Bacteremia and Mortality with Urinary Catheter—Associated Bacteriuria

Author(s): Quratulain F. Kizilbash, MD, MPH; Nancy J. Petersen, PhD; Guoqing J. Chen, MD, MPH, PhD; Aanand D. Naik, MD; Barbara W. Trautner, MD, PhD

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ORIGINAL ARTICLE

Bacteremia and Mortality with Urinary Catheter–Associated Bacteriuria

Quratulain F. Kizilbash, MD, MPH;[1,2] Nancy J. Petersen, PhD;[2,3,4] Guoqing J. Chen, MD, MPH, PhD;[2,3,4] Aanand D. Naik, MD;[2,3,5] Barbara W. Trautner, MD, PhD[1,2,3]

OBJECTIVE. Although catheter-associated urinary tract infection (CAUTI) and catheter-associated asymptomatic bacteriuria (CAABU) are clinically distinct conditions, most literature describing the risks of bacteriuria does not distinguish between them. We studied the relationship between catheter-associated bacteriuria and bacteremia from a urinary source in CAUTI relative to that in CAABU. Second, we investigated whether the presence or absence of urinary symptoms in catheterized patients with bacteriuria was associated with bacteremia from any source or mortality. Finally, we explored the effect of antimicrobial treatment of bacteriuria on subsequent bacteremia from any source and mortality.

DESIGN. We performed a retrospective cohort study with 30 days of follow-up after an initial positive urine culture. CAUTI and CAABU were defined by Infectious Diseases Society of America guidelines.

SETTING. A large tertiary care facility.

PATIENTS. All inpatients with a urinary catheter (external or indwelling) and a positive urine culture between October 2010 and June 2011.

RESULTS. We captured 444 episodes of catheter-associated bacteriuria in 308 patients; 128 (41.6%) patients had CAUTI, and 180 (58.4%) had CAABU. Three episodes of bacteriuria were followed by bacteremia from a urinary source (0.7%). CAUTI, rather than CAABU, was associated with bacteremia from any source, but neither CAUTI nor CAABU predicted subsequent mortality. Use of antimicrobial agents to treat bacteriuria was not associated with either bacteremia from any source or mortality.

CONCLUSIONS. Bacteremia from a urinary source was infrequent, and there was no evidence of an association of mortality with symptomatic versus asymptomatic bacteriuria in this population. Antibiotic treatment of bacteriuria did not affect outcomes.

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Catheter-associated bacteriuria is extremely common worldwide,[1] and it is estimated that more than 30 million indwelling catheters are placed annually in the United States, resulting in several hundred thousand cases of catheter-associated bacteriuria.[2] Potential complications of catheter-associated bacteriuria include catheter-associated urinary tract infection (CAUTI), urinary-source bacteremia, and mortality.

Existing evidence suggests that catheter-associated bacteriuria is associated with a low rate of subsequent bacteremia and may not have a strong causal relationship with mortality. For example, in a prospective study of 1,497 patients with newly placed urinary catheters, 235 (15.7%) developed new-onset catheter-associated bacteriuria, but only 1 (0.07%) of these episodes clearly resulted in bacteremia.[3] The relationship between urinary catheter–associated bacteriuria and mortality is more controversial. Platt et al,[4] in 1982, attributed a 3-fold increase in mortality to catheter-associated bacteriuria. However, subsequent studies using a more standardized adjustment for severity of illness have not supported a causal relationship.[5,6]

Most literature on the clinical consequences of catheter-associated bacteriuria does not distinguish whether the patient had symptoms related to the urinary tract (ie, CAUTI) or whether the bacteriuria was asymptomatic (catheter-associated asymptomatic bacteriuria, or CAABU). Guidelines from the Infectious Diseases Society of America (IDSA) and other organizations have clearly distinguished between these two conditions and strongly advocate against treating CAABU.[7-12] However, with the existing research gap, we do not know whether untreated CAUTI is more likely than

Affiliations: 1. Section of Infectious Diseases, Department of Medicine, Baylor College of Medicine, Houston, Texas; 2. Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; 3. Houston Veterans Affairs Health Services Research and Development Center of Excellence, Houston, Texas; 4. Section of Health Services Research, Department of Medicine, Baylor College of Medicine, Houston, Texas; 5. Section of Geriatrics, Department of Medicine, Baylor College of Medicine, Houston, Texas.

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CAABU to lead to negative outcomes in terms of bacteremia and mortality. Furthermore, we do not yet know whether treatment of CAUTI confers benefits beyond symptom relief, in terms of preventing bacteremia or mortality. Certain patient subgroups with catheter-associated bacteriuria may be at increased risk of bacteremia and thus be good candidates for targeted antimicrobial treatment.[13-15] The idea of restricting antibiotic use to patients who are likely to benefit is a core tenet of the US Centers for Disease Control and Prevention's (CDC's) "Use Wisely" campaign to reduce antibiotic overuse.

We had 3 objectives. First, we sought to describe the relationship between catheter-associated bacteriuria and bacteremia from a urinary source, in CAUTI relative to CAABU. Second, we investigated whether the presence or absence of guidelines-defined urinary symptoms (CAUTI or CAABU) in catheterized patients with bacteriuria was associated with either bacteremia or mortality. Finally, we explored the effect of antimicrobial treatment of bacteriuria on bacteremia and mortality.

METHODS

Setting, Design, and Study Population

We conducted a retrospective cohort study in 5 medicine and 5 extended care wards of a tertiary care facility, with approval from the Baylor College of Medicine Institutional Review Board and the Houston Veterans Affairs (VA) Research and Development Committee. Our extended care wards are in the same building as the acute care wards and encompass long-term assisted care as well as subacute rehabilitation beds. All patients who had both a urinary catheter and a positive urine culture (defined as a culture showing bacterial or fungal growth) between October 2010 and June 2011 were included. Our microbiology laboratory threshold for reporting bacterial or fungal growth in the urine is at least 10^3 organisms/mL, which meets the IDSA definition of CAUTI. We used the microbiology laboratory threshold for positive urine cultures at our institution, as this threshold reflects the clinician's perspective. Both external (condom) catheters and indwelling urinary catheters meet the IDSA definition of urinary catheter use and were thus included in this study.

Classification of Bacteriuria as CAUTI or CAABU

Data were abstracted from the electronic medical records system by trained research personnel using an established chart-based surveillance method validated against a criterion standard of direct observation.[16] Episodes of catheter-associated bacteriuria were classified by 2 investigators as either CAUTI or CAABU after a thorough systematic chart review starting from 2 days before to 1 week after the urine culture sample was collected, using a diagnostic pathway developed from the IDSA practice guidelines for CAUTI.[7,17,18] We defined CAUTI as the presence of at least 10^3 colony-forming units/mL of at least one organism from the urine of a patient with one or more of the following signs and symptoms and no other identifiable cause: urgency, frequency, dysuria, suprapubic tenderness, pelvic discomfort, flank pain, rigors, gross hematuria, delirium, or fever (temperature of at least 100°F). To meet the definition of CAUTI, the patient had to be currently catheterized or to have had the urinary catheter removed within the preceding 48 hours. Frequency, urgency, and dysuria applied only to those patients whose catheter had been removed. We defined CAABU as bacteriuria or candiduria without any of these symptoms or as bacteriuria or candiduria with symptoms clearly attributable to a nonurinary cause.[9] The rationale for using the clinical IDSA criteria rather than the surveillance CDC/NHSN (National Healthcare Safety Network) criteria was that the IDSA guidelines are written from the clinician's perspective and focus on management decisions, while the CDC/NHSN criteria are intended for surveillance rather than to guide clinical decision making. The kappa statistic for the level of agreement between members of the research team regarding classification of cases of catheter-associated bacteriuria as CAABU versus CAUTI was 0.73 (86.7% agreement), or substantial agreement.[19,20] All urine samples cultured within 7 days of the collection of the original positive culture sample were considered part of the same episode.

Detecting Bacteremia and Mortality

All positive blood cultures and all deaths from 1 day before to 30 days after the urine culture (defined as the time the sample for the original positive urine culture was collected) were recorded. Bacteremia was defined as any bacterial or fungal growth from a blood culture specimen, excluding coagulase-negative staphylococci and corynebacteria, as these could potentially have been skin contaminants. To explore the relationship between bacteriuria and bacteremia and to determine whether the bacteremia was potentially from a urinary source, we classified each episode of bacteremia as a definite match, a possible match, or discordant from the organisms isolated in the urine. A definite match meant that the urine and blood organisms were identical on a genus-and-species level, if species-level identification was available. A possible match meant that we had inadequate information to declare a definite match but that the organisms in the blood and urine might be the same. For example, if the urine grew gram-positive organisms, not further identified, and the blood grew *Staphylococcus aureus*, this would be a possible match. When the organisms clearly differed, for example, urine culture with a gram-negative organism and blood culture with *S. aureus*, we classified these cultures as discordant. If the blood cultures were done on the day before or the day of the urine culture, the bacteriuria was considered concurrent with the bacteremia. If the blood cultures were done from 1 to 30 days after the urine culture, the bacteriuria was considered prior to the bacteremia. We studied all-source bacteremia, not just urinary-source bacteremia, as the broad-

spectrum antibiotics often used empirically to treat suspected CAUTI might have a beneficial effect in treating organisms beyond a urinary source.

Determining Antimicrobial Treatment

Data on all antimicrobials prescribed from 7 days before to 30 days after the original urine culture for all urine culture episodes were extracted from the pharmacy database of VA Decision Support System Clinical National Data Extracts.[21] We also reviewed the electronic medical records to determine whether the antimicrobial agents given were intended to treat urinary organisms. We defined 2 variables for antimicrobial use: those given specifically for treatment of bacteriuria (defined as antimicrobials given for bacteriuria) and any antimicrobials given from 7 days before to 30 days after the urine culture (defined as any antimicrobials). The "any antimicrobials" category includes "antimicrobials given for bacteriuria."

STATISTICAL ANALYSIS

Univariate Analysis

Univariate analysis was used to test for differences in characteristics associated with CAUTI and CAABU. A *t* test was performed for continuous variables, Fisher's exact test was used to analyze categorical variables with 2 possible categories, and the χ^2 test was used for categorical variables with more than 2 categories.

Multivariable Analysis

Multivariable analysis was used to explore Aim 2, the relationship between urinary symptoms (CAUTI vs CAABU) and the 2 outcomes of bacteremia from any source and mortality. Hierarchical logistic regression with nesting of urine culture episodes within patients was used to analyze cases of bacteremia from any source, whereas mortality analysis was based on individual patients rather than episodes of bacteriuria. Independent variables included the classification of catheter-associated bacteriuria as CAABU or CAUTI; demographic and clinical characteristics, including age, race, and Charlson comorbidity score; catheter type and duration; and the category of organisms in the urine. Urine microbiology results, including polymicrobial cultures, were placed into 3 mutually exclusive and exhaustive categories: (1) any gram-negative organisms present (with or without other species), (2) *Candida* alone present (no other organisms), and (3) all remaining urine culture results (eg, mixed gram-positive organisms). To explore our third aim, the effect of antimicrobials on the 2 outcomes of bacteremia from any source and mortality, we added a variable for antimicrobial use to the independent variables described above for Aim 2. To assess whether our classification of catheter-associated bacteriuria as CAABU or CAUTI might have resulted in a change in the significance of our findings, we also ran these models while excluding the CAABU-versus-CAUTI variable. All data analyses used SAS statistical software, version 9.2 (SAS Institute). A *P* value of .05 or less was considered statistically significant.

RESULTS

Numbers of Patients and Episodes of Bacteriuria

We captured 444 cases of catheter-associated bacteriuria in 308 unique patients. Table 1 describes the baseline characteristics of the 308 unique patients, based on the last urine culture sample collected from each patient. The mean age of patients was 72.3 years (standard deviation, 11.4), and the mean Charlson comorbidity score was 4.1 (standard deviation, 3.2). The study sample includes 253 (82.1%) patients from the medical wards and 55 (17.9%) from the extended care wards. Of the 308 patients included in our study, all with urinary catheters of some type, 45.5% of the patients in the extended care unit had indwelling catheters, whereas 60.1% in medical care units had indwelling catheters ($P = .047$, χ^2). Among study patients, 277 of 308 (89.9%) received some antimicrobial agent during the period from 7 days before to 30 days after the urine culture. Overall mortality was 21.1% (61 of 308 patients) within 30 days. Among the 444 episodes of positive urine culture, an indwelling catheter was associated with 258 (58.1%) and an external catheter was associated with 186 (41.9%); 285 (64.2%) of these urine cultures had at least one gram-negative organism, 58 (13.1%) had *Candida* alone, and 101 (22.8%) had either exclusively gram-positive organisms or both gram-positive organisms and *Candida*. In order of frequency, the symptoms used to make a diagnosis of CAUTI rather than CAABU were fever, delirium, hematuria, dysuria, suprapubic tenderness, increased frequency, pelvic discomfort, flank pain, urgency, and rigors.

Description of Relationship between Bacteriuria and Bacteremia from a Urinary Source

Among the 444 episodes of positive urine culture, 52 (11.7%) showed bacteremia from any source in the period from 1 day before to 30 days after the urine culture (after 36 episodes in which the organism in the blood culture was either coagulase-negative staphylococci or corynebacteria were excluded). Details of 9 (2% of 444) episodes of bacteriuria in which bacteriuria preceded the bacteremia by at least 1 day and in which the organisms in both blood and urine were either definite or possible matches appear in Table 2. These represent the cases of bacteremia for which treatment targeted at the organism in the urine might presumably have prevented subsequent bacteremia. However, 6 of the 9 cases had, upon further chart review, most likely a nonurinary source (Table 2), leaving 3 (0.7% of 444) cases of bacteremia from a urinary source, out of 444 episodes (0.7%), that could possibly have been prevented. One of these 3 cases was CAABU, while the other 2 were CAUTI.

TABLE 1. Univariate Comparison between CAUTI and CAABU Cases by Patient

Characteristic (N = 308)	Patients with CAUTI (n = 128)	Patients with CAABU (n = 180)	P value
Age, years			.78
≥65	88 (68.8)	121 (67.2)	
<65	40 (31.3)	59 (32.8)	
Sex			.58
Male	123 (96.1)	175 (97.2)	
Female	5 (3.9)	5 (2.8)	
Race			.96
White	65 (50.8)	88 (48.9)	
Black	49 (38.3)	72 (40.0)	
Hispanic	8 (6.3)	10 (5.6)	
Other/unknown	6 (4.7)	10 (5.6)	
Charlson comorbidity score, mean (SD)	3.79 (3.01)	4.25 (3.35)	.22
Urinary catheter type			.30
Indwelling	78 (60.9)	99 (55)	
External	50 (39.1)	81 (45)	
Any antimicrobials received	125 (97.7)	155 (86.1)	<.001
Antimicrobials received for bacteriuria	117 (91.4)	90 (50.0)	<.001
Mortality within 30 days	21 (16.4)	44 (24.4)	.09

NOTE. Unless otherwise specified, data are number (%) of patients. CAUTI, catheter-associated urinary tract infection; CAABU, catheter-associated asymptomatic bacteriuria; SD, standard deviation.

Association of Urinary Symptoms (CAUTI or CAABU) with Bacteremia or Mortality

Of 52 episodes of bacteremia from any source within 30 days, 32 (61.5%) occurred with episodes of CAUTI, and 20 (38.5%) occurred with episodes of CAABU. CAUTI, rather than CAABU, was significantly associated with bacteremia from any source, while having an external catheter rather than an indwelling catheter was protective (see Table 3). The variables significantly associated with mortality were a higher Charlson comorbidity score and having a pure growth of *Candida* versus a gram-negative organism in the urine culture (see Table 3). CAUTI versus CAABU was not associated with mortality.

Effect of Antimicrobial Treatment for Bacteriuria on Bacteremia and Mortality

Administration of antimicrobials for bacteriuria did not affect the risk of bacteremia from any source or mortality within 30 days. We reran the analysis after removing the CAABU-versus-CAUTI variable and again did not find an association between the use of antimicrobials for bacteriuria and bacteremia from any source or mortality. Since all 52 bacteremia episodes were associated with prescription of at least one antimicrobial agent within the period from 7 days before to 30 days after the original positive urine culture, we were unable to analyze whether withholding antimicrobials entirely would have affected the occurrence of bacteremia from any source. When we repeated the multivariate analysis for mortality using the variable of any antimicrobial use from 7 days before to 30 days after the urine culture, there still was no difference in mortality at 30 days between the 2 groups (P = .59).

DISCUSSION

We studied the difference in outcomes between CAUTI and CAABU, as defined by IDSA guidelines. CAUTI, rather than CAABU, was significantly associated with bacteremia from any source but not with mortality. Administration of antimicrobials for bacteriuria did not affect the risk of bacteremia from any source or mortality within 30 days within this group of patients with substantial comorbidities and high underlying antimicrobial use. The lack of effect of antimicrobials was not affected by whether we included presence or absence of urinary symptoms as a variable.

The purpose of treating CAUTI is 2-fold: to relieve symptoms[7] and to prevent bacteremia from a urinary source and, potentially, sepsis and death.[13,22] We found that only 3 of the 52 bacteremias from any source (or 3 of 444 [0.68%] catheter-associated bacteriuria episodes) were actually from a urinary source and potentially preventable by treating the urine organism. Our findings are similar to those of Tambyah and Maki,[3] for whom 1 (0.43%) of 235 patients with bacteriuria developed bacteremia from a urinary source. Also, as in the Tambyah and Maki study, 1 of these 3 bacteremias was asymptomatic, with CAABU rather than CAUTI. Our findings raise the question of whether symptom-based classification of cases as CAUTI rather than CAABU is relevant to the use of antimicrobials to prevent bacteremia from a urinary source. Others have suggested tailoring antibiotic therapy to certain patient subgroups that may be at increased risk of bacteremia.[13-15] Our finding that having CAUTI rather than CAABU was significantly associated with bacteremia from any source was not surprising, because one criterion we used for classifying cases of catheter-associated bacteriuria as CAUTI was

TABLE 2. Episodes of Bacteremia Following a Positive Urine Culture with Either a Possible or a Definite Match to the Urinary Organisms

Episode	Organism(s) on urine culture	Organism(s) on positive blood cultures	Days between urine and blood cultures	Classification of episode	Suspected infectious source of bacteremia	Other conditions	Antimicrobials given for bacteriuria?	Outcome at 30 days
1	GPO	*S. aureus*	7	CAUTI	Balanitis: penile swab grew *S. aureus*	Hypopharyngeal cancer, diabetes	Yes	Alive
2	*Proteus*, GPO	*Proteus*	2	CAABU			No	Alive
		S. aureus	16					
		Enterococcus	27		PICC line (*Proteus*), decubitus ulcer	Colorectal cancer (resolved), dementia		
		Candida	30					
3	*E. coli*, GPO	*S. pneumoniae*	6	CAUTI	Pneumonia	Hypertension, osteoporosis	Yes	Dead
4	*Candida*	*E. coli*	15	CAABU	Cholecystitis, necrotizing pneumonia; PICC line (*Candida*)	Cirrhosis	No	Alive
		Candida	26					
5	GPO	*S. aureus*	8	CAABU	Probable endocarditis	Diabetes, renal cell carcinoma	No	Alive
6	*Candida*	*Candida*, *Enterococcus*	5	CAABU	Urinary	Cirrhosis	Yes	Dead
7	GNR, GPO	*Enterobacter*	29	CAUTI	Urinary	Cirrhosis, diabetes	No	Alive
8	*Candida*, GPO	*S. aureus*	16	CAUTI	Endocarditis	Cirrhosis, diabetes	No	Alive
9	*E. coli*	*E. coli*	1	CAUTI	Urinary	Chemotherapy and steroids for lymphoma	Yes	Alive

NOTE. The day the urine sample for culture is collected is considered to be day 0. CAABU, catheter-associated asymptomatic bacteriuria; CAUTI, catheter-associated urinary tract infection; *E. coli*, *Escherichia coli*; GNR, gram-negative rods; GPO, gram-positive organisms; PICC, peripherally inserted central catheter; *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*.

TABLE 3. Multivariable Model for Analysis of Bacteremia from Any Source and Mortality within 30 Days of Urine Culture

	Bacteremia		Mortality	
Independent variables	Odds ratio	95% CI	Odds ratio	95% CI
CAUTI vs CAABU	**2.8**	**1.24–6.22**	0.8	0.40–1.60
Antimicrobials given for bacteriuria	0.7	0.32–1.71	0.9	0.43–1.69
Charlson comorbidity score	0.9	0.66–1.26	**1.1**	**1.01–1.21**
Urinary catheter type: external vs indwelling	**0.5**	**0.22–0.99**	1.5	0.84–2.84
Organisms on urine culture				
Candida in pure culture vs gram-negative rod	0.9	0.31–2.49	**3.6**	**1.57–8.26**
All remaining organisms vs gram-negative rod	1.0	0.43–2.28	1.2	0.58–2.51
Catheter duration: <2 weeks vs >2 weeks or prior to emergency room	1.3	0.63–2.58	0.8	0.43–1.47
Age	0.9	0.75–1.01	1.1	0.96–1.24
Race/ethnicity				
Black vs white	0.9	0.42–1.81	1.1	0.57–1.94
Hispanic vs white	0.5	0.09–2.50	0.8	0.22–3.23
Other/unknown vs white	1.4	0.37–5.52	1.6	0.46–5.33

NOTE. Data from unique patients were used for mortality, and data from nested urine culture episodes were used for bacteremia from any source. Charlson comorbidity score was analyzed in 3-unit increments, ranging from 0 to 33, with higher scores denoting higher comorbidities. Logistic regression was used to determine the odds ratios and 95% confidence intervals for the independent variables. CAABU, catheter-associated asymptomatic bacteriuria; CAUTI, catheter-associated urinary tract infection, CI, confidence interval.

the presence of fever in the absence of another clear etiology. We found a potentially protective effect of the use of an external catheter rather than an indwelling catheter in terms of bacteremia from any source. This finding should be interpreted with awareness that patients' treatment was often switched from an indwelling catheter to an external catheter and vice versa during the course of follow-up. A plausible biologic explanation is that the external catheters are less likely to cause mucosal trauma than indwelling catheters, thus decreasing the risk of bacteremia.

Our study population had a high mortality rate (21.1%), comparable to the mortality seen among catheterized patients with bacteriuria in past studies (18%–43%).[4-6] Our study population had a high comorbidity score, with an average of 4.1, and a higher Charlson comorbidity score was associated with mortality. Given that patients were admitted with a variety of conditions and that they were not in an intensive care unit at the time of the urine culture, there was no overall score for severity of acute illness that we could have used in our analysis, and we did not examine the reported cause of death. Having a pure growth of *Candida* versus a gram-negative organism in the urine culture was also associated with mortality within 30 days. An association between candiduria and crude mortality has been found in multiple other studies of hospitalized patients and is likely a reflection of heavy prior antimicrobial use in patients with substantial underlying comorbidities.[23-27]

One limitation of our retrospective study design is that classification of urine cultures as CAUTI or CAABU was based on chart review. Providers who added antibiotics to patients with bacteriuria usually provided justification in the notes, documenting whether the antimicrobial agents were added for a urinary or a nonurinary infectious source, and we used this to determine the indication for antimicrobial use. Although it would have been ideal to further clarify antimicrobials as appropriate or inappropriate on the basis of matches to the susceptibility of organism(s) in the urine, this was impractical, given that the catheter-associated bacteriuria was often polymicrobial and that patients' treatment was often switched from one antimicrobial to another. It was disheartening to note that 50% of the patients with CAABU received antimicrobials targeting their urinary tract organisms. Our study results cannot be generalized to all patients with urinary catheters, as most of our patients were men, and condom catheter use may have been more common in this facility than in other settings. The strengths of the study include the emphasis on distinguishing CAUTI from CAABU and the relatively large sample of episodes of bacteriuria. Given the low number of cases of bacteremia of urinary origin, a multicenter study would be necessary to focus specifically on that outcome. We also looked at the greater context of all antimicrobial agents used in our study population, taking into account that patients who develop catheter-associated bacteriuria are likely to receive antimicrobial agents regardless of whether they receive specific treatment for urinary flora.

Our findings document that bacteremia from a urinary source is infrequent in patients with catheter-acquired bacteriuria, and there was no evidence of an association of all-cause mortality with symptomatic versus asymptomatic bacteriuria in this population. Furthermore, antibiotic treatment of bacteriuria, symptomatic or asymptomatic, was not associated with decreased mortality.

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Address correspondence to Barbara Wells Trautner, MD, PhD, MEDVAMC (MCL 111), 2002 Holcombe Boulevard, Houston, TX 77030 (trautner@bcm.edu) or Aanand Naik, MD, MEDVAMC (152), 2002 Holcombe Boulevard, Houston, TX 77030 (anaik@bcm.edu).

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