Clinical Infectious Diseases

VIEWPOINTS

Considerations for Clinical Trials of *Staphylococcus aureus* Bloodstream Infection in Adults

Thomas L. Holland,[1] Henry F. Chambers,[2] Helen W. Boucher,[3] G. Ralph Corey,[1] Rebecca Coleman,[4] Bibiana Castaneda-Ruiz,[4] and Vance G. Fowler Jr[1]

[1]Department of Medicine, Duke University Medical Center, Durham, North Carolina; [2]Department of Medicine, University of California San Francisco; [3]Department of Medicine, Tufts Medical Center, Boston, Massachusetts; and [4]Theravance Biopharma US, Inc., South San Francisco, California

Clinical trials for *Staphylococcus aureus* bloodstream infections (SAB) are broadly grouped into 2 categories: registrational trials intended to support regulatory approval of antibiotics for the treatment of SAB and strategy trials intended to inform clinicians on the best treatment options for SAB among existing antibiotics. Both types of SAB trials are urgently needed but have been limited by cost, complexity, and regulatory uncertainty. Here, we review key SAB trial design considerations for investigators, sponsors, and regulators.

Keywords. *Staphylococcus aureus*; bacteremia; clinical trials.

Staphylococcus aureus bloodstream infections (SAB) is common and often lethal [1]. Despite advances in infection control and prevention, the incidence and mortality of SAB are unchanged [1]. SAB remains among the most frequent infections treated by infectious disease specialists, yet high-quality trials are few [2]. Clinicians who manage SAB lack robust evidence about the optimal agent for initial therapy, efficacy of combination antibiotics, salvage therapy in the face of persistent infection, duration of therapy, and efficacy of oral "stepdown" therapy. In addition, the ever-shifting landscape of antibacterial resistance threatens clinicians' abilities to treat SAB at all. Here, we summarize challenges in the design and execution of interventional clinical trials for SAB, with attention to both registrational and strategy designs, and offer recommendations to address these issues.

CHALLENGES CONFRONTING REGULATORY TRIALS

The ultimate goal of a registrational trial is to obtain marketing approval from the US Food and Drug Administration (FDA). For antibiotics used to treat *S. aureus* infections, initial approval is usually achieved through an indication that is currently referred to as acute bacterial skin and skin structure infections (ABSSSIs). Robust FDA guidance for trial designs and endpoints is available for these infections [3]. ABSSSI trials enable sponsors to obtain safety, efficacy, and pharmacokinetic/pharmacodynamic information while pursuing regulatory approval. Consequently, every antistaphylococcal antibiotic in the last 20 years has entered the marketplace with an FDA indication for ABSSSI. Efficacy in treating ABSSSI, however, does not imply efficacy in treating invasive infections [4, 5]. To determine safety and efficacy for treatment of SAB, an antibiotic must be studied in patients with SAB.

To date, only daptomycin has been approved by the FDA for treatment of SAB and right-sided native valve endocarditis [6], in part, due to a lack of FDA guidance for the treatment of SAB. While FDA guidance for catheter-related bloodstream infection was published in the 1990s, no trials have been completed for this indication [7]. In the absence of specific guidance for SAB, trials have used different patient populations, noninferiority margins, and study endpoints (Table 1) [8]. Currently, 1 registrational trial in SAB is expected to begin enrolling patients soon (clinicaltrials.gov NCT03138733). Two other industry-sponsored phase 3 or phase 4 studies were terminated prematurely (NCT02208063, NCT03148756), underscoring the difficulty of conducting such trials.

CHALLENGES CONFRONTING STRATEGY TRIALS

High-quality trials that test antibiotics or treatment strategies (hereafter, "strategy" trials) are also difficult to complete. While strategy trials typically exhibit greater flexibility in their design than trials intended for regulatory approval, significant challenges remain due to fundamental characteristics of SAB. These include diagnostic delay, the need for empirical antibiotic therapy, and differentiating complicated from uncomplicated SAB (Table 2). Any trial seeking to enroll patients with SAB must address these challenges. Other treatment variables (eg, adjunctive surgical therapy, standard-of-care antibiotics, and use of outpatient parenteral antibiotic therapy) may also be difficult to standardize. Receipt of nonstudy antibiotics may

Received 18 June 2018; editorial decision 27 August 2018; accepted 5 September 2018; published online September 10, 2018.

Correspondence: V. G. Fowler Jr, Division of Infectious Diseases, Department of Medicine, Box 102359, Room 185, Hanes Building, 315 Trent Drive, Duke University Medical Center, Durham, NC 27710 (vance.fowler@duke.edu).

Clinical Infectious Diseases® 2019;68(5):865–72

DOI: 10.1093/cid/ciy774

Table 1. Recent Investigator-initiated and Industry-sponsored *Staphylococcus aureus* Bacteremia Clinical Trials

Study	Intervention	Study Design	Proposed Sample Size	Outcome	Status
Investigator-initiated trials					
ARREST (ISRCTN37666216)	Adjunctive rifampin vs placebo, each in combination with standard of care for SAB	Double-blind RCT	758	Microbiologic failure, disease recurrence, or death at 12 weeks	Completed [9]
National Institutes of Health algorithm (NCT01191840)	Algorithm-based therapy for staphylococcal bacteremia	Open-label RCT	509	Treatment success, safety, and duration of antibiotic therapy	Completed, results in review [10]
CAMERA-1 (ACTRN12610000940077)	Addition of flucloxacillin to vancomycin for MRSA bacteremia	Open-label pilot RCT	60	Duration of bacteremia	Completed [11]
CAMERA-2 (NCT02365493)	Addition of a beta-lactam antibiotic to standard therapy for MRSA bacteremia	Open-label RCT	440	Complication-free 90-day survival	Recruiting
SABATO (NCT01792804)	Early intravenous to oral antibiotic switch in uncomplicated SAB	Open-label RCT	430	SAB-related complications at 90 days	Recruiting
BACSARM (NCT01898338)	Fosfomycin vs placebo, in combination with daptomycin, for MRSA bacteremia	Open-label RCT	167	Clinical response 6 weeks after the end of therapy	Enrollment completed
Industry-sponsored trials					
Primary treatment					
Daptomycin (NCT00093067)	Daptomycin vs standard of care for SAB including endocarditis	Open-label RCT	236	Treatment success 42 days after the end of therapy	Completed [6]
ASSURE (NCT00062647)	Telavancin vs standard of care for uncomplicated SAB	Double-blind RCT	58	Success at 12 weeks	Completed [12]
Dalbavancin (NCT03148756)	Dalbavancin vs standard of care for therapy completion for complicated bacteremia and endocarditis	Open-label RCT	…	Success at 12 weeks	Study terminated by sponsor
Telavancin (NCT02208063)	Telavancin vs standard of care for SAB, including right-sided endocarditis	Open-label RCT	248	Success at 8 weeks	Study terminated by sponsor
Ceftobiprole (NCT03138733)	Ceftobiprole vs daptomycin for SAB, including right-sided endocarditis	Double-blind RCT	390	Success at 10 weeks	Recruiting
Adjunctive immunotherapeutics and other novel approaches					
CF-301 (NCT03163446)	CF-301 (a lysin) vs placebo added to standard therapy for SAB	Double-blind RCT	115	Adverse events, day 14 clinical outcome	Recruiting
SAL200 (NCT03089697)	SAL200 (a lysin) vs placebo for patients with persistent SAB	Double-blind RCT	50	Safety	Recruiting
Tefibazumab (Inhibitex, Alpharetta, GA) (NCT00198302)	Human monoclonal anti-ClfA antibody vs placebo added to standard therapy for SAB	Double-blind RCT	63	Safety, new SAB complication, relapse or death at 8 weeks	Completed [13]
Altastaph (Nabi Biopharmaceuticals, Rockville, MD) (NCT00063089)	Pooled human anticapsular polysaccharides 5 and 8 antibody vs placebo added to standard therapy for SAB	Double-blind RCT	40	Safety, time to resolution of bacteremia, and defervescence	Completed [14]
Aurograb (Novartis, Basel, Switzerland) (NCT00217841)	Single-chain antibody variable fragment against the ABC transporter component GrfA vs placebo added to vancomycin for severe, deep-seated staphylococcal infections	Double-blind RCT	180	Clinical and bacterial response	Completed, results not published
514G3 (NCT02357966)	Human monoclonal antibody against SpA [15] vs placebo added to standard therapy for SAB	Double-blind RCT	52	Safety, time to resolution of bacteremia and defervescence, duration of hospital stay	Enrollment completed
DSRA4637S (Genentech, San Francisco, CA (NCT03162250)	Human monoclonal antibody against *S. aureus* wall-teichoic acids conjugated to a rifamycin derivative [16] vs placebo added to standard therapy for SAB	Double-blind RCT	24	Safety	Recruiting

Abbreviations: ARREST, Adjunctive Rifampicin to Reduce Early Mortality from *S. aureus* Bacteraemia; ASSURE, Telavancin for Treatment of Uncomplicated *S. aureus* Bacteremia; BACSARM, Bacteremia due to Methicillin-Resistant *S. aureus*; CAMERA, Combination Antibiotic Therapy for Methicillin-Resistant *S. aureus* Infection; MRSA, methicillin-resistant *S. aureus*; RCT, randomized controlled trial; *S. aureus*, *Staphylococcus aureus*; SAB, *S. aureus* bacteremia; SABATO, *S. aureus* Bacteremia Antibiotic Treatment Options.

Table 2. Assessment of Complicated vs Uncomplicated *Staphylococcus aureus* Bloodstream Infection [17]

Criterion	Areas of Controversy
Uncomplicated	
Negative follow-up blood culture obtained 2–4 days following initial positive culture	Should positive blood cultures 24–48 hours after the initial set be regarded as evidence of complicated infection?
Defervescence within 72 hours of initiating effective therapy	Should persistent fever be considered a treatment failure?
Exclusion of endocarditis (transesophageal echocardiogram preferred)	Is transthoracic echocardiogram adequate for some patients? Should a negative initial echocardiogram be repeated later in the treatment course?
No evidence of metastatic sites of infection	Should there be standardized imaging to assess for metastatic sites?
No implanted prostheses (eg, prosthetic valves, cardiac devices, and arthroplasties)	Is it necessary to treat patients with extravascular prosthetic material as complicated infection?
Complicated	
Any infection not meeting all of the criteria above	What is the role of alternative imaging modalities such as positron emission tomography/computed tomography in evaluation for complicated infection? What is the optimal duration of therapy for complicated vs uncomplicated infections? Can oral antibiotics replace intravenous antibiotics for some of the treatment duration?

further undermine the ability to attribute the outcome to the study intervention.

ELEMENTS TO CONSIDER IN BACTEREMIA TRIAL DESIGN

A summary of key features to consider in designing an SAB trial is presented in Table 3 and discussed below.

Overall Trial Design

While double-blind SAB trials are desirable, an open-label design is often a practical necessity. Objective endpoints, such as mortality and clearance of bacteremia with use of a blinded adjudication committee to establish key study endpoints, can mitigate observer bias of an open-label design [18]. A superiority trial design is appropriate for study of "add-on" agents to standard therapy for SAB [9, 13, 14, 19]; however, demonstrating superiority to existing therapies for SAB has been difficult [6, 12].

At a minimum, patients enrolled in treatment trials for SAB should have isolation of *S. aureus* from at least 1 blood culture. While *S. aureus* should rarely be considered a bloodstream contaminant, contamination does occur; thus, enrolled patients should also have additional evidence of active infection (eg, fever, localizing signs, or symptoms of infection). Additional issues for consideration prior to enrollment include the following: definitions of complicated vs uncomplicated infections, duration of prior active antibiotic therapy, inclusion of either or both methicillin-susceptible *S. aureus* (MSSA) and methicillin-susceptible *S. aureus* (MRSA), enrollment of patients with renal impairment, inclusion of patients with metastatic sites of infection and how to diagnose them, presence of prosthetic material (such as cardiac or orthopedic devices), source control, and polymicrobial bacteremia.

Complicated vs Uncomplicated Bloodstream Infection

Due to their lower risk of poor outcome, patients with uncomplicated SAB (uSAB) are often treated for shorter durations of therapy than patients with complicated SAB (cSAB); thus, differentiating uSAB from cSAB is critical [20]. uSAB was defined in treatment guidelines for MRSA [17], but the definition is generally applied to MSSA bloodstream infections as well. Because uSAB is uncommon, trials that limit enrollment to patients with uSAB are difficult to enroll. For example, 3 recent studies limited to uSAB (NCT00062647 [12], NCT01191840 [10], NCT01792804) each screened at least 25 patients with SAB to enroll 1 patient into the study (personal communications Steve Barriere, written 5 March 2018; Achim Kaasch, written 6 March 2018; Vance Fowler, written 26 September 2018).

Differentiating uSAB from cSAB at patient enrollment is challenging. Results of follow-up blood cultures and diagnostic imaging require several days. Therefore, patients with cSAB will inevitably be enrolled into studies that evaluate uSAB (and vice versa). In 1 recent trial, approximately one-third of patients meeting criteria for uSAB at enrollment proved to have cSAB (NCT01191840) [10]. Thus, while trials may seek to enrich enrollment for a specific infection type, protocols must account for inclusion of both complicated and uncomplicated *S. aureus* infections.

An additional means to assess severity of infection at randomization is to utilize standardized measures such as the Pitt bacteremia score, Charlson score, or APACHE-II (Acute Physiology and Chronic Health Evaluation II). At least 1 such measure should be ascertained to ensure balance between study arms [21–23].

Duration of Antibiotic Therapy Prior to Randomization

Ideally, patients would be enrolled in a trial before receiving any nonstudy therapy. In reality, this is unachievable. The key consideration is how much does prior antibiotic therapy bias a trial toward a noninferiority finding or, with a superiority design, toward the null hypothesis (ie, type II error). For example, a single day of antibiotics can potentially affect outcomes in patients with community-acquired bacterial pneumonia (CABP) [4]. For this reason, FDA guidance recommends against enrolling patients who have received more than 24 hours of prestudy

Table 3. *Staphylococcus aureus* Bacteremia Trial Design Considerations

Study Design Consideration	Advantages	Disadvantages	Recommendations
Inclusion and exclusion criteria			
Include patients with multiple sources of *S. aureus* bacteremia	Enhances study generalizability; faster enrollment	Diverse study population; requires multiple comparator regimens	Include multiple sources of infection; stratify enrollment according to key characteristics of infection
Limit prerandomization antibiotic therapy	Allows an unadulterated assessment of efficacy of study drug	Makes enrollment more difficult	Allow prerandomization therapy of up to 72 hours from last positive blood culture
Limit to uncomplicated or complicated *S. aureus* bacteremia	Study population more homogenous	Difficult to assess complicated status at the time of enrollment	Formulate an a priori plan to address inevitable inclusion of misclassified infections
Limit enrollment to MRSA	Study population more homogenous	Slower enrollment; requires susceptibility testing prior to enrollment	Enroll all *S. aureus* and stratify randomization and/or analysis by MRSA status
Exclude specific metastatic sites of infection (eg, osteomyelitis)	Study population more homogenous	Slower enrollment	Have a standardized evaluation and management plan for all included metastatic sites
Standardize source control	Helps avoid unnecessary treatment failures	Difficult to standardize surgical therapy	Mandate removal of infected vascular catheters; allow clinical judgment for other specific source control approaches to enhance enrollment and minimize protocol deviations
Evaluation of outcomes			
Objective outcome (eg, mortality)	Simple, easy to collect, clinically meaningful	Requires large sample size to show a difference; does not capture all endpoints of importance to patients	Measure objective endpoint at a fixed time point from randomization
Composite outcome	Improve power of study; can capture additional important outcomes; ordinal scale such as desirability of outcome ranking can allow for superiority comparisons	May be more difficult to interpret	Use a composite clinical outcome as a primary or secondary endpoint
Choice of comparator			
Daptomycin or vancomycin for MRSA	US Food and Drug Administration approved for *S. aureus* bacteremia	Daptomycin often used at higher than approved dose; daptomycin contraindicated in patients with pneumonia	Daptomycin effective against MSSA in the registrational trial and could ethically be used as comparator for either MRSA or MSSA infections
Beta-lactam antistaphylococcal antibiotic for MSSA	Superior to vancomycin as directed therapy for MSSA	No clear advantage over vancomycin as empiric therapy in the first few days; outcomes may not be equivalent for all beta-lactam antibiotics	Allow switch to beta-lactam antibiotic for MSSA
Additional considerations			
Allow limited durations of potentially effective nonstudy antibiotics	Avoid misclassifying patients as treatment failures	May be difficult to establish whether study treatment was truly responsible for successful outcomes	Adjudication committee should determine impact of nonstudy antibiotics
Utilize an independent outcome evaluation committee	Mitigate bias; consistent evaluation criteria for multisite trials	Cost, complexity	Use an adjudication committee for open-label trials

Abbreviations: MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus; S. aureus*, *Staphylococcus aureus.*

antibiotics into registrational trials for CABP [24] and ABSSSI [3]. For patients with SAB, however, no such guidance is available. Thus, decisions on allowable durations of prior antibiotics for clinical trials of treatment for SAB should be made in consultation with the appropriate regulatory authorities. However, less than 72 hours of prestudy antibiotic therapy is unlikely to substantially impair the ability to attribute patient outcomes to study drug in SAB trials, as blood cultures in patients with cSAB commonly remain positive for 2 to 4 days even with effective therapy [20, 25]; the first few days of empirical therapy will constitute a minority of the overall treatment course. Further, duration of therapy of even 7 to 14 days for patients with uSAB is associated with high rates of relapse or mortality [26], highlighting the importance of prolonged therapy in successful outcomes. We suggest that patients who have received less than 72 hours of effective therapy since their last positive blood culture should be eligible.

When clinical circumstances dictate that SAB patients also require treatment for gram-negative or anaerobic bacteria, the study protocol should specify antibiotics with no effectiveness against *S. aureus*, such as aztreonam or metronidazole.

Should Both MSSA and MRSA Patients Be Included?

The decision to enroll patients with both MSSA and MRSA needs to balance a variety of issues. Because most cases of SAB are caused by MSSA, its inclusion speeds enrollment and

reduces study cost. Additionally, regional prevalence of MRSA varies and has declined in most areas [27]. MRSA-only protocols would limit site selection and study generalizability. On the other hand, studies must account for the fact that outcomes differ for MSSA and MRSA SAB [28, 29]. One option to address these differences is to stratify randomization by the methicillin-susceptibility status. While effective in uniformly distributing the proportions of MRSA across both study arms, stratifying by methicillin susceptibility can delay enrollment (and likely prolong administration of potentially effective nonstudy antibiotic therapy), especially if conventional microbiological susceptibility testing methods are used. A second option is to allow enrollment prior to obtaining susceptibility results and then stratify the analysis of outcomes by methicillin susceptibility. This enhances feasibility but risks imbalance in the study arms.

How Should Metastatic Sites of Infection Be Assessed?

Metastatic sites of infection in patients with SAB can impact subgroup assignment and antibiotic duration in a clinical trial [20] but are often unrecognized at enrollment. A standardized evaluation should be undertaken for each study patient with SAB, including a complete history and physical exam, infectious diseases consultation where available, echocardiography, and additional imaging (eg, magnetic resonance imaging [MRI], ultrasound) if clinically indicated. Transthoracic echocardiography is sufficient for a subset of patients with uSAB [2], but transesophageal echocardiography (TEE) is preferred for more complicated cases. For patients at high risk of endocarditis but with a negative initial study, repeat TEE is recommended to fully assess for endocarditis [30]. Although positron emission tomography/computed tomography (PET/CT) is a promising modality for assessing for metastatic sites of infection [31], there is insufficient evidence at present to mandate PET/CT or routine MRI scans.

How Should Source Control Be Approached?

The inclusion of metastatic infections improves trial feasibility but requires a detailed infection-specific plan in the study protocol. Failure to promptly identify and control sources of infection in SAB studies not only compromises patient care [32, 33] but also constitutes a potentially avoidable failure in the primary efficacy endpoint. Thus, it is essential to establish source control. For example, central venous catheters present at the time of bacteremia should be removed. Patients without plans for adequate source control within a prespecified time window from randomization (eg, 3–5 days) should not be enrolled.

For patients with *S. aureus* infective endocarditis (IE), decisions on performance and timing of valve surgery are complex and individualized [34, 35]. For SAB trials that include patients with IE, surgical decision-making should be personalized based on the presence or absence of complications such as heart failure, perivalvular abscess, and embolic complications. Surgery should not be mandated (or withheld) as a trial inclusion criterion, nor should it be automatically considered a treatment failure.

EVALUATION OF OUTCOMES

Efficacy Endpoints

Endpoints for SAB trials have been proposed previously [36]. At a minimum, the primary efficacy endpoint should require that the patient is alive and did not clinically fail treatment.

Prompt identification of a metastatic focus of infection in patients with SAB is problematic from both a clinical and study-design perspective. Metastatic foci discovered shortly after enrollment are likely to have been present prior to patient inclusion in the study. Consequently, their diagnosis immediately following enrollment does not automatically constitute a treatment failure [20]. A practical solution is to pre-specify a post-enrollment "work-up window" of approximately 5 to 7 days in the protocol, during which time newly diagnosed metastatic foci of infection may be considered part of the patient's baseline condition. Beyond that window, newly diagnosed metastatic sites or the need for unplanned source control procedures would be evidence of treatment failure.

Efficacy should be measured at a prespecified time point from randomization, not from end of therapy. A longer interval from randomization to the test-of-cure assessment increases confidence that patients deemed a success are truly cured of their infection and will also increase the risk that patients cured of their SAB will become an administrative failure due to receipt of nonstudy antibiotics or loss to follow-up. Administrative failures can be mitigated by allowing brief courses of nonstudy antibiotics (eg, ≤20% of total duration of study drug) and by allowing telephone contact as the patient's primary efficacy assessment in place of in-person visits with mandatory blood cultures. Since the median time to relapse in patients with SAB is 36 days following end of treatment [37], a practical follow-up period for primary efficacy assessment in an SAB clinical trial is approximately 8 to 10 weeks from randomization. Particular subgroups of SAB patients, such as those with an infected arthroplasty, may require longer follow-up intervals due to the nature of these infections. Key endpoints such as all-cause mortality may also be evaluated at other time points such as 14, 30, and 90 days.

A microbiologic failure endpoint has been a component of prior SAB trials [6], based on ongoing positive cultures that lead to discontinuation of study drug or relapse after initial improvement. This may be part of a composite clinical failure endpoint, assessed by a site investigator and/or a blinded adjudication committee.

Innovative statistical methods such as desirability of outcome ranking (DOOR) [38] and partial credit scoring [39] may be used to enhance and support noninferiority designs. DOOR utilizes ordinal ranking that incorporates both benefits and

harms experienced by a patient into outcomes, allowing for a superiority comparison between 2 treatments. A SAB-specific DOOR score has been developed recently [40].

OTHER CONSIDERATIONS

Choice of Comparator

Vancomycin and daptomycin are standard antibiotics for MRSA, whereas beta-lactam antibiotics nafcillin, oxacillin, flucloxacillin, and cefazolin are preferred agents for MSSA SAB. Vancomycin is inferior to beta-lactams for MSSA [41, 42] and should be used only when a clear contraindication to beta-lactam antibiotics exists.

Cure rates for MRSA and MSSA in the phase 3 daptomycin SAB trial were similar, and daptomycin may be used as a standard-of-care comparator for both MRSA and MSSA [6]. Although the FDA-approved daptomycin dose is 6 mg/kg intravenous every 24 hours (renally adjusted where appropriate), higher doses (eg, 8–10 mg/kg) are preferred [43, 44] and should be allowed in nonregistrational SAB trials.

The benefit of combination antibiotic therapy for SAB and native valve IE is unproven. Neither rifampin nor gentamicin is recommended as adjunctive treatment for SAB or native valve endocarditis [9, 45]. Although a number adjunct agents have been tested (Table 1), none have improved patient outcomes [11, 15, 16, 19, 46, 47].

Geography also influences selection of comparator agents. Availability of potential comparator antibiotics (eg, daptomycin, telavancin, teicoplanin) varies as does standard practice. These facts can necessitate multiple comparator drugs in a global study of SAB, significantly increasing study complexity and expense.

Potentially Effective Nonstudy Antibiotics

Most patients in SAB trials will receive nonstudy antibiotics. If these are active against the patient isolate, they are considered potentially effective nonstudy (PENS) antibiotics and could interfere with efficacy assessment of the study drug or antibiotic duration. In the daptomycin registrational trial, receipt of PENS antibiotics accounted for 36 of 134 (26.9%) treatment failures [6]. Some of these patients were likely cured by study therapy, and an overly conservative approach to interpretation of PENS misclassified them as treatment failures. Sensitivity analyses confirmed that receipt of PENS did not influence the difference between study arms [48]. As with prerandomization antibiotic therapy, the key variables are whether the antibiotic is active against the baseline isolate, the duration of nonstudy therapy, and when in the treatment course it is prescribed. Prespecified criteria describing which PENS antibiotics and durations would be permissible can be incorporated into the study protocol. An independent adjudication committee should review PENS antibiotics and determine their impact on study outcome; the daptomycin trial experience [6] suggests that most PENS antibiotics should not lead to designation of treatment failure.

PENS are most impactful in studies that seek to attribute patient outcomes to a specific drug [6] or treatment duration [10]. They are of less import in strategy trials in which there is flexibility in post-randomization antibiotic use or in trials with a superiority design, in which nonstudy antibiotics do not threaten the validity of the study result.

Independent Outcome Evaluation Committee

An independent outcome evaluation committee should be established to mitigate bias from an open-label design. Committee members should be experienced in management of patients with SAB and in clinical trials and should be blinded to treatment assignment of the patients reviewed. The committee should adjudicate each case for efficacy and safety outcomes based on protocol-specified endpoints and can additionally incorporate information such as defervescence and evolution of inflammatory markers. This has been a consistent feature of previous successful trials [6, 9]. The adjudication committee may also make final determination of the diagnosis of each patient as it relates to complicated vs uncomplicated SAB and the presence of IE and any metastatic sites of infection.

An additional advantage of an adjudication committee is that in studies for which enrollment numbers are low, a group that reviews all patients should provide a consistent approach to the evaluation of individual patient diagnosis and outcomes. Potential drawbacks primarily relate to cost and complexity, as well as the possibility that a blinded committee may lack key insights gained from direct interaction with trial participants. For this reason, key analyses (such as primary efficacy analysis) should be repeated using both adjudicator-derived and site principal investigator–established outcomes if feasible.

CONCLUSIONS

Despite an urgent need for better treatment options for SAB, few high-quality trials have been completed. Clinical trial design is challenging from both regulatory and scientific perspectives. In the absence of a consensus approach, there has been substantial heterogeneity in enrolled populations, choice of comparator agents, and trial endpoints. A consistent approach to trial design may enable investigators, sponsors, and regulatory authorities to generate better data and ultimately to deliver better treatment options to patients with this serious, common infection.

Notes

Acknowledgments. Editorial support was provided by AlphaBioCom, LLC, King of Prussia, Pennsylvania.

Financial support. This work was supported by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health (NIH; grant K24-AI093969 to V. G. F. and grant 5UM1AI104681 to V. G. F. and T. L. H.). Funding for editorial support was provided by Theravance Biopharma US, Inc., South San Francisco, California.

Potential conflicts of interest. T. L. H. has been a consultant for Basilea Pharmaceutica, Genentech, the Medicines Company, Motif Biosciences, and Theravance Biopharma and has received grant support from Basilea Pharmaceutica and Achaogen. H. F. C. has been a consultant for Allergan and Cempra Pharmaceuticals and has received grant support from Allergan and the Medicines Company. G. R. C. has received research funding and been a consultant for Arsanis, ContraFect, Melinta Therapeutics, Merck, and Paratek; has been a consultant for Basilea Pharmaceutica, Cempra, Meiji Seika Pharma Co., Motif Biosciences, Parion Sciences, Quintiles, Regeneron Pharmaceuticals, ScPharmaceuticals, the Medicines Company, and Theravance Biopharma; has served on an adjudication committee for Bio2 Medical; has participated in a SAB study design group for Medtronic; has served on the mortality board for Pfizer; and has received research grants from Tetraphase Pharmaceuticals Inc. R. C. and B. C.-R. are employees of Theravance Biopharma US and may hold stock in Theravance Biopharma. V. G. F. served as chair of the V710 Scientific Advisory Committee (Merck); has received grant support from Cerexa/Actavis/Allergan, Pfizer, Advanced Liquid Logics, NIH, MedImmune, Basilea Pharmaceutica, Karius, ContraFect, Regeneron Pharmaceuticals, and Genentech; has NIH Small Business Technology Transfer/Small Business Innovation Research grants pending with Affinergy, Locus, and Medical Surface; has been a consultant for Achaogen, Astellas Pharma, Arsanis, Affinergy, Basilea Pharmaceutica, Bayer, Cerexa Inc., ContraFect, Cubist, Debiopharm, Durata Therapeutics, Grifols, Genentech, MedImmune, Merck, the Medicines Company, Pfizer, Novartis, NovaDigm Therapeutics Inc., Theravance Biopharma, and XBiotech; has received honoraria from Theravance Biopharma and Green Cross; and has a patent pending in sepsis diagnostics. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev **2015**; 28:603–61.
2. Holland TL, Arnold C, Fowler VG Jr. Clinical management of *Staphylococcus aureus* bacteremia: a review. JAMA **2014**; 312:1330–41.
3. US Food and Drug Administration. Guidance for industry. Acute bacterial skin and skin structure infections: developing drugs for treatment. US Department of Health and Human Services, Food and Drug Administration, **2013**. Available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064980.htm.
4. Pertel PE, Bernardo P, Fogarty C, et al. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clin Infect Dis **2008**; 46:1142–51.
5. Paul M, Bishara J, Yahav D, et al. Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant *Staphylococcus aureus*: randomised controlled trial. BMJ **2015**; 350:h2219.
6. Fowler VG Jr, Boucher HW, Corey GR, et al.; *S. aureus* Endocarditis and Bacteremia Study Group. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. N Engl J Med **2006**; 355:653–65.
7. Boucher H, Miller LG, Razonable RR. Serious infections caused by methicillin-resistant *Staphylococcus aureus.* Clin Infect Dis **2010**; 51(Suppl 2):S183–97.
8. Boucher H. Challenges in anti-infective development in the era of bad bugs, no drugs: a regulatory perspective using the example of bloodstream infection as an indication. Clin Infect Dis **2010**; 50: S4–9.
9. Thwaites GE, Scarborough M, Szubert A, et al.; United Kingdom Clinical Infection Research Group. Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet **2018**; 391:668–78.
10. Holland TL, Raad I, Boucher HW, et al. Effect of algorithm-based therapy vs usual care on clinical success and serious adverse events in patients with Staphylococcal bacteremia. JAMA **2018**; 320:1249–58.
11. Davis JS, Sud A, O'Sullivan MVN, et al. Combination of vancomycin and beta-lactam therapy for methicillin-resistant *Staphylococcus aureus* bacteremia: a pilot multicenter randomized controlled trial. Clin Infect Dis **2016**; 62:173–80.
12. Stryjewski ME, Lentnek A, O'Riordan W, et al. A randomized phase 2 trial of telavancin versus standard therapy in patients with uncomplicated *Staphylococcus aureus* bacteremia: the ASSURE study. BMC Infect Dis **2014**; 14:289.
13. Weems JJ Jr, Steinberg JP, Filler S, et al. Phase II, randomized, double-blind, multicenter study comparing the safety and pharmacokinetics of tefibazumab to placebo for treatment of *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother **2006**; 50:2751–5.
14. Rupp ME, Holley HP Jr, Lutz J, et al. Phase II, randomized, multicenter, double-blind, placebo-controlled trial of a polyclonal anti-*Staphylococcus aureus* capsular polysaccharide immune globulin in treatment of *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother **2007**; 51:4249–54.
15. Barber KE, Rybak MJ, Sakoulas G. Vancomycin plus ceftaroline shows potent in vitro synergy and was successfully utilized to clear persistent daptomycin-non-susceptible MRSA bacteraemia. J Antimicrob Chemother **2015**; 70:311–3.
16. Claeys KC, Smith JR, Casapao AM, et al. Impact of the combination of daptomycin and trimethoprim-sulfamethoxazole on clinical outcomes in methicillin-resistant *Staphylococcus aureus* infections. Antimicrob Agents Chemother **2015**; 59:1969–76.
17. Liu C, Bayer A, Cosgrove SE, et al.; Infectious Diseases Society of America. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis **2011**; 52:e18–55.
18. Ndounga Diakou LA, Trinquart L, Hrobjartsson A, et al. Comparison of central adjudication of outcomes and onsite outcome assessment on treatment effect estimates. Cochrane Database Syst Rev **2016**; 3: MR000043.
19. Sakoulas G, Moise PA, Casapao AM, et al. Antimicrobial salvage therapy for persistent Staphylococcal bacteremia using daptomycin plus ceftaroline. Clin Ther **2014**; 36:1317–33.
20. Fowler VG Jr, Olsen MK, Corey GR, et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. Arch Intern Med **2003**; 163:2066–72.
21. Paterson DL, Ko WC, Von Gottberg A, et al. International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial infections. Ann Intern Med **2004**; 140:26–32.
22. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
23. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med **1985**; 13:818–29.
24. US Food and Drug Administration. Guidance for industry. Community-acquired bacterial pneumonia: developing drugs for treatment. US Department of Health and Human Services, Food and Drug Administration, **2014**. Available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064980.htm.
25. Chang FY, MacDonald BB, Peacock JE Jr, et al. A prospective multicenter study of *Staphylococcus aureus* bacteremia: incidence of endocarditis, risk factors for mortality, and clinical impact of methicillin resistance. Medicine (Baltimore) **2003**; 82:322–32.
26. Chong YP, Moon SM, Bang KM, et al. Treatment duration for uncomplicated *Staphylococcus aureus* bacteremia to prevent relapse: analysis of a prospective observational cohort study. Antimicrob Agents Chemother **2013**; 57:1150–6.
27. Sader HS, Mendes RE, Streit JM, Flamm RK. Antimicrobial susceptibility trends among Staphylococcus aureus isolates from U.S. hospitals: results from 7 years of the ceftaroline (AWARE) surveillance program, 2010 to 2016. Antimicrob Agents Chemother **2017**; 61:e01043–17.
28. Bassetti M, Peghin M, Trecarichi EM, et al. Characteristics of *Staphylococcus aureus* bacteraemia and predictors of early and late mortality. PLoS One **2017**; 12:e0170236.
29. Shurland S, Zhan M, Bradham DD, Roghmann MC. Comparison of mortality risk associated with bacteremia due to methicillin-resistant and methicillin-susceptible *Staphylococcus aureus.* Infect Control Hosp Epidemiol **2007**; 28:273–9.
30. Vieira ML, Grinberg M, Pomerantzeff PM, Andrade JL, Mansur AJ. Repeated echocardiographic examinations of patients with suspected infective endocarditis. Heart **2004**; 90:1020–4.
31. Berrevoets MAH, Kouijzer IJE, Aarntzen EHJG, et al. ^{18}F-FDG PET/CT optimizes treatment in *Staphylococcus aureus* bacteremia and is associated with reduced mortality. J Nucl Med **2017**; 58:1504–10.
32. Chamis AL, Peterson GE, Cabell CH, et al. *Staphylococcus aureus* bacteremia in patients with permanent pacemakers or implantable cardioverter-defibrillators. Circulation **2001**; 104:1029–33.
33. Fowler VG Jr, Sanders LL, Sexton DJ, et al. Outcome of *Staphylococcus aureus* bacteremia according to compliance with recommendations of infectious diseases specialists: experience with 244 patients. Clin Infect Dis **1998**; 27:478–86.
34. Kang DH, Kim YJ, Kim SH, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med **2012**; 366:2466–73.
35. Chirouze C, Alla F, Fowler VG Jr, et al.; ICE Prospective Investigators. Impact of early valve surgery on outcome of *Staphylococcus aureus* prosthetic valve infective endocarditis: analysis in the International Collaboration of Endocarditis-Prospective Cohort Study. Clin Infect Dis **2015**; 60:741–9.

36. Harris PNA, McNamara JF, Lye DC, et al. Proposed primary endpoints for use in clinical trials that compare treatment options for bloodstream infection in adults: a consensus definition. Clin Microbiol Infect **2017**; 23:533–41.
37. Chang FY, Peacock JE Jr, Musher DM, et al. *Staphylococcus aureus* bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. Medicine (Baltimore) **2003**; 82:333–9.
38. Evans SR, Rubin D, Follmann D, et al. Desirability of outcome ranking (DOOR) and response adjusted for duration of antibiotic risk (RADAR). Clin Infect Dis **2015**; 61:800–6.
39. Evans SR, Follmann D. Using outcomes to analyze patients rather than patients to analyze outcomes: a step toward pragmatism in benefit:risk evaluation. Stat Biopharm Res **2016**; 8:386–93.
40. Doernberg S, Gouskova N, Evans S, et al. BAC DOOR: a clinician ranking exercise for better *Staphylococcus aureus* bacteremia trial design. Open Forum Infect Dis **In press**; 3(Suppl 1):Abstract 1066.
41. McDanel JS, Perencevich EN, Diekema DJ, et al. Comparative effectiveness of beta-lactams versus vancomycin for treatment of methicillin-susceptible *Staphylococcus aureus* bloodstream infections among 122 hospitals. Clin Infect Dis **2015**; 61:361–7.
42. Schweizer ML, Furuno JP, Harris AD, et al. Comparative effectiveness of nafcillin or cefazolin versus vancomycin in methicillin-susceptible *Staphylococcus aureus* bacteremia. BMC Infect Dis **2011**; 11:279.
43. Falcone M, Russo A, Venditti M, Novelli A, Pai MP. Considerations for higher doses of daptomycin in critically ill patients with methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis **2013**; 57:1568–76.
44. Figueroa DA, Mangini E, Amodio-Groton M, et al. Safety of high-dose intravenous daptomycin treatment: three-year cumulative experience in a clinical program. Clin Infect Dis **2009**; 49:177–80.
45. Cosgrove SE, Vigliani GA, Fowler VG Jr, et al. Initial low-dose gentamicin for *Staphylococcus aureus* bacteremia and endocarditis is nephrotoxic. Clin Infect Dis **2009**; 48:713–21.
46. del Río A, Gasch O, Moreno A, et al.; FOSIMI Investigators. Efficacy and safety of fosfomycin plus imipenem as rescue therapy for complicated bacteremia and endocarditis due to methicillin-resistant *Staphylococcus aureus*: a multicenter clinical trial. Clin Infect Dis **2014**; 59:1105–12.
47. Fabre V, Ferrada M, Buckel WR, Avdic E, Cosgrove SE. Ceftaroline in combination with trimethoprim-sulfamethoxazole for salvage therapy of methicillin-resistant *Staphylococcus aureus* bacteremia and endocarditis. Open Forum Infect Dis **2014**; 1:ofu046.
48. Boucher H. *S. aureus* bacteremia and endocarditis study efficacy results. In: US Food and Drug Administration, Center for Drug Evaluation and Research: Anti-Infective Drugs Advisory Committee, 6 March 2006. Available at: https://wayback.archive-it.org/7993/20170404052335/https:/www.fda.gov/ohrms/dockets/ac/06/slides/2006-4209S1-index.htm. Accessed 14 May 2018.