

Predictors and Outcomes of Antibiotic Adequacy for Bloodstream Infections in Veterans With Spinal Cord Injury

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ABSTRACT. Evans CT, Burns SP, Chin A, Weaver FM, Hershow RC. Predictors and outcomes of antibiotic adequacy for bloodstream infections in veterans with spinal cord injury. *Arch Phys Med Rehabil* 2009;90:1364-70.

Objective: To identify predictors and outcomes associated with receiving inadequate empirical antimicrobial treatment for bloodstream infections (BSIs) in persons with spinal cord injury (SCI).

Design: Retrospective cohort study from October 1, 1997, through September 30, 2004.

Setting: A Department of Veterans Affairs SCI center that serves approximately 700 patients a year.

Participants: Hospitalized patients with SCI (N=123) who had 1 or more BSIs during the study period.

Interventions: Not applicable.

Main Outcome Measures: Adequacy of antimicrobial treatment (inadequate treatment was defined as the absence of antimicrobial agents for a particular organism within 2 days after the collection of blood cultures and/or the microorganism's resistance to the antimicrobial administered), hospital length of stay (LOS) post-BSI infection, and in-hospital and 30-day mortality. Cluster-adjusted multivariable models were assessed.

Results: Over one third (88; 37.4%) of the 235 episodes of BSI identified received inadequate empirical antibiotic treatment. Having a polymicrobial BSI was associated with inadequate treatment (odds ratio [OR]=3.28; 95% confidence interval [CI]=1.62–6.65; $P=.001$). Factors protective against inadequate therapy included having a comorbid pressure ulcer (OR=0.37; 95% CI=0.21–0.68; $P=.001$) or a BSI that was not primary (OR=0.30; 95% CI=0.15–0.58; $P<.0001$). Mortality did not differ between the inadequate and adequate treatment

groups (11.4% vs 10.9%; $P=.92$). Similarly LOS postinfection was not affected by treatment status (inadequate treatment median=22d vs adequate treatment median=27d; $P=.98$).

Conclusions: Over one third of patients received inadequate empirical treatment, which was associated with having a polymicrobial BSI. However, inadequate treatment was not associated with increased mortality or LOS postinfection.

Key Words: Bacteremia; Drug resistance; Drug therapy; Rehabilitation; Spinal cord injuries.

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BLOODSTREAM INFECTIONS ARE one of the most common hospital-acquired infections in persons with SCI^{1,2} and indicated as the third leading cause of death for persons with SCI who survive at least 24 hours postinjury.³ The most common sites of origin for BSI in persons with SCI are the urinary tract, skin, intravascular catheters, and respiratory tract.^{4,5} Risk factors for BSI in persons with SCI are reported to include tetraplegia, neurologically complete lesion,⁴ older age, indwelling bladder catheter, pressure ulcers, recent surgical procedure, underlying malignancy, chronic ventilator dependency, chronic renal insufficiency, malnutrition, and diabetes mellitus.⁵⁻⁷ The most commonly reported causative organisms of BSI in persons with SCI are coagulase-negative staphylococci, *Staphylococcus aureus*, and gram-negative bacteria^{1,4-7}; 4.9% to 25% of episodes are reported to be polymicrobial.^{4,6}

An ever-increasing level of resistance in pathogens causing BSIs has resulted in increased need to treat more complex infections. Antibiotic resistance appears to have contributed to increasing frequency of administration of inadequate antimicrobial therapy for BSIs.⁸ In addition, evidence suggests that the identification of a BSI as community-acquired or HCA (recent contact with the health care system) is important in determining appropriate antimicrobial treatment. It is unlikely, however, that the HCA category is being readily used by most providers to determine where infection was acquired, and thus,

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List of Abbreviations

BSI	bloodstream infection
CI	confidence interval
HCA	health care-associated
LOS	length of stay
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
OR	odds ratio
SCI	spinal cord injury
sp.	species
UTI	urinary tract infection
VA	Veterans Affairs

inadequate empirical treatment may be prescribed. To the investigators' knowledge, only 1 study involving persons with SCI assessed adequacy of antibiotic treatment for BSIs, although risk factors were not assessed.⁷ Montgomerie et al⁷ defined appropriate antibiotics as those with in vitro activity against the causative organism. This category was further divided into treatment started the day of BSI, the day after BSI, and greater than or equal to 2 days after BSI. Antibiotic regimens that were not active in vitro against the causative organism were considered inadequate treatment. Inadequate antibiotics were given in 7.8% of BSI episodes; overall, 36.9% of BSI episodes were given inadequate antibiotics, or appropriate treatment was delayed 2 or more days after the BSI was identified.⁷

More research on treatment of BSIs has been conducted in the general population; reporting rates of inadequate treatment for BSI range from 22% to 33%.⁸⁻¹¹ The following factors have been shown to be associated with inadequate treatment: nosocomial/hospital-acquired BSI, HCA BSI, residing in a nursing home, previous antibiotic treatment, unknown source of BSI, intravascular device, pressure ulcer, polymicrobial episode, and type of organism (eg, MRSA, *Enterococcus* sp., *Pseudomonas* sp., *Acinetobacter* sp., and *Candida*).⁸⁻¹⁰

The impact of inadequate treatment for BSI on outcomes—overall hospital mortality, BSI-related mortality (mortality found to be directly caused by the BSI), and LOS—has varied. Montgomerie⁷ found that inadequate or delayed antibiotic use did not affect BSI mortality in persons with SCI, although it was a small study with limited statistical power. Among hospitalized patients, mortality has been shown to be higher and LOS longer for those treated inappropriately.^{8,10,12} Other studies have shown that adequacy of treatment did not affect mortality or LOS.^{9,11} However, 2 recent review articles on the assessment of the impact of inadequate treatment suggests that the variability in results is caused by a number of issues. One concern is variation in definitions of inadequate therapy. Some studies included definitions of inadequate therapy defined on the basis of in vitro susceptibility data, while others included guideline-recommended care. There are also concerns with distinguishing between empirical and definitive therapy and controlling for baseline severity of illness.^{13,14} In this study, we focused on patients with SCI to assess the prevalence of inadequate empirical therapy for BSIs, factors associated with receiving inadequate therapy, and outcomes (all-cause mortality and LOS postinfection) that occurred after receiving inadequate empirical therapy.

METHODS

Setting and Design

This study involved a retrospective review of clinical data over a 7-year period (October 1, 1997–September 30, 2004) on patients with SCI admitted at a VA tertiary care hospital that provides primary care and specialized SCI services to approximately 700 patients with SCI each year.

Participants

Patients with SCI who had a positive blood culture during a hospitalization within the study period were eligible to be included in the study. Institutional review board approval was received from the study institution to conduct this study.

Definitions for Bloodstream Infection

BSI was defined as having any documented growth from a blood microbiology culture in which isolated organisms were

subjected to antibiotic susceptibility testing. Common skin contaminants (eg, diphtheroids, *Bacillus* sp., *Propionibacterium* sp., coagulase-negative staphylococci, or micrococci) were excluded from the study because a medical record review was not conducted to determine whether these organisms were clinically relevant. Episodes of BSI in the same patient were counted as separate BSI events. If less than 28 days separated cultures showing growth of the same organism, the second BSI episode was counted as a recurrence and excluded from the study. Polymicrobial BSI was defined as having more than 1 microorganism species found in the same culture or multiple cultures from the same day.

Secondary sources of BSI were defined as a positive culture at another site within 7 days of the BSI that had the same organism as found in the BSI culture.⁵ These sources included the urinary, respiratory, and gastrointestinal tract; pressure ulcer/skin or soft tissue; and catheter cultures (if available). If no other site had a positive culture with the same organism, the BSI was defined as primary.

Antimicrobial resistant BSI was defined as follows^{15,16}: (1) MRSA, defined as an *S aureus* isolate with an antibiogram resistant to oxacillin; (2) vancomycin-resistant *Enterococcus*, defined as enterococci strains with intermediate or high-level resistance to vancomycin; (3) antibiotic-resistant *Pseudomonas aeruginosa*, defined as resistance to 2 or more of the antipseudomonal agents, including piperacillin, ceftazidime, imipenem or aztreonam, ciprofloxacin or levofloxacin, or an aminoglycoside; and (4) multidrug-resistant gram-negative bacilli, defined as resistance to drugs in at least 2 of 4 antibiotic classes: (a) β -lactams, (b) aminoglycosides (2 or more of the following: gentamicin, tobramycin, amikacin), (c) fluoroquinolones, and (d) trimethoprim/sulfamethoxazole.¹⁷ A variable combining resistant microorganisms as described was also created: any resistance versus no resistance. The hospital's microbiology laboratory determined antimicrobial susceptibility of isolates following breakpoints defined by the Clinical and Laboratory Standards Institute, which are updated yearly.¹⁸

BSIs were further categorized into hospital-acquired, HCA, and community-acquired BSI. A hospital-acquired BSI was defined using Centers for Disease Control and Prevention criteria: a positive blood culture identified 48 hours or more after admission to the hospital.¹⁹ HCA infection was defined as a positive blood culture obtained from a patient at the time of hospital admission or within 48 hours of admission plus any of the following criteria: (1) patient received intravenous therapy at home, or received any home care, including wound care or specialized nursing care through a health care agency within 30 days before the BSI; (2) patient attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the 30 days before the BSI; (3) patient was hospitalized in an acute care hospital (VA or non-VA) for 2 or more days in the 90 days before the BSI; or (4) patient resided in a nursing home or other long-term care facility.²⁰ Community-acquired BSI was defined as a positive blood culture obtained at the time of hospital admission or within 48 hours after hospital admission for patients who did not fit the criteria for an HCA infection.

Definitions for Adequate Treatment

Empirical antimicrobial treatment was classified as adequate if it was started within 2 days after collection of blood cultures and if the microorganism subsequently isolated was susceptible in vitro to 1 of the antibiotic drugs given. Inadequate treatment was defined as the absence of antimicrobial agents directed at the particular organism within 2 days after the collection of blood cultures and/or the microorganism's resistance to the antimicrobial agent administered. For polymicrobial BSIs, treatment had to

be adequate for all microorganisms in order to be considered adequate treatment. We also assessed definitive treatment within 5 days using similar criteria.

Outcomes

In-hospital mortality rate was defined as the number of patients with BSI who died in-hospital divided by the total number of patients with BSI. Because of the long LOS in this population, patients with BSI were followed for 30 days from collection of the first blood culture that indicated a positive BSI to assess 30-day mortality. LOS after positive culture was determined from combining the dates from the culture data with the dates for admission and discharge. Patients who died in the hospital were excluded from LOS comparisons.

Data Sources and Covariates

The microbiology data were obtained from the local electronic medical record, including specimen site, collection date and time, microorganism identified, and antibiotic-susceptible profile of the organism, which is categorized as susceptible, intermediate, or resistant.

VA medical encounter databases were used to identify demographic characteristics (age, sex, race, marital status, place of residence), health conditions within the 90 days prior to hospitalization, and comorbid conditions during the hospitalization (myocardial disease [includes myocardial infarct and congestive heart failure], vascular disease [includes peripheral vascular disease and cerebrovascular disease], dementia, chronic obstructive pulmonary disease, liver disease, diabetes, cancer, pressure ulcers, or acquired immune deficiency syndrome). Total LOS and LOS after BSI (defined as LOS after positive culture) were determined from admission, culture, and discharge dates; evidence of mechanical ventilation or other respiratory procedures (including tracheostomy, bronchoscopy, intubation) in the 30 days prior to BSI; and discharge status (which includes death if the patient died in the hospital). Mortality was determined from the "discharge destination" and "date of death" variables available in the inpatient data set and the "date of death" field in the VA Beneficiary Identification Record Locator System death file. The inpatient data set only identifies those veterans who died in the hospital or whose death was reported to the hospital by a survivor. The Beneficiary Identification Record Locator System database contains records of all beneficiaries, including veterans whose survivors applied for death benefits.

The VA Spinal Cord Dysfunction Registry is a national database containing information on SCI characteristics. This database was used to obtain level of injury, age at onset, and duration of injury on the sample.

Antimicrobials used in the inpatient and outpatient settings were obtained from the patient local medical record to determine antibiotic exposure in the previous 30 days as well as adequacy of antibiotic treatment for the BSI.

Statistical Analysis

Statistical analyses were performed using SAS software, version 8.2,^a and STATA 8.0.^b Crude associations between variables and adequacy of treatment are presented with cluster-adjusted *P* values from multivariable logistic regression. For example, age was included in a cluster-adjusted logistic model alone to assess its association with adequacy of treatment. This was repeated with each covariate described. This statistical method was chosen to account for multiple BSI episodes within the same patient and control for nonindependence of BSI episodes within patients. Similar cluster adjusted logistic re-

gression models were fit to assess independent predictors of inadequate treatment, where adjusted OR and 95% CI are presented. Variables for the final model predicting adequacy of treatment were selected based on fit to the model using the likelihood ratio test and whether the variables were statistically significant. Cluster-adjusted *P* values were also calculated to compare the mortality outcomes for those with adequate and inadequate therapy.

LOS postinfection was treated as censored data, where time to discharge or in-hospital death was the event of interest. If a patient had multiple BSIs during an admission, each BSI episode was censored at the start of a new BSI episode, with the final BSI being censored at discharge. Multiple admissions (ie, multiple events of interest) and multiple BSIs were addressed in the model using the Prentice, Williams, and Petersen counting process and gap time model with modified sandwich variance estimators.²¹ The unit of analysis was the BSI episode. The cluster-adjusted *P* values were calculated from this model. *P* values less than .05 (2-sided) and 95% CIs that did not include 1 were considered statistically significant in all data presented.

RESULTS

Between October 1, 1997, and September 30, 2004, veterans with SCI at the study medical center incurred a total of 2202 admissions. Seven-hundred ten positive blood cultures in 182 patients were detected during these admissions. All episodes of BSI were used for this analysis. After removing those with contaminants (455) and recurrent BSI (20), a total of 235 episodes of BSI were identified in 123 patients (mean, 1.9 episodes a patient); 18.3% of these episodes occurred in the same admission. The overall incidence over 7 years was 10.7 episodes per 100 admissions.

The median age of the cohort was 57.5 years and most were men (96.6%). Over half were non-Hispanic white (54.5%), 40.9% were non-Hispanic black, 45.5% had tetraplegia, 43.0% had paraplegia, and 11.5% were missing this information (table 1). Date of injury was missing for 19.2% of the sample, so an "unknown" category was created for age at onset and duration of injury. The median age at onset of SCI and duration of injury were 33.4 years and 20.2 years, respectively, for those with complete information (n=190).

Factors Associated With Inadequate Empirical Therapy

Over one third of the BSI episodes (88; 37.4%) received inadequate empirical antibiotic treatment. Of those who received inadequate therapy, all received at least 1 antibiotic. Table 1 describes demographic and SCI characteristics by adequacy of empirical treatment. There were no significant associations between year, age, ethnicity, known neurologic level (tetraplegia vs paraplegia), age at onset or duration of injury, and adequacy of empirical treatment.

Location of onset of BSI (BSI type), having a preexisting chronic medical condition in the 90 days prior to BSI, or having a comorbid condition at time of BSI was not significantly associated with adequacy of therapy (table 2). However, having a comorbid pressure ulcer (compared with no pressure ulcer) was protective against inadequate therapy (*P*=.003). Antibiotic therapy in the previous 30 days also was associated with adequate treatment for the BSI (*P*=.03). In addition, having a BSI secondary to other infections in the respiratory tract, wound/skin/bone, or the urinary tract (compared with a primary BSI) showed a protective association with inadequate therapy (*P*=.001).

The causative microorganisms associated with receiving inadequate therapy included *Enterococcus faecium* (compared

Table 1: Adequacy of Empirical Treatment in 235 Episodes of BSI in Veterans With SCI by Demographics

Demographics	Inadequate Empirical Treatment n=88 Frequency (%)	Adequate Empirical Treatment n=147 Frequency (%)	Total Frequency (%)	OR (95% CI), Cluster-Adjusted P
Age (y)				
<50	20 (22.8)	37 (25.2)	57 (24.3)	Reference
50–64	34 (38.6)	58 (39.4)	92 (39.1)	1.08 (0.44–2.67), 0.86
65+	34 (38.6)	52 (35.4)	86 (36.6)	1.09 (0.67–1.81), 0.71
Median	58.7	55.4	57.5	0.51
Ethnicity				
White	49 (55.7)	79 (53.7)	128 (54.5)	Reference
Black	34 (38.6)	62 (42.2)	96 (40.8)	0.88 (0.42–1.87), 0.75
Other	5 (5.7)	6 (4.1)	11 (4.7)	1.16 (0.71–1.88), 0.55
Level of injury				
Tetraplegia	36 (40.9)	71 (48.3)	107 (45.5)	Reference
Paraplegia	36 (40.9)	65 (44.2)	101 (43.0)	1.09 (0.51–2.36), 0.82
Unknown	16 (18.2)	11 (7.5)	27 (11.5)	1.69 (1.09–2.64), 0.02
Age at onset of injury (y)				
<24	13 (14.8)	22 (15.0)	35 (14.9)	Reference
25–49	37 (42.0)	63 (42.9)	100 (42.6)	0.99 (0.45–2.21), 0.99
50+	22 (25.0)	33 (22.4)	55 (23.4)	1.06 (0.61–1.86), 0.83
Unknown	16 (18.2)	29 (19.7)	45 (19.1)	0.98 (0.66–1.44), 0.91
Median	36.8	32.4	33.4	0.77
Duration of injury (y)				
<10	18 (20.4)	23 (15.7)	41 (17.5)	Reference
10–29	41 (46.6)	69 (46.9)	110 (46.8)	0.76 (0.21–2.8), 0.68
30+	13 (14.8)	26 (17.7)	39 (16.6)	0.80 (0.40–1.61), 0.53
Unknown	16 (18.2)	29 (19.7)	45 (19.1)	0.89 (0.53–1.50), 0.66
Median	19.4	21.3	20.2	0.89

with *E faecium* not being a cause, $P=.04$) and *S aureus* (compared with no *S aureus*, $P=.03$) (see table 2). Having a polymicrobial BSI was also associated with inadequate therapy ($P=.01$). *Enterococcus* comprised 50% of all polymicrobial BSIs, followed by *S aureus* (26.2%), and most (88.1%) polymicrobial BSIs had an antimicrobial-resistant organism. BSI caused by any antimicrobial-resistant organisms was not associated with adequacy of treatment. In the cluster-adjusted multivariable logistic regression analyses, having a comorbid pressure ulcer and having a secondary BSI remained protective against inadequate therapy, and having a BSI caused by multiple organisms continued to be associated with receiving inadequate therapy (table 3). All other variables were either not significant or did not add significantly to the model, and therefore were dropped from the final model.

Empirical Treatment Outcomes

Twenty-six patients with BSI died in-hospital, which was 21.1% of the 123 patients or 11.1% of the 235 BSI episodes (table 4). In-hospital mortality rates were similar for those with both inadequate and adequate empirical therapy (11.4% vs 10.9%; P value=.92). Because of the long LOS for this patient population, we also assessed 30-day mortality and found that 16 deaths (6.8% of BSI episodes) occurred within 30 days after the last BSI, and this did not differ between the inadequate and adequate treatment groups (9.1% vs 5.4%; $P=.30$).

There were 181 BSIs included in the LOS postinfection analysis from patients who survived the hospitalization. There were no differences in the median LOS postinfection between those with inadequate therapy and those with adequate therapy (22d vs 27d; $P=.98$).

Definitive Treatment

We also assessed definitive adequate therapy that occurred within 5 days after collection of blood cultures and found that

66 (28.1%) of the 235 BSI episodes had inadequate definitive therapy. Therefore, only 22 (25%) of 88 inadequate empirical cases later received adequate definitive treatment. A cluster-adjusted multivariable model showed similar factors, as seen in the empirical treatment model, were associated with adequacy of definitive treatment; having a comorbid pressure ulcer ($OR=0.42$; 95% $CI=0.23-0.76$; $P=.004$) and a secondary BSI ($OR=0.35$; 95% $CI=0.19-0.65$; $P=.001$) were protective against inadequate therapy. However, polymicrobial BSI was not associated with adequate therapy. In-hospital mortality did not significantly differ, but 30-day mortality trended toward significance (see table 4). LOS postinfection between those with inadequate therapy and those with adequate therapy (21d vs 27d; $P=.06$) was similar.

DISCUSSION

The incidence of BSI (10.7 cases per 100 hospital admissions) was high in this study cohort, but similar to other studies in SCI.^{4,5} Studies have shown that the presence of BSI is a risk factor for inadequate antimicrobial treatment.^{11,22} In this study, 37.4% and 28.1% of veterans with SCI received inadequate empirical and definitive antimicrobial treatment, respectively, for BSI. This is slightly higher than what has been reported in the non-SCI literature, ranging from 22% to 33%.^{8-11,23} However, Montgomerie et al⁷ showed a similar rate for SCI, where 36.9% of BSI episodes in persons with SCI were either given inadequate antibiotics or had adequate treatment that was delayed 2 or more days after the BSI was identified.⁷ All episodes had at least 1 antibiotic prescribed, and thus, BSIs do not appear to have been overlooked by physicians. However, inadequate definitive therapy was still provided in 75% of cases where empiric treatment was not adequate.

Having a primary BSI was associated with inadequate treatment. However, patients having BSI secondary to a respiratory tract, wound, or urinary tract infection were less likely to

Table 2: Adequacy of Empirical Treatment in 235 Episodes of BSI in Veterans With SCI by Medical Characteristics

Medical Characteristics	Inadequate Empirical Treatment n=88 Frequency (%)	Adequate Empirical Treatment n=147 Frequency (%)	Total Frequency (%)	OR (95% CI), Cluster-Adjusted P
BSI type				
Nosocomial	46 (52.2)	96 (65.3)	142 (60.4)	Reference
HCA	35 (39.8)	43 (29.3)	78 (33.2)	1.70 (0.93–3.12), 0.09
Community-acquired	7 (8.0)	8 (5.4)	15 (6.4)	1.35 (0.78–2.34), 0.28
Medical conditions				
Preexisting medical condition (\leq 90d prior)	65 (73.9)	119 (80.9)	184 (78.3)	0.66 (0.32–1.37), 0.27
Comorbid condition at hospitalization	59 (67.0)	117 (79.6)	176 (74.9)	0.52 (0.27–1.02), 0.06
Type of comorbid conditions*				
Myocardial disease	12 (13.6)	12 (8.2)	24 (10.2)	1.77 (0.74–4.27), 0.20
Vascular disease	4 (4.5)	7 (4.8)	11 (4.7)	0.95 (0.28–3.23), 0.94
Gastrointestinal ulcer	3 (3.4)	2 (1.4)	5 (2.1)	2.56 (0.26–25.65), 0.42
COPD	11 (12.5)	18 (12.2)	29 (12.3)	1.02 (0.33–3.19), 0.97
Dementia	1 (1.1)	1 (0.7)	2 (0.9)	1.68 (0.10–27.77), 0.72
Renal disease	1 (1.1)	6 (4.1)	7 (3.0)	0.27 (0.02–3.34), 0.31
Liver disease	1 (1.1)	2 (1.4)	3 (1.3)	0.83 (0.20–3.45), 0.80
Diabetes	19 (21.6)	27 (18.4)	46 (19.6)	1.22 (0.57–2.62), 0.60
Pressure ulcers	33 (37.5)	86 (58.5)	119 (50.6)	0.43 (0.24–0.75), 0.003
Cancer	8 (9.1)	9 (6.1)	17 (7.2)	1.53 (0.66–3.59), 0.32
AIDS	0 (0)	11 (7.5)	11 (4.7)	Undefined
Procedures/antibiotic use				
Respiratory procedure in previous 30 days	19 (21.6)	17 (11.6)	36 (15.3)	2.11 (0.90–4.94), 0.09
Antibiotic exposure in previous 30 days	56 (63.6)	115 (78.2)	171 (72.8)	0.49 (0.26–0.92), 0.03
Source of BSI				
Primary	44 (50.0)	38 (25.9)	82 (34.9)	Reference
Secondary	44 (50.0)	109 (74.1)	153 (65.1)	0.35 (0.18–0.67), 0.001
Specific secondary sources				
Primary	44 (50.0)	38 (25.9)	82 (34.9)	Reference
Respiratory tract	3 (3.4)	11 (7.5)	14 (6.0)	0.24 (0.09–0.63), 0.004
Wound/skin/bone	1 (1.1)	10 (6.8)	11 (4.7)	0.29 (0.11–0.80), 0.02
Urinary tract	40 (45.5)	88 (59.8)	128 (54.4)	0.73 (0.58–0.92), 0.01
Microorganism type				
Polymicrobial BSI	23 (26.1)	19 (12.9)	42 (17.9)	2.38 (1.22–4.65), 0.01
Specific causative organisms				
<i>E faecium</i>	19 (21.6)	17 (11.6)	36 (15.3)	2.11 (1.04–4.28), 0.04
<i>E coli</i>	12 (13.6)	23 (15.6)	35 (14.9)	0.85 (0.43–1.70), 0.65
<i>Klebsiella pneumoniae</i>	5 (5.7)	12 (8.2)	17 (7.2)	0.68 (0.24–1.93), 0.47
<i>P aeruginosa</i>	9 (10.2)	20 (13.6)	29 (12.3)	0.72 (0.30–1.74), 0.47
<i>S aureus</i>	40 (45.5)	46 (31.3)	86 (36.6)	1.83 (1.06–3.16), 0.03
Susceptibility data				
MRSA	28 (31.8)	40 (27.2)	68 (28.9)	1.25 (0.71–2.18), 0.44
VRE	5 (5.7)	6 (4.1)	11 (4.7)	1.42 (0.31–6.43), 0.65
Resistant <i>P aeruginosa</i>	5 (5.7)	10 (6.8)	15 (6.4)	0.83 (0.25–2.72), 0.75
Multidrug-resistant gram-negative bacilli	29 (33.0)	52 (35.4)	81 (34.5)	0.90 (0.52–1.54), 0.70
Any antimicrobial resistance	56 (63.6)	96 (65.3)	152 (64.7)	0.93 (0.53–1.62), 0.80

Abbreviations: AIDS, acquired immune deficiency syndrome; COPD, chronic obstructive pulmonary disease; VRE, vancomycin-resistant *Enterococcus*.

*Zero patients had rheumatologic/connective tissue diseases.

receive inadequate therapy. This is in agreement with prior studies indicating a greater likelihood of inadequate therapy when the source of BSI was unknown.¹⁰

Having a comorbid pressure ulcer was found to be protective against inadequate therapy in this study, contrary to a report by Leibovici et al.¹⁰ Pressure ulcers were present in 50.6% of BSI episodes, but presence did not necessarily indicate that the ulcer was a secondary source. In fact, only 11 episodes of BSI (4.7% of all episodes) had wound, skin, or bone identified as secondary sources. Most of those with a comorbid pressure ulcer (60.5%) also had a urinary tract infection as the secondary source of BSI and frequently received adequate treatment.

Although not significant in the multivariable analyses, *E faecium* and *S aureus* were associated with receipt of inadequate therapy and together accounted for nearly two thirds of inadequately treated BSIs, consistent with previous literature.^{8,11} Because of the preeminence of UTIs as causes of secondary bacteremia, clinicians may be inclined to target gram-negative organisms (*Escherichia coli*, *Klebsiella* sp., *Pseudomonas* sp.) more than gram-positive pathogens (*E faecium* and *S aureus*).

Recent antibiotic exposure was not associated with antibiotic therapy in multivariable analyses, which was contrary to other studies.^{8,10} General mechanisms for development of antibiotic resistance suggest that prior antibiotic exposure predisposes

Table 3: Cluster-Adjusted Logistic Multiple Regression Analysis Identifying Independent Predictors of Inadequate Empirical Antimicrobial Treatment in Veterans With SCI (N=235)

Predictor Variables*	Adjusted OR (95% CI),† P
Having a comorbid pressure ulcer	0.37 (0.21–0.68), 0.001
Secondary source of BSI	0.30 (0.15–0.58), <0.0001
Having a polymicrobial BSI	3.28 (1.62–6.65), 0.001

*Reference groups include not having a comorbid pressure ulcer, BSI with 1 causative organism.

†The adjusted OR is the odds of receiving inadequate treatment.

patients to colonization with resistant organisms, and thus, antibiotics prescribed may not have in vitro susceptibility against the organism. However, in this population, antibiotic resistance was not associated with inadequate therapy.

Having a BSI caused by more than 1 organism also was associated with inadequate therapy. This suggests that clinicians should be aware of polymicrobial infection when choosing empirical antibiotic treatment. Nosocomial and/or HCA BSI⁸⁻¹⁰ and antimicrobial resistance have been shown to be associated with inadequate therapy in other studies, but not in the current study population. In this SCI population, those with HCA and community-acquired BSI had the highest proportions of people with inadequate treatment (46.7% and 44.9%, respectively), compared with 32.4% of nosocomial BSI episodes. Although the association between setting of onset of BSI and adequacy of treatment was not significant in these analyses, it suggests that persons with SCI are different from the able-bodied population in factors associated with adequacy of treatment.

The overall mortality for BSI episodes in those with SCI (11.1%) was in the range of mortality rates reported in previous studies (range, 1.7%–29%).⁶⁻¹³ It was speculated in a review of infections in persons with SCI that recurrent UTIs may help persons with SCI develop antibodies that may protect them from BSIs, reducing mortality.²⁴ UTI was the most common secondary source of BSI in our study. Similar to the findings of Montgomerie,⁷ inadequate treatment did not affect mortality in our study, although there was a trend toward significance in those who had definitive inadequate treatment.

Adequacy of treatment did not affect LOS postinfection in this study, although there was a trend toward increased LOS postinfection after inadequate definitive therapy. Other studies have shown a significant impact of adequacy of therapy on LOS, although these studies did not attempt to control for other factors that may have influenced LOS and counted total LOS and not LOS postinfection.^{8,12} In veterans with SCI, LOS may not be a good outcome to assess impact of adequacy of treat-

ment on BSI, particularly because many factors may affect LOS. These may include clinical factors such as long LOS caused by pressure ulcers or other comorbidities, but also social concerns such as whether the caregiver can care for the patient once discharged or whether accessible housing is available for the patient.²⁵

Although poorer outcomes in those with inadequate treatment (empirical or definitive) were not statistically different from those who received adequate treatment, this does not lessen the importance of appropriate use of antibiotics. Antibiotic use can promote antibiotic resistance, resulting in prolonged hospital stay, and increased health care costs.²⁶ In addition, other adverse events could result from antibiotic use, including allergic reactions and other pharmacologic or idiosyncratic effects (diarrhea, headache, dizziness).²⁷ Therefore, unnecessary antibiotic use should be curbed.

Study Limitations

Our definition of adequacy or inadequacy of treatment was based on in vitro susceptibility of causative organisms to prescribed antibiotics. We did not determine whether inadequate empirical therapy by our definition was adequate based on established hospital protocols or antibiograms. However, we used definitions similar to previously published research in this area.^{8,10} The major limitations of this study were that it was retrospective and patients were not randomized to a specific treatment group. The statistical power was also limited in assessing differences in 30-day mortality between the 2 groups. In addition, we only collected data that were available through the VA medical encounter databases; thus, clinical factors that may have further demonstrated severity of illness such as physiologic findings were unavailable. Having these clinical data also would have assisted with identifying attributable mortality caused by BSI. Further, we were unable to determine definitively whether antimicrobial treatment received was for the BSI or other infections. Administration of antimicrobials was guided by individual physician behavior; therefore, hospitals using antibiotic prescribing protocols could have different results. Finally, this study was conducted in 1 hospital, and variation in risk factors may exist across hospitals. However, this hospital represents 1 of 23 hospitals across the country that provide primary and specialty care to veterans with SCI, suggesting a more homogenous sample.

CONCLUSIONS

Over one third of patients with SCI and a BSI received inadequate empirical antimicrobial treatment. Inadequate treatment was associated with having a polymicrobial BSI or BSI of primary or unknown source. Although mortality and LOS were not statistically associated with adequacy of treatment, providers should use hospital antibiogram data to ensure appropriate

Table 4: In-Hospital and 30-Day Outcomes for Type of Treatment

Type of Treatment	In-Hospital Mortality		30-Day Mortality	
	Frequency (%)	Adjusted OR (95% CI),* P	Frequency (%)	Adjusted OR (95% CI),* P
Inadequate empirical (n=88)	10 (11.4)	1.05 (0.43–2.55), 0.92	8 (9.1)	1.74 (0.61–4.94), 0.30
Adequate empirical (n=147)	16 (10.9)	Reference	8 (5.4)	Reference
Inadequate definitive (n=66)	9 (13.6)	1.41 (0.59–3.40), 0.44	8 (12.1)	2.78 (1.00–7.73), 0.06
Adequate definitive (n=169)	17 (10.1)	Reference	8 (4.7)	Reference
Total	26 (11.1)		16 (6.8)	

*The adjusted OR is the odds of death.

treatment. Microbiology cultures should be obtained in a timely manner to adjust treatment if necessary. Additional studies are needed to confirm these results with a larger sample and further assess the effects of duration of treatment and type of treatment (including class of antibiotic) on outcomes.

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Suppliers

- SAS version 8.2; SAS Institute Inc, 100 SAS Campus Dr, Cary, NC 27513-2414.
- STATA 8.0; StataCorp LP, 4905 Lakeway Dr, College Station, TX 77845.