

SUPPLEMENT ARTICLE

Patients at Risk of Complications of *Staphylococcus aureus* Bloodstream Infection

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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. S251.

Staphylococcus aureus is one of the most common causative pathogens of bloodstream infections (BSIs). In approximately one-half of patients with *S. aureus* BSI, no portal of entry can be documented. This group of patients has a high risk of developing septic metastases. Similarly, patient populations at high risk of *S. aureus* BSI and BSI-associated complications include patients receiving hemodialysis, injection drug users, patients with diabetes, and patients with preexisting cardiac conditions or other comorbidities. One of the most severe complications of *S. aureus* BSI is infective endocarditis, and *S. aureus* is now the most common cause of infective endocarditis in the developed world. Patients with methicillin-resistant *S. aureus* BSI or infective endocarditis have higher rates of mortality, compared with patients with methicillin-susceptible *S. aureus* infection. Nasal carriage is the most important source of *S. aureus* BSI. Better eradication and control strategies, including nasal decolonization and more-active antibiotics, are needed to combat *S. aureus* BSIs.

Bacteremia is defined as the presence of viable bacteria in the blood and is not necessarily associated with clinical manifestations of disease [1]. The term bloodstream infection (BSI) has been imposed progressively, and a diagnosis of BSI requires the presence of clinical symptoms of systemic infection in addition to positive blood culture results [2]. BSIs are associated with significant morbidity and mortality, particularly in populations at high risk of infection.

Staphylococcus aureus is the second-most common pathogen causing BSIs worldwide [3, 4], and *S. aureus* is the leading cause of nosocomial BSIs in Europe [4]. In the United States, *S. aureus* is the pathogen that is most frequently isolated from all types of BSI [5]. *S. aureus* BSIs are associated with a high frequency of life-threatening complications, such as metastatic infections, and *S. aureus* is the principal pathogen respon-

sible for infective endocarditis (IE) in industrialized countries [6–16]. Patients with *S. aureus* IE are more clinically debilitated and have a higher prevalence of severe sepsis, major neurological events, and multiple organ failure, compared with patients with IE caused by other pathogens [16, 17]. As a result, *S. aureus* BSIs have a significant impact on mortality, with documented associated mortality rates of 20%–40% [18]. This relatively wide range of reported mortality rates may be reflective of the different characteristics of specific study populations, and patients with prosthetic devices or long-term intravascular catheters may be particularly vulnerable. A study that involved 298 patients with prosthetic devices (long-term catheters and cardiovascular, orthopedic, and other devices) reported an in-hospital *S. aureus*-associated mortality rate of 12%, with a 12-week mortality rate of 17%. Mortality rates among patients with cardiovascular prostheses were considerably higher; the in-hospital *S. aureus*-associated mortality rate was 18%, and this mortality increased to 26% at 12 weeks of follow-up [10]. An overall mortality rate of 19% was observed among patients who received long-term hemodialysis [19]. Nosocomial *S. aureus* BSI dramatically increases the cost of hospitalization, and these costs are further increased

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Clinical Infectious Diseases 2009;48:S246–53

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1058-4838/2009/4810S4-0003\$15.00

DOI: 10.1086/598187

by methicillin resistance in pathogens causing complicated BSIs, including those associated with endocarditis, osteomyelitis, and deep-seated abscesses [10, 19, 20]. Because of the high morbidity and mortality associated with BSIs, efforts to identify patients at high risk of developing BSI and associated complications have intensified.

EPIDEMIOLOGY OF BSIs

Classically, BSIs are stratified according to the environment of acquisition (nosocomial or community-acquired BSIs [CA-BSIs]) and by the presence or absence of identified associated sites of infection. The recent delineation of health care-associated BSIs (HCA-BSIs), which are more closely related to nosocomial BSIs than to CA-BSIs, allows us to define more precisely the population at risk of *S. aureus* BSI (table 1). The features of HCA-BSIs are not consistently defined among studies; however, most authors identify previous hospitalization, receipt of long-term hemodialysis, and residence in a nursing home or long-term care facility as the most important characteristics [5, 21, 22]. Nosocomial BSIs and HCA-BSIs are most frequently associated with intravascular devices [21]. Rates of methicillin resistance among strains causing nosocomial BSIs and HCA-BSIs are generally similar [5, 21] and are higher than those among strains causing CA-BSIs [5]. In a large US study, the frequency of *S. aureus* causing HCA-BSIs, nosocomial BSIs, and CA-BSIs was 25.7%, 29.7%, and 17.8%, respectively, and the frequency of methicillin-resistant strains causing these infections was 41%, 52%, and 26%, respectively [5].

Although *S. aureus* is less frequently isolated from CA-BSIs than from nosocomial BSIs or HCA-BSIs, *S. aureus* CA-BSI remains a serious condition and is associated with high rates of complications and mortality [23]. Analysis of patients with *S. aureus* BSI at a tertiary care center in Switzerland revealed that mortality among patients with CA-BSI was twice as high as mortality among patients with nosocomial infection [24], probably because primary BSIs, which are a potential severity factor (see below), occurred more frequently in the patients with CA-BSI. In addition, patients with CA-BSI may have prolonged undiagnosed *S. aureus* bacteremia, and patients with nosocomial BSI usually receive a diagnosis relatively early. Historically, methicillin-resistant *S. aureus* (MRSA) has been associated primarily with nosocomial BSIs; however, community-acquired MRSA (CA-MRSA) strains with the Panton-Valentine leukocidin locus are causing an epidemic in the United States and are now emerging throughout the world and becoming a cause of a significant proportion of *S. aureus* infections in surveillance studies [25–29]. Of particular concern is CA-MRSA infection in patients with no known risk factors for BSI [27, 30]. CA-MRSA strains are generally susceptible to non- β -lactam antibiotics; however, the increasing proportion of CA-MRSA infections that are caused by highly virulent strains,

together with the emergence of multidrug-resistant strains, emphasizes the importance of rapid initiation of appropriate treatment [31–33].

PRIMARY VERSUS SECONDARY BSIs

A primary BSI is traditionally defined as a BSI associated with bacteremia for which there is no identified portal of entry or associated infected site [1]. Primary BSI accounts for 40%–50% of cases of *S. aureus* bacteremia and occurs much less frequently in patients with nosocomial bacteremia (3%–5%) than it does in patients with community-acquired bacteremia [24, 34]. A secondary BSI is defined as a BSI in which there is a documented portal of bacterial entry (e.g., a skin infection, a catheter, pneumonia, or a urinary tract infection) and/or a known associated site of infection. Infections frequently associated with secondary BSIs include endocarditis, deep-seated abscesses, and osteomyelitis [35]. It is useful to consider primary BSI as part of a continuum of pathology from the initial undetected bacteremia to the secondary seeding of sites (figure 1). These sites may have been seeded either from a primary BSI, if there is bacteremia without a documented portal of entry, or from a secondary BSI, if a portal of entry or primary infection has been established. Therefore, it is clearer to distinguish primary and secondary BSIs on the criterion of an identified portal of entry.

S. AUREUS BSI: THE RISK OF COMPLICATIONS

Approximately one-third of patients with *S. aureus* BSI develop local complications or distant septic metastases [11, 35]. Frequent sites of distant metastases include the bones and joints (especially when prosthetic materials are present), the epidural space and intervertebral discs, and both native and prosthetic cardiac valves. In addition, patients can develop visceral abscesses in the spleen and kidneys. Fowler et al. [35] investigated clinical characteristics that might predict the likelihood of complications developing. The authors identified 4 risk factors associated with complicated *S. aureus* BSIs: namely, the presence of persistent bacteremia (positive blood culture results after 72–96 h of appropriate treatment), community acquisition, the presence of skin lesions suggestive of distant metastases, and persistent fever. In the absence of any of these risk factors, the probability of developing complications was 16%; this risk increased dramatically when ≥ 1 of these risk factors were present [35]. A delay in the administration of appropriate treatment has also been associated with an increase in the risks of complications [3] and higher mortality [36]. These data suggest that persistent bacteremia should alert the clinician to the potential for complications and should prompt further investigation.

Endocarditis is one of the most severe complications of *S. aureus* BSI, and native-valve *S. aureus* IE has a poorer prognosis than does IE caused by other pathogens [37]. Several studies

Table 1. Definitions of bloodstream infections (BSIs) according to means of acquisition.

Category	Definition
HA-BSI	Patients with a first positive blood culture result >2 days after hospital admission and ≤1 day after hospital discharge
HCA-BSI	Patients with a first positive blood culture result >2 days after hospital admission and any of the following: <ul style="list-style-type: none">●hospitalization in an acute care hospital for ≥2 days in the past 90 days,●residence in a nursing home or long-term care facility,●receiving long-term hemodialysis,●receiving IV therapy at home,●previous hospitalization within 2–30 days before hospital admission, or●currently receiving immunosuppression medication or presence of metastatic cancer Patients with long-term intravascular devices to receive either chemotherapy or parenteral nutrition Patients who underwent an invasive procedure that required hospital admission or with BSI occurring within the first 48 h after hospital admission
CA-BSI	Patients who do not meet HA-BSI or HCA-BSI definitions and who had a first positive blood culture result ≤2 days after hospital discharge

NOTE. The definitions are derived from Friedman et al. [21], Shorr et al. [5], and Siegman-Igra et al. [22]. CA-BSI, community-acquired BSI; HA-BSI, hospital-acquired BSI; HCA-BSI, health care-associated BSI; IV, intravenous.

have investigated risk factors for *S. aureus* BSI-associated IE, and these are summarized in table 2. Major risk factors include persistent bacteremia, persistent fever, an unknown source of infection, the presence of prosthetic heart valves, and community acquisition. A previous episode of IE and injection drug use have also been defined as risk factors for IE [38, 40–42]. Although the risk of IE is higher among patients with prosthetic heart valves (43%–51%) than among those without these devices [39, 43], *S. aureus* is currently the primary etiological agent for all types of IE [6], highlighting its ability to infect native valves, even those that are structurally normal [44].

The absence of a documented source of infection and the development of complications are independent risk factors for mortality and are more frequently associated with CA-BSI than with nosocomial BSI [24]. Recent data show that the overall increase in the incidence of *S. aureus* BSI is mainly attributable to an increase in the incidence of MRSA infection [24, 45] and that patients with MRSA BSI have worse prognoses and increased risk of mortality, compared with those with BSI caused by methicillin-susceptible *S. aureus* (MSSA) or other pathogens [5, 17, 41, 46]. The worse prognoses and increased mortality may be attributable, in part, to a higher incidence of comorbidities among patients with MRSA infection and to the fact that patients with MRSA infection more frequently receive inappropriate empirical therapy or are treated with vancomycin, which has been associated with treatment failure and relapse of infection [47–52]. Among patients with MRSA BSI treated with vancomycin, those for whom the vancomycin MIC is ≥1.5 µg/mL have the highest risk of treatment failure [50] and mor-

tality [51]. Overall, the prognosis of *S. aureus* IE is poorer when there are associated complications that preclude valve replacement surgery (e.g., persistent bacteremia, embolic events, and multiorgan failure) or when the patient has non-IE-related comorbidities [53]. Similarly, MRSA IE is associated with a worse prognosis, compared with MSSA IE (table 3) [6, 53, 54]. The mortality associated with MRSA IE varies depending on the patient population but is particularly high among patients with nosocomial infections (67%) [53]. A study that reviewed outcomes in patients with MRSA IE who were receiving hemodialysis reported a mortality rate of 90%; however, this retrospective analysis included only 10 patients who were receiving hemodialysis [54].

Although the risk of developing complications of secondary BSI is lower than the risk of developing complications of primary BSI, the complications of secondary BSI are not insignificant. Catheter-related *S. aureus* BSI is associated with a 13% incidence of hematogenous complications, including septic arthritis, vertebral osteomyelitis, and IE [55]. An experimental model of IE revealed that both the percentage of damaged heart valves that subsequently became infected and the number of colony-forming units per valve were related to the size of the inocula [56]. Consistent with this finding, the risk of developing IE increases as the duration of time that the source of infection remains untreated increases, probably because of an increased number of bacteria entering the bloodstream [57]. Prompt management of the primary source of infection in secondary BSIs (e.g., removal of an intravenous catheter) is therefore recommended to reduce the risk of complications. However, con-

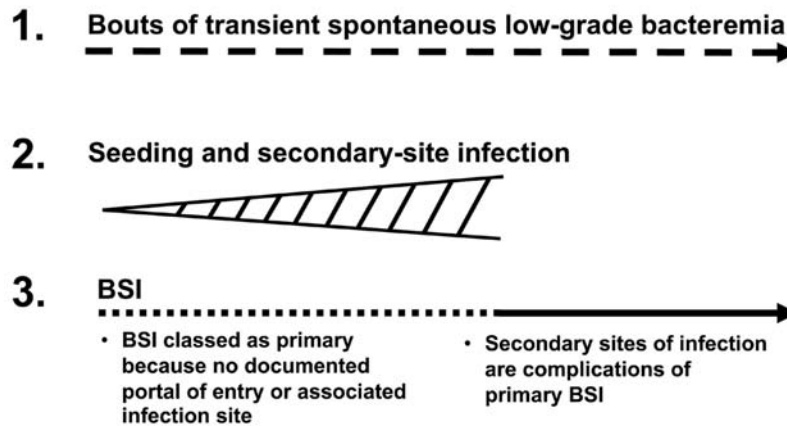


Figure 1. Primary bloodstream infections (BSIs) as a continuum in which secondary seeding can give rise to complications. (1) Episodes of spontaneous low-grade bacteremia may occur repeatedly during normal activities, usually without clinical repercussions. The portal of entry is breached in colonized skin or mucosa. (2) Occasionally, such spontaneous events may result in organ seeding, creating an infected microfocus that will enlarge over time. (3) The microfocus is responsible for discharging bacteria at an increasing frequency, resulting first in primary BSI and then in bacteremia with an identifiable focus.

tinued vigilance is still required, because undetected seeding of bacteria to other sites may have already occurred, and complications may not become apparent until days or weeks after the initial seeding.

The clinical presentation of *S. aureus* BSI in children is different from that in adults [58, 59]. One study revealed that, although children had similar rates of primary and secondary BSIs [59], 86% of *S. aureus* BSIs in infants without a preexisting medical condition had a clinically recognized focus, mostly in osteoarticular sites (59%). In that study, very few children developed IE (1.4% of children), and the mortality associated with *S. aureus* BSIs in infants was low (~0.7%). However, higher prevalence of IE and mortality rates have been reported for pediatric patients with *S. aureus* bacteremia. In a prospective single-center study, 11.8% of children with *S. aureus* bacteremia had definite IE, and 7.8% had possible IE; the combined mortality rate was 40% among children with definite or possible IE [60].

ORIGIN OF *S. AUREUS* ISOLATES IN BSIs

The nares are the main reservoir for *S. aureus* in humans. Approximately 25% of healthy adults are colonized with *S. aureus*, and 1.5%–3.0% are persistently colonized with MRSA [61–63]. Permanent colonization of the nares is more frequent in infants than in adults [64], and persistent carriers are usually members of groups at high risk of infection, such as patients with type I diabetes mellitus, injection drug users, and patients receiving hemodialysis who have extensive skin disease [65–67].

Nasal carriage plays an important role in the pathogenesis of infection. It is associated with an increased risk of *S. aureus* infection after surgery and in patients receiving renal replace-

ment therapy comprising either ambulatory peritoneal dialysis or hemodialysis. One study demonstrated that the vast majority (82.2%) of isolates from cultures of blood samples from patients with *S. aureus* BSI were indistinguishable from the isolates from nares samples from the same patients, and 85.7% of *S. aureus* nasal carriers who developed BSI had identical strains at both sites [64].

Farm animals may represent an additional reservoir for CA-MRSA strains. Recent studies in Europe and worldwide have demonstrated the transmission of MRSA from pigs and veal calves to farmers and veterinarians [68, 69].

PREVENTION AND TREATMENT OF *S. AUREUS* BSIs

Carriers of *S. aureus* who undergo medical procedures are at risk of developing bacteremia. Coello et al. [70] found that ~11% of patients who were colonized with MRSA at hospital admission developed nosocomial MRSA infection, and Pujol et al. [71] found that ~22% of patients colonized with *S. aureus* at the time of admission to the intensive care unit developed bacteremia. MRSA infection was associated with previous use of antibiotics, the presence of ulcers or surgical wounds, and the use of tubes, drains, and catheters [70, 71]. Early commentators suggested that the highest risk of bacteremia occurs during the period immediately after colonization; however, more-recent studies suggest that the risk of infection and mortality may be higher during the first year after colonization (33%) than it is during the second (27%) and third (16%) years [72] or that the risk of infection and mortality may be completely unrelated to the duration of MRSA colonization [73].

These data support the use of methods for decolonization

Table 2. Risk factors for infective endocarditis after *Staphylococcus aureus* bacteremia

Reference	Year	No. of patients	Risk factor
Fowler et al. [35]	2003	724	Community acquisition, persistent fever, persistent bacteremia, and skin examination findings that suggest acute systemic infection
Chang et al. [38]	2003	505	Valvular heart disease, prosthetic valve, previous infective endocarditis, injection drug use, unknown source of bacteremia, persistent bacteremia, nonwhite race, and community acquisition
El-Ahdab et al. [39]	2005	51 ^a	Persistent fever and persistent bacteremia
Hill et al. [40]	2007	132	Unknown source of bacteremia, prosthetic valve, persistent fever, and persistent bacteremia

^a All of these patients had prosthetic valves.

in MRSA nasal carriers who are admitted to the hospital or who are scheduled to undergo inpatient procedures in the near future [73]. Nasal decolonization is effective in a high proportion of patients. A success rate of 87% was achieved after implementation of a decolonization regimen that combined topical treatments (e.g., mupirocin nasal ointment, chlorhexidine mouth rinse, and full-body washes with chlorhexidine soap for 5 days) for nasal and skin colonization with oral vancomycin and trimethoprim-sulphamethoxazole for intestinal and urinary colonization, respectively, and povidone-iodine, chlorhexidine ovula, or octenidine solution for vaginal colonization [74, 75]. With regard to topical mupirocin, a recent study reported a high incidence of resistance in MRSA strains (resistance in 13% of strains and high-level resistance in 9%), despite low levels of in-hospital mupirocin use [76]. Oral administration of rifampicin and doxycycline has also proven to be successful for decolonization [77]. Guidelines recommend screening for MRSA, with prophylaxis for patients at high risk of infection, and preventative measures, such as improved nursing practices, the use of aseptic techniques for catheter placement, and decontamination practices, have proved to be effective against both MRSA and MSSA colonization [78–80]. However, the long-term effects of MRSA decolonization on the incidence of infection remain unclear.

Immunotherapy is a potential preventative strategy that has attracted commercial interest. Several candidates are being investigated in clinical trials; however, 2 of the most advanced compounds—the StaphVAX vaccine and INH-A21, a polyclonal antibody—did not demonstrate adequate protection in phase III clinical trials [81–83]. Trials of the StaphVAX vaccine in patient populations at high risk of infection have recently been completed, and publication of the results is anticipated [84]. In addition to the difficulties in implementing vaccination and/or prophylaxis against an evolving and virulent pathogen

such as *S. aureus*, many relevant epidemiological questions remain unanswered. Which populations should be targeted for vaccination? What is the risk of *S. aureus* BSI in healthy carriers? What is the potential value of MRSA screening for all patients admitted to the hospital or for hospital inpatients in settings with a high prevalence of CA-MRSA or nosocomial MRSA infection, respectively, and what sites should be tested? Which prophylactic treatments are best able to penetrate into the mucosal cells of the nostrils, and are the vaccines able to elicit immunity at this site?

The optimal strategies for treatment of *S. aureus* bacteremia and BSI are still a matter of much debate, and this subject is covered in more detail in an article by Corey [85] in this supplement. No clear guidelines exist for the treatment of *S. aureus* BSI without associated secondary infections; however, treatment for at least 2 weeks with penicillinase-stable β -lactam antibiotics (e.g., nafcillin or cloxacillin) has been recommended for MSSA infection [86]. When there are secondary foci, treatment should adhere to the recommendations for the specific complications [87–90]. The proportion of MRSA isolates is increasing in many countries [91]. Vancomycin is currently the recommended treatment for MRSA BSI, but the rate of treatment failure remains high [8]. Vancomycin is less effective than β -lactams against MSSA infection [49, 92], and there is evidence of a vancomycin MIC creep for both MSSA and MRSA [93]. This evidence has caused increasing concerns about the appropriateness of vancomycin for the treatment of both MSSA and MRSA infections [51, 52, 94] and has led to consideration of the use of more-recently introduced antibiotic agents, such as daptomycin, which has demonstrated efficacy comparable to that of the standard of care for MSSA or MRSA complicated skin and soft-tissue infections and bacteremia with or without IE [8, 95]. The limited success of current treatments for MRSA infection indicates that many challenges are yet to be overcome.

Table 3. Frequency of surgical procedures and mortality associated with methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) infective endocarditis (IE).

Study, type of IE	Type of valve(s)	No. of patients	Frequency of surgical procedures, %	In-hospital mortality, %
Fowler et al. [6]				
MSSA	NV and PV	283	37.5	23.3
MRSA	NV and PV	141	39.0	29.8
Miró et al. [37]				
MSSA	NV	248	24.6	23.2
MRSA	NV	43	25.6	37.2
Hill et al. [53]				
MSSA	NV and PV	56	68	30 ^a
MRSA	NV and PV	16	38	56 ^a

NOTE. NV, native valve; PV, prosthetic valve.

^a Six-month mortality.

CONCLUSIONS

To fully appreciate the risks associated with *S. aureus* BSIs and the implications of these risks for management strategies, the progression from bacteremia to BSI should be considered as a continuum of pathology. The risk of developing MSSA or MRSA bacteremia is related to the source of infection; MRSA bacteremia is more frequently associated with health care environments, whereas MSSA bacteremia is more frequently associated with community settings. Primary *S. aureus* BSIs are often the expression of deep-seated infections that have not been diagnosed and, thus, deserve serious consideration. *S. aureus* carriers are at high risk of developing BSIs, and patients with underlying conditions have an increased risk of developing associated complications. Improved eradication and control strategies are needed to successfully combat the challenges presented by *S. aureus* BSIs.

Acknowledgments

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

Financial support. Spanish Network for Research in Infectious Diseases, Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo (REPI RD06/0008 to J.M.M., A.D.R., C.C., and A.M.; FIS 05/0170, 08/0268, and EC08/00190 to J.M.M., A.D.R., and A.M.), and Institut d'Investigacions Biomèdiques August Pi i Sunyer (to J.M.M.).

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. J.M.M. has received speaking honoraria from, has served on advisory boards for, and/or has received research grants from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Cubist, Novartis, GlaxoSmithKline, Gilead Sciences, Merck, Pfizer, Roche, and Ther-

avance. P.M. has received research support from and has served as an advisor for Johnson & Johnson, Novartis, and Wyeth. All other authors: no conflicts.

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