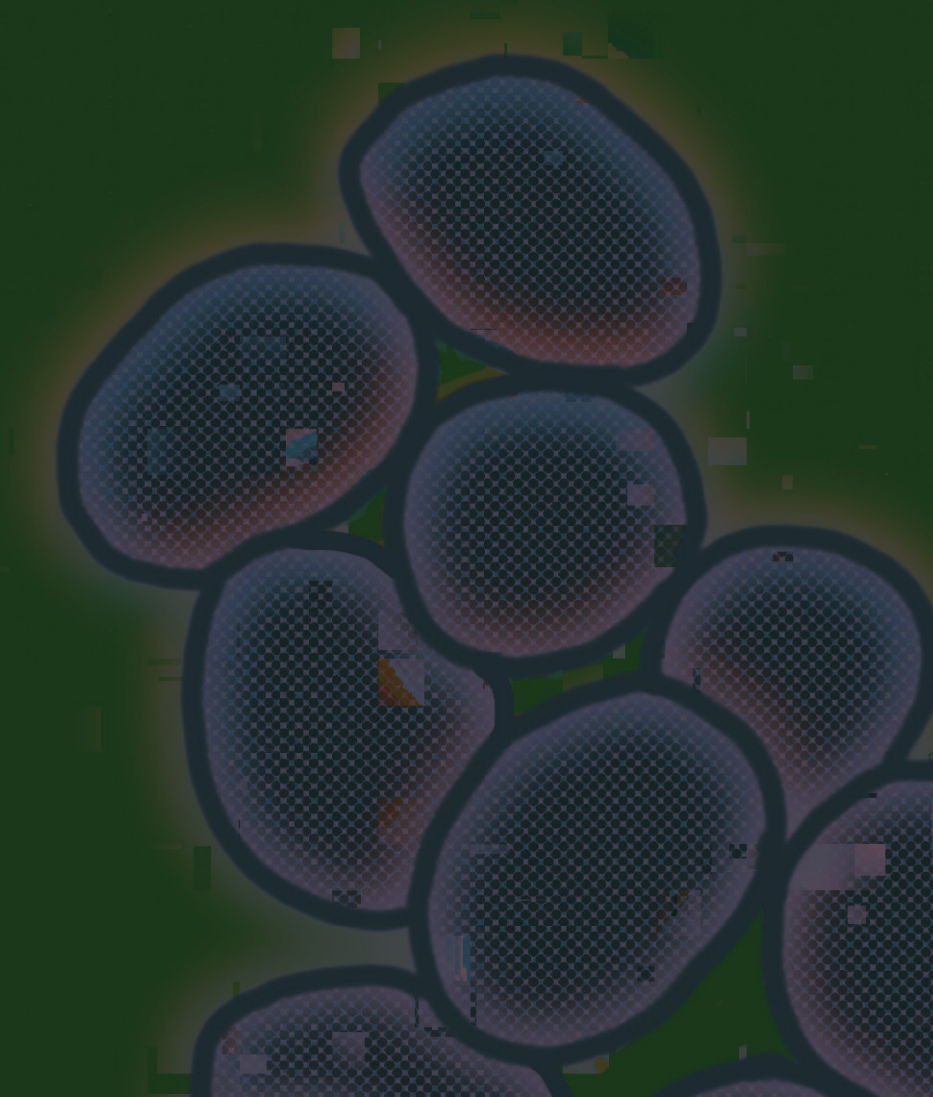
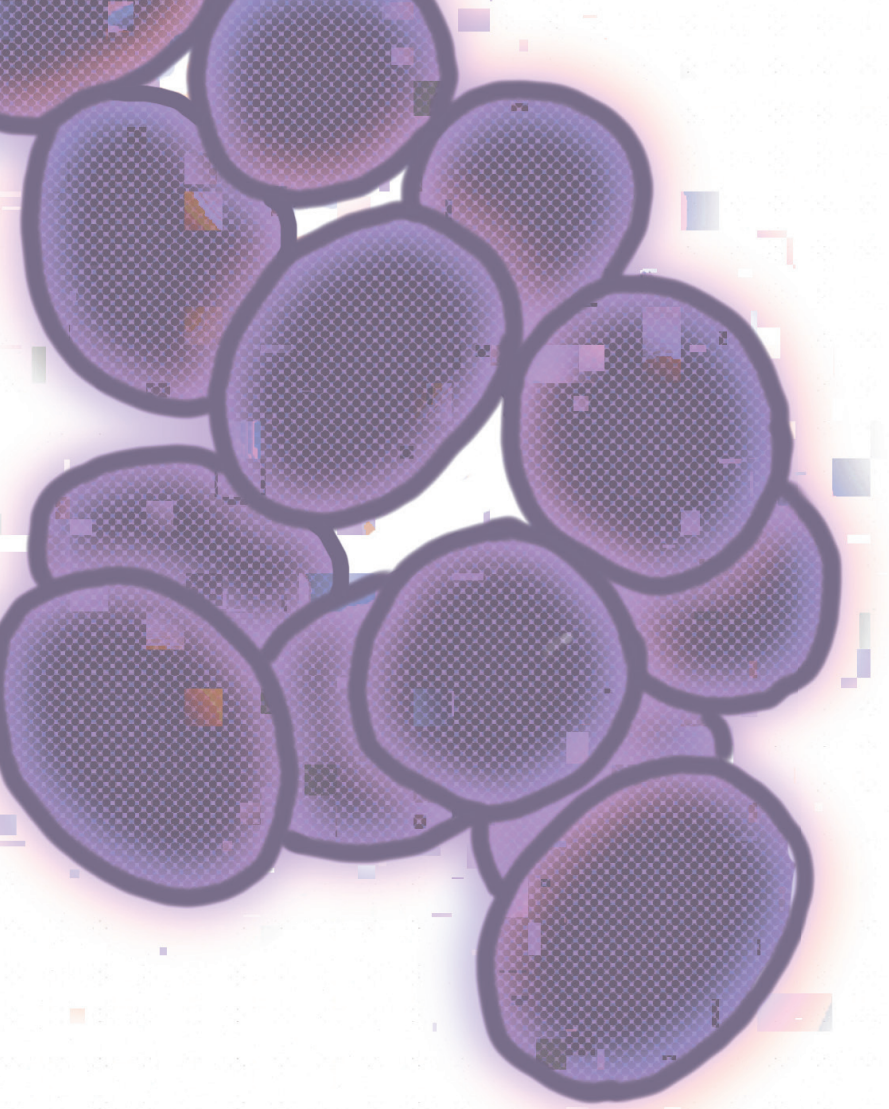
Staphylococcus aureus colonization and infection: optimizing MRSA decolonization and addressing challenges in S. aureus bacteremia management

Westgeest, A.C.

Part 2

Challenges in *Staphylococcus aureus* bacteremia management





Chapter 6

Global differences in the management of *Staphylococcus aureus* bacteremia: no international standard of care

Annette C. Westgeest, David T.P. Buis, Kim C.E. Sigaloff, Felicia Ruffin, Leo G. Visser, Yunsong Yu, Emile F. Schippers, Merel M.C. Lambregts, Steven Y.C. Tong, Mark G.J. de Boer, Vance G. Fowler Jr.

Clin Infect Dis. 2023 Oct 13;77(8):1092-1101.

Abstract

Background

Despite being the leading cause of mortality from bloodstream infections worldwide, little is known about regional variation in treatment practices for *Staphylococcus aureus* bacteremia (SAB). The aim of this study was to identify global variation in management, diagnostics, and definitions of SAB.

Methods

During a 20-day period in 2022, physicians throughout the world were surveyed on SAB treatment practices. The survey was distributed through listservs, e-mails, and social media.

Results

In total, 2031 physicians from 71 different countries on 6 continents (North America [701, 35%], Europe [573, 28%],Asia [409, 20%], Oceania [182, 9%], South America [124, 6%], and Africa [42, 2%]) completed the survey. Management-based responses differed significantly by continent for preferred treatment of methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) bacteremia, use of adjunctive rifampin for prosthetic material infection, and use of oral antibiotics ($P < .01$ for all comparisons). The 18F-FDG PET/CT scans were most commonly used in Europe (94%) and least frequently used in Africa (13%) and North America (51%; $P < .01$). Although most respondents defined persistent SAB as 3–4 days of positive blood cultures, responses ranged from 2 days in 31% of European respondents to 7 days in 38% of Asian respondents ($P < .01$).

Conclusions

Large practice variations for SAB exist throughout the world, reflecting the paucity of high-quality data and the absence of an international standard of care for the management of SAB.

Introduction

Staphylococcus aureus is the leading cause of mortality by bloodstream infections worldwide [1], and methicillin resistant *S. aureus* (MRSA) is the leading cause of mortality attributable to antimicrobial resistance [2]. Despite its global distribution and an incidence of approximately 30 per 100 000 person-years [3, 4], the optimal approach to *S. aureus* bacteremia (SAB) is poorly understood. Despite the fact that SAB has been a major theme in the medical literature for decades, basic treatment elements such as the optimal antibiotic regimen, the role of adjunct and oral antibiotics, the optimal treatment duration, and the definition of persistent SAB remain fundamentally unknown. Even less is known about global differences in treatment practices for SAB.

The aim of this study was to identify global variation in management, diagnostics, and definitions of SAB. To do this, we used a variety of social media platforms to reach a large number of clinicians throughout the world for a survey on SAB treatment practices.

Methods

Survey development and distribution

We conducted this study on geographic practice variation in SAB by modifying a recently developed survey that was deployed in five European countries [5]. The modified survey was tested among an independent expert panel and adjusted where appropriate. The survey focused on unsettled aspects of the disease in clinical practice: first-choice antimicrobial agents, intravenous to oral switch of antimicrobial therapy, treatment duration, the use of 18F-fluoro-deoxyglucose positron emission tomography/computed tomography (PET/CT) (18F-FDG PET/CT) scan, and the definition of persistent SAB (Supplementary Appendix 1). When relevant, questions were provided separately for both methicillin-susceptible *S. aureus* (MSSA) and MRSA bacteremia. The survey was anonymous and voluntary. Country of practice was asked to determine geographic region and subsequently respondents were grouped by continent. The survey was developed in English. Target respondents included infectious diseases, clinical microbiology and internal medicine physicians (both adults and pediatrics) treating SAB patients throughout the world. The survey was distributed through a public URL link on listservs, e-mails, Twitter, and WeChat. Respondents were asked to share the survey link with their professional network. The link was accessible between 2 November and 22 November 2022.

Ethical approval

Given the anonymous and voluntary aspects of the survey, a declaration of exemption was issued by the institutional review board of Duke University.

Definitions

Uncomplicated bacteremia was defined as SAB that was not community-acquired, with <48 hours of positive blood cultures under appropriate antibiotic treatment, and no signs of metastatic infections. Oral switch therapy was defined as prescribing at least part of the treatment course orally. Both definitions were provided with the relevant questions. The estimated percentage of SAB patients in whom oral switch therapy was used was defined as never or uncommonly (<20% of SAB patients), sometimes (20%–60% of SAB patients) or frequently (>60% of SAB patients). All questions concerning antibiotic treatment assumed that the isolate was susceptible to the drug.

Data collection and management

Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Duke University [6]. Respondents who completed 0 or 1 question only were removed from the analysis, as well as respondents that did not enter their country of practice. In order to remove potential non-targeted respondents, records were screened for straightliners (respondents that failed to differentiate between response alternatives by, for example, answering always only the first answer, or only the "other" option to every multiple- choice question) and for nonsensical answers to open-ended questions. Because the survey was distributed through different listservs and social media, the number of times the public survey URL link was opened was used to provide the best estimation of the response rate.

Statistical analysis

Descriptive statistics were used to summarize the data. Data were presented as percentages or proportions of the number of respondents that answered the question for categorical variables, and as medians plus interquartile range (IQR) for continuous variables. Pearson Chi^2 tests were performed to analyze differences between continents. All analyses were carried out using SPSS statistics version 28.0.1.1 (IBM Corporation, Armonk, New York, USA).

Results

A total of 2229 individual survey responses were obtained. The URL link was opened 5679 times (response rate 39%). Nine percent (198/2229) of records were removed from the analyses because of completion of ≤1 questions (88/2229, 4%) or not entering the country of practice (110/2229, 5%). No non-targeted responses were identified. The remaining survey records of 2031 respondents from 71 different countries on 6 continents (North America [701, 35%], Europe [573, 28%], Asia [409, 20%], Oceania [182, 9%], South America [124, 6%], and Africa [42, 2%]) were included in the analysis (Figure 1). Respondents stated they were physicians in adult infectious diseases (74%), clinical microbiology (10%), internal medicine (6%), and pediatric infectious diseases (5%). Thirteen percent of respondents were still in training, and 44% had been registered as a consultant for more than 10 years.

Antimicrobial management of SAB

Antibiotic treatment for SAB differed significantly between continents (Figure 2). For MSSA bacteremia, cefazolin was the first-choice antibiotic treatment in North America (78% of respondents), whereas anti-staphylococcal penicillins were preferred in all other continents (51%–82%; $P < .01$) (Figure 2A). For MRSA bacteremia, vancomycin was the preferred first-choice antibiotic agent in all continents, but with a broad range of 53%–97% of respondents. Daptomycin was identified as the first-choice antibiotic agent for MRSA bacteremia in 23% of European respondents but in <10% of respondents of all other continents (Figure 2B; $P < .01$ for all comparisons above.)

Adjunctive rifampin

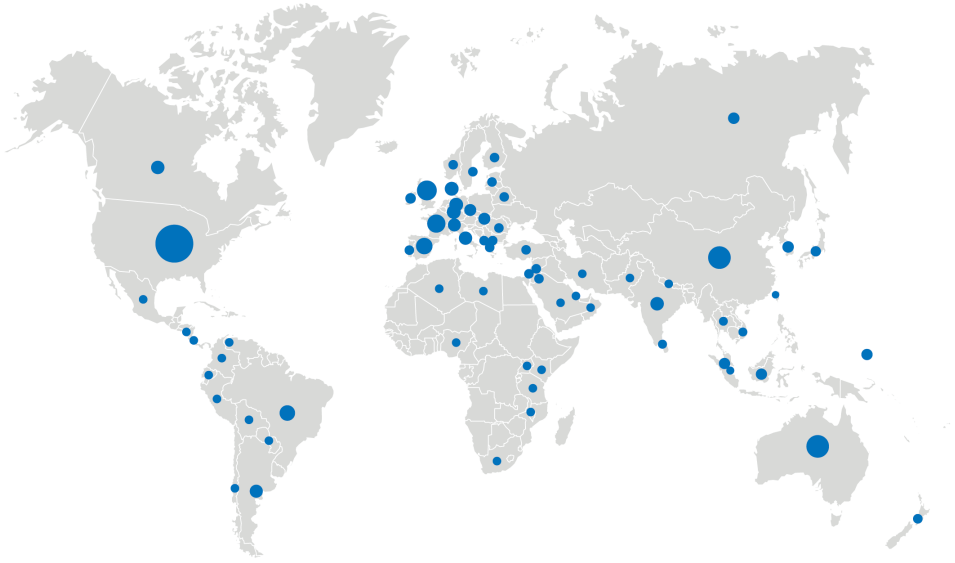
The practice of adding adjunctive rifampin in cases of SAB associated with infected prosthetic material was most frequently reported in Europe: 94% of European respondents would add it in at least 1 of the listed prosthetic material infections (cardiac device, endovascular device, joint prosthesis, prosthetic heart valve, and/or spondylodesis material infection). In Oceania and Africa rifampin was least often used in SAB patients with infected prosthetic material: 26% and 38% never added rifampin for this indication, respectively (Figure 2C).

Oral switch therapy

The estimated percentage of SAB patients in whom oral therapy was used was lowest in North America, where 76% of physicians indicated that they never or uncommonly used oral switch antibiotic therapy. Acceptance of oral therapy was highest in Europe, where 55% of physicians indicated that they used it frequently in their SAB patients

(Figure 3A). The majority of respondents from all continents except Oceania (48%) indicated that they would use oral switch therapy in uncomplicated SAB (57%–71%). Over half (54%–66%) of respondents from every continent identified patients with SAB originating from skin or soft tissue infection as a suitable patient group for safe oral switch therapy. By contrast, respondents differed widely on their views of the acceptability of oral therapy for SAB associated with spondylodiscitis, ranging from 19% in Africa to 60% in Oceania (Table 1). Source control and absence of a central nervous system infection were the only criteria for oral switch therapy for which there was broad agreement among respondents (79% and 69%, respectively) (Supplementary Table 1).

Figure 1. Global distribution of survey respondents. Respondents per country: 71 unique countries participated, and participation ranged from 1 to 654 respondents per country.



Treatment duration

The most commonly identified durations of therapy between geographic regions for SAB-associated syndromes were similar. Thus, the majority of respondents from each continent indicated the same duration of treatment for native valve endocarditis (6 weeks), septic arthritis (4 weeks), and spondylodiscitis (6 weeks). Despite these similarities in practice amongst the majority of practitioners across geographic regions, substantial "within-region" variation existed for these syndromes. For each infectious complication of SAB, individual respondents within each continent indicated longer and shorter durations of therapy (Figure 4).

The finding of blood cultures positive for *S. aureus* after 48–72 hours of appropriate therapy was identified as the most important reason to extend therapy duration in SAB patients beyond 2 weeks in all continents (range: 66% in South America to 90% in North America). Immunocompromised status was identified as an indication to extend antibiotic treatment beyond 2 weeks for most North American physicians (72%) but less than half (43%) of European physicians. By contrast, community acquisition of SAB was considered a reason to extend antibiotic treatment in only 20%–41% of physicians (Table 1; $P < .01$ for all above mentioned comparisons between continents).

18F-FDG PET/CT scan use

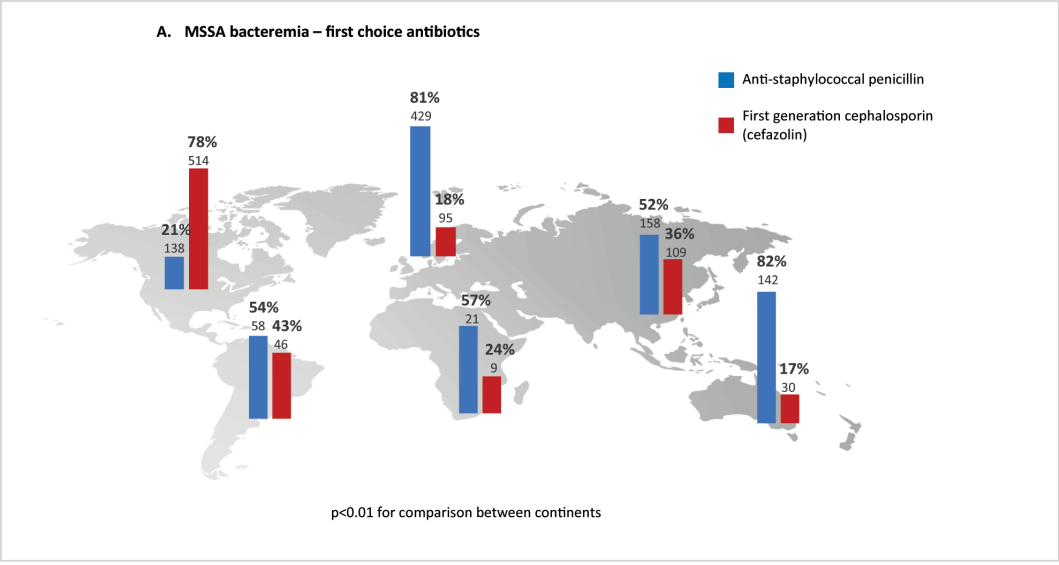
The availability, insurance coverage, and use of 18F-FDG PET/CT scans differed significantly between geographic regions (Table 1). All were highest in Europe and lowest in Africa. The direct availability of 18F-FDG PET/CT scans for SAB patients ranged from 9% in Africa and 29% in South America, to 78% in Europe. 18F-FDG PET/CT scans were used for SAB patients by 94% of European, 83% of Oceanian, 61% of South American, 57% of Asian, and 51% of North American physicians ($P < .01$ for both above mentioned comparisons between continents). Survey respondents indicating that they ordered 18F-FDG PET/CT scans in patients with SAB were asked to specify for which indications they did so. Globally, the most important and most agreed upon indication for 18F-FDG PET/CT scan in SAB was persistent bacteremia: 62%–70% of physicians in every continent ordered 18F-FDG PET/CT scans for this indication (Supplementary Table 2; $P = .66$).

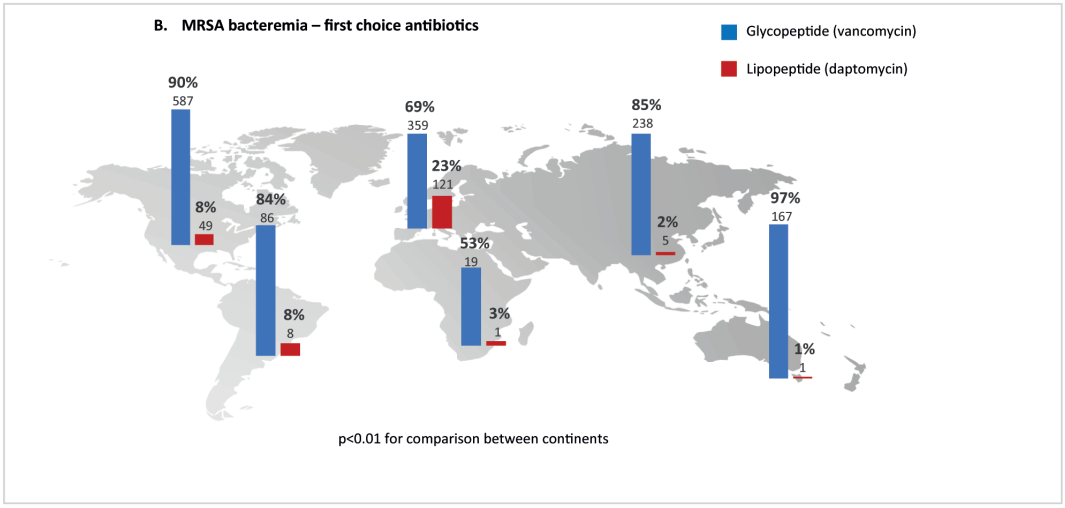
Persistent *S. aureus* bacteremia

The clinical definition of persistent SAB varied widely between continents. The most frequent definition of persistent SAB was a duration of at least 3-4 days of positive blood cultures despite appropriate treatment, identified by >33% of physicians in every continent. However, in Europe (31%) and South America (24%), a significant

minority of survey respondents indicated that persistent SAB was present after only 2 or more days of positive blood cultures. By contrast, 38% of Asian physicians indicated that seven or more days of positive blood cultures were required to constitute persistent SAB (Figure 3B). Almost all physicians indicated that they would order additional diagnostic testing in the setting of persistent SAB (79% in Africa, > 90% in all other continents), and a majority of physicians would also change their medical management (range 64% in Europe to 84% in North America; P < .01 for all above mentioned comparisons between continents) (Table 1).

Figure 2. Antibiotic treatment preferences for *S. aureus* bacteremia per continent. Percentage of total respondents of the question per continent, and count of respondents per continent. *Listed prosthetic materials: cardiac device, endovascular device, joint prosthesis, heart valve, and spondylodesis material.




B. MRSA bacteremia – first choice antibiotics
Glycopeptide (vancomycin)
Lipopeptide (daptomycin)
90%
587
8%
49
84%
86
8%
8
69%
359
23%
121
53%
19
3%
1
85%
238
2%
5
97%
167
1%
1
p<0.01 for comparison between continents

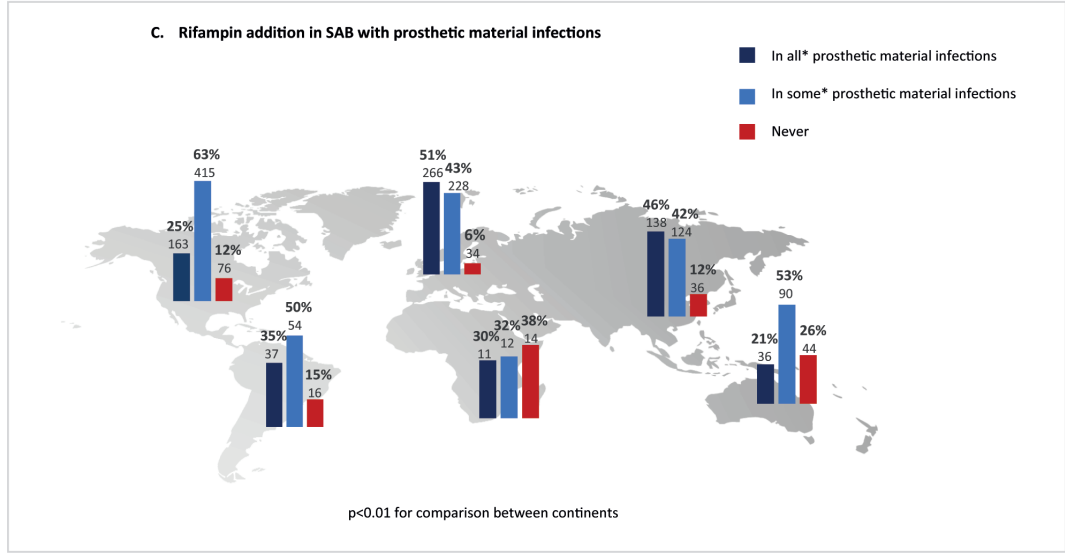

C. Rifampin addition in SAB with prosthetic material infections
In all* prosthetic material infections
In some* prosthetic material infections
Never
63%
415
25%
163
12%
76
50%
54
35%
37
15%
16
51%
266
43%
228
6%
34
30%
11
32%
12
38%
14
46%
138
42%
124
12%
36
53%
90
21%
36
26%
44
p<0.01 for comparison between continents

Figure 3. Oral switch therapy in SAB. Percentage (count) of total respondents of the question per continent. A, Estimated percentage of SAB patients per physician that are treated orally for at least part of the treatment course. B, Days of positive blood cultures while receiving adequate treatment to define persistent bacteremia, in *S. aureus* bacteremia. Abbreviation: SAB, *S. aureus* bacteremia.

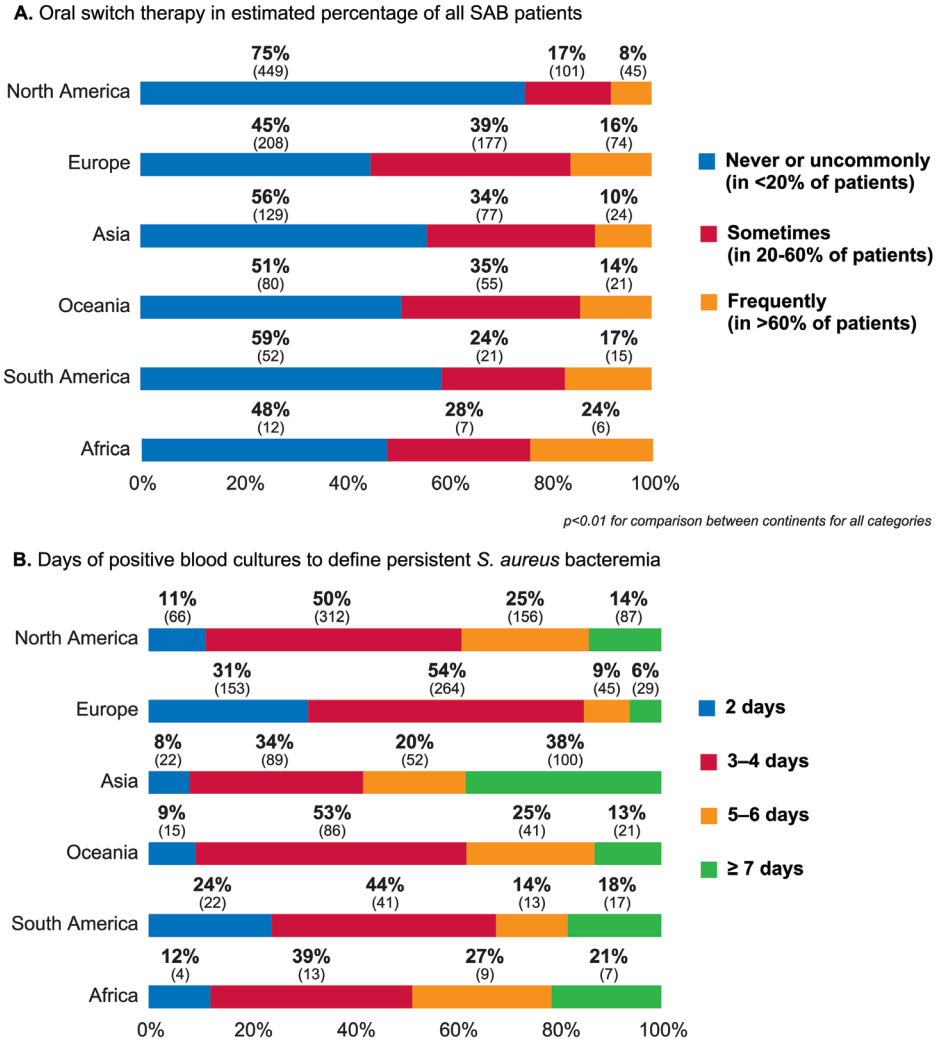
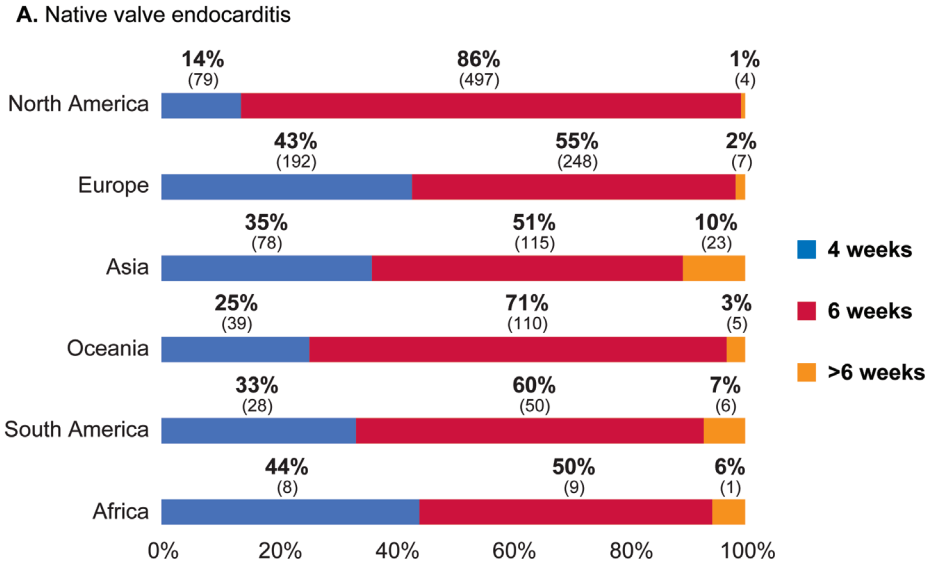


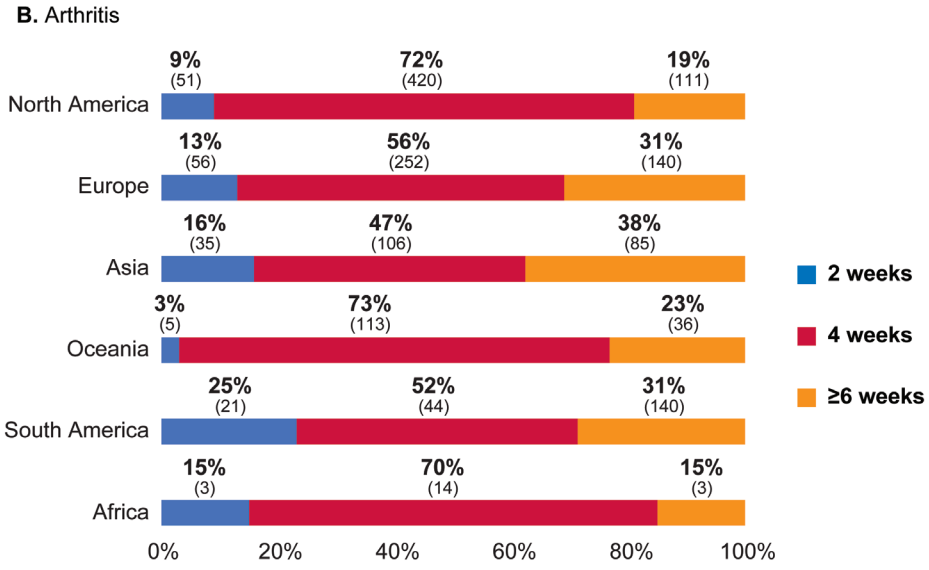
Table 1. Regional practice patterns for *S. aureus* bacteremia

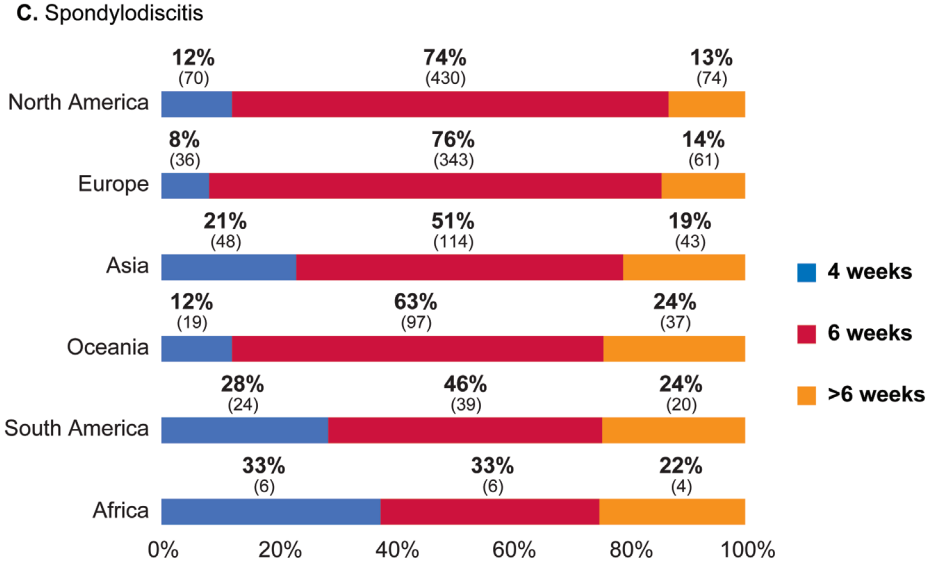
	Total	North America	Europe	Asia	Oceania	South America	Africa	
	N = 2031	N = 701	N = 573	N = 409	N = 182	N = 124	N = 42	p+
Cefazolin vs ASP in MSSAB								<0.01
Regarded equally effective	1470 (81.4)	557 (85.2)	416 (78.8)	235 (76.5)	148 (85.5)	86 (81.1)	28 (75.7)	
Reasons to extend therapy from 2 weeks to 4 weeks or more								<0.01
Positive BC 48-72h after start abx	1248 (84.0)	516 (89.7)	363 (83.3)	169 (76.1)	132 (86.8)	54 (65.9)	14 (77.8)	
Immuno-compromised	873 (59.5)	411 (72.0)	187 (43.2)	134 (62.9)	94 (63.1)	36 (44.4)	11 (55.0)	
Unknown portal of entry	787 (54.3)	386 (68.4)	178 (41.7)	102 (48.1)	87 (58.0)	28 (36.4)	6 (31.6)	
Fever 72h after first positive BC	746 (51.6)	331 (58.8)	203 (47.3)	94 (45.4)	78 (52.0)	32 (41.0)	8 (40.0)	
Community acquisition	460 (31.3)	231 (40.7)	96 (22.1)	44 (20.4)	71 (46.4)	14 (17.9)	4 (21.1)	
Oral switch therapy in different infection foci[1]								
Skin/soft tissue infection	922 (59.3)	330 (56.2)	305 (66.3)	140 (58.8)	85 (54.5)	47 (54.0)	15 (55.6)	0.01
Osteomyelitis	840 (54.0)	260 (44.3)	301 (65.4)	106 (44.5)	105 (67.3)	60 (69.0)	8 (29.6)	<0.01
Spondylodiscitis	659 (42.4)	155 (26.4)	275 (59.8)	84 (35.3)	94 (60.3)	46 (52.9)	5 (18.5)	<0.01
Prosthetic joint septic arthritis	610 (39.2)	144 (24.5)	260 (56.5)	75 (31.5)	89 (57.1)	37 (42.5)	5 (18.5)	<0.01
Prosthetic valve endocarditis	130 (8.4)	24 (4.1)	54 (11.7)	14 (5.9)	32 (20.5)	5 (5.7)	1 (3.7)	<0.01
All of the above	120 (7.7)	22 (3.7)	44 (9.6)	30 (12.6)	16 (10.3)	5 (5.7)	3 (11.1)	<0.01
18F-FDG PET/CT for SAB								
PET/CT readily available	829 (55.6)	278 (48.9)	341 (78.0)	106 (46.7)	78 (51.3)	24 (28.6)	2 (9.1)	<0.01
Covered by insurance for SAB	610 (42.2)	177 (33.2)	332 (77.4)	41 (18.2)	37 (24.3)	21 (25.0)	2 (9.1)	<0.01
PET/CT use in some/all patients	1009 (67.8)	293 (51.1)	409 (93.8)	125 (57.0)	124 (82.8)	50 (61.0)	4 (12.7)	<0.01
Never use PET/CT in SAB patients	479 (32.2)	281 (49.0)	27 (6.2)	96 (43.0)	26 (17.2)	32 (39.0)	17 (77.3)	<0.01
Available, but never use in SAB[2]	101 (12.2)	63 (22.7)	5 (1.5)	24 (23.1)	8 (10.3)	1 (4.2)	-	<0.01
Actions following diagnosis of persistent SAB								
Additional diagnostic testing	1610 (95.8)	605 (97.0)	484 (96.6)	242 (92.0)	161 (97.6)	91 (96.8)	27 (79.4)	<0.01
Change antibiotic management	1246 (74.7)	523 (83.5)	316 (63.8)	207 (80.2)	106 (64.6)	72 (76.7)	22 (68.8)	<0.01

N = the total number of respondents of the survey. Values are counts (%). Not all respondents answered every question, therefore the percentages represent the percentage of the total respondents of the continent who answered this question. Abbreviations: ASP, anti-staphylococcal penicillin; BC, blood culture; h, hours; MSSAB, methicillin-susceptible *Staphylococcus aureus*; PET/CT, positron emission tomography/computed tomography; SAB, *Staphylococcus aureus* bacteremia. [a]Results are still significant with P < .01 when continents with n ≤ 5 were excluded from analysis. [b]This represents the number and percent of respondents that indicated that PET/CT is readily available but still never use PET/CT in SAB patients.

Figure 4. Treatment duration for *S. aureus* bacteremia. Percentage (count) of total respondents of the question per continent. P < .01 for comparison between continents for all categories (χ2 test).




B. Arthritis
North America
9% (51)
72% (420)
19% (111)
Europe
13% (56)
56% (252)
31% (140)
Asia
16% (35)
47% (106)
38% (85)
Oceania
3% (5)
73% (113)
23% (36)
South America
25% (21)
52% (44)
31% (140)
Africa
15% (3)
70% (14)
15% (3)
0%
20%
40%
60%
80%
100%
2 weeks
4 weeks
≥6 weeks


C. Spondylodiscitis
North America
12% (70)
74% (430)
13% (74)
Europe
8% (36)
76% (343)
14% (61)
Asia
21% (48)
51% (114)
19% (43)
Oceania
12% (19)
63% (97)
24% (37)
South America
28% (24)
46% (39)
24% (20)
Africa
33% (6)
33% (6)
22% (4)
0%
20%
40%
60%
80%
100%
4 weeks
6 weeks
>6 weeks

Discussion

This study shows that even the most basic aspects of treating patients with SAB differ profoundly between geographic regions. This variation was most marked in fundamental aspects of decision-making for SAB treatment, including antibiotic choice for MSSA bacteremia, addition of rifampin for prosthetic device infections, and route of administration. An anti-staphylococcal penicillin was treatment of choice for MSSA bacteremia in Europe and Oceania but a distant second to cefazolin in North America. The evidence for superiority of either of the 2 is limited to cohort studies with conflicting results and with underrepresentation of complicated disease [7, 8], emphasizing the need for randomized trials.

The role of adjunctive rifampin in patients with prosthetic material infections also differed by continent. This controversy persists despite the availability of published society guidelines that recommend the use of rifampin in *S. aureus* infections involving prosthetic valves and arthroplasties [9, 10]. However, the recommendation to use rifampin for prosthetic valve infective endocarditis has a very limited evidence base [11]. Thus, well-designed randomized trials are needed to define any potential role of adjunctive rifampin in prosthesis-associated SAB. Importantly, the wide range of practices regarding the use of rifampin in this survey demonstrates the presence of the global equipoise necessary to ethically conduct such a trial. The practice of prescribing part of the treatment course for SAB with oral antibiotics was well accepted in all continents except North America, where only a minority of physicians would consider its routine use. This infrequent use of oral therapy in the United States may be due in part to a high prevalence of MRSA, the presence of a well-organized outpatient parenteral antimicrobial therapy system, or concerns related to medical malpractice. This lack of global consensus on the role of oral switch therapy is also reflected by the lack of consensus on which setting in which it should be considered. In fact, only the criteria of “source control” and “absence of central nervous system infection” were considered essential for oral switch by a clear majority. By contrast, all other listed criteria were regarded as essential by approximately half of the respondents—which implies that these were considered non-essential by the other half. Because oral switch therapy has potential to decrease the number of adverse drug events, catheter-associated problems and costs, and the fact that the survey respondents are in equipoise on the question, the need for a well-designed randomized trial seems clear. Current studies such as SABATO and SNAP might provide answers in the future [12, 13].

Broader global consensus existed for treatment duration of SAB. The worldwide similarity of respondents' views on treatment duration for SAB is noteworthy given that the data for this aspect of SAB is at least as limited as that for the treatment-related aspects outlined above for which there is significant controversy [14, 15]. Although the majority of surveyed physicians throughout the world treat complications of SAB such as endocarditis and osteoarticular infection for a similar duration, a portion of physicians in each continent will treat substantially longer or shorter. This finding suggests that factors influencing treatment duration decision-making may be provider-based and situational rather than simply geographical in nature.

18F-FDG PET/CT use

Our findings also indicate significant geographic variability in the use of 18F-FDG PET/CT as diagnostic tool in SAB, with broad use in Europe and Oceania being balanced by infrequency in other continents. Observational studies have reported that 18F-FDG PET/CT may impact management and reduce mortality in patients with SAB because of higher detection of metastatic foci [16, 17], although the reduced mortality may have been confounded by immortal time bias related to including patients dying before undergoing 18F-FDG PET/CT [18]. Obviously, the associated costs could be a reason to refrain from using 18F-FDG PET/CT in low- and middle-income regions, but this does not explain its highly variable use in high-income regions. Recently, a call to action was published in the United States, advocating for insurance coverage of 18F-FDG PET/CT use in SAB patients [19]. In order to reach that goal, high-quality studies including randomized trials of 18F-FDG PET/CT are warranted.

Definition of persistent SAB

The results of our survey suggest that the identification of persistent SAB may be therapeutically important, as it triggers additional diagnostic testing and changes in medical management for the majority of respondents. However, respondents generally disagreed on how to define it. Although 3–4 days was the most common identified definition of persistent SAB overall, all options in the range of 2–7 or more days were selected by respondents from each continent. Roughly one third of European respondents defined persistent SAB as only 2 days of bacteremia, although a similar portion of Asian respondents indicated that it occurred after 7 or more days. The prognostic significance of persistent SAB has been previously demonstrated [20–22]. Identifying a broadly accepted definition of persistent SAB would thus be helpful to optimize clinical decision-making, as well as to harmonize the terminology used in clinical research.

Perspective

The current study suggests that there is no global standard of practice for SAB. Striking differences were noted, both between and within continents, in what antibiotics were prescribed, and by what route. The lack of a global standard in the management of SAB stands in stark contrast to treatment of other syndromes of comparable lethality. For coronary artery disease, management has been largely standardized by guidelines based on data from randomized controlled trials [23–25]. Coincident with establishing these best treatment practices, the annual US mortality rate from coronary artery disease declined by 17.7% from 2005 to 2015 [26]. By contrast, the 1-month mortality for patients with SAB only decreased by 2.8% over the same time period [27]. The results of this study underscore one key fact: a global standard of care for SAB will be difficult to develop pending more definitive clinical trials data. Indeed, fewer than 3500 patients have been enrolled in published SAB randomized trials over the past 20 years (Supplementary Table 3). Factors other than robust clinical data, such as cultural differences, costs and availability of resources also influence management choices. However, without consensus on best practice, normative and cultural factors gain influence on for example antibiotic prescription behavior [28]. Multinational clinical trials such as the *Staphylococcus aureus* Network Adaptive Platform (SNAP) [13] are thus essential to standardize clinical definitions, identify treatment strategies, and improve patient outcomes of this common and frequently lethal infection.

Strengths and limitations

The current study illustrates the potential of using social media to understand global treatment practices and decision making. Although previous studies on physicians' management of SAB have been conducted [5, 29, 30], none were as extensive and on a global scale as this current study. Our study has several limitations. There were relatively low participation rates from South America and Africa. The respondents were not questioned about their local guideline and adherence to it, and for many countries no national guidelines were available. This made it impossible for us to consider the role of national guidelines in the present study. Given the fact that 71 countries were included in the survey, comparing differences between each of these countries was methodologically infeasible. Therefore, we limited the analyses to continents. We were unable to evaluate spatial clustering of infections. The survey was only available in English, which might have dissuaded non-English speaking physicians. Because the survey was distributed through listservs and social media, the exact number of recipients or proportion of physicians per country is unknown. Therefore, the true response rate is uncertain and could only be estimated by the ratio of the reported surveys and the number of times the URL link was opened.

Finally, because it was impossible to control who filled out the survey, respondents theoretically could have been non-physicians or could have completed the survey multiple times. However, because there was no incentive in responding, and we did not discover any nonsensical answers, this seems unlikely. Overall, the advantage of receiving feedback from over 2000 specialists from all over the world outweighs the potential disadvantages of the use of social media platforms.

Conclusion

Large practice variations for SAB exist throughout the world, reflecting the absence of an international standard of care for the management of patients with SAB. This article sets the stage and the agenda for multinational or global clinical trials and networks, to address the unresolved aspects of this devastating disease.

References

1. GBD 2019 Antimicrobial Resistance Collaborators. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2022; 400:2221–48.
2. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022; 399:629–55.
3. WHO priority pathogens list for R&D of new antibiotics. 2017. Available at: http:// www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/. Accessed 1 November 2022.
4. Jernigan JA, Hatfield KM, Wolford H, et al. Multidrug-resistant bacterial infections in U.S. hospitalized patients, 2012–2017. N Engl J Med 2020; 382:1309–19.
5. Buis DTP, Prins JM, Betica-Radic L, et al. Current clinical practice in antibiotic treatment of Staphylococcus aureus bacteraemia: results from a survey in five European countries. J Antimicrob Chemother 2022; 77:2827–34.
6. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42:377–81.
7. McDanel JS, Roghmann MC, Perencevich EN, et al. Comparative effectiveness of cefazolin versus nafcillin or oxacillin for treatment of methicillin-susceptible Staphylococcus aureus infections complicated by bacteremia: a nationwide cohort Sstudy. Clin Infect Dis 2017; 65:100–6.
8. Miller WR, Seas C, Carvajal LP, et al. The cefazolin inoculum effect is associated with increased mortality in methicillin-susceptible Staphylococcus aureus bacteremia. Open Forum Infect Dis 2018; 5:ofy123.
9. Liu C, Bayer A, Cosgrove SE, et al. 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.
10. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015; 36:3075–128.
11. Ryder JH, Tong SYC, Gallagher JC, et al. Deconstructing the dogma: systematic literature review and meta-analysis of adjunctive gentamicin and rifampin in staphylococcal prosthetic valve endocarditis. Open Forum Infect Dis 2022; 9: ofac583.
12. Kaasch AJ, Fätkenheuer G, Prinz-Langenohl R, et al. Early oral switch therapy in low-risk Staphylococcus aureus bloodstream infection (SABATO): study protocol for a randomized controlled trial. Trials 2015; 16:450.
13. Tong SYC, Mora J, Bowen AC, et al. The Staphylococcus aureus network adaptive platform trial protocol: new tools for an old foe. Clin Infect Dis 2022; 75:2027–34.
14. Bernard L, Dinh A, Ghout I, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non- inferiority, randomised, controlled trial. Lancet 2015; 385:875–82.

15. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the committee on rheumatic fever, endocarditis, and kawasaki disease, council on cardiovascular disease in the young, and the councils on clinical cardiology, stroke, and cardiovascular surgery and anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation 2005; 111:e394–434.
16. Buis DTP, Sieswerda E, Kouijzer IJE, et al. [18f]FDG-PET/CT in Staphylococcus aureus bacteremia: a systematic review. BMC Infect Dis 2022; 22:282.
17. Duval X, Le Moing V, Tubiana S, et al. Impact of systematic whole-body 18F-fluorodeoxyglucose PET/CT on the management of patients suspected of infective endocarditis: the prospective multicenter TEPvENDO Study. Clin Infect Dis 2021; 73:393–403.
18. van der Vaart TW, Prins JM, van Werkhoven CH, et al. Positive impact of [18F] FDG-PET/CT on mortality in patients with Staphylococcus aureus bacteremia explained by immortal time bias. Clin Infect Dis 2023:ciad112.
19. Thottacherry E, Cortés-Penfield NW. Evidence of clinical impact supports a new petition for medicare coverage of 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography in the evaluation of Staphylococcus aureus bacteremia: a focused literature review and call to action. Clin Infect Dis 2022; 75:1457–61.
20. Minejima E, Mai N, Bui N, et al. Defining the breakpoint duration of Staphylococcus aureus bacteremia predictive of poor outcomes. Clin Infect Dis 2020; 70:566–73.
21. Minejima E, Bensman J, She RC, et al. A dysregulated balance of proinflammatory and anti-inflammatory host cytokine response early during therapy predicts persistence and mortality in Staphylococcus aureus bacteremia. Critic Care Med 2016; 44:671–9.
22. Kuehl R, Morata L, Boeing C, et al. Defining persistent Staphylococcus aureus bacteraemia: secondary analysis of a prospective cohort study. Lancet Infect Dis 2020; 20:1409–17.
23. Hochman JS, Lamas GA, Buller CE, et al. Coronary intervention for persistent occlusion after myocardial infarction. N Engl J Med 2006; 355:2395–407.
24. Zijlstra F, Hoorntje JC, de Boer MJ, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999; 341:1413–9.
25. Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. J Am Coll Cardiol 2022; 79:e21–e129.
26. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation 2018; 137:e67–e492.
27. Bai AD, Lo CKL, Komorowski AS, et al. Staphylococcus aureus bacteraemia mortality: a systematic review and meta-analysis. Clin Microbiol Infect 2022; 28: 1076–84.
28. Warreman EB, Lambregts MMC, Wouters RHP, et al. Determinants of in- hospital antibiotic prescription behaviour: a systematic review and formation of a comprehensive framework. Clin Microbiol Infect 2019; 25:538–45.
29. Hagel S, Bahrs C, Schumann R, Pletz M, Weis S. Complicated and uncomplicated S. aureus bacteraemia: an international Delphi survey among infectious diseases experts on definitions and treatment. Clin Microbiol Infect 2022; 28:1026.e7–.e11.
30. Liu C, Strnad L, Beekmann SE, Polgreen PM, Chambers HF. Clinical practice variation among adult infectious disease physicians in the management of Staphylococcus aureus bacteremia. Clin Infect Dis 2019; 69:530–3.

Supplementary data

Appendix 1. Survey questions

In which country do you currently practice? _____

Which of the following best describes your primary area of medical specialty?

- o Clinical microbiology
- o Infectious diseases (adults)
- o Infectious diseases (pediatric)
- o Internal medicine
- o Other

How many years have you been registered as a consultant (i.e. medical specialist)?

- o Still in training for consultant
- o 0-10 years
- o 11-20 years
- o 21-30 years
- o More than 30 years

The following question refers to MSSA bacteremia

What is your first-choice initial antibiotic regimen in patients with confirmed monobacterial MSSA bacteremia without implanted prosthetic material provided the isolate is susceptible to the drug?

- □ Aminoglycoside, e.g. gentamicin
- □ Anti-staphylococcal penicillin, e.g. flucloxacillin dicloxacillin
- □ Carbapenem, e.g. meropenem
- □ Clindamycin
- □ First-generation cephalosporin, e.g. cefazolin
- □ Second-generation cephalosporin, e.g. cefuroxime
- □ Third-generation cephalosporin, e.g. ceftriaxone
- □ Fourth-generation cephalosporin, e.g. cefepime
- □ Fifth generation cephalosporin, i.e. ceftaroline
- □ Fluoroquinolone, e.g. levofloxacin
- □ Glycopeptide, e.g. vancomycin
- □ Linezolid
- □ Lipopeptide, e.g. daptomycin
- □ Piperacillin/tazobactam
- □ Rifampicin
- □ Trimethoprim/sulfamethoxazole
- □ Other

Do you consider first-generation cephalosporins (e.g. cefazoline) to have equivalent clinical effectiveness for MSSA bacteremia without central nervous system infection as anti-staphylococcal penicillins (e.g. flucloxacillin, dicloxacillin)?

- o Yes
- o No

Do you treat patients with *Staphylococcus aureus* bacteremia and the following types of infected prosthetic material which will not be removed with rifampicin as part of combination antibiotic therapy provided the isolate is susceptible to the drug? Mark all that apply.

- □ Cardiac device
- □ Endovascular graft
- □ Joint prosthesis
- □ Prosthetic heart valve
- □ Spondylodesis
- □ All of the above
- □ None of the above

The following question refers to MRSA bacteremia

What is your first-choice initial antibiotic regimen in patients with confirmed monobacterial MRSA bacteremia without implanted prosthetic material provided the isolate is susceptible to the drug?

- □ Aminoglycoside, e.g. gentamicin
- □ Clindamycin
- □ Fifth generation cephalosporin, i.e. ceftaroline
- □ Fluoroquinolone, e.g. levofloxacin
- □ Fosfomycin
- □ Glycopeptide, e.g. vancomycin
- □ Linezolid
- □ Lipopeptide, e.g. daptomycin
- □ Rifampicin
- □ Tetracycline, e.g. doxycycline
- □ Trimethoprim/sulfamethoxazole
- □ Other
- □ Combination therapy

The following questions refer to persistent bacteremia.

After how many days (-or more) of positive blood cultures with *S. aureus* despite adequate antibiotic therapy would you consider it a ‘persistent bacteremia’?

- o 2 days
- o 3 days
- o 4 days
- o 5 days
- o 6 days
- o 7 days
- o >7 days
- o Do not know

Would you order additional diagnostic testing in persistent bacteremia and if yes, after how many days of positive blood cultures?

- o Yes, after … days of adequate antibiotic therapy and persistent positive blood cultures
- o No, I would not order additional diagnostic testing in case of persistent bacteremia

What kind of additional diagnostic testing would you order? Mark all that apply.

- o Transthoracic echocardiography
- o Transesophageal echocardiography
- o CT- scan
- o PET-CT scan
- o MRI scan
- o Other: …..

Would you change medical management (e.g., change antibiotics, increase dose or duration of antibiotics; add 2nd antibiotic) in case of persistent bacteremia and if yes, after how many days of positive blood cultures?

- o Yes, after …….. days of adequate antibiotic therapy and persistent positive blood culture
- o No, I would not change medical management in case of persistent bacteremia

In case of MSSA persistent bacteremia: what would you change in terms of medical management? Mark all that apply.

- o Change antibiotic agents
- o Increase dose of antibiotics
- o Add 2nd (or 3rd) antibiotic agent
- o Prolong treatment
- o Other: …….

In case of MSSA persistent bacteremia: to what antibiotic regimen would you change?

- □ Aminoglycoside, e.g. gentamicin
- □ Anti-staphylococcal penicillin, e.g. flucloxacillin, dicloxacillin
- □ Carbapenem, e.g. meropenem
- □ Clindamycin
- □ First-generation cephalosporin, e.g. cefazolin
- □ Second-generation cephalosporin, e.g. cefuroxime
- □ Third-generation cephalosporin, e.g. ceftriaxone
- □ Fourth-generation cephalosporin, e.g. cefepime
- □ Fifth generation cephalosporin, i.e. ceftaroline
- □ Fluoroquinolone, e.g. levofloxacin
- □ Glycopeptide, e.g. vancomycin

- □ Linezolid
- □ Lipopeptide, e.g. daptomycin
- □ Piperacillin/tazobactam
- □ Rifampicin
- □ Trimethoprim/sulfamethoxazole
- □ Other

In case of MRSA persistent bacteremia: what would you change in terms of medical management? Mark all that apply.

- ○ Change antibiotic agents
- ○ Increase dose of antibiotics
- ○ Add 2nd (or 3rd) antibiotic agent
- ○ Other: …….

In case of MRSA persistent bacteremia: to what antibiotic regimen would you change?

- □ Aminoglycoside, e.g. gentamicin
- □ Clindamycin
- □ Fifth generation cephalosporin, i.e. ceftaroline
- □ Fluoroquinolone, e.g. levofloxacin
- □ Fosfomycin
- □ Glycopeptide, e.g. vancomycin
- □ Linezolid
- □ Lipopeptide, e.g. daptomycin
- □ Rifampicin
- □ Tetracycline, e.g. doxycycline
- □ Trimethoprim/sulfamethoxazole
- □ Other

The following questions refer to oral step-down therapy in MSSA/MRSA bacteremia.

Do you consider oral step-down antibiotic therapy in patients with uncomplicated *Staphylococcus aureus* bacteremia?

- o Yes
- o No

Do you consider oral step-down antibiotic therapy in patients with *Staphylococcus aureus* bacteremia and the following foci of infection? Mark all that apply.

- □ Brain abscess
- □ Central line infection
- □ Epidural abscess
- □ Native joint septic arthritis
- □ Native valve endocarditis
- □ Osteomyelitis
- □ Prosthetic joint septic arthritis
- □ Prosthetic valve endocarditis
- □ Skin- and soft tissue infection without abscess
- □ Urinary tract infection
- □ Vertebral osteomyelitis
- □ None of the above

In your opinion, which of the following criteria must a patient with *Staphylococcus aureus* bacteremia who is able to take oral medication fulfill to be eligible for oral step-down antibiotic therapy? Mark all that apply.

- □ Absence of central nervous system infection
- □ Absence of endovascular infection focus other than endocarditis
- □ Blood culture negativity 48-72 hours after initiation of adequate antibiotic treatment
- □ Blood culture negativity for at least 72 hours
- □ Defervescence within 72 hours after initiation of adequate antibiotic treatment
- □ Afebrile for at least the past 72 hours
- □ Hospital acquired bacteremia
- □ Initiation of adequate antibiotic treatment within 48 hours of blood culture collection
- □ PET-CT without signs of endocarditis and metastatic infections
- □ No evidence of metastatic foci (on clinical of radiologic examination, but radiological imaging is not required if not clinically indicated)
- □ Primary infection focus was line related or skin/soft tissue related
- □ Source control is achieved
- □ Transesophageal echocardiography (TEE) without signs of endocarditis
- □ Transthoracic echocardiography (TTE) without signs of endocarditis
- □ None of the above

If oral drugs are acceptable in your opinion, what is your most commonly prescribed antibiotic regimen for oral step-down therapy in patients with confirmed MSSA bacteremia without implanted prosthetic material provided the isolate is susceptible to the drug? *Choose only one answer, unless you routinely prescribe combination therapy. In that case mark all that apply.*

- □ Anti-staphylococcal penicillin, e.g. flucloxacillin, dicloxacillin
- □ Oral cephalosporin (e.g., cefalexin, cefadroxil)
- □ Clindamycin
- □ Fluoroquinolone, e.g. levofloxacin
- □ Fusidic acid
- □ Linezolid
- □ Macrolide, e.g. erythromycin
- □ Penicillin, e.g. amoxicillin
- □ Rifampicin
- □ Tetracycline, e.g. doxycycline
- □ Trimethoprim/sulfamethoxazole
- □ Probenicid
- □ Other

If oral drugs are acceptable in your opinion, what is your most commonly prescribed antibiotic regimen for oral step-down therapy in patients with confirmed MRSA bacteremia without implanted prosthetic material provided the isolate is susceptible to the drug? Choose only one answer, unless you routinely prescribe combination therapy. In that case mark all that apply.

- □ Clindamycin
- □ Fluoroquinolone, e.g. levofloxacin
- □ Fusidic acid
- □ Linezolid
- □ Macrolide, e.g. erythromycin
- □ Rifampicin
- □ Tetracyclin, e.g. doxycycline
- □ Trimethoprim/sulfamethoxazole
- □ Other

In what estimated percentage of the patients you treat for *Staphylococcus aureus* bacteremia, do you prescribe at least part of the treatment course orally (instead of prescribing IV antibiotics during the entire treatment course)?

- o 0% (I never treat patients with SAB with oral antibiotics, also not temporarily)
- o 1-20%
- o 21-40%
- o 41-60%
- o 61-80%
- o 81-100% (I treat almost every patient with SAB for at least part of the treatment with oral antibiotics)

The following questions refer to treatment duration.

How many weeks of antibiotic treatment (includes both IV and oral) would you prescribe in a patient with *Staphylococcus aureus* bacteremia without implanted prosthetic material and the following foci of infection?

	2 weeks	**4 weeks**	**6 weeks**	**>6 weeks**
Arthritis	○	○	○	○
Native valve endocarditis	○	○	○	○
Long bone osteomyelitis	○	○	○	○
Pneumonia without abscess	○	○	○	○
Septic thrombophlebitis	○	○	○	○
Spondylodiscitis without abscess	○	○	○	○

Would the following factors make you consider extending antibiotic therapy from 2 weeks to 4 weeks in a patient with *Staphylococcus aureus* bacteremia? Assume transesophageal echocardiography (TEE) does not show signs of endocarditis.

	Yes	No
Community-acquisition	○	○
Delay of 48 hours between sampling first positive blood culture and initiation of adequate antibiotic treatment	○	○
Fever at 72 hours after first positive blood culture	○	○
Positive blood cultures after 72 hours of adequate antibiotic treatment	○	○
Unknown portal of entry	○	○
Methicillin resistant *Staphylococcus aureus*	○	○
Age > 75 years	○	○
Immunocompromised patient	○	○

The following questions refer to PET-CT scan.

Is PET-CT readily available in your setting for investigation of SAB?

- Yes
- No

Is PET-CT covered by insurance / reimbursed for the indication of SAB?

- Yes
- No

In which situations do you use PET-CT in patients with *Staphylococcus aureus* bacteremia? Mark all that apply.

- I never use PET-CT in patients with SAB
- In all patients with SAB
- When SAB is community acquired
- In patients with MRSA bacteremia
- In patients with persistent fever >48h after adequate therapy
- In patients with persistent fever >72h after adequate therapy
- In patients with persistent bacteremia
- In patients >75 years old
- In patients with prosthetic joint material
- In patients suspected of endocarditis
- In patients with clinical signs of metastatic infection
- Other, please clarify: …..

Table S1. Criteria that must be fulfilled for oral switch therapy in *S. aureus* bacteremia

	Total	North America	Europe	Asia	Oceania	South America	Africa	
	N=1156	N=399	N=372	N=177	N=120	N=70	N=18	p
Source control achieved	914 (79.1)	325 (81.5)	307 (82.5)	125 (70.6)	87 (72.5)	57 (81.4)	13 (72.2)	<0.01
Absence of central nervous system infection	793 (68.6)	289 (72.4)	248 (66.7)	123 (69.5)	67 (55.8)	53 (75.7)	13 (72.2)	0.01
Negative blood culture 48-72h after start antibiotics	652 (56.4)	247 (61.9)	217 (58.3)	85 (48.0)	52 (43.3)	39 (55.7)	12 (66.7)	<0.01
Absence of endovascular focus	558 (48.3)	202 (50.6)	173 (46.5)	93 (52.5)	45 (37.5)	31 (44.3)	14 (77.8)	0.01
Afebrile for at least 72h	644 (55.7)	206 (51.6)	224 (60.2)	91 (51.4)	64 (53.3)	49 (70.0)	10 (55.6)	0.02
No evidence of metastatic foci	573 (49.6)	217 (54.4)	167 (44.9)	101 (57.1)	41 (34.2)	42 (60.0)	5 (27.8)	<0.01
Negative blood culture for at least 72h	602 (52.1)	220 (55.1)	182 (48.9)	99 (55.9)	63 (52.5)	31 (44.3)	7 (38.9)	0.2

Legend. Values are counts (% of respondents of region who answered the question). N = number of respondents that answered this question. p value refers to difference between continents.

Table S2. Indications for 18F-FDG PET/CT use in *S. aureus* bacteremia patients

	Total N=993	North America N=292	Europe N=398	Asia N=125	Oceania N=124	South America N=50	p
Persistent bacteremia	666 (67.1)	203 (69.5)	269 (67.6)	84 (67.2)	78 (62.9)	31 (62.0)	0.66
Signs of metastatic infection	518 (52.2)	115 (39.4)	247 (62.1)	75 (60.0)	41 (33.1)	38 (76.0)	<0.01
Persistent fever 48-72h	367 (37.0)	95 (32.5)	169 (42.5)	43 (34.4)	38 (30.6)	22 (44.0)	0.03
Prosthetic joint material	279 (28.1)	60 (20.5)	144 (36.2)	32 (25.6)	25 (20.2)	18 (36.0)	<0.01
Suspected endocarditis	311 (31.3)	52 (17.8)	172 (43.2)	34 (27.2)	33 (26.6)	18 (36.0)	<0.01

Legend. Values are counts (% of respondents of region who answered the question). N = number of respondents that answered this question. p value refers to difference between continents. Africa was excluded here because 18F-FDG PET/CT was almost never used.

Table S3. Randomized controlled trials on *S. aureus* bacteremia patients in the past 20 years

Study	Year	Number of patients
Fowler NEJM	2006	246
Weems AAC	2006	63
Ruotsalainen J Int Med	2006	381
Rupp AAC	2007	40
Stryjewski BMC	2014	60
Paul BMJ	2015	91
Davis CID	2016	60
Xbiotech	2016	52
Thwaites Lancet	2017	758
Holland JAMA	2018	116
Pericas CMI	2018	15
Geriak AAC	2019	40
Fowler JCI	2020	116
Tong JAMA	2020	352
Cheng CID	2021	104
Pujol CID	2021	155
Kaasch ECCMID	2022	213
Holland IDWeek	2022	390
Total		**3252**