

Staphylococcus aureus Infections: Epidemiology, Pathophysiology, Clinical Manifestations, and Management

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SUMMARY

Staphylococcus aureus is a major human pathogen that causes a wide range of clinical infections. It is a leading cause of bacteremia and infective endocarditis as well as osteoarticular, skin and soft tissue, pleuropulmonary, and device-related infections. This review comprehensively covers the epidemiology, pathophysiology, clinical manifestations, and management of each of these clinical entities.

The past 2 decades have witnessed two clear shifts in the epidemiology of *S. aureus* infections: first, a growing number of health care-associated infections, particularly seen in infective endocarditis and prosthetic device infections, and second, an epidemic of community-associated skin and soft tissue infections driven by strains with certain virulence factors and resistance to β -lactam antibiotics. In reviewing the literature to support management strategies

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 to 2005, 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 <i>S. aureus</i> 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 infec-

tion; 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 \sim 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 \sim 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 infec-

tions, 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 endocarditisⁱ

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 anti-staphylococcal 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

leukocytes, sequestering host antibodies, hiding from detection via polysaccharide capsule or biofilm formation, and resisting destruction after ingestion by phagocytes.

With the rise in the number of SSTIs caused by CA-MRSA, there has been intense interest in understanding the enhanced pathogenicity of these strains. Multiple virulence factors appear to contribute, including Pantone-Valentine leukocidin (PVL), alpha-hemolysin (also called alpha-toxin), phenol-soluble modulins (PSMs), the arginine catabolic mobile element (ACME), and a regulatory locus referred to as *agr*.

PVL causes lysis of human white blood cells (WBCs). In the early 1990s, it was linked to *S. aureus* cutaneous infections (277, 278) and has been epidemiologically associated with CA-MRSA infections, raising the question of whether it was responsible for increased virulence. Vandenesch et al. assessed 117 CA-MRSA isolates from a widespread geographic area and performed pulsed-field gel electrophoresis (PFGE) and multilocus sequence typing (MLST) to look for common genetic markers (279). All isolates shared a type IV staphylococcal cassette chromosome *mec* (SCC*mec*) element and the *pvl* locus. Similar work in the United States (280) and France (281) established a correlation between the presence of *pvl* and CA-MRSA infections. In a meta-analysis of several studies (282–285), the presence of *pvl* was clearly associated with abscesses and furuncles, with an odds ratio of 10.5 (95% CI, 7.4 to 14.9) (286). However, the quantity of PVL produced in CA-MRSA infections has not been found to correlate with the severity of infection; for example, some high-PVL-producing strains were found in patients with uncomplicated abscesses, whereas patients with necrotizing fasciitis carried *S. aureus* strains with lower levels of PVL production (287). A study of isolates from 142 human infections in England and Wales was similarly unable to document an association between levels of PVL production *in vitro* and clinical severity of infection (288). Furthermore, laboratory models have not found PVL to be the predominant virulence determinant in skin infections. In mice, *pvl*-negative USA300 and USA400 strains caused skin disease comparable to that caused by *pvl*-positive strains (289). However, mice are not an optimal model for human SSTI, in that mouse neutrophils are resistant to the toxic effects of PVL compared to human and rabbit neutrophils (290, 291). In a rabbit model, compared to isogenic *pvl* knockout mutants, *pvl*-positive MRSA strains were also found to exert toxic effects on keratinocytes; after being taken up by host cells, the *pvl*-positive strains were able to escape and induce keratinocyte apoptosis, facilitating local spread and inflammation (292). In another rabbit experimental model (293), *pvl*-positive and *pvl*-negative strains produced similar disease. Thus, despite the strong epidemiological association between *pvl* and abscesses and furuncles (286), evidence from animal models does not conclusively link *pvl* and the pathogenesis of skin lesions.

Substantial attention has also been directed to alpha-hemolysin, a toxin that forms pores in various human cells, not limited to red blood cells, leading to cell lysis. Its role in *S. aureus* virulence has been appreciated for nearly a century (294). In the rabbit skin infection study mentioned above, virulence correlated with transcript levels of alpha-hemolysin and PSM α (293). More recently, it was discovered that alpha-hemolysin interacts with the ADAM10 receptor, and ADAM10-deficient mice are protected from severe skin infection (295). In the virulent Australian sequence type 93 (ST93) MRSA clone (296, 297), high levels of alpha-hemolysin have been associated with more severe cutaneous

lesions (298). Alpha-hemolysin also appears to contribute to the penetration of keratinocytes in skin infection (299). Vaccination against alpha-hemolysin in mice led to less severe skin disease with subsequent challenge (300).

Phenol-soluble modulins are a family of small, amphipathic proteins found in *S. aureus* that lyse human cells, including neutrophils and erythrocytes. A growing body of evidence from both *in vitro* and *in vivo* studies suggests that PSMs may also be important in the development of SSTI. PSMs and their proteolytic products facilitate *S. aureus* colonization (301) and dispersion (302) on skin. PSM deletion in a mouse abscess model led to significantly decreased skin lesions, supporting a role in virulence (303). In a subsequent rabbit skin infection model, alpha-hemolysin, PSM α , and *agr* appeared to contribute to pathogenesis (304). The level of production of phenol-soluble modulins is also significantly higher in USA300 isolates than in other variants of MRSA (303). A recent investigation demonstrated that *in vitro* levels of PSM production were significantly higher among clinical MRSA isolates originating from an SSTI source than in geographically matched MRSA isolates from cases of hospital-acquired pneumonia (HAP) or IE (305).

The success of the USA300 strains has been linked to the presence of ACME (306, 307). Although USA500, the progenitor strain of USA300, has virulence similar to that of USA300 in animal models (308), it has proven less successful in terms of spread in the human population. USA500 notably lacks the ACME locus. Recently, Planet et al. (309) demonstrated that the *speG* gene in the ACME locus confers increased resistance to skin-produced polyamines that are toxic to other *S. aureus* strains, resulting in a likely selective advantage during skin colonization and infection.

Differential gene expression for proteins such as PVL, alpha-toxin, and PSMs appears to also contribute to the enhanced virulence of CA-MRSA. These elements are under the control of *agr*, a regulatory locus that controls the expression of *S. aureus* toxins. In a mouse model, less severe infection ensued after inoculation with *agr*-deleted *S. aureus* strains (310). Similarly, clinical ST93 strains with *agr* mutations produce less alpha-hemolysin and are less virulent than wild-type strains (298).

Other candidate virulence determinants continue to be discovered. The *sasX* gene was found in the *S. aureus* clone most common in Asia. In addition to a putative role in nasal colonization and pleural infection, the presence of this gene was correlated with larger cutaneous abscesses than those in mice infected with *sasX* mutant strains (311).

Clinical Features and Outcomes

Even prior to the rise of CA-MRSA, *S. aureus* was a key contributor to SSTIs (see Fig. 1 for photos of classical *S. aureus* SSTIs).

Impetigo is the most common bacterial skin infection of children (312). In general, impetigo presents as bullous or papular lesions that progress to crusted lesions, without accompanying systemic symptoms, on exposed areas of the body (usually the face or extremities). Recent studies of impetiginous lesions found recovery rates of 29 to 90% and 57 to 81% for *Streptococcus pyogenes* and *S. aureus*, respectively (313–316).

While the hallmark infection of *S. aureus* SSTI is generally regarded as the cutaneous abscess (30, 247, 248, 317–319), other manifestations of skin infection are also encountered clinically. Nonpurulent cellulitis may be caused by *S. aureus* in a minority of cases, although the lack of a diagnostic gold standard and variabil-



FIG 1 *Staphylococcus aureus* skin and soft tissue infections. Shown are abscess (top left), cellulitis surrounding a pustule (top right), embolic infarcts complicating infective endocarditis (bottom left), and impetigo complicating scabies infection (bottom right).

ity introduced by different microbiological methods obscure the true microbiology of this condition (320). While *S. aureus* cellulitis most commonly involves the lower extremities, it may also involve other regions, including the upper extremities, abdominal wall, and face. It vies for primacy with streptococci as a cause of preseptal and orbital cellulitis (321–323).

Necrotizing fasciitis is another cutaneous syndrome caused by *S. aureus*. In a review of 843 patients with wound cultures positive for MRSA, 14 isolates were identified as being associated with necrotizing fasciitis or myositis. Coexisting conditions among those patients included injection drug use in 6/14 (43%) patients, previous MRSA infections in 3/14 (21%), diabetes mellitus in 3/14 (21%), and hepatitis C in 3/14 (21%) (324). In Taiwan, a review of 53 patients with necrotizing fasciitis revealed that 38% of infections were caused by *S. aureus*, 60% of which were caused by MRSA (325).

Pyomyositis can occur with both MSSA and MRSA. It has a tropical predilection, accounting for up to 1 to 4% of hospital admissions in some tropical countries, with *S. aureus* being responsible for an estimated 90% of these presentations (326). It is less common in temperate climates, where it occurs primarily in children and young adults (327, 328) and has been reported in association with HIV (329).

SSIs occur after 2 to 5% of all surgeries (330), although there is considerable heterogeneity depending on the type of procedure, population studied, comorbid illnesses, experience of the surgeon, setting, and antimicrobial prophylaxis utilized. According to 2009–2010 U.S. National Healthcare Safety Network data, *S. aureus* was the most common cause of SSIs overall, accounting for 30% of infections. Of these, 44% of isolates were methicillin resistant (331). In registrational trials of complicated SSTIs, even

higher proportions of SSIs due to *S. aureus* have been found; for example, 49% of SSIs in ATLAS studies (telavancin versus vancomycin) were due to *S. aureus* (332).

A particularly devastating SSI is mediastinitis complicating median sternotomy for cardiac surgery. *S. aureus* is the most common cause of postoperative mediastinitis (333–338). Fowler et al. demonstrated that the presence of SAB in the postoperative period was highly predictive of a diagnosis of mediastinitis, with a likelihood ratio (LR) of 25, compared to blood cultures positive for other pathogens or negative blood cultures (338). These findings were subsequently independently validated (334, 336). Thus, the presence of SAB following sternotomy mandates aggressive investigation to exclude the possibility of postoperative mediastinitis.

Treatment

Numerous RCTs have been conducted for different subsets of SSTIs. These studies (339–361) are summarized in Table 4, and additional comments are presented below.

Impetigo. A 2012 meta-analysis of 68 treatment trials for impetigo (362) concluded that topical antibiotics, including mupirocin, fusidic acid, and retapamulin, are more effective than placebo and as effective as or more effective than oral antibiotics. There was no difference when mupirocin and fusidic acid were compared head-to-head (362). Penicillin was inferior to erythromycin and cloxacillin. However, the majority of these studies were conducted in industrialized countries, and the findings may not be applicable to resource-limited settings, where the greater burden of impetigo lies (363) and where the severity of lesions and likelihood of development of resistance to topical agents are greater. Of the 68 trials included in the meta-analysis, only 5 were from resource-limited settings, and only 1 involved the extensive impe-

TABLE 4 Randomized controlled trials involving skin and soft tissue infections^a

Type of SSTI and authors of study, yr (reference)	Population	Study design	No. of patients	Treatment(s)	Outcome	Description
Impetigo Oranje et al., 2007 (339)	Children and adults with impetigo	Observer-blind RCT	519	1% retapamulin ointment twice daily for 5 days vs 2% sodium fusidate ointment 3 times daily for 7 days	99.1% and 94.0% clinical efficacy in per-protocol populations	60.5% were culture positive for <i>S. aureus</i> , of which 3.5% were positive for MRSA
Koning et al., 2008 (340)	Children and adults with impetigo	Double-blind RCT	210	1% retapamulin ointment twice daily vs placebo, each for 5 days	Retapamulin was superior to placebo in clinical success at 7 days (86% vs 52%) and at 14 days (76% vs 39%)	69.5% were culture positive for <i>S. aureus</i>
Bowen et al., 2014 (316)	Children with impetigo	Investigator-blind RCT	508	Benzathine penicillin i.m. in a single dose vs TMP-SMX twice daily for 3 days or daily for 5 days	TMP-SMX was noninferior to penicillin in mITT (84.7% vs 85.3%) or evaluable populations when assessed for improvement or cure at day 7	81% were culture positive for <i>S. aureus</i> , and 90% were culture positive for <i>S. pyogenes</i> ; 13.3% of <i>S. aureus</i> isolates were MRSA
Uncomplicated SSTI Tack et al., 1997 (341)	Children with uncomplicated SSTI, mostly impetigo (57%), infected dermatitis (9%), wound infection (8%), and cellulitis (7%)	Investigator-blind RCT	394	7 mg/kg cefdinir twice daily vs 10 mg/kg cephalixin 4 times daily, each for 10 days	No difference; high cure rate in both arms (98.3% vs 93.8%) in microbiologically evaluable population	72.1% were culture positive for <i>S. aureus</i>
Bucko et al., 2002 (342)	Adults and children at least 12 yr of age with uncomplicated SSTI	Double-blind RCT	1,685	200 mg or 400 mg cefditoren vs either 250 mg cefuroxime or 500 mg cefadroxil, each given twice daily for 10 days	Similar clinical cure rates at TOC visit (85%, 83%, 88%, and 85%, respectively)	31.1% were culture positive for <i>S. aureus</i> , of which 8% were positive for MRSA
Giordano et al., 2006 (343)	Adults and children at least 13 yr of age with uncomplicated SSTI	Investigator-blind RCT	391	300 mg cefdinir twice daily vs 250 mg cephalixin 4 times daily, each for 10 days	No difference in clinical cure rate at TOC visit in ITT (83% vs 82%) or CE (89% vs 89%) populations; no difference between MRSA and MSSA subgroups was found	38.6% were culture positive for <i>S. aureus</i> , of which 52.3% were positive for MRSA
Rajendran et al., 2007 (344)	Adults with uncomplicated skin abscess who underwent drainage procedure	Double-blind RCT	166	500 mg cephalixin 4 times daily vs placebo, each for 7 days	No difference; high cure rates in both arms (84.1% vs 90.5%)	70.4% were culture positive for <i>S. aureus</i> , of which 87.8% were positive for MRSA
Duong et al., 2010 (345)	Children with uncomplicated skin abscess who underwent drainage procedure	Double-blind RCT	161	TMP-SMX (10–12 mg trimethoprim/kg/day divided into 2 doses, with a maximum dose of 160 mg trimethoprim/dose) vs placebo, each for 7–10 days	No difference; high success rates in both arms (94.7% vs 95.9%); more new lesions at 10 days in placebo-treated group (26% vs 13%) but not at 3 no	88.2% were culture positive for <i>S. aureus</i> , of which 90.8% were positive for MRSA
Schmitz et al., 2010 (346)	Adults with uncomplicated skin abscess who underwent drainage procedure	Double-blind RCT	212	2 tablets of 160/800 mg TMP-SMX twice daily vs placebo, each for 7 days	Nonsignificant difference in treatment failure (17% vs 26%), higher incidence of subsequent new lesions within 30 days in placebo group (28% vs 9%)	62.3% were culture positive for <i>S. aureus</i> , of which 73.5% were positive for MRSA
Pallin et al., 2013 (347)	Adults and children with cellulitis without abscess	Double-blind RCT	146	TMP-SMX vs placebo, each in addition to cephalixin, for 7–14 days	No difference in 30-day cure rates (62% vs 60%)	
Miller et al., 2015 (369)	Adults and children with uncomplicated cellulitis or skin abscess	Double-blind RCT	524	Clindamycin vs TMP-SMX, each for 10 days	No difference in cure rates at 14 days in ITT population (80.3% vs 77.7%) or evaluable population	Among suppurative lesions, <i>S. aureus</i> was found in 218 (42%), 178 (82%) of which were MRSA isolates; there was 14% clindamycin resistance and 0% TMP-SMX resistance among <i>S. aureus</i> isolates

(Continued on following page)

TABLE 4 (Continued)

Type of SSTI and authors of study, yr (reference)	Population	Study design	No. of patients	Treatment(s)	Outcome	Description
Complicated SSTI and ABSSSI ^c Stevens et al., 2000 (348)	Adults with cSSTI suspected to be due to a Gram-positive organism	Double-blind RCT	819	600 mg linezolid i.v. every 12 h vs 2 g oxacillin i.v. every 6 h, each for 10–21 days (mean, 13.4 days), with transition to oral linezolid or dicloxacillin, respectively, when clinically improving	Similar cure rates in ITT population (69.8% vs 64.9%), CE population (88.6% vs 85.8%), and ME population (88.1% vs 86.1%)	23.9% were culture positive for <i>S. aureus</i>
Arbeit et al., 2004 (349)	Adults with cSSTI due to Gram-positive organism and requiring hospitalization and i.v. therapy for ≥4 days	Pooled analysis of 2 evaluator-blind RCTs	1,082	4 mg/kg/day daptomycin vs vancomycin or a penicillinase-resistant penicillin (cloxacillin, nafcillin, oxacillin, or flucloxacillin), each for 7–14 days	No difference in clinical success in ITT population (71.5% vs 71.1%)	<i>S. aureus</i> was cultured in samples from 58.0% of patients, of which 13.9% were positive for MRSA
Weigelt et al., 2005 (350)	Adults with cSSTI requiring hospitalization.	Open-label RCT	1,180	Linezolid vs vancomycin, each for a goal of 7–14 days (minimum, 4 days; maximum, 21 days)	No difference in clinical response in ITT population (92.2% vs 88.5%); linezolid was superior (71% vs 55%) in the subgroup with MRSA	71% culture positive for <i>S. aureus</i> , of which 59% were positive for MRSA
Ellis-Grosse et al., 2005 (351) ^b	Adults with cSSTI	Pooled analysis of 2 double-blind RCTs	1,116	Tigecycline vs vancomycin-aztreonam, each for up to 14 days	No significant difference in cure rates in clinically evaluable populations (86.5% vs 88.6%) at TOC visit	28.6% were culture positive for <i>S. aureus</i> , of which 20.4% were positive for MRSA
Breedt et al., 2005 (352) ^b	Adults with cSSTI	Double-blind RCT	546	Tigecycline vs vancomycin-aztreonam, each for up to 14 days	Tigecycline was noninferior in clinical response in the clinically evaluable mITT population	24.2% were culture positive for <i>S. aureus</i> , of which 9.1% were positive for MRSA
Sachidamand et al., 2005 (353) ^b	Adults with known or suspected cSSSI who required ≥5 days of i.v. antibiotics	Double-blind RCT	573	Tigecycline vs vancomycin-aztreonam, each for up to 14 days	Tigecycline was noninferior in clinical response in the CE population (82.9% vs 82.3%) at TOC visit	20.0% were culture positive for <i>S. aureus</i> , of which 36.5% were positive for MRSA
Jauregui et al., 2005 (354)	Adults with cSSSI suspected or confirmed to harbor a Gram-positive pathogen	Double-blind RCT	854	2:1 distribution of dalbavancin at 1,000 mg on day 1 and 500 mg on day 8 vs 600 mg linezolid every 12 h, each for 14 days (with each dalbavancin dose defined as 7 days of therapy)	Dalbavancin was noninferior in clinical success at TOC visit (88.9% vs 91.2%)	57.6% were culture positive for <i>S. aureus</i> , of which 56.5% were positive for MRSA
Noel et al., 2008 (361)	Adults with cSSSI	Double-blind RCT	828	Ceftopiprole vs vancomycin-ceftazidime, each for 7–14 days	Ceftopiprole was noninferior in cure rate in clinically evaluable (90.5% vs 90.2%) or ITT populations at 7- to 14-day TOC visit	45.4% were culture positive for <i>S. aureus</i> , of which 33% were positive for MRSA
Noel et al., 2008 (355)	Adults with cSSSI	Double-blind RCT	784	Ceftopiprole vs vancomycin, each for 7–14 days	Ceftopiprole was noninferior in cure rate in clinically evaluable (93.3% vs 93.5%) or ITT populations at 7- to 14-day TOC visit	60.9% were culture positive for <i>S. aureus</i> , of which 37.1% were positive for MRSA
Stryjowski et al., 2008 (356)	Adults with cSSSI	Pooled analysis of 2 double-blind RCTs (ATLAS 1 and 2)	1,867	Telavancin vs vancomycin, each for 7–14 days	Telavancin was noninferior in cure among the clinically evaluable population (88.3% vs 87.1%) at 7- to 14-day TOC visit	61.2% were culture positive for <i>S. aureus</i> , of which 62.7% were positive for MRSA
Krievins et al., 2009 (357)	Adults with cSSTI	Double-blind RCT	92	0.8 or 1.6 mg/kg iclaprim vs 1 g vancomycin, each given twice daily for 10 days	No difference in clinical cure rates at TOC visit (92.9% for lower-dose iclaprim, 90.3% for higher-dose iclaprim, and 92.9% for vancomycin)	57% were culture positive for <i>S. aureus</i> , of which 10% were positive for MRSA

ASSIST 1 and 2 (828)	Adults with cSSSI	Pooled results of 2 investigator-blinded RCTs (ASSIST 1 and 2)	991	0.8 mg/kg iclaprim i.v. twice daily vs 600 mg linezolid i.v. twice daily, each for 10–14 days	Iclaprim did not meet prespecified noninferiority criteria for clinical cure rate at TOC visit in ITT and PP populations	59.6% were culture positive for <i>S. aureus</i> , of which 39.4% were positive for MRSA
Craff et al., 2011 (358)	Adults with ABSSSI suspected or proven to be caused by a Gram-positive organism	Double-blind RCT	198	600 mg fusidic acid p.o. twice daily ($n = 43$), fusidic acid at 1,500 mg twice daily for 2 loading doses and then 600 mg twice daily ($n = 78$), or 600 mg linezolid p.o. twice daily ($n = 77$); study outcomes were reported only for the “loading-dose” and linezolid groups	Similar clinical success rates between fusidic acid loading-dose and linezolid groups; among ITT (86% vs 95%), mITT (88% vs 93%), CE (92% vs 99%), and ME (96% vs 98%) populations	71.6% were culture positive for <i>S. aureus</i> , of which 70.3% were positive for MRSA
Friedland et al., 2012 (359)	Adults with cSSSI	Pooled analysis of 2 double-blind RCTs (CANVAS 1 and 2)	1,378	Cefaroline vs vancomycin-aztreonam, each for 5–14 days	Cefaroline was noninferior in cure rates in clinically evaluable (91.6% vs 92.7%) and mITT (85.9% vs 85.5%) populations	53.3% were culture positive for <i>S. aureus</i> , of which 36.9% were positive for MRSA
Prokocimer et al., 2013 (360)	Adults with ABSSSI	Double-blind RCT	667	200 mg tedizolid daily for 6 days vs 600 mg linezolid twice daily for 10 days	Tedizolid was noninferior in early clinical response (79.5% vs 79.4%); results at the end of treatment and 1–2 wk posttherapy were also similar	51.9% were culture positive for <i>S. aureus</i> , of which 51.4% were positive for MRSA
Moran et al., 2014 (373)	Patients aged ≥ 12 yr with ABSSSI	Double-blind RCT	666	200 mg tedizolid i.v. daily for 6 days vs 600 mg linezolid i.v. twice daily for 10 days, with optional oral step-down therapy	Tedizolid was noninferior in early clinical response (85% vs 83%)	48.8% were culture positive for <i>S. aureus</i> , of which 33.5% were positive for MRSA
Corey et al., 2014 (374)	Adults with suspected or proven ABSSSI requiring at least 7 days of i.v. therapy	Double-blind RCT	954	1,200 mg oritavancin i.v. in a single dose vs vancomycin twice daily for 7–10 days	Oritavancin was noninferior in the mITT population (82.3% vs 78.9%) in a composite outcome of (i) cessation of spreading or reduction in lesion size, (ii) absence of fever, and (iii) no rescue antibiotic	60.8% were culture positive, of which 73.8% were positive for <i>S. aureus</i> (47.7% MRSA, 52.3% MSSA)
Boucher et al., 2014 (372)	Adults with ABSSSI requiring at least 3 days of i.v. therapy	Pooled analysis of 2 double-blind RCTs (DISCOVER I and II)	1,312	Dalbavancin i.v. on days 1 and 8 vs vancomycin for at least 3 days +/- linezolid to complete 10–14 days of therapy	Dalbavancin was noninferior in early clinical response (79.7% vs 79.8%)	50.8% were culture positive, of which 77.0% were positive for <i>S. aureus</i> (30.6% MRSA, 69.4% MSSA)

^a cSSSI, skin and soft tissue infection; cSTTI, complicated skin and soft tissue infection; ABSSSI, acute bacterial skin and skin structure infection; cSSSI, complicated skin and skin structure infection; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; TMP-SMX, trimethoprim-sulfamethoxazole; i.m., intramuscular; RCT, randomized controlled trial; ITT, intention to treat; mITT, modified intention to treat; TOC, test of cure; CE, clinically evaluable; ME, microbiologically evaluable; p.o., orally; PP, per protocol.

^b Note that tigecycline has subsequently received an FDA black box warning for an increased risk of death compared to other antibacterial drugs.

^c The FDA has released periodic guidance on clinical trial design for drug development for skin and skin structure infections. The studies enrolling patients with “cSTTI” were performed in accordance with the initial 1998 version of this guidance. This FDA guidance was updated in 2010 and included the newer designation ABSSSI. The oritavancin and dalbavancin trials were performed in accordance with this version of the guidelines. For a comparison of these guidelines, see reference 376. The guideline was updated again in October 2013 (375).

tigo typically seen in these settings. Recently, an RCT of systemic therapy with short-course oral TMP-SMX versus intramuscular benzathine penicillin G in 508 indigenous Australian children with extensive impetigo provided high-quality evidence for the equivalent efficacies of these agents (316). The TMP-SMX regimens are particularly attractive due to the short courses of 3 or 5 days and significantly fewer side effects than with intramuscular benzathine penicillin G injections.

Uncomplicated SSTI. It is not clear whether antibiotic therapy is required for other uncomplicated *S. aureus* SSTIs, especially for cases of abscess when incision and drainage are pursued. In an analysis of retrospective data, Lee et al. (364) noted that in children with culture-proven CA-MRSA skin abscesses (96% of whom underwent a drainage procedure), no significant differences in outcome were seen between those who received an effective antibiotic and those who did not; similar outcomes have been reported by others (365). In a larger cohort of 1,647 patients with SSTIs, 81% received antibiotics, but receipt of inactive initial therapy was not associated with a worse outcome, irrespective of whether a drainage procedure was done (247). This was in contrast to the findings of a subsequent analysis of 492 adults with community-onset uncomplicated SSTIs due to MRSA; in this retrospective review, receipt of active antimicrobial therapy was associated with lower rates of treatment failure (5% versus 13%) (366). However, 84% of those failures were because the patient required an additional incision-and-drainage procedure, leaving in question whether it was antibiotic failure *per se*, as opposed to inadequate surgical therapy, that led to treatment failures. Additionally, in a trial comparing two cephalosporins (cefdinir and cephalexin) for treatment of uncomplicated SSTIs, no difference in clinical cure rates between MSSA and MRSA subgroups was noted (343).

These findings laid the groundwork for several RCTs comparing antibiotics to placebo for the treatment of uncomplicated SSTIs. Rajendran et al. (344) randomized 166 patients with uncomplicated SSTIs to receive 7 days of cephalexin versus placebo, after incision and drainage. Seventy percent of cultures were positive for *S. aureus*, 88% of which were positive for MRSA and 93% of which were PVL positive. Clinical cure rates at 7 days were similar and were >90% in the placebo arm. Duong et al. (345) randomized 161 pediatric patients to receive 10 days of TMP-SMX versus placebo after incision and drainage, with in-person follow-up at 10 to 14 days and phone follow-up at 90 days. Failure rates were similar and were <6% for both groups. Eighty percent of patients had CA-MRSA isolated (100% TMP-SMX susceptible), whereas 9% had MSSA isolated. Patients on antibiotics developed fewer new lesions in the short term but not at the 90-day mark. Schmitz et al. (346) randomized 212 patients to receive TMP-SMX or placebo after incision and drainage. Treatment failure was seen in 17% of those who received TMP-SMX, versus 26% who received placebo, a difference that was not statistically significant. Others (367, 368) have noted that the point estimate of a 9% difference in the failure rate could be clinically significant if confirmed with an adequate sample size and extrapolated over the large number of *S. aureus* SSTIs each year. For uncomplicated cellulitis, the addition of TMP-SMX to cephalexin treatment did not provide benefit (347). Currently, there are larger ongoing clinical trials (ClinicalTrials.gov registration numbers NCT00730028 and NCT00729937) to answer this question more definitively. Miller et al. reported results of a study involving 524 patients with un-

complicated SSTIs, randomized to receive TMP-SMX versus clindamycin, each for 10 days. MRSA was the most common organism isolated. There was no significant difference between treatments (369).

There is some heterogeneity in the definition of “uncomplicated” in these studies; for example, Schmitz et al. (346) excluded immunocompromised patients and those with facial abscesses, whereas Rajendran et al. (344) included those patients. Duong et al. (345) excluded children with diabetes or other chronic health problems. There is consistency, however, in the exclusion of hemodynamically unstable patients or those with an extension of the abscess into deeper structures. A conservative definition of uncomplicated abscess would thus exclude those who are systemically unwell; have comorbidities, including immunosuppression or diabetes; or have abscesses in locations for which complete drainage is difficult, such as the face, hand, or genitalia. Taken together, studies to date suggest that for these uncomplicated cutaneous abscesses for which drainage is pursued, additional antimicrobial therapy may not be required. This is the position taken in IDSA guidelines for the treatment of MRSA infection, although those authors specify that for purulent cellulitis in the absence of a drainable focus of infection, empirical therapy for CA-MRSA is recommended (76). The 2014 IDSA guidelines for SSTI differentiate between mild infections (no systemic signs of infection), for which adjunctive antibiotics are not required, and moderate (systemic signs of infection) or severe (failed initial antibiotic therapy, impaired host defenses, or systemic signs of infection with hypotension) infections, for which antibiotics are indicated (370). For cases of uncomplicated cellulitis, generally defined as those in which the patient is systemically well, current IDSA SSTI guidelines recommend therapy aimed at streptococci, not *S. aureus* (76, 370), with therapy for CA-MRSA being reserved for those patients who do not respond to β -lactam treatment.

The long-held assumption that TMP-SMX is not effective for SSTIs involving *S. pyogenes* is being strongly challenged. It appears that TMP-SMX has *in vitro* efficacy against *S. pyogenes* (371). Two recent clinical trials suggest that TMP-SMX has clinical efficacy for nonsuppurative cellulitis (369) and impetigo due to *S. pyogenes* (316). Thus, TMP-SMX may be an appropriate treatment option for both *S. pyogenes*- and *S. aureus*-related SSTIs.

Complicated SSTI. For complicated SSTI, a number of registrational trials have compared different antimicrobial agents (Table 4). Current IDSA MRSA treatment guidelines recommend vancomycin, linezolid, daptomycin, telavancin, or ceftaroline for patients hospitalized with a severe purulent SSTI (370). In the case of a nonpurulent SSTI, a β -lactam antibiotic is recommended for mild or moderate infection, whereas vancomycin is recommended as part of empirical therapy for severe nonpurulent SSTI. As shown in Table 4, a number of other agents have been studied; dalbavancin (372), tedizolid (373), and oritavancin (374) have obtained FDA approval in 2014 alone. The FDA has released periodic guidance on clinical trial design for drug development for SSTIs. Following the initial 1998 version of this guidance, updates were provided in 2010 (which included the newer designation of acute bacterial skin and skin structure infections [ABSSSIs]) and most recently in 2013 (375; for a discussion of these guidelines, see reference 376).

For necrotizing fasciitis, there are limited data to guide a treatment approach, both because the disease is uncommon and because patients with necrotizing fasciitis have been excluded from

most trials. Empirical therapy should cover MRSA and anaerobes, and recommended combinations include vancomycin plus piperacillin-tazobactam or a carbapenem (370). Directed therapy for *S. aureus* should be an antistaphylococcal penicillin for MSSA or vancomycin for MRSA. Similar considerations extend to pyomyositis, for which *S. aureus* is the primary pathogen. Clindamycin is recommended for necrotizing fasciitis caused by *S. pyogenes*, based on its suppression of streptococcal toxins and two observational studies showing greater efficacy than with β -lactams (377, 378). In an additional observational cohort, the addition of clindamycin was associated with reduced mortality due to invasive *S. pyogenes* infections (379). There are no such data available for *S. aureus* necrotizing fasciitis, and IDSA guidelines do not specifically recommend the addition of clindamycin in this setting (370). Nonetheless, other groups recommend adding clindamycin for its antitoxin effect (380). The successful use of linezolid to switch off toxin production in a surgical wound with *S. aureus*-associated toxic shock syndrome (TSS) has also been reported (381). Our practice is to add clindamycin for *S. aureus* necrotizing fasciitis. There is currently no evidence to recommend a role for i.v. immunoglobulin for *S. aureus* necrotizing fasciitis. Aggressive surgical debridement and antistaphylococcal antibiotics are considered cornerstones of therapy (370).

OSTEOARTICULAR INFECTIONS

S. aureus is the most common pathogen in all three major classes of osteoarticular infection, namely, osteomyelitis (OM) (382–392), native joint septic arthritis (393–401), and prosthetic joint infection (PJI) (402–406). As staphylococcal osteoarticular infections in children are common and have distinctive clinical and management issues compared to those in adults, we include an in-depth discussion of this important subpopulation.

Osteomyelitis

Osteomyelitis is an infection of bone resulting in its inflammatory destruction, bone necrosis, and new bone formation. The Waldvogel classification system (407) describes three types of OM: hematogenous OM, contiguous-focus OM (from adjacent structures such as joint spaces or soft tissues or from trauma or surgery with direct implantation of organisms), and OM with vascular insufficiency (most commonly in patients with diabetes or peripheral vascular disease and generally involving the foot). *S. aureus* is the predominant cause of OM in all of these categories and is identified in 30 to 60% of cases (Table 5). Hematogenous OM generally involves the ends of long bones in children and adolescents and the axial skeleton in older adults (408), partly due to the blood supply to vertebrae in adults being more extensive than that to the long bones. This section principally focuses on hematogenous OM that most commonly manifests as vertebral OM in adults and long bone OM in children, where *S. aureus* is typically the key pathogen.

Epidemiology. The incidence of vertebral OM in adults is increasing. Scandinavian studies reported an incidence of 0.05 per 100,000 person-years in Denmark in 1978 to 1982 (385), compared with 2.2 per 100,000 person-years in Sweden in 1990 to 1995 (388). More recently, the incidence of vertebral OM in Funen County, Denmark, increased during a 14-year period (1995 to 2008), from 2.2 to 5.8 per 100,000 person-years (409). *S. aureus* caused 55% of cases, and the incidence of *S. aureus* vertebral OM increased from 1.6 to 2.5 per 100,000 person-years (409). Else-

where, incidence rates are similar. In New Zealand, from 2000 to 2005, the incidence of vertebral OM was 9.8 per 100,000 person-years in the >65-year age group (410). In a nationwide Japanese study, the incidence increased from 5.3 per 100,000 person-years in 2007 to 7.4 per 100,000 person-years in 2010 (411). The major risk factors for vertebral OM are advancing age (389, 409, 411), diabetes mellitus (384, 386, 411, 412), injection drug use (412, 413), and immunosuppression (389, 412), and the growing incidence of these risk factors, together with increased access to advanced radiological modalities, may explain the increasing incidence of vertebral OM. The majority of patients with vertebral OM and concomitant SAB are >60 years of age (414).

Pathophysiology. Animal models have demonstrated that healthy bone is generally highly resistant to infection and that either direct trauma or a large bacterial inoculum is needed to establish infection (415). *S. aureus*, however, has evolved to overcome the natural resistance of bone to infection. For example, it expresses numerous surface proteins that mediate adherence to components of bone matrix and collagen (416). These bacterial cell surface receptors are known as adhesins or MSCRAMMs (microbial surface components recognizing adhesive matrix molecules) (417, 418). Strains of *S. aureus* lacking genes that encode certain MSCRAMMs are less likely to cause osteoarticular infections in animal models (417, 419, 420). *S. aureus* is also able to form biofilms on foreign materials that act as sanctuary sites, where it is relatively protected from antimicrobial agents and the host immune response (421). Finally, *S. aureus* can invade osteoblasts (422) and form small-colony variants (SCVs) (423) in the intracellular compartment, where they are able to survive in a metabolically inactive state while preserving the integrity of the host cell. Kalinka et al. (424) recently found that *S. aureus* clinical isolates cultured from samples from patients with chronic OM were better able to invade osteoblasts than those from samples from patients with sepsis and nasal colonization. Isolates from acute and chronic OM also formed more biofilm, and compared to isolates from acute OM, those from chronic OM were likely to develop a small-colony-variant phenotype (424).

SCVs of *S. aureus* are important in the pathogenesis of a number of chronic forms of staphylococcal infections, including osteomyelitis (424–426), relapsing prosthetic joint infection (427, 428), skin and soft tissue infection (429), endocarditis (430), and infections involving ventriculoperitoneal shunts (431) and nasal sinuses (432). SCVs are also important in patients with cystic fibrosis (CF) (see Pleuropulmonary Infections, below). SCVs are naturally occurring subpopulations possessing important metabolic and phenotypic differences from ordinary *S. aureus* isolates (comprehensively reviewed in reference 423). SCVs are slower growing, less pigmented, and less hemolytic and produce less coagulase than ordinary *S. aureus* isolates, making them difficult to identify in the laboratory. They are able to survive intracellularly within nonprofessional phagocytes such as fibroblasts and endothelial cells (433, 434) and are relatively resistant to cell wall-active antibiotics and aminoglycosides (435, 436). The basis of these phenotypic changes appears to be a defect in the electron transport chain and auxotrophy (dependence) on certain growth factors, including hemin, menadione, and thymidine (437). Given their slow growth and intracellular survival, SCVs are difficult to eradicate with standard antibiotic therapy. The ideal therapy for these variants is unclear, and there are no randomized trials on which to base recommendations. Most experts recommend the

TABLE 5 Osteoarticular infections and the percentage caused by *Staphylococcus aureus*^a

Type of osteoarticular infection and reference	Study type	No. of cases (no. of cases with microbiologic diagnosis)	Region	Time period (yr)	Population	Predominant causative organism	% of infections caused by <i>S. aureus</i> (% caused by MRSA)
Nonvertebral osteomyelitis							
382	Prospective observational, single center	166	Oxford, UK		Chronic OM	MSSA	32
383	Retrospective, single center	454 (454)	USA	1982–1998	Adults treated at HITH; 52% diabetic foot infections, 6% vertebral infections, 19% long bone infections	MSSA	54
Vertebral osteomyelitis							
384	Retrospective	70 (44)	St. Louis, MO, USA		Adults with hematogenous VOM	MSSA	55 (22)
385	Retrospective	137	Denmark	1978–1982	Adults with hematogenous VOM		
386	Retrospective, multicenter	253	Cleveland, OH, USA	1950–1994	All ages with VOM	MSSA	49
387	Retrospective, single center	129 (74)	Cambridge, UK	1998–2008	All ages with VOM	MSSA	51
388	Retrospective, single center	58	Sweden	1990–2005	All ages with VOM	MSSA	34
Native joint septic arthritis							
393	Retrospective	233	Switzerland	1999–2008	Adults with hematogenous NJSA	MSSA	49.3 (4.7)
394	Retrospective	81 (59)	Cambodia	2007–2011	Children with NJSA and OM	MSSA	49 (2)
395	Retrospective, single center	44 (24)	Victoria, Australia		Children with acute NJSA	MSSA	76 (8)
396	Retrospective, single center	53	Japan	1955–2005	Adults with hematogenous NJSA	MSSA	
397	Retrospective, single center	65 (28)	Saudi Arabia	1997–2006	Children with NJSA	MSSA	39
398	Retrospective, single center	110	Israel	1987–2003	Adults with NJSA	MSSA	40
Prosthetic joint infection							
402	Retrospective, 10 hospitals	147	Victoria, Australia	2006–2008	Early-onset infections	MSSA	53
403	Prospective, 9 hospitals	50	Spain	2004–2006	Adults with hematogenous PJI	MSSA	38
404	Prospective, single center	38 (27)	Norway	1998–2005	Adults with early hip PJI	MSSA	37
405	Prospective, single center	152 (90)	Oxford, UK		Adults with PJI having 2-stage replacements	CoNS	18
403	Prospective, 9 hospitals	139 (132)	Spain	2004–2006	Adults with early PJI	MSSA	40 (12)
406	Retrospective, single center	112	Oxford, UK	1998–2003	Adults with PJI treated with DAIR	MSSA	73 (8)

^a OM, osteomyelitis; VOM, vertebral osteomyelitis; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; CoNS, coagulase-negative *Staphylococcus*; HITH, hospital in the home; PJI, prosthetic joint infection; DAIR, debridement and implant retention; NJSA, native joint septic arthritis.

TABLE 6 Clinical manifestations of vertebral osteomyelitis and septic arthritis caused by *S. aureus*^a

Infection type and reference	No. of patients	Age of patients (yr)	Main symptom(s) (% of patients)	Main sign(s) (% of patients)	Laboratory finding(s) (% of patients)	Description
Vertebral osteomyelitis						
386	253	60 ^b	Limb weakness (25)	Fever (78)	NA	
389	111	60 ^c	Back pain (91), limb weakness (33)	Fever (16)	Raised ESR (95)	
390	49	65 ^c	Back pain (96), limb weakness (53)	Fever (57), limb weakness (53)	NA	
391	40	58 ^c	Back pain (100), limb weakness (48)	Vertebral tenderness (83), fever (65)	Raised CRP level (98), raised ESR (95)	
392	20	72 ^c	Back pain (85), limb weakness (55)	Fever (30)	Raised ESR (95), raised CRP level (100)	
Native joint septic arthritis						
399	47	66.5 ^b	Joint pain (83)	Joint swelling (79), fever (34)	Raised CRP level (98), raised ESR (100)	
400	56	49 ^b	Joint pain (100)	Restricted joint movement (100)		95% single joint, 67% knee joint
401	75	2.5 ^b	Joint pain (85)	Joint swelling (77), fever (44)	Raised CRP level (98), raised ESR (100)	85% single joint, 56% knee joint

^a NA, not available; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

^b Median age.

^c Mean age.

use of antibiotics such as rifampin and quinolones that penetrate host cells but do not act on bacterial cell wall synthesis (423, 438) and also emphasize the role of extensive surgical debridement in the treatment of SCV infections (439).

Clinical manifestations and outcomes. Vertebral OM generally involves the endplates of two adjacent vertebrae and the intervening disc space. The most common route of spread is hematogenous seeding to the vertebral endplates, and from here, the infection spreads directly into the disc space (386). Hence, the term “discitis” is a misnomer, since disc space infection is secondary. The exception is where infection has been directly introduced to the disc space (e.g., following a surgical microdiscectomy). The hallmark of vertebral OM is back pain, being present in 85 to 100% of patients. Localized vertebral percussion tenderness is present in >80% of cases, but fever is present in anywhere from 18 to 83% of cases in various case series (Table 6). A significant minority of patients have signs of nerve compression (such as limb weakness) at presentation, and one-quarter of patients with vertebral OM will ultimately develop paralysis or significant neurologic dysfunction (386). Among 133 consecutive patients with SAB and concomitant vertebral OM, the most frequent primary foci or portals of entry of infection were the skin (21%) and urinary tract (10%). However, 71/133 patients (53%) had no identified primary focus (414). Comparisons between vertebral OM caused by MRSA and that caused by MSSA have found that patients with infections due to MRSA have more comorbidities and are more likely to have had recent nonspinal surgery (390). Lumbar vertebrae are most frequently affected, followed by thoracic and then cervical regions (384, 386, 412). Notably, the diagnosis of vertebral OM is frequently delayed, with an interval of >1 month from symptom onset to diagnosis for the majority of patients (386, 389, 391, 392, 414). Delayed diagnosis has been associated with poorer longer-term outcomes, including death, chronic pain, and residual disability (386).

The peripheral WBC count is raised in a variable proportion of patients with OM, but the erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) level are raised in 95 to 100% of patients with acute osteomyelitis (Table 6). A systematic review of 14 studies of vertebral OM found that the reported yield from blood cultures for a microbiological diagnosis was 58% (range, 30 to 78%) (412). Therefore, in the appropriate clinical and radiological settings, positive blood cultures can eliminate the need for diagnostic biopsy or aspiration of infected bone for culture. However, bone biopsy for culture and histology should be pursued if blood cultures are negative, as it provides a higher diagnostic yield (77%; range, 47 to 100%) (412). Where possible, the biopsy specimen is best obtained prior to antibiotic treatment. Several investigators have found that the microbiological yield from biopsy specimens of patients on antibiotics is ~50% lower than that from biopsy specimens obtained prior to antibiotic treatment (440–442). Where an initial percutaneous biopsy specimen is negative, there may be value in obtaining a second percutaneous biopsy specimen. Gras et al. (443) examined a cohort of 136 patients with vertebral OM who were all blood culture negative and who had not received antibiotics in the previous 2 weeks. Performance of a second biopsy after an initial negative result led to a microbiological diagnosis in 80% (74/93) of cases, versus 44% (60/136) with only one biopsy specimen. While significantly more invasive, open surgical biopsy is also more likely to yield a diagnosis than needle biopsy. For example, in a series of 70 patients from Missouri, an open biopsy had a 93% diagnostic yield, compared with 48% for radiologically guided needle biopsy (384). In summary, a microbiological diagnosis should be sought to guide subsequent therapy. One suggested approach to the diagnosis of vertebral OM begins with blood cultures, followed by an initial percutaneous biopsy, a second percutaneous biopsy if the initial biopsy specimen is sterile, and an open biopsy if clinically indicated (441).

The short-term mortality rates for OM are substantial, at 2.8 to

7.7% for nonvertebral OM (383, 444) and 6 to 16% for vertebral OM (386, 389, 391, 411). Furthermore, health care costs (445, 446) and rates of long-term functional impairment (386, 395, 447) are also high. Akiyama et al. (411) found that for vertebral OM, higher mortality rates were significantly associated with older age (ORs of 2.78, 3.99, and 7.13 for patients aged 60 to 69, 70 to 79, and ≥ 80 years, respectively, compared with those aged ≤ 59 years; $P < 0.001$), hemodialysis use (OR, 10.56; $P < 0.001$), diabetes (OR, 2.37; $P < 0.001$), liver cirrhosis (OR, 2.63; $P = 0.001$), malignancy (OR, 2.68; $P < 0.001$), and IE (OR, 3.19; $P < 0.001$).

Management. The management of vertebral OM caused by *S. aureus* requires prolonged courses of antibiotics. Jensen et al. (414) found that among 114 patients with bacteremic *S. aureus* OM, recurrence was more likely in patients receiving < 8 weeks of antibiotic therapy than in those receiving ≥ 8 weeks of therapy. Park et al. (448) determined that for 62 patients with vertebral OM due to MRSA, patients receiving < 8 weeks of antibiotic treatment were 4.8 times more likely to relapse than those receiving ≥ 8 weeks of therapy. There was no such association for 77 patients with MSSA infections (448). In contrast, Roblot et al. (449) determined that for 120 patients, outcomes were similar for 36 patients treated at one center with a median of 6 weeks of total therapy and for 84 patients treated at another center with a median of 10 weeks total therapy. These data and other observational data (386, 450) have led to recommendations that range from 6 weeks (449, 451) to 12 weeks (441) of antibiotic treatment. Most recently, Bernard et al. (452) compared antibiotic treatments for 6 weeks and 12 weeks for patients with pyogenic vertebral OM. In an open-label, noninferiority clinical trial design powered to achieve an absolute margin of 10%, 359 patients from 71 French medical care centers were randomly assigned to either of the treatment durations. Of these infections, 145 (41%) were due to *S. aureus*, 95% ($n = 137$) of which were due to MSSA. The primary endpoint was defined as the proportion of patients who were classified as being cured at 1 year by a masked independent validation committee. In an intention-to-treat analysis, 6 weeks of antibiotic treatment was noninferior to 12 weeks of antibiotic treatment, suggesting that the standard duration of antibiotic treatment for patients with this infection could be reduced to 6 weeks (452). Where clinical improvement is slow, undrained or unremoved foci exist, the CRP level is slow to normalize, or infection is due to MRSA, we consider it prudent to extend antibiotic therapy to at least 8 weeks. For patients responding well to initial i.v. therapy, observational data suggest that a switch to oral therapy after 2 weeks may be safe (451, 453). Results reported by Bernard et al. (452) are also supportive in that the overall rate of treatment success in their RCT was 91% with a median duration of 14 days of i.v. therapy.

Septic Arthritis

Epidemiology. Native joint septic arthritis is uncommon, with a population-based incidence of 4 to 10 per 100,000 person-years in Western Europe (454–456) but a higher incidence in nonindustrialized countries and disadvantaged populations (e.g., 29.1 per 100,000 person-years in aboriginal Australians [457] and 13.8 per 100,000 person-years in children in Cambodia [394]). In adults, underlying joint diseases such as rheumatoid arthritis and crystal arthropathies are predisposing conditions for septic arthritis (458). In addition to rheumatoid arthritis, other risk factors identified in a prior systematic review included an age of > 80 years, diabetes mellitus, recent joint surgery, and skin infection (459). In

healthy children, septic arthritis is typically related to spreading from contiguous OM affecting the vascular growth plate of long bones. *S. aureus* is the most common causative organism in both children and adults, accounting for 39 to 76% of identified pathogens in various case series (Table 5). There appears to have been no significant change in the distribution of causative organisms in native joint septic arthritis over the past 20 years (460). MRSA remains uncommon in most recent case series, accounting for 2 to 8% of infections (Table 5), but its prevalence may be increasing in some areas, particularly the United States (461).

Pathophysiology. *S. aureus* most commonly gains access to a joint space via bacteremic seeding of the vascular synovial lining of the joint, accounting for up to 70% of cases. Direct implantation, either through trauma or an iatrogenic event (e.g., following an intra-articular steroid injection), accounts for most of the remainder. Rarely, septic arthritis can occur following arthroscopy, the reported incidence of which is 0.01 to 0.23% (462).

As is the case in the pathogenesis of osteomyelitis, *S. aureus* MSCRAMMs mediate adherence to host proteins in the joint extracellular matrix, a process that is more likely to occur in damaged or healing joints (463). Upon seeding the synovial membrane, bacteria pass into the joint space. Synovial fluid inhibits *S. aureus* growth *in vitro* (464), an observation that is at odds with the substantial damage caused by *S. aureus* septic arthritis. Several avenues of investigation have clarified this apparent contradiction. In murine models, there is a rapid recruitment of neutrophils, mediated by formylated peptides (465), after *S. aureus* gains entry to the joint space. Activated macrophages and T cells are recruited as well, and a host of cytokines are induced, including tumor necrosis factor alpha (TNF- α), gamma interferon (IFN- γ), interleukin-1 (IL-1), IL-2, IL-6, and IL-17 (466). Neutrophils, however, play a dual role. They are needed for bacterial clearance, and their absence in experimental models leads to higher mortality rates and worse arthritis (467); however, they also contribute to tissue damage via enzyme release and free radical formation. A study of human synovial fluid also demonstrated that *S. aureus* forms large aggregates with host-derived fibrin, a finding that suggests a possible explanation for *in vivo* resistance to killing by neutrophils, as these aggregates are too large for neutrophil phagocytosis (468).

If the host is able to contain the initial *S. aureus* invasion, the infection may resolve. However, in the absence of an effective early response, the inflammatory process leads to joint destruction. In addition to the damage inflicted by proteases and inflammatory cytokines released by cells of the synovial lining, ischemia due to increased intra-articular pressure may also result (417). Thus, the major deleterious consequence of septic arthritis is the destruction of articular cartilage, leading to degenerative osteoarthritis.

Clinical manifestations and outcomes. Septic arthritis is most commonly monoarticular, but $\sim 10\%$ of cases are polyarticular (469, 470), and this occurs mainly in the context of SAB. The knee is the most commonly involved joint in acute septic arthritis, comprising 50% of cases, followed by the hip and then the shoulder (471, 472). Septic arthritis involving the pubic symphysis or the sacroiliac joint accounts for $\sim 5\%$ of cases and can be difficult to diagnose (473, 474). Sternoclavicular septic arthritis is strongly associated with IDUs but can occur in other settings (475). It accounts for 1% of septic arthritis cases in the general population but up to 17% in IDUs in one series (476).

Patients with septic arthritis generally present acutely with a single swollen, hot, red, and tender joint. Classically, an affected

joint is said to be so inflamed, tense, and tender as to make any movement impossible. However, contrary to traditional teaching, a mobile joint does not rule out septic arthritis. Both joint pain and swelling are present in >80% of cases at presentation, but fever is present in only 30 to 50% of cases (Table 6).

Arthrocentesis is the definitive diagnostic test for septic arthritis. Synovial fluid leukocyte counts are generally in the range of 50,000 to 150,000 cells/mm³, with likelihood ratios (LRs) for bacterial septic arthritis of 7.7 and 28.0 for synovial leukocyte counts of >50,000 cells/mm³ and >100,000 cells/mm³, respectively (459). More than 90% of synovial fluid white blood cells are neutrophils in most cases of culture-confirmed septic arthritis. In a meta-analysis including 6,242 patients with septic arthritis (of all causes but most commonly *S. aureus*), a leukocyte differential consisting of >90% neutrophils was strongly associated with septic arthritis (LR, 3.4; 95% CI, 2.8 to 4.2), while a differential of <90% neutrophils suggested that septic arthritis was absent (LR, 0.34; 95% CI, 0.25 to 0.47) (459). In bacterial septic arthritis in general (including *S. aureus* and other pathogens), Gram stain is positive in 29 to 50% of cases (477), and synovial fluid culture is positive for the majority of patients who have not received prior systemic antibiotics. This is in contrast to gonococcal septic arthritis, where synovial fluid cultures are positive in only ~50% of cases (478, 479). The major clinical differential diagnoses for septic arthritis are acute crystal arthropathies (gout and pseudogout) and acute hemarthrosis. Gout can coexist with septic arthritis, so the presence of crystals does not rule out the diagnosis of concomitant septic arthritis (480, 481).

Between 10 and 30% of patients with septic arthritis suffer long-term decreased joint function or mobility (395, 447, 454, 482). This proportion is higher with *S. aureus* than with other organisms and with delays in diagnosis or surgical intervention (483, 484). *S. aureus* septic arthritis is considered a medical emergency, as it can lead to rapid and irreversible joint damage if it is not treated promptly.

Management. There are no adequately powered randomized trials to guide management of *S. aureus* septic arthritis in adults. Therefore, guidelines have relied primarily upon expert opinion, usually extrapolated from treatment of other invasive staphylococcal infections and from animal and observational human studies (76, 470, 485). Most experts agree that one or more episodes of drainage of the joint space are urgently required in all cases, followed by a minimum of 3 to 4 weeks of antistaphylococcal antibiotic treatment, the initial 2 weeks of which should be intravenously administered. A recent retrospective study from Switzerland suggests that shorter courses of antibiotics may be sufficient for adults with uncomplicated native joint septic arthritis (486). This study included 157 adult patients and found that a total antibiotic duration of 14 days (the initial 7 days being i.v.) was noninferior to longer courses of 4 to 6 weeks, including patients with *S. aureus* infections. In the daptomycin registrational trial for *S. aureus* bacteremia (119), there were 32 patients with osteoarticular infections, 16 of whom had native joint septic arthritis. Comparable success rates were observed among patients treated with daptomycin (7/11; 64%) or with standard therapy (3/5; 60%) (487). The best surgical approach for drainage of the joint is also unclear and depends on the situation. For deep joints such as the hip, arthrotomy and lavage are generally the preferred methods of drainage. For more accessible joints such as the knee, either arthroscopic drainage and lavage or repeated closed-needle

drainage is recommended, with no clear evidence of superiority of either of these two approaches (488, 489). The role, if any, of adjuvant corticosteroids is also unknown; in a murine model, systemic corticosteroid administration was associated with favorable outcomes (490). Two randomized trials and one nonrandomized trial have suggested a benefit of adjunctive dexamethasone in children with native joint septic arthritis (482, 491, 492), but there are no data for adults.

Osteoarticular Infections in Children

Epidemiology. The incidence of osteoarticular infections in children ranges from 7 to 22 per 100,000 person-years based on studies from Europe (493–495). These infections are more common in males than in females (with incidences in French children of 24 per 100,000 person-years for boys and 19 per 100,000 person-years for girls) and in toddlers than in other age groups (494, 495). Some ethnic groups may be at higher risk, with Maori and Pacific Islander populations being overrepresented in a study involving 813 cases of acute OM in New Zealand (496). In the United States, CA-MRSA has become considerably more prominent as a cause of acute osteoarticular infections since 2000. In a study of 158 cases in Tennessee, the proportion of osteoarticular infections due to CA-MRSA rose from 4% to 40% from 2000 to 2004 (497). Similarly, the proportion of cases of acute OM due to CA-MRSA was 6% in 1999 to 2001 compared to 31% in 2001 to 2003 in Dallas, TX (498). In Houston, TX, between 2001 and 2010, 195 of 376 (52%) cases of *S. aureus* OM were due to MRSA (499).

Clinical manifestations and outcomes. Acute hematogenous OM in children presents with fever and malaise, local pain, and point tenderness and most commonly involves the metaphysis of the tibia or the femur, resulting in limping or an inability to walk (500). The pain is often poorly localized but becomes more focal over time. The hallmark of the pain is its constant nature. Overlying redness and swelling are often present, which may create diagnostic confusion. For diagnostic purposes, CRP analysis is highly sensitive and thus has value in excluding the diagnosis of acute osteoarticular infection. In a prospective study of 265 osteoarticular infections in children, using a cutoff of 20 mg/liter, CRP analysis had a sensitivity of 95% for the diagnosis of acute OM; and the combination of CRP and ESR (with a cutoff 20 mm/h) analyses provided a sensitivity of 98% (501). Additionally, CRP analysis can be used to monitor the response to antibiotic treatment (501). Peltola and Paakkonen provide an excellent diagnostic algorithm for acute OM in children (500).

With regard to acute OM caused by *S. aureus*, Ju et al. (502) found four clinical parameters that could predict the probability of acute OM in children due to MRSA compared to MSSA: temperature of >38°C, hematocrit level of <34%, white blood cell count of >12,000 cells/μl, and CRP level of >13 mg/liter. However, this study suffers from having only 11 patients with MRSA and a lack of genotyping data and from its single-center design (502). An attempt to validate this clinical prediction algorithm among 58 patients (MRSA, *n* = 16; MSSA, *n* = 42) in Phoenix, AZ, found the algorithm to have a poor predictive value (503). Without genotyping data, it seems likely that the study by Ju et al. and previous studies that also compared cases of acute OM due to MRSA versus MSSA (498, 502, 504, 505) found discriminators between USA300 and other *S. aureus* clones rather than between MRSA and MSSA *per se*.

With the emergence of CA-MRSA, deep venous thrombosis

(DVT) adjacent to the site of OM has been described by several groups (506–510). DVT with acute OM has been associated with MRSA (506, 508), PVL-positive strains of *S. aureus* (510), and USA300 in particular (507). Compared to patients with acute OM but no DVT, those with DVT were consistently unwell, likely to be bacteremic, and likely to have pulmonary involvement (presumably due to septic pulmonary emboli), and MRSA was overrepresented (511, 512). Thus, a high index of suspicion for DVT is required for children with acute OM who are critically unwell or who have pulmonary involvement, and Doppler ultrasound screening near the site of infection should be considered (511).

Nonetheless, most large series suggest that for acute OM in children, outcomes are generally favorable. Only 1 child out of 1,000 with OM died in a case series from France (494), and of 131 prospectively monitored cases in Finland, only 2 children developed mild sequelae (varus deformity of tibia and ankle pain during exercise) (513). The mean length of hospital stay was 8.6 days in the French series (494).

Management. Empirical treatment for acute OM in children is dictated by the local antibiogram of *S. aureus*. Where the prevalence of MRSA is <10% among community *S. aureus* strains, an antistaphylococcal penicillin or cephalosporin is recommended; where the prevalence of CA-MRSA is >10% and the rate of clindamycin resistance is <10%, clindamycin is recommended; and where both the prevalence of CA-MRSA and the rate of clindamycin resistance are >10%, vancomycin should be used (500). If the child is severely ill and has suspected acute OM or septic arthritis, it is prudent to treat the child with both vancomycin and an antistaphylococcal β -lactam until bacterial susceptibilities are known (499).

For pediatric acute OM caused by MSSA, an early switch to oral therapy appears safe. A prospective study of 70 children with either septic arthritis or OM demonstrated that an algorithmic approach resulted in 59% of children converting to oral therapy after 3 days of i.v. therapy and 86% converting to oral therapy after 5 days. All 70 children had good outcomes at 1 year of follow-up (514). Similarly, Peltola et al. switched 131 patients to oral therapy after a median of 3 to 4 days of i.v. therapy, with excellent outcomes (513). An early switch to oral therapy is particularly important for children, as the risk for central line-related complications is high. Ruebner et al. found that of 75 patients who received >2 weeks of treatment for acute OM through a central venous catheter (CVC), 41% developed at least one CVC-related complication (515).

A prospective, quasirandomized, controlled, open-label trial involving 252 children with osteoarticular infections (82/252 with OM and 189/252 with *S. aureus* [all MSSA]; the proportion of cases of OM with MSSA was not reported) in Finland determined that oral clindamycin or a first-generation cephalosporin was equally efficacious as follow-up therapy (516). The same investigators also determined in an RCT involving 131 children with acute OM (117 with *S. aureus*, all MSSA) that 20 days of total therapy resulted in outcomes equivalent to those with 30 days of total therapy (513). In children with septic arthritis, a separate Finnish study (517) found that a duration of 10 days of total antibiotic therapy was equivalent to 30 days of therapy. Of 130 cases, only 1 developed a late-onset infection following completion of therapy, and this case was in the 30-day arm of the study. A systematic review (518) noted that the above-mentioned RCTs are only of moderate quality, principally due to a lack of blinding, and

concluded that the recommendations of treatment for acute OM of 3 to 4 days of i.v. therapy followed by oral antibiotics for a total treatment duration of 3 weeks should be regarded as being supported by only weak evidence (grade 2B).

Given the severity of osteoarticular infections caused by CA-MRSA and their conspicuous absence in the Finnish studies, it is unknown whether abbreviated i.v. and subsequent oral therapies can effectively treat acute OM due to MRSA. This point is acknowledged by Peltola and Paakkonen (500) and also in IDSA guidelines for MRSA infections (76). Both reports suggest that acute OM due to MRSA should be treated with a minimum of 4 to 6 weeks of total therapy. Additionally, it is recommended that infants <3 months of age receive a longer course of i.v. therapy due to concerns over the absorption and efficacy of oral antibiotics (518).

Only 12% of 130 patients with septic arthritis in a Finnish study (517) required a surgical procedure, and in a separate trial, 62/131 (47%) cases of acute OM received resectional surgery to the bone cortex (513). However, higher rates of surgery have been noted in the United States. For example, Tuason et al. found that of 57 cases of acute OM, 41 (72%) children required surgery, 12 of whom underwent ≥ 2 surgeries (519). Additional concerns are that hip septic arthritis in children can result in ischemic necrosis of the femoral head and that sequelae of septic arthritis may be more common than for OM. An Australian study including 44 children, in whom *S. aureus* was the causative organism in 76% of cases, found that 10% of children at 12 months had residual joint dysfunction (395). Thus, careful clinical assessment and monitoring are mandatory. For patients with extensive disease or where levels of inflammatory markers are not being reduced as expected, ongoing reassessment of the need for surgical intervention is advised.

Adjunctive dexamethasone appears to be a promising intervention to accelerate recovery and decrease residual morbidity in children with native joint septic arthritis. Odio et al. (482) randomized 123 children with septic arthritis (67% of whom had infections due to *S. aureus*) to receive 4 days of adjunctive i.v. dexamethasone in addition to antibiotics. They found that a significantly lower proportion of patients in the dexamethasone group had residual joint dysfunction after 12 months of follow-up (2% versus 26%). Harel et al. (491) randomized 49 children to receive 4 days of dexamethasone or placebo for septic arthritis and found more rapid resolution of fever and pain and a shorter duration of i.v. antibiotics in the dexamethasone group. However, it is unclear if these results apply to *S. aureus* infections, as 65% of patients had no pathogen isolated from joint fluid, and for the remainder of the patients, the most common pathogen was *Kingella kingae*. More rapid early recovery with dexamethasone was also recently found in a double-blind, nonrandomized, prospective clinical trial enrolling 60 children in Pakistan (492).

Prosthetic Joint Infection

Epidemiology. Prosthetic joint replacement is common, with >600,000 procedures being performed in the United States (520) and >77,000 being performed in Australia annually (Australian Orthopaedic Association National Joint Replacement Registry [<https://aoanjrr.dmac.adelaide.edu.au/>]). Older observational studies reported rates of infection of 0.5 to 1% for hip arthroplasties and 1 to 2% for knees (521, 522); more recent data from a large U.S. Medicare data set (including ~70,000 knee replacement patients and 40,000 hip replace-

ment patients) estimate the risk of infection to be ~2% for both hip and knee arthroplasties (523, 524). Hence, PJI is a very common problem and poses a large economic burden in industrialized countries (445, 525). The major risk factors for PJI are prior surgery on the index joint, obesity, rheumatoid arthritis, duration of implantation surgery, and immunosuppression (526–528).

PJIs are usually classified as early postoperative (within 30 days of implantation), late chronic (indolent presentation), and late acute hematogenous (explosive onset in a previously well-functioning joint). High-virulence organisms, primarily *S. aureus* but also beta-hemolytic streptococci, aerobic Gram-negative organisms, and mixed infections, are generally the cause of most early and hematogenous infections. Chronic infections are more likely to be caused by indolent organisms, including coagulase-negative staphylococci, *Enterococcus* spp., and *Propionibacterium* spp. In nearly all case series, for all forms of PJI, *S. aureus* is the most common causative organism, accounting for 18 to 73% of cases (Table 5). In patients with a prosthetic joint *in situ* who develop SAB, a PJI eventuates in 29 to 39% of cases (446, 529, 530).

Pathophysiology. Within a biofilm, bacteria are contained in a polymeric matrix that adheres to prosthetic material. The biofilm acts as a sanctuary site where *S. aureus* is relatively protected from antimicrobial agents and the host immune response. In addition, organisms within a biofilm generally enter a stationary or stringent phase of growth and are thus much more resistant to antimicrobial killing than those in the active or vegetative phase (531). The presence of an implanted foreign body has been shown to reduce the inoculum of *S. aureus* required to establish an infection by a factor of 100,000 (532). An implanted joint prosthesis is avascular, and the bone-prosthesis interface is relatively poorly vascularized. These facts explain why PJIs are so difficult to treat, can occur despite all efforts at prevention, and generally require removal of the prosthesis for definitive cure.

Clinical manifestations. Early PJIs (presenting within 30 days of implantation) generally present as a deep wound infection. The patient is usually acutely ill, with fever and joint inflammation and effusion. Clinical evidence of wound infection in the postoperative period is the strongest risk factor for early PJI, with an odds ratio of 52 (95% CI, 21 to 130) (521).

Chronic infections are more subtle. Often, there is a history of the joint “never being quite right,” with low-grade chronic pain and poor function but no obvious signs of infection. In one case series including 110 patients with PJI, fever was present in only 4.5% of cases (533). The exception is the presence of a discharging sinus. A PJI can be diagnosed with certainty if the sinus can be shown to communicate with the joint space. It can be very difficult to differentiate the chronic pain of the aseptic loosening of a prosthetic joint from that of a low-grade chronic infection. Hemarthrosis, gout, and metallic debris-induced synovitis can also be mistaken for PJI.

A definitive diagnosis of PJI due to *S. aureus* requires the isolation of the organism from operative specimens of joint fluid and/or periprosthetic tissue. When all causative organisms are considered as a group, positive cultures from three operative specimens represent a 95% probability of infection, whereas two positive specimens represent a 20% probability, and one specimen represents a 13% probability of infection (534). However, *S. aureus* is virtually never a nonpathogenic isolate or contaminant (e.g., in comparison to coagulase-negative staphylococci and pro-

tionibacteria). Thus, a single isolate of *S. aureus* in the appropriate clinical setting can be considered diagnostic.

For investigation of suspected PJI, culture of a preoperative closed-needle aspirate of the hip or knee joint for synovial fluid analysis is highly specific for infection (e.g., 95% in a study of 145 revision knee arthroplasties, 40 of which were found to be infected [535]) but lacks sensitivity (73% in the above-mentioned study and 75% in another series of 68 hip and knee replacements [536]). Gram stains of synovial fluid without accompanying growth are difficult to interpret, as fibrin and other artifacts may cause false-positive Gram stains, and the sensitivity is poor; Stirling et al. found a false-negative rate of 78% for 143 positive synovial fluid cultures (537). Hence, it is important if possible to avoid the use of any antibiotics (including preoperative prophylaxis) in the 1 to 2 weeks leading up to a diagnostic sampling of joint fluid or tissue. If PJI is suspected but not proven, the next step is operative exploration, with collection of at least 5 periprosthetic tissue specimens for culture and histology (538).

If the prosthesis itself or its components are removed, they should be cultured. Simple swab or broth cultures of explanted prostheses lack sensitivity because of biofilm-associated organisms, perioperative antibiotic use, or adjacent antibiotic-impregnated cement. The sensitivity can be improved by placing the prosthesis in a sonication bath and culturing the sonicate fluid. This sonication technique has been found to have a sensitivity of 75 to 77% for culturing of microorganisms, compared to 34 to 45% with culturing of multiple periprosthetic tissue specimens, and is particularly valuable if there has been recent antibiotic use (539, 540). However, it may cause problems with false-positive cultures of environmental organisms and other contaminants if appropriate cutoffs are not used (541). The diagnostic role of 16S PCR is uncertain, as in most cases, it appears to add little to culture and may lead to both false-positive and false-negative results (542).

One might expect this discussion to not be relevant to *S. aureus* infections, since *S. aureus* is a nonfastidious and easily cultured organism in most circumstances. However, in the setting of PJI, *S. aureus* is often associated with biofilm and may form SCVs (428), both of which may render it difficult to culture with usual microbiological methods. For further information on the diagnosis of PJI, readers are referred to recent IDSA guidelines (543) and other review articles (544–547).

Management. Staphylococcal early postoperative PJI has been traditionally treated with 2-stage joint replacement, with resultant cure rates of >90% (405, 548). Over the past 2 decades, the debridement and implant retention (DAIR) procedure has been increasingly practiced, and there are accumulating data that this strategy leads to acceptable cure rates of 70 to 80% in appropriately selected patients (549, 550). However, some studies report lower success rates. Cobo et al. (551) retrospectively reported 117 cases of early PJI (most commonly caused by *S. aureus*) and found a 57% cure rate. A systematic review including data from 14 original articles and 710 patients treated with DAIR for “early” (within 6 weeks of implantation) PJI found pooled success rates of 46% for those undergoing a single debridement and 52% if multiple debridements were used, after a mean follow-up of 53 months (552). DAIR is seen as an attractive strategy as it is cheaper and more convenient, avoiding the multiple operations and prolonged immobility associated with 2-stage joint replacements. Zimmerli and colleagues (553) proposed an algorithm for the selection of a sur-

gical treatment strategy for patients with a PJI, which suggests that DAIR should be considered only if the patient meets all of the following criteria: <3 weeks since the onset of symptoms, a stable implant, good soft tissue envelope, and an organism that is susceptible to rifampin and/or quinolones. Other patients should undergo one- or two-stage replacement or, for those who are unfit for any surgery, attempted long-term antibiotic suppression.

There are two main approaches to antibiotic treatment in patients with staphylococcal PJI treated with DAIR, with insufficient evidence to definitively recommend one over the other. The first approach uses 6 weeks of i.v. vancomycin (for MRSA or coagulase-negative staphylococci) or an antistaphylococcal penicillin (for MSSA), following adequate debridement. This approach has had high reported success rates in appropriately selected patients. For example, success rates of 70% at 2 years in early postoperative prosthetic hip joint infections (554) and 71% in 38 early postoperative prosthetic hip joint infections (404) have been reported. Neither of these studies used rifampin.

The second, and increasingly popular, approach uses shorter courses of i.v. vancomycin or an antistaphylococcal penicillin (2 to 6 weeks) along with 3 to 6 months of oral rifampin-based combination therapy (rifampin combined with a second oral agent, most commonly ciprofloxacin or fusidic acid). Zimmerli et al. (555) reported the only prospective controlled trial assessing the role of rifampin for treatment of PJI in 33 adults with staphylococcal infection of various orthopedic implants. Patients with <3 weeks of symptoms prior to initial debridement were randomized to receive either 2 weeks of i.v. flucloxacillin or vancomycin with rifampin or placebo, followed by either ciprofloxacin-rifampin or ciprofloxacin-placebo therapy for 3 to 6 months (555). Those authors reported a successful outcome at 24 months for 12 of 12 patients in the rifampin group, compared with 7 of 12 in the placebo group ($P = 0.02$). This study is problematic for a number of reasons: (i) it contained only 15 patients with PJI, 8 of whom received rifampin-based therapy; (ii) it was not analyzed by intention to treat, as when one includes the 9 patients who were excluded from the analysis due to having received <85% of the study drug, the cure rates are not significantly different between the two groups ($P = 0.10$); and (iii) the control arm received a treatment known to have a significant chance of failure, because a course of 3 to 6 months of ciprofloxacin monotherapy for *S. aureus* often leads to resistance (556). Observational studies of this approach are very heterogeneous; however, they report success rates ranging from 57% (551) to $\geq 85\%$ (549, 550). Despite the flaws of the study by Zimmerli et al. (555), 2013 IDSA guidelines (543) on PJI recommend rifampin-based combination therapy for 3 to 6 months following DAIR, grading this recommendation as level A1 (good evidence from ≥ 1 properly randomized, controlled trial). This recommendation has been criticized (557), as there are actually no properly designed RCTs to support it.

It is important to note the adequacy of surgical debridement as a key source of heterogeneity in all studies of DAIR. This is probably more important than the choice of antibiotic regimen in determining cure rates and ranges from a single operation involving only arthroscopic lavage to multiple operations involving the removal of all infected periprosthetic tissue and loose cement, the exchange of the prosthesis liners, and high-volume lavage with antiseptic-containing solutions. Lora-Tamayo et al. (558) found that polyethylene liner exchange independently predicted treatment success (adjusted OR, 0.65; 95% CI, 0.44 to 0.95).

The role of DAIR for acute hematogenous infection (an explosive onset of symptoms in a previously well-functioning joint, often years after the original implantation surgery) is less certain. Cure rates in this setting appear to be lower than in early postoperative infection, ranging from 50 to 70% (554, 558, 559). As for early postoperative infections, in those for whom DAIR is not considered appropriate, the main curative option is one- or two-stage joint replacement.

Two-stage replacement has higher cure rates than DAIR and is the primary mode of treatment recommended for those with chronic PJI. This involves an initial operation with removal of the prosthesis and all infected bone and cement, followed by a period of i.v. antibiotics (2 to 8 weeks) and then a second operation where a new prosthesis is implanted. There are few data to guide the duration of therapy between the two stages or the choice of antibiotics. Most guidelines recommend vancomycin for MRSA infections and antistaphylococcal penicillins for MSSA, with or without adjunctive rifampin (543). Because vancomycin has poor bone penetration and low clinical cure rates, there is increasing interest in the use of alternative agents for MRSA osteoarticular infections, including linezolid (560, 561), daptomycin (562), and rifampin in combination with either quinolones or fusidic acid (549, 563). The only reported RCT addressing antibiotic choice for staphylococcal PJI in patients undergoing 2-stage replacement compared daptomycin with the “standard of care” (vancomycin, teicoplanin, or nafcillin) for 6 weeks in between the 2 stages in 75 adults with staphylococcal PJI (562). The primary safety outcome of this study was an elevation of creatinine kinase (CK) levels. A raised CK level was found more frequently in the daptomycin group (CK level of > 500 in 19% of patients, compared with 8% in the control group). Based on a stringent definition of success, the rate of successful treatment was higher in the daptomycin group (60% versus 38%). This study is difficult to extrapolate, as the test of cure was at a very early time point (1 to 2 weeks following the second stage). While 2-stage replacement is the most common mode of exchange arthroplasty, one-stage joint replacement (where the infected prosthesis is removed and replaced with a new one at a single operation) appears to have similar success rates in experienced centers. In a meta-analysis including 62 observational studies and 2,500 patients comparing one- and two-stage joint replacements for PJI, successful outcomes at 24 months were reported for 91% of patients following one-stage replacement and for 90% of patients following two-stage replacement (548). For a more detailed discussion on the management of *S. aureus* PJI, the reader is referred to recent IDSA guidelines (543) and recent reviews (545, 564, 565).

OTHER PROSTHETIC DEVICE INFECTIONS

S. aureus is particularly adept at infecting foreign bodies within the human host. Infections of prosthetic cardiac valves and prosthetic joints are described above, but this section provides further background on the formation of biofilms, the pathognomonic feature of device infections. Device infections of implantable cardiac devices, intravascular catheters, and other prostheses are discussed in greater depth.

Formation of Biofilm

S. aureus forms a biofilm on the surface of a foreign device, making eradication of the infection without surgical removal of the device all but impossible. A biofilm is a community of sessile bacteria

encased in an extracellular matrix of water, microbial cells, nutrients, polysaccharides, DNA, and proteins (566–568). The biofilm provides a protective matrix around the encased bacteria and is highly resistant to host immune defenses and antimicrobials (567, 569, 570). Within the endovascular system, the host deposits fibrin (571–573), fibronectin (573), fibrinogen (574), and collagen (575) in a sheath along the surface of an inserted device (571, 572, 576).

The formation of a biofilm occurs in the following 4 steps: (i) initiation, (ii) colonization, (iii) replication, and (iv) dispersal (576). The first step of biofilm formation is the reversible adherence of *S. aureus* to the device (576). The bacteria initially adhere to a protein-coated device via hydrogen bonds, van der Waals forces, and electrostatic interactions (567, 576). Integral to the ability of *S. aureus* to seed prosthetic devices is the MSCRAMM family of bacterial proteins. One of these MSCRAMMs, fibronectin-binding protein A (FnBPA), enables *S. aureus* to bind to fibronectin, a host extracellular matrix molecule that coats the surface of endovascular prostheses such as permanent pacemakers (PPMs) and implantable cardioverter defibrillators (ICDs) (156, 520). This binding of *S. aureus* FnBPA to human fibronectin is thought to be a critical initial step in the pathogenesis of prosthetic device infections (577). Lower et al. showed that specific single nucleotide polymorphisms in *fnbA* were associated with (i) greater *in vitro* binding to fibronectin, as assessed by atomic force microscopy; (ii) a higher number of hydrogen bonds between fibronectin and FnBPA in a simulated model system; and (iii) a higher risk of cardiac device infection (CDI) in patients with SAB (578).

In the second step, colonization, *S. aureus* upregulates the expression of genes necessary to synthesize the extracellular polymeric substance that forms the matrix, an effective barrier to antibiotics and host defenses (576, 579).

In the third step, the bacteria divide to form microcolonies, spreading nonuniformly along the surface of the device (576). In many *S. aureus* strains, the bacteria adhere to each other through polysaccharide intercellular adhesin, also referred to as poly-*N*-acetylglucosamine (PNAG), synthesized by *icaADB*G-encoded enzymes (579–585). Many MRSA isolates also have the capacity to form biofilms through an *icaADB*G-independent mechanism, such as FnBPA and FnBPB as well as major autolysin (Atl) (582, 586, 587). This biofilm phenotype is less virulent than the phenotype of PNAG-mediated biofilm (582).

In the fourth step, some bacteria will switch back to the planktonic state and disperse due to hemodynamic stress, a decrease in nutrient availability, or other unknown physiological causes, leading to bacteremia (576). Overall, *S. aureus* regulates biofilm formation via “quorum sensing,” a cell-cell communication process that enables the bacteria to communicate information about their environment, such as bacterial density, salt stress, and nutrient availability (567, 588, 589).

Cardiac Device Infections

Epidemiology. PPMs and ICDs are critical in managing arrhythmias and hemodynamic instability in low-cardiac-output states and have improved the quality of life of patients worldwide. However, infection poses the threat of serious and significant complications (590). The reported incidence of CDI ranges from 0.7 to 2.2% (591–599). While the incidence of cardiac device implantation has continued to increase, with 42% more cardiac devices

implanted in 1999 than in 1990 in U.S. Medicare beneficiaries, the rate of device infection has increased at a substantially higher rate, with a 124% increase in the infection rate over the same period (600). Similarly, Greenspon et al. found that the incidence of cardiac device implantation increased by 96% while the annual incidence of CDI increased by 210% from 1993 to 2008 in U.S. Medicare beneficiaries (597). This increase in the prevalence of CDIs was tracked with increasing rates of procedures, increasing numbers of medical centers implanting cardiac devices, and significant increases in patient comorbidity indicators in cardiac device recipients.

Permanent pacemakers and ICDs can become infected directly during initial implantation or indirectly via hematogenous seeding from a distant source. A temporal cutoff of 1 year after implantation or surgical manipulation is often used to indicate whether an episode of CDI is most likely due to direct inoculation (early infection, <1 year) or hematogenous seeding (late infection, >1 year) (601, 602). Although the short-term risk for CDI for an individual patient is greatest in the immediate postprocedure period, the majority of CDI cases in patients with SAB are actually late infections (601, 602). This finding is likely to reflect the larger number of patients with long-standing cardiac devices rather than higher rates of seeding. In the case of hematogenous CDI, seeding of the cardiac device usually originates from one of four sources: (i) the generator pocket, (ii) an intravascular catheter, (iii) non-device-related soft tissue infection, or (iv) pneumonia/lung infection (602). *S. aureus* is responsible for 23 to 46% of CDIs (594, 603–606), with up to 51% of these *S. aureus* infections being due to MRSA (602, 604, 607–609). Of patients with SAB and a preexisting cardiac device, there is a high risk of CDI. In a prospective study of 33 patients at Duke University, Chamis et al. found that the incidence of confirmed or possible CDIs in such patients was 45% (601). This high rate of CDIs was subsequently externally validated by Uslan et al. (estimated rate, 55%) (594) and Obeid et al. (estimated rate, 37%) (610). Collectively, these reports underscore that providers must be aware of the likelihood of CDI in patients with SAB who have a preexisting ICD or PPM (601, 602, 611). For patients with SAB and a cardiac device, the rate of CDI is significantly higher among patients with ICDs than among those with PPMs (602, 610). For example, Uslan et al. described the rate of ICD-related infection in patients with SAB to be 60%, versus 24% for patients with PPMs (602). Reasons for the disparity in CDI rates between ICD and PPM patients are unknown, although it has been speculated to be due in part to the higher comorbid burden of patients with ICDs (602, 610). Studies that externally validate this clinical phenomenon and establish its biological basis are needed.

The impact of CDI caused by *S. aureus* is high. The identification of SAB in patients with cardiac devices is associated with a 25% all-cause 12-week mortality rate and per-patient costs of up to \$83,635 in 2004 (612). Le et al. found that *S. aureus* CDIs were associated with a longer duration of bacteremia, longer hospitalization, and greater mortality than similar infections caused by coagulase-negative staphylococci (CoNS) (609). Viola et al. conducted a multicenter, retrospective review of 160 patients with *S. aureus* CDI and nonstaphylococcal CDI and found that the mortality rate was not statistically different between the two groups (613). Cardiac device infections due to MRSA are generally, but not invariably, associated with higher mortality rates than CDIs caused by MSSA. For example, Chu et al. found the distinction to

be statistically significant (612), while Chamis et al. and Roig et al. did not (44% versus 27% [$P = 0.47$] [601] and 24% versus 25% [607], respectively).

Risk factors for *S. aureus* CDI. Cardiac device infections due to any bacterial species, including *S. aureus*, tend to occur in white males over the age of 60 years (596, 597, 604, 606, 613). However, in a Danish PPM registry study that included a large number of children, Johansen et al. also found high CDI rates in children and adolescents (595). Overall, the majority of patients with *S. aureus* CDI tend to have multiple medical comorbidities, such as coronary artery disease, diabetes mellitus, congestive heart failure, and prosthetic heart valves (602). A large retrospective study at the Mayo Clinic found that late *S. aureus* CDI (>1 year after implantation), compared to late CoNS CDI, was commonly associated with hemodialysis (17% versus 4%) and corticosteroid therapy (19% versus 5%) as well as the presence of a prosthetic valve (21% versus 8%), a central venous catheter (15% versus 4%), and a remote source of infection (40% versus 10%) (609). Viola et al. reported that patients with *S. aureus* CDI tended to have more comorbid conditions and more health care-associated infections (81% versus 49%; $P < 0.001$) than patients with nonstaphylococcal CDI. Additionally, *S. aureus* CDI was more frequently associated with a history of bacteremia within the preceding year than nonstaphylococcal CDI (21% versus 4%) (613).

A number of studies have confirmed that the rate of PPM infection is much higher for replacement PPMs (5.3 infections/1,000 device-years after PPM replacement) than for first-time PPM placements (1.82 infections/1,000 device-years after initial PPM placement) (591, 595, 596). The risk for *S. aureus* CDI is increased by recent instrumentation of the device (602). Under-scoring this point, it is estimated that as many as 24% of *S. aureus* CDIs occur within 3 months of cardiac device implantation or revision (602).

Clinical manifestations. The most common clinical manifestations of early *S. aureus* CDI are localized pain and erythema of the generator pocket (602, 603). In contrast, in late *S. aureus* CDI, the leads are most commonly involved, and the generator pocket typically appears normal (602). Patients with *S. aureus* CDI more commonly present with fever, leukocytosis, tachycardia, chills, hypotension, malaise, and anorexia than do patients with CDI due to CoNS (609) or other nonstaphylococcal bacterial causes of CDI (613). Similarly, patients with *S. aureus* CDI are more likely to present with leukocytosis, a higher mean WBC count, an elevated ESR, and bacteremia than are those with nonstaphylococcal CDI (613). It is important to emphasize that the absence of signs or symptoms of systemic infection does not exclude the possibility of *S. aureus* CDI, especially if the infection has been present for an extended period or if it is limited to the generator pocket. In such settings, clinical presentation may be limited to localized inflammatory signs at the site of the pocket, without any systemic symptoms (604, 614).

Management. Sohail et al. proposed guidelines for the diagnosis and management of CDI in 2007 (604). They outlined that the first step in cases of suspected CDI is to obtain at least two blood cultures. In the case of positive blood cultures or prior antibiotic therapy, TEE is warranted. Should TEE demonstrate CDI, surgical removal of the device is warranted, regardless of clinical presentation. The explanted device and leads should be cultured and Gram stained (615), and postoperative blood cultures should be drawn (604). Generator pocket site tissue should be obtained, as culture

of tissue has a higher yield than that of swabs of the pocket site (616). It should also be borne in mind that leads are usually extracted through an open generator pocket and thus prone to lead contamination. Antibiotic treatment without device and lead extraction for *S. aureus* CDI has a high failure rate (604, 611, 617). Therefore, complete device removal is integral to the treatment of CDI (615).

Current American Heart Association guidelines recommend that patients begin i.v. vancomycin until culture susceptibility test results return. Should the *S. aureus* isolate demonstrate susceptibility to methicillin, the patient may switch to a single antistaphylococcal β -lactam such as nafcillin or cefazolin (615). In the case of β -lactam allergy or MRSA infection, vancomycin should be continued (615). While no clinical trials have been conducted to determine the appropriate duration of antibiotic therapy for CDI, current guidelines for CDI recommend 7 to 10 days of antibiotics after device removal if the infection is limited to the pocket site and the extracted device shows only device erosion without inflammatory changes (615). If the CDI does not meet these criteria, the patient should undergo 10 to 14 days of antibiotics (615). A course of at least 2 weeks of antibiotic therapy is recommended after device extraction if the patient had bacteremia, and a course of at least 4 weeks is recommended for patients with >24 h of ongoing positive blood cultures despite device extraction (615). After device removal, the patient should be reevaluated as to whether reimplantation of the device is indicated (615). If replacement is warranted, the new site should be contralateral to the extraction site (615). Additionally, blood cultures should be negative for at least 72 h prior to replacement (615).

Intravascular Catheter Infections

Epidemiology. Intravascular catheters may become directly infected at the hub site during insertion or manipulation (618–620), with the subsequent complication of central line-associated bloodstream infection (CLABSI). The reported incidence of CLABSI ranges from 1.3 to 6.8 events per 1,000 device-days (621–624). Notably, the incidence of CLABSI was found to be >3-fold higher for intensive care units (ICUs) in countries in Latin America, Asia, Africa, and Europe than for ICUs in the United States (622). *S. aureus* follows CoNS as the major bacterium causing CLABSI, responsible for 14 to 41% of CLABSIs (624–627). *S. aureus* CLABSI is associated with a 7 to 21% mortality rate (612, 628–632) and has been estimated to cost \$9,830 to \$14,136 per episode (633).

According to the Centers for Disease Control and Prevention (CDC), there has been a 57% reduction in the number of CLABSIs due to all pathogens over the past 9 years in the United States, with 25,000 fewer cases in 2009 than in 2001 (634). In particular, the number of *S. aureus* CLABSIs has declined by 73% over this time period (634), with reductions in MSSA and MRSA CLABSIs of 74% and 50%, respectively, between 1997 and 2007 (67). This decrease in the incidence of *S. aureus* CLABSI is attributed in part to the dissemination and uptake of MRSA transmission prevention guidelines (67, 635, 636) as well as improved central line insertion practices.

Central venous catheter (CVC) colonization and the subsequent development of CLABSI vary by the site of insertion, with the highest risk for femoral vein insertions and the lowest risk for subclavian vein insertions (625). CVC bacterial colonization increases with an increasing duration of insertion (625), and the presence of a central line extending beyond 30 days significantly

increases the risk for contracting MRSA CLABSI (637). Sadoyama et al. found two independent risk factors for *S. aureus* CLABSI: (i) the presence of *S. aureus* at the insertion site (OR, 6.98; 95% CI, 2.42 to 21.90) and (ii) the presence of *S. aureus* in the tip of the catheter (OR, 7.95; 95% CI, 1.95 to 19.60) (624).

Catheter-related SAB is particularly prominent in hemodialysis patients. Marr et al. monitored 102 patients for 16,081 catheter-days and reported that 40% of patients developed bacteremia, with an incidence of 3.9 episodes per 1,000 catheter-days (638). *S. aureus* was the most commonly isolated organism, occurring in 44% of the cases. Risk factors for catheter-related SAB were a previous episode of bacteremia and an immunocompromised state (638). Rates of SAB in hemodialysis patients differ significantly by the type of vascular access, with the highest rates occurring in patients with a tunneled, cuffed catheter (59.5%), followed by patients with arteriovenous grafts (36%) and finally by patients with arteriovenous fistulas (4.5%) (639).

Clinical manifestations. Clinical features of CLABSI are usually nonspecific. Fever, erythema, tenderness, induration, and/or purulence at the catheter insertion site may suggest catheter infection (628, 630, 632, 640). Purulence at the catheter insertion site is much more common in CLABSIs due to *S. aureus* than in those due to Gram-negative rods (50% versus 2.4%; $P < 0.01$) (641). Blood cultures positive for *S. aureus* in a patient with a catheter but lacking another identifiable source of infection likely indicate catheter infection (642).

Anywhere from 6 to 30% of patients with CLABSI have been reported to develop complications (630, 643, 644) such as native valve IE (9 to 18%) (640, 643, 645), prosthetic valve IE (146), septic arthritis (3.4%), and vertebral OM (2.2%) (643). Fowler et al. found the following five risk factors for hematogenous complications in *S. aureus* CLABSI: (i) the presence of a foreign device, such as a long-term catheter or prosthesis (RR, 4.0; 95% CI, 1.7 to 9.3); (ii) community-onset infection (RR, 2.3; 95% CI, 1.2 to 4.1); (iii) hemodialysis dependence (RR, 3.8; 95% CI, 2.1 to 7.1); (iv) increased symptom duration (OR for each day, 1.1; 95% CI, 1.1 to 1.2); and (v) a higher mean APACHE II score ($P = 0.02$) (643). Other studies have found that immunosuppression and preexisting valvular disease are also host factors that increase the risk for complications associated with *S. aureus* CLABSI (629). Methicillin resistance is also a risk factor for complications stemming from an *S. aureus* CLABSI (643).

Although any hematogenous complication can arise from an episode of *S. aureus* CLABSI, endovascular infections are particularly common (643). In particular, the possibility of septic thrombophlebitis should be considered in every patient with *S. aureus* CLABSI who exhibits persistent bacteremia. In a prospective cohort study, 48 consecutive patients with *S. aureus* CLABSI involving a catheter in the neck or upper torso underwent targeted physical examination (e.g., for upper arm circumference, asymmetric venous markings in the upper chest, and the presence of hand vein collapse when hands are raised above the heart level) and Doppler ultrasonography to evaluate the prevalence of septic thrombophlebitis. Importantly, an ultrasonogram was provided to all enrolled study subjects and was not dependent upon clinical suspicion of underlying septic thrombophlebitis by the treating physicians. Two key findings arose from this study. First, septic thrombophlebitis was common; 71% of the 48 patients had definite or possible hemodynamically significant thrombosis visualized by Doppler ultrasonography. Second, physical examination

was inadequate to exclude the presence of underlying septic thrombophlebitis. The sensitivity of physical examination compared to Doppler ultrasonography was only 24%. Based upon these findings, ultrasonography should be performed on every patient with *S. aureus* CLABSI and persistent bacteremia or persistent fever, even in the setting of a normal physical examination (646, 647).

Prevention and treatment. Rates of *S. aureus* CLABSI have declined significantly in the past decade (67). This reduction has been attributed to improved procedures for catheter insertion and care (67, 648–650). There are extensive and updated guidelines provided by the CDC for the prevention of line-related infections (651). The major areas of emphasis are “1) educating and training health care personnel who insert and maintain catheters; 2) using maximal sterile barrier precautions during central venous catheter insertion; 3) using a > 0.5% chlorhexidine skin preparation with alcohol for antiseptics; 4) avoiding routine replacement of central venous catheters as a strategy to prevent infection; and 5) using antiseptic/antibiotic impregnated short-term central venous catheters and chlorhexidine impregnated sponge dressings if the rate of infection is not decreasing despite adherence to other strategies” (651). The guidelines emphasize the implementation of bundled strategies and documenting and reported rates of compliance with all components of the bundle.

The key tenets for the management of *S. aureus* CLABSI (647) are the removal of the infected catheter, the use of appropriate antibiotics guided by antibiotic susceptibility testing, and a delineation of the SAB into complicated or uncomplicated infection. Uncomplicated SAB should be treated with at least 14 days of parenteral therapy (79, 647). Treatment of *S. aureus* CLABSI for <10 days has been associated with relapse of infection (629, 640) and is ill advised. Complicated SAB associated with a vascular catheter should be managed with 4 to 6 weeks of therapy. In all cases of *S. aureus* CLABSI, removal of the infected catheter is associated with a higher cure rate and a lower mortality rate (629, 632, 647, 652) and should be regarded as the standard of care (647). Rarely, catheter removal is sufficiently problematic in an individual patient with limited i.v. access that the risk imposed by attempting to retain the infected vascular access point is exceeded by the risk of removing it. In such desperate situations, adjunctive antibiotic lock therapy, in which antibiotics are instilled into the catheter lumen for extended periods, should be considered in addition to parenteral therapy (628, 647, 653).

Infections Involving Other Prosthetic Devices

Infection of breast implants. (i) Epidemiology. Approximately 1 to 2.5% of breast prostheses develop infection (654–657). Estimates for the proportion of these infections due to *S. aureus* range from 0 to 75% (655, 658, 659). For example, in a multicenter retrospective cohort of 106 patients with confirmed or suspected breast prosthesis infection, Feldman et al. found that 68% of the 31 culture-positive breast implants grew *S. aureus*, 37% of which grew MRSA (658). In contrast, none of the 65 culture-confirmed silicone breast infections reported by Ahn et al. grew *S. aureus* (659). The true incidence of *S. aureus* infection in breast prostheses is unknown, as there is currently no surveillance network that records the total number of mammoplasties and infections (660).

Breast implantation for reconstructive purposes is a significant risk factor for infection (658, 660, 661), as these patients typically have a higher degree of tissue scarring, ischemia, and delayed

wound healing (660). Other risk factors for infection are (i) hematoma formation secondary to inadequate hemostasis, (ii) seroma formation, (iii) adjuvant chemotherapy or radiation, and (iv) skin irritation (658, 660).

(ii) Pathogenesis. There are four possible routes of *S. aureus* breast implant infection: (i) contaminated implant or saline, (ii) contamination during the surgery, (iii) seeding from a hematogenous source, or (iv) contamination via the patient's skin and mammary ducts (660). The breast tissue is colonized with flora that is similar to that of the skin. The bacteria gain access to the deep breast tissue via the nipple ducts, which provide a passage for bacteria to enter the deep breast tissue from the skin surface (655, 660). This skin flora may be the source of infection during peri-areola or transareola breast surgeries (660).

(iii) Clinical manifestations. Fever, localized pain, fluctuance, erythema, and accumulation of pus in the breast are all symptoms indicative of an infected breast implant (658, 660). Additionally, capsular contraction and change in breast shape may be seen (659).

(iv) Management. A single dose of antistaphylococcal antibiotic prophylaxis prior to surgery is recommended to prevent implant infection (660). Additionally, there may be a role for antimicrobial-impregnated implants, as Darouiche et al. demonstrated the benefit of minocycline-rifampin-impregnated saline-filled silicone breast implants in reducing the incidence of *S. aureus* infection in a rabbit model (662).

The recommended management for an infected breast implant is surgical removal of the implant with postsurgical drainage, accompanied by 10 to 14 days of appropriate antibiotics (520, 660). Removal of the capsule surrounding the implant may be indicated in some cases, and immediate reimplantation is not recommended (660).

Infection of ventricular shunts. (i) Epidemiology and clinical manifestations. The reported frequency of CNS shunt infections ranges from 2 to 39% (663–665). *S. aureus* is the causative organism in 13 to 25% of infected shunts (663, 665, 666). In the most robust analysis of the epidemiology of CNS shunt infections to date, Schoenbaum et al. found that *S. aureus* was the second most common pathogen, accounting for 27% of ventriculoatrial shunts and 21% of ventriculoperitoneal shunts (663).

Some of the important risk factors for shunt infection are (i) the presence of a postoperative cerebrospinal fluid (CSF) leak (664), (ii) age of <6 months, (iii) poor condition of the skin, (iv) the presence of infection at the time of surgery, and (v) shunt reimplantation following removal secondary to infection (667).

Fever is a frequent but nonspecific sign of shunt infection (663). Other common symptoms are malaise, nausea, vomiting, and signs of increased intracranial pressure and meningeal irritation (663, 665).

(ii) Management. Management of an infected ventricular shunt generally requires surgical removal and appropriate parenteral antibiotics (665, 668). Some experts advocate that the surgery should occur in two stages. First, the infected shunt is explanted while an external ventricular catheter is placed to drain CSF and monitor intracranial pressure (520, 666). This external ventricular catheter should be replaced every 5 to 10 days (520). Once CSF culture has confirmed that the infection has been cleared, a new shunt may be implanted on the contralateral side (520).

***S. aureus* infection of penile implants. (i) Epidemiology, clinical manifestations, and risk factors.** The risk of penile prosthesis

infection is ~3 to 5%, with *S. aureus* causing ~8% of those infections (520, 669). Symptoms are typically pain, swelling, and drainage (669). Fever, leukocytosis, and positive blood cultures are less common and typically occur later in the course of infection (669). Spinal injury and steroid use are two significant risk factors for infection of penile prosthesis (669).

(ii) Management. Improved surgical approaches, including the use of antibiotic-coated hydrophilic implants and a “no-touch” surgical technique (with exchange of surgical instruments and gloves immediately prior to insertion of the prosthesis), have reduced the rates of penile implant infection (670). Management of an infected penile prosthesis without complications or bacteremia consists of 2 to 4 weeks of systemic antibiotics, and most experts now recommend a single-stage removal-and-replacement procedure with vigorous irrigation (671).

PLEUROPULMONARY INFECTIONS

S. aureus is an important cause of pneumonia. It was initially implicated as a devastating respiratory complication of influenza during the 1918 pandemic (672). It thereafter remained an infrequent but well-documented cause of community-acquired pneumonia (CAP), even in the absence of preceding influenza infection (673, 674). *S. aureus* has had a more predominant role in hospitalized patients with respiratory infections and has been implicated in each of the three other major subsets of pneumonia: hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and health care-associated pneumonia (HCAP) (675). It is also a common pathogen in patients with cystic fibrosis.

Epidemiology

S. aureus is an important cause of pneumonia in both community-onset presentations and hospital-acquired infections. Hospitalized patients quickly develop oropharyngeal colonization with nosocomial flora and can subsequently manifest lower respiratory tract infections related to these organisms (676–678). Overall, *S. aureus* has consistently been shown to be one of the most common pathogens in these health care-associated infections. For example, *S. aureus* accounted for >40% of culture-positive HCAP cases in a large U.S. retrospective cohort, with a roughly equal distribution of MRSA and MSSA (679). MRSA was found to cause 28% of VAP cases in 31 U.S. community hospitals (680). In the SENTRY Antimicrobial Surveillance Program from 1997 to 2001, *S. aureus* was the most common pathogen isolated in the United States and in Europe and the second most common organism in Latin America (681). Pooled data for Asia (682) are similar albeit with an increased incidence of other Gram-negative pathogens competing for primacy with *S. aureus* and *Pseudomonas aeruginosa*. Patients with MRSA pneumonia incur an increased cost of care compared to patients with MSSA pneumonia (683). At present, then, *S. aureus* remains a well-known pathogen in both CAP and HCAP presentations, and modern isolates are a mix of methicillin-susceptible and methicillin-resistant strains (684–687).

Recently, a new clinical entity of severe necrotizing pneumonia caused by distinct strains of *S. aureus* has emerged. The first report was of fulminant respiratory illness in four children in Minnesota and North Dakota in the late 1990s. These cases were due to infection with a novel community-associated MRSA strain type, USA400, which carried genes for PVL (264). The association between *S. aureus* isolates carrying *pvl* and necrotizing pneumonia was also noted in France (688), and subsequent reports included

otherwise healthy adults presenting with severe CAP (689–695). Despite the attention given to this new entity in both the scientific literature and the lay press, the incidence of *S. aureus* CAP is actually fairly low, estimated at 2 to 3% of all adult CAP cases in the United States, of which approximately half are caused by MRSA (696). For example, among 627 prospectively enrolled patients with CAP from 12 U.S. urban emergency departments in 2006 to 2007, 2.4% had culture-confirmed MRSA (a subset of these isolates were genotyped and were all USA300), and 1.5% had MSSA (697). Patients with MRSA isolated had a more severe clinical presentation. Prospective data from the United Kingdom are similar but with a lower proportion of cases that are due to MRSA. In 1,348 patients hospitalized with pneumonia from 2005 to 2009, a microbiologic diagnosis was made for ~30% of CAP patients, of which 9.3% and 0.6% were due to MSSA and MRSA, respectively. These rates were similar to those in the HCAP population in the same study for MSSA (10.1%) and MRSA (2.2%) (698) but were higher than those reported for a cohort of 885 episodes of CAP from Australia. In the Australian study, a microbiologic diagnosis was made in 46% of episodes, of which 2.5% and 0.2% were due to MSSA and MRSA, respectively (699).

Historically, *S. aureus* has accounted for approximately one-third of cases of empyema (700). Furthermore, *S. aureus* pneumonia or empyema may occur as a result of hematogenous spread, as with septic emboli from an infected cardiac valve, or via local extension from another infected source (701).

Risk factors. Risk factors for MSSA pneumonia are similar to those for pneumonia in general and include low body mass index, smoking, chronic lung disease, history of pneumonia, diabetes, and chronic liver disease. Risk factors for invasive MRSA disease (including, but not limited to, pneumonia) include history of hospitalization, history of surgery, and long-term-care residence (14). MRSA carriage also confers a risk of subsequent invasive disease. In a year-long surveillance study conducted by Huang et al., pneumonia was the most common form of invasive disease that subsequently developed in patients found to be carrying MRSA (702), corroborating similar data reported previously (703). In a study of patients hospitalized with *S. aureus* pneumonia, 37% of which were community-onset cases, risk factors for MRSA (versus MSSA) included tobacco use, illicit drug use, recent antibiotic use, chronic obstructive pulmonary disease (COPD), liver disease, and HIV infection (704).

While knowledge of the general factors that predispose patients to incident pneumonia is useful, the increasing prevalence of pneumonia due to resistant organisms, including MRSA, has spurred interest in identifying those patients at increased risk for these multidrug-resistant (MDR) pathogens (679). The most important risk factors are related to health care contact, which led to formal American Thoracic Society (ATS)/IDSA guidelines delineating the entity of HCAP (675), with corresponding recommendations for empirical broad-spectrum antibiotic therapy for patients meeting HCAP definitions. Patient characteristics that meet definitions for HCAP include residence in a nursing home or extended-care facility, recent hospitalization, recent antimicrobial exposure, the need for long-term hemodialysis, home infusion therapy or home wound care, and underlying immunosuppression. While these risk factors have been corroborated in other geographic settings (687, 705–708), the prevalence of potentially resistant pathogens causing HCAP in these regions varies considerably (709).

TABLE 7 Risk score for methicillin-resistant *S. aureus* pneumonia^a

Variable	No. of points assigned
Age of <30 or >79 yr	1
Recent hospitalization (≥ 2 days within the last 90 days)	2
Nursing home/long-term acute-care exposure within the last 90 days	1
Prior i.v. antibiotic therapy within the last 30 days	1
Intensive care unit admission	2
Cerebrovascular disease	1
Dementia	1
Female with diabetes mellitus	1

^a Adapted from reference 712.

Nonetheless, the overall incidence of MDR pathogens, including MRSA, is relatively low in patients with HCAP (710). To help identify patients at risk of HCAP with MDR pathogens, Shorr et al. developed and validated a clinical prediction model: 4 points were assigned for recent hospitalization, 3 points were assigned if the patient presented from a long-term-care facility, 2 points were assigned if the patient was undergoing chronic hemodialysis, and 1 point was assigned if the patient was admitted to the ICU within 24 h of evaluation in the emergency department, for a possible maximum score of 10. Those patients with a score of zero had a prevalence of resistant organisms of ~15%, whereas nearly 75% of those with a score of 6 to 10 had a resistant pathogen (711). This same group developed a separate score (derived from a different set of patients over the period of 2005 to 2009 and in a population with an overall prevalence of MRSA pneumonia of 14%) that aims to predict MRSA specifically (Table 7) (712). As might be expected, it is difficult to predict the presence of a single pathogen based on clinical features alone. While the latter scoring system could divide patients into low-risk (score of 0 or 1), medium-risk (score of 2 to 5), and high-risk (score of 6 to 10) strata, in the validation cohort, the low-risk group still had an MRSA prevalence of ~10%, while prevalence in the high-risk group was just over 30%.

Rates of HCAP caused by MDR bacteria are lower in most parts of Europe than in the United States (713). For example, although more than half of a recent cohort of 935 Italian pneumonia patients had ≥ 1 HCAP risk factor, only 6.1% had an MDR pathogen isolated, the most common of which was MRSA. Notably, MSSA was more common than MRSA among those with no risk factors (12.4% versus 2.7% of all culture-positive patients). Among those with HCAP risk factors, MSSA and MRSA were equally prevalent (12.4% and 14.4%, respectively). Recent hospitalization, nursing home residency, and chronic renal failure were predictive of isolation of MDR pathogens. Overall, *S. aureus* was the second most common bacterium isolated. Thus, it was possible to develop another prediction score for this setting (714), an undertaking that has since been repeated in other geographic settings (715).

Pathophysiology

The presence of *S. aureus* in the respiratory tract can lead to a wide range of outcomes, from asymptomatic colonization to fulminant invasive disease, and the host immune response is a significant determinant of this outcome. Of the numerous virulence factors important in staphylococcal infections, several appear to be specifically implicated in the development of pleuropulmonary infec-

tions, especially in the most severe manifestation of *S. aureus* pneumonia, the hemorrhagic necrotizing phenotype. Massive polymorphonuclear leukocyte influx into the lung parenchyma and the formation of microabscesses are typical findings of *S. aureus* pneumonia (716) and have been associated with PVL positivity (688). In a murine model, Labandeira-Rey et al. demonstrated that PVL is sufficient to cause pneumonia and does so by inducing changes in the transcription of genes that encode secreted and cell wall-anchored proteins, including *spa* (717). Similar findings were noted in a rabbit model (718). However, a recent meta-analysis of studies examining the role of PVL in clinical staphylococcal disease found that PVL positivity, while common in SSTIs, was comparatively rare in pneumonia (286). Importantly, Bubeck-Wardenburg et al. found that another pore-forming toxin, called alpha-hemolysin, but not PVL, was essential for the pathogenesis of clinical pneumonia (719). At the cellular level, proposed mechanisms for the action of alpha-hemolysin include activation of the NLRP3 inflammasome, leading to necrotic lung injury (720), and alpha-hemolysin promotion of platelet-neutrophil aggregates, which then dysregulate inflammatory responses and contribute to tissue destruction (721). Notably, immunization against alpha-hemolysin is protective against lethal pneumonia in mice (722, 723).

Clinical Features and Outcomes

There are distinct clinical phenotypes associated with health care-associated MRSA (HCA-MRSA) and CA-MRSA pneumonia. HCA-MRSA tends to occur in elderly patients with multiple comorbid illnesses and follows a clinical course similar to that of pneumonia caused by Gram-negative organisms. Bacteremia, when it occurs, is a poor prognostic indicator. In a retrospective review of 60 patients with nosocomial bacteremic *S. aureus* pneumonia (42 with MRSA and 18 with MSSA), the mortality rate was >50% in both MSSA and MRSA cases (724). Vidaur et al. noted higher mortality rates and higher medical resource utilization, including longer time on a ventilator, for patients with MRSA VAP than for patients infected other pathogens, including MSSA (725). This excess mortality with MRSA, however, has not been demonstrated by other investigators (726).

Staphylococcal PVL-positive necrotizing pneumonia was initially described in young, previously healthy patients with a preceding flu-like illness, with rapid onset of severe symptoms, high fever, leukopenia, cavitory pneumonia, and a fulminant course with mortality rates of 56% (727, 728). During the 2009 influenza A virus H1N1 pandemic in France, among 103 patients admitted to the ICU with confirmed influenza A virus H1N1 2009 infections, 48 had bacterial coinfection (54% due to *Streptococcus pneumoniae* and 31% due to *S. aureus*) (729). The median age of those with bacterial coinfection was 43 years, and the mortality rate was 21%. In this setting, procalcitonin levels of >0.8 µg/liter had a sensitivity of 91% for detecting bacterial coinfection (729). However, previously well patients with influenza virus infections are not the only patient group affected by PVL-positive necrotizing pneumonia: in a retrospective review of 15 patients with CA-MRSA CAP, only 1 had evidence of preceding influenza, there was no seasonal pattern, and half of the patients were immunocompromised. Pleural effusions were present in 9/15 patients, and the mortality rate was 13% (730). An examination in France of 133 PVL-producing *S. aureus* pneumonia cases found a mortality rate of 39%, and methicillin resistance was not an independent predic-

tor of mortality (731), in keeping with similar findings from a prior meta-analysis of 107 cases (732).

In patients with CF, poor clearance of viscous airway secretions leads to colonization and subsequent clinical infections with pathogenic bacteria. *S. aureus* is the most common of these pathogens, an increasing proportion of which are MRSA (733). *S. aureus* may form biofilms in the airways of patients with CF (734), contributing to the persistence of colonization and antibiotic failure. SCVs are also found frequently in patients with CF; 17% of 252 CF patients in a German study (735) and 24% of 100 children with CF in a U.S. study (736) (15) had airways colonized with SCVs, which is associated with worse lung disease (735, 736). Colonization with MRSA appears to be an independent predictor of mortality in CF patients (737).

Management

With the advent of guidelines recommending empirical antibiotics targeting MRSA in high-risk patients with pneumonia, the question has naturally arisen as to whether such guideline-concordant therapy improves outcomes. In a retrospective review of 757 patients with HCAP (27% of whom had MRSA), inappropriate initial antimicrobial therapy and the absence of empirical anti-MRSA antibiotics were associated with a higher risk of mortality (738). In a similar investigation of patients admitted with pneumonia in Canada, only 10 of 1,220 patients with culture-positive infection had MRSA isolated, and guideline-concordant therapy did not influence HCAP mortality (739). Similar findings have been documented in other settings of low MRSA prevalence (740). Some authors have found higher mortality rates with the use of guideline-concordant empirical therapy, with a trend toward higher mortality rates even in the subset with MRSA (741, 742). A more nuanced view emerged from Madaras-Kelly et al., in which receipt of “guideline-similar therapy” increased the 30-day mortality rate overall but appeared to improve mortality in the subset of patients with an *a priori* increased risk of resistance to ceftriaxone or moxifloxacin (743).

Two major clinical trials have compared the uses of vancomycin and linezolid in known cases of MRSA pneumonia. Rubinstein et al. randomized patients with nosocomial pneumonia to receive vancomycin or linezolid, each in combination with aztreonam (744). Given the few MRSA patients in either group, the trial was then extended to include an additional 345 patients (745). Clinical cure rates did not differ between vancomycin and linezolid treatments, while the microbiologic success rate was slightly higher in the linezolid group. In a *post hoc* MRSA subgroup analysis, linezolid was associated with cure in 36/61 (59%) patients, compared to 22/62 (36%) for vancomycin ($P < 0.01$), and also improved survival of 60/75 (80%) patients in the linezolid group, versus 54/85 (64%) patients in the vancomycin group ($P = 0.03$) (746). Interpretation of these results was complicated by the use of a vancomycin dosing regimen that was less aggressive than would be recommended under current dosing guidelines (747). This uncertainty paved the way for ZEPHYR, a subsequent randomized, double-blind trial of 1,184 patients from 154 sites over 6 years that aimed to address these issues (748). In ZEPHYR, cure was defined as resolution of clinical signs and symptoms of pneumonia compared with the baseline, improvement or lack of progression determined by chest imaging, and no requirement for additional antibacterial treatment, and it was assessed at the end of the study (defined as 7 to 30 days after the end of therapy) by the investiga-

tors, with “occasional override by the sponsor.” Patients treated with linezolid had a higher clinical cure rate (58% versus 47% in the per-protocol population; $P = 0.042$), but the 60-day mortality rate was not significantly different between groups (15.7% in the linezolid group versus 17% in the vancomycin group) (748). Strengths of this study included the large sample size, the attention to vancomycin MIC values and trough levels, and extension of therapy in bacteremic patients (749). Limitations of ZEPHYR included an imbalance between per-protocol groups, as more patients in the vancomycin group had bacteremia and required mechanical ventilation. Additionally, vancomycin trough levels were suboptimal in >50% of patients (750–752). Therefore, there is uncertainty regarding the optimal antimicrobial agent for MRSA pneumonia.

In the setting of known MRSA pneumonia, ATS/IDSA guidelines recommend vancomycin, linezolid, or clindamycin, noting a stronger evidence base for vancomycin and linezolid than for clindamycin. The suggested duration of therapy is 7 to 21 days, depending on the clinical response. British Thoracic Society (BTS) guidelines advocate for vancomycin, linezolid, or teicoplanin (a glycopeptide antibiotic that is not available in the United States). However, a special case is made for PVL-producing *S. aureus*, for which the use of linezolid or clindamycin (depending on susceptibility results) in addition to rifampin is recommended, with the further addition of i.v. immunoglobulin for those with clinical deterioration or features of severe disease (753). The preference for linezolid and clindamycin over vancomycin in this setting is based upon the hypothesis that linezolid and clindamycin, which suppress toxin production, may improve survival with this specific infection, for which toxin production is a key virulence factor. This improved survival has been demonstrated in a rabbit model of necrotizing MRSA pneumonia (754) and in a pig pneumonia model (755). Two retrospective studies suggest that there may be a clinical benefit for suppression of toxins in such cases (756, 757).

Daptomycin should not be used for MRSA pneumonia, as it is inactivated by surfactant (758). However, in the case of hematogenous septic pulmonary emboli, as from right-sided endocarditis, daptomycin may be an option (119).

Ceftaroline fosamil is a broad-spectrum cephalosporin with bactericidal activity against Gram-positive pathogens, including MRSA, as well as some Gram-negative pathogens. It was studied in two identical registrational trials (FOCUS 1 and FOCUS 2) that compared ceftaroline with ceftriaxone in the treatment of adults hospitalized with CAP but not requiring ICU care and with a Pneumonia Outcomes Research Team risk class III or IV status (759). Known MRSA was an exclusion criterion (since ceftriaxone does not have significant activity against MRSA), and ultimately, only 2 patients, both in the ceftriaxone group, had cultures positive for MRSA. Ceftaroline was noninferior to ceftriaxone overall, and in the MSSA group, clinical cure was reported for 18/25 (72%) patients with ceftaroline, versus 18/30 (60%) patients with ceftriaxone. Thus, ceftaroline appears to have a potential role in the treatment of CAP, although it remains unstudied in MRSA pneumonia and in more severe CAP presentations necessitating ICU care.

For patients with CF, two ongoing studies are examining the role of decolonization (760, 761); currently, there is no clear role for attempted decolonization. It is also unknown whether a different treatment strategy should be used for acute flares due to

MRSA in CF patients (762); vancomycin and linezolid are recommended first-line therapies, as for MRSA pulmonary infections in other patient populations.

OTHER STAPHYLOCOCCAL CLINICAL SYNDROMES

Epidural Abscess

Epidural abscesses can be intracranial or spinal. Intracranial epidural abscesses are much less common than spinal epidural abscesses and usually follow surgery or trauma. Discussion in this section is limited to spinal epidural abscesses.

Epidemiology. Although a rare infection (~1 in 20,000 hospitalized patients [763]), spinal epidural abscess is the second most common infectious cause of medical malpractice in the United States (764). The incidence of epidural abscess appears to have increased over the past 30 years (765). This is likely to be in part due to the increasing availability of magnetic resonance imaging (MRI) (which is much more sensitive than previous modalities) and partly due to the increasing use of epidural catheters and electrodes for pain management. *S. aureus* is the most common causative agent of spinal epidural abscess, accounting for 60 to 73% of all cases (766–768).

Pathophysiology and clinical manifestations. An epidural abscess may arise by hematogenous seeding from an episode of SAB, by contiguous spread from an adjacent focus (such as psoas abscess or vertebral OM), or due to direct inoculation from trauma, spinal surgery, or the placement of epidural catheters (766). Although a spinal epidural abscess may occur anywhere from the cervical to the sacral spine, it is generally more likely to occur where the epidural space is larger. Thus, posterior epidural space involvement is more common than anterior epidural space involvement, and lumbar and lower thoracic epidural abscesses are more common than cervical epidural abscesses (769). Because the epidural space is a continuous vertical region, epidural abscesses generally spread over several vertebral levels and rarely may involve the entire spine. The most important potential consequence of spinal epidural abscesses is damage to the spinal cord and nerve roots, which can occur due to direct compression of the cord by an expanding collection of pus (770) or indirectly through arterial or venous ischemia. The major risk factors for *S. aureus* spinal epidural abscess include diabetes mellitus (766), injection drug use (766, 768), recent spinal surgery or trauma, and recent placement of epidural injections, catheters, or stimulating wires (771, 772). Approximately 2.5% of patients with SAB have epidural abscesses (69). Thus, any patient with SAB who complains of new or changing back pain should undergo spinal imaging, preferably with MRI, to evaluate the possibility of an epidural abscess.

The classic clinical triad for epidural abscess is back pain, fever, and neurological signs; however, the complete triad is present in only a minority of patients at presentation (773). For this reason, the diagnosis of spinal epidural abscess is often not initially considered. For example, only 40% of admitting diagnoses included spinal epidural abscess as the suspected diagnosis for one series of 43 patients ultimately found to have epidural abscess (763). Darouiche et al. (763, 765) described the following clinical staging system, which is useful for determining the timing and nature of management of spinal epidural abscesses: stage 1, back pain at the affected vertebral level; stage 2, nerve root pain radiating from the involved area; stage 3, objective motor and sensory loss and/or bladder and bowel dysfunction; and stage 4, paralysis. This staging

system is important because once patients enter stages 2 and 3, their spinal cord is under threat, and urgent surgical decompression is required.

Management. In general, surgical decompression (laminectomy, debridement of infected or necrotic tissue, and drainage of pus) is required to achieve a successful outcome in cases of *S. aureus* spinal epidural abscess. This is in conjunction with a long course of high-dose i.v. antibiotic therapy (766). Because of the possibility of permanent paralysis, spinal epidural abscess is a medical and surgical emergency. Once paralysis is established for >24 to 48 h, the damage is likely to be permanent. Thus, the key step is the early recognition of the possibility of spinal epidural abscess and rapid investigation to confirm the diagnosis. Most authors suggest that surgical decompression be performed urgently (within 24 h of diagnosis) in patients with *S. aureus* spinal epidural abscess (763, 774–776). However, it is increasingly being recognized that select patients may not require surgical intervention. Such patients include those in whom paralysis has been present for >48 h and those with early (clinical stage 1) infection with small abscesses, where a pathogen has been identified by blood culture or computed tomography (CT)-guided aspiration of the abscess (777, 778). MSSA spinal epidural abscesses should be treated with ~6 weeks of a high-dose i.v. antistaphylococcal β -lactam (e.g., 2 g nafcillin every 4 h [q4h] i.v.). For MRSA, treatment with vancomycin for a similar duration is advised, aiming for plasma levels of 15 to 20 mg/liter.

Meningitis

Epidemiology and pathophysiology. *S. aureus* is an uncommon cause of bacterial meningitis, accounting for 4.9 to 6.4% of cases (779–784). *S. aureus* meningitis may either arise by hematogenous spread from a non-CNS focus of infection or be secondary to neurosurgical intervention (785, 786). Hematogenous *S. aureus* meningitis is usually community acquired (780, 785) and, compared with postsurgical *S. aureus* meningitis, typically affects older individuals (mean age of 59 years versus 40 years; $P = 0.04$) (787) with severe medical comorbidities such as diabetes or chronic kidney disease (780, 787). The initial source of hematogenous *S. aureus* meningitis is generally IE, pneumonia, or SSTI (788). The mortality rate for hematogenous *S. aureus* meningitis is higher (43 to 50%) than that occurring postsurgically (14 to 25%) (780, 787). Among *S. aureus* meningitis cases, methicillin resistance has been increasing in recent years (786, 789–791). Specifically, Pintado et al. conducted a retrospective, multicenter study examining MRSA meningitis in adults over a 25-year period (1981 to 2005). This group found that nearly half of MRSA meningitis cases arose in the last 5 years of the study. The 30-day mortality rate for these patients was 31%. Most MRSA meningitis cases are nosocomial and postsurgical (786, 789).

Clinical manifestations and risk factors. Because meningitis is a rare complication for patients with SAB, occurring in 1.7% of 724 prospectively identified patients with SAB, clinicians need to be alert to its possibility (69). *S. aureus* meningitis typically presents with one or more of the following signs or symptoms: persistent fever, headache, stiff neck, and vomiting (786, 787, 792). Fever and change in consciousness are the two most common clinical symptoms (782, 789). Patients with hematogenous *S. aureus* meningitis typically have a greater degree of CSF leukocytosis than do postsurgical patients (787).

The major predisposing factors for postsurgical meningitis are

(i) the presence of an intrathecal device or ventriculoperitoneal shunt (780, 787, 792), (ii) recent neurosurgery, and (iii) a CSF leak (780). Of note, *S. aureus* is the second leading cause of bacterial meningitis among patients with a ventriculoperitoneal shunt (793) (see the section on *S. aureus* CNS shunt infection, above). Intravenous drug use is an important risk factor for hematogenous *S. aureus* meningitis, being present in 52% of patients in a recent series of 21 cases of hematogenous *S. aureus* meningitis from a single center in the United States (780, 794) but in only 12.5% of 96 cases from a nationwide Danish study (794).

Risk factors for mortality among patients with *S. aureus* meningitis include a hematogenous compared with a postsurgical source (e.g., 56% mortality for a hematogenous source versus 18% for a postsurgical source within a national Danish study [795]), increasing age and number of comorbidities (794), the presence of septic shock (787), and concurrent IE (782, 784).

Management. The IDSA recommends high-dose i.v. nafcillin or oxacillin to treat MSSA meningitis and vancomycin for MRSA meningitis (668). Vancomycin has poor penetration into the CSF of ~1% through uninflamed and 5% through inflamed meninges (782, 789), and in practice, it can be difficult to achieve therapeutic levels within the CSF. This is even more of an issue when the vancomycin MIC of an MRSA isolate approaches or exceeds 2 $\mu\text{g/ml}$. In such dire settings, consideration can be given to unproven adjunctive therapies such as the intrathecal administration of vancomycin (796, 797) or the addition of antibiotics such as linezolid (CSF penetration, 66% [79]), TMP-SMX (CSF penetration, ~50% [798]), or daptomycin (CSF penetration, 6% [799]).

Toxic Shock Syndrome

Epidemiology. *S. aureus* toxic shock syndrome (TSS) was first described in 1978 by Todd et al., who reported the illness in a group of 7 children (800). Shortly thereafter, *S. aureus* TSS became linked with superabsorbent tampons in menstruating women in the 1980s (801, 802), reaching an annual infection rate of 13.7 per 100,000 menstruating women (803). After the removal of highly absorbent tampons from the market, the annual incidences of *S. aureus* TSS declined to 1 per 100,000 menstruating women and 0.3 per nonmenstruating persons (804–806). The incidence of *S. aureus* TSS has remained stable since that time, with the current annual incidences reported to be 0.69 per 100,000 menstruating women and 0.32 per 100,000 total population (804). Currently, the numbers of menstrual and nonmenstrual cases of staphylococcal TSS are similar, and the most common foci of infection in nonmenstrual cases are SSTIs (804, 807). Nonmenstrual cases have been associated with a higher mortality rate than menstrual cases (807).

Pathophysiology, clinical manifestations, and diagnosis. *S. aureus* TSS is a superantigen-mediated process. Some strains of *S. aureus* secrete an exotoxin called toxic shock syndrome toxin 1 (TSST-1) (808). TSST-1 cross-links the T-cell receptor with major histocompatibility complex class II (MHC-II) on antigen-presenting cells, triggering large-scale T-cell activation and massive cytokine release (802, 809, 810). This leads to an overwhelming systemic inflammatory response syndrome and is manifested by septic shock with organ failure. The CDC reported diagnostic criteria for staphylococcal TSS (811). A confirmed case must meet all of the following criteria: (i) a fever of >38.9°C, (ii) shock (systolic blood pressure of <90 mm Hg despite adequate fluid resuscitation), (iii) a diffuse macular erythematous rash (typically followed

1 to 2 weeks later by desquamation), and (iv) specific abnormalities involving at least three organ systems. The organ system involvements that can be included are as follows: (i) gastrointestinal, with vomiting or diarrhea; (ii) musculoskeletal, with severe myalgia or creatinine kinase levels >2 times the upper limit of normal (ULN); (iii) renal, with serum creatinine levels >2 times the ULN; (iv) hepatic, with bilirubin or transaminase levels >2 times the ULN; (v) hematologic, with platelet counts of <100,000 platelets/ μ l; and (vi) CNS, with delirium without focal signs.

Management. The key aspects of treatment of *S. aureus* TSS include identifying and removing the source of *S. aureus* toxin production (e.g., tampon or surgical wound) and supportive care (812, 813). In the setting of postoperative *S. aureus* TSS, the involved surgical wound often appears normal (807, 814, 815). However, this benign appearance in no way reduces the need for surgical debridement in patients with wound-associated *S. aureus* TSS. Antibiotics, in contrast, play a secondary role in the management of TSS. Because it can block the production of exotoxins by the bacterial ribosome, clindamycin or linezolid is often added to standard antibiotic therapy (381). Intravenous immunoglobulin may also be effective, although clinical evidence of benefit is not well established, and there is less evidence supporting the use of i.v. immunoglobulin to treat staphylococcal TSS than for streptococcal TSS. Nonetheless, it is recommended that i.v. immunoglobulin be considered for patients who have had no clinical response to aggressive supportive therapy within 6 h (807, 813).

Urinary Tract Infection

Epidemiology, clinical manifestations, and risk factors. *S. aureus* is a rare cause of urinary tract infection (UTI) in the community, accounting for only 0.5 to 1% of positive urine cultures (816, 817). *S. aureus* UTI is more frequent in patients with an indwelling urinary catheter (818). Muder et al. conducted a longitudinal study of 102 patients at a long-term veteran care facility with documented *S. aureus* bacteriuria and found that 33% of the patients with *S. aureus* isolated from their urine had UTI symptoms, and 13% were bacteremic (818). Importantly, when *S. aureus* is isolated from urine in patients without an obvious urinary focus, it can reflect SAB, and thus, it is imperative to perform blood cultures for any patient with *S. aureus* bacteriuria (819). The most common symptom of *S. aureus* UTI is fever (818). Other symptoms are hematuria, altered mental status, dysuria, suprapubic pain, and, less commonly, flank pain (818). MRSA UTI is associated with longer stays in health care facilities, recent antibiotic use, and urinary catheterization (818, 820).

Management. Because catheters are a frequent cause of UTI, it is important to reduce the use of urinary catheterization to only individuals who have a clear indication for it and to remove the device as soon as clinically indicated (821). It is recommended that patients with catheter-associated UTI (once SAB is excluded) receive 10 to 14 days of appropriate antibiotics, as determined by culture susceptibility results, as well as removal and replacement of the catheter (821).

Septic Thrombophlebitis

S. aureus septic thrombophlebitis has been reported to occur in up to 8% of all patients with SAB (69). In selected populations, however, such as patients with CVC-associated SAB, the prevalence of associated thrombosis has been reported to be as high as 71%

(646) (see the section on intravascular catheter infections, above, for further details on CLABSI and septic thrombophlebitis).

S. aureus thrombophlebitis less commonly manifests as Lemierre syndrome, involving the internal jugular veins (822–824), or septic pelvic thrombophlebitis (825). *S. aureus* Lemierre syndrome may manifest as severe neck pain, nausea, vomiting, and weakness (822). Septic pelvic thrombophlebitis manifests as high fever despite antibiotics and acute abdominal pain (825). In adults, it is almost entirely associated with pelvic procedures. In children, there have been a number of reports of deep venous thrombosis associated with CA-MRSA infections (507, 510).

Treatment with anticoagulation therapy and appropriate antibiotics is recommended for cases of pelvic septic thrombophlebitis (825). For patients with central venous catheter-associated septic thrombophlebitis, Crowley et al. found a trend toward lower mortality rates in those with who received anticoagulation therapy (646). A systematic review of the use of i.v. heparin for the treatment of all forms of septic thrombophlebitis concluded that heparin was a useful addition to the antimicrobial treatment regimen and that the risk of complications from anticoagulation therapy is low (826). Thus, guidelines for the management of CLABSI suggest that anticoagulation therapy with heparin should be considered for the treatment of individuals with septic thrombophlebitis (647).

CONCLUSIONS

Clinical infections with *S. aureus* will likely remain both common and serious. Not only have there been waves of increasing antimicrobial resistance (827), but the spectrum of clinical disease also continues to change. In the past 2 decades, we have witnessed two clear shifts in the epidemiology of *S. aureus* infections: first, a growing number of health care-associated infections, particularly seen in IE and prosthetic device infections, and second, an epidemic of community-associated SSTIs driven by strains with particular virulence factors. There is no doubt that there will continue to be a shifting landscape in the interactions between host and pathogen in the decades to come.

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