EDITORIAL

Treatment Algorithms for Staphylococcal Bacteremia
Improving Clinical Care and Enhancing Antimicrobial Stewardship

Eli N. Perencevich, MD, MS; Preeti N. Malani, MD, MSJ

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Antimicrobial resistance is among the most important threats to human health.[1] Lost in the episodic outbreaks of emerging pathogens such as 2009 H1N1 influenza, Ebola, and Zika virus has been the steady increase in resistance to commonly used antibiotics in frequently seen bacterial infections. Confronting antimicrobial resistance requires investment in 3 critical areas including (1) antimicrobial discovery, (2) rapid diagnostics, and (3) infection prevention and antimicrobial stewardship. In particular, algorithms based on clinical practice guidelines, that promote appropriate antibiotics and durations of therapy and limit unnecessary treatment, have the potential to enhance care for individual patients and improve public health more broadly.

In this issue of *JAMA*, Holland and colleagues[2] report the findings of a multicenter randomized trial of an algorithm compared with usual care for the treatment of staphylococcal bacteremia. The study was conducted at 16 academic medical centers, predominately in the United States, over 6 years. Patients were randomly assigned to algorithm-based therapy (n = 255) or usual practice (n = 254). Diagnostic evaluation, antibiotic selection, and duration of therapy were predefined for the algorithm-based therapy group, whereas care in the usual practice group was determined by the treating clinicians. Coprimary outcomes were (1) clinical success, as determined by a blinded adjudication committee and tested for noninferiority within a 15% margin; and (2) serious adverse event rates in the intention-to-treat population, tested for superiority. Patients with known or suspected complicated infection at the time of randomization were excluded.

Clinical success was documented in 209 of 255 patients assigned to algorithm-based therapy and 207 of 254 assigned to usual practice (82.0% vs 81.5%; difference, 0.5% [1-sided 97.5% CI, −6.2% to ∞). Serious adverse events were reported among 32.5% of patients in the algorithm-based therapy group and 28.3% of those in the usual practice group (difference, 4.2%; 95% CI, −3.8% to 12.2%). In a per-protocol analysis, among patients with simple or uncomplicated bacteremia, mean duration of therapy was 4.4 days in the algorithm-based therapy group vs 6.2 days in the usual practice group (difference, −1.8 days [95% CI, −3.1 to −0.6). Although interpretation was limited by wide confidence intervals, the rates of serious adverse events were not significantly different between the groups.

Staphylococcal bacteremia encompasses 2 clinically distinct pathogens. *Staphylococcus aureus* causes both health care–associated and community-acquired bacteremia, with an annual incidence ranging as high as 38.2 per 100 000 person-years in the United States and mortality rates of approximately 20%.[3] *Staphylococcus aureus* is typically divided into methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) strains, the latter of which have been associated with higher mortality.[4] The heterogeneous species group of coagulase-negative staphylococci, apart from *Staphylococcus lugdunensis*, are much less virulent than *S aureus* and together comprise the most common cause of health care–associated bacteremia.[5]

Optimal care of patients with *S aureus* bacteremia includes source control (eg, device removal or surgical drainage), echocardiography to evaluate for possible endocarditis, infectious disease consultation, and appropriate antibiotic selection once susceptibilities are known.[6] Even though optimal therapy selection for MSSA bacteremia has not been well established with randomized trials,[3] parenteral cefazolin or an antistaphylococcal penicillin are preferred. The majority of coagulase-negative staphylococci are methicillin resistant and, similar to MRSA, are treated with vancomycin or daptomycin, an approach based on limited clinical trial evidence.[7]

Despite the recognized severity of *S aureus* bacteremia, the optimal duration of therapy has not been established with prospective clinical trials. Current recommendations, based on low-quality evidence, recommend 4 to 6 weeks for complicated *S aureus* bacteremia and a minimum of 14 days after the first negative surveillance blood culture result for uncomplicated bacteremia.[3] Similarly, the therapeutic duration for coagulase-negative staphylococcus bacteremia is based on limited evidence but ranges from 0 to 3 days for simple bacteremia (often a contaminant), 5 to 7 days for uncomplicated bacteremia in the setting of a removable central venous catheter, and multiple weeks of therapy for complicated bacteremia in the setting of persistent positive blood culture results, retained foreign bodies, or endocarditis.[5]

Given limited evidence supporting treatment (both drug choice and duration), it may be surprising to see a clinical trial evaluating an algorithm with formalized clinical definitions and guidance on antibiotic selection and treatment duration. Furthermore, the algorithm evaluated by Holland et al addresses bacteremia caused both by *S aureus* (typically undertreated and associated with relatively poor outcomes) and coagulase-negative staphylococci (frequently overtreated and associated with minimal morbidity). Current antimicrobial stewardship guidelines recommend targeted improvements in antibiotic use for clinical syndromes such

as *S aureus* bacteremia.[8] Although stewardship guidelines do not specifically mention coagulase-negative staphylococci, some programs report success using rapid diagnostics to differentiate coagulase-negative staphylococci from *S aureus*.[9]

Despite uncertainties around optimal treatment, Holland et al successfully implemented a treatment algorithm for 5 related clinical syndromes. Importantly, they achieved the primary outcome of noninferiority for clinical success while demonstrating a nearly 2-day reduction in antibiotic duration overall, including a 3-day reduction in therapy for uncomplicated coagulase-negative staphylococcus bacteremia. Given that vancomycin is the most commonly prescribed antibiotic in US acute care hospitals,[10] a 3-day reduction for a high-incidence condition such as uncomplicated coagulase-negative staphylococcus bacteremia could have a sizable public health effect.

A particular strength of this study was the use of a blinded adjudication committee of infectious diseases experts that confirmed primary outcomes, bacteremia-attributable mortality, and possible bias introduced by nonstudy antibiotics. Although bacteremia-related mortality was not a prespecified outcome, it is reassuring that despite reduced therapeutic duration, the adjudication committee identified lower attributable mortality among patients treated with the algorithm. Another key exploratory finding was the higher clinical success among patients with complicated *S aureus* bacteremia treated with the algorithm compared with usual practice (82.6% vs 35.7%). This observation adds to existing evidence that bundled processes of care for this serious infection can improve outcomes.[6] The authors use their results to further highlight an important caveat—2 weeks of therapy for uncomplicated *S aureus* bacteremia should be used with caution and only after careful evaluation for metastatic infection.[2]

Although the results reported by Holland et al are intriguing, the study also has several potential limitations. First, while the study was multicenter and multiyear, there were only an average of 5 patients contributed per hospital per year and about 1 case of *S aureus* bacteremia per year. Thus, this small subsample might not be generalizable to all acute care settings.

Second, the study sites all had access to infectious diseases consultants. While infectious diseases consultation has been associated with improved outcomes in *S aureus* bacteremia,[6] many hospitals currently lack on-site access to infectious diseases expertise, potentially limiting the generalizability of these findings in resource-limited or rural settings. It is possible that this clinical algorithm could be more efficacious in those settings, but further research is needed.

Third, as noted by the authors, the algorithm was randomized at the individual patient level within hospitals, suggesting the potential for contamination among clinicians treating patients in both study groups.[11] This could result in the usual practice group being treated similarly to the algorithm-based therapy group over time and would bias the results toward the null. As such, it would have been interesting to evaluate the results over time. If contamination was determined to significantly bias the results, future studies could reduce contamination through hospital-level cluster randomization.[11]

The report by Holland et al is an elegant addition to the evidence base of how to best manage staphylococcal bacteremia, and these results will likely influence the next iteration of treatment guidelines. The algorithm-defined antibiotic duration targets should be considered for inclusion in antimicrobial stewardship programs and guidelines. However, algorithms cannot simply be applied in a vacuum without ongoing monitoring and adjustment based on an individual patient's clinical course. Moreover, algorithms can only be as good as the clinical evidence supporting their recommendations. The limited quality of evidence used in this algorithm, through no fault of the investigators, is an important reminder that future investment in clinical trials targeting optimal antibiotic selection and duration are essential to continued progress. Successful response to the antimicrobial resistance crisis demands better evidence and dedicated resources to support future investigations.

ARTICLE INFORMATION

Author Affiliations: Division of General Internal Medicine, Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City (Perencevich); Iowa City VA Health Care System, Iowa City, Iowa (Perencevich); Division of Infectious Diseases, Department of Internal Medicine, University of Michigan, Ann Arbor (Malani); Associate Editor, *JAMA* (Malani).

Corresponding Author: Preeti N. Malani, MD, MSJ, F4135 University Hospital South, 1500 E Medical Center Dr, SPC 5226, Ann Arbor, MI 48109-5226 (pmalani@umich.edu).

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JAMA | Original Investigation

Effect of Algorithm-Based Therapy vs Usual Care on Clinical Success and Serious Adverse Events in Patients with Staphylococcal Bacteremia
A Randomized Clinical Trial

Thomas L. Holland, MD; Issam Raad, MD; Helen W. Boucher, MD; Deverick J. Anderson, MD; Sara E. Cosgrove, MD, MS; P. Suzanne Aycock, MSN; John W. Baddley, MD, MSPH; Anne-Marie Chaftari, MD; Shein-Chung Chow, PhD; Vivian H. Chu, MD; Manuela Carugati, MD; Paul Cook, MD; G. Ralph Corey, MD; Anna Lisa Crowley, MD; Jennifer Daly, MD; Jiezhun Gu, PhD; Ray Hachem, MD; James Horton, MD; Timothy C. Jenkins, MD; Donald Levine, MD; Jose M. Miro, MD, PhD; Juan M. Pericas, MD, PhD; Paul Riska, MD; Zachary Rubin, MD; Mark E. Rupp, MD; John Schrank Jr, MD; Matthew Sims, MD, PhD; Dannah Wray, MD; Marcus Zervos, MD; Vance G. Fowler Jr, MD, MHS; for the Staphylococcal Bacteremia Investigators

IMPORTANCE The appropriate duration of antibiotics for staphylococcal bacteremia is unknown.

OBJECTIVE To test whether an algorithm that defines treatment duration for staphylococcal bacteremia vs standard of care provides noninferior efficacy without increasing severe adverse events.

DESIGN, SETTING, AND PARTICIPANTS A randomized trial involving adults with staphylococcal bacteremia was conducted at 16 academic medical centers in the United States (n = 15) and Spain (n = 1) from April 2011 to March 2017. Patients were followed up for 42 days beyond end of therapy for those with *Staphylococcus aureus* and 28 days for those with coagulase-negative staphylococcal bacteremia. Eligible patients were 18 years or older and had 1 or more blood cultures positive for *S aureus* or coagulase-negative staphylococci. Patients were excluded if they had known or suspected complicated infection at the time of randomization.

INTERVENTIONS Patients were randomized to algorithm-based therapy (n = 255) or usual practice (n = 254). Diagnostic evaluation, antibiotic selection, and duration of therapy were predefined for the algorithm group, whereas clinicians caring for patients in the usual practice group had unrestricted choice of antibiotics, duration, and other aspects of clinical care.

MAIN OUTCOMES AND MEASURES Coprimary outcomes were (1) clinical success, as determined by a blinded adjudication committee and tested for noninferiority within a 15% margin; and (2) serious adverse event rates in the intention-to-treat population, tested for superiority. The prespecified secondary outcome measure, tested for superiority, was antibiotic days among per-protocol patients with simple or uncomplicated bacteremia.

RESULTS Among the 509 patients randomized (mean age, 56.6 [SD, 16.8] years; 226 [44.4%] women), 480 (94.3%) completed the trial. Clinical success was documented in 209 of 255 patients assigned to algorithm-based therapy and 207 of 254 randomized to usual practice (82.0% vs 81.5%; difference, 0.5% [1-sided 97.5% CI, −6.2% to ∞]). Serious adverse events were reported in 32.5% of algorithm-based therapy patients and 28.3% of usual practice patients (difference, 4.2% [95% CI, −3.8% to 12.2%]). Among per-protocol patients with simple or uncomplicated bacteremia, mean duration of therapy was 4.4 days for algorithm-based therapy vs 6.2 days for usual practice (difference, −1.8 days [95% CI, −3.1 to −0.6]).

CONCLUSIONS AND RELEVANCE Among patients with staphylococcal bacteremia, the use of an algorithm to guide testing and treatment compared with usual care resulted in a noninferior rate of clinical success. Rates of serious adverse events were not significantly different, but interpretation is limited by wide confidence intervals. Further research is needed to assess the utility of the algorithm.

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Visual Abstract

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Staphylococcal Bacteremia Investigators are listed at the end of this article.

Corresponding Author: Vance G. Fowler Jr, MD, MHS, Trent Drive, Box 102359, Hanes Building, 315, Room 185, Duke University Medical Center, Durham, NC 27710 (fowle003@mc.duke.edu).

Staphylococci are the most commonly identified pathogens in both hospital-acquired and community-onset bloodstream infections.[1] Despite its frequency, the optimal duration of treatment for staphylococcal bacteremia is unknown. Consensus guidelines recommend prolonged courses of antibiotics for complicated staphylococcal bacteremia and shorter courses of therapy for uncomplicated staphylococcal bacteremia, but these are primarily based on low-quality evidence and expert opinion.[2-4] As a result, there is considerable variation in treatment practices.[5]

Unnecessarily treating patients who have uncomplicated staphylococcal bacteremia with prolonged courses of antibiotics leads to antibiotic overuse and increases the likelihood for drug-related adverse events.[6] By contrast, patients with complicated staphylococcal bacteremia who incorrectly receive abbreviated courses of therapy are at risk for relapse, morbidity, and mortality.[7] A standardized strategy to classify patients with complicated and uncomplicated staphylococcal bacteremia and treat them with the appropriate duration of antibiotics would thus improve patient care.

This trial assessed the efficacy and safety of an algorithm that defines treatment duration for staphylococcal bacteremia based on clinical characteristics and evaluated the effect of its use on the duration of antibiotic therapy.

Key Points

Question What is the effect of an algorithm used to define antibiotic choice and duration on clinical success and serious adverse events in patients with staphylococcal bacteremia?

Findings In this randomized trial that included 509 adults with staphylococcal bacteremia, use of an algorithm compared with usual care resulted in a clinical success rate of 82.0% vs 81.5%, respectively, a difference that met the noninferiority margin of 15%. Serious adverse events occurred in 32.5% vs 28.3% of patients, a difference that was not statistically significant but with wide confidence intervals.

Meaning The use of an algorithm to guide testing and treatment compared with usual care resulted in a noninferior rate of clinical success; although there was not a significant difference in serious adverse events, interpretation is limited by wide confidence intervals.

Methods

Study Design

The trial protocol and statistical analysis plan are available in Supplement 1. In brief, this multicenter open-label randomized trial was conducted between April 2011 and March 2017 at 16 sites in the United States and Spain. The institutional review board at each site approved the study, and written informed consent was obtained from all participants or their authorized representatives. The data were analyzed by study statisticians (S.C.C., J.G.) in collaboration with all of the authors.

Eligible patients were 18 years or older and had 1 or more blood cultures positive for either *Staphylococcus aureus* or coagulase-negative staphylococci. Patients were excluded if they had known or suspected complicated infection at the time of randomization, had polymicrobial bacteremia with at least 1 nonstaphylococcal pathogen, or had creatinine clearance less than 30 mL/min. Full eligibility criteria are listed in eAppendix 1 in Supplement 2.

Patients were randomized to either algorithm-based therapy or usual practice. Classification of bacteremia, antibiotic choice, and treatment duration were predefined for algorithm patients (**Table 1**). All patients were required to have follow-up blood cultures obtained every 24 to 48 hours until clearance was documented. Care of patients in the usual practice group was otherwise unrestricted with regard to antibiotic choice, duration, and clinical management.

Definitions

Race and ethnicity were classified by the investigators, based on categories defined by the National Institutes of Health (NIH), as per NIH requirements. Patients were classified as having simple, uncomplicated, or complicated bacteremia (Table 1) according to signs or symptoms of local or metastatic sites of infection on physical examination, number and timing of positive blood culture results, and echocardiography.

The intention-to-treat population included all randomized patients. All patients in the intention-to-treat population were included in the safety population. The per-protocol population included all randomized patients except those who received a potentially effective nonstudy antibiotic before final test of cure, did not undergo removal of an intravenous catheter (with the exception of patients with simple coagulase-negative staphylococcal bacteremia, in whom the catheter could be retained), discontinued study medication prematurely for reasons other than clinical failure, did not undergo final test-of-cure assessment, violated inclusion/exclusion criteria or other key protocol elements, died within 3 days of randomization, or were classified as nonevaluable. *Nonevaluable* was defined as failure for administrative reasons, eg, patients who withdrew consent, discontinued treatment against medical advice, were withdrawn from the study, or were lost to follow-up. Nonevaluable patients were considered to have experienced treatment failure in the intention-to-treat analyses. *Treatment failure* was defined as death, persistent or relapsing infection (eAppendix 2 in Supplement 2), diagnosis of a complicated staphylococcal infection after completion of antibiotic therapy, or change of treatment because of unsatisfactory clinical response.

Randomization, Treatment, and Monitoring

Patients were assigned to algorithm-based therapy vs usual practice in computer-generated permuted randomized blocks by site, with block sizes of 2, 4, or 6. Patients in the algorithm group were treated with vancomycin or daptomycin for methicillin-resistant staphylococci and an intravenous antistaphylococcal penicillin or cefazolin for methicillin-susceptible staphylococci. Vancomycin was dosed per local standard practice, with a recommendation that it be dosed in accordance with published guidelines.[8] Vancomycin minimum inhibitory concentration (MIC) testing was performed at study sites per standard local practice.

The choice and duration of antibiotics in the usual practice group was determined by the treating physician. In the algorithm group, duration of therapy was prespecified

by the algorithm-defined category (Table 1). Patients with simple coagulase-negative staphylococcal bacteremia could have received up to 3 days of treatment before randomization (to account for empirical therapy before receipt of culture results). For patients with simple coagulase-negative staphylococci randomized to the algorithm, antibiotics were discontinued at randomization or not started if the patient had not yet initiated antibiotic therapy at the time of randomization. Patients with uncomplicated coagulase-negative staphylococcal bacteremia who were randomized to the algorithm received 5 days of parenteral therapy. Patients randomized to the algorithm for uncomplicated *S aureus* bacteremia received 14 days of parenteral antibiotics.

Patients known or suspected to have complicated staphylococcal bacteremia (either coagulase-negative staphylococci or *S aureus*) at the time of randomization were ineligible for study participation. If complicated bacteremia was recognized after randomization but before completion of study treatment, the patient was retained in the study and his or her care managed for complicated bacteremia. Patients with complications diagnosed after the end of therapy were considered to have experienced treatment failure. Patients in the algorithm group with complicated coagulase-negative staphylococci received 7 to 28 days of parenteral antibiotic therapy. Patients with complicated *S aureus* bacteremia were treated for 28 to 42 days. Antibiotic days were calculated as the total duration of effective antistaphylococcal antibiotics, beginning with the date of the qualifying blood culture. Any day that a patient received a dose of effective therapy was considered an antibiotic day.

Test-of-cure evaluation occurred 28 days after the end of study antibiotic treatment for coagulase-negative staphylococcal bacteremia and 42 days after the end of treatment for *S aureus* bacteremia. To be considered cured, patients must have had microbiologic and clinical resolution of bacteremia, without relapse or development of new manifestations of staphylococcal infection. Telephone test-of-cure evaluation was permissible when a clinic visit was not possible.

Table 1. Clinical Classification of Bacteremia and Duration of Algorithm-Based Therapy

Definition	Duration of Therapy (Range), d
***Staphylococcus aureus* Bacteremia**	
Uncomplicated	14 (±2)
Intravascular catheter source of infection (if present) removed within 5 d	
Negative follow-up blood culture 24-72 h after initial positive culture	
Defervescence within 72 h of initial positive culture	
Echocardiogram without evidence of endocarditis	
No symptoms or signs of metastatic infection	
No indwelling intravascular prosthetic devices	
Complicated	28-42 (±2)
Positive follow-up blood culture for *S aureus*, OR	
Persistent fever, OR	
Echocardiography with evidence of endocarditis, OR	
Symptoms or signs of metastatic infection	
Coagulase-negative Staphylococcal Bacteremia	
Simple	0-3 (+1)[a]
Single blood culture positive for coagulase-negative staphylococci	
Negative follow-up blood culture	
No signs or symptoms of local infection at a catheter site	
No symptoms or signs of metastatic infection	
No indwelling intravascular prosthetic devices	
Uncomplicated	5 (±1)
≥2 blood cultures positive for coagulase-negative staphylococci drawn ≤24 h apart, OR	
Single blood culture positive for coagulase-negative staphylococci, PLUS symptoms or signs of infection at a catheter site	
Complicated	7-28 (±2)
≥2 blood cultures positive for coagulase-negative staphylococci from samples drawn >24 h apart, OR	
Echocardiography with evidence of endocarditis, OR	
Symptoms or signs of metastatic infection	

[a] For patients with simple coagulase-negative staphylococcal bacteremia, treatment was discontinued on randomization to algorithm-based therapy. Thus, if clinicians suspected that the positive culture result was attributable to contamination and had not initiated therapy, those patients did not receive any study antibiotic therapy.

Echocardiography

Echocardiography was required for all patients in the algorithm-based therapy group who had *S aureus* bacteremia. Transesophageal echocardiography was preferred.[3] All echocardiograms for patients in the algorithm-based therapy group were reviewed by a study echocardiography core laboratory. Echocardiography core laboratory interpretations were blinded to treatment assignment, site interpretation, and clinical details. Echocardiography for patients in the usual practice group was at the discretion of the local clinician.

Outcomes

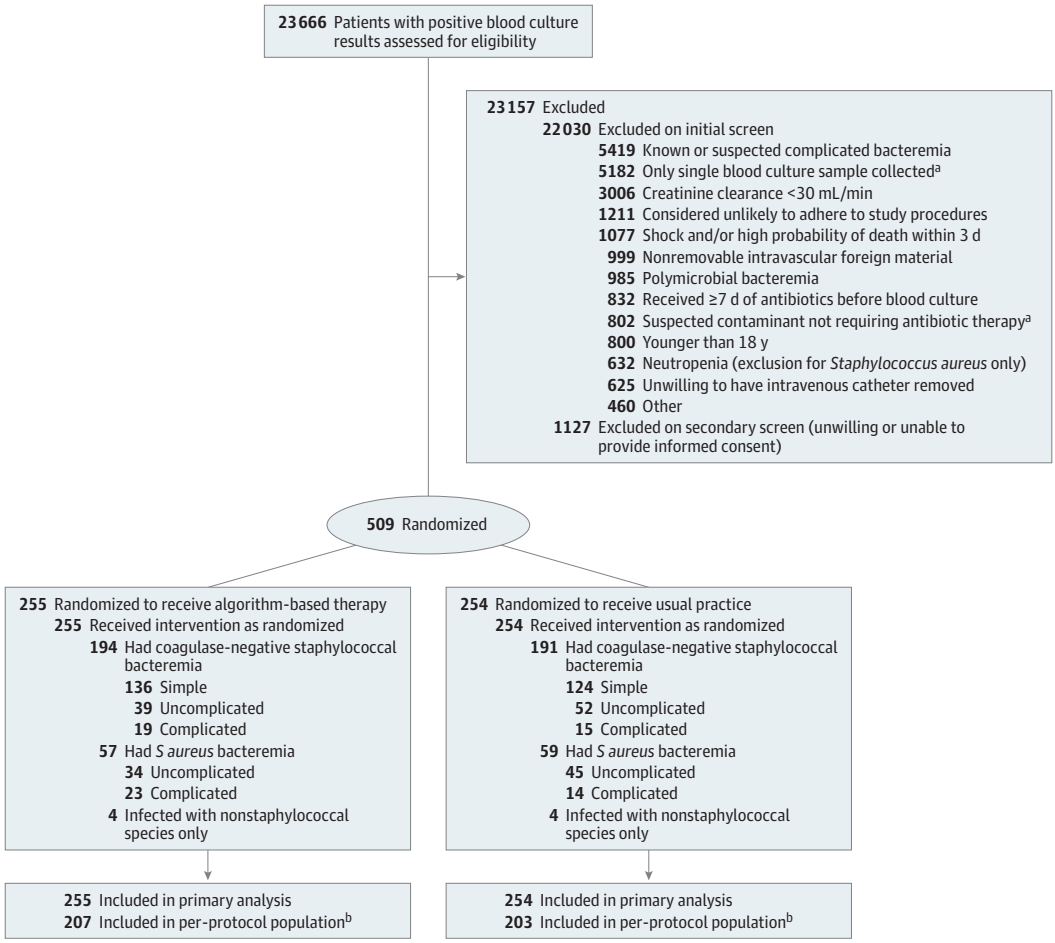
Adjudication Committee

An adjudication committee of 3 experts (D.J.A., H.W.B., S.E.C.) blinded to treatment assignment reviewed clinical data from each patient to establish the primary clinical outcome (success, failure, or nonevaluable). For all patients who died during the study period, the adjudication committee blindly reviewed case records to establish whether the death was attributable to the staphylococcal infection. The adjudication committee also reviewed all potentially effective nonstudy antibiotics administered to each patient from randomization until test of cure to ensure that patient outcome was solely attributable to the duration of study antibiotics.

Primary Outcomes

The primary outcomes in the intention-to-treat population were (1) success rate at the test-of-cure evaluation and (2) investigator-reported serious adverse event rate in the 2 treatment groups. The study would be considered negative if the algorithm resulted in either inferior clinical outcomes (ie, lower success rate) or a statistically higher rate of serious adverse events. Patients were classified as having experienced treatment success if they were judged to be cured by the adjudication committee and exhibited none of the criteria for failure

Figure. Flow of Participants Through the Staphylococcal Bacteremia Trial



[a] Prior to an amendment allowing inclusion of these patients.

[b] Details for reasons for exclusion from the per-protocol population are provided in eTable 8 in Supplement 2.

or nonevaluable outcomes. Serious adverse events were those adverse events that resulted in death; were life-threatening; caused persistent or significant disability or incapacity; inpatient hospitalization or prolongation of existing hospitalization; congenital abnormality or birth defect; or were considered important medical events.

Secondary Outcome

The prespecified secondary outcome was antibiotic days in the per-protocol population with simple or uncomplicated staphylococcal bacteremia.

Exploratory Outcomes

Exploratory outcome measures included (1) cure rate and antibiotic duration in both the intention-to-treat and per-protocol populations among the following subgroups: all patients with coagulase-negative staphylococcus, the subgroups with simple and uncomplicated coagulase negative staphylococcus, all *S aureus*, and the subgroup with uncomplicated *S aureus*; and (2) the association between vancomycin MIC and clinical outcomes. A post hoc analysis of clinical success among patients with complicated *S aureus* was also performed. The frequency of mortality events judged to be attributable to staphylococcal infection by the blinded adjudication review was compared in the 2 treatment groups. This comparison was not prespecified before trial initiation.

Statistical Analysis

Assuming a 75% cure rate in each treatment group, statistical power of 90%, and a 2-sided significance level of .05, we estimated that 362 patients would need to be enrolled to demonstrate noninferiority within a margin of 15%, using the large-sample *z* test. This margin was lower than that allowed in the only previous *S aureus* bloodstream infection registrational trial[9] and is consistent with contemporary noninferiority margins currently considered by the US Food and Drug Administration for trials seeking an indication in *S aureus* bloodstream infection. We additionally estimated that based on previous trial experience,[9] approximately 28% of enrolled patients would be excluded from the per-protocol population. To have sufficient power for the secondary outcome, a sample size of 500 patients was selected. The efficacy analyses are based on 97.5%

Table 2. Characteristics of Patients in the Intention-to-Treat Population

Characteristic	Algorithm-Based Therapy (N = 255)	Usual Practice (N = 254)
Age, median (range), y	58 (19-91)	60 (18-94)
Men, No. (%)	146 (57.3)	137 (53.9)
Race, No. (%)[a]		
White	175 (68.6)	174 (68.5)
Black or African American	63 (24.7)	60 (23.6)
Other[b]	17 (6.7)	20 (7.9)
Ethnicity, No. (%)		
Hispanic or Latino	21 (8.2)	23 (9.1)
Not Hispanic or Latino	234 (91.8)	231 (90.9)
Body mass index, median (range)[c]	27.6 (11.1-63.5)	27.4 (13.5-71.0)
Creatinine clearance (MDRD equation), median (range), mL/min/1.73m^2	82.7 (12.1-873.6)	88.0 (9.7-834.9)
Risk factor, No. (%)		
Immunosuppressed condition[d]	75 (29.4)	72 (28.3)
Diabetes mellitus	63 (24.7)	72 (28.3)
Chronic liver disease	25 (9.8)	20 (7.9)
Surgery within previous 30 d	24 (9.4)	20 (7.9)
Trauma within previous 30 d	9 (3.5)	12 (4.7)
Injection drug use	9 (3.5)	12 (4.7)
Preexisting valvular heart disease	9 (3.5)	9 (3.5)
Chronic renal insufficiency	8 (3.1)	5 (2.0)
History of *S aureus* infection within the past year	7 (2.7)	5 (2.0)
Hypertrophic cardiomyopathy	5 (2.0)	6 (2.4)
Congenital heart disease	1 (0.4)	1 (0.4)
Previous infective endocarditis	0	0
Setting of infection, No. (%)		
Nosocomial	85 (33.3)	82 (32.3)
Health care-associated, community-onset	92 (36.1)	88 (34.6)
Community-acquired	78 (30.6)	84 (33.1)
Classification by diagnosis, No. (%)[e]		
Simple or uncomplicated bacteremia	209 (81.9)	221 (87.0)
Simple coagulase-negative staphylococci	136 (53.3)	124 (48.8)
Uncomplicated coagulase-negative staphylococci	39 (15.3)	52 (20.5)
Uncomplicated *S aureus*	34 (13.3)	45 (17.7)
Complicated bacteremia	42 (16.4)	29 (11.4)
Complicated coagulase-negative staphylococci	19 (7.5)	15 (5.9)
Complicated *S aureus*	23 (9.0)	14 (5.5)
Nonstaphylococcal infection	4 (1.6)	4 (1.6)
Echocardiogram performed, among patients with *S aureus*, No./total (%)	56/57 (98.2)	58/59 (98.3)
Transesophageal echocardiogram	25/57 (43.9)	27/59 (45.8)
Diagnosed with endocarditis[f]	4/57 (7.0)	1 (1.7)
Median vancomycin minimum inhibitory concentration, µg/mL	1.0	1.0
Median daptomycin dose (IQR), mg/kg	6.0 (5.8-7.6) [n = 42]	6.0 (5.8-7.0) [n = 43]
Median vancomycin trough (IQR), µg/mL, No.[g]	13.6 (10.1-20.4) [n = 111]	13.1 (9.5-19.8) [n = 100]
S aureus	17.4 (7.2-21.2) [n = 35]	12.4 (9.0-22.5) [n = 39]
Coagulase-negative staphylococci	13.4 (10.3-19.8) [n = 76]	13.3 (9.5-18.8) [n = 61]
Not simple coagulase-negative staphylococcus and intravenous catheter not removed, No. (%)[h]	1 (0.4)	2 (0.8)
S aureus treatment characteristics, No./total (%)		
Patients with *S aureus* receiving appropriate empirical antibiotic therapy[i]	57/57 (100)	58/59 (98.3)
MRSA receiving appropriate empirical therapy	12/12 (100)	21/21 (100)
MSSA receiving appropriate empirical therapy	45/45 (100)	37/38 (97.4)
MSSA receiving empirical beta-lactam therapy	39/45 (86.7)	28/38 (73.7)
Infectious diseases consultation for *S aureus* bacteremia	41/57 (71.9)	37/59 (62.7)

Abbreviations: IQR, interquartile range, MDRD, Modification of Diet in Renal Disease; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

[a] Race was determined by the investigators and based on predefined categories.

[b] The algorithm-based therapy group included 10 patients with race unknown or not reported and 4 multiracial, 2 Asian, and 1 American Indian/Alaska Native patients. The usual practice group included 12 patients with race unknown or not reported and 4 Asian, 2 multiracial, 1 American Indian/Alaska Native, and 1 Native Hawaiian or other Pacific Islander patients.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Defined as chronic low-dose (>10 mg prednisone for >50 d) or acute high-dose (>40 mg prednisone for >7 d) corticosteroid administration or other immunomodulatory agents (eg, monoclonal agents, methotrexate).

[e] This was the classification after the completion of the baseline evaluation, including follow-up blood cultures and echocardiography. The patients with complicated bacteremia were enrolled with suspected simple or uncomplicated bacteremia but were subsequently found to have complicated infection at baseline.

[f] Using the modified Duke criteria for diagnosis of endocarditis.[9] Local site interpretations and core laboratory echocardiogram interpretations resulted in concordant endocarditis diagnoses (rejected, possible, or definite endocarditis) in all cases.

[g] Vancomycin trough levels were not mandatory but were recorded when obtained as part of routine care.

[h] Intravenous catheters could be retained in patients meeting a definition of having simple coagulase-negative staphylococci. These 3 patients were recorded as protocol deviations and were excluded from per-protocol analyses.

[i] Appropriate empiric therapy defined as treatment in the first 48 hours after the index blood culture was drawn, with either vancomycin or daptomycin for MRSA isolates and with vancomycin, daptomycin, or an antistaphylococcal beta-lactam for MSSA isolates.

1-sided testing with a 2.5% significance threshold. The other end points are based on 2-sided testing with a 5% significance threshold. Patients who had missing data for the test of cure were considered as having experienced treatment failure for both the intention-to-treat and per-protocol analyses.

A prespecified sensitivity analysis, in which missing data were treated as missing, was also performed. Additionally, post hoc multiple imputation analysis was performed to address missing data at the test-of-cure visit. A post hoc mixed-effects analysis, treating site as a random effect, was performed to assess for site effect. Except for the coprimary end points and the antibiotic duration secondary end point, all other analyses were

Table 3. Outcomes at Test-of-Cure Visit

Criteria	No./Total No. (%)		Difference, % (1-Sided 97.5% CI)
	Algorithm-Based Therapy	Usual Practice	
Overall success in the ITT population[a]	209/255 (82.0)	207/254 (81.5)	0.5 (−6.2 to ∞)
Success according to assessment of complication[b]			
Simple or uncomplicated bacteremia	173/209 (82.8)	191/221 (86.4)	−3.7 (−10.5 to 3.2)
Complicated bacteremia	36/42 (85.7)	16/29 (55.2)	30.5 (9.6 to 51.5)
Success according to clinical category			
All *Staphylococcus aureus*	43/57 (75.4)	39/59 (66.1)	9.3 (−7.1 to ∞)
Uncomplicated *S aureus*	24/34 (70.6)	34/45 (75.6)	−5.0 (−24.8 to ∞)
Complicated *S aureus*	19/23 (82.6)	5/14 (35.7)	46.9 (17.4 to ∞)
All coagulase-negative staphylococci	166/194 (85.6)	168/191 (88.0)	−2.4 (−9.2 to ∞)
Simple coagulase-negative staphylococci	115/136 (84.6)	109/124 (87.9)	−3.3 (−11.7 to ∞)
Observed without antibiotics	37/46 (80.4)	35/38 (92.1)	−11.7 (−26.0 to ∞)
Treated with antibiotics	78/90 (86.7)	74/86 (86.0)	0.6 (−9.5 to ∞)
Uncomplicated coagulase-negative staphylococci	34/39 (87.2)	48/52 (92.3)	−5.1 (−17.9 to ∞)
Complicated coagulase-negative staphylococci	17/19 (89.5)	11/15 (73.3)	16.1 (−10.2 to ∞)
Overall success in the per-protocol population	185/207 (89.4)	178/203 (87.7)	1.7 (−4.5 to ∞)
Success according to pathogen in the ITT population[c]			
S aureus			
Methicillin-susceptible	33/45 (73.3)	23/38 (60.5)	12.8 (−7.4 to ∞)
Methicillin-resistant	10/12 (83.3)	16/21 (76.2)	7.1 (−20.7 to ∞)
Coagulase-negative staphylococci			
Methicillin-susceptible	81/90 (90.0)	82/88 (93.2)	−3.2 (−11.3 to ∞)
Methicillin-resistant	84/98 (85.7)	86/100 (86.0)	−0.3 (−10.0 to ∞)

Abbreviation: ITT, intention-to-treat.

[a] In a sensitivity analysis in which missing data were treated as missing, results were similar (success, 209/223 [93.7%] in the algorithm-based therapy group vs 207/221 [93.7%] in the usual practice group; difference, 0.1 [1-sided 97.5% CI, −4.5 to ∞]). In the post hoc multiple imputation analysis, results were also similar (difference, 0.2 [1-sided 97.5% CI, −5.6 to ∞]). See also eTable 6 in Supplement 2.

[b] Final classification as simple, uncomplicated, or complicated bacteremia was established after completion of the baseline evaluation, including follow-up blood cultures and echocardiography. Patients with complicated bacteremia were enrolled with suspected simple or uncomplicated bacteremia but were subsequently found to have complicated infection at baseline.

[c] Methicillin susceptibility testing was not available for 9 (2.3%) coagulase-negative staphylococci isolates (5 with simple coagulase-negative staphylococci and 1 with uncomplicated coagulase-negative staphylococci in the algorithm-based therapy group, and 2 with simple coagulase-negative staphylococci and 1 with uncomplicated coagulase-negative staphylococci in the usual practice group).

not adjusted for multiple comparisons and should be interpreted as exploratory and hypothesis-generating.

All analyses were conducted using SAS version 9.4 (SAS Institute Inc).

Data and Safety Monitoring Board

An independent data and safety monitoring board, appointed and managed by the National Institute of Allergy and Infectious Diseases, regularly reviewed the data and made recommendations regarding study conduct.

Results

Patients

A total of 255 patients (146 [57.3%] men) were randomized to algorithm-based therapy and 254 (137 [54.0%] men) to usual practice (**Figure**; eAppendix 3 in Supplement 2); 480 (94.3%) completed the trial (eTable 8 in Supplement 2). Demographic and clinical characteristics in the 2 groups were similar (**Table 2**; eTables 1-3 in Supplement 2). Among enrolled patients, 385 (76%) had coagulase-negative staphylococcal bacteremia and 116 (23%) had *S aureus* bacteremia. Blood cultures for 4 patients in each group ultimately yielded only a nonstaphylococcal species.

Altogether, 260 patients had simple staphylococcal bacteremia, 170 had uncomplicated staphylococcal bacteremia (91 coagulase-negative staphylococci, 79 *S aureus*), and 71 had complicated staphylococcal bacteremia (34 coagulase-negative staphylococci, 37 *S aureus*). Eighty-four patients with simple coagulase-negative staphylococcal bacteremia were observed without antibiotic therapy.

Vancomycin MICs were similar in each group, with a median of 1 µg/mL. There were no *S aureus* isolates with vancomycin MIC greater than 2 µg/mL.

Echocardiography was performed in all but 1 patient with *S aureus* in each treatment group; transesophageal echocardiography was performed in 25 of 57 patients (43.9%) in the algorithm-based therapy group and 27 of 59 (45.8%) in the usual practice group. Definite endocarditis[10] was diagnosed in 5 patients (4 algorithm, 1 usual practice). Blinded echocardiography core laboratory interpretations were concordant with local site interpretations.

Primary Outcomes

In the intention-to-treat population, clinical success occurred in 209 of 255 patients in the algorithm group and 207 of 254 in the usual practice group (82.0% vs 81.5%; difference, 0.5% [1-sided 97.5% CI, −6.2% to ∞]) (**Table 3**; eTables 4 and 5 in Supplement 2). Since the lower limit of the confidence interval was greater than −15%, algorithm-based therapy was determined to be noninferior to usual practice. There were 65 patients (12.8%) missing the primary efficacy end point. Sensitivity analyses in which missing data were treated as missing, as well as post hoc multiple imputation analysis and mixed-effects analysis treating site as a random effect, were consistent with the primary analysis (Table 3; eTable 6 in Supplement 2).

The overall serious adverse event frequency was not significantly different in the algorithm and usual practice groups (32.5% vs 28.3%; difference, 4.2% [95% CI, −3.8% to 12.2%]). Adverse events leading to study drug discontinuation were reported in 4 patients in the algorithm group and 1 in the usual practice group (**Table 4**; eTable 7 in Supplement 2). Although 161 of 509 patients (31.6%) had at least 1 adverse event, adverse events related to study drug were infrequent (14/509 [2.8%]). A total of 16 patients (6.3%) in the algorithm-based therapy group and 14 (5.5%) in the usual practice group died before the test-of-cure assessment (difference, 0.8% [95% CI, −3.3% to 4.9%]). The blinded adjudication committee attributed 2 of the deaths in the algorithm group to infection, compared with 3 in the usual practice group; all of these deaths were among patients with *S aureus* infection (Table 4). Serious adverse events related to infections occurred in 10.6% of patients in the algorithm group, compared with 11.0% in the usual practice group.

Secondary Outcome

Among per-protocol patients with simple or uncomplicated bacteremia, duration of therapy was significantly shorter in the algorithm-based therapy group than in the usual practice group (4.4 days vs 6.2 days; difference, −1.8 days [95% CI, −3.1 to −0.6 days]) (**Table 5**; eTable 8 in Supplement 2). This difference was primarily attributable to shorter duration of therapy in patients in the algorithm-based therapy group who had uncomplicated coagulase-negative staphylococcal bacteremia (5.3 days vs 8.4 days; difference, −3.1 days [95% CI, −4.9 to −1.3 days]). When the group of patients with simple coagulase-negative staphylococcal bacteremia who were observed without antibiotic therapy were excluded from the analysis, duration of therapy remained significantly shorter in the algorithm group (5.8 days vs 7.7 days; difference, −1.9 days [95% CI, −3.4 to −0.5 days]).

Exploratory Outcomes

Within prespecified subgroup analyses, success rates were not significantly different among patients with simple coagulase-negative staphylococcal bacteremia; uncomplicated coagulase-negative staphylococcal bacteremia; and uncomplicated *S aureus* bacteremia (Table 3; eTables 9 and 10 in Supplement 2).

Among patients with simple coagulase-negative staphylococci in both the algorithm and the usual practice groups, clinical success occurred in 72 of 84 patients (85.7%) who re-

Table 4. Safety Outcomes

Criteria	Algorithm-Based Therapy	Usual Practice
Serious adverse events in the ITT population, No./total (%)[a]	83/255 (32.5)	72/254 (28.3)
Mortality, No./total (%)[b,c]	16/255 (6.3)	14/254 (5.5)
No. related to infection per blinded adjudication/ total deaths (%)	2/16 (12.5)	3/14 (21.4)
According to clinical category, No./total		
Simple coagulase-negative staphylococci	0/6	0/4
Uncomplicated coagulase-negative staphylococci	0/0	0/3
Complicated coagulase-negative staphylococci	0/3	0/1
Uncomplicated *Staphylococcus aureus*	1/5	1/3
Complicated *S aureus*	1/2	2/3
Serious adverse events by organ system class, No. (%)[d]	n = 255	n = 254
Infections and infestations	27 (10.6)	28 (11.0)
Renal and urinary disorders	12 (4.7)	4 (1.6)
Respiratory, thoracic, and mediastinal disorders	10 (3.9)	13 (5.1)
Blood and lymphatic system disorders	9 (3.5)	7 (2.8)
Gastrointestinal disorders	8 (3.1)	11 (4.3)
General disorders and administration site conditions	8 (3.1)	6 (2.4)
Cardiac disorders	8 (3.1)	5 (2.0)
Metabolism and nutrition disorders	6 (2.4)	4 (1.6)
Injury, poisonings, and procedural complications	6 (2.4)	4 (1.6)
Vascular disorders	5 (2.0)	2 (0.8)
Nervous system disorders	4 (1.6)	6 (2.4)
Psychiatric disorders	4 (1.6)	3 (1.2)
Investigations	4 (1.6)	1 (0.4)
Neoplasms	3 (1.2)	3 (1.2)
Hepatobiliary disorders	3 (1.2)	3 (1.2)
Musculoskeletal and connective tissue disorders	2 (0.8)	2 (0.8)
Immune system disorders	1 (0.4)	2 (0.8)
Reproductive system and breast disorders	1 (0.4)	0
Endocrine disorders	1 (0.4)	0
Product issues	0	2 (0.8)
Skin and subcutaneous tissue disorders	0	1 (0.4)
Adverse events associated with study drug, No. (%)	9 (3.5)	5 (2.0)
Adverse events leading to study drug discontinuation, No. (%)	4 (1.6)	1 (0.4)

Abbreviation: ITT, intention-to-treat.

[a] Difference, 4.2% (95% CI, −3.8% to 12.2%).

[b] Difference, 0.8% (95% CI, −3.3% to 4.9%).

[c] No patients died during study antibiotic therapy.

[d] Patients could have more than 1 event.

Table 5. Duration of Therapy Among Per-Protocol Patients With Simple or Uncomplicated Staphylococcal Bacteremia[a]

	Algorithm-Based Therapy			Usual Practice			Difference of Means, d (95% CI)
	Mean	Median (IQR)	No.	Mean	Median (IQR)	No.	
Duration of therapy, d	4.4	3.0 (1.0 to 5.0)	171	6.2	3.0 (1.0 to 13.0)	183	−1.8 (−3.1 to −0.6)
Simple coagulase-negative staphylococci	1.8	2.0 (0.0 to 3.0)	114	1.8	1.0 (0.0 to 3.0)	103	0.0 (−0.5 to 0.6)
Uncomplicated coagulase-negative staphylococci	5.3	5.0 (5.0 to 6.0)	33	8.4	7.5 (5.0 to 14.0)	42	−3.1 (−4.9 to −1.3)
Uncomplicated *Staphylococcus aureus*	15.3	14.0 (14.0 to 15.0)	24	15.9	16.0 (14.0 to 17.0)	38	−0.6 (−3.4 to 2.2)

Abbreviation: IQR, interquartile range.

[a] In an exploratory analysis in patients with complicated bacteremia, patients with complicated coagulase-negative staphylococci had a mean duration of therapy of 10.6 days (median, 9.0; IQR, 7.0-13.0) in algorithm-based therapy and 14.5 days (median, 13.0; IQR, 10.0-16.0) in usual practice (difference of means, 3.9 days [95% CI, −8.9 to 1.1]). Patients with complicated *S aureus* bacteremia had a mean duration of therapy of 30.2 days (median, 29.0; IQR, 24.0-33.0) in algorithm-based therapy and 27.5 days (median, 31.0; IQR, 17.0-33.0) in usual practice (difference of means, 2.7 days [95% CI, −3.9 to 9.3]). Additional information is available in eTables 4 and 5 in Supplement 2.

ceived no antibiotic therapy, compared with 152 of 176 (86.4%) who received antibiotics.

Among patients with uncomplicated *S aureus* bacteremia, 21 of 79 (26.6%) were classified as having experienced treatment failure. Of these, 9 (11.4%) were classified as experiencing failure because of nonevaluable status, whereas 12 (15.2%) experienced clinical failure (eTable 4 in Supplement 2).

In a post hoc analysis of patients with complicated *S aureus* bacteremia, success rates were higher in the algorithm group (19/23 [82.6%] vs 5/14 [35.7%]; difference, 46.9% [1-sided 97.5% CI, 17.4% to ∞]). No significant differences were identified in success rates by methicillin susceptibility or by vancomycin MIC of the bloodstream isolate.

Discussion

In this study, among patients with staphylococcal bacteremia, the use of an algorithm to guide testing and treatment compared with usual care resulted in a noninferior rate of clinical success. There was no significant difference in rates of serious adverse events, although the upper bound of the 95% confidence interval suggests the possibility of a higher rate of adverse events with abbreviated therapy.

Algorithm-based therapy reduced median antibiotic duration by 29%, compared with usual practice, for evaluable patients with simple or uncomplicated bacteremia. The difference was most notable among patients with uncomplicated coagulase-negative staphylococcal bacteremia, for whom antibiotic duration was reduced by 3.1 days (37%). Consensus guidelines recommend short-course antibiotic therapy of 5 to 7 days for uncomplicated coagulase-negative staphylococcal catheter-related bacteremia.[4] However, to our knowledge, before the current study there were no randomized trial data to support these recommendations. The results of this study also provide evidence that simple coagulase-negative staphylococcal bacteremia, which is frequently regarded as a contaminant,[11] may not require antibiotic therapy.

The essential risk of abbreviated therapy is undertreated infection, which would be expected to manifest as any or all of the following: lower cure rates, higher relapse rates, and higher rates of infection-related adverse events, including mortality. In this trial, in addition to noninferior clinical success rates, use of the algorithm was not significantly associated with more infection-related severe adverse events. Although the difference in overall mortality was not statistically significant, the upper confidence limit was 4.9% worse in patients randomized to the algorithm. While the blinded adjudication committee attributable mortality outcome was not a prespecified end point, the committee attributed fewer deaths to infection in the algorithm group. The relatively high rate of serious adverse events experienced by patients in this trial may therefore reflect the severity of concurrent illnesses among hospitalized patients with staphylococcal bacteremia.

The duration of therapy for uncomplicated *S aureus* bacteremia has been a point of controversy since at least 1976, when 10 to 21 days was proposed for *S aureus* bacteremia associated with a removable focus of infection.[12] A meta-analysis evaluating the duration of therapy for catheter-associated *S aureus* bacteremia found that the complication rate of short-course therapy (defined as 2 weeks) was 6.1% and concluded that durations of antibiotics longer than 2 weeks should be used until a means exists to accurately identify patients with underlying complications.[7] In the current study, patients randomized to algorithm-based therapy or usual practice for uncomplicated *S aureus* bacteremia had similar durations of therapy (≈15 days), suggesting that 2 weeks of therapy may be a standard medical practice for this diagnosis in many centers. Despite the widespread acceptance of this treatment duration, however, approximately 15% of the patients with uncomplicated *S aureus* bacteremia in the study were classified as having experienced treatment failure for nonadministrative reasons (antibiotic therapy changed because of an unsatisfactory clinical response, new metastatic infection, persistent or relapsing infection, or death). In addition, 32% of study patients with *S aureus* bacteremia without suspected metastatic infection at enrollment were ultimately diagnosed with complicated *S aureus* bacteremia. Collectively, these results suggest that a 2-week course of therapy for uncomplicated *S aureus* bacteremia should be used with caution and only if patients have undergone a careful evaluation for metastatic infection.[2-4,13]

Patients with complicated *S aureus* bacteremia in the algorithm group experienced higher cure rates than those in the

usual practice group. While this is an exploratory subgroup analysis and may reflect chance, it is consistent with other recent studies[14] and suggests that this algorithm incorporates a comprehensive set of management principles that can improve outcomes for patients with *S aureus* bacteremia.[14]

Limitations

This study had several limitations. First, this study was deliberately not powered to compare subgroups such as patients with uncomplicated *S aureus* bacteremia. Instead, it was designed and powered to address a more clinically applicable question: how to define the optimal treatment duration for a patient with staphylococcal bacteremia and no evidence of metastatic infection. Second, the open-label design of the study could have introduced bias.[15] However, primary study end points were established by a blinded adjudication committee. Third, repeated exposure to the algorithm may have influenced management decisions in clinicians caring for patients receiving algorithm-based therapy as well as those receiving usual practice. This possibility is suggested by similar durations of therapy in the patients with uncomplicated *S aureus* bacteremia in both treatment groups. However, this potential bias would have underestimated the difference in duration of therapy between algorithm-based therapy and usual practice. Fourth, intravenous catheters were removed in all patients except those with simple coagulase-negative staphylococcal bacteremia. Thus, this trial does not establish the optimal duration of therapy for patients with staphylococcal bacteremia in whom a catheter-retention strategy is pursued. Fifth, this study was conducted at academic institutions. Thus, medical practices in the study may not reflect those of other health care organizations.

Conclusions

Among patients with staphylococcal bacteremia, the use of an algorithm to guide testing and treatment compared with usual care resulted in a noninferior rate of clinical success. Rates of serious adverse events were not significantly different, but interpretation is limited by wide confidence intervals. Further research is needed to assess the utility of the algorithm.

ARTICLE INFORMATION

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Author Affiliations: Duke University Medical Center, Durham, North Carolina (Holland, Anderson, Chu, Carugati, Corey, Crowley, Fowler); Duke Clinical Research Institute, Durham, North Carolina (Holland, Aycock, Chow, Gu, Fowler); The University of Texas MD Anderson Cancer Center, Houston (Raad, Chaftari, Hachem); Tufts Medical Center, Boston, Massachusetts (Boucher); Johns Hopkins University School of Medicine, Baltimore, Maryland (Cosgrove); University of Alabama at Birmingham (Baddley); San Gerardo Hospital, Monza, Italy (Carugati); Brody School of Medicine, East Carolina University, Greenville, North Carolina (Cook); University of Massachusetts Medical School, Worcester (Daly); Carolinas Medical Center, Charlotte, North Carolina (Horton); Denver Health, Denver, Colorada (Jenkins); Wayne State University, Detroit, Michigan (Levine); Hospital Clinic–IDIBAPS, University of Barcelona, Barcelona, Spain (Miro, Pericas); Albert Einstein College of Medicine, Bronx, New York (Riska); David Geffen School of Medicine, University of California at Los Angeles (Rubin); University of Nebraska Medical Center, Omaha (Rupp); Greenville Health System, Greenville, South Carolina (Schrank); Beaumont Health System, Royal Oak, Michigan (Sims); Medical University of South Carolina, Charleston (Wray); Henry Ford Health System, Detroit, Michigan (Zervos).

Author Contributions: Dr Fowler had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Holland, Raad, Boucher, Chow, Corey, Gu, Levine, Rupp, Schrank, Zervos, Fowler.
Acquisition, analysis, or interpretation of data: Holland, Boucher, Anderson, Cosgrove, Aycock, Baddley, Chaftari, Chow, Chu, Carugati, Cook, Crowley, Daly, Gu, Hachem, Horton, Jenkins, Levine, Miro, Pericas, Riska, Rubin, Rupp, Schrank, Sims, Wray, Zervos, Fowler.
Drafting of the manuscript: Holland, Raad, Boucher, Anderson, Aycock, Gu, Horton, Pericas, Zervos, Fowler.
Critical revision of the manuscript for important intellectual content: Holland, Raad, Boucher, Anderson, Cosgrove, Baddley, Chaftari, Chow, Chu, Carugati, Cook, Corey, Crowley, Daly, Hachem, Horton, Jenkins, Levine, Miro, Pericas, Riska, Rubin, Rupp, Schrank, Sims, Wray, Zervos, Fowler.
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Supervision: Holland, Raad, Aycock, Chow, Hachem, Pericas, Rupp, Schrank, Zervos, Fowler.

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Group Information: Staphylococcal Bacteremia Principal Investigators: *Spain*: Jose M. Miro, Hospital Clinic-IDIBAPS, University of Barcelona; *United States*: John W. Baddley, University of Alabama; Vivian H. Chu, Duke University Medical Center; John Schrank Jr, Greenville Hospital System; Donald Levine, Wayne State University; Mark E. Rupp, University of Nebraska Medical Center; Issam Raad, MD Anderson Center; Timothy C. Jenkins, Denver Health Medical Center; Dannah Wray, Medical University of South Carolina; Marcus Zervos, Henry Ford Hospital; Zachary Rubin, David Geffen School of Medicine at UCLA; Paul Riska, Albert Einstein College of Medicine; Paul Cook, Brody School of Medicine at East Carolina; James Horton, Carolinas Medical Center; Jennifer Daly, UMass Memorial Medical Center; Mathew Sims, Beaumont Hospital.

Additional Collaborators: *Hospital Clinic-IDIBAPS, University of Barcelona*: M. Almela, J. Ambrosioni, Y. Armero, J.A. Arnaiz, X. Castañeda, C. Cervera, A. del Rio, C. Falces, C. Garcia-de-la-Maria, I. Hoyo-Ulloa, F. Marco, C.A. Mestres, A. Moreno, D. Nicolas, S. Ninot, J.C. Pare, J.M. Pericas, E. Quintana, I. Ruiz-Zamora, D. Soy. *University of Nebraska Medical Center:* R.J. Cavalieri. *Denver Health Medical Center*: H. Young.

Data Sharing Statement: See Supplement 3.

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