

LESS IS MORE

Overtreatment of Enterococcal Bacteriuria

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Background: The purposes of this study were to investigate the clinical outcomes of enterococcal bacteriuria and to determine whether current management is adherent to Infectious Diseases Society of America guidelines.

Methods: We conducted a retrospective medical record review of patients from 2 academic teaching hospitals for 3 months (September 1 through November 30, 2009). Patients were classified as having urinary tract infection (UTI) or asymptomatic bacteriuria (ABU) by applying the guidelines. Antibiotic use was deemed appropriate in patients with UTI and inappropriate in ABU. Medical records were reviewed for *Enterococcus* cultured from another sterile site within 30 days.

Results: A total of 375 urine cultures growing *Enterococcus* were reviewed, with 339 cultures meeting inclusion criteria. Of these 339 episodes, 183 (54.0%) were classified as ABU and 156 (46.0%) as UTI. In 289 epi-

sodes accompanied by urinalysis, pyuria was associated with UTI in 98 of 140 episodes (70.0%) compared with 63 of 149 episodes of ABU (42.3%) (odds ratio, 3.19; 95% CI, 1.96-5.18). Providers inappropriately treated 60 of 183 episodes of ABU (32.8%) with antibiotics. In multivariate analysis, only pyuria was associated with the inappropriate use of antibiotics (odds ratio, 3.27; 95% CI, 1.49-7.18). Only 7 subsequent infections with *Enterococcus* occurred in the 339 episodes of bacteriuria overall (2.1%), with 2 of the 183 cases of ABU (1.1%) having distant infection.

Conclusions: Providers often overtreat enterococcal ABU with antibiotics, particularly in patients with pyuria. Given the low incidence of infectious complications, efforts should be made to optimize the use of antibiotics in enterococcal bacteriuria.

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URINARY TRACT INFECTIONS (UTIs) are among the most common indications for antibiotic use in the community and health care settings.¹⁻⁵ Despite the presence of evidence-based guidelines on the diagnosis and management of UTIs vs asymptomatic bacteriuria (ABU), in practice, ABU is often misdiagnosed as UTI and inappropriately treated.^{6,9} Enterococci have become an increasingly common cause of UTI, accounting for greater than 30% of all bacterial isolates causing UTI among hospitalized patients.¹⁰⁻¹³ Enterococci are intrinsically resistant to many antimicrobials and can rapidly develop resistance to a broad range of antibiotics, implying that overuse of antibiotics for enterococcal bacteriuria should be avoided.^{14,15}

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The presence of enterococci in the urinary tract is often asymptomatic.^{16,17} According to current Infectious Diseases So-

ciety of America (IDSA) guidelines, also endorsed by the US Preventive Services Task Force, ABU should not be treated with antibiotics except in a limited number of patients, such as pregnant women and patients undergoing urologic manipulation.^{18,19} The increasing frequency of enterococcal urinary tract colonization and its association with indwelling urinary catheters may influence physicians to overtreat ABU caused by enterococci.^{6,9,20} Unfortunately, broad-spectrum antibiotic use is a risk factor for developing vancomycin-resistant *Enterococcus* (VRE),^{21,22} and colonization with VRE is in turn associated with increased rates of morbidity and mortality.²³⁻²⁵

See Invited Commentary at end of article

With the growing awareness of the role of antimicrobial stewardship in limiting the spread of resistant organisms, it is important to understand how providers manage enterococcal bacteriuria and its clinical outcomes. However, existing reports of enterococcal bacteriuria have generally not

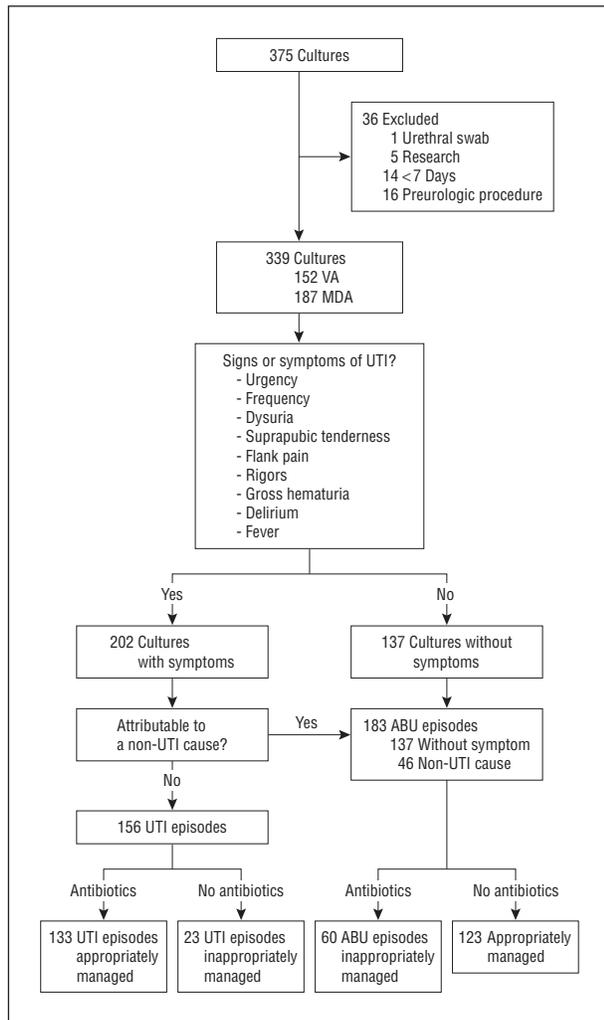


Figure. Patient inclusion and exclusion criteria and Infectious Diseases Society of America–based algorithm used to classify patients. ABU indicates asymptomatic bacteriuria; MDA, MD Anderson Cancer Center; UTI, urinary tract infection; and VA, Veterans Affairs Medical Center.

distinguished between UTI and ABU and have not used definitions of ABU that fit currently accepted standards.^{16,17,26,27} Our objectives were to study enterococcal bacteriuria with an awareness of the distinction between UTI and ABU, to investigate clinical situations in which providers are likely to mistakenly treat enterococcal ABU with antibiotics, and to describe the clinical outcomes of *Enterococcus* in the urine.

METHODS

STUDY POPULATION

We performed a retrospective medical record review at 2 tertiary care, academic teaching hospitals in Houston, Texas: the Michael E. DeBakey Veterans Affairs Medical Center (VA) and the MD Anderson Cancer Center (MDA). This study was approved by the institutional review boards of both hospitals. Patients were included if *Enterococcus* sp were cultured from their urine (regardless of colony-forming units [CFU] or presence of other organisms) from September 1 through November 30, 2009. The lower limit of detection for the microbiology laboratories of the 2 study hospitals was 10^3 CFU/mL of urine. All urine cultures had been

ordered by the patients' health care providers. Patients were excluded if the culture had been collected before a urologic procedure, for research, or from a urethral swab (Figure).

DATA COLLECTION

The unit of analysis was an episode of bacteriuria; patients could therefore have multiple episodes of bacteriuria during the study period. We considered additional urine cultures within 7 days to be part of the same episode. One of us reviewed all episodes of bacteriuria from the VA (E.L.), and another reviewed all episodes of bacteriuria from the MDA (Y.B.). Thirty medical records at each site (60 episodes total) were reviewed by both of us to establish interobserver reliability. For each episode of bacteriuria, the reviewers abstracted demographic data, certain comorbidities, urinary catheterization status, and relevant clinical data. Laboratory data collected included urine bacterial and cell counts and serum leukocyte counts. We reviewed microbiology records for 30 days after each episode of enterococcal bacteriuria to determine whether the patient developed *Clostridium difficile* or an enterococcal infection at a distant, normally sterile body site. Adverse drug reactions within 30 days of antibiotic use were sought in the medical records.

GUIDELINES FOR DETERMINING DIAGNOSIS AND APPROPRIATENESS OF TREATMENT

Each episode of bacteriuria was classified as either UTI or ABU based on an algorithm derived from the IDSA guidelines^{19,28} (Figure). We defined *UTI* as the presence of bacteriuria with 1 or more of the following signs and symptoms and no other identifiable cause: urgency, frequency, dysuria, suprapubic tenderness, flank pain, rigors, gross hematuria, delirium, or fever (temperature $\geq 37.8^\circ\text{C}$). We defined *ABU* as bacteriuria without any of these symptoms or as bacteriuria with symptoms clearly attributable to a nonurinary cause. Antibiotic use was considered *appropriate* for a UTI or if the provider did not prescribe antibiotics for an ABU. Likewise, an antibiotic treatment decision was *inappropriate* if antibiotics were given for ABU or if antibiotics were not given for a UTI (Figure). For study purposes, *appropriate* refers only to whether antibiotics were indicated, not to whether the correct antibiotic was chosen for the organism isolated.

OTHER DEFINITIONS

Immunocompromise was defined as having any of the following conditions: potentially bone marrow suppressive chemotherapy within 30 days of urine culture, infiltrative hematologic disease of the bone marrow, concomitant use of systemic corticosteroids, diagnosis of human immunodeficiency virus regardless of CD4 cell count, and neutropenia (absolute neutrophil count $< 500/\mu\text{L}$ [to convert to $\times 10^9/\text{L}$, multiply by 0.001]). *Catheterization* refers to the presence of a Foley, condom, or suprapubic catheter for 48 hours or more. *Catheter duration* was calculated by measuring the number of days between the first day of catheterization and the day of the urine culture collection, including any catheter-free period of 48 hours or less. *Chronic catheterization* was defined as catheter duration of more than 30 days. A serum white blood cell count greater than $10\,000/\mu\text{L}$ (to convert to $\times 10^9/\text{L}$, multiply by 0.001) was considered *leukocytosis*. More than 10 red blood cells and 10 white blood cells per high-power field via automated microscopy of the urine defined *microscopic hematuria* and *pyuria*, respectively.

Table 1. Association Between Patient Characteristics and UTI^a

Characteristic	No. (%) of Episodes			OR (95% CI)	P Value
	Combined (N = 339)	UTI	ABU		
Age ≥65 y	177 (52.2)	90/156 (57.7)	87/183 (47.5)	1.50 (0.98-2.31)	.06
Male sex	216 (63.7)	105/156 (67.3)	111/183 (60.7)	1.34 (0.85-2.09)	.20
Specific comorbidities					
Immunocompromise	85 (25.1)	38/156 (24.4)	47/183 (25.7)	0.93 (0.57-1.53)	.78
Diabetes mellitus	77 (22.7)	36/156 (23.1)	41/183 (22.4)	1.04 (0.62-1.73)	.88
Neurogenic bladder	36 (10.6)	20/156 (12.8)	16/183 (8.7)	1.53 (0.77-3.08)	.22
Neutropenia (ANC <1000/μL) (n = 337)	24 (7.1)	17/155 (11.0)	7/182 (3.8)	3.08 (1.24-7.64)	.02 ^b
Location					
Inpatient and emergency department	260 (76.7)	117/156 (75.0)	143/183 (78.1)	0.84 (0.51-1.39)	.50
Outpatient clinic	79 (23.3)	39/156 (25.0)	40/183 (21.9)	1.19 (0.72-1.97)	.50
Catheter (n = 332)					
Present (>48 h)	111 (33.4)	63/151 (41.7)	48/181 (26.5)	1.98 (1.25-3.15)	.004
Chronic (>30 d)	55 (16.6)	35/151 (23.2)	20/181 (11.0)	2.43 (1.33-4.42)	.003
Vancomycin resistance (n = 292)	38 (13.0)	17/138 (12.3)	21/154 (13.6)	0.89 (0.45-1.77)	.74
Quantity >10 ⁵ CFU/mL (n = 338)	95 (28.1)	64/156 (41.0)	31/182 (17.0)	3.39 (2.05-5.59)	<.001
Peripheral leukocytosis (WBC count >10 × 10 ⁹ /L) (n = 287)	101 (35.2)	43/127 (33.8)	58/160 (36.2)	0.90 (0.55-1.47)	.67
Urinalysis collected (n = 289)					
Pyuria (>10 WBCs/HPF)	161 (55.7)	98/140 (70.0)	63/149 (42.3)	3.19 (1.96-5.18)	<.001
Microscopic hematuria (>10 RBCs/HPF)	97 (34.0)	62/140 (44.3)	35/149 (23.5)	2.59 (1.56-4.29)	<.001
Antibiotics prescribed	193 (57.0)	133/156 (85.2)	60/183 (32.9)	11.85 (6.91-20.33)	<.001

Abbreviations: ABU, asymptomatic bacteriuria; ANC, absolute neutrophil count; CFU, colony-forming units; HPF, high-power field; OR, odds ratio; RBC, red blood cell; UTI, urinary tract infection; WBC, white blood cell.

SI conversion factors: To convert ANC and WBC count to ×10⁹/L, multiply by 0.001.

^aThis table presents a univariate analysis of patient characteristics and the risk of UTI over ABU using combined data from both sites. Results are given as the number (percentage) of episodes unless otherwise specified. Some episodes are excluded for missing data, resulting in a sample size of less than 339. The χ^2 test was used to calculate *P* values except when specified.

^bBy the Fisher exact test.

STATISTICAL ANALYSIS

Demographic data were analyzed using the *t* test for continuous variables and the χ^2 or Fisher exact test for categorical variables. To determine the characteristics significantly associated with UTI, univariate analysis was performed on the demographic, clinical, and laboratory data by calculating odds ratios (ORs). To identify factors associated with the inappropriate use of antibiotics, univariate analysis was also performed on the subset of ABU episodes treated with antibiotics. Multivariable logistic regression analysis was performed using variables that were significantly associated with the use of antibiotics in patients with ABU episodes by univariate analyses (*P* < .05). A sensitivity analysis was performed by including variables with *P* < .10 by univariate analysis and a variable indicating whether the culture was from the MDA or the VA. All data analysis was performed using SAS statistical software, version 9.2 (SAS Institute, Inc).

RESULTS

PATIENT DEMOGRAPHICS

We analyzed a total of 375 urine cultures positive for *Enterococcus* sp, with 185 from the VA and 190 from the MDA. A total of 36 cultures was excluded from the study for reasons shown in the Figure, resulting in 339 unique episodes of enterococcal bacteriuria (152 from the VA and 187 from the MDA) from 328 unique patients (141 from the VA and 187 from the MDA). There were 38 total

episodes of VRE isolated from 292 cultures with reported sensitivities to antibiotics (13.0%), with 23 of 139 isolates (16.5%) with VRE at the VA and 15 of 153 (9.8%) with VRE at the MDA (*P* = .12).

DIAGNOSIS OF UTI

Of these 339 episodes, we classified 183 as ABU and 156 as UTI (Figure). The interobserver reliability was significant between the 2 reviewers (Cohen κ of 0.87). The diagnosis of UTI at both sites was based on similar symptoms, with the 3 most common presenting symptoms being fever (41.7%), dysuria (30.1%), and delirium (14.1%). Of note, 93 episodes of bacteriuria were accompanied by a documented fever (temperature $\geq 37.8^\circ\text{C}$) within 48 hours, but only 65 of these were classified as UTI because the other 28 episodes had an evident, non-urinary cause for fever.

We analyzed characteristics associated with UTI as opposed to ABU (Table 1). Whereas immunocompromise of any cause was not significantly associated with UTI compared with ABU, the neutropenic (absolute neutrophil count <1000/μL) subset was more than 3 times more likely to have UTI than nonneutropenic patients. Catheterization was associated with a nearly 2-fold increase in UTI compared with ABU. Having at least 10⁵ CFU/mL of *Enterococcus* was associated with a 3 times greater likelihood of having UTI compared with ABU, with a sensitivity of 41% and a specificity of 83%. Whereas

Table 2. Summary of Distant Infectious Complications by *Enterococcus* Within 30 Days of Bacteriuria

Patient No.	Comorbidities	Symptoms	Diagnosis	Treatment	Infection Site
1	None	Delirium, fever	UTI	Ampicillin	Bacteremia
2	Diabetes mellitus	Fever	UTI	None	Bacteremia
3	None	Fever	UTI	Vancomycin hydrochloride	Bacteremia
4	Immunocompromise	None	ABU	None	Peritonitis
5	Immunocompromise	Urgency, fever	UTI	Linezolid, daptomycin	Bacteremia
6	Immunocompromise	Fever	UTI	Vancomycin, amoxicillin-clavulanate, ciprofloxacin	Bacteremia
7	None	None	ABU	Linezolid, trimethoprim-sulfamethoxazole	Bacteremia

Abbreviations: ABU, asymptomatic bacteriuria; UTI, urinary tract infection.

peripheral leukocytosis was not associated with UTI, pyuria was 3.2 times and microscopic hematuria was 2.6 times more likely to be associated with UTI as opposed to ABU. However, the sensitivity and specificity were low for the relationship of pyuria to UTI (70% sensitivity and 58% specificity) and the relationship of microscopic hematuria to UTI (44% sensitivity and 77% specificity).

TREATMENT OF BACTERIURIA

Patients with episodes of symptomatic UTI were almost 12 times more likely to receive antibiotics than those with episodes of ABU by univariate analysis (Table 1). However, 60 of 183 patients with ABU episodes (32.8%) still were inappropriately given antibiotics. Conversely, 23 of 156 patients with UTI episodes (14.7%) were inappropriately undertreated (no antibiotics given). Of the 193 instances when providers prescribed antibiotics for enterococcal bacteriuria, 60 (31.1%) actually had ABU. Taken together, 83 of 339 total episodes (24.5%) were managed incorrectly.

We analyzed the subset of episodes of ABU treated with antibiotics to determine the characteristics associated with inappropriate use of antibiotics. Of all characteristics studied, only pyuria and microscopic hematuria were associated with the use of inappropriate antibiotics by univariate analysis (for pyuria: OR, 4.43; 95% CI, 2.16-9.08; for hematuria: OR, 4.02; 95% CI, 1.82-8.87). On multivariate analysis, only pyuria showed significant association with the use of inappropriate antibiotics, with a 3.27-fold increase in use of antibiotics in episodes of ABU (95% CI, 1.49-7.18). This finding persisted on sensitivity analysis.

COMPLICATIONS AFTER BACTERIURIA

Of the 339 episodes of enterococcal bacteriuria, only 7 subsequent infections with *Enterococcus* occurred within 30 days of the bacteriuria, for an overall rate of 2.1% (Table 2). All subsequent infectious episodes occurred in unique patients. Six of these infectious complications were bacteremia and 1 was a case of peritonitis. Of these episodes of distant enterococcal infection, 5 followed UTI and 2 followed ABU. The rates of distant infectious complications after UTI compared with ABU were not statistically different, with 5 of 156 cases of UTI (3.2%) having distant infection and 2 of 183 cases of ABU (1.1%) having distant infection ($P = .25$). Of 133 episodes of treated UTI, 4 (3.0%) were followed by a subsequent in-

fection, whereas 1 of 23 untreated episodes of UTI (4.3%) resulted in distant infection ($P = .55$). When the original urinary isolates and subsequent sterile site isolates were compared, 3 had the same susceptibility to vancomycin hydrochloride, 3 differed in their susceptibility to vancomycin, and in 1 episode the susceptibility pattern of the urinary isolate had not been determined. Both of the distant infections that followed ABU occurred in patients with significant comorbidities.

ANTIBIOTIC USE

The most commonly used antibiotics were fluoroquinolones and vancomycin (Table 3). Quinolone use was nearly equivalent between the UTI and ABU groups ($P = .73$). On the other hand, use of vancomycin was more common for UTI ($P = .04$). Of the 193 instances of patients receiving antibiotics for their bacteriuria, the use in 5 episodes (2.6%) resulted in adverse effects, with 4 cases of *C difficile* and 1 case of drug-related rash. Three of these episodes occurred in patients treated for ABU (2 episodes of *C difficile* and drug-related rash), with the other 2 episodes of *C difficile* occurring in patients treated for UTI.

COMMENT

To our knowledge, this is the largest study to date investigating the clinical significance and the appropriateness of antibiotic use in patients with enterococcal bacteriuria. Despite published evidence-based guidelines, nearly one-third of episodes of enterococcal ABU were inappropriately treated with antibiotics, particularly when pyuria was also present. Moreover, the low complication rate in the entire study population provides additional evidence against prescribing antibiotics in patients with enterococcal ABU, even in those patients with medical comorbidities.

The challenge of appropriately diagnosing and treating UTI is an area of active investigation, especially given the recent emphasis on cost-effective medical treatment. Recently, Rotjanapan et al⁸ documented that most noncatheterized patients receiving antibiotics for UTI in 2 nursing homes did not meet the McGeer surveillance criteria for having a UTI.²⁹ Nonspecific symptoms, such as fever, can be misleading in catheterized patients, as was documented more than 2 decades ago by Warren et al,³⁰ where more than one-third of febrile episodes in 47 women in nursing homes were clearly attributable to a

Table 3. Antibiotics Used to Treat Bacteriuria by *Enterococcus*^a

Antibiotic	No. (%) of Cases			P Value
	Total Drug (N = 193)	UTI (n = 133)	ABU (n = 60)	
Quinolone	100 (52)	70 (53)	30 (50)	.73 ^b
Vancomycin	44 (23)	36 (27)	8 (13)	.04
Ampicillin	32 (17)	26 (20)	6 (10)	.14
Linezolid	23 (12)	19 (14)	4 (7)	.16
Trimethoprim-sulfamethoxazole	18 (9)	10 (8)	8 (13)	.28
Carbapenem	15 (8)	11 (8)	4 (7)	.78
Nitrofurantoin	8 (4)	4 (3)	4 (7)	.26

Abbreviations: ABU, asymptomatic bacteriuria; UTI, urinary tract infection.

^aThis table includes the 193 patients who received antibiotics for enterococcal bacteriuria. Only antibiotics used in more than 6 episodes are listed in this table; antibiotics used 6 or fewer times in order of decreasing frequency were daptomycin, tetracycline, aminoglycosides, clindamycin, tigecycline, and penicillin. All P values were calculated using the Fisher exact test, unless otherwise specified, to compare episodes of enterococcal bacteriuria treated with a specific antibiotic to all episodes treated with other antibiotic.

^bBy the χ^2 test.

nonurinary cause. Our study confirms prior reports that laboratory values, such as colony count and pyuria, play a limited role in distinguishing UTI from ABU.³¹

Despite the limited utility of pyuria in making the diagnosis of enterococcal UTI, we found that it was associated with a more than 3-fold increase in the inappropriate use of antibiotics. Recent guidelines specifically state that “pyuria accompanying asymptomatic bacteriuria is not an indication for antimicrobial treatment.”¹⁹ That physicians are not following practice guidelines suggests either a lack of awareness of the guidelines and their contents or a lack of agreement with the recommendations.³² Our IDSA-based algorithm may help improve guideline adherence because our high interrater reliability implies that the algorithm can be applied reliably and consistently by providers to distinguish between ABU and UTI.

There is a paucity of literature characterizing the appropriate choice of antibiotics for enterococcal UTI. Consistent with this lack of data, prescribers used a wide variety of drugs to treat enterococcal UTI. Although quinolones are not considered to be highly active against enterococci,^{15,33} these agents were the most commonly prescribed for both UTI and ABU. Our data suggest that enterococcal UTIs are associated with low complication rates independent of the agent chosen for therapy, making the case for use of narrow-spectrum agents when feasible.

An important strength of our study is that we collected data from 2 very different types of hospitals, thus making our findings more broadly applicable. However, its retrospective nature posed several challenges. For example, we assumed that the absence of recorded symptoms meant that the symptoms were absent, but it is possible that the health care provider did not record such symptoms, leading to misclassification bias. Similarly, although it was impossible to eliminate reviewer bias, the use of a more objective algorithm with high interobserver reliability suggests a mitigation of that bias. Finally, the fact that we did not have access to the bacterial isolates means that we cannot definitively ascribe infectious complications that followed isolation of enterococci from the urinary tract as being due to the same organism. Thus, it is possible that we overestimated the complication rate.

The management of enterococcal ABU is often not in accord with evidence-based practice guidelines. We found that infectious complications with *Enterococcus* were rare, lending support to the recommendation not to treat ABU, even in our patient population with multiple medical comorbidities.

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INVITED COMMENTARY

Enhancing the Safety of Hospitalized Patients

Who Is Minding the Antimicrobials?

All things are preceded by the mind . . .

Siddhārtha Gautama

Guidelines have long recommended against using antimicrobials in hospitalized patients who have bacteriuria but no symptoms of a urinary tract infection (UTI). Asymptomatic bacteriuria is com-

monly found in hospitalized patients, often when urine cultures are appropriately ordered in patients with complex problems for which UTI may provide one of many possible explanations. Unfortunately, when asymptomatic bacteriuria is identified, antimicrobials often follow.¹ In this issue of the *Archives*, Lin and colleagues² evaluate antimicrobial use in patients with enterococcal bacteriuria. The authors retrospectively reviewed medi-