

# Uncomplicated *Staphylococcus aureus* Bacteremia Treatment Duration and Outcomes at an Academic Medical Center

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We compared outcomes and clinical characteristics of uncomplicated *Staphylococcus aureus* bacteremia planned for a 14-day or >14-day course of intravenous antibiotics. Treatment failure was infrequent in both groups (0% and 5%, respectively). Catheter-associated deep vein thrombosis, immunosuppression, and valvular dysfunction were associated with a longer planned duration of therapy.

**Keywords:** antibiotic duration; staphylococcal infections; uncomplicated bacteremia.

*Staphylococcus aureus* (SAB) is a common condition, with an incidence of 4.3–38.2 per 100 000 person-years in the United States [1], and is associated with a 30-day all-cause mortality rate of about 20% [1]. High-quality studies evaluating the optimal duration of antimicrobial therapy are lacking. The Infectious Diseases Society of America (IDSA) 2011 Guidelines on Methicillin-Resistant *Staphylococcus aureus* Infections recommend a treatment duration of 4–6 weeks unless criteria are met for uncomplicated SAB, wherein a duration of 14 days may be considered [2]. A prospective study evaluating the use of a clinical algorithm in the management of SAB showed a 15.2% rate of clinical failure among patients with uncomplicated SAB treated with ~14 days of antimicrobial therapy [3]. In this study, we describe our hospital's management practices and outcomes related to uncomplicated SAB, specifically in relation to the planned duration of therapy.

## METHODS

We retrospectively reviewed patients aged  $\geq 18$  years with uncomplicated SAB admitted to a 700-bed tertiary care center in Boston, Massachusetts, between October 2015 and June 2019. Inpatients with at least 1 in-house blood culture positive for *Staphylococcus aureus* (SA) who met the strict definition of uncomplicated SAB adapted from Holland et al. (2018) and Liu et al. (2011) were included [2, 3]. This definition required blood culture negativity and resolution of fever within 72 hours of the initial positive culture, no echocardiographic evidence of endocarditis, no metastatic infection (including septic arthritis, osteomyelitis, deep abscess, and necrotizing pneumonia), no indwelling intravascular prosthetic devices (intracardiac devices, hemodialysis access grafts, nondialysis arterial grafts in place for <90 days, noncoronary vascular stents in place for <42 days, cardiac prosthetic valves or support rings), and removal of an infected intravascular catheter within 5 days of initial positive culture.

Patients were excluded if they were discharged to hospice, transitioned to “comfort measures only” during admission, discharged against medical advice, pregnant, had neutropenic fever at the time of bacteremia, were lost to follow-up, died after discharge of unknown causes, died before a plan for antibiotic duration was determined, had bacteremia from a non-SA organism leading to alteration in the treatment regimen, or developed complicated SAB before hospital discharge. Exclusions were based on ICD-10 diagnostic codes for the initial hospitalization and manual chart review.

Patients were divided into 2 groups based on the planned duration of intravenous antimicrobial therapy at the time of discharge: 14 days and >14 days. The planned antibiotic duration was determined by chart review of infectious disease consultation notes and discharge summaries. The antibiotic start date generally correlated with both source control and blood culture negativity. Oral linezolid was considered an intravenous equivalent.

The primary outcome was treatment failure at 90 days after hospital discharge, which was defined as diagnosis of a complicated staphylococcal infection after discharge, change in treatment because of unsatisfactory clinical response, death due to SA infection (determined by chart review), or relapsed infection. Secondary outcomes included drug-related adverse events (requiring readmission or change in antimicrobial therapy) and catheter-associated adverse events (bloodstream infection, thrombosis, cellulitis, dislodgement, or malpositioning of a central or midline catheter).

We sought to identify correlates of a planned duration of >14 days of antibiotics. We hypothesized that the following

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factors may influence this decision: age, oxacillin sensitivity, community onset (SAB within 48 hours of admission without clear hospital acquisition), symptoms for  $\geq 3$  days before admission, catheter-associated deep vein thrombosis, immunosuppression (transplant recipients, active cancer, corticosteroid use, or use of other immunomodulatory agents), and significant valvular disease determined by echocardiography.

Statistical significance was set at a  $P$  value  $< .05$ . Variables were evaluated using univariable logistic regression. Exact multivariable logistic regression was used to evaluate variables that had a statistically significant correlation with planned treatment duration in the univariable analysis. The Fisher exact test was used for comparing catheter-associated adverse events. SAS was used for statistical analysis (version 9.4; SAS Institute Inc.).

## RESULTS

A total of 612 unique patients were identified as having at least 1 positive culture for SA during the study period. Patients were excluded for the following reasons: skeletal or another deep focus of infection (193); endocarditis, endovascular, or cardiac device infection (177); hospice discharge, discharge against medical advice, or care transitioned to comfort measures only (82); loss to follow-up, including 2 patients who died without a clear cause (48); fevers or positive blood cultures after 72 hours (19); an infected central line removed  $> 5$  days after blood culture positivity (8); unrecognized bacteremia or death before an antibiotic plan was established (7); or other reasons for exclusion as listed above (14). Sixty-four patients met study inclusion criteria. Forty-three patients (67%) had a planned duration of therapy of  $> 14$  days, and 21 patients had a planned duration of 14 days (33%) (Table 1).

Seven potential correlates of antibiotic duration were evaluated. Valvular disease, catheter-associated deep vein thrombosis, and immunosuppression were significantly associated with a planned antibiotic duration of  $> 14$  days (Table 2). Using multivariable logistic regression, valvular disease ( $P = .04$ ), but not immunosuppression ( $P = .06$ ) or deep vein thrombosis ( $P = .06$ ), remained statistically significant.

Regarding the primary outcome, overall 2 of 64 patients (3%) failed treatment for uncomplicated SAB: 2/43 (5%) in the  $> 14$ -day group vs 0/21 (0%) in the 14-day group. One had recurrent bacteremia likely due to severe cutaneous graft-vs-host disease, and the other had recurrent bacteremia of unclear etiology 89 days after discharge. Neither patient died during the study period. The number of study patients was insufficient to ensure adequate statistical power to detect a significant difference for this outcome. The percentage of patients with catheter-associated adverse events was higher in the  $> 14$ -day group (16%) than in the 14-day group (0%;  $P = .05$ ) (Table 2).

**Table 1. Characteristics of Patients With Uncomplicated *Staphylococcus aureus* Bacteremia by Planned Duration of Intravenous Antibiotics**

	14 d	$> 14$ d	$P$ Value (Unadjusted)
Patients, No.	21	43	
Demographics			
Age, median [IQR], y	60 [51–70]	64 [50–74]	.80
Sex, male, No. (%)	10 (48)	23 (53)	
Actual antibiotic duration, median [IQR], d	14 [14–14]	28 [28–40.5]	
Characteristics of patients/disease, No. (%)			
Oxacillin sensitivity	17 (81)	27 (63)	.15
Community onset	15 (71)	30 (70)	.89
Symptoms for $\geq 3$ d before admission	3 (14)	11 (26)	.31
Presence of valvular disease	0	8 (19)	.03
Catheter-associated deep vein thrombosis	0	8 (19)	.03
Immunosuppression	3 (14)	19 (44)	.03
Hemodialysis dependency	0 (0)	5 (12)	
Diabetes	6 (29)	17 (40)	
Cirrhosis	3 (14)	3 (7)	
Injection drug use	0	1 (2)	
Uninvolved orthopedic hardware	0	5 (12)	
Bacteremia source, No. (%)			
Central venous line	2 (10)	20 (47)	
Peripheral venous line	2 (10)	1 (2)	
Skin/soft tissue infection	8 (38)	8 (19)	
Pulmonary	0	6 (14)	
Other	2 (10)	3 (7)	
Unknown	7 (33)	5 (12)	
Hospitalization details, No. (%)			
Transthoracic echocardiography	20 (95)	43 (100)	
Transesophageal echocardiography	2 (10)	17 (40)	
Intensive care unit admission	3 (14)	17 (40)	
Infectious disease consultation	21 (100)	43 (100)	
Definitive therapy, No. (%)			
Cefazolin	15 (71)	19 (44)	
Nafcillin	1 (5)	7 (16)	
Ceftriaxone	1 (5)	0	
Vancomycin	3 (14)	11 (26)	
Daptomycin	0	6 (14)	
Linezolid	1 (5)	0	

Abbreviation: IQR, interquartile range.

## DISCUSSION

Providers at our institution prescribed prolonged courses of intravenous antimicrobial therapy ( $> 14$  days) for most cases of uncomplicated SAB, which differs from the shorter

**Table 2. Outcomes by Planned Duration of Intravenous Antibiotics**

	14 d	>14 d	PValue
Treatment failure, No. (%)	0 (0)	2 (5)	
Death due to <i>Staphylococcus aureus</i>	0	0	
Relapsed bacteremia	0 (0)	2 (5)	
All-cause mortality, No. (%)	2 (10)	2 (5)	
Catheter-associated adverse event, No. (%)	0	7 (16)	.05
Adverse drug events, No. (%)	5 (24)	7 (16)	.47
<i>Clostridioides difficile</i> infection	4 (19)	1 (2)	
Other	1 (5)	6 (14)	

durations in similar cohorts at other institutions [3, 4]. In our setting, prolonged treatment durations were likely chosen because of the perceived risk of treatment failure associated with factors such as immunosuppression, valvular disease, and catheter-associated deep vein thrombosis. Current definitions of uncomplicated bacteremia do not address these factors.

Incorporation of the host's immune status into treatment duration decisions in SAB is highly variable. In a survey of >700 practicing infectious disease physicians in the United States and Canada, 48% of respondents indicated that they would extend the duration of antibiotics for SAB from 2 weeks to 4–6 weeks if the patient had an immunocompromising condition [5]. Retrospective analyses have identified immunocompromising conditions as risk factors for mortality in SAB [6, 7], though others have failed to demonstrate an association [8]. Further studies are needed to elucidate the relationship between antibiotic duration and treatment failure in patients with SAB and an immunocompromising condition or therapy.

The presence of a deep vein thrombosis in the setting of a catheter-associated bloodstream infection raises concern for suppurative thrombophlebitis. The IDSA's catheter-related infection guidelines suggest that suppurative thrombophlebitis should be suspected in patients with persistent bacteremia despite 3 days of adequate antimicrobial therapy [9]. However, in patients *without* persistent bacteremia, determination of whether a thrombus is actively infected is difficult, and guidance is lacking. Regardless of duration of bacteremia, thrombosis in this setting has been associated with poor outcomes if treated with <28 days of antibiotic therapy [10]. The presence of thrombosis should therefore be considered when determining the treatment duration in SAB.

Valvular disease and hemodialysis dependency are established risk factors for endocarditis [1, 11]. All patients included in our study with these risk factors received >14 days of intravenous antibiotics. Given the limited sensitivity of transthoracic echocardiography for detection of valvular vegetations and our limited use of transesophageal echocardiography (30% overall), the concern for undiagnosed SA endocarditis may

have influenced providers to prescribe a prolonged antibiotic course for these patients. Guidelines are ambiguous regarding the need for transesophageal echocardiography in specific patient populations with SAB, adding complexity to interdisciplinary decision-making.

Small sample size limited the power of our study to detect a clinically significant difference, or lack thereof, in the primary outcome. While we cannot establish the influence of treatment duration on clinical failure, the low failure rate in our overall population is notable (3%). This differs from the 15.2% failure rate determined by Holland et al., though this may be related to their inclusion of non-SAB mortality as failure [3]. Our definition of failure, including only SAB-related mortality, may more accurately reflect the true incidence of antibiotic failure. Additionally, our study was limited by the number of patients excluded because they were lost to follow-up (48/612), which may have introduced bias if specific clinical features or comorbidities were disproportionately represented in this group.

Further studies are needed to determine whether intravenous therapy given for >14 days is beneficial in specific cases of SAB that have historically been defined as uncomplicated but have features that may confer a higher risk for treatment failure. This potential benefit will need to be weighed against the increased risk of adverse events with prolonged intravenous antimicrobial therapy.

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