for these clinical manifestations, we also highlight the paucity of high-quality evidence for many key clinical questions.

INTRODUCTION

Staphylococcus aureus is both a commensal bacterium and a human pathogen. Approximately 30% of the human population is colonized with *S. aureus* (1). Simultaneously, it is a leading cause of bacteremia and infective endocarditis (IE) as well as osteoarticular, skin and soft tissue, pleuropulmonary, and device-related infections. Our aim in this review is to summarize recent developments in the epidemiology, pathophysiology, clinical manifestations, and management of these key *S. aureus* clinical infection syndromes. We do not address in any significant depth issues regarding colonization or mechanisms of drug resistance and refer readers to recent reviews (1–6).

STAPHYLOCOCCUS AUREUS BACTEREMIA

Bacteremia is perhaps the best-described manifestation of *S. aureus* infection. Multiple studies have now documented the prevalence, prognosis, and outcome of *S. aureus* bacteremia (SAB) in industrialized regions of the world. However, many basic questions about the epidemiology of SAB, particularly in the world's nonindustrialized regions, remain unanswered. Furthermore, there continues to be a paucity of high-quality evidence to guide the management of SAB.

Epidemiology

Longitudinal trends. In the industrialized world, the population incidence of SAB ranges from 10 to 30 per 100,000 person-years (7). Longitudinal data from Denmark provide considerable insight into the impact of changes in access to health care interventions on SAB incidence. Between 1957 and 1990, the incidence of SAB increased from 3 per 100,000 person-years to 20 per 100,000 person-years (8). Rates of both hospital admissions and invasive medical interventions increased exponentially in Denmark during the same period. As a result, nosocomial acquisition was a key contributor to these overall increases in the incidence of SAB. Since 1990, however, the overall SAB incidence in Denmark has been relatively stable at ~21.8 per 100,000 person-years (9).

While overall rates of SAB may have stabilized over the past 20 years, the contribution of methicillin-resistant *S. aureus* (MRSA) has fluctuated. For example, in Quebec, Canada, the incidence of MRSA bacteremia increased from 0 per 100,000 person-years to 7.4 per 100,000 person-years from 1991 to2005, despite stable rates of methicillin-susceptible *S. aureus* (MSSA) bacteremia during the same period (10). Similar trends of increasing MRSA bacteremia incidence over this time period were seen in Minnesota from 1998 to 2005 (11); Calgary, Canada, from 2000 to 2006 (12); and Oxfordshire, United Kingdom, from 1997 to 2003 (13). In North America, epidemic community-associated clones of MRSA (e.g., USA300) have been largely responsible for the increase in the incidence of MRSA bacteremia (12, 14), while in the United Kingdom, epidemic health care-associated clones of MRSA (United Kingdom EMRSA-15 and EMRSA-16) have been responsible (15). Since 2005, most of these same regions have experienced significant reductions in rates of MRSA bacteremia, almost certainly linked to improvements in infection control procedures. These reductions were especially evident in the United Kingdom, where rates of MRSA bacteremia were halved between 2004 and 2011 (16, 17), but have also been documented in the United States (18), Australia (19), and France (20).

Nonindustrialized settings. Far less is known about the incidence and burden of SAB in the nonindustrialized and newly industrialized regions of the world. Although the overall incidence of community-acquired SAB during 2004 to 2010 in northeast Thailand was 2.5 per 100,000 person-years (21), this study reported incidence rates for community-acquired SAB only. Incomplete case ascertainment may also have contributed to this low reported incidence. In contrast, the incidences of SAB were 27 per 100,000 person-years among children <5 years of age in Kilifi, Kenya (22); 48 per 100,000 person-years among children <15 years of age in Manhica District, Mozambique (23); and 26 per 100,000 person-years among children <13 years of age in Soweto, South Africa (24). Collectively, these reports underscore the clear need for population-based studies to determine the burden of *S. aureus* in nonindustrialized regions of the world.

Risk groups. Age is a powerful determinant of SAB incidence, with the highest rates of infection occurring at either extreme of life (7, 10–12, 14, 25–28). Studies consistently demonstrate high rates in the first year of life, a low incidence through young adulthood, and a gradual rise in incidence with advancing age. For example, the incidence of SAB is >100 per 100,000 person-years among subjects >70 years of age (7) but is only 4.7 per 100,000 person-years in younger, healthier U.S. military personnel (29). Male gender is consistently associated with increased SAB incidence (10, 14, 25, 26, 29), with male-to-female ratios of ~1.5. The basis for this increased risk is not understood.

The incidence of SAB is also associated with ethnicity. In the United States, the incidence of invasive MRSA in the black population (66.5 per 100,000 person-years) is over twice that in the white population (27.7 per 100,000 person-years) (14, 18). In Australia, the incidence of SAB in the indigenous population is 5.8 to 20 times that of nonindigenous Australians (30–32). Similarly, Maori and Pacific Island people have significantly higher rates of incidence of SAB than do those of European ethnicity in New Zealand (33, 34). Differences in markers of the socioeconomic status of indigenous compared to nonindigenous populations do not fully explain the disparity between these groups (31). The contribution of host genetic susceptibility to these ethnic differences has not yet been investigated.

The HIV-infected population has a significantly increased incidence of SAB. Two studies reported incidences of SAB in HIV-infected patients of 494 per 100,000 person-years (35) and 1,960 per 100,000 person-years (36), or 24 times that of the non-HIV-infected population (35). Although much of this increase results from high rates of injection drug use in the HIV-infected population, even the non-injection drug-using HIV-infected population exhibits higher rates of SAB than those in the non-HIV-infected population (35). Among HIV-infected individuals, a low CD4 count was independently associated with SAB. Also, compared to injection drug users (IDUs), men who have sex with men (MSM) were likely to have a low CD4 count and to have nosocomial SAB (35). Thus, HIV-infected IDUs tend to acquire community-onset SAB as a consequence of injection drug use, whereas MSM have higher rates of nosocomial SAB.

The high risk of SAB in the overall IDU population can be inferred from a Dutch study that monitored 758 IDUs for 1,640 person-years and determined that there were 10 confirmed episodes of *S. aureus* IE (37). Based on these figures, the incidence of

TABLE 1 Incidence of *S. aureus* bacteremia per 100,000 person-years in different subpopulations and geographical regions

Population	Region(s)	Time period (yr)	Incidence per 100,000 person-years for all *S. aureus* isolates (incidence for MRSA isolates)[a]	Reference
All	Denmark	1957–1990	3–20 (NA)	8
Adults ≥21 yr of age	Denmark	1981–2000	18.2–30.5 (NA)	49
All	Denmark	1995–2008	22.7 (0.18)	9
Adults ≥18 yr of age	Iceland	1995–2008	24.5 (0.15)	25
All	Finland	1995–2001	14 (<0.14)	27
All	7 countries	2000–2008	26.1 (1.9)	7
All	Sweden	2003–2005	33.9 (0)	55
All	Finland	2004–2007	20 (NA)	50
All	Netherlands	2009	19.3 (0.18)	51
All	North Rhine-Westphalia, Germany	2009	NA (5.76)	51
Adults ≥18 yr of age	Quebec	1991–2005	24.1–32.4 (0–7.4)	10
Adults ≥18 yr of age	Olmsted County, MN, USA	1998–2005	38.2 (12.4)	11
All	New Zealand	1998–2005	21.5 (0.08)	26
All	Calgary, Canada	2000–2006	19.7 (2.2)	12
All	USA	2004–2005	NA (31.8)	14
All, military	USA	2005–2010	4.7 (2)	29
All	NT, Australia	2006–2007	65 (16)	30
All	Australia	2007–2010	11.2 (16)	31
All, CA	Northeast Thailand	2004–2010	2.6 (0.1)	21
Children ≤20 yr of age	Denmark	1971–2000	4.5–8.4 (NA)	52
Children ≤18 yr of age	Calgary	2000–2006	6.5 (0.05)	53
Children <5 yr of age	Kenya	1998–2002	27 (NA)	22
Children <15 yr of age	Mozambique	2001–2006	48 (4.3)	23
Children <5 yr of age	Ghana	2007–2009	630 (105)	54
Children <13 yr of age	South Africa	2005–2006	26 (10)	24
HIV, ≥16 yr of age	Denmark	1995–2007	494 (4.9)	35
HIV, adult	USA	2000–2004	1,960 (850)	36
Hemodialysis	Ireland	1998–2009	17,000 (5,600)	42
All dialysis	Taiwan	2003–2008	1,809 (1,131)	41

[a] NA, not available.

SAB was at least 610 per 100,000 person-years. In the setting of injection of material into the bloodstream, additional factors contributing to the high incidence of SAB include an increased prevalence of *S. aureus* colonization compared to that in the general population (38), frequent skin and soft tissue infections (SSTIs) (39), and a drug-using environment that facilitates the person-to-person transmission of *S. aureus* (40).

Hemodialysis patients are also at a greatly increased risk of SAB. The incidences of SAB in hemodialysis-dependent patients were 3,064 per 100,000 person-years in Taiwan (41), 17,900 per 100,000 person-years in Ireland (42), and 4,045 to 5,015 per 100,000 person-years in the United States (18). The predominant risk factor for these patients is the presence of an intravascular access device and in particular the use of a cuffed, tunneled catheter (e.g., permacath) for dialysis (42). However, other host factors that result in an impairment of the host immune defense, including neutrophil dysfunction (43), iron overload (44), diabetes (45), and increased rates of colonization (45), may also increase the likelihood of invasive *S. aureus* infections. The infrequent vancomycin dosing strategy often used among hemodialysis-dependent patients may not maintain an adequate trough level in high-flux, large-pore-size artificial kidneys (46–48), increasing the risk for relapsing SAB.

Table 1 summarizes the incidences of SAB from the above-mentioned studies and other studies (49–55).

Clinical Manifestations

Although there are many different primary clinical foci or manifestations of SAB, there are consistent patterns across cohorts. In several recent studies involving consecutive patients with either SAB (MSSA and MRSA) (12, 31, 32, 56–60) or only MRSA bacteremia (61–66), common primary clinical foci or sources of infection are vascular catheter-related infections, SSTIs, pleuropulmonary infections, osteoarticular infections, and IE (Table 2). These common primary clinical foci represent a subset of the common general clinical manifestations of *S. aureus* infections. However, a focus of infection is not found in ~25% of cases.

As the clinical epidemiology of *S. aureus* infections changes, it is likely that the proportion of cases of SAB with these individual primary clinical foci will change. For example, reductions in catheter-related infections following improved infection control practices and implementation of central line bundles have resulted in catheter-related SAB contributing to a smaller fraction of all cases of SAB (67). Similarly, rates of SSTI-associated SAB are highest in communities with large numbers of cutaneous infections. Examples include an increase in the incidence of USA300 community-

TABLE 2 Primary foci of infection in cohorts with *S. aureus* bacteremia[a]

Region (reference)	% of MRSA cases in cohort	% of HCA cases in cohort	No. (%) of cases with focus of infection							Total no. of cases
			Infective endocarditis	Osteoarticular	SSTI	Pleuropulmonary	Line related	No focus/unknown	Other	
Central Australia (32)	21.6	25.6	9 (7.2)	20 (16)	42 (34)	11 (8.8)	9 (7.2)	30 (24)	4 (3.2)	125
Australia (59)	24.8	79.1	433 (6)	956 (13)	1,415 (20)	519 (7.2)	1,387 (19)	1,100 (15)	1,421 (20)	7,231
Sydney, Australia (65)	100	92	15 (3.8)	37 (9.3)	80 (20)	52 (13)	140 (35)	40 (10)	35 (8.8)	399
Calgary, Canada (12)[b]	11.3	75.3	79 (5.5)	227 (16)	224 (16)	220 (15)		586 (41)	104 (7.2)	1,440
Missouri, USA (64)	100	92.6	0 (0)	0 (0)	39 (24)	0 (0)	37 (23)	70 (43)	17 (10)	163
New York, USA (61)	100	97.9	91 (14)	72 (11)	112 (17)	55 (8.4)	302 (46)	0 (0)	20 (3.1)	652
Birmingham, UK (66)	100	99.5	6 (3.1)	3 (1.5)	37 (19)	0 (0)	73 (37)	68 (35)	8 (4.1)	195
Italy (57)	53.9	85.5	0 (0)	0 (0)	14 (9.3)	7 (4.6)	23 (15)	104 (69)	3 (2)	151
Israel (56)	42.8	100	55 (4.4)	71 (5.6)	294 (23)	144 (11)	172 (14)	298 (24)	227 (18)	1,261
Thailand (58)	27.6	55.1	8 (11)	9 (12)	20 (27)	16 (22)	10 (14)	0 (0)	10 (14)	73
South Korea (63)	100	95.1	9 (3.4)	16 (6)	35 (13)	24 (9)	132 (49)	36 (13)	16 (6)	268
Japan (62)	100	NA	0 (0)	0 (0)	17 (15)	10 (8.7)	27 (23)	23 (20)	38 (33)	115
Multisite (60)	11.7	NA	282 (8.3)	456 (13)	502 (15)	178 (5.2)	942 (28)	641 (19)	394 (12)	3,395
Total										15,468

[a] The mean percentages of patients for each primary focus of infection from all the studies were as follows: 5% for infective endocarditis, 8% for osteoarticular, 19% for SSTI, 9% for pleuropulmonary, 26% for line related, 24% for no focus/unknown, and 11% for other foci. MRSA, methicillin-resistant *S. aureus*; HCA, health care associated; SSTI, skin and soft tissue infection.

[b] Line-related bacteremia was not reported in this study.

associated MRSA (CA-MRSA) bacteremia with the widespread emergence of USA300 MRSA SSTIs (68) as well as high incidences of both SSTI and SAB in indigenous populations (30).

SAB can be classified as "complicated" or "uncomplicated." These designations have significant implications for the extent and type of diagnostic evaluation, duration of antibiotic treatment, and overall prognosis. A single-center study of 724 episodes of SAB defined complicated infection as one that resulted in attributable mortality, central nervous system (CNS) involvement, an embolic phenomenon, metastatic sites of infection, or recurrent infection within 12 weeks (69). Predictors of complicated SAB were community acquisition, positive follow-up blood cultures at 48 to 96 h, persistent fever at 72 h, and skin findings suggesting an acute systemic infection (petechiae, vasculitis, infarcts, ecchymoses, or pustules) (69). The association between positive follow-up blood cultures and persistent fever with complicated SAB and subsequently poorer outcomes has been independently validated, as recently reviewed (70). The primary source of infection also predicts 30-day mortality, with higher mortality rates for bacteremia without a focus (22 to 48%), IE (25 to 60%), and pulmonary infections (39 to 67%), compared to lower rates for catheter-related bacteremia (7 to 21%), SSTIs (15 to 17%), and urinary tract infections (UTIs) (10%) (70). Similar findings have recently been described in a pooled analysis of five prospective observational studies (60).

Outcomes and Management

In the preantibiotic era, the case fatality rate (CFR) for SAB was ~80% (71). Although the introduction of penicillin to treat SAB immediately reduced this high mortality rate (72), CFRs for SAB have plateaued at 15 to 50% over the past several decades (70). This lack of improvement in patient outcomes reflects both a relative plateau in antibiotic efficacy and larger numbers of older, "sicker" patients that now acquire SAB. Indeed, predictors of mortality from SAB include increasing age; the presence of comorbid conditions; the source, extent, and persistence of infection; and failure to remove eradicable foci (70). Guidelines for the management of SAB are available (73–76), and evidence to support various recommendations has been comprehensively reviewed (77). A striking impression from these documents is the poor quality of evidence that informs clinical management of SAB. For example, in a recent systematic review of evidence for the role of transesophageal echocardiography (TEE) and optimal antibiotic therapy in SAB, only one study met GRADE (grading of recommendation, assessment, development, and evaluation) criteria for high-quality evidence (78). Robust clinical trials are needed to address many outstanding questions regarding the management and treatment of this common and potentially lethal infection.

Despite the need for further high-quality evidence, broadly accepted key tenets in the management of SAB include (i) defining patients as having either uncomplicated or complicated infection; (ii) identifying and removing infected foci; and (iii) applying appropriate antimicrobial therapy with regard to the agent, dose, and duration. The Infectious Diseases Society of America (IDSA) has published guidelines with the following criteria to define uncomplicated SAB: (i) exclusion of IE by echocardiography, (ii) no implanted prostheses, (iii) negative results of follow-up blood cultures drawn 2 to 4 days after the initial set, (iv) defervescence within 72 h after the initiation of effective antibiotic therapy, and (v) no evidence of metastatic infection (79). Any other patient should be considered to have complicated SAB. Establishing the status of individual patients with regard to each of these criteria allows appropriate decisions to be made about subsequent treatment duration.

Infectious diseases consultation. An infectious diseases (ID) consultation can play a key role in facilitating the process of appropriate investigation and management of patients with SAB. ID consultation for patients with SAB is associated with higher rates of various quality-of-care metrics, including (i) obtaining follow-up blood cultures to assess the clearance of SAB (80–86), (ii)

obtaining an echocardiograph (69, 81, 83, 85, 87, 88), (iii) removing infected foci (80, 86, 89), (iv) providing a longer duration of treatment for complicated SAB (80–84, 86–89), and (v) administering β-lactam antibiotics for MSSA infections (80, 81, 83, 86, 88, 89). Eleven studies also reported that ID consultation for SAB is associated with reduced patient mortality rates (61, 62, 80–85, 87, 88, 90). Collectively, these results suggest that ID consultation should be regarded as the standard of care in institutions where this subspecialty service is available.

Role of transesophageal echocardiography. Imaging of the cardiac valves is required to determine if there is underlying IE present in a patient with SAB. However, whether transesophageal echocardiography (TEE) is required in all such patients is unresolved. Among four studies that evaluated IE with both TEE and transthoracic echocardiography (TTE), rates of detection of IE were higher with TEE (14 to 25%) than with TTE (2 to 14%) (91–94). However, the increased sensitivity of TEE for the detection of IE compared to that of TTE needs to be balanced by the associated costs, risks, and availability of TEE. Esophageal perforation occurs in ~1 in 5,000 TEEs performed (95). To risk stratify situations where TEE may not be required, a number of studies have proposed criteria to identify a low-risk subset of patients with SAB: (i) negative TTE results (92, 96), (ii) nosocomial acquisition of bacteremia (96, 97), (iii) negative follow-up blood cultures (93, 98), (iv) absence of an intracardiac device (92, 93, 96–98), (v) absence of hemodialysis dependence (98), and (vi) no clinical signs of endocarditis or metastatic foci (92, 93, 97, 98). Currently, it may be reasonable to avoid TEE in patients meeting all of these criteria. However, such recommendations would clearly be strengthened by a prospective trial with robust clinical outcomes comparing universal TEE to only targeted TEE for those patients with low-risk features.

Antibiotics. The recommended duration of intravenous (i.v.) antibiotics for uncomplicated SAB is at least 2 weeks. In a recent prospective cohort study of uncomplicated SAB (as defined by IDSA criteria), receipt of antibiotic therapy for <2 weeks was associated with a relapse rate of 8% (compared to 0% for those treated for at least 2 weeks) (99). This relapse rate is consistent with the 6% rate of late complications (inclusive of relapse and metastatic complications) for intravascular catheter-associated SAB treated for <2 weeks identified in a 1993 meta-analysis of 11 studies (100). Although a few observational studies have suggested that as little as 7 days of i.v. antibiotics may be adequate (reviewed by Thwaites et al. [77]), such abbreviated courses must be regarded as investigational pending robust, generalizable evidence. Until such evidence exists, all patients with uncomplicated SAB should receive at least 2 weeks of i.v. antibiotics (73, 78, 79). Two-week courses of therapy, both with (101–104) and without (102) adjunctive aminoglycosides, have also been used successfully for uncomplicated, IDU-associated, right-sided *S. aureus* IE. Cure rates in these studies ranged from 77 to 94% (101–103, 105) and were similar for those who did and those who did not receive adjunctive aminoglycosides. However, cure rates were lower for patients who received glycopeptides (e.g., vancomycin and teicoplanin) than for those receiving antistaphylococcal penicillins (101, 105). Thus, patients being treated with vancomycin for right-sided IE should receive >2 weeks of therapy. For complicated SAB, 4 to 6 weeks of i.v. therapy has been the standard practice for over half a century and continues to be recommended (73, 75, 79, 106).

There is evidence that β-lactam therapy is better than glycopeptides for MSSA bacteremia from both randomized controlled trials (RCTs) (104, 105, 107) and observational studies (108–118). Vancomycin and daptomycin are currently the only antibiotics that are approved by the U.S. Food and Drug Administration (FDA) for MRSA bacteremia and right-sided IE. The sole high-quality RCT involving patients with MRSA bacteremia demonstrated that for the MRSA subgroup, daptomycin at 6 mg/kg of body weight i.v. once daily was noninferior to vancomycin (119). Treatment success at 42 days after completion of therapy was found for 20/45 (44%) daptomycin recipients, versus 14/44 (32%) patients receiving vancomycin plus low-dose, short-course gentamicin (absolute difference, 12.6%; 95% confidence interval [CI], −7.4% to 32.6%; $P = 0.28$). Vancomycin has also been compared to teicoplanin (120), trimethoprim-sulfamethoxazole (TMP-SMX) (121), linezolid (122, 123), and dalbavancin (124) in open-label RCTs. None of these antibiotics were shown to be significantly superior to vancomycin. Thus, at this stage, vancomycin and daptomycin are the first-line therapies for MRSA bacteremia.

INFECTIVE ENDOCARDITIS

S. aureus is now the most common cause of IE in the industrialized world (125). Due to its propensity to cause severe disease and its frequent antibiotic resistance, *S. aureus* is a dreaded cause of IE. Although our ability to rigorously study IE was previously limited by its relative infrequency at any single institution, large multinational collaborations such as the International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) (126) and robust population-level studies (127–129) have provided critical insights into the epidemiology and prognosis of IE in general and *S. aureus* IE in particular.

Epidemiology

Traditionally, the overall incidence of IE was estimated to be 1.5 to 6 per 100,000 person-years. These figures were derived from a systematic review of studies from Europe and the United States with population-level data for the period from 1970 to 2000 (130). The proportion of IE cases due to *S. aureus* ranged from 16 to 34%, with no temporal trend to suggest microbiologic shifts. More recent studies, however, have identified important changes in the epidemiology of *S. aureus* IE. Based on data from a nationwide inpatient sample (NIS) in the United States, the incidence of IE was calculated to increase from 11.4 per 100,000 person-years in 1999 to 16.6 per 100,000 person-years in 2006 (131), with most of the increase in incidence being driven by an increase in the incidence of *S. aureus* IE. *S. aureus* IE was also associated with increased mortality compared to other causative pathogens, a finding in keeping with most contemporary studies (125, 132–135). In a separate analysis of this NIS data set, the incidence of IE increased from 9.3 per 100,000 person-years in 1998 to 12.7 per 100,000 person-years in 2009. The proportion of IE cases coded as being due to *S. aureus* increased from 24% to 32% between 1998 and 2009 (136).

Although the incidence of IE elsewhere in the industrialized world has been reported to be severalfold lower than that in the United States, *S. aureus* remains the most common causative agent in those regions. In France, the overall incidence of IE remained stable at ~3.5 per 100,000 person-years from 1991 to 2008, but the proportion of *S. aureus* IE increased from 16% to 26% during the same period (127). In Veluto, Italy, the incidence

of IE increased from 4.1 per 100,000 person-years to 4.9 per 100,000 person-years from 2000 to 2008. *S. aureus* predominated, causing ~40% of cases (128). Similarly, the incidence of IE in New South Wales, Australia, from 2001 to 2005 was 4.7 per 100,000 person-years. Again, *S. aureus* was the most common cause (32%) (129). Collectively, these studies confirm the predominance of *S. aureus* as a cause of IE across different industrialized countries. In contrast, the epidemiology of IE in nonindustrialized or newly industrialized settings involves primarily viridans group streptococci as the major pathogen infecting rheumatic heart valves (137–141).

It is apparent from population-based studies in industrialized regions (127–129, 142) and the prospective cohort studies from the ICE-PCS cohort (125, 132, 133, 143, 144) that the prevalence of health care-associated IE, particularly due to *S. aureus*, has increased. For example, Benito and colleagues reported that over one-third (34%) of a large cohort of 1,622 non-IDU patients with native valve IE had health care-associated infections (133). Cases of health care-associated IE were more likely to be caused by *S. aureus* (125, 133, 142). Thus, in contrast to previous IE series where *S. aureus* comprised <10% of cases (71, 145), *S. aureus* is now consistently the cause of IE in >25% of cases (125–129, 146). In conclusion, *S. aureus* has emerged over the last decade to become the most common cause of IE in the industrialized world, with a primary risk factor for this infection being health care contact.

Prosthetic valve endocarditis. For patients with an underlying prosthetic valve, the yearly incidence of prosthetic valve IE ranges from 0.8 to 3.6% (147–149). *S. aureus* is now the most common cause of prosthetic valve IE (150, 151), responsible for 23 to 33% of cases (150, 152). This development is due in part to the frequency of *S. aureus* as a cause of health care-associated bacteremia and the high risk of hematogenous seeding of prosthetic valves by *S. aureus* once it gains access to the bloodstream. For example, in one prospective cohort study of patients with a prosthetic cardiac valve who developed SAB, the risk of IE was ~51% (153). Fang et al. (154) reported a similar risk for developing prosthetic valve IE (15 of 34 cases; 44%) in a subgroup of their patients with SAB. These results emphasize the high risk of prosthetic valve IE associated with SAB (153, 154) and indicate that all patients with a prosthetic valve who develop SAB should be evaluated for IE, preferably by TEE.

The probability of developing *S. aureus* prosthetic valve IE is highest within the first 12 months after valve replacement surgery (149, 150) and is likely associated with the incomplete endothelialization of the prosthetic valve after placement (150) and also ongoing health care contact (150). Two large studies found that patients with mechanical valves are at a significantly higher risk for early prosthetic valve IE than are patients with porcine prosthetic valves, although there was no difference in the cumulative 5-year risk (148, 149). In contrast, neither the location (e.g., aortic or mitral) nor the composition (e.g., mechanical versus bioprosthetic) of the valve appears to significantly increase the risk of having *S. aureus* prosthetic valve IE in bacteremic patients (149, 153).

Grover et al. found that the most significant predictor of prosthetic valve IE due to any pathogen was active IE at the time of implantation of the prosthetic valve (7.4% versus 0.9%) (147). Other risk factors for prosthetic valve IE are previous episodes of endocarditis, persistent bacteremia, health care-associated infections, and injection drug use (150). The presence of multivalvular disease as well as male sex are risk factors for early prosthetic valve IE (147, 149), while superficial wound infection (relative risk [RR], 3.5; $P = 0.004$) is a risk factor for late prosthetic valve IE (147). Although Wang et al. (150) found that the mean age of patients developing prosthetic valve IE is significantly older than that of patients with native valve IE (65 versus 56 years; $P < 0.001$), Guerrero et al. (146) reported no significant difference in age distribution regarding patients who have *S. aureus* native valve or prosthetic valve IE (60 versus 58 years; $P > 0.05$).

Pathophysiology

The formation of a nidus for bacterial colonization and infection begins with damage to the cardiac endothelium, either by direct trauma (e.g., intravascular catheters and electrodes, injected particulate matter from injection drug use, or turbulent blood flow resulting from valvular abnormalities) or inflammation (e.g., secondary to rheumatic heart disease or degenerative valvular disease). The exposure of subendothelial cells elicits the production of extracellular matrix proteins and tissue factor and the deposition of fibrin and platelets to form sterile vegetations. If these thrombotic vegetations become colonized by bacteria, IE can result (155).

S. aureus has a number of cell wall-associated factors that allow it to attach to extracellular matrix proteins, fibrin, and platelets (156). In particular, clumping factors A and B (ClfA and ClfB, respectively; also known as fibrinogen-binding proteins) are key for attachment to and colonization of the valvular tissue. Fibronectin-binding protein A (FnBPA) and FnBPB facilitate binding to both fibrinogen and fibronectin and also play a role in subsequent endothelial cell invasion and inflammation (157, 158). In addition, Clf, FnBP, and the serine-aspartate repeat protein SdrE induce platelet aggregation and activation (159, 160). These findings have been demonstrated in studies involving the knockout of genes encoding these proteins in *S. aureus* as well as experiments where the expression of these proteins in the normally nonpathogenic bacterium *Lactococcus lactis* results in the ability to cause IE (161, 162). More recent studies have determined the importance of host-derived ultralarge von Willebrand factor fibers in mediating adhesion (probably via cell wall teichoic acids) of *S. aureus* to intact endothelial cells (163) and the role of the prothrombin-activating proteins staphylocoagulase and von Willebrand factor-binding protein in binding prothrombin and converting fibrinogen into fibrin (164). Staphylococcal superantigens have also been shown to be critical to the formation of vegetations, probably through a combined effect of systemic hypotension and direct toxicity to endothelial cells (165).

Although *in vitro* and animal model studies have provided key experimental data in delineating the role of various virulence factors, studies involving large cohorts of patients are essential to link these clues with clinical disease. Several studies have described (166) and confirmed (167) that isolates with distinct bacterial genotypes are associated with specific disease phenotypes, including IE (166–168). For example, clinical *S. aureus* isolates within clonal complex 30 (CC30) have been shown to be significantly more likely to be associated with IE (166, 167) and are more likely to have adhesion- and superantigen-encoding genes such as *clfB*, *cna*, and *eap* (167). The relevance of this epidemiologic association was further strengthened by the recent observation that CC30

TABLE 3 Clinical and demographic characteristics of large cohorts of patients with *S. aureus* infective endocarditis[i]

Characteristic	Value reported in reference:					
	125	170	146	173	171	172
No. of patients	558	260	133	74	61	27
Region	Multinational	Denmark	Spain	Finland	France	Australia
Study type	Multicenter	Multicenter	Single center	Multicenter	Single center	Single center
Period (yr)	2000–2003	1982–1991	1985–2006	1999–2002	1990–2000	1991–2006
Age (yr)	57[a]	68[a]	NA	55[b]	57[b]	64[a]
No. (%) of patients						
Males	341 (61)	145 (56)	89 (77)	47 (64)	42 (69)	18 (67)
With acquisition type						
HCA	218 (39)	88[c] (33)	29[c] (22)	34[c] (46)	NA	26 (96)
Community	326 (58)	172 (67)	104 (78)	40 (54)	NA	1 (4)
IDU	117 (21)	0[d] (0)	62 (47)	20 (27)	NA	1 (4)
On dialysis	79 (14)	NA	NA	6 (8)	7 (11)	1 (4)
With diabetes	110 (20)	35 (13)	2 (6)	19 (26)	12 (20)	8 (30)
With intravascular device	159 (28)	23 (9)	NA	10 (14)	11 (17)	14 (52)
With native valve	401 (72)	215 (83)	113 (85)	57 (77)	55 (90)	17 (63)
With prosthetic valve	86 (15)	24 (9)	20 (15)	17 (23)	6 (10)	10 (37)
With location of vegetations						
Aortic	143 (29)	84 (32)	21 (16)	26 (35)	22 (36)	6 (22)
Mitral	224 (46)	100 (38)	42 (32)	22 (30)	28 (46)	15 (56)
Tricuspid/pulmonary	132 (27)	13 (5)	58 (47)	16 (22)	11 (18)	2 (7)
With MRSA	283/424 (67)	0 (0)	8 (6)	0[e] (0)	NA	27[f] (100)
With complication						
Stroke	119 (21)	91 (35)	30 (23)	13 (18)	21 (34)	9 (35)
Cardiac failure	161 (29)	139 (53)	36 (27)	NA	19 (31)	4 (15)
Intracardiac abscess	71 (13)	NA	12 (9)	3 (4)	14 (23)	3 (12)
With in-hospital mortality	125 (22)	164[g] (63)	37 (28)	17[h] (23)	21 (34)	15 (66)
With surgery	211 (38)	27 (10)	39 (29)	7 (9)	20 (33)	16 (59)

[a] Median age.
[b] Mean age.
[c] For several studies, only nosocomial versus community-onset data were collected.
[d] IDUs were excluded from the study.
[e] MRSA was excluded from the study.
[f] Only MRSA was reported in this study.
[g] This study included 83 patients not clinically known to have *S. aureus* IE but who were subsequently diagnosed at autopsy.
[h] This study referred to 28-day mortality.
[i] HCA, health care associated; IDU, intravenous drug user; MRSA, methicillin-resistant *S. aureus*; NA, not available.

isolates were more likely to cause IE in a rabbit endocarditis model than other common, clinically relevant strains (169).

Clinical Manifestations and Outcomes

The clinical manifestations of *S. aureus* IE are now well understood through the ICE-PCS cohort (125) as well as national cohorts (170) and long-term single-center studies (146, 171, 172). Patient characteristics associated with *S. aureus* IE include injection drug use, health care-associated infections, a shorter duration of symptoms prior to diagnosis, persistent bacteremia, the presence of a presumed intravascular device source, stroke, and diabetes mellitus (125, 171).

Table 3 outlines the major demographic and clinical features of *S. aureus* IE. Left-sided valvular disease is more common than right-sided disease, and the mitral valve is more commonly involved than the aortic valve, in a ratio of ~1.5:1. Right-sided disease is usually secondary to either injection drug use or the presence of a central catheter. However, *S. aureus* IE in IDUs is not restricted to the tricuspid valve. Approximately 30% of cases of IE in IDUs are left sided (125, 173). Complications for *S. aureus* IE are common, particularly for left-sided IE, in which embolism of the systemic circulation and heart failure frequently occur.

For those with SAB and a prosthetic valve, clinical manifestations suggesting *S. aureus* prosthetic valve IE are persistent fever (odds ratio [OR], 4.4; 95% CI, 1.0 to 19.1) and persistent SAB (OR, 11.7; 95% CI, 2.9 to 47.7) (153). Other clinical findings in *S. aureus* prosthetic valve IE are peripheral emboli, splenomegaly, or new regurgitant murmurs (174–177). El-Ahdab et al. (153) found that of patients with SAB and a prosthetic valve who underwent TEE, 23% showed valvular vegetation and 11% showed evidence of a valvular abscess. Patients with *S. aureus* prosthetic valve IE generally develop a new murmur less frequently than do patients with *S. aureus* native valve IE (146) and typically have a shorter duration of symptoms before a diagnosis is made (146).

Diagnosis of *S. aureus* IE is generally established by the application of modified Duke criteria (178), which incorporate a combination of factors, including history and physical exam, blood culture results, and echocardiography results. In a minority of cases, however, standard blood or tissue culture results will not detect *S. aureus*. Real-time PCR (RT-PCR) targeting 16S rRNA genes may

be a useful adjunct for the microbiological diagnosis of endocarditis in this setting (179). In an analysis of 48 patients in France with culture-negative IE, *S. aureus* was detected by PCR in 10/48 (20.4%) patients (180). In a similar analysis of 69 patients in the United Kingdom and Ireland with culture-negative IE, 2 patients had *S. aureus* infection identified by PCR of explanted valve tissue (181).

The overall mortality rate for *S. aureus* IE ranges from 22 to 66% and is consistently higher than those for other causes of IE. Across the broad categories of *S. aureus* IE, left-sided IE has a poorer prognosis than right-sided IE, health care-associated IE has a poorer prognosis than community-associated IE, prosthetic valve IE has a poorer prognosis than native valve IE, and non-IDU-associated IE has a poorer prognosis than IDU-associated IE (125, 173). In addition, consistent predictors of mortality are increasing age, stroke, and heart failure (125, 170). Stroke is a grave but frequent complication arising from *S. aureus* prosthetic valve IE, afflicting 23 to 33% of patients (177, 182, 183), and is a significant prognostic indicator of mortality (146, 177, 182, 183). Sohail et al. found that of patients with *S. aureus* prosthetic valve IE, an American Society of Anesthesiologists class IV status and the presence of bioprosthetic (compared to mechanical) valves were also independent predictors of mortality (177).

Management

Antimicrobial therapy. All patients with *S. aureus* IE require prolonged i.v. antibiotics. Detailed guidelines have been reported by professional societies in the United States and Europe (79, 106, 184, 185). An addition found in the most recent guidelines is the recognition of daptomycin as an option for treatment of *S. aureus* IE. In the key registrational trial, daptomycin was noninferior to standard therapy for SAB (119). On the basis of these results, daptomycin gained an indication for treatment of SAB and right-sided *S. aureus* IE, including infections due to MRSA. The relatively small number of patients in the trial with left-sided *S. aureus* IE ($n = 18$) prevented meaningful conclusions regarding daptomycin's utility in this setting. Nonsusceptibility to daptomycin developed in 5 of 45 patients with MRSA bacteremia (and 2 of 74 patients with MSSA) treated with daptomycin. Nonetheless, daptomycin treatment is now recommended in United Kingdom guidelines for native valve MRSA IE where the isolate has a vancomycin MIC of >2 mg/liter (106) and in IDSA guidelines for all cases of native valve MRSA IE (79). The recommended dose is 6 mg/kg, but higher doses (8 to 10 mg/kg) are increasingly being used and appear to be safe (186, 187). Registries for the use of daptomycin have included 86 patients with MRSA IE; outcomes appear favorable (186, 187). However, these were not comparative studies, and a large proportion of patients received concomitant therapy with other antibacterial agents. Carugati et al. (188) examined the ICE-Daptomycin substudy database and compared 29 patients (12 with *S. aureus* and 7 with MRSA) who received high-dose daptomycin (median, 9.2 mg/kg) with 149 patients (74 with *S. aureus* and 18 with MRSA) who received the standard of care for Gram-positive IE. Clearance of MRSA bacteremia was significantly faster in the daptomycin cohort than in the standard-of-care cohort (1.0 days versus 5.0 days).

The clinical syndrome of treatment-emergent nonsusceptibility to daptomycin in MRSA has been noted in a number of studies at rates of 11% (5 of 45 patients) (119), 11% (6/54) (187), 60% (6/10) (189), and 39% (7/18) (190). The risk of this phenomenon appears greatest in those patients without adequate source control (119), suboptimal daptomycin dosing (189), and persistent MRSA bacteremia (189, 190). To reduce the risk of treatment-emergent resistance and to provide the possibility for synergy, a number of investigators have evaluated the addition of a second antibiotic to daptomycin *in vitro* and in animal studies. These second agents have included gentamicin (191–198); rifampin (191–196, 198); β-lactam antibiotics (195, 199–204), including ceftaroline (202, 203); TMP-SMX (201); and linezolid (201). Clinical successes with combination therapy have also been reported with rifampin (205), TMP-SMX (206, 207), fosfomycin (208, 209), and β-lactams (210, 211). Unfortunately, an RCT comparing daptomycin to daptomycin combined with gentamicin was terminated after recruiting only 24 patients (ClinicalTrials.gov registration number NCT00638157). Thus, the role of combination therapy with daptomycin remains to be defined, and the development of treatment-emergent resistance to daptomycin must be closely monitored, particularly among patients with residual sites of infection or persistent bacteremia (212).

Various guidelines (79, 106, 184, 185) recommend that prosthetic valve MRSA IE be treated with a combination of vancomycin, gentamicin, and rifampin. These recommendations are based largely on expert opinion and on small retrospective studies of methicillin-resistant coagulase-negative staphylococci (CoNS) (213, 214). Given that neither rifampin nor gentamicin appears to improve outcomes for native valve *S. aureus* IE and that these antibiotics are in fact associated with adverse side effects (215, 216), there is a clear need for further research to determine the optimal antimicrobial therapy for prosthetic valve *S. aureus* IE.

Surgery. Recent studies have underscored the importance of early surgery in the treatment of IE in general and *S. aureus* IE in particular. Following a period of controversy over the results of various cohort studies and the lack of adjustment for bias in these studies (217–223), the benefit of surgery for native valve IE was demonstrated in an analysis of the ICE-PCS cohort (224). This study used propensity-based matching to adjust for treatment selection bias, survivor bias, and hidden bias. The subgroups with *S. aureus* IE, as well as patients with paravalvular complications and those with systemic embolization, were found to benefit from early surgery (224). Early surgery reduced the risk of subsequent embolic events in an RCT for patients with native valve IE and large vegetations or severe valvular disease (225). However, there were only eight patients with *S. aureus* IE in this study, thus precluding conclusions specifically regarding the *S. aureus* subgroup.

The timing of surgery following stroke is controversial. For patients with intracerebral hemorrhage, there is consensus that surgery should be delayed by at least 1 month. For those patients with ischemic stroke, a number of studies (reviewed by Rossi et al. [226]) have suggested that surgery does not need to be delayed if there are indications for surgery. Although an analysis of the ICE cohort specifically addressing this question concluded that early surgery is not associated with increased mortality, concerns have been raised regarding the adjusted OR for in-hospital mortality being 2.3 (95% CI, 0.94 to 5.7) for those receiving surgery within 7 days of stroke compared to delayed surgery (227, 228). Further studies with more detailed stratification, including a subset of patients with *S. aureus* IE, and inclusion of data on long-term neurological outcomes will be required to determine which patients will truly benefit from early compared to delayed surgery following ischemic stroke.

Several studies have concluded that all patients with *S. aureus* prosthetic valve IE, regardless of whether they have complications, benefit from surgery, citing the lower mortality rates found with the combination of medical and surgical treatments (146, 152, 153, 183, 229–232). For example, Fernandez Guerrero et al. found that of the 65% of patients who underwent valve replacement surgery, only 15% died, whereas all of the 35% of patients who did not receive surgery died (146). An analysis of all patients with prosthetic valve IE in the ICE cohort found no overall benefit with early surgery compared to medical therapy after adjustment for treatment selection and survivor bias (151). In a *post hoc* analysis that did not adjust for survivor bias, improved survival was found for those with the highest probability of receiving surgery. Those with the highest probability for surgery typically had factors that current recommendations suggest should receive surgery, including heart failure and uncontrolled infection (including paravalvular abscesses) (106, 184, 185). The role of early valve surgery in *S. aureus* prosthetic valve IE was specifically addressed by Chirouze et al. (233) with the ICE-PCS cohort. As expected, the 1-year mortality rate was significantly higher among patients with *S. aureus* prosthetic valve IE than among patients with non-*S. aureus* prosthetic valve IE (48.2% versus 32.9%; $P = 0.003$), and patients with *S. aureus* prosthetic valve IE who underwent early valve surgery had a significantly lower 1-year mortality rate (33.8% versus 59.1%; $P = 0.001$) than did those who did not. However, in multivariate, propensity-adjusted models, receipt of early valve surgery for *S. aureus* prosthetic valve IE was not associated with reduced 1-year mortality rates. Based on these findings, the decision to pursue early valve surgery in cases of *S. aureus* prosthetic valve IE should be individualized for each patient based upon infection-specific characteristics rather than solely upon the identification of *S. aureus* as the causative pathogen.

In summary, one recent RCT and several well-designed cohort studies have now provided strong supportive evidence for early surgery in IE patients with heart failure, uncontrolled infection, and a high risk of emboli. It is likely that these findings apply to patients with *S. aureus* IE in particular. Given the poorer outcomes associated with *S. aureus* native valve IE, the absolute benefit of early surgery (and hence the number needed to treat to demonstrate a clinically meaningful difference) may be even more favorable.

SKIN AND SOFT TISSUE INFECTIONS

S. aureus causes a variety of SSTIs, ranging from the benign (e.g., impetigo and uncomplicated cellulitis) to the immediately life-threatening. It is the most common pathogen isolated from surgical site infections (SSIs), cutaneous abscesses, and purulent cellulitis. Here we review the epidemiology, pathophysiology, clinical features, and treatment of *S. aureus* SSTIs, with an emphasis on the recent epidemic of community-associated MRSA (CA-MRSA).

Epidemiology

While *S. aureus* has traditionally been the leading cause of SSTIs, its importance has ballooned in the past 15 years with the emergence of a worldwide epidemic of CA-MRSA SSTIs (234, 235). Because the rise of CA-MRSA was previously explored in detail (236), it is reviewed here briefly.

MRSA was described shortly after the introduction of methicillin but was uncommon outside the health care environment until the 1990s. Around that time, reports emerged of patients presenting with MRSA who did not have traditional health care risk factors. These reports included both children and adults in various geographic locations presenting predominately with SSTI (237–251), with community clusters among athletes, men who have sex with men, correctional facilities (252–254), homeless persons and IDUs (255), military personnel (256–258), and indigenous populations (30, 239, 250, 259).

Over time, it became apparent that the CA-MRSA epidemic was not simply replacing endemic SSTI strains but was significantly increasing the incidence of SSTIs. For example, Pallin et al. (260) estimated that the number of emergency department (ED) visits for SSTIs in the United States increased from 1.2 million in 1993 to 3.4 million in 2005. These data were corroborated by others. Hersh et al. (261) queried U.S. national survey data and found an increase in the number of coded SSTI encounters from 32.1 to 48.1 per 1,000 population from 1997 to 2005, largely in younger and black patients. Inpatient admissions for SSTIs exhibited the same trend. Edelsberg et al. (262) estimated that there were 675,000 admissions for SSTI in the United States in 2000, compared to 869,800 in 2004, with the most notable increases being seen for younger and urban patients. Frei et al. (263) found that among pediatric patients, the numbers of hospitalizations for both MSSA and CA-MRSA increased from 1996 to 2006. More recent U.S. data suggest that the MRSA SSTI incidence may have peaked around 2007 to 2008. For example, from 2005 to 2010, the proportion of all community-onset SSTIs due to MRSA in Department of Defense beneficiaries declined from 62% to 52%, although overall *S. aureus* SSTI rates did not change (29).

When CA-MRSA was first recognized in the United States in the late 1990s, molecular typing demonstrated that the predominant clone was USA400 (236, 264). Since 2000, USA400 has largely been supplanted by a single epidemic clone, USA300, which has been responsible for the rapid shift in epidemiology in the United States. King et al. (265) found that the USA300 clone was the cause of most community-onset *S. aureus* SSTIs. Among 389 patients in a Georgia health system, 72% of all *S. aureus* SSTIs were caused by MRSA, and ~85% of these were caused by USA300. Similar findings were seen concurrently in cohorts of patients presenting to emergency departments elsewhere in the United States (266–270).

Increasing rates of SSTIs have also been noted in Australia and the United Kingdom. In the United Kingdom, from 1991 to 2006, there was a 3-fold increase in admission rates for abscesses and cellulitis and increases in the numbers of prescriptions for antistaphylococcal antibiotics from primary care settings (271, 272). In Australia, there was a 48% increase in the number of hospitalizations for cutaneous abscesses between 1999 and 2008 (273), with a concurrent increasing proportion of outpatient *S. aureus* strains attributed to CA-MRSA (251). Notably, the increasing incidence of SSTIs in these regions cannot be attributed to USA300, which is an infrequent cause of staphylococcal infections in Europe (274) and Australia (251).

Pathophysiology

The pathogenesis of *S. aureus* SSTI has been comprehensively reviewed elsewhere (275, 276) and is summarized briefly here. The primary defense against *S. aureus* infection is the neutrophil response. When *S. aureus* enters the skin, neutrophils and macrophages migrate to the site of infection. *S. aureus* evades this response in a multitude of ways, including blocking chemotaxis of