Clinical Consensus Conference: Survey on Gram-Positive Bloodstream Infections with a Focus on *Staphylococcus aureus*

Christoph K. Naber,[1,a] Larry M. Baddour,[5] Evangelos J. Giamarellos-Bourboulis,[8] Ian M. Gould,[9] Mathias Herrmann,[2] Bruno Hoen,[10] Adolf W. Karchmer,[6] Yoshio Kobayashi,[11] Roman S. Kozlov,[12] Daniel Lew,[13] José M. Miró,[15] Robert C. Moellering, Jr.,[6] Philippe Moreillon,[14] Georg Peters,[3] Ethan Rubinstein,[16] Harald Seifert,[4] and G. Ralph Corey[7]

[1]Department of Cardiology, West-German Heart Center, Essen, [2]Institute of Medical Microbiology and Hygiene, University of Saarland Hospital, Homburg, [3]Institute of Medical Microbiology University Clinics, University of Muenster, Muenster, and [4]Institute for Medical Microbiology, Immunology and Hygiene, University of Cologne, Cologne, Germany; [5]Mayo Clinic College of Medicine, Division of Infectious Disease, Rochester, Minnesota; [6]Division of Infectious Diseases, Beth Israel Deaconess Medical Center, and Harvard Medical School, Boston, Massachusetts; [7]Duke University Medical Center, Durham, North Carolina; [8]Department of Internal Medicine, University of Athens, Medical School, Athens, Greece; [9]International Society of Chemotherapy Medical Microbiology, Aberdeen Royal Infirmary, Aberdeen, United Kingdom; [10]Department of Infectious Diseases, University Medical Center of Besançon, Besançon, France; [11]Department of Clinical Laboratories, Division of Clinical Microbiology, Keio University Hospital, Tokyo, Japan; [12]Institute of Antimicrobial Chemotherapy, Smolensk State Medical Academy, Smolensk, Russia; [13]Department of Internal Medicine, Division of Infectious Diseases, University of Geneva Hospitals, Geneva, and [14]Department of Fundamental Microbiology, University of Lausanne, Lausanne, Switzerland; [15]Infectious Diseases Service, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi-Sunyer, University of Barcelona, Barcelona, Spain; and [16]Department of Internal Medicine, University of Manitoba Faculty of Medicine, Winnipeg, Canada

This supplement is based on the proceedings of a Novartis-sponsored session at the 9th International Symposium of Modern Concepts in Endocarditis and Cardiovascular Infections, June 2007; for sponsorship details, see p. S269.

The increased incidence over the past decade of bloodstream infections (BSIs) caused by gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus*, highlights the critical need for a consistent approach to therapy. However, there is currently no international consensus on the diagnosis and management of gram-positive BSIs. The Clinical Consensus Conference on Gram-Positive Bloodstream Infections was convened as a session at the 9th International Symposium on Modern Concepts in Endocarditis and Cardiovascular Infections held in 2007. Participants discussed various aspects of the practical treatment of patients who present with gram-positive BSI, including therapeutic options for patients with BSIs of undefined origin, the selection of appropriate empirical therapy, and treatment of complicated and uncomplicated BSIs. The opinions of participants about these key issues are reflected in this article.

Despite the increasing importance of gram-positive bacterial infections [1, 2] and, in particular, the clinical problems related to methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia [3–5], there is no international consensus on the diagnosis and management of gram-positive bloodstream infections (BSIs). This article summarizes the findings of the Clinical Consensus Conference on Gram-Positive Bloodstream Infections, which convened as a session at the 9th International Symposium on Modern Concepts in Endocarditis and Cardiovascular Infections held in June 2007. The objectives were to poll the opinions of participants and to provide an open forum to discuss practical aspects of the clinical management of gram-positive BSIs.

Three "state-of-the-art" presentations were given; these focused on the clinical microbiology of gram-positive BSI, patient groups at particular risk of developing gram-positive BSIs, and the management of

[a] Present affiliation: Department for Cardiology and Angiology, Centre for Cardiovascular Medicine, Elisabeth Hospital Essen, Essen, Germany.

Reprints or correspondence: Dr. Christoph K. Naber, Dept. for Cardiology and Angiology, Centre for Cardiovascular Medicine, Elisabeth Hospital Essen, Klara Kopp Weg 1, 45138 Essen, Germany (cknaber@web.de).

Clinical Infectious Diseases 2009; 48:S260–70
© 2009 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2009/4810S4-0005$15.00
DOI: 10.1086/598185

gram-positive BSIs, with special reference to *S. aureus* bacteremia. The presentations were followed by a discussion among conference participants and an international panel of experts in the diagnosis and treatment of BSIs and their associated complications. Consensus opinion was not necessarily sought from participants. This article reflects the outcomes of the discussion and the results of an integral keypad voting process with both open and predefined questions and answers.

METHODS

Participants were asked to respond to a series of multiple-choice questions by selecting 1 answer from a numbered selection of 2–6 possible responses. Answers were registered using series 8 VGD1.01 keypads (provided by Key Audio Visual), which were distributed to unallocated seats before the admittance of participants. To vote, each participant pressed the number that corresponded to their chosen answer. The display on the keypad prompted each participant to vote and displayed their vote. Participants were able to change their vote during the voting period of 10 s by pressing "C" on the keypad and re-entering their vote. After an explanation of the voting process, participants were familiarized with the operation of the keypads (including brief details on the time allocated for voting and the attribution of answers to individual keypads) with use of a test question (the response to this test question was not included in the analyses).

All questions were predetermined by an expert panel, which included the invited speakers. Three initial questions requested the age, specialty, and country of work of the participants. Additional questions were displayed after each of the 3 presentations, and visual voting cues were displayed before each set of questions, in addition to the chairman's instructions. The scores for each of the responses were displayed as percentages of the total number of evaluable votes. After keypad voting, sessions were open to discussion, and although not quantitative, viewpoints that were expressed during this discussion are included in Results.

RESULTS

Participant demographic characteristics. A total of 206 physicians participated in the conference, the discussion, and the keypad voting. The mean number of responses per question was 167 (range, 153–179 responses per question). The key demographic characteristics of the participants are summarized in table 1. The main specialties were infectious diseases (75 respondents [45%]), cardiology (30 [18%]), and microbiology (clinical, 18 [11%]; unspecified, 12 [7%]), and the majority (119 [71%]) of respondents were European.

Defining a clinically relevant BSI. In general, a single blood culture positive for gram-positive pathogenic bacteria was considered to be insufficient evidence of a clinically relevant BSI. A small majority (99 [59%]) of respondents required the presence of clinical signs of infection or an additional independent positive blood culture result to secure a diagnosis of a clinically relevant infection (figure 1, *top*). However, there was general agreement that any blood culture positive for *S. aureus* should be regarded as relevant because of the intrinsic pathogenicity of this organism in the bloodstream and the high number and frequency of complications associated with *S. aureus* BSIs. In addition, 35 respondents (23%) suggested that the definition of a clinically relevant BSI will vary depending on the causative pathogen (figure 1, *top*).

In the case of a suspected *S. aureus* BSI, approximately two-thirds of respondents agreed that the initial diagnostic examination should include at least 1 laboratory test or imaging technique, in addition to a full blood profile, blood culture,

Table 1. Participant demographic characteristics.

Characteristic	No. (%) of respondents
Specialty	
Infectious diseases	75 (45)
Cardiology	30 (18)
Clinical microbiology	18 (11)
Academic research	15 (9)
Microbiology	12 (7)
Pharmaceutical industry	10 (6)
Surgery	4 (2)
Dental medicine	2 (1)
Geographic region	
North America	26 (15)
Scandinavia	19 (11)
Spain	22 (12)
Germany	15 (8)
Southern Europe	15 (8)
Benelux	13 (7)
Eastern Europe	13 (7)
Middle East	11 (5)
Italy	9 (5)
United Kingdom and Ireland	9 (5)
Asia	5 (3)
France	6 (3)
Australasia	4 (2)
South America	4 (2)
Switzerland	4 (2)
Africa	2 (1)
Age group, years	
25–35	38 (24)
36–45	45 (28)
46–55	47 (29)
>55	30 (19)

NOTE. Data on specialty were available for 166 participants, data on geographic region were available for 177 participants, and data on age were available for 160 participants.

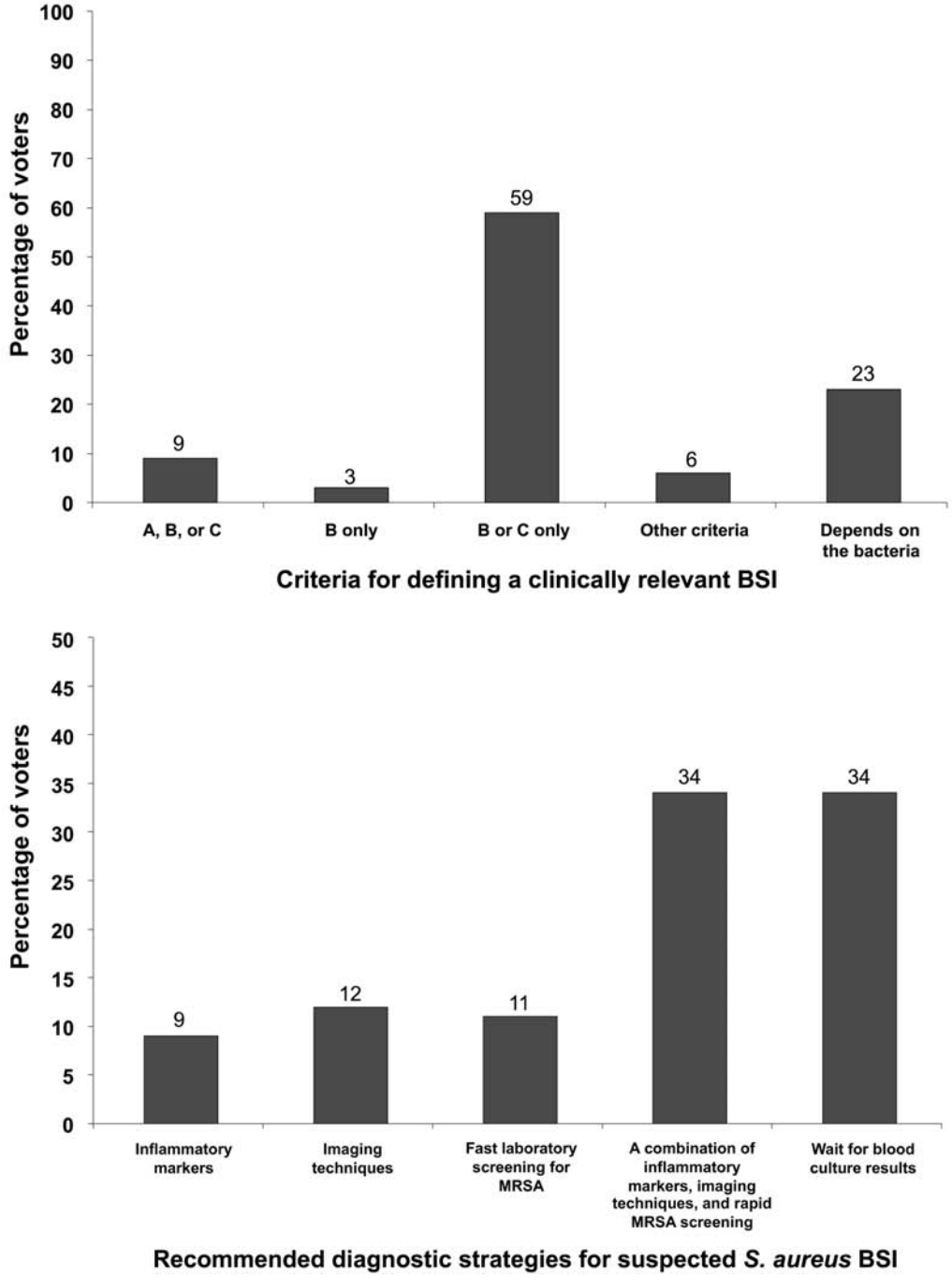

Figure 1. The definition and diagnosis of a clinically relevant bloodstream infection (BSI). *Top,* Percentage of responses to the following question: after a blood culture positive for gram-positive pathogenic bacteria, which of the following satisfies your definition of a clinically relevant BSI: (A) the single blood culture, with no clinical signs of infection; (B) an additional independent blood culture, with no clinical signs of infection; or (C) the single blood culture plus clinical signs of infection? A total of 153 participants responded to this question. *Bottom,* Percentage of responses to the following question: in addition to a full blood profile, blood culture, bacterial identification, and susceptibility testing, what should be included in the initial standard diagnostic examination for suspected *Staphylococcus aureus* BSI? Methicillin-resistant *S. aureus* (MRSA) screening methods included PCR and other fast laboratory tests. A total of 165 participants responded to this question.

bacterial identification, and susceptibility testing. Of these respondents, 28 (17%) responded that screening for MRSA with use of rapid laboratory tests, such as PCR, should be included, and approximately one-half (85 [51.5%]) responded that a combination of inflammatory markers, imaging techniques, and MRSA screening should be included (figure 1, *bottom*). Some participants suggested that definitions of clinically relevant infection should encompass a range of clinical parameters

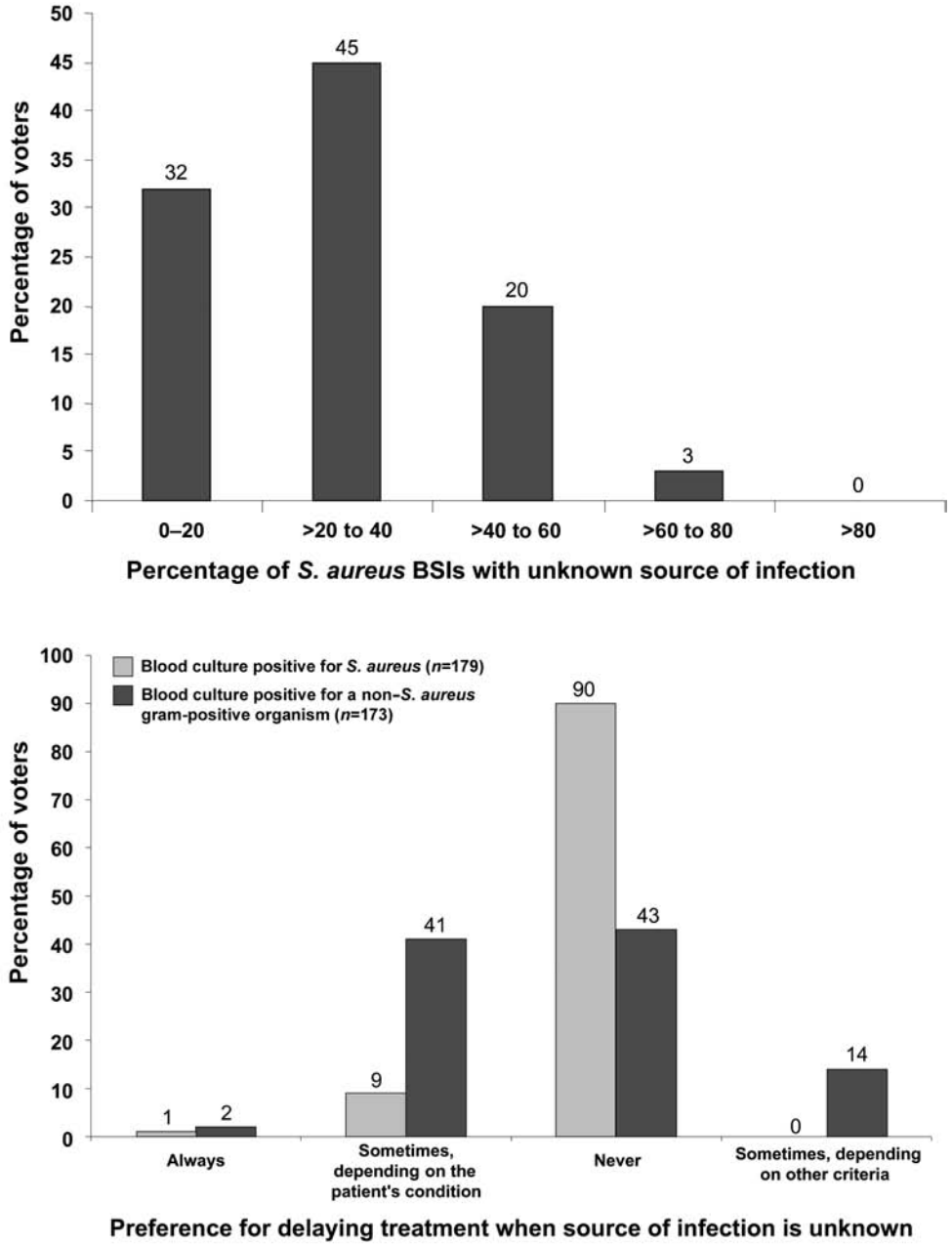

Figure 2. Treatment initiation for a bloodstream infection (BSI) of unknown origin. *Top,* Percentage of responses to the following question: in your experience, for what proportion of *Staphylococcus aureus* BSIs does the source remain unknown despite extensive diagnostics? A total of 158 participants responded to this question. *Bottom,* Percentage of responses to the following question: would you delay treatment initiation in the case of either a blood culture positive for *S. aureus* or for a non–*Staphylococcus aureus* gram-positive organism because the source of infection is unknown? A total of 158 participants responded to this question.

that would be applicable to the individual patient and useful for epidemiological purposes.

BSIs of unknown source. Although establishment of the probable source of infection may facilitate the selection of an appropriate intervention and enable monitoring of the effect of treatment, it is not always possible. In the experience of 158 respondents (68%), the source of *S. aureus* BSI remained unknown in >20% of cases, despite extensive diagnostic procedures (figure 2, *top*). There was an overwhelming consensus (158 respondents [90%]) that, in the case of a blood culture positive for *S. aureus,* treatment initiation should not be delayed because the source of infection is unknown. However, when participants considered blood cultures negative for *S. aureus* but positive for another gram-positive organism, only 68 re-

spondents (43%) thought that treatment should never be delayed when the source was unknown, and 65 (41%) reported that the decision to initiate therapy should take into account the patient's condition (figure 2, *bottom*). It was reasoned that, because patients may be bacteremic for some time before presentation of clinical symptoms, bacteremia might be indicative of a deep-seated infection.

Preferred antibiotic treatments for BSIs. Participants were asked to consider the factors that are most likely to trigger empirical anti-MRSA therapy for a suspected *S. aureus* infection. Individual clinical risk factors were most likely to trigger empirical treatment against MRSA for 75 respondents (45%), whereas 65 (39%) reported that local epidemiology was the primary trigger (figure 3, *top*). A small proportion (22 [13%]) of respondents reported that MRSA was always assumed in cases of suspected *S. aureus* infection; 20 (90%) of these participants were from regions with a high prevalence of MRSA infection.

The majority (144 [86%]) of respondents preferred β-lactams as the backbone antibiotic regimens directed against methicillin-susceptible *S. aureus* (MSSA) infections, whereas glycopeptides were the anti-MSSA agent of choice for 10 respondents (6%) (figure 3, *bottom*). Glycopeptides were the preferred backbone of antibiotic regimens directed against MRSA infections for 127 respondents (76%).

For empirical therapy of suspected nonstaphylococcal gram-positive BSI, β-lactams were the agents of choice for the majority (125 [75%]) of respondents; glycopeptides and fluoroquinolones were selected by a minority (23 [14%] and 7 [4%], respectively) of respondents (figure 3, *bottom*). Daptomycin was the backbone of preferred antimicrobial regimens for 23 respondents (14%) for treatment of MRSA BSIs and for 10 respondents (6%) for treatment of MSSA infections.

The treatment of uncomplicated* S. aureus *BSIs. Participants were unable to reach consensus on a definition of uncomplicated *S. aureus* bacteremia; 45 respondents (27%) suggested that uncomplicated *S. aureus* bacteremia does not exist. However, despite the failure to reach consensus, criteria for defining uncomplicated *S. aureus* bacteremia were proposed. This definition required the patient to have catheter-associated infection, with negative results of a follow-up blood culture; to defervesce within 72 h after initiation of therapy; to have normal transesophageal echocardiography (TEE) findings; to be free of prosthetic material in the joints or cardiovascular space; and to lack any clinical evidence suggestive of metastatic infection.

The majority (119 [71%]) of respondents preferred monotherapy for uncomplicated *S. aureus* BSIs (figure 4, *top*). However, a substantial minority (37 [22%]) of respondents preferred combination therapy with 2 agents (including an aminoglycoside), which alluded to the usefulness of increased cidal activity. The voting results suggested that the standard duration of treatment for uncomplicated *S. aureus* BSIs was 7–14 days for 79 respondents (45%), whereas 69 respondents (39%) preferred treatment for 15–21 days (figure 4, *bottom*). However, it was noted that there are no clinical data to demonstrate that a 7-day course of treatment is equivalent to 14 days of therapy, and after discussion, there appeared to be consensus favoring treatment for 14 days.

Complications of BSI. Because *S. aureus* BSIs are frequently associated with infective endocarditis (IE), participants were polled about their use of TEE for patients with *S. aureus* BSI. Forty-one percent of physicians reported that they routinely performed TEE for all patients with *S. aureus* BSI; many of these physicians thought that TEE was a cost-effective method for the determination of the duration of treatment for patients. Of the remaining 99 respondents (59%), some assessed the probability of a patient having endocarditis or waited for the results of transthoracic echocardiography, whereas others deferred the decision to a cardiologist.

Monitoring treatment success of patients with BSI. In addition to the clinical progress of the patient, for the majority (139 [82%]) of respondents, blood culture was the best method to monitor treatment response, although follow-up blood culture was not always deemed necessary, depending on the microorganisms involved. However, in the case of *S. aureus* infection, follow-up blood cultures were considered to be mandatory. The majority (98 [58%]) of respondents considered that, in addition to blood cultures, inflammatory markers, such as C-reactive protein and procalcitonin, could be important tools for monitoring clinical progress (figure 5).

DISCUSSION

S. aureus is a leading cause of BSIs [6], and the management of such infections continues to present a number of significant challenges to the treating physicians. The initial clinical features of *S. aureus* BSIs are often nonspecific, and the patient may be asymptomatic [7]. In addition, signs of sepsis (e.g., hypothermia and hypotension) exist beyond the classic symptom of fever [8]; thus, a sizeable number of patients have positive blood culture results in the absence of fever (G.R.C., personal communication). The indication for performing a blood culture in the absence of clinical signs of infection was therefore questioned. Of no surprise, the majority of participants considered a single positive blood culture result to be insufficient evidence of a clinically relevant BSI. There was, however, recognition that the definition of a clinically relevant BSI might vary depending on the causative pathogen. For example, coagulase-negative staphylococci (CoNS) are an important cause of BSIs, but they are also the most common contaminant of blood

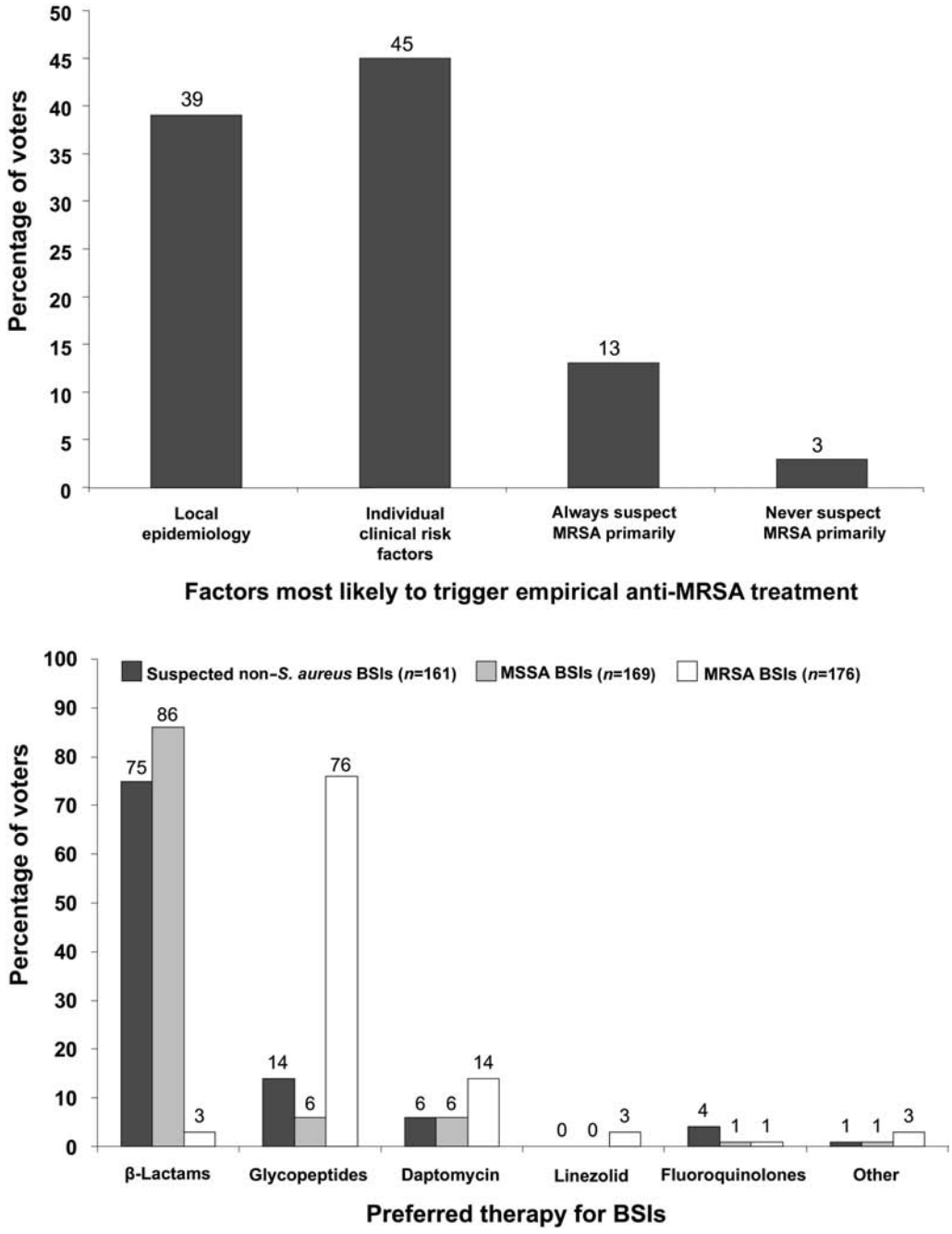

Figure 3. Comparison of treatment preferences for suspected and confirmed bloodstream infections (BSIs). *Top,* Percentage of responses to the following question: which factors are most likely to trigger empirical anti–methicillin-resistant *Staphylococcus aureus* (MRSA) treatment in a patient with suspected *S. aureus* BSI? *Bottom,* Percentage of responses to the following question: what forms the backbone of your preferred empirical treatment regimen for suspected non-*Staphylococcus* gram-positive BSIs, confirmed methicillin-susceptible *S. aureus* (MSSA) BSIs, and confirmed MRSA BSIs?

cultures [9, 10]. In a recent report that evaluated the significance of 405 CoNS blood culture isolates, 78% of CoNS isolates were judged to be contaminants [9]. Because of the possibility of recovering 2 independent CoNS contaminants from a patient, CoNS isolates should be identified to the species level, and genotypic analysis should be used in selected cases to determine whether the strains are identical or different.

By agreeing that all blood cultures positive for *S. aureus* should be treated as clinically relevant, participants appeared to support the notion that some other microorganisms should

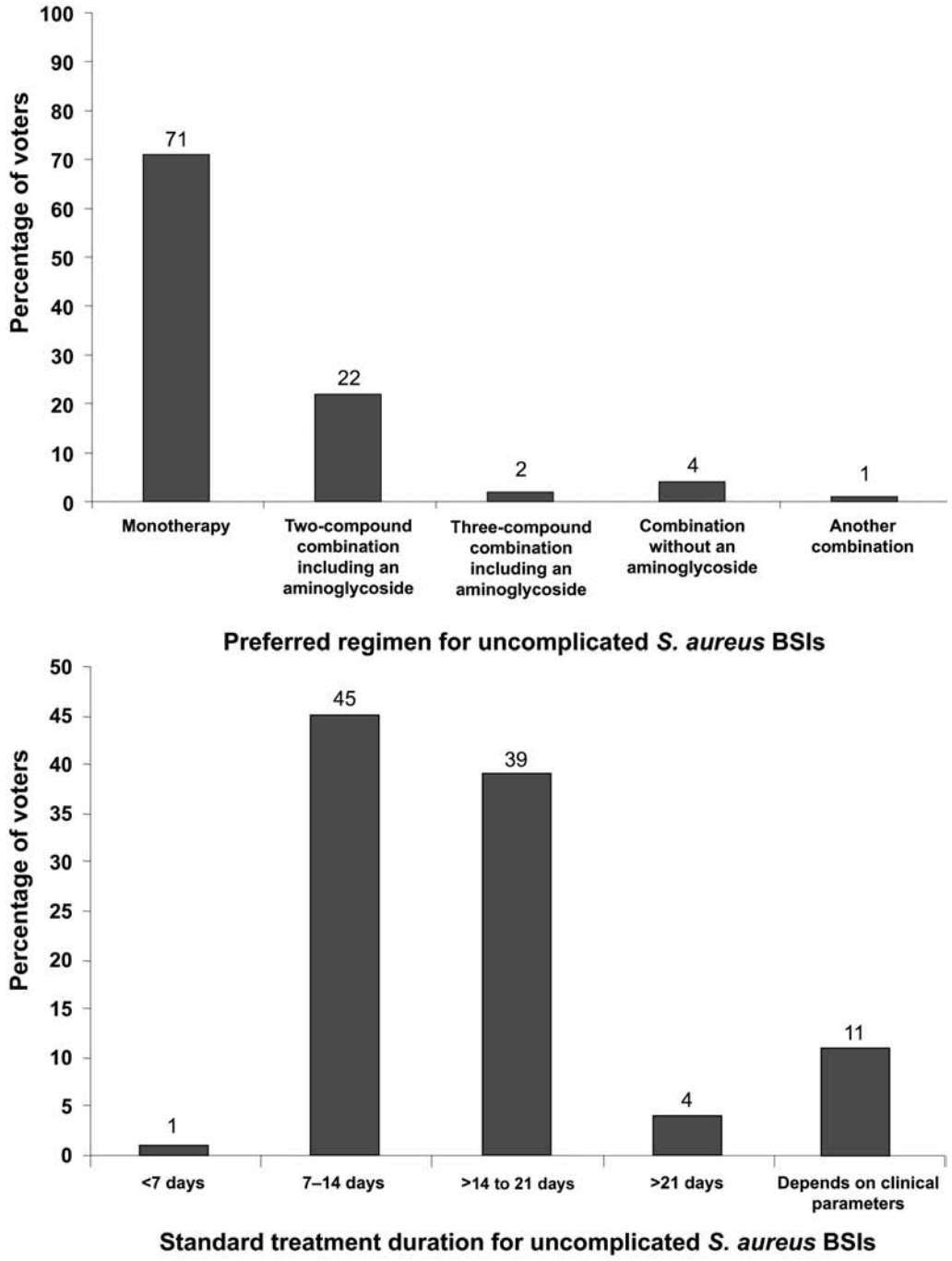

Figure 4. Treatment of an uncomplicated *Staphylococcus aureus* bloodstream infection (BSI). *Top,* Percentage of responses to the following question: which best describes your preferred regimen for uncomplicated *S. aureus* BSIs? A total of 167 participants responded to this question. *Bottom,* Percentage of responses to the following question: what is your usual standard treatment duration for uncomplicated *S. aureus* BSIs? A total of 176 participants responded to this question.

be regarded as categorical pathogens. This is reflective of the significant pathology associated with *S. aureus* BSIs if they are left untreated or are misdiagnosed. Complications include serious metastatic infection, sepsis, and mortality; therefore, accurate diagnosis with use of both traditional and modern techniques is recommended [7].

A substantial proportion of participants felt that inflammatory markers were a valuable addition to blood cultures for

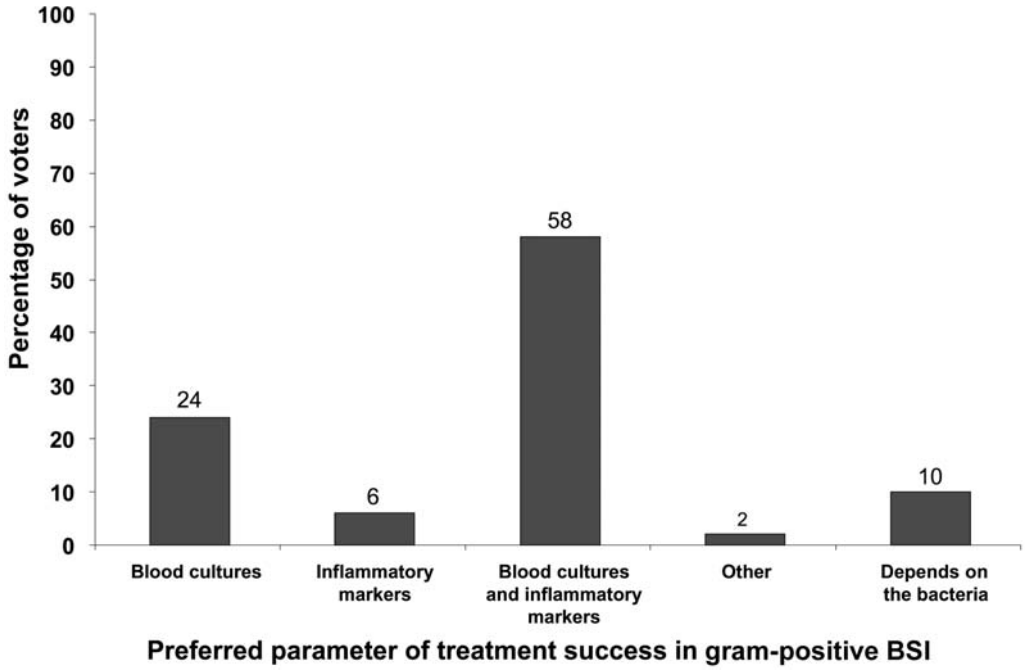

Figure 5. Parameters for treatment success in gram-positive bloodstream infections (BSIs). The participants were asked: in addition to the clinical progress of the patient, which is the best parameter of treatment success for gram-positive BSIs? A total of 169 participants responded to this question.

the evaluation of treatment success. Both C-reactive protein and procalcitonin have demonstrated high sensitivity when used as indices of therapeutic success [11, 12]. In addition, recent data suggest that serial monitoring of procalcitonin levels may have health care–related economic benefits, because it enables an earlier discontinuation of antibiotic therapy [13]. Notwithstanding, the potential of these markers to complicate rather than assist in the assessment of treatment success was highlighted. Elevation of the C-reactive protein level, for example, can occur in the context of conditions other than infection; in addition, the C-reactive protein level may remain elevated in patients after resolution of infection. Publications regarding the diagnostic and prognostic use of procalcitonin level measurement are contradictory. Furthermore, patient characteristics and clinical settings vary markedly, and the data have been difficult to interpret and are often extrapolated inappropriately to clinical use. Although high levels of procalcitonin occur frequently in infection, the procalcitonin level is also elevated in some noninfectious conditions. Thus, procalcitonin level is not a specific indicator of either infection or BSI [14].

Published studies of *S. aureus* bacteremia report an undefined source of infection in 12%–43% of patients [15–17]. Consistent with this finding, the majority of participants reported that the source of BSI remained unknown in >20% of cases. An undefined source of *S. aureus* bacteremia has been identified as an independent predictor of 30-day mortality [15]. The timely delivery of effective antimicrobial therapy is critical for the successful treatment of *S. aureus* BSI. Delaying the initiation of treatment by as little as 45 h from the time of the first blood culture positive for *S. aureus* can increase the duration of hospitalization and can increase the risk of infection-related mortality [18]. Therefore, the vast majority of participants did not delay initiation of therapy in the case of a blood culture positive for *S. aureus* with an unknown source of infection. However, when participants considered blood cultures negative for *S. aureus* but positive for another gram-positive organism, the response was strikingly different, with more than one-half of the participants reporting that they might delay treatment. Antibiotic therapy targeted at simply resolving the bacteremia alone might not adequately address the underlying infection, thereby increasing the risk of recurrence, with potentially serious complications. Some participants felt that, for patients with an underlying infection, it may be beneficial to identify the source of infection before initiation of therapy if the patient's condition remains stable.

Use of an inadequate empirical treatment regimen is known to have detrimental effects and is associated with higher in-hospital mortality [18, 19], irrespective of the pathogen or other risk factors for mortality [20]. It has been suggested that the selection of empirical treatment regimens for suspected *S. aureus* BSI should be guided by both the local prevalence of MRSA

infection and the patient's history [7]. When the factors that might influence the decision to prescribe empirical anti-MRSA therapy for a suspected *S. aureus* infection were considered, participant opinion was almost equally divided; individual clinical risk factors were key in the decision to initiate empirical anti-MRSA therapy for 45% of respondents, whereas 39% considered local epidemiology to be of primary importance.

The participants' choice of antimicrobial agents for treatment of *S. aureus* infections was primarily in accordance with current UK guidelines that, for reasons of overall patient safety, convenience, and cost [21], recommend β-lactams as the preferred agents for treatment of documented or suspected MSSA infection. This recommendation is supported by 2 large prospective studies. Chang et al. [22] found that patients with MSSA bacteremia who received vancomycin therapy had a higher rate of relapse and microbiological failure, compared with patients who received nafcillin treatment, whereas Stryjewski et al. [23] found significantly higher rates of treatment failure and recurrent infection at 12 weeks after the initiation of treatment among patients with MSSA bacteremia who received vancomycin treatment, compared with patients who received cefazolin treatment. Therefore, the use of glycopeptides for the treatment of MSSA infection is recommended only for patients who are allergic to penicillins [24]. Guidelines for the prophylaxis and treatment of MRSA infection in the United Kingdom recommend glycopeptides as the mainstay of anti-MRSA therapy, particularly for bacteremia, complicated skin and soft-tissue infections, and bone infections [21].

The need to update guidelines as new evidence emerges on the use of recently approved antimicrobial agents has been acknowledged [21, 25]. Daptomycin is a novel cyclic lipopeptide antibacterial agent that has demonstrated efficacy in clinical trials for the treatment of both MSSA and MRSA complicated skin and soft-tissue infections and *S. aureus* bacteremia, with and without right-sided IE [26, 27]. The results of this consensus conference suggest that daptomycin is now also proving to be effective in clinical practice.

Uncomplicated BSIs have been characterized by the isolation of *S. aureus* from blood cultures of samples from patients without evidence of metastatic spread [27], the absence of sustained BSI, rapid clinical response (normalization of temperature) to antibacterial therapy, and the absence of complications within a given follow-up period [28]. However, such definitions are usually specific to a particular clinical study, and no definitive criteria to identify uncomplicated *S. aureus* bacteremia have been accepted. The failure of participants to reach consensus on this issue might reflect the difficulties in superimposing a definition on a condition with a wide spectrum of clinical presentations.

An alternative strategy has been to identify patients with good prognostic features who are thus at low risk of developing complications of *S. aureus* bacteremia [7, 28]. In a similar approach, participants felt that the establishment of criteria to identify patients who can be treated safely for 14 days was more important than the definition. This would entail a risk-benefit assessment incorporating all the stakeholders to balance the cost of long-term intravenous therapy against the risk of patients returning with recurrent *S. aureus* bacteremia or complications such as endocarditis. The established criteria are comparable to a previously recommended treatment duration of 10–14 days for *S. aureus* infection in patients with good prognostic characteristics (i.e., those who have normal examination findings, lack a prosthetic device, and are afebrile, with a negative blood culture result 72 h after presentation) [7]. After some discussion, participants agreed on a 14-day treatment period but cautioned that patients should be followed up to monitor their condition and to treat any complications that develop. No specific recommendations regarding the duration of this follow-up monitoring period were made. However, there was agreement that the majority of relapses occur within the first month after treatment. This is at variance with published data suggesting that the relapse rate generally remains constant during the first 3 months after treatment [29].

IE is arguably the most common complication associated with *S. aureus* BSI. Echocardiography can play a central role in the diagnosis and management of IE, as evidenced by the recommendation of the American Heart Association that echocardiography be performed in all cases of suspected IE [30]. Patients may undergo TEE (or transthoracic echocardiography), depending on the particular clinical circumstances. Transthoracic echocardiography is less invasive, more widely available, and easier and cheaper to perform, compared with TEE [7, 31]. It is typically performed as the first option for patients at low risk of IE and for patients for whom there is the greatest likelihood of definitive images (e.g., children and those with a low body mass index) [30]. TEE has the potential to provide high-quality images of the heart [31], and it is recommended for patients for whom clinical suspicion of IE or its complications is high (i.e., those with staphylococcal bacteremia, prosthetic valves, or a new atrioventricular block) or for whom imaging may be difficult [30]. In addition, TEE was shown to be a cost-effective method to determine the duration of therapy for patients with clinically uncomplicated bacteremia [32]. Despite these recommendations, fewer than one-half of participants thought that TEE was necessary to adequately evaluate the risk of complication.

The clinical consensus conference provided valuable insight into the opinions and working practices of a range of primarily European clinicians with an interest in BSIs, particularly those caused by *S. aureus.* Outcomes should, however, be interpreted with recognition that the participants were self-selected and

that voting was preceded by "state-of-the-art" presentations from leading experts.

There was consensus on some key aspects regarding the management of BSIs caused by *S. aureus* (compared with BSIs caused by other gram-positive pathogens) and the preferred treatment regimens for MSSA and MRSA infections. However, the discussions have highlighted several differences in therapeutic approaches to gram-positive infections (particularly those caused by *S. aureus*), such as the appropriate treatment duration and the usefulness of inflammatory markers in the diagnosis and/or management of BSIs. Definitive evidence-based guidelines for both the diagnosis and optimal treatment of *S. aureus* BSIs are required, and this subject deserves further study.

Acknowledgments

Support for this supplement was provided by Chameleon Communications International with Novartis Pharma AG sponsorship.

Supplement sponsorship. This article was published as part of a supplement entitled "Clinical Overview of Gram-Positive Bloodstream Infections," sponsored by a medical grant from Novartis, and has been derived from a session entitled "A Clinical Consensus Conference on Gram-Positive Bloodstream Infections" that was held at the 9th International Symposium on Modern Concepts in Endocarditis and Cardiovascular Infections (supported financially by Astellas, Medtronic, Novartis, and Wyeth) and that was organized by the ISC Working Group on Infective Endocarditis and Bloodstream Infections.

Potential conflicts of interest C.K.N. has served as a consultant for Astellas, Biotronik, Boston Scientific, Cordis, GHIP Netherlands, and Novartis; has received speaking honoraria from Cordis and Novartis; and has received research grants from Bayer HealthCare and St. Jude Medical. L.M.B. has served as a consultant for Enturia. E.J.G.-B. has received research grants from Abbott and Wyeth Ayerst SA. I.M.G. has received financial support from Johnson & Johnson, Novartis, Pfizer, Phico Therapeutics, and Wyeth. M.H. has received research grants and speaker honoraria from BayerVital, Novartis, Wyeth, Merck Sharp & Dohme, and Pfizer. B.H. has served as a consultant for Novartis. A.W.K. has served as a consultant for Cubist, Pfizer, Merck, Ortho-McNeil, and Theravance-Astellas; has received research grants from Merck and Pfizer; and owns stock in Cubist and Pfizer. J.M.M. has received research grants and speaker honoraria from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Chiron, Cubist, Novartis, GlaxoSmithKline, Gilead Sciences, Oxford Immunotec, Pfizer, Roche, and Theravance. R.C.M. has served as a consultant for Cubist, Novartis, and Pfizer. P.M. has received research support from and serves as an advisor for Johnson & Johnson, Novartis, and Wyeth. E.R. has served as a consultant for Astellas, Atox, Bayer, Pfizer, Replydine, Theravance, and Wyeth. H.S. has received speaker honoraria from Bayer, Gilead, Novartis, Oxoid, Pfizer, and Wyeth. G.R.C. has received research support from Cerexa/Forest Pharmaceuticals, Cubist, Cypress Pharmaceuticals, Innocol, Skyline Ventures, Theravance, and United Therapeutics. All other authors: no conflicts.

References

1. Gaynes R, Edwards JR. Overview of nosocomial infections caused by gram-negative bacilli. Clin Infect Dis **2005**; 41:848–54.
2. Schaberg DR, Culver DH, Gaynes RP. Major trends in the microbial etiology of nosocomial infection. Am J Med **1991**; 91:72S–5S.
3. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol **2005**; 26:166–74.
4. Lodise TP, McKinnon PS. Clinical and economic impact of methicillin resistance in patients with *Staphylococcus aureus* bacteremia. Diagn Microbiol Infect Dis **2005**; 52:113–22.
5. Reed SD, Friedman JY, Engemann JJ, et al. Costs and outcomes among hemodialysis-dependent patients with methicillin-resistant or methicillin-susceptible *Staphylococcus aureus* bacteremia. Infect Control Hosp Epidemiol **2005**; 26:175–83.
6. Health Protection Agency. Polymicrobial bacteraemias and fungaemias in England, Wales, and Northern Ireland: 2007. Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1213946128496. Accessed 5 January **2009**.
7. Mitchell DH, Howden BP. Diagnosis and management of *Staphylococcus aureus* bacteraemia. Intern Med J **2005**; 35(Suppl 2):S17–24.
8. O'Grady NP, Barie PS, Bartlett JG, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. Crit Care Med **2008**; 36:1330–49.
9. Beekmann SE, Diekema DJ, Doern GV. Determining the clinical significance of coagulase-negative staphylococci isolated from blood cultures. Infect Control Hosp Epidemiol **2005**; 26:559–66.
10. Dobbins BM, Kite P, Kindon A, McMahon MJ, Wilcox MH. DNA fingerprinting analysis of coagulase negative staphylococci implicated in catheter related bloodstream infections. J Clin Pathol **2002**; 55:824–8.
11. Povoa P, Coelho L, Almeida E, et al. Pilot study evaluating C-reactive protein levels in the assessment of response to treatment of severe bloodstream infection. Clin Infect Dis **2005**; 40:1855–7.
12. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis **2007**; 7:210–7.
13. Schuetz P, Christ-Crain M, Wolbers M, et al. Procalcitonin guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: a prospective, multicenter, randomized controlled trial. BMC Health Serv Res **2007**; 7:102.
14. Becker KL, Snider R, Nylen ES. Procalcitonin assay in systemic inflammation, infection, and sepsis: clinical utility and limitations. Crit Care Med **2008**; 36:941–52.
15. Mylotte JM, Tayara A. *Staphylococcus aureus* bacteremia: predictors of 30-day mortality in a large cohort. Clin Infect Dis **2000**; 31:1170–4.
16. Khatib R, Riederer K, Saeed S, et al. Time to positivity in *Staphylococcus aureus* bacteremia: possible correlation with the source and outcome of infection. Clin Infect Dis **2005**; 41:594–8.
17. Jensen AG, Wachmann CH, Espersen F, Scheibel J, Skinhoj P, Frimodt-Moller N. Treatment and outcome of *Staphylococcus aureus* bacteremia: a prospective study of 278 cases. Arch Intern Med **2002**; 162:25–32.
18. Lodise TP, McKinnon PS, Swiderski L, Rybak MJ. Outcomes analysis of delayed antibiotic treatment for hospital-acquired *Staphylococcus aureus* bacteremia. Clin Infect Dis **2003**; 36:1418–23.
19. Khatib R, Saeed S, Sharma M, Riederer K, Fakih MG, Johnson LB. Impact of initial antibiotic choice and delayed appropriate treatment on the outcome of *Staphylococcus aureus* bacteremia. Eur J Clin Microbiol Infect Dis **2006**; 25:181–5.
20. Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. J Intern Med **1998**; 244:379–86.
21. Gemmell CG, Edwards DI, Fraise AP, Gould FK, Ridgway GL, Warren RE. Guidelines for the prophylaxis and treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the UK. J Antimicrob Chemother **2006**; 57:589–608.
22. 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.
23. Stryjewski ME, Szczech LA, Benjamin DK Jr, et al. Use of vancomycin or first-generation cephalosporins for the treatment of hemodialysis-dependent patients with methicillin-susceptible *Staphylococcus aureus* bacteremia. Clin Infect Dis **2007**; 44:190–6.
24. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the

diagnosis and management of skin and soft-tissue infections. Clin Infect Dis **2005**; 41:1373–406.
25. Dandache P, Aronow WS, Sakoulas G. Clinical update on the diagnosis and treatment of bacterial endocarditis. Compr Ther **2007**; 33:192–207.
26. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis **2004**; 38:1673–81.
27. Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus.* N Engl J Med **2006**; 355:653–65.
28. Fowler VG Jr, Olsen MK, Corey GR, et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. Arch Intern Med **2003**; 163: 2066–72.
29. Johnson LB, Almoujahed MO, Ilg K, Maolood L, Khatib R. *Staphylococcus aureus* bacteremia: compliance with standard treatment, long-term outcome and predictors of relapse. Scand J Infect Dis **2003**; 35: 782–9.
30. 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.
31. Murray RJ. *Staphylococcus aureus* infective endocarditis: diagnosis and management guidelines. Intern Med J **2005**; 35(Suppl 2):S25–44.
32. Rosen AB, Fowler VG Jr, Corey GR, et al. Cost-effectiveness of transesophageal echocardiography to determine the duration of therapy for intravascular catheter–associated *Staphylococcus aureus* bacteremia. Ann Intern Med **1999**; 130:810–20.