that drug dosage might be adjusted on so-called mutation prevention concentration, which is two to four times higher than the MIC, rather than on MIC.[354] However, the clinical relevance of mutation prevention concentrations has not yet been assessed.

Alternative Treatments

Treatment of infections from multiresistant HCA-MRSA may be problematic. The activity of all available drugs must be tested against the isolate to establish whether some could still be used. Evaluation of the severity of the disease is also important because not all drugs are equally appropriate in serious conditions.

Alternatives Against Non–Life-Threatening Infections

Superficial and non–life-threatening infections may respond to a variety of drugs, including TMP-SMX, to which HCA-MRSA and CA-MRSA are often susceptible, combined or not with other substances such as rifampin. Other alternatives include the agents discussed in the following sections.

Tigecycline

A modified version of minocycline from the tetracycline family of molecules, tigecycline is almost universally active against gram-negative and gram-positive pathogens, with the notorious exception of *Pseudomonas aeruginosa* and a few other gram-negative organisms that can extrude the drug via efflux pumps.[355] Tigecycline overcomes current *S. aureus* tetracycline-resistance mechanisms, including ribosome protection and active efflux, and thus is effective against all tetracycline-resistant isolates. It is approved in the United States and Europe for the treatment of complicated SSTI. However, it is strictly bacteriostatic, and no trials on *S. aureus*–specific severe infections have been reported. It is still uniformly efficacious against MRSA in recent antimicrobial surveys.[356] The drug must be administered intravenously. Increased mortality in the aggregated clinical trials is also a concern.[357] The drug should not be used in severe situations.

Aminomethylcyclines

This new class of minocycline derivatives, structurally related to tigecycline, includes two recently approved drugs, omadacycline (see Chapter 26) and eravacycline. Both have promising in vitro activity against *S. aureus*, both methicillin-susceptible and methicillin-resistant isolates, but insufficient clinical data to estimate their use.

Quinupristin-Dalfopristin

Quinupristin-dalfopristin combines a streptogramin B (quinupristin) and a streptogramin A (dalfopristin).[358] It is active against both MLS_B-susceptible and MLS_B-resistant staphylococci. It is highly bactericidal against MLS_B-susceptible isolates, but tends to be less bactericidal in the case of constitutive MLS_B resistance, which is practically always the case with HCA-MRSA. Standard dosage is 7.5 mg/kg IV q12h, but larger doses (7.5 mg/kg q8h) have been suggested against constitutive MLSB resistant strains. Experimental data indicate that combining quinupristin-dalfopristin with a β-lactam increases its activity against MRSA, even though the β-lactam is inactive on its own.[359] One limitation of quinupristin-dalfopristin is its venotoxicity, which makes it necessary to administer the drug through a central catheter. Arthralgia and myalgia are significant side effects.

Lipoglycopeptides

Semisynthetic derivatives of glycopeptides, lipoglycopeptides carry modifications of specific functional groups. Three lipoglycopeptides are currently approved for SSTIs in the United States: telavancin, dalbavancin, and oritavancin.[237,360,361] Like vancomycin, they bind to the D-ala-D-ala terminal of peptidoglycan precursors, thus inhibiting both transpeptidation and transglycosylation. In addition, the presence of lipophilic pharmacophores allows the molecules to interact with the plasma membrane, which leads to dispersion of the membrane potential and rapid bacterial killing. Their lipophilic nature confers high binding (≥90%) to plasma proteins and thus prolongs their plasma half-life.[362] For instance, dalbavancin can be given only once a week.

All three compounds are active against antibiotic-susceptible and antibiotic-resistant (including vancomycin) gram-positive pathogens and showed efficacy in various animal infection models. In a double-blind complicated SSTI trial, dalbavancin given once weekly for 2 weeks (1 g at day 1 and 0.5 g at day 8, IV) was highly effective (success rate, >90%) and comparable to linezolid given twice a day (600 mg IV q12h; may be later switched to oral therapy) for the same length of time.[363] Oritavancin given 1200 mg IV once for acute SSTI, including MRSA infections, gave comparable results to vancomycin 1 g (or 15 to 20 mg/kg) IV q12h for 7 to 10 days.[364] The high cost of dalbavancin and oritavancin appears to factor in the cost of intravenous vancomycin administration.

Of note, however, high binding to plasma protein may hamper diffusion of the drug inside therapeutic sanctuaries such as abscesses or infected vegetations. This limitation was demonstrated years ago with teicoplanin[365] and might have been responsible for recently described treatment failure of dalbavancin in right-sided *S. aureus* endocarditis.[366] Data are lacking regarding use of this drug family against severe *S. aureus* infections.

Alternatives Against Severe Infections

There is a notorious lack of good alternatives for use in deep-seated or life-threatening infection. Vancomycin is one of the first choices in such situations. However, poor response to vancomycin may occur in a substantial proportion of patients because the drug is poorly bactericidal and selects for resistant mutants.[282,283,297]

Combination Therapy

Combining vancomycin with an aminoglycoside increases in vitro bactericidal activity. However, the clinical benefit of adding aminoglycosides to vancomycin is not demonstrated, and both kidney and ototoxicity are a matter of concern.[367]

An interesting alternative is to take advantage of the vancomycin–β-lactam or vancomycin-daptomycin seesaw effects,[318] as discussed in the "Daptomycin" section earlier. The fact that resistance to methicillin or daptomycin and resistance to vancomycin are mutually exclusive has yielded several successful therapeutic attempts.[368] An open-label study in MRSA bacteremia demonstrated that combining vancomycin with flucloxacillin shortened the duration of bacteremia to 1.94 days, as compared with 3 days with vancomycin.[369] Moreover, the so-called CAMERA2 trial is now studying vancomycin or daptomycin combinations with antistaphylococcal β-lactams (flucloxacillin, cloxacillin, or cefazolin) on a larger scale.[370]

In addition, there is a growing interest in combining fosfomycin plus β-lactams (e.g., imipenem) as a rescue therapy for complicated MRSA bacteremia or endocarditis.[371] This combination is still being evaluated.

β-Lactams With Improved Penicillin-Binding Protein 2A Affinity

Improving the affinity of β-lactams for MRSA-specific PBP2A has been the purpose of intensive research.[278] Work on the structure of PBP2A and potential blocking of PBP2A–β-lactams indicates that the active site of the enzyme is closed in the resting state and thus difficult to reach with the drug. However, when the enzyme is exposed to cell wall precursors or β-lactams with appropriate pharmacophores, allosteric interactions at other portions of PBP2A trigger opening of the active site, providing access to the precursors or to the blocking drug.[372] The success of this interaction probably depends on the hydrophobic pentaglycine side chain of the precursor (see Figs. 194.12 and 194.13) and thus on the presence of hydrophobic pharmacophores on the β-lactam molecule.[278] This poses solubility problems, which were solved by delivering the compound as a prodrug, as in ceftobiprole medocaril.

Ceftaroline is the first of these agents approved for use in the United States for complicated skin and skin structure infections and nonstaphylococcal community-acquired pneumonia (CAP). It has activity against MSSA and MRSA, with MICs for MRSA of 0.5 to 2 mg/L, and 0.12 to 0.25 mg/L for MSSA. The "AWARE" susceptibility survey, which gathered 21,046 *S. aureus* isolates from 42 US centers from 2010 to 2016, showed persistent (>97%) susceptibility to ceftaroline.[341] Ceftaroline was equivalent to ceftriaxone in MSSA pneumonia; MRSA pneumonia was not

systematically studied. Ceftaroline has been examined in parallel studies of complicated skin and skin structure *S. aureus* infections in comparison with vancomycin-aztreonam. The ceftaroline-vancomycin population microbiologic profiles consisted of 73.4% and 84% *S. aureus* infection (34.3% and 32% MRSA; 39.9% and 50.9% MSSA), respectively. Clinical cure rates were 95.1% and 91.4%, respectively, with microbiologic and adverse event outcomes that were similar to those in the comparator.[373,374] The clinical use of the drug is compromised by the lack of a comparative study in major MRSA diseases, such as bacteremia, endocarditis, and osteomyelitis. Multiple reports have focused on its activity in vitro against isolates nonsusceptible to vancomycin and daptomycin, and its clinical use in combination with other agents for the treatment of severe MRSA infections such as bacteremia and endocarditis, which does not answer the question of whether ceftaroline alone would be an effective treatment.[341,374–376] Case series of salvage treatment in refractory MRSA bacteremia, pneumonia, and endocarditis (including prosthetic valve infection) have been reported and suggest that the drug may be an effective option, alone or in combination.[319,377–380]

Development of Nonantibiotic and Vaccine Strategies

A number of nonantibiotic strategies are being investigated to circumvent *S. aureus* antibiotic resistance. These encompass novel AMPs, virulence modulators, antibiotic resensitization, immunomodulation, bacteriophages (phages), phage endolysins (lysins), and vaccines.

Antimicrobial Peptides

AMPs include primarily cathelicidin-like peptides purified from various animal or insect venoms, and synthetic derivatives of them.[381,382] AMPs are positively charged amphiphilic peptides. It was recently shown that artificially increasing their charges increased their bactericidal activity as well.[383] On the other hand, *S. aureus* resists the detrimental effect of AMPs by increasing the charge of its own cell wall or plasma membrane via the *dlt* operon and *mprF,* which act as repelling factors (discussed in "Immune Evasion" earlier).[142] Whether increasing the AMP charges will upset the bacterial resistance mechanism is not clear. Moreover, AMPs still have relatively high MICs for *S. aureus*.[383]

Virulence Modulation

Virulence modulators include primarily inhibitors of SortA, which block the anchoring of *S. aureus* surface adhesins[96,98]; iron-capturing determinants, which also promote infection[97,99,102,384]; and inhibitors of *agr,* which block the secretion of toxins.[61,64] Although the blocking of surface protein and toxin secretion is conceptually sound, none of these methods reached total protection in animal models.[385,386]

Because *S. aureus* virulence results from the intertwining of both surface-attached and secreted factors, one should ideally administer the two kinds of inhibitors simultaneously to prevent or damper infection severity. However, although promising, this method will probably not offset the need to eradicate the microorganisms from the infection site.

Immunomodulation

Reports on the production of IL-17A by γ/δ T cells and the benefit of IL-17A in stimulating innate immunity and impeding skin and nasal colonization by *S. aureus* are quite promising[156,157] (see also "Escaping Cell-Mediated Immunity" earlier). Another strategy consists of sensitizing *S. aureus* cells to complement and phagocytes, referred to as "lysibodies"[387]; this is described in the "Phage Lysins" section later. Whether prescribing IL-17A or lysibodies will be beneficial in humans remains to be determined.

Antibiotic Resensitization

Statins have pleiotropic effects that alter membrane compartmentalization in both eukaryotes and prokaryotes[388] and were associated with improved clinical outcomes in infected patients.[389,390] In the case of MRSA, it was recently shown that antibiotic resensitization was due to altered PBP2A positioning.[391] The authors demonstrated that PBP2A positioning in the cell membrane depended on the dynamics of "functional membrane micro-domains" (FMMs), which are the bacterial equivalent of membrane rafts in eukaryotic cells. FMMs depend on the interaction of membrane lipids with the scaffold protein "flotillin," with which statins interfere. Thus, statins alter both eukaryotes and prokaryotes,[388] in which they may restore susceptibility to antibiotics—that is, to methicillin and its derivatives in the case of MRSA. This remarkable antibacterial benefit of statins, associated with additional in vitro[392] and clinical observations,[389,390] warrants further scrutiny.

Another antibiotic sensitization study addressed the eradication of intracellular *S. aureus* persistence. It showed that conjugating antibody and antibiotics in a system in which antibiotics became activated only in the phagolysosomes was superior to vancomycin in eliminating intracellular *S. aureus* and treating bacteremia in mice.[393] However, once again, the limitation may be the antiphagocytic strategies of *S. aureus.*

Phage Lysins

Phage lysins and phage therapy are coming close to clinical applicability.[394,395] Phages produce peptidoglycan hydrolases (lysins) to burst the host bacteria and release their progeny at the end of their replication cycle. Lysins can be purified and used to lyse gram-positive bacteria very effectively from the outside. Gram-negative bacteria are protected from outside-in lysin diffusion by their outer membrane and are thus naturally resistant to lysin therapy. Several anti–*S. aureus* phage lysins were produced, and demonstrated potent in vitro and in vivo activity in animal models[396–398]; however, few successful cases of treatment of refractory *S. aureus* skin infections in humans have been reported.[399] Lysins are not yet available for routine clinical use, but two prospective clinical trials are underway in *S. aureus* dermatitis[400] and BSIs (https://clinicaltrials.gov/ct2/show/NCT03163446?term=cf-301&rank=1).

An interesting development of lysins in the field of immunomodulation is via so-called lysibodies.[387] It consists of fusing a lysin peptidoglycan-binding domain to an IgG Fc fragment. The lysin peptidoglycan-binding domain of the construct binds to the conserved peptidoglycan and exposes its Fc portion at the bacterial surface. The Fc portion attracts complement and professional phagocytes and promoted bacterial clearance both in vitro and in a mouse sepsis model.[387] It remains to be determined whether *S. aureus* will be able to circumvent lysibodies via their immune escape armamentarium (discussed in "Immune Evasion" earlier).

Phage Therapy

The strategy of phage therapy is generating growing interest.[395] Phages have been used against bacteria since the early 1920s, but were abandoned in Western countries after the introduction of antibiotics. In contrast, phages were continuously developed in the countries of the former Soviet Union, particularly at the Eliava Institute in Tbilisi, Georgia.[401] Phages are very rapidly bactericidal and can synergize with antibiotics.[402] Aside from ample experience from the Eastern countries, no reported phase III comparative clinical trials on phage therapy have been performed, with the exception of the multicenter European Phagoburn study on burn wounds infected with *P. aeruginosa* (http://www.phagoburn.eu), the results of which are still preliminary. On the other hand, there are recent case reports on successful phage therapy of *S. aureus* osteomyelitis and diabetic ulcers,[401,403] and at least one ongoing phase I study using anti–*S. aureus* phages in chronic rhinosinusitis is planned (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=368275). Phage therapy is promising, but it still requires careful comparative assessment.

Vaccines

Vaccination is a very important area of research both in human and in veterinary medicine. However, considering the arsenal of immune evasion strategies of *S. aureus* (discussed in "Immune Evasion" earlier), this issue is an immense challenge. Vaccines pursue one of three aims: blocking the effect of toxins, blocking the functional surface adhesins or other relevant proteins, or stimulating phagocytosis. Experimental vaccines have been developed by a variety of means, including DNA vaccines, and against constituents as diverse as the capsule or specific surface determinants, including PBP2A and adhesins. Most of these vaccines conferred some protection in experimental models, and in one trial a conjugated capsular vaccine conferred promising but transient

protection in patients on hemodialysis.[404] A trial using a vaccine targeted on the IsdB iron-binding LPXTG-bound protein to prevent deep sternal wound infections did not provide protection and paradoxically increased the mortality rate in *S. aureus*–infected patients.[405]

One critical point regarding extrapolation of results in mouse models to human is that mouse thrombocytes do not carry a platelet immunoglobulin Fc receptor similar to FcγRIIA in human thrombocytes.[406] As discussed in the "Contribution of Coagulation" section, *S. aureus* activates platelets and hijacks them to colonize tissues with inflamed or injured endothelia. Hence, antibodies directed to the *S. aureus* surface expose Fc fragments that in turn activate platelets via FcγRIIA (in humans) instead of binding complement and attracting leukocytes, and help channel staphylococcal aggregates to injured tissues. In contrast, this is not expected to occur in the case of neutralizing antibodies that are directed against soluble toxins, which might be a better option. These opposed effects of surface-directed versus toxin-directed antibodies are convincingly supported by studies examining vaccination against experimental PVL-related pneumonia.[407]

As yet, no approved antistaphylococcal vaccine is available for clinical use, but there is one pending phase I/II study targeting leukocidins (https://clinicaltrials.gov/ct2/show/results/NCT01011335?term=staphylococcus+aureus&draw=5&rank=43), and hope still exists regarding the targeting of mixtures of *S. aureus* surface-bound and secreted determinants.[408]

CLINICAL ASPECTS AND EPIDEMIOLOGY

Over the last 2 decades, the increase in medical procedures such as major operations, chronic dialysis, organ transplantation, and cancer chemotherapy has profoundly modified the epidemiology of *S. aureus* infections worldwide. With the recent rise in invasive procedures, *S. aureus* has become a leading cause of nosocomial and health care–related infections.[409,410] Along with the pressure toward shorter lengths of stay in acute-care settings, increasing numbers of such health care–related *S. aureus* infections are now diagnosed in subacute or long-term care facilities.[411,412]

S. aureus invasive infections consistently result in mortality rates as high as 20% to 30%,[413–415] especially when associated with antibiotic resistance (i.e., methicillin resistance)[411] or when occurring in acutely critically ill patients[416] or in patients with chronic conditions such as hemodialysis.[417] This translates to an important social and economic burden: Inpatients with *S. aureus* infection had a hospital stay that was three times longer (14.3 vs. 4.5 days), charges that were three times higher (US $48,824 vs. $14,141), and a risk of in-hospital death that was five times greater (11.2% vs. 2.3%).[418] Additional costs incurred because of methicillin resistance were estimated in 2015 to be approximately $3.3 billion yearly for US intensive care units (ICUs).[419]

Clinical Spectrum

S. aureus is responsible for an array of infections wherein it is either present at the infection site or acts at a distance by secreting toxins (see "Regulation and Virulence Determinants" section). Incidence rates range between 28.4 and 35.4 per 100,000 inhabitants per year[413,420]; it causes mainly skin and soft tissue infection (40%), lower respiratory tract infection (20%), and BSI (20%).[421]

A rising incidence of *S. aureus* health care–related infections has been observed and can be attributed to medical progress.[422] The increasing number of invasive procedures and the use of inserted or implanted foreign bodies has indeed created a unique niche for this versatile bacterium, which is very well equipped with numerous virulence factors (see "The Journey to Invasive Disease" earlier). Accordingly, *S. aureus* is a leading cause of surgical site infections (SSIs; 20%–45% of cases),[409,423] catheter-related bloodstream infections (CRBSIs; 13%–40% of cases),[409,424] and ventilator-associated pneumonia (25%–28% of cases).[409,425]

In the community, it is also one of the primary causes of native and prosthetic valve endocarditis (23%–30% of cases)[422,426–428] and the leading organism responsible for osteoarticular infections (40%–70% of cases).[429–431] Finally, *S. aureus* is the second most frequent cause of community-onset bacteremia after *Escherichia coli* (15%–23.5%).[432]

Risk Factors for *Staphylococcus aureus* Infection

Population-based studies have consistently identified male and very young and elderly individuals as being at increased risk for *S. aureus* infections. Moreover, two studies showed that the most important risk factor is necessity for dialysis, either peritoneal (relative risk [RR], 150–204) or hemodialysis (RR, 257–291). Other conditions that increase the risk of invasive *S. aureus* infections include diabetes (RR, 7), cancer (RR, 7.1–12.9), rheumatoid arthritis (RR, 2.2–9.2), human immunodeficiency virus (HIV) infection (RR, 23.7), intravenous drug use (RR, 10.1), and alcohol abuse (RR, 8.2; Table 194.7).[420,433]

Rare but classic predisposing factors also encompass chemotactic and phagocytosis defects. Inheritable chemotactic defects include Job syndrome, Chédiak-Higashi syndrome, Wiskott-Aldrich syndrome, and Down syndrome. *Job syndrome* is a condition that involves recurrent eczema with repeated skin infections and cold abscesses. *Chédiak-Higashi syndrome* is defined clinically by albinism and recurrent *S. aureus* infections and cytologically by giant granules in phagocytic and other cells. Acquired chemotactic defects are also relatively rare and include rheumatoid arthritis and decompensated acidotic diabetes mellitus. Opsonic defects, whether inherited or acquired, are predisposing factors for all kinds of pyogenic infections and are not specific for *S. aureus*. They are exemplified by selective or combined hypogammaglobulinemias and various kinds of complement defects.

However, one of the most important factors that independently adds to all these predisposing conditions is chronic *S. aureus* nasal carriage (see later discussion). Whether they are in the hospital or in the community, patients mostly become infected with their own carriage strain.[24] Therefore it has been proposed that patients at high risk for *S. aureus* nasal or cutaneous carriage should be screened, and in positive cases should be decontaminated with mupirocin ointments or other means (Table 194.8).[434] Implementation of this policy for selected patients admitted to the hospital should be considered.[26]

The Burden of Antibiotic Resistance

At the beginning of last decade, MRSA was one of the most commonly identified antibiotic-resistant pathogens in many parts of the world.[247,421] During the period from 2000 to 2005, the proportion of hospital-onset *S. aureus* infections that were methicillin resistant peaked to 56.2% in US hospitals,[435] a proportion that was even higher (64.4%) in US ICUs. For some years now, surveillance programs from various areas have reported a steady decrease in the incidence of MRSA infections in the community[436] and in health care[437] or military settings,[438] the largest decrease being observed among hospital-onset MRSA infections[411] (see "Methicillin-Resistant *Staphylococcus aureus*" earlier).

In contrast to the diversity of strains observed in diseases caused by MSSA, MRSA outbreaks are caused by a limited number of successful clones.[439,440] In the health care setting, HCA-MRSA infections are associated with greater lengths of stay,[441] higher mortality,[442] and increased costs.[419] Whether MRSA is more virulent than MSSA is still a matter of debate. The molecular typing of thousands of carriage- and disease-associated *S. aureus* strains revealed that MRSA did not represent specific lineages and that all types of *S. aureus* can become invasive given the appropriate circumstances.[443] On the other hand, most MRSA infections are mainly of nosocomial origin and manifest as complications of health care procedures or underlying disorders. In this specific context, patient differences could account for the variation in mortality because a greater number of older patients with severe underlying disease contract MRSA infections.[442] In addition, ineffective or delay in effective antibiotic therapy could also play a large role in suboptimal response to therapy.[444]

CA-MRSA has now become the most frequent cause of SSTIs acquired in the community.[445] Groups with high-intensity physical contact are particularly affected. This includes competitive athletes, children in daycare centers, military recruits, injections drug users, jailed inmates, and men who have sex with men.[254] Five percent to 10% of CA-MRSA infections are invasive and can cause severe, sometimes fatal disease, such as necrotizing pneumonia, bacteremia, or necrotizing fasciitis[446] (see "Methicillin-Resistant *Staphylococcus aureus*" earlier). Successful CA-MRSA clones have established themselves as nosocomial pathogens and are now a common cause of health care–associated

TABLE 194.7 Risk of Invasive *Staphylococcus aureus* Infection Associated With Selected Underlying Conditions in Adults 20 Years Old or Older

UNDERLYING CONDITION	NO. OF PATIENTS WITH INVASIVE *S. AUREUS* INFECTION (*N* = 226)	ANNUAL INCIDENCE, PER 100,000	RR (95% CI)	*P* VALUE
Hemodialysis	24	7692	257.2 (161.0–393.6)	<.001
Peritoneal dialysis	3	4918	150.0 (30.5–44.1)	<.001
HIV infection	4	778	23.7 (6.4–61.4)	<.001
Solid-organ transplantation	3	683	20.7 (4.2–61.3)	<.001
Heart disease	114	362	20.6 (15.8–27.0)	<.001
Cancer	47	348	12.9 (9.1–17.8)	<.001
Illicit intravenous drug use	13	321	10.1 (5.3–17.7)	<.001
Alcohol abuse	31	241	8.2 (5.4–12.0)	<.001
Diabetes mellitus	48	192	7.0 (5.0–9.7)	<.001
Stroke	16	200	6.4 (3.6–10.6)	<.001
Chronic obstructive pulmonary disease	26	120	3.9 (2.5–5.9)	<.001
Systemic lupus erythematosus	2	80	2.4 (0.3–8.7)	.3
Rheumatoid arthritis	5	74	2.2 (0.7–5.3)	.1

CI, Confidence interval; *HIV,* human immunodeficiency virus; *RR,* relative risk.
Modified from Laupland KB, Church DL, Mucenski M, et al. Population-based study of the epidemiology of and the risk factors for invasive Staphylococcus aureus *infections.* J Infect Dis. *2003;187:1452–1459.*

TABLE 194.8 Example of Decontaminating Scheme for Patients Colonized or Infected With Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Protective Measures

Put patient in contact isolation (one or several contaminated patients in single room with restricted access)
Use protective gown and gloves
Use protective mask and glasses if risk for splashing of contaminated liquids
Clean hands with alcoholic solution at glove removal and between caregiving procedures
Leave any disposable item in room and discard for sterilization in special containers

Decontamination Measures

Apply nasal mupirocin (2%) every 8 hours for 5–7 days
Apply chlorhexidine-based oral spray three to four times a day for 5–7 days
Take daily shower or clean body thoroughly with chlorhexidine-based soap for 5–7 days
In the case of dental prostheses, clean and soak the prosthesis daily in chlorhexidine-based solution for 5–7 days

Control Cultures and Decision

Take control swabs of any contaminated sites 48 and 96 hours after the end of treatment
Keep isolation measures in force until laboratory results are available
If no MRSA is present in control cultures, consider patient decontaminated; discontinue isolation, and swab weekly for follow-up cultures.
If MRSA is present in control cultures, pursue isolation measures and repeat whole decontamination scheme

Modified from Current Recommendations at the University Hospital of Lausanne, Switzerland.

hospital-onset infections, especially BSIs.[447,448] Compared with HCA-MRSA, CA-MRSA retained susceptibility to many non–β-lactam antibiotics. If hospital-associated MRSA infections appear to be on the decline, only modest changes have been reported for CA-MRSA so far.[449]

Carriage of *Staphylococcus aureus*

The primary reservoirs of *S. aureus* are the anterior nares, but the organism can be isolated from other sites, especially the throat.[450] Traditionally, three patterns of carriage have been distinguished: persistent carriers (20% of healthy people, range 12%–30%), intermittent carriers (30% of healthy people, 16%–70%), and noncarriers (50% of healthy people, 16%–69%).[20] Persistent carriers differ markedly from others: They carry the same strain for extended periods of time, have higher *S. aureus* loads, and are at higher risk of acquiring *S. aureus* infections.[22,451] Because intermittent carriers and noncarriers share similar characteristics, such as a low risk of infection, identical *S. aureus* nasal elimination kinetics, and comparable antistaphylococcal antibody profiles, it has been proposed that *S. aureus* carriage be reclassified such that only persistent carriers are distinguished from others.[451]

Bacterial and host determinants for *S. aureus* carriage have been thoroughly investigated.[452] In contrast to toxins, staphylococcal cell surface–associated and immune evasion molecules seem to be important for colonization efficacy[453] (see "The Journey to Invasive Disease" earlier). If some results suggest a role for cell wall teichoic acid, SdrC, SdrD, and SasG in binding to squamous cells in vitro, only ClfB and IsdA have been shown to be associated with *S. aureus* carriage in humans.[454,455] Patients exposed to skin lesions have a greater risk of *S. aureus* nasal carriage. They include patients with insulin-dependent diabetes, patients undergoing hemodialysis or peritoneal dialysis, intravenous drug users, patients with recurrent *S. aureus* skin infections or atopic dermatitis, patients with HIV, and healthy patients receiving repeated injections for allergies.[452]

Carriage rates vary with geographic location, age, sex, and ethnicity. Most infants become colonized shortly after birth, usually with the same strain as their mother. Carriage then decreases with age (40%–60% at 2 months, and 21%–28% at 6 months), reflecting both the development of an immune response to *S. aureus* and competition between microorganisms in the nasopharynx. This is particularly true for *S. aureus* and *S. pneumoniae* because being a *S. pneumoniae* carrier is inversely associated with *S. aureus* carriage and vice versa.[456,457] Children and adolescents younger than 20 years seem to have higher persistent carriage rates than adults. Since 2000, the reported prevalence rate of *S. aureus* nasal colonization has decreased to 20% to 30%.[458] Explanations for this decline might include improved personal hygiene, changes in socioeconomic class, and smaller families.[22]

Traditionally, control of *S. aureus* has been focused on preventing cross-infection between patients. However, at least three sets of observations indicate that nasal carriage of *S. aureus* is an important risk factor for sepsis: persistent carriers have higher rates of infections than others[22]; a large proportion of nosocomial *S. aureus* infections originate from patients' own flora[24]; and eradication of carriage reduces nosocomial infections, especially after orthopedic and cardiosurgery-related infections.[26,459]

Carriage of Methicillin-Resistant *Staphylococcus aureus*

The prevalence of MRSA colonization increased from 0.8% in 2001 to 2002 to 3% in 2011 to 2012.[460,461] MRSA colonization is particularly important in the hospital environment because colonized and infected patients represent the most important reservoir of MRSA in health care facilities. Factors associated with MRSA carriage at time of hospital admission include prior health care exposure (i.e., nursing home resident or hospitalization in past 12 months), prior contact with nosocomial pathogens (i.e., history of MRSA and/or vancomycin-resistant enterococci [VRE] carriage, history of *Clostridioides difficile* [formerly *Clostridium difficile*] infection), or selected comorbid conditions such as diabetes, chronic obstructive pulmonary disease (COPD), and congestive heart failure, probably because those conditions lead to repeated hospital exposure.[462]

Despite the increasing rate of CA-MRSA infections, the prevalence rate of MRSA among persons without typical risk factors remains relatively low, and most MRSA colonization and infection still develop among those who have health care–associated risk factors or contact with other persons who have such risks. When patients known to be colonized with nosocomial MRSA are discharged from the hospital or nursing home into the community, spread to family members or close contacts can occur. Rates of transmission between positive case patients and household members range from less than 10% to 43%. About one-half of MRSA carriers are colonized for 2 months or less, but an estimated 20% are persistent MRSA carriers who remain positive for months or years.[463]

Preventive Measures to Limit Health Care–Associated Infections Methicillin-Resistant *Staphylococcus aureus* Infections

Health care–associated infections is a leading cause of preventable illness. As a major cause of such infections, MRSA has been given priority in infection-control strategies; the United Kingdom and several US states have even mandated anti-MRSA strategies. Typical methods to limit infections by MRSA include a comprehensive set of interventions. Infection-control measures should always involve the laboratory. Determining the clonality of MRSA recovered from several patients is important in order to differentiate sporadic cases of MRSA from more problematic epidemic situations (see "Molecular Typing" earlier).

Improving the rational use of antibiotics and the implementation of standard precaution and hand hygiene are clearly cornerstones of MRSA prevention and control. Other anti-MRSA bundle measures (e.g., systematic active screening using either rapid or conventional testing, isolation and decolonization of carriers; see Table 194.8) when implemented routinely in settings with endemic MRSA are effective, but their use is a matter of debate because they are economically not cost-effective.[464–466]

Screening and isolation of MRSA carriers at admission is a resource-consuming protective measure still widely used worldwide. Both rapid PCR tests and standard culture methods can help decrease MRSA infection rates in hospitals, particularly in settings with hyperendemic MRSA cross-infections.[465] Decolonization of MRSA carriage has been an important part of the control of MRSA dissemination so far. Most decontamination regimens recommend a 1-week daily total body washing with a chlorhexidine-based soap, plus nasal mupirocin application (see Table 194.8). Low-level mupirocin resistance (MIC, 8–256 mg/L) and high-level resistance (MIC, >512 mg/L) exist but are uncommon and usually follow prolonged administration.[467] Monitoring susceptibility is essential to detect appearance of resistance to the decolonizing agent.

Recent Dutch guidelines, which use an aggressive "search and destroy" strategy, achieved a rate of up to 80% of eradication.[468] They differentiate between uncomplicated carriers, who have no associated MRSA infections, and complicated carriers, who may have skin or deeper infection. Uncomplicated carriers are treated only with topical measures (see Table 194.8), whereas complicated carriers receive concomitant systemic antibiotic such as TMP-SMX (160/800 mg, orally q12h) plus rifampin (600 mg orally q12h) for 1 week.[468] Nevertheless, eradication of MRSA carriage is often difficult, and the role of MRSA decolonization in the infection-control measure remains uncertain.[459]

About 5% of health care workers become colonized with MRSA, and it has long been recommended to decolonized them.[469] However, health care workers most frequently act as vectors of transmission, not as main sources of MRSA. A study reported in 2017 demonstrated the limited role of the environment and health care workers in transmission of *S. aureus* to patients.[458] The worrying trend of increasing rates of MRSA has now been reversed in many high-income countries. In this context, should we still target high-risk pathogens, or should we instead protect patient populations that are susceptible to infection from many health care–associated pathogens? Indeed, universal practices such as hand hygiene and chlorhexidine body washings[470] or specific measures to reduce the rate of CRBSIs including use of chlorhexidine sponges[471,472] helped decrease the rates of infection not only with MRSA but also with other pathogens.[473] Infection-control measures should therefore be regarded as a whole and should not target only a specific pathogen.[474]

CLINICAL SYNDROMES

Infection begins with the colonization of target tissues by the microbes. Further spread results from more specific invasion processes, during which bacteria interact directly or indirectly (e.g., via toxins) with the host. Thus, any localized infection has the potential to become the seeding site of a more severe infection by means of contiguous extension, distant spread through the blood circulation, or production of toxins including TSST-1 and PVL (see "The Journey to Invasive Disease" earlier). Pyogenic infections are described subsequently

Skin and Soft Tissues Infections

Classification

S. aureus SSTIs include primary pyoderma (such as folliculitis, furuncles, carbuncles, and impetigo) and soft tissue infections (i.e., cellulitis, erysipelas, and pyomyositis). They are commonly classified according to the anatomic structure involved (Fig. 194.14): (1) infection of the epidermis—impetigo; (2) infection of the superficial dermis—folliculitis; (3) infection of deep dermis—furuncles, carbuncles, and hidradenitis suppurativa; and (4) infection of subcutaneous cellular tissues—erysipelas, cellulitis, fasciitis, and pyomyositis.

The diagnosis of an *S. aureus* SSTI is most frequently made clinically. The basic anatomic lesion induced is a pyogenic exudate or an abscess. Superficial infections can often be treated with local care, surgical drainage, and rarely, systemic antibiotics. When the infection penetrates to the deeper subcutaneous tissue and/or surgery is required, it is considered complicated; erysipelas, lymphangitis, lymphadenitis, cellulitis, and necrotizing fasciitis are severe diseases that may be life-threatening. They require hospitalization, systemic antibiotic therapy, and prompt surgical drainage and débridement[184] (Tables 194.9 and 194.10).

Impetigo

Impetigo is a superficial infection of the skin that involves only the epidermis. It affects mostly children, usually on exposed areas of the

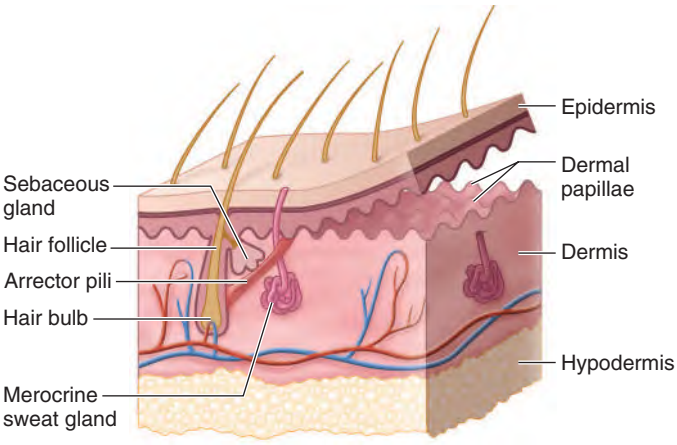

FIG. 194.14 Skin anatomy delineating various levels at which *Staphylococcus aureus* infection can occur (see text for details).

TABLE 194.9 Initial Management of Adults With Community-Acquired Purulent Skin and Soft Tissue Infections Presumed to Be Staphylococcal (Dosages Given for Patients With Normal Renal Function)

1. Incise and drain purulent foci. Consider heat, elevation, and immobilization of site.
2. Obtain wound Gram stain, culture, and two blood cultures with susceptibility testing.
3. Consider admitting for observation patients who require extensive débridement, have large areas of erythema, are elderly, are immunosuppressed, have important comorbidities (such as chronic renal failure, morbid obesity, diabetes mellitus), are unable to take medication reliably, or who are clinically unstable.
4. Administer intravenous therapy for hospitalized patients
   - A. Initially cover MRSA with
     - a. Vancomycin: 15 mg/kg IV q12h
     - b. Alternatives include:
       - i. Daptomycin: 6 mg/kg IV q24h
       - ii. Ceftaroline: 600 mg IV q12h
   - B. If cultures grow MSSA, can switch to:
     - a. Oxacillin, nafcillin, or flucloxacillin (not in United States): 2 g IV q4h, or
     - b. Cefazolin: 2 g IV q8h
5. Patients appropriate for outpatient therapy (with follow-up scheduled for 48–72 h): trimethoprim-sulfamethoxazole—2 double-strength tablets (320/1600 mg orally q12h)
   Alternatives include:
   - A. Clindamycin: 300–450 mg orally q8h
   - B. Doxycycline or minocycline: 100 mg orally q12h
   - C. Linezolid: 600 mg orally q12h
   - D. Tedizolid: 200 mg orally q24h
   - E. Oritavancin: 1.2 g IV over 3 h once, or dalbavancin 1 g IV over 30 min, followed by 500 mg IV 1 week later
   - F. If cultures grow MSSA can switch to:
     - a. Dicloxacillin: 500 mg orally q6h
     - b. Cephalexin: 500 mg orally q6h

MRSA, Methicillin-resistant *Staphylococcus aureus*; *MSSA,* methicillin-susceptible *S. aureus.*

FIG. 194.15 Infective skin lesions in staphylococcal impetigo.

body (e.g., the face and the legs). Primary impetigo occurs via direct bacterial invasion of intact healthy skin, whereas secondary impetigo occurs via infection at sites of minor skin trauma such as abrasions, insect bites, or eczema. Most cases of impetigo are caused by *S. aureus, S. pyogenes* or mixed infections of staphylococci and streptococci.[475]

The disease usually starts as a red macule that evolves into vesicles that contain cloudy fluid based on the area of erythema (Fig. 194.15). Bullous impetigo is mostly exclusively due to *S. aureus* strains producing exfoliative toxins (see "Exfoliative Toxins and Staphylococcal Scalded Skin Syndrome" earlier). The bullae are the result of epidermolytic toxins of the serine protease family. The vesicles rapidly rupture and leave a yellowish, thick, wet crust with a diameter exceeding 1 cm that is surrounded by erythema. Most affected children present with multiple lesions of various ages. General symptoms are absent, but a local inflammatory lymph node reaction is a rule. At the beginning, the differential diagnosis includes other vesicular eruptions, such as herpes simplex and varicella. However, the evolution is typical and rapidly differentiates the diseases. Although of mild severity, the disease is extremely contagious and the affected child should be kept apart from other children until an effective treatment has been applied. A basic treatment that combines disinfection with a chlorhexidine-based or povidone-iodine–based soap and additional bacitracin zinc ointment in patients with limited lesions, or fusidic acid cream (not available in the United States) in cases of more extensive lesions, is generally sufficient. Oral antibiotics are rarely needed. Mupirocin should be reserved for the treatment of *S. aureus* nasal carriage.

Folliculitis

Folliculitis is defined as a pyoderma that involves the hair follicle and its immediate surroundings. It manifests as a series of raised painful reddish lesions with indurated bases, each of them centered on a hair follicle. Extensive folliculitis of the bearded area of the face is called *sycosis barbae.* General symptoms are usually absent, and local antiseptic measures are the treatment of choice.

Furuncles and Carbuncles

Furuncles (boils) represent extension of the infectious process involving the hair follicle and are located, by definition, on the hairy areas of the body, with a predilection for the face, neck, axilla, and buttocks. The disease starts as a painful red nodule and rapidly evolves into a hot, painful, raised, and indurated lesion with a diameter of 1 to 2 cm. Its evolution is characterized by the appearance of a yellowish area in its center. On rupture (either spontaneous or surgical), it liberates a small amount of yellowish creamy discharge of purulent and necrotic material. Secondary foci from autoinoculation are frequent. General symptoms are normally absent. Local treatment is usually sufficient. In case of recurrent episodes, testing for nasal carriage and appropriate eradication may be necessary, although its effectiveness in reducing the risk of recurrence is not clearly shown.

CA-MRSA is a particular issue in furuncles.[254,445] They are often centered by a necrotic spot, are multiple, and occur in outbreaks. Lesions can progress to abscesses and cellulitis. In young patients with boils and systemic signs of infection, one must remember the risk of severe hemorrhagic pneumonia (see Fig. 194.8) or necrotizing fasciitis[446] (discussed in "The Journey to Invasive Disease" earlier).

Another remarkable situation is when furuncles are located around the nares or upper lip. Such lesions may lead to life-threatening septic thrombophlebitis of the cavernous sinus. Therefore, furuncles in this location should be treated with high-dose parenteral antibiotics.

Carbuncles are deep-seated infections that involve several hair follicles and result from the coalescence and spreading of the infectious process into the depths of subcutaneous tissue. They are usually localized at the base of the neck. The disease leads to the development of a central necrotic crater, which heals with the development of a hard hypertrophic violaceous scar. Fever and malaise are generally present. Carbuncles may be the source of bacteremia and require parenteral antibiotic therapy.

Hidradenitis Suppurativa

Hidradenitis suppurativa is a pyogenic infection of the apocrine sweat glands that manifests as crops of furuncles that develop in the axillary, perineal, and genital areas. After spontaneous drainage, hypertrophic scarring may occur. As in furunculosis, treatment is primarily limited to local care and topical disinfectants. Administration of oral antimicrobials is indicated only in the case of systemic symptoms.

Mastitis

Symptoms of *mastitis* occur in up to 25% of mothers in the United States who are breastfeeding, but the incidence of staphylococcal mastitis necessitating therapy is approximately 2.5%.[476] The infection develops most commonly during the second or third week of the puerperium. The diagnosis of mastitis is usually clinical, with patients presenting with focal tenderness in one breast accompanied by fever and malaise.

TABLE 194.10 Suggested Therapy for Native Valve and Prosthetic Valve Endocarditis Caused by Staphylococci

ANTIBIOTIC	FREQUENCY, DOSAGE, AND ROUTE	DURATION	COMMENTS
Native Valves ***Methicillin-Susceptible Staphylococci***			
Flucloxacillin (not in United States) or oxacillin or nafcillin	2 g IV q4h	4–6 wk	Addition of gentamicin no longer recommended for native valve endocarditis
Cefazolin (or other first-generation cephalosporins)[a]	2 g IV q8h	4–6 wk	Alternative for patients allergic to penicillins (not in case of immediate-type penicillin hypersensitivity)
Methicillin-Resistant Staphylococci			
Vancomycin	15–20 mg/kg IV q12h	4–6 wk	
Daptomycin	8–10 mg/kg IV q24h	4–6 wk	
Prosthetic Valves ***Methicillin-Susceptible Staphylococci***[b]			
Flucloxacillin (not in United States) or oxacillin or nafcillin	2 g IV q4h	≥6 wk	
with rifampin	900 mg IV q24h or 300 mg orally q8h	≥6 wk	Rifampin increases hepatic metabolism of numerous drugs, including warfarin
and gentamicin	3 mg/kg IV q24h or 1 mg/kg IM q8h	2 wk	
Methicillin-Resistant Staphylococci			
Vancomycin	15–20 mg/kg IV q12h	≥6 wk	
plus rifampin	900 mg IV q24h or 300 mg orally q8h	≥6 wk	
and gentamicin	3 mg/kg IV q24h or 1 mg/kg IM q8h	2 wk	

[a]American Heart Association.
[b]Rifampin plays a special role in prosthetic device infection because it helps kill bacteria attached to foreign material. Rifampin should never be used alone because it selects for resistance at a high frequency (about 10^{-6}).
Modified from Que YA, Moreillon P. Infective endocarditis. Nat Rev Cardiol. *2011;6:322–336; and Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America.* Circulation. *2015;132:1435–1486.*

Treatment includes analgesics, changing breastfeeding technique, and reversing milk stasis, often with the assistance of a lactation consultant. Continued breastfeeding should be encouraged in the presence of mastitis and generally does not pose a risk to the infant. Evidence has suggest that mastitis can be either prevented[477] or treated[478] with probiotics such as lactobacilli. When antibiotics are needed (i.e., in the presence of acute pain, systemic symptoms, or fever), those effective against *S. aureus* are preferred. Breast abscess is the most common complication of mastitis. It can be prevented with early treatment of mastitis and continued breastfeeding. Once an abscess occurs, surgical drainage or needle aspiration is needed.

Surgical Site Infection

SSIs are infections that occur at or near the incision site within 30 days of the procedure, or within 90 days if prosthetic material is implanted at surgery; they account for 20% to 30% of all hospital-acquired infections.[410] The commonly reported incidence rate of 2% to 5% of patients undergoing inpatient surgery is probably underestimated because of inadequate postdischarge surveillance.[479] *S. aureus* is the most prevalent pathogen that causes SSI for most types of surgery (15%–45% of cases),[409,410,423] especially after clean procedures. Gram-negative rods and enterococci are, however, the most prevalent pathogens that cause SSI after abdominal surgery.[435] Most infections are caused by *S. aureus* strains that are carried by the patient at admission to the hospital.[24] Hence, nasal carriage of *S. aureus* is a risk factor for subsequent infection in patients undergoing surgery, and decolonization has been recommended, especially for patients undergoing orthopedic or cardiothoracic procedures.[480]

SSIs are characterized by progressive edema, erythema, and pain around the surgical incision. General symptoms are frequently associated. Careful inspection of the wound, ulcer, or lesion is essential. If deeper structures are not involved, release of the stitches, repeated cleansing, and antibiotic coverage for 7 to 10 days is usually curative. If the infection involves deeper structures (e.g., bone) or foreign material (e.g., prosthetic devices), prolonged parenteral antibiotic therapy (4–6 weeks) may be necessary, and removal of the foreign material is warranted.[184] The evolution of wound infection is highly dependent on the patient's comorbidities. Healing may be delayed, particularly in vascular insufficiency and diabetes.

Erysipelas, Cellulitis, and Fasciitis

Superficial or deep extension of infection may result in erysipelas, cellulitis, and fasciitis. Erysipelas and fasciitis are commonly the result of *S. pyogenes*, but not exclusively. Fasciitis can arise from hematogenous seeding. An important common feature of all three entities is severe pain. In the case of erysipelas, soreness is associated with typical skin lesions. In the case of cellulitis or fasciitis, on the other hand, severe pain symptoms are disproportional with regard to the visible anatomic lesions (Fig. 194.16). Hence, high fever, severe local pain, and relatively meager clinical findings at visible examination are highly suggestive of one of these entities. The consideration is important because emergency surgical drainage is indicated in the case of fasciitis, and prompt intervention may be delayed because of the confounding picture.

Erysipelas is a superficial cellulitis with prominent lymphatic involvement, with an indurate, "peau d'orange" appearance with a raised border that is demarcated from normal skin. It often complicates edematous extremities and skin ulcers such as in varicose limbs. As in impetigo, it may be the result of mixed *S. pyogenes* and *S. aureus* infection. Clinical signs of sepsis with high fever are present. In most cases, an etiologic diagnosis is not established. Local sampling with puncture may be attempted, and blood cultures must be drawn. Prompt empirical treatment

FIG. 194.16 ***Staphylococcus aureus*** **cellulitis of the elbow in cancer patient with low neutrophil counts.** Pain was disproportional to visual appearance of the lesion. Patient was bacteremic.

should be started with parenteral antibiotics covering at least both staphylococci and streptococci.

In patients with underlying conditions, such as diabetic foot, mixed pictures of erysipelas and cellulitis may occur and may also be the result of gram-negative bacteria, including *P. aeruginosa.* Therefore the spectrum of empirical treatment should be broadened to cover these agents until the microbiologic results are available. If gram-negative bacteria or MRSA is suspected, the addition of aminoglycoside or vancomycin to a broad-spectrum β-lactam may be warranted.

Cellulitis involves deeper anatomic structures and does not produce the typical geographic skin lesion of erysipelas (see Fig. 194.16). Therefore it is more confusing and may be mistaken for nonspecific lesions such as trauma. Associated pain and fever are important signs. Cellulitis may be from multiple other organisms, including gram-negative bacteria, especially in patients with immunocompromise. Therefore, microbiologic sampling (including blood cultures) should be promptly followed by broad-spectrum antibiotic therapy with both anti–gram-positive and anti–gram-negative coverage. Radiologic examination is unnecessary in most cases of cellulitis. Computed tomography (CT) is useful when subjacent osteomyelitis is suspected, whereas magnetic resonance imaging (MRI) helps to differentiate cellulitis from necrotizing fasciitis and osteomyelitis from adjacent soft tissue infection.

Necrotizing fasciitis is the most severe condition and paradoxically causes the least superficial signs at visual observation of the skin and soft tissues. The pain may be so intense that opiate administration is required for relief. The condition is often the result of *S. pyogenes,* but *S. aureus* may be involved, especially in the presence of CA-MRSA.[254] Gram-negative bacteria, including *P. aeruginosa,* may be responsible, especially in patients with immunocompromise, and must be considered in the choice of initial empirical treatment.

Whatever its cause, fasciitis is an absolute emergency that necessitates immediate and generous surgical débridement and drainage. The evolution is a matter of minutes rather than hours and may rapidly result in amputation or death. Prompt clinical diagnosis and multidisciplinary evaluation are warranted. Imaging may help delineate the lesions, but urgent surgical exploration and fasciotomy should not be delayed. High-dose and broad-spectrum antibiotic therapy is necessary and can be readjusted after the bacterial pathogen has been isolated. In the case of *S. pyogenes* and severe refractory shock, compassionate use of intravenous immunoglobulins has been proposed[186] (see also "Nonmenstrual Toxic Shock Syndrome" earlier).

Management of Skin and Soft Tissue Infection

Localized lesions can be handled with disinfectant or topical antibiotics such as fusidic acid. However, increasing rates of resistance to topical agents have been reported. Mupirocin should be reserved for the treatment of *S. aureus* nasal carriage. Moderate and severe SSI should be treated with systemic antibiotic. A decision to hospitalize a patient is made based on clinical judgment (large abscesses, signs of systemic infection) and the at-risk characteristics of the patients (age <6 months, diabetes, or immunodeficiency). Surgical drainage is a major part of treatment, and most benign SSTIs are cured with drainage alone.[184]

Empirical therapy of health care–associated SSTI should cover multiresistant HCA-MRSA and thus include vancomycin or maybe linezolid. Empirical therapy of community-acquired SSTI is complicated by the occurrence of CA-MRSA. β-Lactams should be used with caution and according to the local epidemiology. Unlike HCA-MRSA, CA-MRSA is often susceptible to clindamycin and TMP-SMX, sometimes to tetracyclines, and mostly to linezolid. However, if coinfection with *S. pyogenes* is found and antibiotics are required, linezolid, vancomycin, or maybe tigecyclin should be considered for first-line treatment. If toxin secretion is an issue, linezolid might be preferred.[481]

Bloodstream Infection

BSI is defined as one or several positive blood cultures associated with general symptoms such as fever or hypotension.[482] Its incidence rate increased from 7.4 episodes per 1000 admissions in the 1950s[483] to 31.2 episodes per 1000 admissions in 2006.[484] Population-based studies have estimated the rate of BSI to be around 140 to 160 BSIs per 100,000 inhabitants/year in high-income countries.[432] The most common isolates are *E. coli* and *S. aureus,* with incidence rates estimated at 30 to 50 per 100,000 inhabitants/year and 20 to 35 per 100,000 inhabitants/year, respectively.[432,485] Higher incidence rates of *S. aureus* BSI are observed in countries with a greater burden of MRSA, in men, or at either extreme of life (<1 year and >75 years). Mortality of *S. aureus* BSI (15%–25%) has stabilized since the 1990s and varies as a function of age and underlying conditions.[414] Despite the increased prevalence of SSTI from CA-MRSA in outpatients in the United States, a parallel increase in CA-MRSA bacteremia or endocarditis has not been reported.[485] Studies have suggested that PVL-positive strains are more likely to infect skin and soft tissues (see previous section).

BSI is usually divided into two categories: nosocomial BSI, wherein positive blood cultures occur 2 days or more after hospital entry; and community-acquired BSI, which occurs in the community or before 2 days of hospitalization. However, the increasing number of individuals treated in outpatient programs makes these two categories progressively overlapping. Hence, community-acquired BSI may be more appropriately referred to as *community-onset BSI,* which is further subdivided into *health care–associated BSI* (HCA-BSI) and *community-associated BSI* (CA-BSI). The subdivision is similar to that made between HCA-MRSA and CA-MRSA.

Community-Onset Bacteremia

Community-onset HCA-BSI is comparable with nosocomial BSI in terms of risk factors of multiresistant organisms. These include intravenous devices, a history of surgical treatment, and dialysis. In contrast, community-onset CA-BSI, which occurs in patients without underlying conditions, is mostly from antibiotic-susceptible organisms and always associated with a detectable infected focus, including SSTI, deep-seated abscesses, pneumonia, osteoarticular infections, or infective endocarditis.[486] Of note, patients on dialysis are at particularly high risk for staphylococcal endocarditis and represent a distinct at-risk group for this disease.[426,487]

Nosocomial and Health Care–Associated Bloodstream Infection

S. aureus is the leading cause of nosocomial BSI and HCA-BSI, together with CoNS.[409,410] These are mostly associated with the presence of intravascular catheters or devices, procedures in contaminated sites, SSI, and sometimes *S. aureus* pneumonia.[409] Complications involve peripheral metastatic foci, which can reveal themselves later. Nosocomial *S. aureus* bacteremia enters in the differential diagnosis of any hospital-related febrile or septic episodes. The risk for patients with catheter-induced *S. aureus* bacteremia to develop infective endocarditis is about 10%.[280,488] Thus, catheter-related *S. aureus* bacteremia must be taken very seriously and consideration given to excluding infective endocarditis with transesophageal echocardiography.[489–491]

Management of *Staphylococcus aureus* Bloodstream Infection

With *S. aureus,* even a single positive blood culture should prompt initiation of antibiotic therapy, sampling of blood for follow-up cultures, determination of the source and extent of infection, and finally search for endocarditis with transesophageal echocardiography.[490] Approximately one-third of patients with *S. aureus* BSI develop metastatic complications, especially in cases involving prosthetic material. The strongest indicators of clinical complication are a positive result of follow-up blood culture after 48 to 96 hours of treatment and persistent fever at 72 hours.[492]

Removal of the original focus is a golden rule, especially in the case of infected intravascular material or prosthetic devices. Failure to do so is strongly associated with recurrence. In the case of difficult-to-remove implanted catheters, the use of antibiotic locks between infusions may be attempted, but success is variable.[493] In case of a removable infection source (e.g., a catheter), a 10-day to 14-day post–catheter removal antibiotic treatment may be appropriate: (1) after the removal of all prosthetic material and endovascular catheter; (2) after the exclusion of endocarditis; (3) as long as the follow-up blood cultures drawn 2 to 4 days after initial positive cultures are negative for *S. aureus*; (4) if the fever has vanished within 72 hours after the initiation of antistaphylococcal therapy; and (5) when the absence of metastatic foci has been confirmed.[493,494]

Although no consensus recommendations exist regarding therapy, most authorities advocate a 14-day course of antibiotic treatment in case of BSI related to a removable catheter or drainable localized infection.[495] Deeper infections, such as arthritis, osteomyelitis, and endocarditis, must be treated with antibiotics for 4 to 6 weeks, with or without surgery depending on individual circumstances (see Chapters 80, 81, 103, 104, and 105 for more detailed recommendations). Empirical antibiotic treatment must take into account the probability of methicillin-resistant staphylococci, which may represent more than 50% of staphylococcal infections in the hospital milieu.[490]

Infective Endocarditis

Infective endocarditis is one the most severe complications of *S. aureus* bacteremia. The disease is uniformly lethal if not treated with antibiotics with or without surgery. *S. aureus* endocarditis typically follows an acute course with multiple peripheral septic emboli, valve destruction, myocarditis, and mixed cardiogenic and septic shock. Appropriate care involves a multidisciplinary evaluation, including infectious disease and microbiology experts, cardiologists, intensive care specialists, cardiac surgeons, and sometimes neurologists.[489,491]

Epidemiology

In spite of improved health care, the overall incidence rate of infective endocarditis has remained at 2 to 8 cases per 100,000 population per year over the last 40 years.[426–428,496] Risk factors have, however, been changing. Chronic rheumatic heart disease, which was a prime risk factor in the preantibiotic era, is being replaced by other at-risk groups, including patients with age-related degenerative valve lesions, prosthetic valves,[497] intracardiac devices, or intravascular prostheses. Coexisting conditions such as hemodialysis,[498] diabetes, intravenous drug use, or HIV infection increase the risk for infective endocarditis.[487]

As a consequence, the epidemiology of infective endocarditis has changed; the mean age of patients with infective endocarditis has increased from 30 years in the 1950s to older than 60 years since the 1990s. The incidence of infective endocarditis is now highest in men aged 75 to 79 years.[427] Oral streptococci, which are still a leading cause in developing countries, have been supplanted by *S. aureus* and CoNS, especially in industrialized countries.[422,427,499,500] This finding also correlates with the fact that the portal of entry has become more often cutaneous or procedure related than dental. Accordingly, patients with health care–associated infective endocarditis may represent up to one-fourth to one-third of all cases of infective endocarditis in recent studies.[427,499]

Pathogenesis

Role of Bacterial Adhesins

The pathogenesis of *S. aureus* endocarditis implicates a close relationship between certain *S. aureus* surface adhesins (MSCRAMMs) and host proteins present on the surface of damaged or inflamed valves. Physically damaged endothelia are covered by a meshwork of fibrin, platelets, and numerous host matrix proteins.[501]

S. aureus is extremely well equipped with both surface-bound and secreted factors that mediate tissue colonization and invasion (see Table 194.3 and "The Journey to Invasive Disease" earlier). With a system developed in *Lactococcus lactis,*[502] Que and colleagues[81,503] showed that *S. aureus* ClfA was necessary and sufficient for early valve colonization and infection in rats with experimental infective endocarditis but not sufficient for invasive and persistent disease. The same authors showed that fibronectin-binding protein A (FnBPA) promoted both early valve colonization and persistent infection. FnBPA is a peculiar MSCRAMM that carries at least three binding specificities, to fibronectin, to fibrinogen, and to elastin.[504] Construction of truncated and chimera proteins indicated that although fibrinogen binding was necessary and sufficient for early valve colonization, as observed with ClfA, fibronectin binding was necessary for further invasion and persistence. This invasive phenotype was associated with the capacity of fibronectin binding to trigger active internalization of staphylococci into eukaryotic cells, both in vitro and in vivo. Thus, valve infection proceeds through consecutive binding to fibrinogen, for early colonization, and fibronectin, for invasion and persistence.[81] Such interadhesin cooperation could also occur between other MSCRAMMs, adding even more flexibility to the already wealthy set of *S. aureus* surface determinants.[81,82]

In the case of physically intact but inflamed endothelia, *S. aureus* fibronectin-binding proteins might be of primary importance. During inflammation, endothelial cells express integrins of the β_1 family, which can bind plasma fibronectin at the luminal pole of the cell. The resulting fibronectin coat functions as a ligand surface for circulating *S. aureus* that expresses fibronectin-binding proteins. The contact between the adhesin and its ligand triggers the active internalization of *S. aureus* by endothelial cells and by other cells.[505] Once internalized, *S. aureus* may either persist locally, protected from host defenses and antimicrobial therapy, or multiply and secrete hemolysins (see Tables 194.1 and 194.3), which lyse the host cell and allow bacteria to spread both locally and to distant organs. This second scenario probably explains many cases of infective endocarditis on anatomically normal valves.

Role of Platelets

The role of coagulation is critical in funneling circulating *S. aureus* clumps toward damaged endothelia (see "Contribution of Coagulation" earlier). However, bacteria-induced platelet activation is a double-edged sword. On the one hand, platelets contribute to the formation of the vegetation. On the other hand, platelets also contribute to antiinfective host defenses by releasing AMPs and inflammatory mediators. These cationic AMPs are contained in the α-granules of thrombocytes and are released into the surroundings by activated platelets. They kill numerous gram-positive organisms by perturbing their membrane potential.[506,507]

Experimental evidence indicates that platelet-resistant mutants of staphylococci or streptococci have an increased ability to produce endocarditis in animals. In addition, clinical studies have indicated that isolates of *S. aureus* recovered from patients with endocarditis are more often resistant to platelet-induced killing than *S. aureus* isolated from other infected sites.[508] Resistance of *S. aureus* to AMPs is mediated by the *dlt* and *mrp* operons (see "Immune Evasion" section earlier). Additional resistance strategies include binding and inactivation of AMPs by staphylococcal proteases such as Sak and Aur (see Table 194.1).[507,509]

Experiments have confirmed that fibrinogen adherence and platelet aggregation cooperated to induce experimental endocarditis in rats.[510] In addition, interaction with vWF is also involved.[120] Finally, retrospective studies suggested that patients on prior aspirin therapy were significantly less likely to have vegetations on cardiovascular implantable electronic device leads or heart valves than those who had not received it,[511] yet without any impact on survival[511] or embolism.[512,513]

This raises the question regarding whether antiaggregant therapy might be useful in the prevention or treatment of infective endocarditis. Experimental antiaggregant prophylaxis is therefore being revisited in experimental models and has generated promising results.[121] Likewise, antiaggregant therapy with acetosalicylic acid decreases the severity of experimental endocarditis from *S. aureus.*[514]

One randomized, double-blind, placebo-controlled trial showed that a daily dose of aspirin (325 mg orally q24h) in addition to the conventional antibiotic therapy did not reduce the risk of embolic events in patients with infective endocarditis and was even associated with an increased risk of bleeding.[515] Similarly, anticoagulants increased the risk of secondary bleeding at the site of septic emboli, including hemorrhagic stroke, and are not recommended.[516,517] However, these studies did not look at endocarditis prevention sensu stricto, because the studied patients had already developed valve infection and thus were more prone to have secondary bleeding. A more realistic protocol should include patients who are at risk of endocarditis and are taking or not taking prophylactic antiaggregants, and test whether or not they have a modified risk of contracting endocarditis.

Host Defenses and Prevention

The role of host defenses is marginal in infective endocarditis. Once staphylococci have colonized the valves, their intrinsic procoagulant activities (e.g., fibrinogen polymerization by coagulase and platelet activation by fibrinogen-binding protein) trigger further deposition of platelets and fibrin on top of the microorganisms, thus providing a protective niche inside the vegetation. Moreover, *S. aureus* can be internalized into endothelial cells via bridging with fibronectin (see previous discussion). Both cases result in a failure of professional phagocytes to eradicate the organisms (see also "Immune Evasion" earlier).

Killing by T-cell–mediated effectors is not operative in endocarditis. Therefore, the only alternative is antibody-mediated protection, which could act before colonization by blocking *S. aureus* surface adhesins or by increasing the speed of blood clearance via opsonization. Active research is dedicated to such an approach, but few promising results are available yet. The limitation of preventive vaccines in endocarditis might be the short (1-minute to 2-minute) delay between blood invasion and valve colonization, which leaves a small window for antibodies to be active.

Other preventive measures are scarce. Because *S. aureus* is a ubiquitous skin colonizer, prevention starts with hygiene and disinfection. Decontamination of carriers and proper antisepsis at the site of injection and catheter placement is mandatory. Antibiotic prophylaxis may be useful but is limited to cases of medicosurgical procedures in the area of well-defined infective foci (see Chapter 83 for details). Thus, detection of patients with risk factors, and respect for proper hygiene and antisepsis measures, remain the cornerstones of *S. aureus* endocarditis prevention.

Clinical Spectrum

S. aureus infective endocarditis often manifests as an acute septic syndrome with fever, tachycardia, and often hypotension. Dyspnea may be present from congestive heart and from septic pulmonary emboli in the case of right-sided endocarditis. General signs such as arthralgia or myalgia, back pain, and pleuritic pain are present in 10% to 50% of cases. Specific signs include a new cardiac murmur, usually of valve regurgitation, in about 90% of cases; septic emboli in the form of petechiae and Janeway lesions; and central nervous system manifestations in up to one-third of patients (Figs. 194.17, 194.18, and 194.19).

Cardiac failure is a major indication for emergency valve replacement. A defect in atrioventricular conduction may represent a mycotic aneurysm of the sinus of Valsalva, usually the noncoronary cusp. Transesophageal echocardiography is useful in detecting this complication. Large vegetations (≥1 cm) are relatively frequent in *S. aureus* endocarditis and have been associated with an increased risk of embolization. However, the risk of embolization rapidly decreases within the first days of efficacious therapy.[518]

Vascular Complications

Embolic skin lesions encompass Janeway spots, occurring in acute endocarditis and often containing bacteria (see Fig. 194.17), or more delayed immune-related vasculitis (Roth spots) that are a sign of relatively chronic infection and are not a usual feature of acute *S. aureus* endocarditis. Larger septic emboli from broken-off vegetations can occlude the coronary or peripheral arteries, especially in the brain. Mycotic aneurysms are found in up to 15% of patients with bacterial endocarditis, and probably more frequently in *S. aureus* endocarditis. They may arise either from direct invasion of the arterial wall by the infecting organisms, from septic embolization of the vasa vasorum, or from the deposition of immune complexes that trigger local inflammation and weakening of the arterial wall.

FIG. 194.17 Embolic skin lesions (Janeway spots) in framework of acute mitral valve endocarditis caused by *Staphylococcus aureus*.

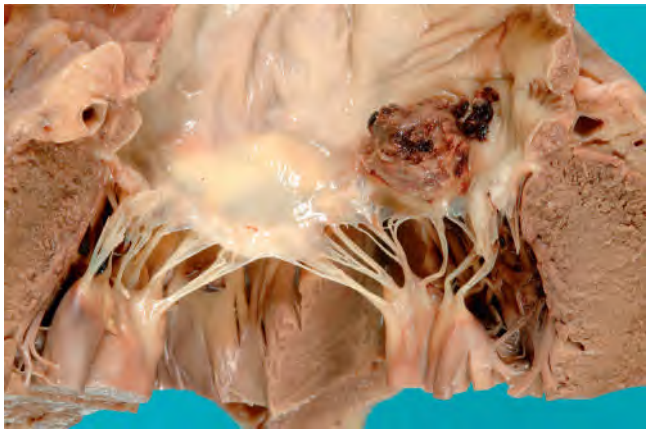

FIG. 194.18 *Staphylococcus aureus* endocarditis of the mitral valve. Note large ulcerovegetative lesion on anterior leaflet. *(Courtesy Drs. A. Lobrinus and I. Letovanec, Pathology Institute, Lausanne University.)*

Neurologic Complications

Cerebral complications are frequent, occurring in 15% to 25% of patients[517,519] and are associated with poor outcome.[520] Systematic brain imaging with MRI may reveal cerebral events in up to 80% of patients; among them, 50% are asymptomatic.[521] Lesions include ischemic and hemorrhagic stroke, transient ischemic attacks, silent cerebral embolism,

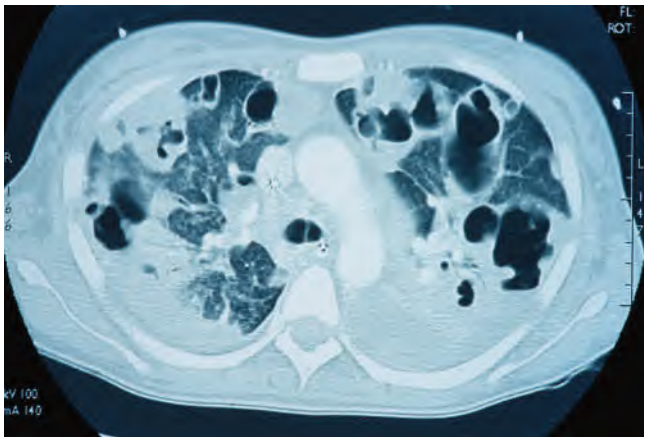

FIG. 194.19 Chest computed tomography scan of 30-year-old intravenous drug user with tricuspid valve *Staphylococcus aureus* endocarditis and bilateral lung abscesses and empyema.

abscesses, mycotic aneurysms, encephalopathy, and meningitis.[517,519,521] Control of the infection is essential because embolization sharply decreases thereafter.[518] Patients with large mobile mitral vegetations are at higher risk of embolism.[517] Recurrent embolization after the onset of efficacious therapy may be an indication for urgent valve replacement. This decision is difficult because anticoagulation therapy during extracorporeal circulation and after valve replacement puts the patients at increased risk of secondary intracerebral hemorrhage.[489,517] However, recent studies have indicated that early surgery (i.e., within the hospital stay) is usually beneficial.[522]

Diagnosis

Criteria for the diagnosis of infective endocarditis changed with the use of echocardiography and are discussed in detail in Chapter 80. In *S. aureus* endocarditis, the first two blood cultures are positive in more than 90% of cases. The volume of blood cultures is critical because persistent bacteremia in infective endocarditis is often of low level, representing 1 to 100 bacteria per milliliter of blood. For each culture, 8 to 12 mL of blood should be drawn, with careful antiseptic precautions.

Management of *Staphylococcus aureus* Endocarditis

Treatment options are listed in Table 194.10[489,491] (see Chapters 80 and 81).

Management of Right-Sided Endocarditis in Injection Drug Users

S. aureus is the most common, yet not unique, pathogen in right-sided endocarditis in intravenous drug users.[523] Although standard treatment of left-sided *S. aureus* endocarditis requires 4 to 6 weeks of antibiotic therapy (see Table 194.10 and Chapter 80), the duration of treatment for right-sided endocarditis can be considerably shortened in injection drug users[489,491,524,525] because right-sided endocarditis has somewhat different physiopathologic features and is easier to cure or can heal spontaneously in experimental models. Moreover, the prognosis is less severe than in left-sided valve infection. Agents proven appropriate for 2-week treatment of right-sided endocarditis are nafcillin and oxacillin. Combination with an aminoglycoside was shown to be not necessary.[524,525] However, short-course therapy is limited to favorable conditions, including infection with an MSSA, prompt response to treatment, infection limited to the tricuspid valve, <20-mm vegetations, absence of extracardiac infected sites such as empyema, and absence of severe immunodepression (>200 CD4 cells/mL) in HIV-infected patients.[489,491,524]

Another proposed regimen that may allow intravenous-oral switch therapy is ciprofloxacin plus rifampin.[526,527] Today newer anti–gram-positive quinolones (e.g., levofloxacin or moxifloxacin) should be preferred to ciprofloxacin, because they are less prone to select for resistance. Some authors do not start rifampin until 3 days of effective therapy have been given, hoping to reduce the chance of secondary rifampin resistance. Daptomycin is an alternative for *S. aureus* right-sided infective endocarditis therapy (see Chapter 31).[236] However high doses (10 mg/kg/24 h) should be used, and combination with oxacillin or fosfomycin to avoid the development of resistance has been suggested (see "Daptomycin" section earlier). On the other hand, glycopeptides (vancomycin or teicoplanin) should not be used for short-course treatment because of their lack of bactericidal activity and poor vegetation penetration.

Infections of the Central Nervous System

Meningitis

S. aureus meningitis is an uncommon disease that accounts for about 5% of cases of bacterial meningitis.[528] Two different modes of pathogenesis have been described: (1) postoperative meningitis, associated with neurosurgical procedures, shunt devices, or head trauma; and (2) hematogenous meningitis, sometimes in the context of infective endocarditis.[529]

Postoperative and spontaneous *S. aureus* meningitis are two different clinical syndromes. *Postoperative meningitis* usually appears as hospital-acquired infection in young people, and most cases are associated with ventricular shunt devices,[530] recent neurosurgery, or cerebrospinal fluid leak. On the other hand, *spontaneous meningitis* is a community-acquired infection associated with a variety of clinical sources (primary bacteremia, infective endocarditis, osteomyelitis) that mainly affects older patients with severe underlying conditions.[529] The mortality rate associated with *S. aureus* meningitis is high, around 50%; the mortality rate of spontaneous meningitis is usually higher than that of postoperative meningitis.[530–532]

Spinal Epidural Abscess

Spinal epidural abscess is a rare infection of the central nervous system, usually occurring after operation or trauma, that can be associated with damage to the spinal cord and nerve roots. *S. aureus* is the leading bacterial pathogen causing spinal epidural abscess, accounting for about two-thirds of cases. Classically, patients have back pain, fever, and neurologic signs.[533] In general, surgical decompression and a long course of intravenous antibiotics are required in order to achieve a successful outcome.

Pulmonary Infections

Epidemiology

S. aureus is responsible for 2% to 5% of CAP for which hospitalization is required,[534,535] but for 20% to 30% of hospital-acquired pneumonia (HAP).[409] The prevalence of *S. aureus* CAP varies widely by country and continent.[536] Although *S. aureus* CAP cases may cluster with influenza cases, *S. aureus* CAP occurs year round. In recent studies, patients with *S. aureus* CAP had similar demographic characteristics, comorbidities, and presenting signs and symptoms compared with those with non–*S. aureus* CAP.[534] Mortality is high (10%–15%) compared with pneumococcal CAP (about 5%),[534] and is often associated with a more severe course.[535]

In the hospital, *S. aureus* is becoming the pathogen most frequently responsible for nosocomial pneumonia. Its frequency increased from 13% of the cases between 1981 and 1986 to 25% between 2011 and 2014,[409] with a proportion of MRSA that peaked at 55% during the last decade.

Clinical Spectrum

The clinical manifestations of *S. aureus* pneumonia are frequently indistinguishable from those of pneumonia caused by other pathogens,[534] although the pneumonia caused by *S. aureus* is typically a necrotizing infection with rapid progression to tissue destruction and cavitation. The infection may result either from airborne contamination or aspiration or from hematogenous seeding during bacteremia or right-sided endocarditis. In both cases, the pulmonary infection can lead to local complications, such as abscesses and pleural empyema.

Pneumonia in young, previously healthy adults with a preceding influenza-like illness characterized by severe respiratory symptoms, hemoptysis, high fever, leukopenia, very high C-reactive protein level (>400 mg/L), hypotension, and a chest radiograph that shows multilobar cavitating alveolar infiltrates should lead one to suspect CA-MRSA infection.[411] The fatality rate of CA-MRSA necrotizing pneumonia can be as high as 60%.[537] Airway bleeding, erythroderma, and leukopenia are strong predictors of mortality.[537] Fig. 194.8 illustrates a case of acute

hemorrhagic pneumonia from PVL toxin–secreting *S. aureus* associated with influenza A infection in a 20-year-old patient (see "Killing Leukocytes" section earlier).

S. aureus remains a common cause of pleural empyema and accounts for about one-fifth of the cases.[538] Acute empyema usually arises by means of direct extension from *S. aureus* pneumonia or lung abscess. It is also often seen as a complication of thoracic surgery. Radiologic findings on CT scan or ultrasound scan confirm the clinical suspicion. Demonstration of a pleural air-fluid level in the absence of a previous thoracocentesis suggests a bronchopleural fistula, another feared complication of *S. aureus* infection. Fig. 194.19 illustrates the case of multiple lung abscesses and pleural effusion in a young patient with right-sided endocarditis.

Therapy

Rapid institution of appropriate antibiotic therapy is essential. Delay is associated with poor outcome. Because the rapid determination of the etiology of severe pneumonia is possible only in a limited number of cases, initial broad-spectrum antibiotic therapy that treats MRSA and other nosocomial pathogens should be instituted early in the cases of health care–associated pneumonia. However, deescalation therapy should occur whenever possible; in particular, a switch to a more rapidly bactericidal β-lactam agent should be done whenever possible according to susceptibility testing. Because of the low prevalence of MRSA in CAP,[534,536] routine empirical anti-MRSA antibiotics are not recommended in the initial treatment of CAP.[539]

For years, vancomycin was the only treatment for MRSA pneumonia, but the cure rate was disappointing. This led to the recommendation to increase trough concentrations of vancomycin in the serum to 15–20 μg/mL for severe infections. Linezolid is an alternative to vancomycin for the treatment of MRSA pneumonia. Clinical outcomes of *S. aureus* HAP and VAP treated with linezolid therapy were found to be significantly better than in those treated with vancomycin in retrospective subgroups analysis. However, these results were not confirmed in a randomized trial. Thus it is still unclear whether one drug is better than the other. For patients with pneumonia caused by MRSA strains with vancomycin MICs of 1.0 mg/mL or more who require concomitant nephrotoxic therapy or who have preexisting renal failure, linezolid (600 mg IV, q12h, with possible later switch to oral therapy) is advised.[540]

The duration of treatment of *S. aureus* pneumonia is determined by the general picture of the disease. The less complicated cases of CAP without overt tissue destruction and without associated deep-seated infections respond to appropriate antibiotic therapy in 10 to 15 days. With the exception of MRSA pneumonia, 7 to 8 days of treatment is sufficient for most patients with HAP or VAP without bacteremia. In the case of surgical drainage of empyema, the treatment duration is adjusted according to cultures and persistence of the pleural effusion. In the case of right-sided endocarditis, therapy is prolonged to 4 weeks according to standard recommendations for endocarditis treatment (see previous discussion).

Osteoarticular Infections

S. aureus is the leading cause of bone and joint infections in both children and adults.[541] The prevalence of those infections is increasing, mainly because of a longer life expectancy, the rise in chronic diseases such as diabetes mellitus, and the increasing use of bone fixation devices and prosthetic joints in the elderly.[542]

Osteomyelitis

Epidemiology

Osteomyelitis has been described since antiquity. Its epidemiology has, however, dramatically changed over the last decades, in parallel with the increased use of medical devices in orthopedic surgery; the higher incidence of chronic disease, especially diabetes mellitus; and the emergence of resistant bacterial strains (e.g., MRSA and CA-MRSA).[543] In parallel, immunization programs led to the disappearance of causative organisms such as *Haemophilus influenzae,* and improved identification methods revealed new causative microorganisms (i.e., *Kingella kingae*). Nevertheless, *S. aureus* continues to be the leading organism, isolated in 30% to 60% of cases (Table 194.11).[486,544]

TABLE 194.11 Frequency of Osteomyelitis Caused by Various Microorganisms

	FREQUENCY OF OSTEOMYELITIS (%)			
	BLYTH ET AL.[547]	TICE ET AL.[557]	KREMERS ET AL.[542]	MURILLO ET AL.[543]
Microorganisms				
Staphylococcus aureus	65	ND	44	59
Coagulase-negative staphylococci	5	13.9	17	3
Non–group D streptococci	30	13.7	16	17
Pseudomonas aeruginosa	ND	4.4	7	2
Other	0	13.8	16	19
Total	100	100	100	100
Demographics				
No. of patients or episodes	20	454	760	618
Age (yr; median)	0.1–12 (5.4)	6–92 (51)	52 +/- 25	53–77 (65)

ND, Not determined.

The mortality of osteomyelitis has markedly decreased since the introduction of antibacterial therapy. In one pediatric case review, the mortality rate decreased from more than 30% before the introduction of sulfa derivatives (years 1936 through 1940) to approximately 13% afterward (from 1941 to 1945).[545] The mortality rate from osteomyelitis continued to decline with modern antibiotics and is now stabilizing at around 5%.[546]

The reported incidence of osteomyelitis has risen from around 3 cases per 100,000 population per year in 1997[547] to 24.4 cases per 100,000 population per year in recent population-based studies.[542] Whereas the incidence of osteomyelitis is increasing in adults, it has been declining in children younger than 13 years; in the area of the Greater Glasgow Board Health Center (United Kingdom), the incidence rate of osteomyelitis declined by about three times over the last 30 years and by two times during the 1990s.[547] Some studies reported, however, an increased incidence in children related to CA-MRSA.[548]

The incidence of osteomyelitis varies with age and the presence of underlying risk factors such as male sex (men are affected twice as often as women) or diabetes. Other risk factors include individuals with an increased risk of bacteremia, such as patients undergoing hemodialysis or intravenous drug users, and immunosuppression.

Pathogenesis

Lew and Waldvogel differentiated three different groups of osteomyelitis etiologies: (1) hematogenous osteomyelitis occurring mostly in children; (2) osteomyelitis due to local spread from a contiguous source after trauma or surgery; and (3) secondary osteomyelitis in patients with vascular insufficiency or concomitant neuropathy, with most of the cases following a foot soft tissue infection.[549] Some authors propose the addition of a fourth etiologic group of osteomyelitis occurring in special hosts with an increased risk for bone infection, including intravenous drug users, individuals with sickle cell anemia, and patients with Gaucher disease.

Healthy bone is generally highly resistant to infection. The two ways by which bacteria can infect the bones are: 1, hematogenous seeding; and 2, contiguous contamination. Both have epidemiologic and pathogenic correlates. Bone infection requires certain predisposing circumstances. In children with hematogenous osteomyelitis, the disease is usually located at the distal end of the long bone metaphysis, including the humerus, femur, and tibia.[548] The nature of the blood flow close to the growing plate may be responsible. Terminal arterioles followed by stagnant blood in the venous sinusoids may facilitate the settlement of

blood-borne staphylococci. A similar model may apply for vertebral osteomyelitis (Fig. 194.20A), wherein blood flow at the vertebral interface is somewhat similar. In addition, microtrauma (or macrotrauma) to bone may facilitate infection by affecting the local blood supply or exposing host matrix proteins to which staphylococci can adhere.

On the bacterial side, *S. aureus* is equipped with several surface adhesins or MSCRAMMs (see Tables 194.1 and 194.3, and "The Journey to Invasive Disease" earlier), including collagen-binding protein and sialoprotein-binding protein, which were shown to promote experimental osteoarticular infection. After local settlement, secreted proteases, such as aureolysin, and toxins, such as alpha-type PSMs,[550] promote profound alteration in bone remodeling, tissue destruction, and invasion, as indicated by a decreased virulence of *sae, sar,* and *agr* mutants that are affected in secretion of virulence factors.[551,552] The combined effect of both *S. aureus* factors and immune cell-mediated production of oxygen radicals and cytokines results in local necrosis and abscess formation. If adequate antibacterial therapy is given, the nascent abscess can heal totally. Alternatively, bone remodeling and necrosis can extend and circumscribe devitalized bone fragments, or sequestra, floating in the abscess cavity (see Fig. 194.20B). The formation of necrosis and sequestra exemplifies the evolution of acute osteomyelitis to the chronic form (see subsequent discussion) and requires the combination of antibiotics and surgical débridement and sequestrectomy for successful treatment.

FIG. 194.20 Osteomyelitis. (A) T1-weighted magnetic resonance image of L4-L5 lumbar osteomyelitis after injection of gadolinium contrast medium. (B) Chronic osteomyelitis of left tibia. A vast necrotic cavern containing sequestrum surrounded by air can be seen. A fistula with drainage to the skin is also present. *(Courtesy Dr. U. Flückiger, Hirslanden Klinik, Aarau, Switzerland.)*

Clinical Features

Osteomyelitis can be classified according to pathogenesis, to localization, to the presence of an implant, or to anatomy and comorbidity. It is conventionally divided into acute and chronic disease. Acute osteomyelitis is defined as a first episode that responds to medical treatment within 6 weeks. It is usually hematogenous and predominant in children and elderly patients. Symptoms are those of an acute septic syndrome with chills, high fever, malaise, and local pain and swelling. Blood cultures are positive in about 50% of cases, and blood or tissue cultures in 65% of cases.

Chronic osteomyelitis is considered in all other situations, including the relapse of previously treated or untreated disease and infection arising by contiguity. The process can evolve over months or even years and is characterized by low-grade inflammation, the presence of necrosis, sequestra, pus, fistula, and recurrences.[549]

Aside from open-wound fractures, contiguous osteomyelitis involves diabetes-related and unrelated vascular diseases and prosthesis-related osteomyelitis. Diabetes-related osteomyelitis and vascular-related osteomyelitis principally involve the feet. They complicate chronic ulcers, which may be paradoxically painless because of associated neuritis. The ulcerative lesion should be explored gently, but in depth, with a surgical probe. If the probe encounters the bone surface, osteomyelitis is present.[553] Other investigations involve radiology and surgical biopsy. Cultures of deep tissues and bone biopsy are mandatory for microbiologic diagnosis. Cultures of surface swabs and fistula fluids mostly yield skin contaminants but not the responsible pathogen.

Diagnosis

Diagnosis of osteomyelitis integrates clinical signs, radiology, and microbiology. However, clinical signs may be scarce in chronic infection. Imaging techniques are of primary importance, and dominated now by MRI because it is highly sensitive and provides information on both solid and soft tissues. Nuclear studies (bone scans) are performed only if metal hardware precludes MRI or CT.

Microbiologic cultures are indispensable to guide therapy. Whenever possible, both blood cultures and tissue biopsies should be performed. Important to note, chronic infection may be associated with persistent forms of *S. aureus,* such as SCVs (small colony variants), especially if aminoglycosides have been used in conjunction with osteosynthetic material (see earlier "Culture and Identification" section).[554] The diagnostic laboratory should be made aware of this possibility so appropriate measures may be taken.

Therapy

Rapid institution of antibiotic therapy is mandatory to prevent bone necrosis and the passage of acute osteomyelitis to more problematic chronic disease. The duration of drug treatment in most studies is 4 and 6 weeks but may vary up to 10 weeks or more in complicated situations. A trial suggested that 6 weeks of treatment is noninferior to 12 weeks.[430] Empirical treatment of osteomyelitis should include adequate coverage of MRSA in areas where CA-MRSA is endemic. Adequate representative cultures should be obtained to ensure the early identification of MRSA.

The classic regimens are as follows: (1) for penicillin-susceptible *S. aureus,* intravenous penicillin G, 4 millions units IV q6h; (2) for penicillin-resistant *S. aureus,* intravenous nafcillin, oxacillin, or, outside the United States, flucloxacillin, 2 g IV q6h; and (3) for MRSA, intravenous vancomycin, 1 g IV q12h (followed a loading dose as proposed in "Therapeutic Monitoring of Vancomycin in Adult Patients"). Clindamycin might be a good alternative to vancomycin in the presence of susceptible CA-MRSA (see Chapter 104).

In children with hematogenous *S. aureus* osteomyelitis, a relatively short course (4–7 days) of intravenous treatment is often followed by oral therapy. A series comparing 131 children showed equivalence

between short (total of 20 days) and long (total of 30 days) treatment durations.[555] Intravenous treatment (median 3.7 days) was followed by oral amoxicillin, first-generation cephalosporin, or clindamycin for the remaining period. Oral treatment is currently not recommended in adults, although newer quinolones may be appropriate because of their high bioavailability. However, outpatient therapy is also increasingly used. Although controversial, some workers use ceftriaxone (2 g once a day), which was shown to be effective against *S. aureus* osteomyelitis in two studies.[556,557]

Finally, osteomyelitis from multiresistant MRSA remains difficult to treat. Although vancomycin is still recommended as first-line therapy, daptomycin and linezolid are good alternatives.[558]

Native Joint Septic Arthritis

Septic arthritis is a disease that usually arises in elderly people and very young children.[546,559] *S. aureus* remains the most frequent cause of septic arthritis in both children and adults.[429,543] Previous joint pathology (e.g., rheumatoid arthritis, osteoarthritis, crystal arthropathy) and diabetes are risk factors. The disease may follow both hematogenous seeding and local trauma and may be of iatrogenic nature in the case of joint puncture or arthroscopy. Postarthroscopic septic arthritis has a prevalence of around 14 cases per 10,000 procedures.[560] Symptoms associated are acute pain and joint swelling. Joint destruction occurs within a few days from both bacterial and host inflammatory factors and probably also ischemic lesions from the increased intraarticular hydrostatic pressure. Therefore, patients with underlying arthritis with acute pain in a single joint should undergo aspiration immediately; the fluid should be examined for cell count, chemistry, and gout crystals (if appropriate), and culture should be performed.

The prognosis of hematogenous arthritis in children is good. In adults, the mortality rate is around 11%[429] and the prognosis is mostly associated with that of the underlying disease (i.e., rheumatoid arthritis or endocarditis or other deep-seated condition responsible for the initial bacteremia). Medical treatment is identical to that of osteomyelitis. Open joint drainage is usually unnecessary, except for hip infections in children, where it may help prevent necrosis of the femoral head.

Septic Bursitis

Septic bursitis is an acute infection that involves the periarticular bursa. It is most often located in pressure areas such as the olecranon and the patella. It manifests as an acute juxtaarticular inflammation. The overlying skin is usually inflamed. Unlike arthritis and osteomyelitis, the underlying bone and joint are usually painless at pressure or mobilization. The portal of entry is likely to be local, such as spread from cellulitis. More than 80% of bursitis is the result of *S. aureus*.[561] Diagnosis is made with puncture and examination of the bursa fluid. Important to note, septic bursitis may be at the origin of both local and distant septic complication. Thus, careful clinical evaluation is mandatory. The prognosis is good but requires 2 to 3 weeks of appropriate antibiotic therapy. Repeated aspiration of the bursa is preferable to incision and drainage for patient with persistent swelling and pain. Patients with complicated cases may require hospitalization and intravenous treatment. Surgical excision of the bursa may be considered in the case of recurrences, once inflammation has subsided.

Prosthetic Joint Infections

With the use of perioperative antimicrobial prophylaxis and laminar airflow operating rooms, prosthetic joint infections are fairly rare, with an estimated incidence rate of 1.5 infections per 1000 joint-years.[431] The infection rate after primary joint replacement is usually less than 1% in hip and shoulder prostheses, less than 2% in knee prostheses, and less than 9% in elbow prostheses.[562] Sixty percent to 70% of infections occur during the first 2 years after surgery. Infection rates after surgical revision are usually considerably higher.

Implant-associated infections are typically caused by microorganisms that grow in structures known as biofilms. *S. aureus* and CoNS are the main causative organisms.[431,562] Infections within the 12 first weeks after implantation are considered early, or acute; infections that occur from 12 weeks to 24 months after implantation are considered delayed, or low-grade, infections; and those that occur after 24 months are considered late, or chronic.[562]

S. aureus is mostly responsible for early infection.[431] As for prosthetic heart valves, the organisms usually originate from the skin and are likely to be introduced at the time of operation. Although early symptoms may be acute, patients with low-grade or chronic infection may have few general symptoms, and the clinical signs may become centered around local pain and loosening of the prosthesis. Prosthetic joints remain susceptible to hematogenous seeding during their entire lifetime. The overall risk for prosthetic joint infection after *S. aureus* bacteremia is high, ranging from 30% to 40%.[563,564]

Blood culture results are often negative. Cultures of the fluid from the artificial joint are critical, preferably with broth culture, but can have negative results as well. Molecular diagnosis with PCR should be considered (see "Culture and Identification" earlier). If the prosthesis is surgically removed, multiple microbiologic samples should be taken at various sites of the prosthesis and bone cavity because bacteria may remain clustered in circumscribed areas.

Successful treatment combines surgical intervention and antibiotics. The suggested antibiotic duration is 3 months for hip prostheses and 6 months for knee prostheses. Intravenous therapy should be administrated for the first 2 to 4 weeks.[431] The addition of rifampin to a conventional antistaphylococcal regimen appeared clearly useful in patients with prosthetic joint infections. Rifampin has an excellent activity on slow-growing and adherent staphylococci. In general, retention of the implant should not be attempted. Débridement with retention is an option only for patients with early postoperative or acute hematogenous infection, if duration of clinical signs and symptoms is less than 3 weeks, if the implant is stable, and if effective therapy against biofilm microorganisms is available. The prerequisites for one-stage exchange are satisfactory condition of soft tissue, the absence of severe coexisting illnesses, and the absence of difficult-to-treat bacteria. In all other cases, a two-stage exchange is preferred, with a 2-week to 4-week interval between procedures (see Chapter 105).[431,565]

Pyomyositis

Primary pyomyositis, also called tropical myositis, infective myositis, pyogenic myositis, and myositis purulenta tropica, is a rare subacute purulent infection of skeletal muscles. It does not follow contiguous contamination and is most probably of hematogenous origin. The rarity of the disease is attributed to the resistance of muscles to infection. A history of muscle trauma is often reported.

Pyomyositis is frequently seen in Africa and the South Pacific, but it is rare in the Northern Hemisphere. Hence, it could be related to particular local conditions or bacterial properties. In a review of 676 cases, the disease occurred in all age groups. However, it was about twice as frequent in children and adults younger than 30 years than in older adults, and males were predominantly affected.[566] Any muscle may be involved, but the quadriceps and iliopsoas muscles were most often implicated, in 26% and 14%, respectively. *S. aureus* was the etiologic agent in about 80% of cases. In a series from the Amazon Basin of Peru, 11 of 12 patients carried the Panton-Valentine toxin suggesting that PVL might be involved (see "Killing Leukocytes" section earlier).[567]

Clinical symptoms evolve in three stages. They first start with the insidious onset of dull cramping and low-grade fever, general malaise, and muscle aches. Because only the aponeurosis is innervated, overt muscle pain may be delayed for 1 or 2 weeks, before frank abscess formation. Second, the formation of muscle abscess becomes symptomatic, with pain, muscle swelling, tenderness, and sepsis. Most patients are seen at this stage. If left untreated, the disease evolves into the third stage, with muscle destruction, local extension with osteomyelitis, or osteoarthritis, septicemia, and distant dissemination. Diagnosis involves radiographic imaging (CT and MRI) and bacteriologic diagnosis with blood cultures and muscle puncture. Treatment is essentially based on antibiotic therapy. Treatment duration is a matter of debate. Parenteral treatment is often recommended for 7 to 14 days, followed by oral treatment for up to 6 weeks. The prognosis before stage 3 is usually excellent.

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Key References

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1. Lowy FD. *Staphylococcus aureus* infections. *N Engl J Med*. 1998;339:520–532.
2. Spaulding AR, Salgado-Pabon W, Kohler PL, et al. Staphylococcal and streptococcal superantigen exotoxins. *Clin Microbiol Rev*. 2013;26:422–447.
5. Brosnahan AJ, Schlievert PM. Gram-positive bacterial superantigen outside-in signaling causes toxic shock syndrome. *FEBS J*. 2011;278:4649–4667.
7. Feng Y, Chen CJ, Su LH, et al. Evolution and pathogenesis of *Staphylococcus aureus*: lessons learned from genotyping and comparative genomics. *FEMS Microbiol Rev*. 2008;32:23–37.
9. Foster TJ. Immune evasion by staphylococci. *Nat Rev Microbiol*. 2005;3:948–958.
10. Lindsay J, Holden M. Understanding the rise of the superbug: investigation of the evolution and genomic variation of *Staphylococcus aureus*. *Funct Integr Genomics*. 2006;6:186–201.
12. Kloos WE. *The Prokaryotes. A Handbook on the Biology of Bacteria: Ecophysiology, Isolation, Identification, Applications*. 2nd ed. New York: Springer-Verlag; 1992.
13. Novick RP, Ram G. The floating (pathogenicity) island: a genomic dessert. *Trends Genet*. 2016;32:114–126.
20. Kluytmans J, van Belkum A, Verbrugh H. Nasal carriage of *Staphylococcus aureus*: epidemiology, underlying mechanisms, and associated risks. *Clin Microbiol Rev*. 1997;10:505–520.
22. Wertheim HF, Melles DC, Vos MC, et al. The role of nasal carriage in *Staphylococcus aureus* infections. *Lancet Infect Dis*. 2005;5:751–762.
24. von Eiff C, Becker K, Machka K, et al. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. Study Group. *N Engl J Med*. 2001;344:11–16.
26. Bode LG, Kluytmans JA, Wertheim HF, et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *N Engl J Med*. 2010;362:9–17.
30. Proctor RA, Balwit JM, Vesga O. Variant subpopulations of *Staphylococcus aureus* as cause of persistent and recurrent infections. *Infect Agents Dis*. 1994;3:302–312.
47. Ito T, Hiramatsu K, Tomasz A, et al. Guidelines for reporting novel mecA gene homologues. *Antimicrob Agents Chemother*. 2012;56:4997–4999.
55. Enright MC, Robinson DA, Randle G, et al. The evolutionary history of methicillin-resistant *Staphylococcus aureus* (MRSA). *Proc Natl Acad Sci USA*. 2002;99:7687–7692.
61. Novick RP, Geisinger E. Quorum sensing in staphylococci. *Annu Rev Genet*. 2008;42:541–564.
63. Balasubramanian D, Harper L, Shopsin B, et al. *Staphylococcus aureus* pathogenesis in diverse host environments. *Pathog Dis*. 2017;75.
64. Novick RP, Ross HF, Projan SJ, et al. Synthesis of staphylococcal virulence factors is controlled by a regulatory RNA molecule. *EMBO J*. 1993;12:3967–3975.
65. Cheung AL, Bayer AS, Zhang G, et al. Regulation of virulence determinants in vitro and in vivo in *Staphylococcus aureus*. *FEMS Immunol Med Microbiol*. 2004;40:1–9.
77. Lioliou E, Sharma CM, Caldelari I, et al. Global regulatory functions of the *Staphylococcus aureus* endoribonuclease III in gene expression. *PLoS Genet*. 2012;8:e1002782.
81. Que YA, Haefliger JA, Piroth L, et al. Fibrinogen and fibronectin binding cooperate for valve infection and invasion in *Staphylococcus aureus* experimental endocarditis. *J Exp Med*. 2005;201:1627–1635.
91. Dufour P, Jarraud S, Vandenesch F, et al. High genetic variability of the agr locus in *Staphylococcus* species. *J Bacteriol*. 2002;184:1180–1186.
96. Patti JM, Allen BL, McGavin MJ, et al. MSCRAMM-mediated adherence of microorganisms to host tissues. *Annu Rev Microbiol*. 1994;48:585–617.
97. Roche FM, Massey R, Peacock SJ, et al. Characterization of novel LPXTG-containing proteins of *Staphylococcus aureus* identified from genome sequences. *Microbiology*. 2003;149(Pt 3):643–654.
117. Liesenborghs L, Verhamme P, Vanassche T. *Staphylococcus aureus*, master manipulator of the human hemostatic system. *J Thromb Haemost*. 2018;16:441–454.
121. Veloso TR, Que YA, Chaouch A, et al. Prophylaxis of experimental endocarditis with antiplatelet and antithrombin agents: a role for long-term prevention of infective endocarditis in humans? *J Infect Dis*. 2015;211:72–79.
133. Thammavongsa V, Kern JW, Missiakas DM, et al. *Staphylococcus aureus* synthesizes adenosine to escape host immune responses. *J Exp Med*. 2009;206:2417–2427.
139. Brinkmann V, Reichard U, Goosmann C, et al. Neutrophil extracellular traps kill bacteria. *Science*. 2004;303:1532–1535.
151. Saeed K, Gould I, Espositio S, et al. Panton-Valentine leukocidin-positive *Staphylococcus aureus*: a position statement from the International Society of Chemotherapy. *Int J Antimicrob Agents*. 2018;51:16–25.
197. Wright JS 3rd, Traber KE, Corrigan R, et al. The agr radiation: an early event in the evolution of staphylococci. *J Bacteriol*. 2005;187:5585–5594.
205. Price LB, Stegger M, Hasman H, et al. *Staphylococcus aureus* CC398: host adaptation and emergence of methicillin resistance in livestock. *MBio*. 2012;3:e00305–e00311.
221. Chambers HF, Hartman BJ, Tomasz A. Increased amounts of a novel penicillin-binding protein in a strain of methicillin-resistant *Staphylococcus aureus* exposed to nafcillin. *J Clin Invest*. 1985;76:325–331.
223. International Working Group on the Classification of Staphylococcal Cassette Chromosome E. Classification of staphylococcal cassette chromosome mec (SCCmec): guidelines for reporting novel SCCmec elements. *Antimicrob Agents Chemother*. 2009;53:4961–4967.
252. Gustave CA, Tristan A, Martins-Simoes P, et al. Demographic fluctuation of community-acquired antibiotic-resistant *Staphylococcus aureus* lineages: potential role of flimsy antibiotic exposure. *ISME J*. 2018;8:1879–1894.
254. DeLeo FR, Otto M, Kreiswirth BN, et al. Community-associated meticillin-resistant *Staphylococcus aureus*. *Lancet*. 2010;375:1557–1568.
262. Strauss L, Stegger M, Akpaka PE, et al. Origin, evolution, and global transmission of community-acquired *Staphylococcus aureus* ST8. *Proc Natl Acad Sci USA*. 2017;114:E10596–E10604.
286. Hiramatsu K, Hanaki H, Ino T, et al. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. *J Antimicrob Chemother*. 1997;40:135–136.
313. Silverman JA, Mortin LI, Vanpraagh AD, et al. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. *J Infect Dis*. 2005;191:2149–2152.
320. Weisblum B. Erythromycin resistance by ribosome modification. *Antimicrob Agents Chemother*. 1995;39:577–585.
391. Garcia-Fernandez E, Koch G, Wagner RM, et al. Membrane microdomain disassembly inhibits MRSA antibiotic resistance. *Cell*. 2017;171:1354–1367, e1320.
394. Fischetti VA. Bacteriophage endolysins: a novel anti-infective to control Gram-positive pathogens. *Int J Med Microbiol*. 2010;300:357–362.
401. Cisek AA, Dabrowska I, Gregorczyk KP, et al. Phage therapy in bacterial infections treatment: one hundred years after the discovery of bacteriophages. *Curr Microbiol*. 2017;74:277–283.
432. Laupland KB. Incidence of bloodstream infection: a review of population-based studies. *Clin Microbiol Infect*. 2013;19:492–500.
443. Melles DC, Gorkink RF, Boelens HA, et al. Natural population dynamics and expansion of pathogenic clones of *Staphylococcus aureus*. *J Clin Invest*. 2004;114:1732–1740.
451. van Belkum A, Verkaik NJ, de Vogel CP, et al. Reclassification of *Staphylococcus aureus* nasal carriage types. *J Infect Dis*. 2009;199:1820–1826.
468. Ammerlaan HS, Kluytmans JA, Berkhout H, et al. Eradication of carriage with methicillin-resistant *Staphylococcus aureus*: effectiveness of a national guideline. *J Antimicrob Chemother*. 2011;66:2409–2417.
489. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36:3075–3128.
518. Dickerman S, Abrutyn E, Barsic B, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). *Am Heart J*. 2007;154:1086–1094.
549. Lew DP, Waldvogel FA. Osteomyelitis. *Lancet*. 2004;364:369–379.
565. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med*. 2004;351:1645–1654.

References

1. Lowy FD. *Staphylococcus aureus* infections. *N Engl J Med*. 1998;339:520–532.
2. Spaulding AR, Salgado-Pabon W, Kohler PL, et al. Staphylococcal and streptococcal superantigen exotoxins. *Clin Microbiol Rev*. 2013;26:422–447.
3. Ladhani S, Joannou CL, Lochrie DP, et al. Clinical, microbial, and biochemical aspects of the exfoliative toxins causing staphylococcal scalded-skin syndrome. *Clin Microbiol Rev*. 1999;12:224–242.
4. Lamand V, Dauwalder O, Tristan A, et al. Epidemiological data of staphylococcal scalded skin syndrome in France from 1997 to 2007 and microbiological characteristics of *Staphylococcus aureus* associated strains. *Clin Microbiol Infect*. 2012;18:E514–E521.
5. Brosnahan AJ, Schlievert PM. Gram-positive bacterial superantigen outside-in signaling causes toxic shock syndrome. *FEBS J*. 2011;278:4649–4667.
6. Jarraud S, Peyrat MA, Lim A, et al. egc, a highly prevalent operon of enterotoxin gene, forms a putative nursery of superantigens in *Staphylococcus aureus*. *J Immunol*. 2001;166:669–677.
7. Feng Y, Chen CJ, Su LH, et al. Evolution and pathogenesis of *Staphylococcus aureus*: lessons learned from genotyping and comparative genomics. *FEMS Microbiol Rev*. 2008;32:23–37.
8. Baba T, Takeuchi F, Kuroda M, et al. Genome and virulence determinants of high virulence community-acquired MRSA. *Lancet*. 2002;359:1819–1827.
9. Foster TJ. Immune evasion by staphylococci. *Nat Rev Microbiol*. 2005;3:948–958.
10. Lindsay J, Holden M. Understanding the rise of the superbug: investigation of the evolution and genomic variation of *Staphylococcus aureus*. *Funct Integr Genomics*. 2006;6:186–201.
11. Gotz F, Bannerman T, Schleifer K-H. The genera *Staphylococcus* and *Macrococcus*. In: Balows A, Truper AG, Dworkin M, et al, eds. *The Prokaryotes*. Vol. 4. 3rd ed. New York: Springer Science+Business Media; 2006:1–75.
12. Kloos WE. *The Prokaryotes. A Handbook on the Biology of Bacteria: Ecophysiology, Isolation, Identification, Applications*. 2nd ed. New York: Springer-Verlag; 1992.
13. Novick RP, Ram G. The floating (pathogenicity) island: a genomic dessert. *Trends Genet*. 2016;32:114–126.
14. Kuroda M, Ohta T, Uchiyama I, et al. Whole genome sequencing of meticillin-resistant *Staphylococcus aureus*. *Lancet*. 2001;357:1225–1240.
15. Ogston A. Micrococcus poisoning. *J Anat Physiol*. 1883;17:24–58.
16. Takeuchi F, Watanabe S, Baba T, et al. Whole-genome sequencing of *Staphylococcus haemolyticus* uncovers the extreme plasticity of its genome and the evolution of human-colonizing staphylococcal species. *J Bacteriol*. 2005;187:7292–7308.
17. Kuroda M, Yamashita A, Hirakawa H, et al. Whole genome sequence of *Staphylococcus saprophyticus* reveals the pathogenesis of uncomplicated urinary tract infection. *Proc Natl Acad Sci USA*. 2005;102:13272–13277.
18. Gill SR, Fouts DE, Archer GL, et al. Insights on evolution of virulence and resistance from the complete genome analysis of an early methicillin-resistant *Staphylococcus aureus* strain and a biofilm-producing methicillin-resistant *Staphylococcus epidermidis* strain. *J Bacteriol*. 2005;187:2426–2438.
19. Borjesson S, Gomez-Sanz E, Ekstrom K, et al. *Staphylococcus pseudintermedius* can be misdiagnosed as *Staphylococcus aureus* in humans with dog bite wounds. *Eur J Clin Microbiol Infect Dis*. 2015;34:839–844.
20. Kluytmans J, van Belkum A, Verbrugh H. Nasal carriage of *Staphylococcus aureus*: epidemiology, underlying mechanisms, and associated risks. *Clin Microbiol Rev*. 1997;10:505–520.
21. Williams RE. Healthy carriage of *Staphylococcus aureus*: its prevalence and importance. *Bacteriol Rev*. 1963;27:56–71.
22. Wertheim HF, Melles DC, Vos MC, et al. The role of nasal carriage in *Staphylococcus aureus* infections. *Lancet Infect Dis*. 2005;5:751–762.
23. Senn L, Clerc O, Zanetti G, et al. The stealthy superbug: the role of asymptomatic enteric carriage in maintaining a long-term hospital outbreak of ST228 methicillin-resistant *Staphylococcus aureus*. *MBio*. 2016;7:e02039-02015.
24. von Eiff C, Becker K, Machka K, et al. Nasal carriage as a source of *Staphylococcus aureus* bacteremia. Study Group. *N Engl J Med*. 2001;344:11–16.
25. Dufour P, Gillet Y, Bes M, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* infections in France: emergence of a single clone that produces Panton-Valentine leukocidin. *Clin Infect Dis*. 2002;35:819–824.
26. Bode LG, Kluytmans JA, Wertheim HF, et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *N Engl J Med*. 2010;362:9–17.
27. Kuehnert MJ, Kruszon-Moran D, Hill HA, et al. Prevalence of *Staphylococcus aureus* nasal colonization in the United States, 2001-2002. *J Infect Dis*. 2006;193:172–179.
28. Compernolle V, Verschraegen G, Claeys G. Combined use of Pastorex Staph-Plus and either of two new chromogenic agars, MRSA ID and CHROMagar MRSA, for detection of methicillin-resistant *Staphylococcus aureus*. *J Clin Microbiol*. 2007;45:154–158.
29. Walsh TR, Bolmstrom A, Qwarnstrom A, et al. Evaluation of current methods for detection of staphylococci with reduced susceptibility to glycopeptides. *J Clin Microbiol*. 2001;39:2439–2444.
30. Proctor RA, Balwit JM, Vesga O. Variant subpopulations of *Staphylococcus aureus* as cause of persistent and recurrent infections. *Infect Agents Dis*. 1994;3:302–312.
31. Wolter DJ, Emerson JC, McNamara S, et al. *Staphylococcus aureus* small-colony variants are independently associated with worse lung disease in children with cystic fibrosis. *Clin Infect Dis*. 2013;57:384–391.
32. Baumert N, von Eiff C, Schaaff F, et al. Physiology and antibiotic susceptibility of *Staphylococcus aureus* small colony variants. *Microb Drug Resist*. 2002;8:253–260.
33. Edwards AM. Phenotype switching is a natural consequence of *Staphylococcus aureus* replication. *J Bacteriol*. 2012;194:5404–5412.
34. Latimer J, Forbes S, McBain AJ. Attenuated virulence and biofilm formation in *Staphylococcus aureus* following sublethal exposure to triclosan. *Antimicrob Agents Chemother*. 2012;56:3092–3100.
35. Chatterjee I, Kriegeskorte A, Fischer A, et al. In vivo mutations of thymidylate synthase (encoded by thyA) are responsible for thymidine dependency in clinical small-colony variants of *Staphylococcus aureus*. *J Bacteriol*. 2008;190:834–842.
36. Jonsson IM, von Eiff C, Proctor RA, et al. Virulence of a hemB mutant displaying the phenotype of a *Staphylococcus aureus* small colony variant in a murine model of septic arthritis. *Microb Pathog*. 2003;34:73–79.
37. Bates DM, Eiff Cv C, McNamara PJ, et al. *Staphylococcus aureus* menD and hemB mutants are as infective as the parent strains, but the menadione biosynthetic mutant persists within the kidney. *J Infect Dis*. 2003;187:1654–1661.
38. Vaudaux P, Francois P, Bisognano C, et al. Increased expression of clumping factor and fibronectin-binding proteins by hemB mutants of *Staphylococcus aureus* expressing small colony variant phenotypes. *Infect Immun*. 2002;70:5428–5437.
39. Williamson DA, Heffernan H, Nimmo G. Contemporary genomic approaches in the diagnosis and typing of *Staphylococcus aureus*. *Pathology*. 2015;47:270–275.
40. Carretto E, Bardaro M, Russello G, et al. Comparison of the *Staphylococcus* QuickFISH BC test with the tube coagulase test performed on positive blood cultures for evaluation and application in a clinical routine setting. *J Clin Microbiol*. 2013;51:131–135.
41. Laub RR, Knudsen JD. Clinical consequences of using PNA-FISH in Staphylococcal bacteraemia. *Eur J Clin Microbiol Infect Dis*. 2014;33:599–601.
42. Huletsky A, Lebel P, Picard FJ, et al. Identification of methicillin-resistant *Staphylococcus aureus* carriage in less than 1 hour during a hospital surveillance program. *Clin Infect Dis*. 2005;40:976–981.
43. Zhang K, McClure JA, Elsayed S, et al. Novel multiplex PCR assay for simultaneous identification of community-associated methicillin-resistant *Staphylococcus aureus* strains USA300 and USA400 and detection of mecA and Panton-Valentine leukocidin genes, with discrimination of *Staphylococcus aureus* from coagulase-negative staphylococci. *J Clin Microbiol*. 2008;46:1118–1122.
44. Okolie CE, Wooldridge KG, Turner DP, et al. Development of a new pentaplex real-time PCR assay for the identification of poly-microbial specimens containing *Staphylococcus aureus* and other staphylococci, with simultaneous detection of staphylococcal virulence and methicillin resistance markers. *Mol Cell Probes*. 2015;29:144–150.
45. Harbarth S, Masuet-Aumatell C, Schrenzel J, et al. Evaluation of rapid screening and pre-emptive contact isolation for detecting and controlling methicillin-resistant *Staphylococcus aureus* in critical care: an interventional cohort study. *Crit Care*. 2006;10:R25.
46. Mendes RE, Watters AA, Rhomberg PR, et al. Performance of BD max StaphSR for screening of methicillin-resistant *Staphylococcus aureus* isolates among a contemporary and diverse collection from 146 institutions located in nine U.S. census regions: prevalence of mecA dropout mutants. *J Clin Microbiol*. 2016;54:204–207.
47. Ito T, Hiramatsu K, Tomasz A, et al. Guidelines for reporting novel mecA gene homologues. *Antimicrob Agents Chemother*. 2012;56:4997–4999.
48. Garcia-Alvarez L, Holden MT, Lindsay H, et al. Meticillin-resistant *Staphylococcus aureus* with a novel mecA homologue in human and bovine populations in the UK and Denmark: a descriptive study. *Lancet Infect Dis*. 2011;11:595–603.
49. Proulx MK, Palace SG, Gandra S, et al. Reversion from methicillin susceptibility to methicillin resistance in *Staphylococcus aureus* during treatment of bacteremia. *J Infect Dis*. 2016;213:1041–1048.
50. Sogawa K, Watanabe M, Ishige T, et al. Rapid discrimination between methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* using MALDI-TOF mass spectrometry. *Biocontrol Sci*. 2017;22:163–169.
51. Ruppe E, Cherkaoui A, Lazarevic V, et al. Establishing genotype-to-phenotype relationships in bacteria causing hospital-acquired pneumonia: a prelude to the application of clinical metagenomics. *Antibiotics (Basel)*. 2017;6.
52. Styers D, Sheehan DJ, Hogan P, et al. Laboratory-based surveillance of current antimicrobial resistance patterns and trends among *Staphylococcus aureus*: 2005 status in the United States. *Ann Clin Microbiol Antimicrob*. 2006;5:2.
53. Kanjilal S, Sater MRA, Thayer M, et al. Trends in Antibiotic Susceptibility in *Staphylococcus aureus* in Boston, Massachusetts, from 2000 to 2014. *J Clin Microbiol*. 2018;56.
54. Cai Y, Venkatachalam I, Tee NW, et al. Prevalence of healthcare-associated infections and antimicrobial use among adult inpatients in Singapore acute-care hospitals: results from the first national point prevalence survey. *Clin Infect Dis*. 2017;64(suppl_2):S61–S67.
55. Enright MC, Robinson DA, Randle G, et al. The evolutionary history of methicillin-resistant *Staphylococcus aureus* (MRSA). *Proc Natl Acad Sci USA*. 2002;99:7687–7692.
56. Oliveira DC, Tomasz A, de Lencastre H. Secrets of success of a human pathogen: molecular evolution of pandemic clones of meticillin-resistant *Staphylococcus aureus*. *Lancet Infect Dis*. 2002;2:180–189.
57. Enright MC, Day NP, Davies CE, et al. Multilocus sequence typing for characterization of methicillin-resistant and methicillin-susceptible clones of *Staphylococcus aureus*. *J Clin Microbiol*. 2000;38:1008–1015.
58. Robinson DA, Enright MC. Evolutionary models of the emergence of methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2003;47:3926–3934.
59. Kuhn G, Francioli P, Blanc DS. Double-locus sequence typing using clfB and spa, a fast and simple method for epidemiological typing of methicillin-resistant *Staphylococcus aureus*. *J Clin Microbiol*. 2007;45:54–62.
60. Rasigade JP, Laurent F, Lina G, et al. Global distribution and evolution of Panton-Valentine leukocidin-positive methicillin-susceptible *Staphylococcus aureus*, 1981-2007. *J Infect Dis*. 2010;201:1589–1597.
61. Novick RP, Geisinger E. Quorum sensing in staphylococci. *Annu Rev Genet*. 2008;42:541–564.
62. Pragman AA, Schlievert PM. Virulence regulation in *Staphylococcus aureus*: the need for in vivo analysis of virulence factor regulation. *FEMS Immunol Med Microbiol*. 2004;42:147–154.
63. Balasubramanian D, Harper L, Shopsin B, et al. *Staphylococcus aureus* pathogenesis in diverse host environments. *Pathog Dis*. 2017;75.
64. Novick RP, Ross HF, Projan SJ, et al. Synthesis of staphylococcal virulence factors is controlled by a regulatory RNA molecule. *EMBO J*. 1993;12:3967–3975.
65. Cheung AL, Bayer AS, Zhang G, et al. Regulation of virulence determinants in vitro and in vivo in *Staphylococcus aureus*. *FEMS Immunol Med Microbiol*. 2004;40:1–9.
66. Gupta RK, Luong TT, Lee CY. RNAIII of the *Staphylococcus aureus* agr system activates global regulator MgrA by stabilizing mRNA. *Proc Natl Acad Sci USA*. 2015;112:14036–14041.
67. Giraudo AT, Cheung AL, Nagel R. The sae locus of *Staphylococcus aureus* controls exoprotein synthesis at the transcriptional level. *Arch Microbiol*. 1997;168:53–58.
68. Yarwood JM, McCormick JK, Schlievert PM. Identification of a novel two-component regulatory system that acts in global regulation of virulence factors of *Staphylococcus aureus*. *J Bacteriol*. 2001;183:1113–1123.

69. Fournier B, Hooper DC. A new two-component regulatory system involved in adhesion, autolysis, and extracellular proteolytic activity of *Staphylococcus aureus*. *J Bacteriol*. 2000;182:3955–3964.
70. Berends ET, Horswill AR, Haste NM, et al. Nuclease expression by *Staphylococcus aureus* facilitates escape from neutrophil extracellular traps. *J Innate Immun*. 2010;2:576–586.
71. Luong TT, Dunman PM, Murphy E, et al. Transcription Profiling of the mgrA Regulon in *Staphylococcus aureus*. *J Bacteriol*. 2006;188:1899–1910.
72. Said-Salim B, Dunman PM, McAleese FM, et al. Global regulation of *Staphylococcus aureus* genes by Rot. *J Bacteriol*. 2003;185:610–619.
73. Chan PF, Foster SJ. The role of environmental factors in the regulation of virulence-determinant expression in *Staphylococcus aureus* 8325-4. *Microbiology*. 1998;144(Pt 9):2469–2479.
74. Bischoff M, Dunman P, Kormanec J, et al. Microarray-based analysis of the *Staphylococcus aureus* sigmaB regulon. *J Bacteriol*. 2004;186:4085–4099.
75. Entenza JM, Moreillon P, Senn MM, et al. Role of sigmaB in the expression of *Staphylococcus aureus* cell wall adhesins ClfA and FnbA and contribution to infectivity in a rat model of experimental endocarditis. *Infect Immun*. 2005;73:990–998.
76. Lorenz U, Huttinger C, Schafer T, et al. The alternative sigma factor sigma B of *Staphylococcus aureus* modulates virulence in experimental central venous catheter-related infections. *Microbes Infect*. 2008;10:217–223.
77. Lioliou E, Sharma CM, Caldelari I, et al. Global regulatory functions of the *Staphylococcus aureus* endoribonuclease III in gene expression. *PLoS Genet*. 2012;8:e1002782.
78. Priest NK, Rudkin JK, Feil EJ, et al. From genotype to phenotype: can systems biology be used to predict *Staphylococcus aureus* virulence? *Nat Rev Microbiol*. 2012;10:791–797.
79. Mayville P, Ji G, Beavis R, et al. Structure-activity analysis of synthetic autoinducing thiolactone peptides from *Staphylococcus aureus* responsible for virulence. *Proc Natl Acad Sci USA*. 1999;96:1218–1223.
80. Cheung AL, Eberhardt KJ, Chung E, et al. Diminished virulence of a sar-/agr- mutant of *Staphylococcus aureus* in the rabbit model of endocarditis. *J Clin Invest*. 1994;94:1815–1822.
81. Que YA, Haefliger JA, Piroth L, et al. Fibrinogen and fibronectin binding cooperate for valve infection and invasion in *Staphylococcus aureus* experimental endocarditis. *J Exp Med*. 2005;201:1627–1635.
82. Piroth L, Que YA, Widmer E, et al. The fibrinogen- and fibronectin-binding domains of *Staphylococcus aureus* fibronectin-binding protein A synergistically promote endothelial invasion and experimental endocarditis. *Infect Immun*. 2008;76:3824–3831.
83. Cheung AL, Nast CC, Bayer AS. Selective activation of sar promoters with the use of green fluorescent protein transcriptional fusions as the detection system in the rabbit endocarditis model. *Infect Immun*. 1998;66:5988–5993.
84. Yarwood JM, McCormick JK, Paustian ML, et al. Repression of the *Staphylococcus aureus* accessory gene regulator in serum and in vivo. *J Bacteriol*. 2002;184:1095–1101.
85. Goerke C, Wolz C. Adaptation of *Staphylococcus aureus* to the cystic fibrosis lung. *Int J Med Microbiol*. 2010;300:520–525.
86. Smyth DS, Kafer JM, Wasserman GA, et al. Nasal carriage as a source of agr-defective *Staphylococcus aureus* bacteremia. *J Infect Dis*. 2012;206:1168–1177.
87. Boles BR, Horswill AR. Agr-mediated dispersal of *Staphylococcus aureus* biofilms. *PLoS Pathog*. 2008;4:e1000052.
88. Archer NK, Mazaitis MJ, Costerton JW, et al. *Staphylococcus aureus* biofilms: properties, regulation, and roles in human disease. *Virulence*. 2011;2:445–459.
89. Ji G, Beavis R, Novick RP. Bacterial interference caused by autoinducing peptide variants. *Science*. 1997;276:2027–2030.
90. Kahl BC, Becker K, Friedrich AW, et al. agr-dependent bacterial interference has no impact on long-term colonization of *Staphylococcus aureus* during persistent airway infection of cystic fibrosis patients. *J Clin Microbiol*. 2003;41:5199–5201.
91. Dufour P, Jarraud S, Vandenesch F, et al. High genetic variability of the agr locus in *Staphylococcus* species. *J Bacteriol*. 2002;184:1180–1186.
92. Weidenmaier C, Kokai-Kun JF, Kristian SA, et al. Role of teichoic acids in *Staphylococcus aureus* nasal colonization, a major risk factor in nosocomial infections. *Nat Med*. 2004;10:243–245.
93. O'Brien LM, Walsh EJ, Massey RC, et al. *Staphylococcus aureus* clumping factor B (ClfB) promotes adherence to human type I cytokeratin 10: implications for nasal colonization. *Cell Microbiol*. 2002;4:759–770.
94. Roche FM, Meehan M, Foster TJ. The *Staphylococcus aureus* surface protein SasG and its homologues promote bacterial adherence to human desquamated nasal epithelial cells. *Microbiology*. 2003;149(Pt 10):2759–2767.
95. Corrigan RM, Miajlovic H, Foster TJ. Surface proteins that promote adherence of *Staphylococcus aureus* to human desquamated nasal epithelial cells. *BMC Microbiol*. 2009;9:22.
96. Patti JM, Allen BL, McGavin MJ, et al. MSCRAMM-mediated adherence of microorganisms to host tissues. *Annu Rev Microbiol*. 1994;48:585–617.
97. Roche FM, Massey R, Peacock SJ, et al. Characterization of novel LPXTG-containing proteins of *Staphylococcus aureus* identified from genome sequences. *Microbiology*. 2003;149(Pt 3):643–654.
98. Mazmanian SK, Liu G, Ton-That H, et al. *Staphylococcus aureus* sortase, an enzyme that anchors surface proteins to the cell wall. *Science*. 1999;285:760–763.
99. Bradshaw WJ, Davies AH, Chambers CJ, et al. Molecular features of the sortase enzyme family. *FEBS J*. 2015;282:2097–2114.
100. Askarian F, Ajayi C, Hanssen AM, et al. The interaction between *Staphylococcus aureus* SdrD and desmoglein 1 is important for adhesion to host cells. *Sci Rep*. 2016;6.
101. Geoghegan JA, Corrigan RM, Gruszka DT, et al. Role of surface protein SasG in biofilm formation by *Staphylococcus aureus*. *J Bacteriol*. 2010;192:5663–5673.
102. Mazmanian SK, Skaar EP, Gaspar AH, et al. Passage of heme-iron across the envelope of *Staphylococcus aureus*. *Science*. 2003;299:906–909.
103. Clement S, Vaudaux P, Francois P, et al. Evidence of an intracellular reservoir in the nasal mucosa of patients with recurrent *Staphylococcus aureus* rhinosinusitis. *J Infect Dis*. 2005;192:1023–1028.
104. Nouwen J, Boelens H, van Belkum A, et al. Human factor in *Staphylococcus aureus* nasal carriage. *Infect Immun*. 2004;72:6685–6688.
105. Grothe C, Taminato M, Belasco A, et al. Prophylactic treatment of chronic renal disease in patients undergoing peritoneal dialysis and colonized by *Staphylococcus aureus*: a systematic review and meta-analysis. *BMC Nephrol*. 2016;17:115.
106. Chirouze C, Alla F, Fowler VG Jr, et al. Impact of early valve surgery on outcome of *Staphylococcus aureus* prosthetic valve infective endocarditis: analysis in the International Collaboration of Endocarditis-Prospective Cohort Study. *Clin Infect Dis*. 2015;60:741–749.
107. McDevitt D, François P, Vaudaux P, et al. Molecular characterization of the clumping factor (fibrinogen receptor) of *Staphylococcus aureus*. *Mol Microbiol*. 1994;11:237–248.
108. Massey RC, Kantzanou MN, Fowler T, et al. Fibronectin-binding protein A of *Staphylococcus aureus* has multiple, substituting, binding regions that mediate adherence to fibronectin and invasion of endothelial cells. *Cell Microbiol*. 2001;3:839–851.
109. Massey RC, Dissanayeke SR, Cameron B, et al. Functional blocking of *Staphylococcus aureus* adhesins following growth in ex vivo media. *Infect Immun*. 2002;70:5339–5345.
110. Kroh HK, Panizzi P, Bock PE. Von Willebrand factor-binding protein is a hysteretic conformational activator of prothrombin. *Proc Natl Acad Sci USA*. 2009;106:7786–7791.
111. Rooijakkers SH, Ruyken M, van Roon J, et al. Early expression of SCIN and CHIPS drives instant immune evasion by *Staphylococcus aureus*. *Cell Microbiol*. 2006;8:1282–1293.
112. Peetermans M, Vanassche T, Liesenborghs L, et al. Plasminogen activation by staphylokinase enhances local spreading of S. aureus in skin infections. *BMC Microbiol*. 2014;14:310.
113. van Wamel WJ, Rooijakkers SH, Ruyken M, et al. The innate immune modulators staphylococcal complement inhibitor and chemotaxis inhibitory protein of *Staphylococcus aureus* are located on beta-hemolysin-converting bacteriophages. *J Bacteriol*. 2006;188:1310–1315.
114. Resch G, Francois P, Morisset D, et al. Human-to-bovine jump of *Staphylococcus aureus* CC8 is associated with the loss of a beta-hemolysin converting prophage and the acquisition of a new staphylococcal cassette chromosome. *PLoS ONE*. 2013;8:e58187.
115. Patti JM, Bremell T, Krajewska-Pietrasik D, et al. The *Staphylococcus aureus* collagen adhesin is a virulence determinant in experimental septic arthritis. *Infect Immun*. 1994;62:152–161.
116. Xu Y, Rivas JM, Brown EL, et al. Virulence potential of the staphylococcal adhesin CNA in experimental arthritis is determined by its affinity for collagen. *J Infect Dis*. 2004;189:2323–2333.
117. Liesenborghs L, Verhamme P, Vanassche T. *Staphylococcus aureus*, master manipulator of the human hemostatic system. *J Thromb Haemost*. 2018;16:441–454.
118. Loughman A, Fitzgerald JR, Brennan MP, et al. Roles for fibrinogen, immunoglobulin and complement in platelet activation promoted by *Staphylococcus aureus* clumping factor A. *Mol Microbiol*. 2005;57:804–818.
119. Ruggeri ZM, Ware J. von Willebrand factor. *FASEB J*. 1993;7:308–316.
120. Claes J, Liesenborghs L, Peetermans M, et al. Clumping factor A, von Willebrand factor-binding protein and von Willebrand factor anchor *Staphylococcus aureus* to the vessel wall. *J Thromb Haemost*. 2017;15:1009–1019.
121. Veloso TR, Que YA, Chaouch A, et al. Prophylaxis of experimental endocarditis with antiplatelet and antithrombin agents: a role for long-term prevention of infective endocarditis in humans? *J Infect Dis*. 2015;211:72–79.
122. Claes J, Vanassche T, Peetermans M, et al. Adhesion of *Staphylococcus aureus* to the vessel wall under flow is mediated by von Willebrand factor-binding protein. *Blood*. 2014;124:1669–1676.
123. Kupferwasser LI, Yeaman MR, Shapiro SM, et al. In vitro susceptibility to thrombin-induced platelet microbicidal protein is associated with reduced disease progression and complication rates in experimental *Staphylococcus aureus* endocarditis: microbiological, histopathologic, and echocardiographic analyses. *Circulation*. 2002;105:746–752.
124. Bayer AS, Prasad R, Chandra J, et al. In vitro resistance of *Staphylococcus aureus* to thrombin-induced platelet microbicidal protein is associated with alterations in cytoplasmic membrane fluidity. *Infect Immun*. 2000;68:3548–3553.
125. Bayer AS, Cheng D, Yeaman MR, et al. In vitro resistance to thrombin-induced platelet microbicidal protein among clinical bacteremic isolates of *Staphylococcus aureus* correlates with an endovascular infectious source. *Antimicrob Agents Chemother*. 1998;42:3169–3172.
126. Resch A, Rosenstein R, Nerz C, et al. Differential gene expression profiling of *Staphylococcus aureus* cultivated under biofilm and planktonic conditions. *Appl Environ Microbiol*. 2005;71:2663–2676.
127. Kim HK, Thammavongsa V, Schneewind O, et al. Recurrent infections and immune evasion strategies of *Staphylococcus aureus*. *Curr Opin Microbiol*. 2012;15:92–99.
128. Guerra FE, Borgogna TR, Patel DM, et al. Epic immune battles of history: neutrophils vs. *Staphylococcus aureus*. *Front Cell Infect Microbiol*. 2017;7:286.
129. Wolf AJ, Underhill DM. Peptidoglycan recognition by the innate immune system. *Nat Rev Immunol*. 2018.
130. Chavakis T, Hussain M, Kanse SM, et al. *Staphylococcus aureus* extracellular adherence protein serves as anti-inflammatory factor by inhibiting the recruitment of host leukocytes. *Nat Med*. 2002;8:687–693.
131. Higgins J, Loughman A, van Kessel KP, et al. Clumping factor A of *Staphylococcus aureus* inhibits phagocytosis by human polymorphonuclear leucocytes. *FEMS Microbiol Lett*. 2006;258:290–296.
132. Thiel M, Caldwell CC, Sitkovsky MV. The critical role of adenosine A2A receptors in downregulation of inflammation and immunity in the pathogenesis of infectious diseases. *Microbes Infect*. 2003;5:515–526.
133. Thammavongsa V, Kern JW, Missiakas DM, et al. *Staphylococcus aureus* synthesizes adenosine to escape host immune responses. *J Exp Med*. 2009;206:2417–2427.
134. Smith EJ, Visai L, Kerrigan SW, et al. The Sbi protein is a multifunctional immune evasion factor of *Staphylococcus aureus*. *Infect Immun*. 2011;79:3801–3809.
135. Zipfel PF. Complement and immune defense: from innate immunity to human diseases. *Immunol Lett*. 2009;126:1–7.
136. Lee LY, Hook M, Haviland D, et al. Inhibition of complement activation by a secreted *Staphylococcus aureus* protein. *J Infect Dis*. 2004;190:571–579.
137. Sharp JA, Echague CG, Hair PS, et al. *Staphylococcus aureus* surface protein SdrE binds complement regulator factor H as an immune evasion tactic. *PLoS ONE*. 2012;7:e38407.
138. Beavers WN, Skaar EP. Neutrophil-generated oxidative stress and protein damage in *Staphylococcus aureus*. *Pathog Dis*. 2016;74.
139. Brinkmann V, Reichard U, Goosmann C, et al. Neutrophil extracellular traps kill bacteria. *Science*. 2004;303:1532–1535.
140. Lehrer RI, Ganz T. Antimicrobial peptides in mammalian and insect host defence. *Curr Opin Immunol*. 1999;11:23–27.
141. Peschel A, Collins LV. Staphylococcal resistance to antimicrobial peptides of mammalian and bacterial origin. *Peptides*. 2001;22:1651–1659.

142. Sass P, Bierbaum G. Native graS mutation supports the susceptibility of *Staphylococcus aureus* strain SG511 to antimicrobial peptides. *Int J Med Microbiol*. 2009;299:313–322.
143. Dinges MM, Orwin PM, Schlievert PM. Exotoxins of *Staphylococcus aureus*. *Clin Microbiol Rev*. 2000;13:16–34. Table of contents.
144. Wang R, Braughton KR, Kretschmer D, et al. Identification of novel cytolytic peptides as key virulence determinants for community-associated MRSA. *Nat Med*. 2007;13:1510–1514.
145. Bhakdi S, Tranum-Jensen J. Alpha-toxin of *Staphylococcus aureus*. *Microbiol Rev*. 1991;55:733–751.
146. Berube BJ, Bubeck Wardenburg J. *Staphylococcus aureus* alpha-toxin: nearly a century of intrigue. *Toxins (Basel)*. 2013;5:1140–1166.
147. Wilke GA, Bubeck Wardenburg J. Role of a disintegrin and metalloprotease 10 in *Staphylococcus aureus* alpha-hemolysin-mediated cellular injury. *Proc Natl Acad Sci USA*. 2010;107:13473–13478.
148. Popov LM, Marceau CD, Starkl PM, et al. The adherens junctions control susceptibility to *Staphylococcus aureus* alpha-toxin. *Proc Natl Acad Sci USA*. 2015;112:14337–14342.
149. Towle KM, Lohans CT, Miskolzie M, et al. Solution Structures of Phenol-Soluble Modulins alpha1, alpha3, and beta2, Virulence Factors from *Staphylococcus aureus*. *Biochemistry*. 2016;55:4798–4806.
150. von Eiff C, Friedrich AW, Peters G, et al. Prevalence of genes encoding for members of the staphylococcal leukotoxin family among clinical isolates of *Staphylococcus aureus*. *Diagn Microbiol Infect Dis*. 2004;49:157–162.
151. Saeed K, Gould I, Espositio S, et al. Panton-Valentine leukocidin-positive *Staphylococcus aureus*: a position statement from the International Society of Chemotherapy. *Int J Antimicrob Agents*. 2018;51:16–25.
152. Sanchini A, Del Grosso M, Villa L, et al. Typing of Panton-Valentine leukocidin-encoding phages carried by methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* from Italy. *Clin Microbiol Infect*. 2014;20:O840–O846.
153. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant S. aureus infections among patients in the emergency department. *N Engl J Med*. 2006;355:666–674.
154. Lina G, Piemont Y, Godail-Gamot F, et al. Involvement of Panton-Valentine leukocidin-producing *Staphylococcus aureus* in primary skin infections and pneumonia. *Clin Infect Dis*. 1999;29:1128–1132.
155. Nielsen MM, Witherden DA, Havran WL. gammadelta T cells in homeostasis and host defence of epithelial barrier tissues. *Nat Rev Immunol*. 2017;17:733–745.
156. Archer NK, Adappa ND, Palmer JN, et al. Interleukin-17A (IL-17A) and IL-17F are critical for antimicrobial peptide production and clearance of *Staphylococcus aureus* nasal colonization. *Infect Immun*. 2016;84:3575–3583.
157. Cho JS, Pietras EM, Garcia NC, et al. IL-17 is essential for host defense against cutaneous *Staphylococcus aureus* infection in mice. *J Clin Invest*. 2010;120:1762–1773.
158. Tomi NS, Kranke B, Aberer E. Staphylococcal toxins in patients with psoriasis, atopic dermatitis, and erythroderma, and in healthy control subjects. *J Am Acad Dermatol*. 2005;53:67–72.
159. Bancsi MJ, Veltrop MH, Bertina RM, et al. Role of phagocytosis in activation of the coagulation system in *Streptococcus sanguis* endocarditis. *Infect Immun*. 1996;64:5166–5170.
160. Patel R. Biofilms and antimicrobial resistance. *Clin Orthop Relat Res*. 2005;437:41–47.
161. Begun J, Gaiani JM, Rohde H, et al. Staphylococcal biofilm exopolysaccharide protects against *Caenorhabditis elegans* immune defenses. *PLoS Pathog*. 2007;3:e57.
162. Gerke C, Kraft A, Sussmuth R, et al. Characterization of the N-acetylglucosaminyltransferase activity involved in the biosynthesis of the *Staphylococcus epidermidis* polysaccharide intercellular adhesin. *J Biol Chem*. 1998;273:18586–18593.
163. Heilmann C, Schweitzer O, Gerke C, et al. Molecular basis of intercellular adhesion in the biofilm-forming *Staphylococcus epidermidis*. *Mol Microbiol*. 1996;20:1083–1091.
164. Francois P, Tu Quoc PH, Bisognano C, et al. Lack of biofilm contribution to bacterial colonisation in an experimental model of foreign body infection by *Staphylococcus aureus* and *Staphylococcus epidermidis*. *FEMS Immunol Med Microbiol*. 2003;35:135–140.
165. Periasamy S, Joo HS, Duong AC, et al. How *Staphylococcus aureus* biofilms develop their characteristic structure. *Proc Natl Acad Sci USA*. 2012;109:1281–1286.
166. Von Rittershain GR. Die exfloliative dermatitis jungere senglinge. *Z Kinderheilkd*. 1878;2.
167. Yamaguchi T, Nishifuji K, Sasaki M, et al. Identification of the *Staphylococcus aureus* etd pathogenicity island which encodes a novel exfoliative toxin, ETD, and EDIN-B. *Infect Immun*. 2002;70:5835–5845.
168. Ladhani S. Understanding the mechanism of action of the exfoliative toxins of *Staphylococcus aureus*. *FEMS Immunol Med Microbiol*. 2003;39:181–189.
169. Staiman A, Hsu DY, Silverberg JI. Epidemiology of staphylococcal scalded skin syndrome in U.S. children. *Br J Dermatol*. 2017.
170. Becker K, Friedrich AW, Lubritz G, et al. Prevalence of genes encoding pyrogenic toxin superantigens and exfoliative toxins among strains of *Staphylococcus aureus* isolated from blood and nasal specimens. *J Clin Microbiol*. 2003;41:1434–1439.
171. Nishifuji K, Sugai M, Amagai M. Staphylococcal exfoliative toxins: "molecular scissors" of bacteria that attack the cutaneous defense barrier in mammals. *J Dermatol Sci*. 2008;49:21–31.
172. Nishifuji K, Shimizu A, Ishiko A, et al. Removal of amino-terminal extracellular domains of desmoglein 1 by staphylococcal exfoliative toxin is sufficient to initiate epidermal blister formation. *J Dermatol Sci*. 2010;59:184–191.
173. Lina G, Bohach GA, Nair SP, et al. Standard nomenclature for the superantigens expressed by *Staphylococcus*. *J Infect Dis*. 2004;189:2334–2336.
174. Fraser JD, Proft T. The bacterial superantigen and superantigen-like proteins. *Immunol Rev*. 2008;225:226–243.
175. Stevens F. The occurrence of *Staphylococcus aureus* infection with a scarlatiniform rash. *JAMA*. 1927;88:1957–1958.
176. Shands KN, Schmid GP, Dan BB, et al. Toxic-shock syndrome in menstruating women: association with tampon use and *Staphylococcus aureus* and clinical features in 52 cases. *N Engl J Med*. 1980;303:1436–1442.
177. Shupp JW, Jett M, Pontzer CH. Identification of a transcytosis epitope on staphylococcal enterotoxins. *Infect Immun*. 2002;70:2178–2186.
178. Stolz SJ, Davis JP, Vergeront JM, et al. Development of serum antibody to toxic shock toxin among individuals with toxic shock syndrome in Wisconsin. *J Infect Dis*. 1985;151:883–889.
179. Reingold AL, Hargrett NT, Shands KN, et al. Toxic shock syndrome surveillance in the United States, 1980 to 1981. *Ann Intern Med*. 1982;96(6 Pt 2):875–880.
180. McCormick JK, Yarwood JM, Schlievert PM. Toxic shock syndrome and bacterial superantigens: an update. *Annu Rev Microbiol*. 2001;55:77–104.
181. Hajjeh RA, Reingold A, Weil A, et al. Toxic shock syndrome in the United States: surveillance update, 1979 1996. *Emerg Infect Dis*. 1999;5:807–810.
182. Adalat S, Dawson T, Hackett SJ, et al. In association with the British Paediatric Surveillance U. Toxic shock syndrome surveillance in UK children. *Arch Dis Child*. 2014;99:1078–1082.
183. Lamagni TL, Neal S, Keshishian C, et al. Severe *Streptococcus pyogenes* infections, United Kingdom, 2003-2004. *Emerg Infect Dis*. 2008;14:202–209.
184. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis*. 2014;59:147–159.
185. Stevens DL, Gibbons AE, Bergstrom R, et al. The Eagle effect revisited: efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis. *J Infect Dis*. 1988;158:23–28.
186. Shah SS, Hall M, Srivastava R, et al. Intravenous immunoglobulin in children with streptococcal toxic shock syndrome. *Clin Infect Dis*. 2009;49:1369–1376.
187. Kadri SS, Swihart BJ, Bonne SL, et al. Impact of intravenous immunoglobulin on survival in necrotizing fasciitis with vasopressor-dependent shock: a propensity score-matched analysis from 130 US hospitals. *Clin Infect Dis*. 2017;64:877–885.
188. Schwameis M, Roppenser B, Firbas C, et al. Safety, tolerability, and immunogenicity of a recombinant toxic shock syndrome toxin (rTSST)-1 variant vaccine: a randomised, double-blind, adjuvant-controlled, dose escalation first-in-man trial. *Lancet Infect Dis*. 2016;16:1036–1044.
189. Argudin MA, Mendoza MC, Rodicio MR. Food poisoning and *Staphylococcus aureus* enterotoxins. *Toxins (Basel)*. 2010;2:1751–1773.
190. Fitzgerald JR, Reid SD, Ruotsalainen E, et al. Genome diversification in *Staphylococcus aureus*: molecular evolution of a highly variable chromosomal region encoding the Staphylococcal exotoxin-like family of proteins. *Infect Immun*. 2003;71:2827–2838.
191. Petersson K, Pettersson H, Skartved NJ, et al. Staphylococcal enterotoxin H induces V alpha-specific expansion of T cells. *J Immunol*. 2003;170:4148–4154.
192. Yarwood JM, Leung DY, Schlievert PM. Evidence for the involvement of bacterial superantigens in psoriasis, atopic dermatitis, and Kawasaki syndrome. *FEMS Microbiol Lett*. 2000;192:1–7.
193. Semic-Jusufagic A, Bachert C, Gevaert P, et al. *Staphylococcus aureus* sensitization and allergic disease in early childhood: population-based birth cohort study. *J Allergy Clin Immunol*. 2007;119:930–936.
194. Matsubara K, Fukaya T. The role of superantigens of group A *Streptococcus* and *Staphylococcus aureus* in Kawasaki disease. *Curr Opin Infect Dis*. 2007;20:298–303.
195. Feil EJ, Cooper JE, Grundmann H, et al. How clonal is *Staphylococcus aureus*? *J Bacteriol*. 2003;185:3307–3316.
196. Robinson DA, Monk AB, Cooper JE, et al. Evolutionary genetics of the accessory gene regulator (agr) locus in *Staphylococcus aureus*. *J Bacteriol*. 2005;187:8312–8321.
197. Wright JS 3rd, Traber KE, Corrigan R, et al. The agr radiation: an early event in the evolution of staphylococci. *J Bacteriol*. 2005;187:5585–5594.
198. Kang CK, Cho JE, Choi YJ, et al. agr dysfunction affects staphylococcal cassette chromosome mec type-dependent clinical outcomes in methicillin-resistant *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2015;59:3125–3132.
199. McAdam PR, Templeton KE, Edwards GF, et al. Molecular tracing of the emergence, adaptation, and transmission of hospital-associated methicillin-resistant *Staphylococcus aureus*. *Proc Natl Acad Sci USA*. 2012;109:9107–9112.
200. Fitzgerald JR. Livestock-associated *Staphylococcus aureus*: origin, evolution and public health threat. *Trends Microbiol*. 2012;20:192–198.
201. Drougka E, Foka A, Koutinas CK, et al. Interspecies spread of *Staphylococcus aureus* clones among companion animals and human close contacts in a veterinary teaching hospital. A cross-sectional study in Greece. *Prev Vet Med*. 2016;126:190–198.
202. Schwaber MJ, Navon-Venezia S, Masarwa S, et al. Clonal transmission of a rare methicillin-resistant *Staphylococcus aureus* genotype between horses and staff at a veterinary teaching hospital. *Vet Microbiol*. 2013;162:907–911.
203. Steinman A, Masarwa S, Tirosh-Levy S, et al. Methicillin-Resistant *Staphylococcus aureus* spa Type t002 Outbreak in Horses and Staff at a Veterinary Teaching Hospital after Its Presumed Introduction by a Veterinarian. *J Clin Microbiol*. 2015;53:2827–2831.
204. Armand-Lefevre L, Ruimy R, Andremont A. Clonal comparison of *Staphylococcus aureus* isolates from healthy pig farmers, human controls, and pigs. *Emerg Infect Dis*. 2005;11:711–714.
205. Price LB, Stegger M, Hasman H, et al. *Staphylococcus aureus* CC398: host adaptation and emergence of methicillin resistance in livestock. *MBio*. 2012;3:e00305–e00311.
206. Sakwinska O, Kuhn G, Balmelli C, et al. Genetic diversity and ecological success of *Staphylococcus aureus* strains colonizing humans. *Appl Environ Microbiol*. 2009;75:175–183.
207. Rooijakkers SH, Ruyken M, Roos A, et al. Immune evasion by a staphylococcal complement inhibitor that acts on C3 convertases. *Nat Immunol*. 2005;6:920–927.
208. Katayama Y, Baba T, Sekine M, et al. Beta-hemolysin promotes skin colonization by *Staphylococcus aureus*. *J Bacteriol*. 2013;195:1194–1203.
209. Verkade E, Bergmans AM, Budding AE, et al. Recent emergence of *Staphylococcus aureus* clonal complex 398 in human blood cultures. *PLoS ONE*. 2012;7:e41855.
210. Larsen J, Petersen A, Sorum M, et al. Meticillin-resistant *Staphylococcus aureus* CC398 is an increasing cause of disease in people with no livestock contact in Denmark, 1999 to 2011. *Euro Surveill*. 2015;20.
211. Brennan GI, Abbott Y, Burns A, et al. The emergence and spread of multiple livestock-associated clonal complex 398 methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* strains among animals and humans in the Republic of Ireland, 2010-2014. *PLoS ONE*. 2016;11:e0149396.
212. Wardyn SE, Forshey BM, Farina SA, et al. Swine farming is a risk factor for infection with and high prevalence of carriage of multidrug-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2015;61:59–66.
213. Lowder BV, Guinane CM, Ben Zakour NL, et al. Recent human-to-poultry host jump, adaptation, and pandemic spread of *Staphylococcus aureus*. *Proc Natl Acad Sci USA*. 2009;106:19545–19550.
214. Boss R, Cosandey A, Luini M, et al. Bovine *Staphylococcus aureus*: subtyping, evolution, and zoonotic transfer. *J Dairy Sci*. 2016;99:515–528.

215. Lindsay JA, Ruzin A, Ross HF, et al. The gene for toxic shock toxin is carried by a family of mobile pathogenicity islands in *Staphylococcus aureus*. *Mol Microbiol*. 1998;29:527–543.
216. Ruzin A, Lindsay J, Novick RP. Molecular genetics of SaPI1–a mobile pathogenicity island in *Staphylococcus aureus*. *Mol Microbiol*. 2001;41:365–377.
217. Tormo-Mas MA, Mir I, Shrestha A, et al. Moonlighting bacteriophage proteins derepress staphylococcal pathogenicity islands. *Nature*. 2010;465:779–782.
218. Ubeda C, Maiques E, Knecht E, et al. Antibiotic-induced SOS response promotes horizontal dissemination of pathogenicity island-encoded virulence factors in staphylococci. *Mol Microbiol*. 2005;56:836–844.
219. Katayama Y, Ito T, Hiramatsu K. A new class of genetic element, *Staphylococcus* cassette chromosome mec, encodes methicillin resistance in *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2000;44:1549–1555.
220. Ito T, Okuma K, Ma XX, et al. Insights on antibiotic resistance of *Staphylococcus aureus* from its whole genome: genomic island SCC. *Drug Resist Updat*. 2003;6:41–52.
221. Chambers HF, Hartman BJ, Tomasz A. Increased amounts of a novel penicillin-binding protein in a strain of methicillin-resistant *Staphylococcus aureus* exposed to nafcillin. *J Clin Invest*. 1985;76:325–331.
222. Zhang HZ, Hackbarth CJ, Chansky KM, et al. A proteolytic transmembrane signaling pathway and resistance to beta-lactams in staphylococci. *Science*. 2001;291:1962–1965.
223. International Working Group on the Classification of Staphylococcal Cassette Chromosome E. Classification of staphylococcal cassette chromosome mec (SCCmec): guidelines for reporting novel SCCmec elements. *Antimicrob Agents Chemother*. 2009;53:4961–4967.
224. Wu Z, Li F, Liu D, et al. Novel type XII staphylococcal cassette chromosome mec harboring a new cassette chromosome recombinase, CcrC2. *Antimicrob Agents Chemother*. 2015;59:7597–7601.
225. Ito T, Katayama Y, Asada K, et al. Structural comparison of three types of staphylococcal cassette chromosome mec integrated in the chromosome in methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2001;45:1323–1336.
226. Ma XX, Ito T, Tiensasitorn C, et al. Novel type of staphylococcal cassette chromosome mec identified in community-acquired methicillin-resistant *Staphylococcus aureus* strains. *Antimicrob Agents Chemother*. 2002;46:1147–1152.
227. Diep BA, Gill SR, Chang RF, et al. Complete genome sequence of USA300, an epidemic clone of community-acquired meticillin-resistant *Staphylococcus aureus*. *Lancet*. 2006;367:731–739.
228. Diep BA, Stone GG, Basuino L, et al. The arginine catabolic mobile element and staphylococcal chromosomal cassette mec linkage: convergence of virulence and resistance in the USA300 clone of methicillin-resistant *Staphylococcus aureus*. *J Infect Dis*. 2008;197:1523–1530.
229. Bouchiat C, Curtis S, Spiliopoulou I, et al. MRSA infections among patients in the emergency department: a European multicentre study. *J Antimicrob Chemother*. 2017;72:372–375.
230. Glaser P, Martins-Simoes P, Villain A, et al. Demography and intercontinental spread of the USA300 community-acquired methicillin-resistant *Staphylococcus aureus* lineage. *MBio*. 2016;7:e02183-02115.
231. Petersen A, Stegger M, Heltberg O, et al. Epidemiology of methicillin-resistant *Staphylococcus aureus* carrying the novel mecC gene in Denmark corroborates a zoonotic reservoir with transmission to humans. *Clin Microbiol Infect*. 2013;19:E16–E22.
232. Ba X, Harrison EM, Lovering AL, et al. Old drugs to treat resistant bugs: methicillin-resistant *Staphylococcus aureus* isolates with mecC are susceptible to a combination of penicillin and clavulanic acid. *Antimicrob Agents Chemother*. 2015;59:7396–7404.
233. Francioli M, Bille J, Glauser MP, et al. Beta-lactam resistance mechanisms of methicillin-resistant *Staphylococcus aureus*. *J Infect Dis*. 1991;163: 514–523.
234. Mancini S, Laurent F, Veloso TR, et al. In vivo effect of flucloxacillin in experimental endocarditis caused by mecC-positive *Staphylococcus aureus* showing temperature-dependent susceptibility in vitro. *Antimicrob Agents Chemother*. 2015;59:2435–2438.
235. Lowy FD. Antimicrobial resistance: the example of *Staphylococcus aureus*. *J Clin Invest*. 2003;111: 1265–1273.
236. Fowler VG Jr, Boucher HW, Corey GR, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by *Staphylococcus aureus*. *N Engl J Med*. 2006;355:653–665.
237. Abbas M, Paul M, Huttner A. New and improved? A review of novel antibiotics for Gram-positive bacteria. *Clin Microbiol Infect*. 2017;23:697–703.
238. Watanabe S, Ohnishi T, Yuasa A, et al. The first nationwide surveillance of antibacterial susceptibility patterns of pathogens isolated from skin and soft-tissue infections in dermatology departments in Japan. *J Infect Chemother*. 2017;23:503–511.
239. Goffin C, Ghuysen JM. Multimodular penicillin-binding proteins: an enigmatic family of orthologs and paralogs. *Microbiol Mol Biol Rev*. 1998;62:1079–1093.
240. Gillespie MT, May JW, Skurray RA. Antibiotic resistance in *Staphylococcus aureus* isolated at an Australian hospital between 1946 and 1981. *J Med Microbiol*. 1985;19:137–147.
241. Stefanaki C, Ieronymaki A, Matoula T, et al. Six-Year Retrospective Review of Hospital Data on Antimicrobial Resistance Profile of *Staphylococcus aureus* Isolated from Skin Infections from a Single Institution in Greece. *Antibiotics (Basel)*. 2017;6.
242. Richter SS, Doern GV, Heilmann KP, et al. Detection and Prevalence of Penicillin-Susceptible *Staphylococcus aureus* in the United States in 2013. *J Clin Microbiol*. 2016;54:812–814.
243. Nguyen HM, Jones RN. Treatment of methicillin-susceptible *Staphylococcus aureus* osteoarticular and prosthetic joint infections: using the oxacillin minimum inhibitory concentration to guide appropriate ceftriaxone use. *Clin Infect Dis*. 2013;57:161–162.
244. Kang N, Housman ST, Nicolau DP. Assessing the Surrogate Susceptibility of Oxacillin and Cefoxitin for Commonly Utilized Parenteral Agents against Methicillin-Susceptible *Staphylococcus aureus*: focus on Ceftriaxone Discordance between Predictive Susceptibility and in Vivo Exposures. *Pathogens*. 2015;4:599–605.
245. Jevons MP, Coe AW, Parker MT. Methicillin resistance in staphylococci. *Lancet*. 1963;1:904–907.
246. Panlilio AL, Culver DH, Gaynes RP, et al. Methicillin-resistant *Staphylococcus aureus* in U.S. hospitals, 1975-1991. *Infect Control Hosp Epidemiol*. 1992;13:582–586.
247. Song Y, Du X, Li T, et al. Phenotypic and molecular characterization of *Staphylococcus aureus* recovered from different clinical specimens of inpatients at a teaching hospital in Shanghai between 2005 and 2010. *J Med Microbiol*. 2013;62(Pt 2):274–282.
248. Klein EY, Mojica N, Jiang W, et al. Trends in methicillin-resistant *Staphylococcus aureus* hospitalizations in the United States, 2010-2014. *Clin Infect Dis*. 2017;65:1921–1923.
249. Walter J, Noll I, Feig M, et al. Decline in the proportion of methicillin resistance among *Staphylococcus aureus* isolates from non-invasive samples and in outpatient settings, and changes in the co-resistance profiles: an analysis of data collected within the Antimicrobial Resistance Surveillance Network, Germany 2010 to 2015. *BMC Infect Dis*. 2017;17:169.
250. Li L, Fortin E, Tremblay C, et al. Hospital-acquired methicillin-resistant *Staphylococcus aureus* bloodstream infections in Quebec: impact of guidelines. *Infect Control Hosp Epidemiol*. 2017;38:840–847.
251. Rolain JM, Abat C, Brouqui P, et al. Worldwide decrease in methicillin-resistant *Staphylococcus aureus*: do we understand something? *Clin Microbiol Infect*. 2015;21:515–517.
252. Gustave CA, Tristan A, Martins-Simoes P, et al. Demographic fluctuation of community-acquired antibiotic-resistant *Staphylococcus aureus* lineages: potential role of flimsy antibiotic exposure. *ISME J*. 2018;8:1879–1894.
253. Johnson AC, Jurgens MD, Nakada N, et al. Linking changes in antibiotic effluent concentrations to flow, removal and consumption in four different UK sewage treatment plants over four years. *Environ Pollut*. 2017;220(Pt B):919–926.
254. DeLeo FR, Otto M, Kreiswirth BN, et al. Community-associated meticillin-resistant *Staphylococcus aureus*. *Lancet*. 2010;375:1557–1568.
255. Dietrich DW, Auld DB, Mermel LA. Community-acquired methicillin-resistant *Staphylococcus aureus* in southern New England children. *Pediatrics*. 2004;113:e347–e352.
256. Salgado CD, Farr BM, Calfee DP. Community-acquired methicillin-resistant *Staphylococcus aureus*: a meta-analysis of prevalence and risk factors. *Clin Infect Dis*. 2003;36:131–139.
257. Qiao Y, Dong F, Song W, et al. Hospital- and community-associated methicillin-resistant *Staphylococcus aureus*: a 6-year surveillance study of invasive infections in Chinese children. *Acta Paediatr*. 2013;102:1081–1086.
258. Miller LG, Perdreau-Remington F, Rieg G, et al. Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. *N Engl J Med*. 2005;352:1445–1453.
259. Vandenesch F, Naimi T, Enright MC, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* carrying Panton-Valentine leukocidin genes: worldwide emergence. *Emerg Infect Dis*. 2003;9:978–984.
260. Coombs GW, Daly DA, Pearson JC, et al. Community-onset *Staphylococcus aureus* Surveillance Programme annual report, 2012. *Commun Dis Intell Q Rep*. 2014;38:E59–E69.
261. Diekema DJ, Richter SS, Heilmann KP, et al. Continued emergence of USA300 methicillin-resistant *Staphylococcus aureus* in the United States: results from a nationwide surveillance study. *Infect Control Hosp Epidemiol*. 2014;35:285–292.
262. Strauss L, Stegger M, Akpaka PE, et al. Origin, evolution, and global transmission of community-acquired *Staphylococcus aureus* ST8. *Proc Natl Acad Sci USA*. 2017;114:E10596–E10604.
263. Williamson DA, Roberts SA, Ritchie SR, et al. Clinical and molecular epidemiology of methicillin-resistant *Staphylococcus aureus* in New Zealand: rapid emergence of sequence type 5 (ST5)-SCCmec-IV as the dominant community-associated MRSA clone. *PLoS ONE*. 2013;8:e62020.
264. Labandeira-Rey M, Couzon F, Boisset S, et al. *Staphylococcus aureus* Panton-Valentine leukocidin causes necrotizing pneumonia. *Science*. 2007;315:1130–1133.
265. Voyich JM, Otto M, Mathema B, et al. Is Panton-Valentine leukocidin the major virulence determinant in community-associated methicillin-resistant *Staphylococcus aureus* disease? *J Infect Dis*. 2006;194:1761–1770.
266. Spaan AN, Henry T, van Rooijen WJ, et al. The staphylococcal toxin Panton-Valentine Leukocidin targets human C5a receptors. *Cell Host Microbe*. 2013;13:584–594.
267. Prince A, Wang H, Kitur K, et al. Humanized mice exhibit increased susceptibility to *Staphylococcus aureus* pneumonia. *J Infect Dis*. 2017;215:1386–1395.
268. Rouzic N, Janvier F, Libert N, et al. Prompt and successful toxin-targeting treatment of three patients with necrotizing pneumonia due to *Staphylococcus aureus* strains carrying the Panton-Valentine leukocidin genes. *J Clin Microbiol*. 2010;48:1952–1955.
269. Gauduchon V, Cozon G, Vandenesch F, et al. Neutralization of *Staphylococcus aureus* Panton Valentine leukocidin by intravenous immunoglobulin in vitro. *J Infect Dis*. 2004;189:346–353.
270. Hryniewicz MM, Garbacz K. Borderline oxacillin-resistant *Staphylococcus aureus* (BORSA) - a more common problem than expected? *J Med Microbiol*. 2017;66:1367–1373.
271. de Jonge BL, Tomasz A. Abnormal peptidoglycan produced in a methicillin-resistant strain of *Staphylococcus aureus* grown in the presence of methicillin: functional role for penicillin-binding protein 2A in cell wall synthesis. *Antimicrob Agents Chemother*. 1993;37:342–346.
272. de Lencastre H, Tomasz A. Reassessment of the number of auxiliary genes essential for expression of high-level methicillin resistance in *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 1994;38:2590–2598.
273. Berger-Bachi B. Expression of resistance to methicillin. *Trends Microbiol*. 1994;2:389–393.
274. Pinho MG, de Lencastre H, Tomasz A. An acquired and a native penicillin-binding protein cooperate in building the cell wall of drug-resistant staphylococci. *Proc Natl Acad Sci USA*. 2001;98:10886–10891.
275. Lim D, Strynadka NC. Structural basis for the beta lactam resistance of PBP2a from methicillin-resistant *Staphylococcus aureus*. *Nat Struct Biol*. 2002;9:870–876.
276. Que YA, Entenza JM, Francioli P, et al. The impact of penicillinase on cefamandole treatment and prophylaxis of experimental endocarditis due to methicillin-resistant *Staphylococcus aureus*. *J Infect Dis*. 1998;177:146–154.
277. Tomasz A. Intelligence coup" for drug designers: crystal structure of *Staphylococcus aureus* beta-lactam resistance protein PBP2A. *Lancet*. 2003;361:795–796.
278. Guignard B, Entenza JM, Moreillon P. Beta-lactams against methicillin-resistant *Staphylococcus aureus*. *Curr Opin Pharmacol*. 2005;5:479–489.
279. Bal AM, David MZ, Garau J, et al. Future trends in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection: an in-depth review of newer antibiotics active against an enduring pathogen. *J Glob Antimicrob Resist*. 2017;10:295–303.
280. Chang FY, Peacock JE Jr, Musher DM, et al. *Staphylococcus aureus* bacteremia: recurrence and the impact of antibiotic treatment in a prospective multicenter study. *Medicine (Baltimore)*. 2003;82: 333–339.

281. CLSI. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically: Approved Standard; 2012.
282. Soriano A, Marco F, Martinez JA, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2008;46:193–200.
283. Mavros MN, Tansarli GS, Vardakas KZ, et al. Impact of vancomycin minimum inhibitory concentration on clinical outcomes of patients with vancomycin-susceptible *Staphylococcus aureus* infections: a meta-analysis and meta-regression. *Int J Antimicrob Agents*. 2012;40:496–509.
284. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66:82–98.
285. Song KH, Kim M, Kim CJ, et al. Impact of Vancomycin MIC on Treatment Outcomes in Invasive *Staphylococcus aureus* Infections. *Antimicrob Agents Chemother*. 2017; 61.
286. Hiramatsu K, Hanaki H, Ino T, et al. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. *J Antimicrob Chemother*. 1997;40:135–136.
287. Sieradzki K, Roberts RB, Haber SW, et al. The development of vancomycin resistance in a patient with methicillin-resistant *Staphylococcus aureus* infection. *N Engl J Med*. 1999;340:517–523.
288. Hiramatsu K, Aritaka N, Hanaki H, et al. Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. *Lancet*. 1997;350:1670–1673.
289. Charles PG, Ward PB, Johnson PD, et al. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus*. *Clin Infect Dis*. 2004;38:448–451.
290. Pereira PM, Filipe SR, Tomasz A, et al. Fluorescence ratio imaging microscopy shows decreased access of vancomycin to cell wall synthetic sites in vancomycin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2007;51:3627–3633.
291. Kuroda M, Kuroda H, Oshima T, et al. Two-component system VraSR positively modulates the regulation of cell-wall biosynthesis pathway in *Staphylococcus aureus*. *Mol Microbiol*. 2003;49:807–821.
292. Neoh HM, Cui L, Yuzawa H, et al. Mutated response regulator graR is responsible for phenotypic conversion of *Staphylococcus aureus* from heterogeneous vancomycin-intermediate resistance to vancomycin-intermediate resistance. *Antimicrob Agents Chemother*. 2008;52:45–53.
293. Howden BP, Stinear TP, Allen DL, et al. Genomic analysis reveals a point mutation in the two-component sensor gene graS that leads to intermediate vancomycin resistance in clinical *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2008;52:3755–3762.
294. Howden BP, McEvoy CR, Allen DL, et al. Evolution of multidrug resistance during *Staphylococcus aureus* infection involves mutation of the essential two component regulator WalKR. *PLoS Pathog*. 2011;7:e1002359.
295. Chen CJ, Huang YC, Chiu CH. Multiple pathways of cross-resistance to glycopeptides and daptomycin in persistent MRSA bacteraemia. *J Antimicrob Chemother*. 2015;70:2965–2972.
296. Dubrac S, Bisicchia P, Devine KM, et al. A matter of life and death: cell wall homeostasis and the WalKR (YycGF) essential signal transduction pathway. *Mol Microbiol*. 2008;70:1307–1322.
297. Moreillon P, Bizzini A, Giddey M, et al. Vancomycin-intermediate *Staphylococcus aureus* selected during vancomycin therapy of experimental endocarditis are not detected by culture-based diagnostic procedures and persist after treatment arrest. *J Antimicrob Chemother*. 2012;67:652–660.
298. Yusof A, Engelhardt A, Karlsson A, et al. Evaluation of a new Etest vancomycin-teicoplanin strip for detection of glycopeptide-intermediate *Staphylococcus aureus* (GISA), in particular, heterogeneous GISA. *J Clin Microbiol*. 2008;46:3042–3047.
299. Arthur M, Courvalin P. Genetics and mechanisms of glycopeptide resistance in enterococci. *Antimicrob Agents Chemother*. 1993;37:1563–1571.
300. Noble WC, Virani Z, Cree RG. Co-transfer of vancomycin and other resistance genes from *Enterococcus faecalis* NCTC 12201 to *Staphylococcus aureus*. *FEMS Microbiol Lett*. 1992;72:195–198.
301. Walters MS, Eggers P, Albrecht V, et al. Vancomycin-Resistant *Staphylococcus aureus* - Delaware, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64:1056.
302. Centers for Disease Control and Prevention. Vancomycin-resistant *Staphylococcus aureus*–New York, 2004. *MMWR Morb Mortal Wkly Rep*. 2004;53:322–323.
303. Dezfulian A, Aslani MM, Oskoui M, et al. Identification and characterization of a high vancomycin-resistant *Staphylococcus aureus* harboring VanA gene cluster isolated from diabetic foot ulcer. *Iran J Basic Med Sci*. 2012;15:803–806.
304. Rossi F, Diaz L, Wollam A, et al. Transferable vancomycin resistance in a community-associated MRSA lineage. *N Engl J Med*. 2014;370:1524–1531.
305. Panesso D, Planet PJ, Diaz L, et al. Methicillin-Susceptible, Vancomycin-Resistant *Staphylococcus aureus*, Brazil. *Emerg Infect Dis*. 2015;21:1844–1848.
306. Icgen B. VanA-type MRSA (VRSA) emerged in surface waters. *Bull Environ Contam Toxicol*. 2016;97:359–366.
307. Scott WR, Baek SB, Jung D, et al. NMR structural studies of the antibiotic lipopeptide daptomycin in DHPC micelles. *Biochim Biophys Acta*. 2007;1768:3116–3126.
308. Baltz RH, Miao V, Wrigley SK. Natural products to drugs: daptomycin and related lipopeptide antibiotics. *Nat Prod Rep*. 2005;22:717–741.
309. Murray KP, Zhao JJ, Davis SL, et al. Early use of daptomycin versus vancomycin for methicillin-resistant *Staphylococcus aureus* bacteremia with vancomycin minimum inhibitory concentration >1 mg/L: a matched cohort study. *Clin Infect Dis*. 2013;56:1562–1569.
310. Carugati M, Bayer AS, Miro JM, et al. High-dose daptomycin therapy for left-sided infective endocarditis: a prospective study from the international collaboration on endocarditis. *Antimicrob Agents Chemother*. 2013;57:6213–6222.
311. Seaton RA, Gonzalez-Ruiz A, Cleveland KO, et al. Real-world daptomycin use across wide geographical regions: results from a pooled analysis of CORE and EU-CORE. *Ann Clin Microbiol Antimicrob*. 2016;15: 18.
312. Guleri A, Utili R, Dohmen P, et al. Daptomycin for the treatment of infective endocarditis: results from European Cubicin((R)) Outcomes Registry and Experience (EU-CORE). *Infect Dis Ther*. 2015;4:283–296.
313. Silverman JA, Mortin LI, Vanpraagh AD, et al. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. *J Infect Dis*. 2005;191:2149–2152.
314. Rose WE, Leonard SN, Sakoulas G, et al. daptomycin activity against *Staphylococcus aureus* following vancomycin exposure in an in vitro pharmacodynamic model with simulated endocardial vegetations. *Antimicrob Agents Chemother*. 2008;52:831–836.
315. Cui L, Tominaga E, Neoh HM, et al. Correlation between reduced daptomycin susceptibility and vancomycin resistance in vancomycin-intermediate *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2006;50:1079–1082.
316. Patel JB, Jevitt LA, Hageman J, et al. An association between reduced susceptibility to daptomycin and reduced susceptibility to vancomycin in *Staphylococcus aureus*. *Clin Infect Dis*. 2006;42:1652–1653.
317. Roch M, Gagetti P, Davis J, et al. Daptomycin resistance in clinical MRSA strains is associated with a high biological fitness cost. *Front Microbiol*. 2017;8:2303.
318. Renzoni A, Kelley WL, Rosato RR, et al. Molecular bases determining daptomycin resistance-mediated resensitization to beta-lactams (seesaw effect) in methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2017;61.
319. Shafiq I, Bulman ZP, Spitznogle SL, et al. A combination of ceftaroline and daptomycin has synergistic and bactericidal activity in vitro against daptomycin nonsusceptible methicillin-resistant *Staphylococcus aureus* (MRSA). *Infect Dis (Lond)*. 2017;49:410–416.
320. Weisblum B. Erythromycin resistance by ribosome modification. *Antimicrob Agents Chemother*. 1995;39:577–585.
321. Levin TP, Suh B, Axelrod P, et al. Potential clindamycin resistance in clindamycin-susceptible, erythromycin-resistant *Staphylococcus aureus*: report of a clinical failure. *Antimicrob Agents Chemother*. 2005;49:1222–1224.
322. Putnam SD, Sader HS, Farrell DJ, et al. Antimicrobial characterisation of solithromycin (CEM-101), a novel fluoroketolide: activity against staphylococci and enterococci. *Int J Antimicrob Agents*. 2011;37:39–45.
323. Davis KA, Crawford SA, Fiebelkorn KR, et al. Induction of telithromycin resistance by erythromycin in isolates of macrolide-resistant *Staphylococcus* spp. *Antimicrob Agents Chemother*. 2005;49:3059–3061.
324. Schaumburg F, Idelevich EA, Peters G, et al. Trends in antimicrobial non-susceptibility in methicillin-resistant *Staphylococcus aureus* from Germany (2004-2011). *Clin Microbiol Infect*. 2014;20:O554–O557.
325. Ross JI, Eady EA, Cove JH, et al. Identification of a chromosomally encoded ABC-transport system with which the staphylococcal erythromycin exporter MsrA may interact. *Gene*. 1995;153:93–98.
326. Clancy J, Petitpas J, Dib-Hajj F, et al. Molecular cloning and functional analysis of a novel macrolide-resistance determinant, mefA, from *Streptococcus pyogenes*. *Mol Microbiol*. 1996;22:867–879.
327. Vallianou N, Evangelopoulos A, Hadjisoteriou M, et al. Prevalence of macrolide, lincosamide, and streptogramin resistance among staphylococci in a tertiary care hospital in Athens, Greece. *J Chemother*. 2015;27:319–323.
328. Shashindran N, Nagasundaram N, Thappa DM, et al. Can Panton Valentine leukocidin gene and clindamycin susceptibility serve as predictors of community origin of MRSA from skin and soft tissue infections? *J Clin Diagn Res*. 2016;10:DC1–DC4.
329. Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. *Clin Infect Dis*. 2012;54:621–629.
330. Falagas ME, Manta KG, Ntziora F, et al. Linezolid for the treatment of patients with endocarditis: a systematic review of the published evidence. *J Antimicrob Chemother*. 2006;58:273–280.
331. Watkins RR, Lemonovich TL, File TM Jr. An evidence-based review of linezolid for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA): place in therapy. *Core Evid*. 2012;7:131–143.
332. Chen CJ, Chiu CH, Lin TY, et al. Experience with linezolid therapy in children with osteoarticular infections. *Pediatr Infect Dis J*. 2007;26:985–988.
333. Stevens DL, Ma Y, Salmi DB, et al. Impact of antibiotics on expression of virulence-associated exotoxin genes in methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*. *J Infect Dis*. 2007;195:202–211.
334. Beekmann SE, Gilbert DN, Polgreen PM, et al. Toxicity of extended courses of linezolid: results of an Infectious Diseases Society of America Emerging Infections Network survey. *Diagn Microbiol Infect Dis*. 2008;62:407–410.
335. Meka VG, Gold HS. Antimicrobial resistance to linezolid. *Clin Infect Dis*. 2004;39:1010–1015.
336. Mendes RE, Deshpande LM, Castanheira M, et al. First report of cfr-mediated resistance to linezolid in human staphylococcal clinical isolates recovered in the United States. *Antimicrob Agents Chemother*. 2008;52:2244–2246.
337. Long KS, Poehlsgaard J, Kehrenberg C, et al. The Cfr rRNA methyltransferase confers resistance to Phenicols, Lincosamides, Oxazolidinones, Pleuromutilins, and Streptogramin A antibiotics. *Antimicrob Agents Chemother*. 2006;50:2500–2505.
338. Mendes RE, Deshpande LM, Bonilla HF, et al. Dissemination of a pSCFS3-like cfr-carrying plasmid in *Staphylococcus aureus* and *Staphylococcus epidermidis* clinical isolates recovered from hospitals in Ohio. *Antimicrob Agents Chemother*. 2013;57:2923–2928.
339. Shore AC, Lazaris A, Kinnevey PM, et al. First report of cfr-carrying plasmids in the pandemic sequence type 22 methicillin-resistant *Staphylococcus aureus* staphylococcal cassette chromosome mec type IV clone. *Antimicrob Agents Chemother*. 2016;60:3007–3015.
340. Flamm RK, Mendes RE, Hogan PA, et al. Linezolid surveillance results for the United States (LEADER surveillance program 2014). *Antimicrob Agents Chemother*. 2016;60:2273–2280.
341. Sader HS, Mendes RE, Streit JM, et al. Antimicrobial susceptibility trends among *Staphylococcus aureus* isolates from U.S. hospitals: results from 7 years of the ceftaroline (AWARE) surveillance program, 2010 to 2016. *Antimicrob Agents Chemother*. 2017;61.
342. Rybak JM, Roberts K. Tedizolid phosphate: a next-generation oxazolidinone. *Infect Dis Ther*. 2015.
343. Lepak AJ, Marchillo K, Pichereau S, et al. Comparative pharmacodynamics of the new oxazolidinone tedizolid phosphate and linezolid in a neutropenic murine *Staphylococcus aureus* pneumonia model. *Antimicrob Agents Chemother*. 2012;56:5916–5922.
344. Shorr AF, Lodise TP, Corey GR, et al. Analysis of the phase 3 ESTABLISH trials of tedizolid versus linezolid in acute bacterial skin and skin structure infections. *Antimicrob Agents Chemother*. 2015;59:864–871.
345. Dholakia N, Rolston KV, Ho DH, et al. Susceptibilities of bacterial isolates from patients with cancer to levofloxacin and other quinolones. *Antimicrob Agents Chemother*. 1994;38:848–852.
346. Coombs GW, Nimmo GR, Daly DA, et al. Australian *Staphylococcus aureus* Sepsis Outcome Programme annual report, 2013. *Commun Dis Intell Q Rep*. 2014;38:E309–E319.
347. Jacoby GA. Mechanisms of resistance to quinolones. *Clin Infect Dis*. 2005;41 Suppl 2:S120–S126.

348. Arsene S, Leclercq R. Role of a qnr-like gene in the intrinsic resistance of *Enterococcus faecalis* to fluoroquinolones. *Antimicrob Agents Chemother*. 2007;51:3254–3258.
349. Yoshida H, Bogaki M, Nakamura S, et al. Nucleotide sequence and characterization of the *Staphylococcus aureus* norA gene, which confers resistance to quinolones. *J Bacteriol*. 1990;172:6942–6949.
350. Fournier B, Hooper DC. Mutations in topoisomerase IV and DNA gyrase of *Staphylococcus aureus*: novel pleiotropic effects on quinolone and coumarin activity. *Antimicrob Agents Chemother*. 1998;42:121–128.
351. Entenza JM, Vouillamoz J, Glauser MP, et al. Levofloxacin versus ciprofloxacin, flucloxacillin, or vancomycin for treatment of experimental endocarditis due to methicillin-susceptible or -resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 1997;41:1662–1667.
352. Remy JM, Tow-Keogh CA, McConnell TS, et al. Activity of delafloxacin against methicillin-resistant *Staphylococcus aureus*: resistance selection and characterization. *J Antimicrob Chemother*. 2012;67:2814–2820.
353. Craig WA. Does the dose matter? *Clin Infect Dis*. 2001;33 Suppl 3:S233–S237.
354. Cui J, Liu Y, Wang R, et al. The mutant selection window in rabbits infected with *Staphylococcus aureus*. *J Infect Dis*. 2006;194:1601–1608.
355. Chopra I. Glycylcyclines: third-generation tetracycline antibiotics. *Curr Opin Pharmacol*. 2001;1:464–469.
356. Yang Q, Xu YC, Kiratisin P, et al. Antimicrobial activity among gram-positive and gram-negative organisms collected from the Asia-Pacific region as part of the Tigecycline Evaluation and Surveillance Trial: comparison of 2015 results with previous years. *Diagn Microbiol Infect Dis*. 2017;89:314–323.
357. Yahav D, Lador A, Paul M, et al. Efficacy and safety of tigecycline: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2011;66:1963–1971.
358. Cocito C, Di Giambattista M, Nyssen E, et al. Inhibition of protein synthesis by streptogramins and related antibiotics. *J Antimicrob Chemother*. 1997;39 Suppl A:7–13.
359. Vouillamoz J, Entenza JM, Feger C, et al. Quinupristin-dalfopristin combined with beta-lactams for treatment of experimental endocarditis due to *Staphylococcus aureus* constitutively resistant to macrolide-lincosamide-streptogramin B antibiotics. *Antimicrob Agents Chemother*. 2000;44:1789–1795.
360. Billeter M, Zervos MJ, Chen AY, et al. Kurukularatne C. Dalbavancin: a novel once-weekly lipoglycopeptide antibiotic. *Clin Infect Dis*. 2008;46:577–583.
361. Allen NE, Nicas TI. Mechanism of action of oritavancin and related glycopeptide antibiotics. *FEMS Microbiol Rev*. 2003;26:511–532.
362. Al Jalali V, Zeitlinger M. Clinical Pharmacokinetics and Pharmacodynamics of Telavancin Compared with the Other Glycopeptides. *Clin Pharmacokinet*. 2018.
363. Jauregui LE, Babazadeh S, Seltzer E, et al. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. *Clin Infect Dis*. 2005;41:1407–1415.
364. Corey GR, Good S, Jiang H, et al. Single-dose oritavancin versus 7-10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study. *Clin Infect Dis*. 2015;60:254–262.
365. Cremieux AC, Maziere B, Vallois JM, et al. Evaluation of antibiotic diffusion into cardiac vegetations by quantitative autoradiography. *J Infect Dis*. 1989;159:938–944.
366. Steele JM, Seabury RW, Hale CM, et al. Unsuccessful treatment of methicillin-resistant *Staphylococcus aureus* endocarditis with dalbavancin. *J Clin Pharm Ther*. 2018;43:101–103.
367. Falagas ME, Matthaiou DK, Bliziotis IA. The role of aminoglycosides in combination with a beta-lactam for the treatment of bacterial endocarditis: a meta-analysis of comparative trials. *J Antimicrob Chemother*. 2006;57:639–647.
368. Davis JS, Van Hal S, Tong SY. Combination antibiotic treatment of serious methicillin-resistant *Staphylococcus aureus* infections. *Semin Respir Crit Care Med*. 2015;36:3–16.
369. Davis JS, Sud A, O'Sullivan MVN, et al. Combination of vancomycin and beta-lactam therapy for methicillin-resistant *Staphylococcus aureus* bacteremia: a pilot multicenter randomized controlled trial. *Clin Infect Dis*. 2016;62:173–180.
370. Tong SY, Nelson J, Paterson DL, et al. CAMERA2 - combination antibiotic therapy for methicillin-resistant *Staphylococcus aureus* infection: study protocol for a randomised controlled trial. *Trials*. 2016;17:170.
371. Pericas JM, Moreno A, Almela M, et al. Efficacy and safety of fosfomycin plus imipenem versus vancomycin for complicated bacteraemia and endocarditis due to methicillin-resistant *Staphylococcus aureus*: a randomized clinical trial. *Clin Microbiol Infect*. 2018.
372. Fuda C, Hesek D, Lee M, et al. Mechanistic basis for the action of new cephalosporin antibiotics effective against methicillin- and vancomycin-resistant *Staphylococcus aureus*. *J Biol Chem*. 2006;281:10035–10041.
373. Corey GR, Wilcox MH, Talbot GH, et al. CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *J Antimicrob Chemother*. 2010;65 Suppl 4:iv41–iv51.
374. Vidaillac C, Leonard SN, Rybak MJ. In vitro activity of ceftaroline against methicillin-resistant *Staphylococcus aureus* and heterogeneous vancomycin-intermediate S. aureus in a hollow fiber model. *Antimicrob Agents Chemother*. 2009;53:4712–4717.
375. Sakoulas G, Moise PA, Casapao AM, et al. Antimicrobial salvage therapy for persistent staphylococcal bacteremia using daptomycin plus ceftaroline. *Clin Ther*. 2014;36:1317–1333.
376. Valour F, Trouillet-Assant S, Riffard N, et al. Antimicrobial activity against intraosteoblastic *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 2015;59:2029–2036.
377. Ho TT, Cadena J, Childs LM, et al. Methicillin-resistant *Staphylococcus aureus* bacteraemia and endocarditis treated with ceftaroline salvage therapy. *J Antimicrob Chemother*. 2012;67:1267–1270.
378. Pasquale TR, Tan MJ, Trienski TL, et al. Methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia patients treated with ceftaroline: retrospective case series of 10 patients. *J Chemother*. 2015;27:29–34.
379. Pagani L, Bonnin P, Janssen C, et al. Ceftaroline for the treatment of prosthetic valve endocarditis due to methicillin-resistant *Staphylococcus aureus*. *J Heart Valve Dis*. 2014;23:219–221.
380. Lin JC, Aung G, Thomas A, et al. The use of ceftaroline fosamil in methicillin-resistant *Staphylococcus aureus* endocarditis and deep-seated MRSA infections: a retrospective case series of 10 patients. *J Infect Chemother*. 2013;19:42–49.
381. Perumal Samy R, Stiles BG, Franco OL, et al. Animal venoms as antimicrobial agents. *Biochem Pharmacol*. 2017;134:127–138.
382. de Breij A, Riool M, Cordfunke RA, et al. The antimicrobial peptide SAAP-148 combats drug-resistant bacteria and biofilms. *Sci Transl Med*. 2018;10.
383. Tajbakhsh M, Karimi A, Tohidpour A, et al. The antimicrobial potential of a new derivative of cathelicidin from *Bungarus fasciatus* against methicillin-resistant *Staphylococcus aureus*. *J Microbiol*. 2018;56:128–137.
384. Torres VJ, Pishchany G, Humayun M, et al. *Staphylococcus aureus* IsdB is a hemoglobin receptor required for heme iron utilization. *J Bacteriol*. 2006;188:8421–8429.
385. McAdow M, Kim HK, Dedent AC, et al. Preventing *Staphylococcus aureus* sepsis through the inhibition of its agglutination in blood. *PLoS Pathog*. 2011;7:e1002307.
386. Sully EK, Malachowa N, Elmore BO, et al. Selective chemical inhibition of agr quorum sensing in *Staphylococcus aureus* promotes host defense with minimal impact on resistance. *PLoS Pathog*. 2014;10:e1004174.
387. Raz A, Serrano A, Lawson C, et al. Lysibodies are IgG Fc fusions with lysin binding domains targeting *Staphylococcus aureus* wall carbohydrates for effective phagocytosis. *Proc Natl Acad Sci USA*. 2017;114:4781–4786.
388. Ko HHT, Lareu RR, Dix BR, et al. Statins: antimicrobial resistance breakers or makers? *PeerJ*. 2017;5:e3952.
389. Janda S, Young A, Fitzgerald JM, et al. The effect of statins on mortality from severe infections and sepsis: a systematic review and meta-analysis. *J Crit Care*. 2010;25:656, e7–e22.
390. Caffrey AR, Timbrook TT, Noh E, et al. Evidence To Support Continuation of Statin Therapy in Patients with *Staphylococcus aureus* Bacteremia. *Antimicrob Agents Chemother*. 2017;61.
391. Garcia-Fernandez E, Koch G, Wagner RM, et al. Membrane microdomain disassembly inhibits MRSA antibiotic resistance. *Cell*. 2017;171:1354–1367, e1320.
392. Thangamani S, Mohammad H, Abushahba MF, et al. Exploring simvastatin, an antihyperlipidemic drug, as a potential topical antibacterial agent. *Sci Rep*. 2015;5:16407.
393. Lehar SM, Pillow T, Xu M, et al. Novel antibody-antibiotic conjugate eliminates intracellular S. aureus. *Nature*. 2015;527:323–328.
394. Fischetti VA. Bacteriophage endolysins: a novel anti-infective to control Gram-positive pathogens. *Int J Med Microbiol*. 2010;300:357–362.
395. Nobrega FL, Costa AR, Kluskens LD, et al. Revisiting phage therapy: new applications for old resources. *Trends Microbiol*. 2015;23:185–191.
396. Pastagia M, Euler C, Chahales P, et al. A novel chimeric lysin shows superiority to mupirocin for skin decolonization of methicillin-resistant and -sensitive *Staphylococcus aureus* strains. *Antimicrob Agents Chemother*. 2011;55:738–744.
397. Yang H, Zhang Y, Yu J, et al. Novel chimeric lysin with high-level antimicrobial activity against methicillin-resistant *Staphylococcus aureus* in vitro and in vivo. *Antimicrob Agents Chemother*. 2014;58:536–542.
398. Channabasappa S, Durgaiah M, Chikkamadaiah R, et al. Efficacy of novel antistaphylococcal ectolysin P128 in a rat model of methicillin-resistant *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2018;62.
399. Totte JEE, van Doorn MB, Pasmans S. Successful treatment of chronic *Staphylococcus aureus*-related dermatoses with the topical endolysin staphefekt SA. 100: a report of 3 cases. *Case Rep Dermatol*. 2017;9: 19–25.
400. Totte J, de Wit J, Pardo L, et al. Targeted anti-staphylococcal therapy with endolysins in atopic dermatitis and the effect on steroid use, disease severity and the microbiome: study protocol for a randomized controlled trial (MAAS trial). *Trials*. 2017;18:404.
401. Cisek AA, Dabrowska I, Gregorczyk KP, et al. Phage therapy in bacterial infections treatment: one hundred years after the discovery of bacteriophages. *Curr Microbiol*. 2017;74:277–283.
402. Oechslin F, Piccardi P, Mancini S, et al. Synergistic interaction between phage therapy and antibiotics clears *Pseudomonas aeruginosa* infection in endocarditis and reduces virulence. *J Infect Dis*. 2017;215:703–712.
403. Fish R, Kutter E, Wheat G, et al. Bacteriophage treatment of intransigent diabetic toe ulcers: a case series. *J Wound Care*. 2016;25 Suppl 7:S27–S33.
404. Shinefield H, Black S, Fattom A, et al. Use of a *Staphylococcus aureus* conjugate vaccine in patients receiving hemodialysis. *N Engl J Med*. 2002;346:491–496.
405. Fowler VG, Allen KB, Moreira ED, et al. Effect of an investigational vaccine for preventing *Staphylococcus aureus* infections after cardiothoracic surgery: a randomized trial. *JAMA*. 2013;309:1368–1378.
406. Fitzgerald JR, Loughman A, Keane F, et al. Fibronectin-binding proteins of *Staphylococcus aureus* mediate activation of human platelets via fibrinogen and fibronectin bridges to integrin GPIIb/IIIa and IgG binding to the FcgammaRIIa receptor. *Mol Microbiol*. 2006;59:212–230.
407. Spaulding AR, Salgado-Pabon W, Merriman JA, et al. Vaccination against *Staphylococcus aureus* pneumonia. *J Infect Dis*. 2014;209:1955–1962.
408. Mohamed N, Wang MY, Le Huec JC, et al. Vaccine development to prevent *Staphylococcus aureus* surgical-site infections. *Br J Surg*. 2017;104:e41–e54.
409. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. *Infect Control Hosp Epidemiol*. 2016;37:1288–1301.
410. Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med*. 2014;370:1198–1208.
411. Dantes R, Mu Y, Belflower R, et al. National burden of invasive methicillin-resistant *Staphylococcus aureus* infections, United States, 2011. *JAMA Intern Med*. 2013;173:1970–1978.
412. Malani PN. National burden of invasive methicillin-resistant *Staphylococcus aureus* infection. *JAMA*. 2014;311:1438–1439.
413. Laupland KB, Church DL, Mucenski M, et al. Population-based study of the epidemiology of and the risk factors for invasive *Staphylococcus aureus* infections. *J Infect Dis*. 2003;187:1452–1459.
414. van Hal SJ, Jensen SO, Vaska VL, et al. Predictors of mortality in *Staphylococcus aureus* Bacteremia. *Clin Microbiol Rev*. 2012;25:362–386.
415. Goto M, Schweizer ML, Vaughan-Sarrazin MS, et al. Association of evidence-based care processes with mortality in *Staphylococcus aureus* bacteremia at Veterans Health Administration hospitals, 2003-2014. *JAMA Intern Med*. 2017;177:1489–1497.
416. Lambert ML, Suetens C, Savey A, et al. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. *Lancet Infect Dis*. 2011;11: 30–38.

417. Nguyen DB, Shugart A, Lines C, et al. National Healthcare Safety Network (NHSN) dialysis event surveillance report for 2014. *Clin J Am Soc Nephrol*. 2017;12:1139–1146.
418. Noskin GA, Rubin RJ, Schentag JJ, et al. National trends in *Staphylococcus aureus* infection rates: impact on economic burden and mortality over a 6-year period (1998-2003). *Clin Infect Dis*. 2007;45:1132–1140.
419. Gidengil CA, Gay C, Huang SS, et al. Cost-effectiveness of strategies to prevent methicillin-resistant *Staphylococcus aureus* transmission and infection in an intensive care unit. *Infect Control Hosp Epidemiol*. 2015;36:17–27.
420. Jacobsson G, Dashti S, Wahlberg T, et al. The epidemiology of and risk factors for invasive *Staphylococcus aureus* infections in western Sweden. *Scand J Infect Dis*. 2007;39:6–13.
421. Diekema DJ, Pfaller MA, Schmitz FJ, et al. Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997-1999. *Clin Infect Dis*. 2001;32 Suppl 2:S114–S132.
422. Fowler VG, Miro JM, Hoen B, et al. *Staphylococcus aureus* endocarditis: a consequence of medical progress. *JAMA*. 2005;293:3012–3021.
423. Worth LJ, Bull AL, Spelman T, et al. Diminishing surgical site infections in Australia: time trends in infection rates, pathogens and antimicrobial resistance using a comprehensive Victorian surveillance program, 2002-2013. *Infect Control Hosp Epidemiol*. 2015;36:409–416.
424. Mimoz O, Lucet JC, Kerforne T, et al. Skin antisepsis with chlorhexidine-alcohol versus povidone iodine-alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial. *Lancet*. 2015;386:2069–2077.
425. Lee MS, Walker V, Chen LF, et al. The epidemiology of ventilator-associated pneumonia in a network of community hospitals: a prospective multicenter study. *Infect Control Hosp Epidemiol*. 2013;34:657–662.
426. Que YA, Moreillon P. Infective endocarditis. *Nat Rev Cardiol*. 2011;8:322–336.
427. Selton-Suty C, Celard M, Le Moing V, et al. Preeminence of *Staphylococcus aureus* in infective endocarditis: a 1-year population-based survey. *Clin Infect Dis*. 2012;54:1230–1239.
428. Hoen B, Duval X. Clinical practice. Infective endocarditis. *N Engl J Med*. 2013;368:1425–1433.
429. Mathews CJ, Weston VC, Jones A, et al. Bacterial septic arthritis in adults. *Lancet*. 2010;375:846–855.
430. Bernard L, Dinh A, Ghout I, et al. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. *Lancet*. 2015;385:875–882.
431. Tande AJ, Patel R. Prosthetic joint infection. *Clin Microbiol Rev*. 2014;27:302–345.
432. Laupland KB. Incidence of bloodstream infection: a review of population-based studies. *Clin Microbiol Infect*. 2013;19:492–500.
433. Laupland KB, Ross T, Gregson DB. *Staphylococcus aureus* bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000-2006. *J Infect Dis*. 2008;198:336–343.
434. van Rijen M, Bonten M, Wenzel R, et al. Mupirocin ointment for preventing *Staphylococcus aureus* infections in nasal carriers. *Cochrane Database Syst Rev*. 2008;(4):CD006216.
435. Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. *Infect Control Hosp Epidemiol*. 2008;29:996–1011.
436. Acree ME, Morgan E, David MZ. S. aureus infections in Chicago, 2006-2014: increase in CA MSSA and decrease in MRSA incidence. *Infect Control Hosp Epidemiol*. 2017;38:1226–1234.
437. Kallen AJ, Mu Y, Bulens S, et al. Health care-associated invasive MRSA infections, 2005-2008. *JAMA*. 2010;304:641–648.
438. Landrum ML, Neumann C, Cook C, et al. Epidemiology of *Staphylococcus aureus* blood and skin and soft tissue infections in the US military health system, 2005-2010. *JAMA*. 2012;308:50–59.
439. Chambers HF, Deleo FR. Waves of resistance: *Staphylococcus aureus* in the antibiotic era. *Nat Rev Microbiol*. 2009;7:629–641.
440. Uhlemann AC, Otto M, Lowy FD, et al. Evolution of community- and healthcare-associated methicillin-resistant *Staphylococcus aureus*. *Infect Genet Evol*. 2014;21:563–574.
441. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis*. 2006;42 Suppl 2:S82–S89.
442. Yaw LK, Robinson JO, Ho KM. A comparison of long-term outcomes after meticillin-resistant and meticillin-sensitive *Staphylococcus aureus* bacteraemia: an observational cohort study. *Lancet Infect Dis*. 2014;14:967–975.
443. Melles DC, Gorkink RF, Boelens HA, et al. Natural population dynamics and expansion of pathogenic clones of *Staphylococcus aureus*. *J Clin Invest*. 2004;114:1732–1740.
444. Cameron DR, Howden BP, Peleg AY. The interface between antibiotic resistance and virulence in *Staphylococcus aureus* and its impact upon clinical outcomes. *Clin Infect Dis*. 2011;53:576–582.
445. Miller LG, Daum RS, Creech CB, et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. *N Engl J Med*. 2015;372:1093–1103.
446. David MZ, Daum RS. Community-associated methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic. *Clin Microbiol Rev*. 2010;23:616–687.
447. Seybold U, Kourbatova EV, Johnson JG, et al. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* USA300 genotype as a major cause of health care-associated blood stream infections. *Clin Infect Dis*. 2006;42:647–656.
448. Jenkins TC, McCollister BD, Sharma R, et al. Epidemiology of healthcare-associated bloodstream infection caused by USA300 strains of methicillin-resistant *Staphylococcus aureus* in 3 affiliated hospitals. *Infect Control Hosp Epidemiol*. 2009;30:233–241.
449. Planet PJ. Life after USA300: the rise and fall of a superbug. *J Infect Dis*. 2017;215(suppl_1):S71–S77.
450. Mertz D, Frei R, Periat N, et al. Exclusive *Staphylococcus aureus* throat carriage: at-risk populations. *Arch Intern Med*. 2009;169:172–178.
451. van Belkum A, Verkaik NJ, de Vogel CP, et al. Reclassification of *Staphylococcus aureus* nasal carriage types. *J Infect Dis*. 2009;199:1820–1826.
452. Sollid JU, Furberg AS, Hanssen AM, et al. *Staphylococcus aureus*: determinants of human carriage. *Infect Genet Evol*. 2014;21:531–541.
453. Burian M, Wolz C, Goerke C. Regulatory adaptation of *Staphylococcus aureus* during nasal colonization of humans. *PLoS ONE*. 2010;5:e10040.
454. Wertheim HF, Walsh E, Choudhurry R, et al. Key role for clumping factor B in *Staphylococcus aureus* nasal colonization of humans. *PLoS Med*. 2008;5:e17.
455. Clarke SR, Mohamed R, Bian L, et al. The *Staphylococcus aureus* surface protein IsdA mediates resistance to innate defenses of human skin. *Cell Host Microbe*. 2007;1:199–212.
456. Lebon A, Labout JA, Verbrugh HA, et al. Dynamics and determinants of *Staphylococcus aureus* carriage in infancy. The generation R study. *J Clin Microbiol*. 2008.
457. van Gils EJ, Hak E, Veenhoven RH, et al. Effect of seven-valent pneumococcal conjugate vaccine on *Staphylococcus aureus* colonisation in a randomised controlled trial. *PLoS ONE*. 2011;6:e20229.
458. Price JR, Cole K, Bexley A, et al. Transmission of *Staphylococcus aureus* between health-care workers, the environment, and patients in an intensive care unit: a longitudinal cohort study based on whole-genome sequencing. *Lancet Infect Dis*. 2017;17:207–214.
459. Simor AE. Staphylococcal decolonisation: an effective strategy for prevention of infection? *Lancet Infect Dis*. 2011;11:952–962.
460. Gorwitz R, Kruszon-Moran D, McAllister S, et al. Changes in the prevalence of nasal colonization with *Staphylococcus aureus* in the United States, 2001-2004. *J Infect Dis*. 2008;197:1226–1234.
461. Fuller C, Robotham J, Savage J, et al. The national one week prevalence audit of universal meticillin-resistant *Staphylococcus aureus* (MRSA) admission screening 2012. *PLoS ONE*. 2013;8:e74219.
462. McKinnell JA, Miller LG, Eells SJ, et al. A systematic literature review and meta-analysis of factors associated with methicillin-resistant *Staphylococcus aureus* colonization at time of hospital or intensive care unit admission. *Infect Control Hosp Epidemiol*. 2013;34:1077–1086.
463. Davis MF, Iverson SA, Baron P, et al. Household transmission of meticillin-resistant *Staphylococcus aureus* and other staphylococci. *Lancet Infect Dis*. 2012;12:703–716.
464. Fatkenheuer G, Hirschel B, Harbarth S. Screening and isolation to control meticillin-resistant *Staphylococcus aureus*: sense, nonsense, and evidence. *Lancet*. 2015;385:1146–1149.
465. Kock R, Becker K, Cookson B, et al. Systematic literature analysis and review of targeted preventive measures to limit healthcare-associated infections by meticillin-resistant *Staphylococcus aureus*. *Euro Surveill*. 2014;19.
466. Robotham JV, Deeny SR, Fuller C, et al. Cost-effectiveness of national mandatory screening of all admissions to English National Health Service hospitals for meticillin-resistant *Staphylococcus aureus*: a mathematical modelling study. *Lancet Infect Dis*. 2016;16:348–356.
467. Loeb M, Main C, Walker-Dilks C, et al. Antimicrobial drugs for treating methicillin-resistant *Staphylococcus aureus* colonization. *Cochrane Database Syst Rev*. 2003;(4):CD003340.
468. Ammerlaan HS, Kluytmans JA, Berkhout H, et al. Eradication of carriage with methicillin-resistant *Staphylococcus aureus*: effectiveness of a national guideline. *J Antimicrob Chemother*. 2011;66:2409–2417.
469. Albrich WC, Harbarth S. Health-care workers: source, vector, or victim of MRSA? *Lancet Infect Dis*. 2008;8:289–301.
470. Climo MW, Yokoe DS, Warren DK, et al. Effect of daily chlorhexidine bathing on hospital-acquired infection. *N Engl J Med*. 2013;368:533–542.
471. Timsit JF, Mimoz O, Mourvillier B, et al. Randomized controlled trial of chlorhexidine dressing and highly adhesive dressing for preventing catheter-related infections in critically ill adults. *Am J Respir Crit Care Med*. 2012;186:1272–1278.
472. Timsit JF, Schwebel C, Bouadma L, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. *JAMA*. 2009;301:1231–1241.
473. Derde LPG, Cooper BS, Goossens H, et al. Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial. *Lancet Infect Dis*. 2014;14:31–39.
474. Huang SS, Septimus E, Kleinman K, et al. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med*. 2013;368:2255–2265.
475. Bowen AC, Tong SY, Chatfield MD, et al. The microbiology of impetigo in indigenous children: associations between *Streptococcus pyogenes*, *Staphylococcus aureus*, scabies, and nasal carriage. *BMC Infect Dis*. 2014;14:727.
476. Lee IW, Kang L, Hsu HP, et al. Puerperal mastitis requiring hospitalization during a nine-year period. *Am J Obstet Gynecol*. 2010;203:332, e331–e336.
477. Fernandez L, Cardenas N, Arroyo R, et al. Prevention of infectious mastitis by oral administration of Lactobacillus salivarius PS2 during late pregnancy. *Clin Infect Dis*. 2016;62:568–573.
478. Arroyo R, Martin V, Maldonado A, et al. Treatment of infectious mastitis during lactation: antibiotics versus oral administration of Lactobacilli isolated from breast milk. *Clin Infect Dis*. 2010;50:1551–1558.
479. Anderson DJ, Podgorny K, Berrios-Torres SI, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014;35:605–627.
480. Allegranzi B, Bischoff P, de Jonge S, et al. New WHO recommendations on preoperative measures for surgical site infection prevention: an evidence-based global perspective. *Lancet Infect Dis*. 2016;16:e276–e287.
481. McClain SL, Bohan JG, Stevens DL. Advances in the medical management of skin and soft tissue infections. *BMJ*. 2016;355:i6004.
482. Eggimann P, Sax H, Pittet D. Catheter-related infections. *Microbes Infect*. 2004;6:1033–1042.
483. McGowan JE Jr, Barnes MW, Finland M. Bacteremia at Boston City Hospital: occurrence and mortality during 12 selected years (1935-1972), with special reference to hospital-acquired cases. *J Infect Dis*. 1975;132:316–335.
484. Rodríguez-Créixems M, Alcalá L, Muñoz P, et al. Bloodstream infections: evolution and trends in the microbiology workload, incidence, and etiology, 1985-2006. *Medicine (Baltimore)*. 2008;87:234–249.
485. Laupland KB, Lyytikainen O, Sogaard M, et al. The changing epidemiology of *Staphylococcus aureus* bloodstream infection: a multinational population-based surveillance study. *Clin Microbiol Infect*. 2013;19:465–471.
486. Tong SY, Davis JS, Eichenberger E, et al. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. *Clin Microbiol Rev*. 2015;28:603–661.
487. Moreillon P, Que YA. Infective endocarditis. *Lancet*. 2004;363:139–149.
488. Gouello JP, Asfar P, Brenet O, et al. Nosocomial endocarditis in the intensive care unit: an analysis of 22 cases. *Crit Care Med*. 2000;28:377–382.

489. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36:3075–3128.
490. Holland TL, Arnold C, Fowler VG Jr. Clinical management of *Staphylococcus aureus* bacteremia: a review. *JAMA*. 2014;312:1330–1341.
491. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132:1435–1486.
492. Fowler VG Jr, Olsen MK, Corey GR, et al. Clinical identifiers of complicated *Staphylococcus aureus* bacteremia. *Arch Intern Med*. 2003;163:2066–2072.
493. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1–45.
494. Cosgrove SE, Fowler VG Jr. Management of methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin Infect Dis*. 2008;46 Suppl 5:S386–S393.
495. Daneman N, Shore K, Pinto R, et al. Antibiotic treatment duration for bloodstream infections in critically ill patients: a national survey of Canadian infectious diseases and critical care specialists. *Int J Antimicrob Agents*. 2011;38:480–485.
496. Duval X, Delahaye F, Alla F, et al. Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: three successive population-based surveys. *J Am Coll Cardiol*. 2012;59:1968–1976.
497. Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA*. 2007;297:1354–1361.
498. Kamalakannan D, Pai RM, Johnson LB, et al. Epidemiology and clinical outcomes of infective endocarditis in hemodialysis patients. *Ann Thorac Surg*. 2007;83:2081–2086.
499. Benito N, Miro JM, de Lazzari E, et al. Health care-associated native valve endocarditis: importance of non-nosocomial acquisition. *Ann Intern Med*. 2009;150:586–594.
500. Murdoch DR, Corey GR, Hoen B, et al. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med*. 2009;169:463–473.
501. Moreillon P, Que YA, Bayer AS. Pathogenesis of streptococcal and staphylococcal endocarditis. *Infect Dis Clin North Am*. 2002;16:297–318.
502. Que YA, Haefliger JA, Francioli P, et al. Expression of *Staphylococcus aureus* clumping factor A in *Lactococcus lactis* subsp. *cremoris* using a new shuttle vector. *Infect Immun*. 2000;68:3516–3522.
503. Que YA, Francois P, Haefliger JA, et al. Reassessing the role of *Staphylococcus aureus* clumping factor and fibronectin-binding protein by expression in *Lactococcus lactis*. *Infect Immun*. 2001;69:6296–6302.
504. Foster TJ, Geoghegan JA, Ganesh VK, et al. Adhesion, invasion and evasion: the many functions of the surface proteins of *Staphylococcus aureus*. *Nat Rev Microbiol*. 2014;12:49–62.
505. Josse J, Laurent F, Diot A. Staphylococcal adhesion and host cell invasion: fibronectin-binding and other mechanisms. *Front Microbiol*. 2017;8:2433.
506. Yeaman MR. Platelets: at the nexus of antimicrobial defence. *Nat Rev Microbiol*. 2014;12:426–437.
507. Andersson DI, Hughes D, Kubicek-Sutherland JZ. Mechanisms and consequences of bacterial resistance to antimicrobial peptides. *Drug Resist Updat*. 2016;26:43–57.
508. Fowler VG, McIntyre LM, Yeaman MR, et al. In vitro resistance to thrombin-induced platelet microbicidal protein in isolates of *Staphylococcus aureus* from endocarditis patients correlates with an intravascular device source. *J Infect Dis*. 2000;182:1251–1254.
509. Anaya-Lopez JL, Lopez-Meza JE, Ochoa-Zarzosa A. Bacterial resistance to cationic antimicrobial peptides. *Crit Rev Microbiol*. 2013;39:180–195.
510. Veloso TR, Chaouch A, Roger T, et al. Use of a human-like low-grade bacteremia model of experimental endocarditis to study the role of *Staphylococcus aureus* adhesins and platelet aggregation in early endocarditis. *Infect Immun*. 2013;81:697–703.
511. Habib A, Irfan M, Baddour LM, et al. Impact of prior aspirin therapy on clinical manifestations of cardiovascular implantable electronic device infections. *Europace*. 2013;15:227–235.
512. Chan KL, Tam J, Dumesnil JG, et al. Effect of long-term aspirin use on embolic events in infective endocarditis. *Clin Infect Dis*. 2008;46:37–41.
513. Snygg-Martin U, Rasmussen RV, Hassager C, et al. The relationship between cerebrovascular complications and previously established use of antiplatelet therapy in left-sided infective endocarditis. *Scand J Infect Dis*. 2011;43:899–904.
514. Kupferwasser LI, Yeaman MR, Shapiro SM, et al. Acetylsalicylic acid reduces vegetation bacterial density, hematogenous bacterial dissemination, and frequency of embolic events in experimental *Staphylococcus aureus* endocarditis through antiplatelet and antibacterial effects. *Circulation*. 1999;99:2791–2797.
515. Chan KL, Dumesnil JG, Cujec B, et al. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. *J Am Coll Cardiol*. 2003;42:775–780.
516. Tornos P, Almirante B, Mirabet S, et al. Infective endocarditis due to *Staphylococcus aureus*: deleterious effect of anticoagulant therapy. *Arch Intern Med*. 1999;159:473–475.
517. Garcia-Cabrera E, Fernandez-Hidalgo N, Almirante B, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. *Circulation*. 2013;127:2272–2284.
518. Dickerman S, Abrutyn E, Barsic B, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). *Am Heart J*. 2007;154:1086–1094.
519. Thuny F, Di Salvo G, Belliard O, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study. *Circulation*. 2005;112:69–75.
520. Sonneville R, Mirabel M, Hajage D, et al. Neurologic complications and outcomes of infective endocarditis in critically ill patients: the ENDOcardite en REAnimation prospective multicenter study. *Crit Care Med*. 2011;39:1474–1481.
521. Duval X, Iung B, Klein I, et al. Effect of early cerebral magnetic resonance imaging on clinical decisions in infective endocarditis: a prospective study. *Ann Intern Med*. 2010;152:497–504, W175.
522. Thuny F, Grisoli D, Collart F, et al. Management of infective endocarditis: challenges and perspectives. *Lancet*. 2012;379:965–975.
523. Sousa C, Botelho C, Rodrigues D, et al. Infective endocarditis in intravenous drug abusers: an update. *Eur J Clin Microbiol Infect Dis*. 2012;31:2905–2910.
524. Miro JM, Moreno A, Mestres CA. Infective endocarditis in intravenous drug abusers. *Curr Infect Dis Rep*. 2003;5:307–316.
525. Ribera E, Gomez-Jimenez J, Cortes E, et al. Effectiveness of cloxacillin with and without gentamicin in short-term therapy for right-sided *Staphylococcus aureus* endocarditis. A randomized, controlled trial. *Ann Intern Med*. 1996;125:969–974.
526. Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. *Am J Med*. 1996;101:68–76.
527. Al-Omari A, Cameron DW, Lee C, et al. Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review. *BMC Infect Dis*. 2014;14:140.
528. Dzupova O, Rozsypal H, Prochazka B, et al. Acute bacterial meningitis in adults: predictors of outcome. *Scand J Infect Dis*. 2009;41:348–354.
529. Aguilar J, Urday-Cornejo V, Donabedian S, et al. *Staphylococcus aureus* meningitis: case series and literature review. *Medicine (Baltimore)*. 2010;89:117–125.
530. Pintado V, Meseguer MA, Fortun J, et al. Clinical study of 44 cases of *Staphylococcus aureus* meningitis. *Eur J Clin Microbiol Infect Dis*. 2002;21:864–868.
531. Pedersen M, Benfield TL, Skinhoej P, et al. Haematogenous *Staphylococcus aureus* meningitis. A 10-year nationwide study of 96 consecutive cases. *BMC Infect Dis*. 2006;6:49.
532. Pintado V, Pazos R, Jimenez-Mejias ME, et al. Methicillin-resistant *Staphylococcus aureus* meningitis in adults: a multicenter study of 86 cases. *Medicine (Baltimore)*. 2012;91:10–17.
533. Grewal S, Hocking G, Wildsmith JA. Epidural abscesses. *Br J Anaesth*. 2006;96:292–302.
534. Self WH, Wunderink RG, Williams DJ, et al. *Staphylococcus aureus* community-acquired pneumonia: prevalence, clinical characteristics, and outcomes. *Clin Infect Dis*. 2016;63:300–309.
535. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373:415–427.
536. Aliberti S, Reyes LF, Faverio P, et al. Global initiative for meticillin-resistant *Staphylococcus aureus* pneumonia (GLIMP): an international, observational cohort study. *Lancet Infect Dis*. 2016;16:1364–1376.
537. Gillet Y, Vanhems P, Lina G, et al. Factors predicting mortality in necrotizing community-acquired pneumonia caused by *Staphylococcus aureus* containing Panton-Valentine leukocidin. *Clin Infect Dis*. 2007;45:315–321.
538. Meyer CN, Rosenlund S, Nielsen J, et al. Bacteriological aetiology and antimicrobial treatment of pleural empyema. *Scand J Infect Dis*. 2011;43:165–169.
539. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44 Suppl 2:S27–S72.
540. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:e18–e55.
541. Davis JS. Management of bone and joint infections due to *Staphylococcus aureus*. *Intern Med J*. 2005;35 Suppl 2:S79–S96.
542. Kremers HM, Nwojo ME, Ransom JE, et al. Trends in the epidemiology of osteomyelitis: a population-based study, 1969 to 2009. *J Bone Joint Surg Am*. 2015;97:837–845.
543. Murillo O, Grau I, Lora-Tamayo J, et al. The changing epidemiology of bacteraemic osteoarticular infections in the early 21st century. *Clin Microbiol Infect*. 2015;21:254, e251–e258.
544. Zimmerli W. Clinical practice. Vertebral osteomyelitis. *N Engl J Med*. 2010;362:1022–1029.
545. White M, Dennison WM. Acute heamatogeneous osteitis in childhood: a review of 212 cases. *J Bone Joint Surg Br*. 1952;34-B:608–623.
546. Grammatico-Guillon L, Baron S, Gettner S, et al. Bone and joint infections in hospitalized patients in France, 2008: clinical and economic outcomes. *J Hosp Infect*. 2012;82:40–48.
547. Blyth MJ, Kincaid R, Craigen MA, et al. The changing epidemiology of acute and subacute haematogenous osteomyelitis in children. *J Bone Joint Surg Br*. 2001;83:99–102.
548. Dartnell J, Ramachandran M, Katchburian M. Haematogenous acute and subacute paediatric osteomyelitis: a systematic review of the literature. *J Bone Joint Surg Br*. 2012;94:584–595.
549. Lew DP, Waldvogel FA. Osteomyelitis. *Lancet*. 2004;364:369–379.
550. Peschel A, Otto M. Phenol-soluble modulins and staphylococcal infection. *Nat Rev Microbiol*. 2013;11:667–673.
551. Loughran AJ, Gaddy D, Beenken KE, et al. Impact of sarA and Phenol-Soluble Modulins on the Pathogenesis of Osteomyelitis in Diverse Clinical Isolates of *Staphylococcus aureus*. *Infect Immun*. 2016;84:2586–2594.
552. Cassat JE, Hammer ND, Campbell JP, et al. A secreted bacterial protease tailors the *Staphylococcus aureus* virulence repertoire to modulate bone remodeling during osteomyelitis. *Cell Host Microbe*. 2013;13:759–772.
553. Butalia S, Palda VA, Sargeant RJ, et al. Does this patient with diabetes have osteomyelitis of the lower extremity? *JAMA*. 2008;299:806–813.
554. Proctor RA, Kriegeskorte A, Kahl BC, et al. *Staphylococcus aureus* Small Colony Variants (SCVs): a road map for the metabolic pathways involved in persistent infections. *Front Cell Infect Microbiol*. 2014;4:99.
555. Peltola H, Paakkonen M, Kallio P, et al; Osteomyelitis-Septic Arthritis Study G. Short- versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood: prospective, randomized trial on 131 culture-positive cases. *Pediatr Infect Dis J*. 2010;29:1123–1128.
556. Guglielmo BJ, Luber AD, Paletta D Jr, et al. Ceftriaxone therapy for staphylococcal osteomyelitis: a review. *Clin Infect Dis*. 2000;30:205–207.
557. Tice AD, Hoaglund PA, Shoultz DA. Risk factors and treatment outcomes in osteomyelitis. *J Antimicrob Chemother*. 2003;51:1261–1268.
558. Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. *Clin Infect Dis*. 2015;61:e26–e46.
559. Russell CD, Ramaesh R, Kalima P, et al. Microbiological characteristics of acute osteoarticular infections in children. *J Med Microbiol*. 2015;64(Pt 4):446–453.

560. Geirsson AJ, Statkevicius S, Vikingsson A. Septic arthritis in Iceland 1990-2002: increasing incidence due to iatrogenic infections. *Ann Rheum Dis*. 2008;67:638–643.
561. Lieber SB, Fowler ML, Zhu C, et al. Clinical characteristics and outcomes of septic bursitis. *Infection*. 2017;45:781–786.
562. Trampuz A, Zimmerli W. Prosthetic joint infections: update in diagnosis and treatment. *Swiss Med Wkly*. 2005;135:243–251.
563. Sendi P, Banderet F, Graber P, et al. Periprosthetic joint infection following *Staphylococcus aureus* bacteremia. *J Infect*. 2011;63:17–22.
564. Lalueza A, Morales-Cartagena A, Chaves F, et al. Risk factors for metastatic osteoarticular infections after a long follow-up of patients with *Staphylococcus aureus* bacteraemia. *Clin Microbiol Infect*. 2015;21:1010, e1011–e1015.
565. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med*. 2004;351:1645–1654.
566. Bickels J, Ben-Sira L, Kessler A, et al. Primary pyomyositis. *J Bone Joint Surg Am*. 2002;84-A:2277–2286.
567. Garcia C, Hallin M, Deplano A, et al. *Staphylococcus aureus* causing tropical pyomyositis, Amazon Basin, Peru. *Emerg Infect Dis*. 2013;19:123–125.

195 *Staphylococcus epidermidis* and Other Coagulase-Negative Staphylococci

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SHORT VIEW SUMMARY

Microbiology

- A heterogeneous group of more than 40 species, coagulase-negative staphylococci are gram-positive cocci that are closely related to the intrinsically more virulent *Staphylococcus aureus* and differentiated from *S. aureus* by their inability to produce coagulase.
- *Staphylococcus epidermidis,* the most common clinically encountered species of coagulase-negative staphylococci, is a prominent part of the normal commensal flora of human skin. *S. epidermidis* owes its pathogenic success to three factors: (1) its normal niche on human skin, giving it access to any device inserted or passed through the skin; (2) its ability to adhere to biomaterials and elaborate biofilm; and (3) changes in the human host population resulting in greater numbers of immunosuppressed patients and greater use of bioprosthetic devices.[1–3]
- Other noteworthy species of coagulase-negative staphylococci include *Staphylococcus saprophyticus,* a common cause of uncomplicated urinary tract infection in sexually active women; *Staphylococcus haemolyticus,* often resistant to glycopeptides; and *Staphylococcus lugdunensis,* a more virulent coagulase-negative *Staphylococcus* that mimics infections due to *S. aureus.*

Epidemiology

- *S. epidermidis* is a prominent cause of intravascular catheter–related infection and infection of a variety of medical devices, such as prosthetic joints, artificial heart valves, and cerebrospinal fluid shunts.
- Strains of *S. epidermidis* can establish predominance in hospital environments and spread from unit to unit, hospital to hospital, and country to country.

Diagnosis

- Differentiating "true" infection-causing coagulase-negative staphylococci from contaminants can, at times, be a diagnostic challenge. Finding coagulase-negative staphylococci at high numbers or repetitively in situations clinically consistent with infection is indicative of a true infection. Unfortunately, in some situations, infections due to coagulase-negative staphylococci can be indolent and diagnosis is difficult.

Therapy

- Most nosocomial *S. epidermidis* strains are multidrug resistant, and glycopeptide or alternative antistaphylococcal antibiotics directed at methicillin-resistant strains are used in treatment. Isolates of *S. epidermidis* with an oxacillin minimal inhibitory concentration (MIC) of 0.25 μg/mL or less may be treated with oxacillin or nafcillin. Vancomycin is the drug with which there is the most clinical experience in coagulase-negative staphylococcal infections, although case reports support use of daptomycin and linezolid. Most species are susceptible in vitro to the newer agents telavancin, dalbavancin, oritavancin, ceftaroline, and tedizolid, and to the older agents quinupristin-dalfopristin and tigecycline, but their clinical utility for coagulase-negative staphylococcal infections remains to be defined.
- In some situations, rifampin is added to the regimen for better activity against biofilm-associated organisms.
- Information is accruing with regard to treatment of biomaterial-based infections with the device in situ, but most of these data are anecdotal. In general, infected devices should be removed whenever possible. A number of biofilm-directed therapeutic modalities appear to hold promise.

Prevention

- Biomedical devices must be inserted or implanted with scrupulous attention to aseptic practices. There is great interest in developing biomedical devices that are less prone to bacterial adherence and infection.

The genus *Staphylococcus,* with more than 80 recognized species and subspecies (https://www.dsmz.de/bacterial-diversity/prokaryotic-nomenclature-up-to-date/prokaryotic-nomenclature-up-to-date.html) is one of the most abundant microbes inhabiting normal human skin and mucous membranes.[1,4] They infrequently cause primary invasive disease and are most commonly encountered by clinicians as contaminants of microbiologic cultures. However, because of relatively recent changes in the practice of medicine and changes in underlying host populations, coagulase-negative staphylococci, most notably *Staphylococcus epidermidis,* have arisen to become formidable pathogens.[2] *S. epidermidis* is a very common cause of primary bacteremia and is frequently encountered in infections of indwelling medical devices.[3–5] *S. epidermidis* owes its pathogenic success to two major features: its natural niche on human skin, thus resulting in ready access to any device inserted or implanted across the skin, and its ability to adhere to biomaterials and form a biofilm.[3–7] Infections caused by *S. epidermidis* are often indolent and may be clinically difficult to diagnose. Differentiation of culture contamination from true infection can be challenging. Treatment is made more difficult by increasing rates of antibiotic resistance in coagulase-negative staphylococci and by the effect of biofilms on host defense and antimicrobial susceptibility. Unfortunately, infected prosthetic devices must often be removed to exact cure. Because the use of indwelling medical devices will most likely continue to increase, it is anticipated that the clinical significance of coagulase-negative staphylococci will similarly increase.

MICROBIOLOGY AND ECOLOGY

The staphylococci are members of the family Micrococcaceae, which also includes *Micrococcus, Stomatococcus,* and *Planococcus.* These bacteria are catalase-positive, gram-positive cocci that divide in irregular clusters, producing a "grapelike cluster" appearance when viewed under the microscope. *Staphylococcus* comprises at least 80 defined species and subspecies (Table 195.1).[7,8] In the clinical microbiology laboratory, staphylococci are typically categorized as those that have the ability to coagulate rabbit plasma (i.e., coagulase-positive staphylococci or *Staphylococcus aureus*) and those that do not (i.e., coagulase-negative staphylococci). The most common coagulase-negative staphylococci associated with human disease include *S. epidermidis, Staphylococcus saprophyticus, Staphylococcus lugdunensis,* and *Staphylococcus haemolyticus.* However, numerous other species have less commonly been associated with disease

TABLE 195.1 Taxonomy of Coagulase-Negative Staphylococci

Human

Species Frequently Associated With Disease

Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus lugdunensis
Staphylococcus saprophyticus

Species Rarely Associated With Human Disease

Staphylococcus auricularis
Staphylococcus capitis
Staphylococcus caprae
Staphylococcus carnosus
Staphylococcus cohnii
Staphylococcus hominis
Staphylococcus pasteuri
Staphylococcus petrasii
Staphylococcus pettenkoferi
Staphylococcus pulvereri
Staphylococcus saccharolyticus
Staphylococcus schleiferi
Staphylococcus simulans
Staphylococcus warneri
Staphylococcus xylosus

Animal

Staphylococcus agnetis
Staphylococcus arlettae
Staphylococcus caseolyticus
Staphylococcus chromogenes
Staphylococcus condimenti
Staphylococcus delphini
Staphylococcus devriesei
Staphylococcus equorum
Staphylococcus felis
Staphylococcus fleurettii
Staphylococcus gallinarum
Staphylococcus hyicus
Staphylococcus intermedius
Staphylococcus kloosii
Staphylococcus lentus
Staphylococcus lutrae
Staphylococcus muscae
Staphylococcus nepalensis
Staphylococcus piscifermentans
Staphylococcus pseudintermedius
Staphylococcus rostri
Staphylococcus sciuri
Staphylococcus simiae
Staphylococcus succinus
Staphylococcus vitulinus

(see Table 195.1). An alternative to the coagulase test commonly used in clinical microbiology laboratories includes rapid agglutination kits (containing antibody bound to beads) that target specific *S. aureus* antigens. The ability to identify coagulase-negative staphylococci to the species level correctly is difficult because of the number of biochemical tests required to yield accurate results.[8,9] However, most phenotypic systems used in clinical laboratories today can accurately identify those species most commonly isolated from human disease, including *S. aureus, S. epidermidis, S. haemolyticus,* and *S. saprophyticus*.[9,10] A simplified scheme used to identify *S. lugdunensis* from other coagulase-negative staphylococci includes a positive pyrrolidonyl aminopeptidase (PYR) and ornithine decarboxylase test.[10,11] Owing to complexities of identifying bacteria through phenotypic means, clinical laboratories are increasingly using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) to identify bacterial pathogens, including staphylococci.[12–14,27,28] In addition, US Food and Drug Administration (FDA)–approved polymerase chain reaction (PCR) platforms are commonly used to rapidly detect staphylococci (both *S. aureus* and coagulase-negative *Staphylococcus*) from positive blood culture bottles.[15,16] Indeed, the use of MALDI and rapid PCR identification testing systems will most certainly replace phenotypic identification of *Staphylococcus* species in the near future. Lastly, research-based PCR assays that identify coagulase-negative staphylococci to the species level primarily target 16S-23S rRNA regions,[17] *hsp60,*[10,18] *rpoB,*[10] *sodA,*[10] *tuf,*[10] and transfer RNA intergenic spacer length polymorphisms.[19]

Coagulase-negative staphylococci are normal commensal skin and mucous membrane microbes and are indigenous to a variety of mammalian hosts. Depending on the anatomic site, healthy human skin or mucous membranes support from 10^1 to 10^6 colony-forming units (CFUs) per square centimeter of coagulase-negative staphylococci. We are just now beginning to investigate the fundamental biologic significance of staphylococcal skin colonization. For example, recent data demonstrate that *S. epidermidis* colonization augments the local T-cell response, providing protection against *Leishmania major* infection in mice.[20] Furthermore, Nakatsuji and colleagues found evidence of bacterial communities extending beneath the dermal layer to the basement membrane, indicating interactions with various cell types.[21] Indeed, future studies to document the biologic function of coagulase-negative staphylococci and other skin commensals may be of utmost importance in the understanding of normal skin development and immunity. Of interest, the *S. epidermidis* protease Esp has the ability to inhibit biofilm formation of *S. aureus,* suggesting that some strains of *S. epidermidis* may be important in the inhibition of *S. aureus* colonization in humans.[22,23] More recent studies have found that *S. lugdunensis, Staphylococcus hominis,* and *S. epidermidis* produce antimicrobial peptides (AMPs) that, in some cases, synergize with the human AMP LL-37, to inhibit *S. aureus* growth on skin.[24,25] These interactions between coagulase negative staphylococci and *S. aureus* appear to be vital in the pathogenesis of staphylococcal infections in atopic dermatitis.[25] In addition, Horswill and colleagues found that a strain of *Staphylococcus caprae* was able to inhibit *S. aureus* dermonecrosis in a mouse model by inhibition of the Agr quorum sensing system via synthesis of its own autoinducing peptide.[26] Thus, the study of coagulase-negative staphylococci and their interactions with other commensal flora (e.g., *Cutibacterium acnes*) and potential pathogens, including *S. aureus*, is a fertile area of investigation that may lead to novel prevention strategies.

Aptly named, *S. epidermidis* is one of the most prevalent species found on human skin, with the average person consistently carrying 10 to 24 different strains.[1,8,9] Because of varying characteristics of human skin, including varying moisture content, nutrient substances, pH range, and temperature, *S. epidermidis* must adapt to a variety of environmental conditions. Certain species of coagulase-negative staphylococci are well adapted to exist in specialized niches, such as *Staphylococcus capitis* (human scalp), *Staphylococcus auricularis* (human ear canal), and *S. saprophyticus* (human alimentary and genitourinary tracts); however, the loci that function in staphylococcal skin colonization are not well characterized.

ANTIBIOTIC RESISTANCE

Coagulase-negative staphylococci isolated from nosocomial environments are almost always resistant to multiple antimicrobial agents. In two large surveillance studies from the United States and North America, 73% to 88% of isolates were resistant to oxacillin, 55% to 66% were resistant to levofloxacin, 70% to 73% were resistant to erythromycin, 35% to 52% were resistant to clindamycin, and 35% to 48% were resistant to trimethoprim-sulfamethoxazole.[29,30] Similar results were obtained from the United Kingdom.[31] Although resistance determinants have been defined in some cases, little resistance is observed clinically to agents such as linezolid, tedizolid, daptomycin, quinupristin-dalfopristin, tigecycline, ceftaroline, dalbavancin, telavancin, and oritavancin, or to the investigational agents ceftobiprole and iclaprim.[30,32–45] A few coagulase-negative staphylococci with *van* genes have been isolated from nonclinical sources.[50] In addition, isolates with elevated minimal inhibitory concentrations (MICs) to glycopeptide antibiotics, especially within *S. haemolyticus,* have been reported.[46–49] To date, "vancomycin creep" as found in *S. aureus* has not been observed in coagulase-negative staphylococci.[50] The ability to isolate subpopulations of *S. epidermidis* clinical isolates with markedly elevated vancomycin MICs (>32 g/mL) has not been associated with a clinical consequence to date.[51–53]

Phenotypic expression of methicillin (oxacillin) resistance in coagulase-negative staphylococci is much more heterotypic than that observed in *S. aureus,* meaning that the percentage of the population

that expresses high-level oxacillin resistance is smaller. To address this expression difference, the MIC breakpoint to detect oxacillin resistance is lower for coagulase-negative staphylococci (except *S. lugdunensis*) than *S. aureus* (≥0.5 μg/mL vs. >4 μg/mL, respectively).[59] Regardless of the degree of heterotypy observed, all isolates containing *mecA* (the gene conferring oxacillin resistance) are clinically resistant to all β-lactam antibiotics.[55] Alternative methods to detect oxacillin resistance include a cefoxitin disk test, which is used as a surrogate to detect *mecA*-mediated oxacillin resistance,[54] PCR assay for *mecA* detection,[56] and commercial assays to detect PBP2A production (gene product of *mecA*).[57] However, in some coagulase-negative staphylococci, PBP2A is detected only after oxacillin induction. Note that *mecA*, and thus oxacillin resistance, is rapidly detected with PCR-based blood culture identification systems.[15,58,59]

A particularly onerous aspect of treatment of most coagulase-negative staphylococcal infections is their ability to form biofilms on biomaterials (e.g., catheters, prostheses; see later). Tolerance to antibiotics and persister cells is a common theme with staphylococci and other bacteria growing within a biofilm; these facts need to be taken into consideration during treatment.[60,61] Studies testing the effectiveness of antibiotics against staphylococci growing in a biofilm have demonstrated that they are significantly less effective than when treating planktonic cells.[62] However, antibiotic combinations containing daptomycin alone or in combination with rifampin seem promising in treating or at least reducing the bacterial burden of staphylococcal biofilm infections.[63,64] Interesting to note, studies have shown that staphylococci growing in a biofilm lead to the establishment of an antiinflammatory environment.[65,66] Redirecting this response with proinflammatory macrophages can lead to partial clearance of *S. aureus* biofilm, suggesting that the combination of antibiotics plus a cell-based therapy could be a promising approach in the future.[67]

MOLECULAR EPIDEMIOLOGY

Pulsed-field gel electrophoresis (PFGE) is the gold standard method for addressing the short-term molecular epidemiology of *S. epidermidis* and other coagulase-negative staphylococci. There is extreme diversity in pulsed-field patterns when *S. epidermidis* epidemiology is studied.[68,69] Therefore the finding of indistinguishable PFGE patterns within the context of an outbreak assessment is highly relevant. Longer-term, population-based relationships and trends are better addressed with multilocus sequence typing (MLST) analysis, which suggests that the population structure of *S. epidermidis* is epidemic and that nine clonal lineages are disseminated worldwide.[70] One major clone, CC2, represented 74% of isolates worldwide in one study; similar results were found in other MLST studies.[70–74]

Interesting to note, population structure and the presence or absence of five genetic markers (*icaA, IS256, sesD, mecA,* and the ACME pathogenicity island) have the ability to discriminate between hospital and nonhospital sources of *S. epidermidis*.[75] However, rapid evolution (and thus PFGE patterns) occurs through frequent transfer of mobile genetic elements and recombination, possibly through insertion sequence elements. Other molecular typing methods, including sequence analysis of repeat regions of *sdrG/aap* genes and MLVA (multiple-locus variable-number tandem repeat analysis), have been developed and have yielded similar discriminatory power as MLST or PFGE.[76,77]

PATHOGENESIS

In contrast to *S. aureus,* which produces an array of toxins and adherence factors, there are few defined virulence factors in *S. epidermidis* (Table 195.2) and other coagulase-negative staphylococci. However, significant advances made in the past 20 years have helped define the pathogenesis of infections caused by *S. epidermidis*.[78] The ability of *S. epidermidis* to adhere and form biofilm on the surface of biomaterials is thought to be the most significant virulence factor associated with this bacterium.[79–81] However, other factors, such as the secretion of poly-gamma-DL-glutamic acid (PGA)[82] and phenol-soluble modulins (PSMs),[83,84] appear to complement and increase virulence.

Virulence Factors

Biofilm

Staphylococcal biofilm formation is thought to occur in multiple stages, including adherence to a surface, multiplication, maturation and tower development, and subsequent dispersal (Fig. 195.1).[85] It is well established that bacteria growing within a biofilm are unique compared with those growing exponentially in the planktonic phase. Microarray studies have demonstrated that both *S. epidermidis* and *S. aureus* growing in a biofilm state have unique transcriptional responses compared with cells growing exponentially.[86–88] For example, these experiments have shown that staphylococci growing in a biofilm shift their physiology toward anaerobic or microaerobic metabolism and downregulate protein, cell wall, and DNA synthesis. Although these experiments have been extremely helpful in defining the "average" transcriptional response of biofilm growth (as all cells growing in a biofilm were examined), it is also well established

TABLE 195.2 Defined and Proposed Virulence Factors of *Staphylococcus epidermidis*

DEFINED AND PUTATIVE VIRULENCE FACTORS	PROPOSED MECHANISM
Biofilm	**Immune System Avoidance, Antimicrobial Tolerance**
Polysaccharide intercellular adhesin (PIA)	Polysaccharide component of biofilm
Accumulation-associated protein (Aap)	Accumulation of biofilm
Bap homologue protein (Bhp)	Accumulation of biofilm
Extracellular DNA	Structure of biofilm
Adhesin Molecules	**Adherence to Host Proteins or Plastic**
Autolysin, adhesin (Aae)	Binds fibrinogen, vitronectin, fibronectin
Autolysin (AtlE)	Binds vitronectin
Bap homologue protein (Bhp)	Binds polystyrene
Elastin-binding protein (Ebp)	Binds elastin
Extracellular matrix binding protein (EmbP)	Binds fibronectin
Fibrinogen-binding protein (Fbe)	Binds fibrinogen
Glycerol ester hydrolase (GehD)	Binds collagen
Staphylococcal conserved antigen (ScaA)	Binds fibrinogen, vitronectin, fibronectin
Staphylococcal conserved antigen (ScaB)	Binds undefined ligand
Serine aspartate repeat protein F (SdrF)	Binds collagen
Serine aspartate repeat protein G (SdrG)	Binds fibrinogen
Staphylococcal surface protein 1 (Ssp-1)	Binds polystyrene
Staphylococcal surface protein 2 (Ssp-2)	Binds polystyrene
Teichoic acid	Binds fibronectin
Other Putative Virulence Factors	**Mechanisms**
Peptidoglycan, lipoteichoic acid	Stimulates cytokine production
Phenol-soluble modulins	Immune system modulation, biofilm dispersion
Poly-D-glutamic acid	Immune system avoidance, resistance to antimicrobial peptides
Delta toxin	Immune system avoidance
Exoenzymes	
Fatty acid–modifying enzyme (FAME)	Inactivates fatty acids on skin, skin colonization
Lipases	Skin and wound colonization
Proteases	Destruction of host tissue
Elastase	Immune modulation, skin colonization
Lantibiotics	
Epidermin, epilancin, epicidin, Pep5, K7	Bacterial interference and skin colonization

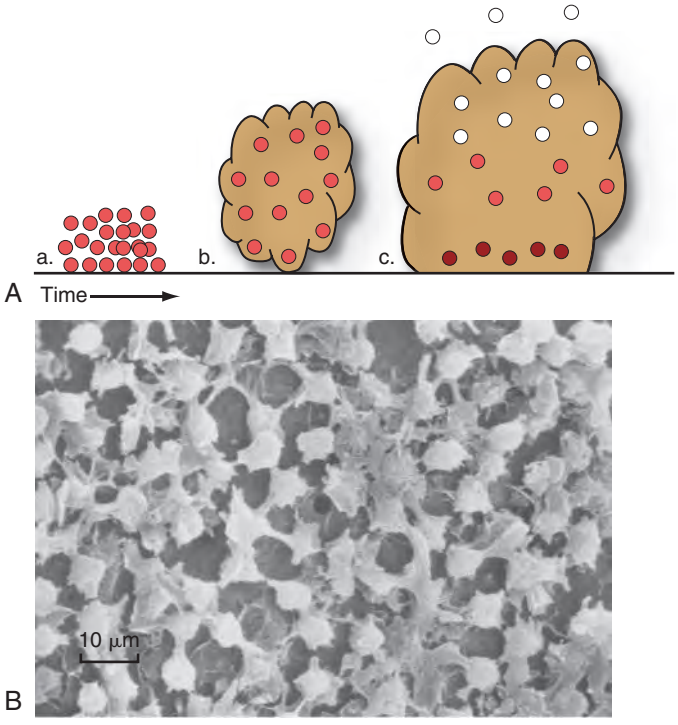

FIG. 195.1 Biofilm formation in *Staphylococcus epidermidis.* (A) Model of biofilm formation in *S. epidermidis.* Staphylococci initially adhere to biomaterial by binding to serum matrix proteins coated on the biomaterial and through direct biomaterial interactions *(a).* Once bound, *S. epidermidis* produces extracellular polymeric substances (polysaccharide intercellular adhesin, environmental DNA) and other proteinaceous factors (Aap, Embp, Bap), which facilitate intercellular adherence *(b).* A mature biofilm has multiple metabolic states, including cells growing under aerobic conditions (white cells), microaerobic or anaerobic conditions (bright red cells), and dormant cells (dark red cells) *(c).* Through the action of phenol-soluble modulins, cells disperse from the biofilm, which facilitates colonization at other sites. (B) Scanning electron micrograph of *S. epidermidis* biofilm adhering to a tissue cage in a guinea pig model (×1360).

that cells growing within a biofilm have spatial and temporal responses to their immediate environment (e.g., nutrient and oxygen availability and interactions with metabolic waste).[89] It is hypothesized that these unique physiologic states found within a biofilm allow for tolerance to antibiotics and development of persister and/or dormant cells.[60]

Adherence

Biomaterials placed within a human host are rapidly coated with serum matrix proteins, including fibrinogen and fibronectin. Genome and functional analyses have suggested that *S. epidermidis* possesses at least the ability to bind fibrinogen, fibronectin, collagen, vitronectin, and elastin.[90–95] Furthermore, there is evidence that *S. epidermidis* autolysins have the ability to bind directly to plastic and contain matrix protein binding sites.[96,97] Lipase (GehD), in addition to its enzymatic function, has been shown to bind collagen.[94] Mutants that do not have the ability to bind fibrinogen or produce autolysin are less virulent in pertinent in vivo models, suggesting that initial adherence to serum matrix proteins is critical.[98,99] Lastly, the bifunctional protein accumulation-associated protein (Aap) has been shown to bind to catheters in a rat catheter model, but the binding partner within serum or host cells is currently unknown.[100–102]

Maturation

After adherence to the biomaterial, intercellular adherence of the bacteria is primarily mediated by polymeric molecules. It has been shown that extracellular DNA is a major component of both *S. aureus* and *S. epidermidis* biofilms, and mutants defective in DNA release produce deficient biofilms.[103] Some clinical strains of *S. epidermidis* produce an abundance of polysaccharide intercellular adhesin (PIA), but not all strains produce PIA and it is a minor component of an *S. aureus* biofilm.[104,105] PIA (or poly-*N*-acetylglucosamine [PNAG]) is a β-1,6-linked *N*-acetylglucosamine[78] synthesized by the *ica* operon gene products.[105,106] The *ica* operon is composed of four genes: *icaA, icaD, icaB,* and *icaC.*[81] A divergently transcribed repressor, *icaR,* is found just upstream of *ica.*[107] PIA appears to be important in *S. epidermidis* surface colonization, biofilm formation, and immune system evasion.[108,109] Regulation of *icaADBC* transcription has been an intense area of study and involves SarA, SarZ, σB, IcaR, and the TCA cycle, among others.[110–116] In *S. aureus,* PIA enhances virulence in murine systemic disease models and is a vaccine candidate for both *S. aureus* and *S. epidermidis.*[117–119] It is important to reiterate that approximately 50% of clinically relevant strains of *S. epidermidis* do not contain the *icaADBC* operon, and other alternative, proteinaceous biofilm maturation strategies exist (e.g., AAP, Embp, Bap).[92–95,104,120–124] PIA-positive strains of *S. epidermidis* may be selected for in niches of high shear stress such as the catheter lumen; indeed, isolates obtained from high-shear environments are more likely to produce PIA-mediated biofilms than those isolates obtained from other sources, suggesting that an additional function of PIA is related to stability of the biofilm structure under high shear.[104] Furthermore, allelic replacement of *icaADBC* confers increased fitness during colonization of human skin as compared with the isogenic wild-type isolate.[125] Therefore, although production of PIA is highly advantageous to the organism during the infection process, PIA production may be deleterious to the organism during colonization of human skin. An additional well-studied protein that functions in biofilm maturation and accumulation is Aap. Once Aap binds to its target, the N-terminal portion of the protein is cleaved via an *S. epidermidis* protease, SepA, and intracellular accumulation occurs via Aap proteins on neighboring cells.[102]

Dispersal

The last stage of biofilm development is dispersal and subsequent spread to other potential sites. The production of PSMs by *S. epidermidis* has been shown in flow cell biofilm experiments to mediate the detachment of the upper layers of the biofilm, although other mechanisms may exist, including nuclease-mediated dispersal.[85,87] PSMs, which are regulated by the quorum-sensing global regulator *agr,* act as surfactants, leading to loss of cellular clusters. In addition, *S. epidermidis* PSMs are proinflammatory and have been shown to recruit, activate, and lyse human neutrophils during infection with *S. aureus.*[126,127]

Other Virulence Factors

Phenol Soluble Modulins

S. epidermidis typically produces five PSMs, a family of amphipathic α-helical peptides that have many functions, including spread on epithelial surfaces.[128] However, some PSMs, including those produced by *S. aureus,* have cytolytic activities. A study by Otto and coworkers found that PSM-mec, which is encoded within SCC*mec,* the genomic island conferring methicillin resistance within the staphylococci, contributes significantly in a mouse model of sepsis.[129] These data may be particularly relevant to neonatal sepsis, which is typically mediated by methicillin-resistant *S. epidermidis* strains encoding *psm-mec.*

Poly-Gamma-DL-Glutamic Acid

A somewhat surprising finding is that in contrast to *S. aureus,* multiple species of coagulase-negative staphylococci, including *S. epidermidis,* produce PGA.[82] PGA is a cell surface–associated, antiphagocytic polymer first described as a virulence factor in *Bacillus anthracis.*[130,131] PGA appears to have a bifunctional role in *S. epidermidis* and functions to inhibit innate host defense and facilitate colonization of human skin.

Antimicrobial Peptide Resistance

Although *S. epidermidis* does not produce multiple toxins to protect against professional phagocytes, several other mechanisms are used to defend against phagocytosis. First, as previously mentioned, biofilm production is itself antiinflammatory, and production of PIA is antiphagocytic.[132] Second, the Aps system can sense the presence of AMPs and upregulate mechanisms to protect the cell against this injury; this includes

increased D-alanylation of teichoic acids and lysylation of phospholipids, thus increasing the overall positive charge of the bacterium.[133]

Lantibiotics

S. epidermidis produces several lantibiotics (e.g., epidermin, Pep5, epilancin, epicidin), which are bacteriocins. These thioether amino acid–containing AMPs are active against a variety of bacteria and may function in bacterial interference and successful colonization and persistence on human skin.[134]

Other Coagulase-Negative Species

Because of the lack of well-developed genetic systems within other coagulase-negative staphylococci, investigation of virulence mechanisms in other staphylococcal species is limited. However, significant progress has been made with *S. saprophyticus* and *S. lugdunensis*. *S. saprophyticus* shows strong adherence to uroepithelial cells and erythrocytes and produces urease, facilitating the growth of this pathogen in urine.[135–138] In addition, genome sequencing has revealed that *S. saprophyticus* ATCC15305 is particularly adapted to growth in urine because of expansion of systems involved in osmotolerance and inorganic ion transport.[136] *S. lugdunensis* does not produce toxins and adherence factors similar to *S. aureus* despite its apparently increased virulence.[10,11] However, several studies have found that *S. lugdunensis* binds human host matrix proteins, including collagen, immunoglobulin G (IgG), fibrinogen, laminin, vitronectin, fibronectin, thrombospondin, von Willebrand factor, and plasminogen.[91,136,139,140] In addition, although it contains the *icaADBC* locus, *S. lugdunensis* appears to produce protein-dependent biofilms that are not PIA dependent, similar to *S. aureus*.

EPIDEMIOLOGY AND CLINICAL SYNDROMES

Previously disregarded as nonvirulent contaminants, coagulase-negative staphylococci have more recently been increasingly recognized as true pathogens. Coagulase-negative staphylococci cause a wide variety of clinical infections, many related to foreign bodies and prosthetic medical devices.

Colonization and Transmission

Certain species of coagulase-negative staphylococci have a predilection for specific niches on the human body that may predispose to certain types of infections. At times, the species names reflect the anatomic site where the particular species is most frequently encountered. For example, *S. auricularis* colonizes the external ear and *S. capitis* is frequently recovered from the scalp. *S. haemolyticus* and *S. hominis* prefer apocrine glands found in the axilla and pubis. Similarly, *S. lugdunensis* is frequently found to colonize the perineum and groin region. Consequently, it is not surprising that *S. capitis* has been associated with cerebrospinal fluid (CSF) shunt infections nor *S. auricularis* with middle ear infections, and *S. lugdunensis* has caused bacteremia and endocarditis after surgical procedures involving the groin and scrotum. As previously mentioned, *S. epidermidis* is well suited to colonize human skin. It possesses a number of osmoprotective systems to cope with the harsh environmental conditions and high salt concentrations encountered on the dermal surface.[141] Most strains of *S. epidermidis* (and some strains of *S. haemolyticus* and *S. capitis*) contain the arginine catabolic mobile element (ACME), which is thought to improve the organism's ability to colonize the skin and mucosal membranes.[142] In general, body sites with greater moisture are favored, and thus coagulase-negative staphylococci are more readily recovered from the axilla, groin, gluteal, umbilical, antecubital, popliteal, and plantar foot and toe web areas, in addition to mucosal surfaces such as the nares, conjunctiva, and vagina.[50] *S. epidermidis* is also well suited to survive in hospital environments. It can survive on fabrics and inanimate surfaces for weeks to months[143] and is often resistant to multiple antibiotics.[3] *S. epidermidis* often possesses efflux pumps, making it less susceptible to certain antiseptics and other biocides.[144] *S. epidermidis* produces PSMs that are proinflammatory cytolysins and appear to exact selective antimicrobial activity against other organisms, including *S. aureus,* thus helping *S. epidermidis* to outcompete other microbes for dominion of the skin niche.[145,146] Similarly, *S. epidermidis* serine protease Esp appears to inhibit nasal colonization by *S. aureus*.[19,23] These findings hold promise that certain strains of *S. epidermidis* may someday be used as probiotics to exclude the more pathogenic *S. aureus* from skin and nasal colonization.

Investigators have documented in various patient groups that shortly after admission to the hospital, a patient's endogenous, usually antibiotic-susceptible, *S. epidermidis* flora is replaced by nosocomial, usually antibiotic-resistant, strains of *S. epidermidis*.[147–149] Predominant clones of *S. epidermidis* often emerge and can persist in hospitals for decades.[149,150] Health care providers may be carriers of these endemic *S. epidermidis* strains and spread them from patient to patient.[151,152] Furthermore, under the selective pressure of antimicrobial use, these highly successful strains of *S. epidermidis* have been shown to spread from unit to unit, hospital to hospital, and even country to country.[47,72,153–156] Although nosocomial spread of coagulase-negative staphylococci primarily occurs via contact with health care providers' hands, fomites, or contaminated environmental surfaces, nosocomial strains of *S. epidermidis* have been recovered from hospital air.[157] In addition, coagulase-negative staphylococci appear to serve as a pool for the horizontal transfer of antibiotic-resistant genes to *S. aureus*.[158,159] Interesting to note, at least part of the ability of community-associated methicillin-resistant *S. aureus* (MRSA) (strain USA300) to rapidly spread in the human population is thought to be due to the transfer of ACME from coagulase-negative staphylococci to *S. aureus*. Some authors have suggested that in order to better control the emergence and spread of multidrug-resistant *S. aureus,* infection-control measures should be introduced to detect and prevent the spread of multidrug-resistant *S. epidermidis*.[160] However, practical and feasible methods to control the spread of multidrug-resistant *S. epidermidis* are completely undefined.

Bacteremia

Coagulase-negative staphylococci are the most common cause and account for approximately 30% of health care–associated bloodstream infections. Most of these infections are caused by involvement of intravascular catheters or other prosthetic medical devices. Immunosuppressed patients, particularly neonates or those with severe neutropenia, are at increased risk of bloodstream infection with coagulase-negative staphylococci. In addition to intravascular catheters, mucosal breakdown caused by cytotoxic chemotherapy may precipitate infection in oncology patients.

Because coagulase-negative staphylococci, particularly *S. epidermidis,* occupy such a prominent position in the commensal flora of human skin and mucous membranes, they are frequently encountered as culture contaminants. Approximately 1% to 6% of blood cultures are contaminated, and coagulase-negative staphylococci are responsible for 70% to 80% of cases.[161–163] Typically, rates of true bacteremia range from 10% to 35% when coagulase-negative staphylococci are isolated from blood cultures.[163–167]

Determining the clinical significance of coagulase-negative staphylococci isolated from blood cultures is difficult, and a variety of clinical and laboratory parameters should be examined when making this determination. This is not a trivial issue because contaminants treated as true pathogens result in unnecessary antibiotic treatment, emergence of antibiotic resistance, excessive use of laboratory resources, antibiotic-associated side effects and toxicity, and greater expense.[168] Many clinicians use fever or other signs of infection (e.g., leukocytosis or leukopenia, hypotension) to assist with the interpretation of blood cultures that yield coagulase-negative staphylococci, and a number of studies have offered support.[161,162,165,169] However, most blood cultures are obtained because of a clinical suspicion of bacteremia, and other investigators have not found clinical signs and symptoms helpful in differentiating contamination from infection.[166,170,171] Another parameter often used is the number or proportion of cultures that yield coagulase-negative staphylococci. Most studies relate that the likelihood of true bacteremia increases when multiple cultures are obtained and yield coagulase-negative staphylococci,[172] but this has not been universally observed.[172,173] The problem is compounded in neonates, from whom it is common practice to obtain only one blood culture when entertaining the possible diagnosis of bacteremia. A study examining the usefulness of a single-sample strategy for blood culture found that the positive predictive values for a "true" bloodstream infection were 3.5%, 61.1%, 78.9%, and 100% when one, two, three, and four or more blood culture

bottles yielded coagulase-negative staphylococci.[174] However, Seybold and colleagues noted through use of molecular typing methods that contamination may be frequent even when two or more blood cultures reveal coagulase-negative staphylococci in a 24-hour period.[175] A shorter time to growth or a greater burden of bacteria in quantitative blood cultures has also been used to differentiate true bacteremia from contamination, with mixed success.[176] In general, a time to positivity of less than 24 hours is considered consistent with true bacteremia.[167] Savithri and colleagues noted that a time to positivity of less than 24 hours for blood cultures yielding coagulase-negative staphylococci was associated with a higher organ failure score and a trend toward increased 28-day mortality in a group of critical care unit patients.[177] Schnell and colleagues formulated an algorithm to assess the clinical significance of coagulase-negative staphylococcal bacteremia, taking into account the number of positive cultures, antibiogram, clinical signs, and source of infectious foci, and they related positive and negative predictive values of 78% and 68%, respectively.[178] Similarly, Garcia-Vasquez and colleagues formulated an algorithm to predict clinically significant coagulase-negative staphylococcal bacteremia with a 62% sensitivity and 93% specificity; this algorithm included Charlson score ≥3, Pitt score ≥1, neutropenia, presence of a central venous catheter (CVC), time to culture positivity of <16 hours, and *S. epidermidis* speciation.[167]

In differentiating intravascular catheter–associated coagulase-negative staphylococci bloodstream infection from bacteremia from other sources, the differential time for a blood culture to become positive between peripheral blood and catheter blood can now be readily determined with most automated blood culture methods. When the catheter blood is positive 2 or more hours sooner than the peripheral blood, this can be taken as an indicator that the catheter is the source of bacteremia.[145,146,179,180] Other laboratory parameters that may have some usefulness for differentiating contaminants from pathogens in certain settings include C-reactive protein (CRP)[181] and serum procalcitonin levels,[182] molecular typing,[183,184] antibiogram,[185] biofilm production,[186] presence of adhesins, and absence of *bap* gene.[181–187] Kitao and colleagues noted that more than half of *S. epidermidis* isolates obtained from blood cultures possessed genes for biofilm production *(icaAB)* and methicillin resistance *(mecA),* whereas only 1.5% of isolates from the skin were positive by PCR for these potential markers for clinical infection.[188]

Methods that have been used to prevent blood culture contamination include use of effective skin antiseptics, phlebotomy teams, culture bottle preparation, blood culture kits, and double-needle bottle inoculation.[161,162,189] More recently, a device that diverts and sequesters the initial 1.0 mL to 1.5 mL of blood has proven very effective in preventing blood culture contamination thought to stem from dislodged skin cells.[190] In general, blood cultures should be obtained with careful aseptic technique in persons in whom a clinical suspicion for bacteremia exists. Paired cultures should be drawn, and if a CVC source is being considered, one of the blood samples should be obtained from the catheter. The site (catheter or periphery) and time of obtainment should be recorded. Patients with clinical signs of sepsis, with multiple positive cultures for coagulase-negative staphylococci that reveal growth in less than 24 hours, are much more likely to have true bacteremia. Although the low virulence of coagulase-negative staphylococci is well known, coagulase-negative staphylococcal infections can at times be severe, even in the absence of a biomaterial-based process. Chu and coworkers noted that 8% of all cases of native valve endocarditis were caused by coagulase-negative staphylococci, and these patients experienced a mortality rate that is similar to that associated with *S. aureus* endocarditis (approximately 25%).[191] Among 87 patients with clinically significant bacteremia, Pien and colleagues noted an attributable mortality of approximately 2%.[163]

Intravascular Catheter Infections

Intravascular catheter infections are discussed more fully in Chapter 300. More than 150 million intravascular catheters are used in the United States annually. Although the incidence of central line–associated bloodstream infections (CLA-BSIs) decreased by 50% in US acute-care hospitals between 2008 and 2014, tens of thousands of patients continued to experience CLA-BSI each year, resulting in substantial morbidity, mortality, and increased cost.[192,193] The mean rate of CLA-BSIs in US hospitals ranges from 0 to 2.9 per 1000 CVC days depending on the type of unit.[192,194] The rate of CLA-BSI in Western Europe is generally comparable to rates reported in the United States.[195] Unfortunately, the incidence of CLA-BSI in limited-resource countries is substantially higher (1.6–44.6 per 1000 CVC days).[195a] Coagulase-negative staphylococci are the most common cause of these infections (Fig. 195.2). For the years 2009 and 2010, 27,766 CLA-BSIs were defined in the Centers for Disease Control and Prevention's National Healthcare Safety Network, of which 20.5% were caused by coagulase-negative staphylococci. Over a 6-year observation period in Quebec, from 2003 to 2009, coagulase-negative staphylococci were responsible for 53% of CLA-BSIs.[196] A detailed discussion of the pathogenesis of CVC-associated bloodstream infection is beyond the scope of this chapter. Briefly, for peripheral intravascular catheters and nontunneled CVCs, infection most commonly results from coagulase-negative staphylococci entering via the cutaneous surface of the catheter to the bloodstream. The tissue around the intravascular catheter appears to be an important niche for microbes, and large numbers of coagulase-negative staphylococci can be cultured from pericatheter tissue.[197] For tunneled CVCs, hub colonization and passage of organisms along the lumen appear to be an important route of infection. In a cohort of hemodialysis patients with tunneled CVCs, endoluminal colonization by *S. epidermidis* was detected a median of 31.5 days before a clinically evident catheter-related bloodstream infection was defined.[198] The ability of coagulase-negative staphylococci to adhere to the catheter and elaborate biofilm are crucial traits that allow them to cause infection of vascular catheters.[199]

FIG. 195.2 Infected central venous catheter. Although many infected central venous catheters appear innocuous, this *Staphylococcus epidermidis*–infected implanted catheter site exhibits erythema, tenderness, and purulent drainage at the skin exit site.

The diagnosis of coagulase-negative staphylococci CVC bloodstream infection can be difficult because most infected CVCs have no obvious local evidence of inflammation or infection[199] and, as already discussed, coagulase-negative staphylococci are most often clinically encountered as blood culture contaminants.[199] In the past, diagnosis of CVC-associated bloodstream infection was considered to require removal of the catheter and semiquantitative or quantitative culture of the catheter tip.[200,201] Many clinicians take advantage of automated, continuously monitored blood culture systems and use a 2-hour cutoff differential time to positivity assessment on blood cultures drawn from the periphery and CVC.[180] The limitations of this technique are discussed in greater detail in Chapter 300.

In general, short-term, nontunneled CVCs infected with coagulase-negative staphylococci should be removed because these infections can be associated with sepsis and increased morbidity.[202,203] In patients with coagulase-negative staphylococci–infected tunneled CVCs who do not exhibit signs of severe sepsis, it is permissible to attempt catheter salvage. If the CVC is retained, it is advisable to use systemic antimicrobials, based on susceptibility testing, through all the lumens of the catheter for 7 to 14 days.[179] Antimicrobial lock therapy, discussed in greater detail in Chapter 300, is increasingly employed in attempt to treat CVC-related infection with the catheter in situ. Various antimicrobial

agents have been used, either alone or in combination, in lock solutions used to treat coagulase-negative staphylococcal CVC-related bloodstream infection, including vancomycin, daptomycin, minocycline, cephalosporins, aminoglycosides, fluoroquinolones, hydrochloric acid, alcohol, and various chelators.[204] In general, success rates of 80% to 90% are noted, with a relapse of 20% to 30%. Similarly, lock therapy can be used to prevent CVC-associated bloodstream infection.[205,206] If fever or bacteremia persists for more than 3 days after initiating therapy, the CVC should usually be removed. In a group of 23 patients with coagulase-negative staphylococcal bacteremia lasting for longer than 48 hours despite appropriate antibiotics, antibiotic lock therapy was successful in only 30% of patients.[207] Most health care–associated coagulase-negative staphylococci are methicillin resistant, and vancomycin is most frequently used to treat these infections. If once-daily daptomycin is used, each dose should be distributed among all the lumens of a multiport catheter. As mentioned, if the catheter is retained, the clinician should be alert for relapse because this occurs in a substantial minority of patients.[204,208] Tunnel track or port pocket infections necessitate catheter removal, whereas exit site infections can usually be successfully treated with the CVC in place.

Endocarditis

Prosthetic valve endocarditis (PVE), although uncommon, is caused by coagulase-negative staphylococci in 15% to 40% of cases.[209–213] Both bioprosthetic and mechanical valves can be infected, as can valves replaced via a transcatheter approach.[213,214] The infection is usually health care related (resulting from inoculation at the time of surgery) and manifests within 12 months of valve placement.

Coagulase-negative staphylococci cause approximately one-third of early-onset PVE (onset <2 months after valve insertion) and 40% of intermediate-onset disease (onset 2–12 months after valve insertion).[212] These isolates are likely to be methicillin resistant. The cases of PVE that present after this time period are less commonly caused by the coagulase-negative staphylococci, usually associated with trauma to mucosal surfaces or incidental infection and, if caused by coagulase-negative staphylococci, are more apt to be methicillin susceptible.[215] Coagulase-negative staphylococci cause 10% to 20% of late-onset PVE (>12 months after valve insertion).[211,212] The aortic valve is most frequently involved, and patients may present in an acute or more indolent fashion. An acute presentation is characterized by fever and physical evidence of valve dysfunction, whereas peripheral stigmata of endocarditis are more commonly observed in patients exhibiting a more indolent course. The diagnosis is usually confirmed by documenting repeatedly positive blood cultures and vegetations with transesophageal echocardiography. Positron emission tomography (PET)/computed tomography (CT) is being increasingly used in ambiguous cases and should be interpreted by a specialist with expertise in cardiac imaging and the findings integrated into the clinical context.[216] Heart failure occurs in 54% of cases, and more than 80% of patients have complications, including prosthetic valve dysfunction and intracardiac abscesses. Typically, antibiotic therapy consists of vancomycin and rifampin for at least 6 weeks combined with gentamicin for the first 2 weeks (see Chapter 81).[217,218] Isolates susceptible to penicillinase-stable penicillins should be treated with oxacillin or nafcillin instead of vancomycin. There is increasing concern regarding vancomycin "MIC creep," and clinicians are sometimes turning to daptomycin or other vancomycin alternatives. Valve replacement surgery is usually necessary. Despite aggressive therapy, the mortality caused by coagulase-negative staphylococci PVE remains high, at approximately 25%.[211,213]

Unlike PVE, native valve endocarditis caused by coagulase-negative staphylococci is relatively rare, occurring in only 5% to 12% of endocarditis cases.[191,209,213,219,220] This infection is the result of hematogenous seeding of previously damaged heart valves and endocardium. The incidence of endocarditis caused by coagulase-negative staphylococci appears to be increasing and is probably driven by an increase in health care–associated interventions (e.g., intravenous catheters, hemodialysis), and the causative isolates are usually methicillin resistant.[221] In the rare cases of polymicrobic endocarditis, coagulase-negative staphylococci are involved in approximately 50% of cases.[219] Prolonged symptoms and physical signs (fever, vascular or immunologic findings) before diagnosis are relatively common,[156] and patients often have a complicated clinical course because of embolic events, rhythm conduction abnormalities, and congestive heart failure.[191,222] At times, PCR may be helpful in defining the causative role of coagulase-negative staphylococci when cultures of blood and tissue are sterile.[223] The aortic valve is most frequently involved (70%), and more than half of these cases require valve replacement. Despite aggressive combined medical-surgical treatment, mortality continues to be approximately 25%.

Cardiovascular Implantable Electronic Devices

Cardiovascular implantable electronic device (CIED) infection (pacemakers, defibrillators) occurs in 1% to 2% of device placement procedures (see Chapter 82); coagulase-negative staphylococci (predominantly *S. epidermidis*) account for approximately 50% to 60% of these infections.[224–230] Unfortunately, the incidence of CIED infection has increased and has paralleled the increased use of implantable cardiac devices.[231] A particularly challenging subset of patients includes those with a CIED infection who also have a left ventricular assist device in place.[232,233] Infection can be limited to the pocket or can spread via intravascular leads to involve endocardial tissue. One-fourth of pacemaker infections manifest acutely within 1 month of insertion, but delays of up to 1 to 2 years are commonly observed.[231] Factors associated with increased risk of CIED infection include older age, diabetes, end-stage renal disease, chronic obstructive pulmonary disease, corticosteroid use, history of previous device infection, malignancy, heart failure, preprocedural fever, anticoagulant drug use, and skin disorders.[233] Clinically, most patients present with inflammation at the pocket site, whereas systemic symptoms are less frequently observed. Diagnosis is generally made through culture of the generator pocket, culture of the device itself, or multiple positive sequential blood cultures with the same strain of coagulase-negative staphylococci. However, only about one-third of patients with implantable cardiac device infection are bacteremic.[226,228] Transesophageal echocardiography is recommended for all patients and is much more sensitive than transthoracic echocardiography.[225,234,235] Interesting to note, coagulase-negative staphylococci can be cultured from a substantial number of explanted devices from asymptomatic patients, particularly if sonication is used.[236,237] Some of these patients go on to develop device infection with the same species, leading to the thought that the devices can be colonized without overt infection.[236] Successful treatment of implanted electrical cardiac devices generally requires complete removal of the device. Although some clinicians are reluctant to remove leads for fear of associated complications, these concerns have been minimized with use of laser extraction. Complete lead extraction can be safely achieved in more than 90% of patients with minimal risk of significant morbidity.[238] Relapse rates and mortality are substantially increased if complete removal of the device is not accomplished.[225–227, 229,235,239] A multivariate analysis demonstrated a sevenfold increase in 30-day mortality if the CIED was not removed.[234] Antibiotic therapy typically consists of vancomycin or daptomycin, with or without rifampin, continued for 14 days after device removal for patients with infection limited to the pocket and for 6 weeks for patients with bacteremia, lead involvement, or endocarditis.[234] Device reimplantation, if necessary, should be at a new site when the patient is no longer bacteremic.

Vascular Grafts

Although infection is a relatively rare complication of arterial reconstruction (<1%–6%, depending primarily on location of the graft), coagulase-negative staphylococci are one of the most common causes (20%–30%) of this feared entity.[240–242] The coagulase-negative staphylococci, usually *S. epidermidis,* causing these infections are thought to be inoculated at the time of surgery from the patient's skin. Major risk factors include a groin incision, diabetes, emergency aortic aneurysm repair, steroid therapy, and remote infections. Most cases of vascular graft infection caused by coagulase-negative staphylococci present in an indolent fashion, months to years after surgery, and manifest as a false aneurysm, fistula or sinus tract formation, or hemorrhage at the anastomotic site. Diagnosis is usually entertained on the basis of local physical findings and supported by radiographic modalities, such as CT, magnetic resonance imaging

(MRI), or ultrasonography. Blood cultures are often negative because infection may not extend to the graft lumen. Radiographic-guided aspiration of perigraft fluid can be helpful in establishing the diagnosis.[242]

Confirmation of the causative role of coagulase-negative staphylococci is maximized by sonication of the explanted graft at the time of surgery to recover biofilm-associated organisms.[243] Optimum treatment requires a combined medical and surgical approach. Intensive and prolonged antibiotic therapy is important, but surgery is required for cure. "Conservative" therapy with antibiotics and without surgery is associated with a high mortality rate and should be avoided if possible.[244] Treatment failure has been associated with antibiotic regimens that did not include rifampin.[245] Surgical strategy can be summarized as graft excision with extraanatomic bypass or graft excision with in situ reconstruction using a prosthetic conduit, allograft, or autogenous tissue. These techniques have been summarized elsewhere but are all associated with mortality of approximately 10% to 25%. As expected, in situ reconstruction is associated with less risk of amputation but an increased risk (15%–20%) of recurrent infection. There is some support for the use of antibiotic-treated or silver-coated grafts in the treatment of vascular graft infection or, similar to their application in orthopedic surgery, the placement of antibiotic-impregnated beads into the infected tissue bed.[246] A systematic review and meta-analysis of perioperative strategies to prevent infection in patients undergoing peripheral arterial reconstruction has confirmed the beneficial role of prophylactic antibiotics but did not find benefit associated with rifampin-bonded Dacron grafts, suction groin wound drainage, or perioperative bathing with antiseptic agents.[241]

Orthopedic Prosthetic Device Infections

Coagulase-negative staphylococci, usually *S. epidermidis,* are responsible for 30% to 43% of cases and are the most common cause of infection of prosthetic orthopedic devices (see Chapter 105).[247–249] These organisms are generally inoculated at the time of the arthroplasty and, because of their relatively avirulent nature, may be quite indolent in their clinical presentation. Risk factors consistently observed include previous joint surgery, perioperative wound complications, and rheumatoid arthritis.[250] Risk factors observed in some studies but not others include history of malignancy, diabetes, corticosteroid use, obesity, age, nutritional status, infection at remote site at time of surgery, psoriasis, hemophilia, sickle cell anemia, dialysis, acquired immunodeficiency syndrome (AIDS), and solid-organ transplantation. Infections can be classified as early (within 3 months of surgery and are often caused by *S. aureus*); delayed (3 months to 2 years postoperatively; most frequently caused by coagulase-negative staphylococci); and late (longer than 2 years after surgery; usually caused by hematogenous inoculation of organisms from some other source). Delayed infections caused by coagulase-negative staphylococci are usually indolent and manifest as pain at the affected joint, without fever or other systemic manifestations. The diagnosis is supported by the presence of an elevated erythrocyte sedimentation rate or CRP level.[251] Radiographic imaging studies may be helpful but are often limited by poor sensitivity and specificity or imaging artifact caused by metallic components of the implant. Labeled leukocyte scans combined with either technetium or gallium bone scans may be helpful.[251] PET scanning has been reported to offer an 82% sensitivity and 87% specificity in defining prosthetic joint infection.[252] Aspiration and synovial fluid analysis or tissue biopsy may also be helpful but can be limited by the localized nature of inflammation or infection and potential contamination. Diagnostic yield is improved by obtaining five or six periprosthetic tissue specimens for bacterial culture.[253] The recovery of organisms can be optimized by sonication of the prosthesis at the time of removal or by prolonging incubation time to 15 days.[247,254,255] In addition, PCR has proven helpful in some circumstances, but is also associated with "false-positive" results.[256] Coagulase-negative staphylococci may also be a prominent cause of culture-negative prosthetic joint infection manifesting as aseptic loosening of the joint.[257] It is thought that prior antibiotic therapy and the presence of a metabolically quiescent population of coagulase-negative staphylococci encased in biofilm may explain this condition. In addition, small colony variants are noted in approximately one-third of prosthetic joint infections caused by *S. epidermidis.*[258] Prosthetic joint infection caused by *S. epidermidis* small colony variants appear to have a more indolent presentation, but are not associated with excess treatment failure compared with infections caused by strains with a normal phenotype.[258] Finally, unsuspected prosthetic joint infection, defined by positive cultures at the time of revision surgery, is noted in a small proportion of patients undergoing repeat joint replacement surgery.[259] Such patients, undergoing knee revision, had inferior infection-free survival compared with patients with sterile cultures.[259]

Surgical management of prosthetic joint infections consists of débridement and resection of the prostheses or replacement of the prostheses in one-stage or two-stage procedures.[260] Depending on the type of surgical procedure, antibiotic therapy, usually using vancomycin directed at the methicillin-resistant strains of coagulase-negative staphylococci, lasts from 4 to 6 weeks to up to 6 months.[251,260] In two-stage procedures, the use of antibiotic spacers may improve outcome. Rifampin is recommended in combination therapy in cases of rifampin-susceptible coagulase-negative staphylococcal infection.[248,260] Success rates of 90% to 95% are noted.[261] Decreased susceptibility to vancomycin in strains of coagulase-negative staphylococci isolated from prosthetic joint infections has been noted.[262] Coagulase-negative staphylococci are also occasionally noted to cause osteomyelitis or septic joints in the absence of orthopedic devices.[263,264] There are limited data regarding treatment with vancomycin alternatives, such as linezolid, daptomycin, telavancin, ceftobiprole, or ceftaroline.[265–267] Prevention strategies include the use of laminar flow operating suites, antimicrobial prophylaxis, and antibiotic-impregnated bone cement.[268–271]

Cerebrospinal Fluid Shunt Infections

Infection is one of the most significant complications associated with CSF shunt implantation, ranging in incidence from 1.5% to 38%, but more recently occurring in approximately 5% of patients (see Chapter 92). Coagulase-negative staphylococci, most predominantly *S. epidermidis,* are the most common cause and are responsible for approximately one-third to one-half of cases.[272] Risk factors predisposing to infection include age younger than 6 months, shunt revision surgery, scalp dermatitis, long duration of procedure, proficiency of the surgeon, and intraoperative use of a neuroendoscope. One study found that in 80% of cerebral spinal fluid shunt implant procedures, the gloves of neurosurgeons and other members of the surgical team quickly became contaminated with coagulase-negative staphylococci, and the authors hypothesized that this may be the route of inoculation and infection.[273] Patients who receive a short-term ventriculostomy (external ventricular drain) are at substantial risk (approximately 10%) of developing ventriculitis or meningitis, and coagulase-negative staphylococci are the predominant pathogens,[274–276] although some reports have indicated a shift toward gram-negative pathogens.[277] The long duration of catheterization appears to be the major risk factor for infection that is not substantially modified by catheter exchange or prophylactic antibiotics. Other risk factors are intraventricular blood and previous trauma.[274] Signs and symptoms of shunt infection typically develop within 2 months of shunt insertion and should be suspected in patients with local signs of inflammation; nausea or vomiting; signs of increased intracranial pressure; or shunt malfunction. The diagnosis is confirmed by means of isolation of coagulase-negative staphylococci from CSF obtained from the shunt. PCR may prove helpful in timely identification of coagulase-negative staphylococci or other pathogens.[278] A modest pleocytosis is usually evident, accompanied by an elevated protein level. Positive blood cultures are observed in patients with infected ventriculoatrial shunts.

Most infections are caused by methicillin-resistant strains of coagulase-negative staphylococci, and combination therapy with vancomycin, gentamicin, and rifampin is a traditional regimen. Vancomycin and gentamicin are often delivered intraventricularly. Rifampin achieves excellent CSF concentration with systemic administration. Experience with newer antistaphylococcal agents, such as linezolid or daptomycin, is limited. Successful treatment usually requires shunt removal,[227] but some selected patients may be treated successfully with the shunt in situ.[272,279] In patients with coagulase-negative staphylococcal infections and normal CSF findings, reshunting can be performed on the third day after shunt removal. If CSF abnormalities are present,

7 days of therapy are generally recommended before reshunting as long as repeat CSF cultures are sterile and the CSF protein level is lower than 200 mg/dL. In a systematic review and meta-analysis of 17 trials involving 2134 patients, the administration of perioperative (24 hours) prophylactic antibiotics in CSF shunt surgery significantly decreased the risk of infection.[280] Additional reduction in infection was observed through application of strict operative aseptic technique.[281] Although most studies examining the use of antimicrobial-impregnated catheters for prevention of CSF shunt infection are not randomized trials, meta-analysis indicates a reduction in the risk of infection, but use of antibiotic-impregnated shunt catheters has been associated with inconsistent results.[282–286] There is some concern that antibiotic-impregnated extraventricular drains may result in false-negative surveillance cultures and an increased risk of infection with implantation of a permanent shunt.[287]

Ommaya reservoirs are subcutaneous devices used to deliver chemotherapy into the CSF of patients with cancer. Approximately 5% of patients with Ommaya reservoirs develop infection, and approximately 50% are caused by coagulase-negative staphylococci.[288] Treatment generally requires device removal along with systemic and intra-Ommaya administration of vancomycin. In one series, approximately 15% of patients were successfully treated with retention of the Ommaya reservoir.[288]

Surgical Site Infections

Surgical site infections caused by the coagulase-negative staphylococci occur frequently; these organisms are third only to *S. aureus* and *E. coli* as a causative agent.[289] Coagulase-negative staphylococci are more often causative of superficial incisional infections than of deep incisional infections and rarely cause organ or space infections. A notable exception is mediastinitis after median sternotomy for cardiac surgery (see Chapter 85). In addition, coagulase-negative staphylococci are more likely to cause infections involving clean procedures than those classified as contaminated (e.g., bowel, genitourinary). Superficial incisional infections generally manifest within 5 to 10 days after the procedure and usually result from inoculation of organisms from the patient's endogenous flora or, less frequently, from the operating personnel or environment. Risk factors include long duration of the surgical procedure; host factors (e.g., extremities of age, obesity, poor nutritional status); and experience of the surgeon and surgical staff. Signs and symptoms of a surgical site infection include pain, tenderness, swelling, warmth, erythema, drainage at the incisional site, leukocytosis, and fever. The causative pathogen is confirmed by recovery of coagulase-negative staphylococci from wound cultures. Culture results require careful interpretation because coagulase-negative staphylococci are commonly regarded as contaminants or colonizers. In general, coagulase-negative staphylococci are interpreted to be the causative agent of the infection if they are the predominant or only isolate from purulent drainage and/or are repeatedly cultured from the same source. Treatment depends on the severity of the infection and ranges from topical wound care alone to surgical débridement and parenteral antibiotics. Preventive measures should be emphasized, and detailed guidelines are available (see Chapter 313 and Berrios-Torres and colleagues[290]). Because many coagulase-negative staphylococcal surgical site infections are caused by strains that are resistant to traditional prophylactic antibiotics, some interest has been expressed in broader use of glycopeptide-containing regimens.[290] Other preventive strategies include use of perioperative mupirocin and antiseptic body washes.[291] Triclosan-coated sutures did not prevent coagulase-negative staphylococcal sternal wound infections.[292]

Peritoneal Dialysis Catheter–Associated Infections and Peritoneal Dialysis–Associated Peritonitis

Coagulase-negative staphylococci, accounting for 25% to 50% of cases, are the most frequent cause of peritonitis in patients undergoing peritoneal dialysis.[293] *S. epidermidis* is responsible for 50% to 80% of infections caused by coagulase-negative staphylococci, with a wide variety of other coagulase-negative staphylococcal species less frequently observed[294]; clonal spread of coagulase-negative staphylococci has been documented at some centers.[293–296] Coagulase-negative staphylococci gain access to the peritoneum from the patient's skin via the intraluminal route or from the exit site via the periluminal route. Factors for the development of peritoneal dialysis-associated peritonitis include age, diabetes, heart failure, anemia, and low serum albumin.[297] Obese patients appear to be at particular risk of peritonitis due to coagulase-negative staphylococci.[298]

Clinically, compared with infection with S. *aureus,* peritonitis caused by coagulase-negative staphylococci is relatively benign and infrequently leads to catheter removal.[299] Peritonitis caused by biofilm-producing strains of coagulase-negative staphylococci is associated with worse outcome compared with biofilm-negative strains.[299] Signs and symptoms of infection include abdominal pain and tenderness, fever, nausea, and vomiting. Diagnosis is confirmed by documentation of more than 100 white blood cells per milliliter in dialysate fluid and recovery of coagulase-negative staphylococci in cultures of the fluid. When culturing the dialysate, it is necessary to culture large volumes of fluid (>100 mL) or to use a filter technique or broth enrichment to detect small numbers of organisms. However, care must be taken because it may be difficult to differentiate contaminants from causative pathogens.[293] Although historically most of these infections were caused by methicillin-susceptible strains, the antimicrobial susceptibility pattern has recently shifted, and most causative strains are now methicillin resistant.[299,300] Treatment with vancomycin via the dialysate fluid is a relatively convenient administration method and is often successful. Recalcitrant or recurrent peritonitis is often an indication for catheter removal.[301]

Prevention of infection depends on proper catheter placement, exit site care, infusion with Y sets and twin bag systems, disconnect systems, mupirocin application at the exit site, and careful training of patients regarding aseptic practices.[302] Perioperative antibiotic prophylaxis significantly reduces the risk of early peritonitis but not exit site or tunnel infections.[303,304]

Endophthalmitis

Coagulase-negative staphylococci are readily recovered from conjunctival cultures of preophthalmologic surgery patients, and thus it is not surprising that they are the most frequent cause of postoperative endophthalmitis or infection following intravitreal injection, responsible for 33% to 70% of cases (see Chapter 114).[305–309] Symptoms typically develop within 1 week of surgery and usually consist of pain, redness, and decreased visual acuity.[310] Fever is generally absent and leukocyte count is normal. The physical examination reveals conjunctival injection and a hypopyon. Optimal treatment consists of vitrectomy and intravitreal administration of antibiotics.[311] A large proportion of coagulase-negative staphylococci causing eye infections are multidrug resistant.[312] Vancomycin is usually administered at an intravitreal dose of 1 mg, and bactericidal concentrations usually persist up to 2 to 3 days.[313] Intraocular lens removal is generally not required. Although prognosis largely depends on presenting visual acuity, residual visual impairment is frequently observed. Postinfection visual acuity is generally better preserved when the infection is due to coagulase-negative staphylococci compared with other pathogens.[310]

Urinary Tract Infection

Urinary tract infections (UTIs) caused by the coagulase-negative staphylococci fall into two major groups. The first is caused by *S. saprophyticus,* which is covered more fully in a separate section of this chapter (also see Chapter 72). The second group is uncommon and occurs almost exclusively in hospitalized patients with underlying urinary tract complications. Most of these patients have a urinary catheter in place and have recently undergone urinary tract surgery or a kidney transplantation, or they have experienced kidney stone disease or have a neurogenic bladder or obstructive uropathy. Coagulase-negative staphylococci cause approximately 3% of nosocomial UTIs, with *S. epidermidis* responsible for 90% of these isolates.[289] Additional risk factors include advanced age and extended length of hospital stay. Approximately 1% of UTIs in outpatients are caused by coagulase-negative staphylococci.[314] Infection with coagulase-negative staphylococci is associated with a lesser degree of pyuria than infection with gram-negative bacilli (mean urine leukocyte count, of 39 vs. 121 white blood cells per milliliter), and most of these patients are asymptomatic.[315] Coagulase-negative staphylococci causing

nosocomial UTIs are usually methicillin resistant, and treatment, if required, should be based on the susceptibility profile of the organism. Coagulase-negative staphylococci have also been noted as a cause of chronic prostatitis, and strains causing this condition are more frequently noted to inhibit lysozyme and platelet microbicidal protein than strains isolated from the semen of healthy men.[316]

Infections of Genitourinary Prostheses

S. epidermidis is responsible for 35% to 60% of infections of synthetic urinary sphincters and penile prostheses, in which an overall infection rate of 2% to 4% is observed.[317] Coagulase-negative staphylococcal infections of penile prostheses are often indolent and may take up to a year from the date of implantation to manifest clinically. Those with infected prostheses exhibit local pain, swelling, induration, and erythema of the penis. Occasionally fistula formation is observed, and malfunction or impairment of the device is frequent. Rarely do systemic signs of infection occur. Diagnosis is made clinically and by culture of any drainage or of the device itself. Surgical removal of the device is usually required, accompanied by 10 to 14 days of systemic antibiotics for uncomplicated infection.[318] Treatment with retention of the prosthesis has been successful in selected patients.[319] In prevention of infection, alcoholic chlorhexidine appears to be superior to povidone iodine in reduction of skin flora at the surgical site in patients undergoing genitourinary prosthetic surgery.[320] In addition to fastidious surgical technique and antibiotic prophylaxis, the use of antibiotic-coated prostheses appears promising as a means to prevent infection.[321,322]

Mastitis and Infections of Breast Implants

Although *S. aureus* is the major etiologic agent of mastitis in lactating women, coagulase-negative staphylococci may also play a role.[323] Causative strains usually produce biofilm and are antibiotic resistant. Infection associated with breast implant surgery occurs in approximately 1% to 2% of patients and is most often caused by coagulase-negative staphylococci (27%).[324–326] The rate of infection is highest in patients undergoing mastectomy and immediate tissue expander reconstruction (6%).[326] *S. epidermidis* inhabits the glandular tissue ducts of the breast and from there may gain access to the space surrounding the implant.[327] Infection may manifest acutely or may be indolent. Signs and symptoms are predominantly localized and include erythema, tenderness, pain, swelling, induration, and drainage. Acute infections are often associated with systemic findings, such as fever and leukocytosis. Diagnosis is confirmed by culture of the drainage or fluid surrounding the implant or of the implant itself. Recovery of coagulase-negative staphylococci is increased by sonication of the implant.[328] Treatment consists of antibiotic therapy and a two-stage replacement procedure.[327] Capsular contracture remains the most common complication after breast augmentation. Increasing evidence points to chronic low-grade or subclinical infection with coagulase-negative staphylococci as a cause for capsular contracture.[329] *S. epidermidis* is also seen as a cause of infection after nipple piercing and insertion of nipple rings or studs.

Miscellaneous Prosthetic Device Infections, Implant Infections, and Other Infections

Almost any biomaterial or device that is inserted or implanted across the skin or mucous membranes can become colonized or infected by coagulase-negative staphylococci. Miscellaneous devices that have been associated with infections caused by coagulase-negative staphylococci include ventricular assist devices, coronary stents, hemodialysis shunts and catheters, implantable neurologic stimulators and peripheral nerve catheters, cochlear implants, fracture fixation devices and other orthopedic implants, ureteral or urethral stents, and surgical mesh. It can be anticipated that infection caused by coagulase-negative staphylococci will parallel the increasing use of such devices.[318,330]

In recent years, a large number of infections have been characterized as biofilm associated. It is therefore not surprising that coagulase-negative staphylococci, whose chief virulence determinant is the ability to elaborate a biofilm, have been incriminated as a cause of a variety of biofilm-associated infections such as otitis, osteomyelitis, endocarditis, and chronic cystitis.

PATIENT POPULATIONS AT INCREASED RISK OF INFECTION WITH COAGULASE-NEGATIVE STAPHYLOCOCCI

Transplant Patients and Neutropenic Hosts

Solid-organ or hematopoietic stem cell transplant patients are susceptible to coagulase-negative staphylococcal infections owing to immunosuppression, intravascular catheterization, and mucosal or skin breakdown.[331,332] These infections most often manifest as an *S. epidermidis* bloodstream infection and are due to an infected intravenous catheter. However, empirical therapy directed toward coagulase-negative staphylococci is discouraged in patients with febrile neutropenia.[333,334] Mucositis and the breakdown of gastrointestinal mucosal integrity, related to cytotoxic chemotherapy or radiation therapy, may be an alternate source for coagulase-negative staphylococcal bacteremia.[335,336] The Centers for Disease Control and Prevention surveillance definition for CLA-BSI takes into account mucosal breakdown as a source for bacteremia due to coagulase-negative staphylococci and other organisms that frequently colonize mucosal membranes.[335] Cardiac transplant patients are at increased risk of sternal wound infections and mediastinitis caused by coagulase-negative staphylococci (see Chapter 85).

Neonates

Early-onset neonatal sepsis (occurring at less than 72 hours of life) is rarely due to coagulase-negative staphylococci. In contrast, late-onset neonatal sepsis is frequently caused by coagulase-negative staphylococci, and the incidence varies, depending on the degree of maturity and birth weight, from 0.6% to 14.2%.[337] Over one-half of these infections are caused by coagulase-negative staphylococci.[337–339] *S. epidermidis* accounts for 60% to 93% of the infections caused by coagulase-negative staphylococci, with lesser contributions by *S. haemolyticus, S. hominis, Staphylococcus warneri, S. saprophyticus, Staphylococcus cohnii, S. capitis,* and other species. After implementation of infection-prevention measures directed primarily at reducing intravascular catheter–associated infection, some centers have noted a dramatic fall in the incidence of neonatal sepsis due to coagulase negative staphylococci.[53]

Neonates become colonized with coagulase-negative staphylococci on their skin and in their nares, umbilicus, pharynx, and gastrointestinal tract within days of their admission to the neonatal intensive care unit (NICU), and in most cases these organisms do not originate from the mother but are acquired from the hospital environment and health care workers.[340] The neonatal gut, in particular, appears to be a niche quickly colonized by antibiotic-resistant strains of coagulase-negative staphylococci.[340–342] In one study using multiple molecular epidemiologic typing methods, 62% of NICU nurses harbored methicillin-resistant strains of coagulase-negative staphylococci that were identical to bacteremic strains.[343] Risk factors for developing coagulase-negative staphylococcal bacteremia include low birth weight, the presence and duration of use of CVCs and umbilical catheters, mechanical ventilation, and total parenteral nutrition, especially with intravenous lipid emulsions.[338,344–346]

Coagulase-negative staphylococcal bacteremia in neonates is often indolent, and signs of infection may include abdominal distention, apnea, bradycardia, inability to maintain body temperature, feeding difficulties, lethargy, neutropenia, thrombocytopenia, hyperglycemia, and metabolic acidosis.[344,345] Procalcitonin may be a more useful test in diagnosis of infection due to coagulase-negative staphylococci than CRP, white blood cell count, or immature-to-total neutrophil ratio.[339,347] Persistent bacteremia was associated with the ability to produce biofilm in one study.[348] Although most bloodstream infections occur in infants with indwelling catheters, some cases are also found when there are no intravenous catheters present. These may be the result of skin lesions or respiratory or gastrointestinal colonization by these organisms.[341] Differentiating true bacteremia from contamination is made even more difficult in neonates for several reasons, including the difficulty in obtaining blood from low-birth-weight infants, the small volume of

blood generally obtained (0.1–1 mL), and the common practice of obtaining a single sample of blood for culture to preserve blood volume.[338,349] It is usually necessary to correlate other laboratory findings along with the clinical presentation and the blood culture results to arrive at the correct diagnosis.[338] In addition to bacteremia, coagulase-negative staphylococci can also cause skin infections, pneumonia, UTIs, and meningitis in the newborn. A particularly common problem, conjunctivitis, is reported to occur in 4% to 22% of neonates.[350] Coagulase-negative staphylococci are the most frequently isolated pathogen. Erythema toxicum neonatorum, a benign self-limited eruption, may be caused by an innate immune response to coagulase-negative staphylococci that have colonized the hair follicles. Similarly, there are data associating *S. epidermidis* and neonatal necrotizing enterocolitis.[337,351] Coagulase-negative staphylococcal infections in the neonate infrequently result in mortality but are often associated with morbidity necessitating many additional days of care in the hospital while the infant receives antimicrobial therapy. Prevention of coagulase-negative staphylococcal infection in neonates has largely concentrated on prevention of intravascular catheter–associated infection. Catheters should be inserted with meticulous attention to aseptic practices. Staff should adhere to appropriate protocol in caring for the catheter site and in accessing the catheter, including thorough disinfection of the catheter connector valve or hub.[205] With some restrictions in place, usually based on gestational age, most NICUs in the United States report the use of chlorhexidine as a skin disinfectant to prevent intravascular catheter infection.[352–354] Other preventive measures have included use of prophylactic antibiotics or antimicrobial flush solutions. A meta-analysis of five randomized controlled trials that evaluated the safety and efficacy of prophylactic vancomycin in preventing late-onset sepsis in neonates has confirmed a beneficial effect.[355] However, mortality and length of stay were not significantly different between the two groups. There were insufficient data to evaluate the risk of development of vancomycin-resistant organisms. Similarly, a trial of a vancomycin-heparin catheter lock solution proved beneficial in preventing bloodstream infections.[356]

Burn Patients

Not surprisingly, burn patients have an exceptionally high rate of bloodstream infection. The rate of CLA-BSI is higher in burn units (2.9 per 1000 CVC days) than in any other surveyed unit, and methicillin-resistant coagulase-negative staphylococci are among the most frequently isolated pathogens.[194,357] These infections are associated with increased morbidity and length of hospital stay,[357–359] which emphasizes the need for scrupulous attention to CVC insertion and care guidelines.

NON–*STAPHYLOCOCCUS EPIDERMIDIS* SPECIES OF COAGULASE-NEGATIVE STAPHYLOCOCCI

In addition to *S. epidermidis,* several other species of coagulase-negative staphylococci should be specifically discussed because of their pathogenic potential and other unique features.

Staphylococcus haemolyticus

S. haemolyticus is typically the second or third most common species of coagulase-negative staphylococci to be incriminated as a cause of infection.[360,361] These infections are usually nosocomial bloodstream infections related to intravascular catheters, but skin and soft tissue infection, UTI, meningitis, endocarditis, and a variety of device-associated infections have been described.[362–365] *S. haemolyticus* has been implicated in outbreaks, most often in NICUs. Companion animals have been noted to be colonized with antibiotic-resistant strains of *S. haemolyticus.*[366] *S. haemolyticus* contains several putative virulence factors, including phenol soluble modulins.[367] Approximately 75% of clinical isolates of *S. haemolyticus* produce biofilm. The most noteworthy feature of *S. haemolyticus* is that it is often resistant to multiple antibiotics, including glycopeptides.[368,369] The glycopeptide-resistant strains possess highly cross-linked peptidoglycans with serine instead of glycine in their cross bridges. It has been suggested that *S. haemolyticus* serves as a reservoir of resistance genes for other species of staphylococci.[360] Outbreaks of infection due to linezolid-resistant strains of *S. haemolyticus* have been described.[370]

Staphylococcus lugdunensis

S. lugdunensis, first described in 1988, is a constituent of the normal human skin flora and an increasingly described human pathogen. *S. lugdunensis* behaves clinically in a manner similar to *S. aureus* and has been described to cause fulminant native valve endocarditis, endocarditis associated with implanted cardiac electrical devices, PVE, skin and soft tissue infection, adenitis, bacteremia, ocular infection, UTI, peritoneal catheter infection, central nervous system infection, bone and joint infection, and peritonitis.[10,11,371–378] When MALDI-TOF-MS is used to associate coagulase-negative species with clinical significance, 40% of *S. lugdunensis* isolates are associated with infection risk.[379] *S. lugdunensis* appears to colonize various skin and mucous membrane sites much more frequently than *S. aureus*, which may explain a propensity for *S. lugdunensis* to cause infectious complications, including endocarditis, after vasectomy.[380,381] It is thought that *S. lugdunensis* is more virulent than other coagulase-negative staphylococci because of the production of several virulence factors, including a delta toxin–like hemolytic peptide; a variety of adhesins promoting adherence to collagen, fibronectin, fibrinogen, laminin, and vitronectin; a variety of enzymes, including DNase and lipase; lysozyme resistance; and biofilm formation.[10,11,382–384] Its prominent role in native valve endocarditis may be the result of the production of a von Willebrand factor–binding protein that allows it to bind to endothelial lesions.[91] In addition, it possesses an accessory gene regulator system (*agr* locus), similar to *S. aureus.*

Identification of this species in the clinical laboratory can be difficult. *S. lugdunensis* can be easily confused with *S. aureus* if identification is based only on the latex agglutination test because the production of clumping factor by *S. lugdunensis* will yield a positive test result.[10,11] Detection of genes encoding tannase production can be used to quickly identify *S. lugdunensis.*[385] It is commonly susceptible to most antistaphylococcal antibiotics because β-lactamase production is found in only about 25% of strains, but methicillin resistance is now reported in populations (dialysis patients) commonly colonized with multidrug-resistant pathogens.[386] Infections due to *S. lugdunensis* are treated similarly to those caused by *S. aureus.* The interested reader is referred to reviews on *S. lugdunensis.*[10,11,387] Although similar putative virulence determinants that have been noted in *S. lugdunensis* have also been described in *Staphylococcus schleiferi,* this species is only rarely associated with disease in humans.[6,7] However, it appears to be a significant cause of skin disease and otitis in companion animals.[388]

Staphylococcus saprophyticus

S. saprophyticus colonizes the rectum or urogenital tracts of approximately 5% to 10% of women[314] and is a frequent causative agent of uncomplicated UTIs in young, sexually active women.[389–392] *S. saprophyticus* is only rarely implicated as a cause of UTI in men. *S. saprophyticus* UTIs in women have a seasonal predilection (late summer and fall), often follow sexual intercourse or menstruation, and may occur concomitantly with vaginal candidiasis.[393] Of patients with *S. saprophyticus* UTIs, 90% are symptomatic with dysuria, frequency, or urgency, and 80% have pyuria or hematuria. Whole-genome sequence of *S. saprophyticus* has been defined, which has allowed for greater insight into the pathogenesis of UTI.[136] *S. saprophyticus* possesses a unique adhesion protein, UafA, which allows it to adhere to human uroepithelial cells and mediates hemagglutination.[135] In addition, this bacterium encodes several transport proteins, enabling it to adjust rapidly to osmotic and pH changes, and it produces abundant urease, allowing it to proliferate in urine.[137] Data regarding the molecular epidemiology of *S. saprophyticus* remain relatively scarce, and it is unclear whether specific strains or clones are preferentially responsible for UTI.[394] Timely identification of *S. saprophyticus* can be achieved through PCR testing.[395] *S. saprophyticus* can also be differentiated from other coagulase-negative staphylococci because of its resistance to novobiocin. However, it remains susceptible to other antimicrobial agents, and *S. saprophyticus* UTIs are usually successfully treated with urinary tract antimicrobials, with only rarely reported sequelae. Rare cases of native valve endocarditis, endophthalmitis, and septicemia have been cited in the literature.

OTHER SPECIES OF COAGULASE-NEGATIVE STAPHYLOCOCCI

A large number of other species of coagulase-negative staphylococci are increasingly described as infrequent causes of human infection. Some of the more noteworthy reports include linezolid-resistant *S. cohnii, Staphylococcus kloosii,* and *Staphylococcus pettenkoferi*[396,397]; native valve endocarditis due to *Staphylococcus simulans*[398]; brain abscess due to *Staphylococcus massiliensis*[399]; a multicenter outbreak of bloodstream infections in neonates due to methicillin-resistant *S. capitis* with reduced susceptibility to vancomycin[400]; a series of orthopedic infections due to *S. warneri*[401]; meningitis caused by *S. capitis* without underlying trauma or implant[402]; and finally, an infection due to a relatively newly defined species,[396–402] *Staphylococcus petrasii.*[403] *Staphylococcus pseudintermedius* is a cause of infections in dogs but may occur in humans, usually as a skin and soft tissue infection in a dog owner.[404] However, in general, coagulase-negative staphylococci do not appear to be shared between dogs and their owners.[404] Methicillin resistance is common, and susceptibility testing using cefoxitin as a surrogate for methicillin resistance is not reliable.[405,406]

NOVEL THERAPEUTIC OPTIONS FOR INFECTIONS DUE TO COAGULASE-NEGATIVE STAPHYLOCOCCI

The increasing prevalence of multidrug-resistant *S. epidermidis* and a greater understanding of the pathogenesis of *S. epidermidis* infections and the role of biofilm have prompted investigators to explore novel therapeutic modalities.[407] Developmental agents, many of which are thought to interfere with *S. epidermidis* biofilm, include cinnamon oil,[408] ultrashort cinnamic acid peptide derivatives, cathelicidin[409] berberine,[410] furanones,[411] cationic lipopeptides, flavonoids (quercetin), pleuromutilins,[412] and various other AMPs such as short salt-resistant synthetic peptides.[408–416] Biomedical engineers continue to work on prosthetic devices that are coated or impregnated with constituents that inhibit staphylococcal adherence or proliferation.[417] Antibiofilm approaches and other innovative technologies include immunoprophylaxis (*S. epidermidis* vaccine),[418] quorum sensing interference,[417] impairment of *S. epidermidis* adhesion or biofilm accumulation,[419] immunotherapy (bacteriophage)[420] enzymatic disruption or removal of biofilm,[421] immunomodulation, and use of nanoparticles to deliver antibiofilm agents.[417–422] Some evidence indicates that other microbes produce substances that inhibit *S. epidermidis* biofilm,[423] and an extract from medicinal maggots *(Lucilia sericata)* has a strong impact on biofilm.[423,424] Similarly, a defensin derived from bedbugs appears to have antimicrobial activity against *S. epidermidis.*[425] Although some of these developments appear promising, at the present, coagulase-negative staphylococci continue to offer vexing challenges to patients, clinicians, and medical microbiologists. Unfortunately, with the increased use of medical devices, the challenge of coagulase-negative staphylococcal infections is not likely to diminish.

Key References

The complete reference list is available online at Expert Consult.

1. Grice EA, Kong HH, Conlan S, et al. Topographical and temporal diversity of the human skin microbiome. *Science*. 2009;324:1190–1192.
3. Rogers KL, Fey PD, Rupp ME. Epidemiology of infections due to coagulase-negative staphylococci. In: Crossley KB, Jefferson KK, Archer G, et al, eds. *Staphylococci in Human Disease*. 2nd ed. Chichester, West Sussex. Hoboken, NJ: Wiley-Blackwell; 2009:310–332.
6. O'Gara JP, Humphreys H. *Staphylococcus epidermidis* biofilms: importance and implications. *J Med Microbiol*. 2001;50:582–587.
7. von Eiff C, Peters G, Heilmann C. Pathogenesis of infections due to coagulase-negative staphylococci. *Lancet Infect Dis*. 2002;2:677–685.
11. Frank KL, Del Pozo JL, Patel R. From clinical microbiology to infection pathogenesis: how daring to be different works for *Staphylococcus lugdunensis*. *Clin Microbiol Rev*. 2008;21:111–133.
23. Iwase T, Uehara Y, Shinji H, et al. *Staphylococcus epidermidis* esp inhibits *Staphylococcus aureus* biofilm formation and nasal colonization. *Nature*. 2010;465:346–349.
25. Nakatsuji T, Chen TH, Narala S, et al. Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. *Sci Transl Med*. 2017;9:10.1126/scitranslmed.aah4680.
26. Paharik AE, Parlet CP, Chung N, et al. Coagulase-negative staphylococcal strain prevents *Staphylococcus aureus* colonization and skin infection by blocking quorum sensing. *Cell Host Microbe*. 2017;22:746–756.e5.
50. Becker K, Heilmann C, Peters G. Coagulase-negative staphylococci. *Clin Microbiol Rev*. 2014;27:870–926.
60. Lewis K. Persister cells, dormancy and infectious disease. *Nat Rev Microbiol*. 2007;5:48–56.
61. Fey PD. Modality of bacterial growth presents unique targets: how do we treat biofilm-mediated infections? *Curr Opin Microbiol*. 2010;13:610–615.
78. Otto M. *Staphylococcus epidermidis*–the 'accidental' pathogen. *Nat Rev Microbiol*. 2009;7:555–567.
81. Heilmann C, Schweitzer O, Gerke C, et al. Molecular basis of intercellular adhesion in the biofilm-forming *Staphylococcus epidermidis*. *Mol Microbiol*. 1996;20:1083–1091.
89. Stewart PS, Franklin MJ. Physiological heterogeneity in biofilms. *Nat Rev Microbiol*. 2008;6:199–210.
97. Heilmann C, Hussain M, Peters G, et al. Evidence for autolysin-mediated primary attachment of *Staphylococcus epidermidis* to a polystyrene surface. *Mol Microbiol*. 1997;24:1013–1024.
121. Rohde H, Burandt EC, Siemssen N, et al. Polysaccharide intercellular adhesin or protein factors in biofilm accumulation of *Staphylococcus epidermidis* and *Staphylococcus aureus* isolated from prosthetic hip and knee joint infections. *Biomaterials*. 2007;28:1711–1720.
156. Li X, Arias CA, Aitken SL, et al. Clonal emergence of invasive multidrug-resistant *Staphylococcus epidermidis* deconvoluted via a combination of whole-genome sequencing and microbiome analyses. *Clin Infect Dis*. 2018;67:398–406.
162. Hall KK, Lyman JA. Updated review of blood culture contamination. *Clin Microbiol Rev*. 2006;19:788–802.
165. Asaad AM, Ansar Qureshi M, Mujeeb Hasan S. Clinical significance of coagulase-negative staphylococci isolates from nosocomial bloodstream infections. *Infect Dis (Lond)*. 2016;48:356–360.
166. Elzi L, Babouee B, Vogeli N, et al. How to discriminate contamination from bloodstream infection due to coagulase-negative staphylococci: a prospective study with 654 patients. *Clin Microbiol Infect*. 2012;18:E355–E361.
179. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1–45.
191. Chu VH, Woods CW, Miro JM, et al. Emergence of coagulase-negative staphylococci as a cause of native valve endocarditis. *Clin Infect Dis*. 2008;46:232–242.
197. Broekhuizen CA, Schultz MJ, van der Wal AC, et al. Tissue around catheters is a niche for bacteria associated with medical device infection. *Crit Care Med*. 2008;36:2395–2402.
201. Sherertz RJ, Heard SO, Raad II. Diagnosis of triple-lumen catheter infection: comparison of roll plate, sonication, and flushing methodologies. *J Clin Microbiol*. 1997;35:641–646.
208. Raad I, Davis S, Khan A, et al. Impact of central venous catheter removal on the recurrence of catheter-related coagulase-negative staphylococcal bacteremia. *Infect Control Hosp Epidemiol*. 1992;13:215–221.
215. Karchmer AW, Archer GL, Dismukes WE. *Staphylococcus epidermidis* causing prosthetic valve endocarditis: microbiologic and clinical observations as guides to therapy. *Ann Intern Med*. 1983;98:447–455.
217. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation*. 2005;111:e394–e434.
232. Carrasco F, Anguita M, Ruiz M, et al. Clinical features and changes in epidemiology of infective endocarditis on pacemaker devices over a 27-year period (1987-2013). *Europace*. 2016;18:836–841.
247. Trampuz A, Piper KE, Jacobson MJ, et al. Sonication of removed hip and knee prostheses for diagnosis of infection. *N Engl J Med*. 2007;357:654–663.
248. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med*. 2004;351:1645–1654.
260. Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56:e1–e25.
279. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267–1284.
290. Berrios-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for disease control and prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surg*. 2017;152:784–791.
318. Darouiche RO. Treatment of infections associated with surgical implants. *N Engl J Med*. 2004;350:1422–1429.
327. Pittet B, Montandon D, Pittet D. Infection in breast implants. *Lancet Infect Dis*. 2005;5:94–106.
360. Czekaj T, Ciszewski M, Szewczyk EM. *Staphylococcus haemolyticus* - an emerging threat in the twilight of the antibiotics age. *Microbiology*. 2015;161:2061–2068.
373. Zinkernagel AS, Zinkernagel MS, Elzi MV, et al. Significance of *Staphylococcus lugdunensis* bacteremia: report of 28 cases and review of the literature. *Infection*. 2008;36:314–321.
392. Lo DS, Shieh HH, Barreira ER, et al. High frequency of *Staphylococcus saprophyticus* urinary tract infections among female adolescents. *Pediatr Infect Dis J*. 2015;34:1023–1025.

References

1. Grice EA, Kong HH, Conlan S, et al. Topographical and temporal diversity of the human skin microbiome. *Science*. 2009;324:1190–1192.
2. Rupp ME, Archer GL. Coagulase-negative staphylococci: pathogens associated with medical progress. *Clin Infect Dis*. 1994;19:231–243, quiz 244–5.
3. Rogers KL, Fey PD, Rupp ME. Epidemiology of infections due to coagulase-negative staphylococci. In: Crossley KB, Jefferson KK, Archer G, et al, eds. *Staphylococci in Human Disease*. 2nd ed. Chichester, West Sussex. Hoboken, NJ: Wiley-Blackwell; 2009:310–332.
4. Gemeinschaft L Prokaryotic nomenclature up-to-date. https://www.dsmz.de/bacterial-diversity/prokaryotic-nomenclature-up-to-date/prokaryotic-nomenclature-up-to-date.html. Accessed June 6, 2018.
5. Mack D, Horstkotte MA, Rhode H, et al. Coagulase-negative staphylococci. In: Pace JL, Rupp ME, Finch RG, eds. *Biofilms, Infection, and Antimicrobial Therapy*. Boca Raton, FL: Taylor & Francis; 2006:109–153.
6. O'Gara JP, Humphreys H. *Staphylococcus epidermidis* biofilms: importance and implications. *J Med Microbiol*. 2001;50:582–587.
7. von Eiff C, Peters G, Heilmann C. Pathogenesis of infections due to coagulase-negative staphylococci. *Lancet Infect Dis*. 2002;2:677–685.
8. Bannerman TL, Peacock SJ. *Staphylococcus, micrococcus,* and other catalase-positive cocci. In: Murray PR, Baron EJ, eds. *Manual of Clinical Microbiology*. 9th ed. Washington, D.C: ASM Press; 2007:390–411.
9. Kloos WE, Musselwhite MS. Distribution and persistence of *Staphylococcus* and *Micrococcus* species and other aerobic bacteria on human skin. *Appl Microbiol*. 1975;30:381–385.
10. Becker K, Von Eiff C. *Staphylococcus, micrococcus,* and other catalase-positive cocci. In: Versalovic J, Carroll KC, Funke G, et al, eds. *Manual of Clinical Microbiology*. 10th ed. Washington, DC: ASM Press; 2011:308–330.
11. Frank KL, Del Pozo JL, Patel R. From clinical microbiology to infection pathogenesis: how daring to be different works for *Staphylococcus lugdunensis*. *Clin Microbiol Rev*. 2008;21:111–133.
12. Zhu W, Sieradzki K, Albrecht V, et al. Evaluation of the biotyper MALDI-TOF MS system for identification of *Staphylococcus* species. *J Microbiol Methods*. 2015;117:14–17.
13. Clark AE, Kaleta EJ, Arora A, et al. Matrix-assisted laser desorption ionization-time of flight mass spectrometry: a fundamental shift in the routine practice of clinical microbiology. *Clin Microbiol Rev*. 2013;26:547–603.
14. Dubois D, Leyssene D, Chacornac JP, et al. Identification of a variety of *Staphylococcus* species by matrix-assisted laser desorption ionization-time of flight mass spectrometry. *J Clin Microbiol*. 2010;48:941–945.
15. Salimnia H, Fairfax MR, Lephart PR, et al. Evaluation of the FilmArray blood culture identification panel: results of a multicenter controlled trial. *J Clin Microbiol*. 2016;54:687–698.
16. Dierkes C, Ehrenstein B, Siebig S, et al. Clinical impact of a commercially available multiplex PCR system for rapid detection of pathogens in patients with presumed sepsis. *BMC Infect Dis*. 2009;9:126. 2334-9-126.
17. Jensen MA, Webster JA, Straus N. Rapid identification of bacteria on the basis of polymerase chain reaction-amplified ribosomal DNA spacer polymorphisms. *Appl Environ Microbiol*. 1993;59:945–952.
18. Kwok AY, Chow AW. Phylogenetic study of *Staphylococcus* and *Macrococcus* species based on partial hsp60 gene sequences. *Int J Syst Evol Microbiol*. 2003;53(Pt 1):87–92.
19. Maes N, De Gheldre Y, De Ryck R, et al. Rapid and accurate identification of *Staphylococcus* species by tRNA intergenic spacer length polymorphism analysis. *J Clin Microbiol*. 1997;35:2477–2481.
20. Naik S, Bouladoux N, Wilhelm C, et al. Compartmentalized control of skin immunity by resident commensals. *Science*. 2012;337:1115–1119.
21. Nakatsuji T, Chiang HI, Jiang SB, et al. The microbiome extends to subepidermal compartments of normal skin. *Nat Commun*. 2013;4:1431.
22. Sugimoto S, Iwamoto T, Takada K, et al. *Staphylococcus epidermidis* esp degrades specific proteins associated with *Staphylococcus aureus* biofilm formation and host-pathogen interaction. *J Bacteriol*. 2013;195:1645–1655.
23. Iwase T, Uehara Y, Shinji H, et al. *Staphylococcus epidermidis* esp inhibits *Staphylococcus aureus* biofilm formation and nasal colonization. *Nature*. 2010;465:346–349.
24. Zipperer A, Konnerth MC, Laux C, et al. Human commensals producing a novel antibiotic impair pathogen colonization. *Nature*. 2016;535:511–516.
25. Nakatsuji T, Chen TH, Narala S, et al. Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. *Sci Transl Med*. 2017;9:10.1126/scitranslmed.aah4680.
26. Paharik AE, Parlet CP, Chung N, et al. Coagulase-negative staphylococcal strain prevents *Staphylococcus aureus* colonization and skin infection by blocking quorum sensing. *Cell Host Microbe*. 2017;22:746–756.e5.
27. Seng P, Drancourt M, Gouriet F, et al. Ongoing revolution in bacteriology: routine identification of bacteria by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. *Clin Infect Dis*. 2009;49:543–551.
28. Cherkaoui A, Hibbs J, Emonet S, et al. Comparison of two matrix-assisted laser desorption ionization-time of flight mass spectrometry methods with conventional phenotypic identification for routine identification of bacteria to the species level. *J Clin Microbiol*. 2010;48:1169–1175.
29. Streit JM, Jones RN, Sader HS, et al. Assessment of pathogen occurrences and resistance profiles among infected patients in the intensive care unit: report from the SENTRY antimicrobial surveillance program (north america, 2001). *Int J Antimicrob Agents*. 2004;24:111–118.
30. Jones RN, Ross JE, Castanheira M, et al. United states resistance surveillance results for linezolid (LEADER program for 2007). *Diagn Microbiol Infect Dis*. 2008;62:416–426.
31. Hope R, Livermore DM, Brick G, et al; BSAC Working Parties on Resistance Surveillance. Non-susceptibility trends among staphylococci from bacteraemias in the UK and ireland, 2001-06. *J Antimicrob Chemother*. 2008;62(suppl 2):ii65–ii74.
32. Karlowsky JA, Adam HJ, Poutanen SM, et al; Canadian Antimicrobial Resistance Alliance (CARA). In vitro activity of dalbavancin and telavancin against staphylococci and streptococci isolated from patients in Canadian hospitals: results of the CANWARD 2007-2009 study. *Diagn Microbiol Infect Dis*. 2011;69:342–347.
33. Draghi DC, Sheehan DJ, Hogan P, et al. In vitro activity of linezolid against key gram-positive organisms isolated in the united states: results of the LEADER 2004 surveillance program. *Antimicrob Agents Chemother*. 2005;49:5024–5032.
34. Stuart JI, John MA, Milburn S, et al. Susceptibility patterns of coagulase-negative staphylococci to several newer antimicrobial agents in comparison with vancomycin and oxacillin. *Int J Antimicrob Agents*. 2011;37:248–252.
35. Arhin FF, Draghi DC, Pillar CM, et al. Comparative in vitro activity profile of oritavancin against recent gram-positive clinical isolates. *Antimicrob Agents Chemother*. 2009;53:4762–4771.
36. Perez F, Salata RA, Bonomo RA. Current and novel antibiotics against resistant gram-positive bacteria. *Infect Drug Resist*. 2008;1:27–44.
37. Fritsche TR, Sader HS, Jones RN. Antimicrobial activity of ceftobiprole, a novel anti-methicillin-resistant *Staphylococcus aureus* cephalosporin, tested against contemporary pathogens: results from the SENTRY antimicrobial surveillance program (2005-2006). *Diagn Microbiol Infect Dis*. 2008;61:86–95.
38. Durkin MJ, Corey GR. New developments in the management of severe skin and deep skin structure infections - focus on tedizolid. *Ther Clin Risk Manag*. 2015;11:857–862.
39. Tattevin P, Boutoille D, Vitrat V, et al. Salvage treatment of methicillin-resistant staphylococcal endocarditis with ceftaroline: a multicentre observational study. *J Antimicrob Chemother*. 2014;69:2010–2013.
40. Cidral TA, Carvalho MC, Figueiredo AM, et al. Emergence of methicillin-resistant coagulase-negative staphylococci resistant to linezolid with rRNA gene C2190T and G2603T mutations. *APMIS*. 2015;123:867–871.
41. Wessels C, Strommenger B, Klare I, et al. Emergence and control of linezolid-resistant *Staphylococcus epidermidis* in an ICU of a german hospital. *J Antimicrob Chemother*. 2018;73:1185–1193.
42. Layer F, Vourli S, Karavasilis V, et al. Dissemination of linezolid-dependent, linezolid-resistant *Staphylococcus epidermidis* clinical isolates belonging to CC5 in german hospitals. *J Antimicrob Chemother*. 2018;73:1181–1184.
43. Sader HS, Farrell DJ, Flamm RK, et al. Antimicrobial activity of ceftaroline and comparator agents when tested against numerous species of coagulase-negative *Staphylococcus* causing infection in US hospitals. *Diagn Microbiol Infect Dis*. 2016;85:80–84.
44. Sader HS, Castanheira M, Farrell DJ, et al. Tigecycline antimicrobial activity tested against clinical bacteria from Latin American medical centres: results from SENTRY antimicrobial surveillance program (2011-2014). *Int J Antimicrob Agents*. 2016;48:144–150.
45. Bensaci M, Sahm D. Surveillance of tedizolid activity and resistance: in vitro susceptibility of gram-positive pathogens collected over 5 years from the united states and Europe. *Diagn Microbiol Infect Dis*. 2017;87:133–138.
46. Sieradzki K, Villari P, Tomasz A. Decreased susceptibilities to teicoplanin and vancomycin among coagulase-negative methicillin-resistant clinical isolates of staphylococci. *Antimicrob Agents Chemother*. 1998;42:100–107.
47. Sieradzki K, Roberts RB, Serur D, et al. Heterogeneously vancomycin-resistant *Staphylococcus epidermidis* strain causing recurrent peritonitis in a dialysis patient during vancomycin therapy. *J Clin Microbiol*. 1999;37:39–44.
48. Nunes AP, Teixeira LM, Iorio NL, et al. Heterogeneous resistance to vancomycin in *Staphylococcus epidermidis, Staphylococcus haemolyticus* and *Staphylococcus warneri* clinical strains: characterisation of glycopeptide susceptibility profiles and cell wall thickening. *Int J Antimicrob Agents*. 2006;27:307–315.
49. Froggatt JW, Johnston JL, Galetto DW, et al. Antimicrobial resistance in nosocomial isolates of *Staphylococcus haemolyticus*. *Antimicrob Agents Chemother*. 1989;33:460–466.
50. Becker K, Heilmann C, Peters G. Coagulase-negative staphylococci. *Clin Microbiol Rev*. 2014;27:870–926.
51. Berglund B, Claesson C, Nilsson LE, et al. High prevalence of heterogeneously glycopeptide-intermediate coagulase-negative staphylococci in sternal wounds. *Antimicrob Agents Chemother*. 2016;60:5097–5098.
52. Chong J, Quach C, Blanchard AC, et al. Molecular epidemiology of a vancomycin-intermediate heteroresistant *Staphylococcus epidermidis* outbreak in a neonatal intensive care unit. *Antimicrob Agents Chemother*. 2016;60:5673–5681.
53. Bizzarro MJ, Shabanova V, Baltimore RS, et al. Neonatal sepsis 2004-2013: the rise and fall of coagulase-negative staphylococci. *J Pediatr*. 2015;166:1193–1199.
54. Clinical and Laboratory Standards Institute: Performance standards for antimicrobial susceptibility testing: twenty-third information supplement. Clinical and Laboratory Standards Institute (CLSI). 2013;CLSI Document M100-MS23.
55. Vazquez GJ, Archer GL. Antibiotic therapy of experimental *Staphylococcus epidermidis* endocarditis. *Antimicrob Agents Chemother*. 1980;17:280–285.
56. Prere MF, Baron O, Cohen Bacrie S, et al. Genotype MRSA, a new genetic test for the rapid identification of staphylococci and detection of mecA gene. *Pathol Biol (Paris)*. 2006;54:502–505.
57. Knausz M, Ghidan A, Grossato A, et al. Rapid detection of methicillin resistance in teicoplanin-resistant coagulase-negative staphylococci by a penicillin-binding protein 2' latex agglutination method. *J Microbiol Methods*. 2005;60:413–416.
58. Frye AM, Baker CA, Rustvold DL, et al. Clinical impact of a real-time PCR assay for rapid identification of staphylococcal bacteremia. *J Clin Microbiol*. 2012;50:127–133.
59. Arroyo MA, Denys GA. Parallel evaluation of the MALDI sepsityper and verigene BC-GN assays for rapid identification of gram-negative bacilli from positive blood cultures. *J Clin Microbiol*. 2017;55:2708–2718.
60. Lewis K. Persister cells, dormancy and infectious disease. *Nat Rev Microbiol*. 2007;5:48–56.
61. Fey PD. Modality of bacterial growth presents unique targets: how do we treat biofilm-mediated infections? *Curr Opin Microbiol*. 2010;13:610–615.
62. Saginur R, Stdenis M, Ferris W, et al. Multiple combination bactericidal testing of staphylococcal biofilms from implant-associated infections. *Antimicrob Agents Chemother*. 2006;50:55–61.
63. Olson ME, Slater SR, Rupp ME, et al. Rifampicin enhances activity of daptomycin and vancomycin against both a polysaccharide intercellular adhesin (PIA)-dependent and -independent *Staphylococcus epidermidis* biofilm. *J Antimicrob Chemother*. 2010;65:2164–2171.
64. Dominguez-Herrera J, Docobo-Perez F, Lopez-Rojas R, et al. Efficacy of daptomycin versus vancomycin in an experimental model of foreign-body and systemic infection caused by biofilm producers and methicillin-resistant *Staphylococcus epidermidis*. *Antimicrob Agents Chemother*. 2012;56:613–617.
65. Thurlow LR, Hanke ML, Fritz T, et al. *Staphylococcus aureus* biofilms prevent macrophage phagocytosis and attenuate inflammation in vivo. *J Immunol*. 2011;186:6585–6596.
66. Heim CE, Vidlak D, Odvody J, et al. Human prosthetic joint infections are associated with myeloid-derived suppressor cells (MDSCs): implications for infection persistence. *J Orthop Res*. 2018;36:1605–1613.

67. Hanke ML, Heim CE, Angle A, et al. Targeting macrophage activation for the prevention and treatment of *Staphylococcus aureus* biofilm infections. *J Immunol*. 2013;190:2159–2168.
68. Miragaia M, Carrico JA, Thomas JC, et al. Comparison of molecular typing methods for characterization of *Staphylococcus epidermidis*: proposal for clone definition. *J Clin Microbiol*. 2008;46:118–129.
69. Jamaluddin TZ, Kuwahara-Arai K, Hisata K, et al. Extreme genetic diversity of methicillin-resistant *Staphylococcus epidermidis* strains disseminated among healthy Japanese children. *J Clin Microbiol*. 2008;46:3778–3783.
70. Miragaia M, Thomas JC, Couto I, et al. Inferring a population structure for *Staphylococcus epidermidis* from multilocus sequence typing data. *J Bacteriol*. 2007;189:2540–2552.
71. Wisplinghoff H, Rosato AE, Enright MC, et al. Related clones containing SCCmec type IV predominate among clinically significant *Staphylococcus epidermidis* isolates. *Antimicrob Agents Chemother*. 2003;47:3574–3579.
72. Kozitskaya S, Olson ME, Fey PD, et al. Clonal analysis of *Staphylococcus epidermidis* isolates carrying or lacking biofilm-mediating genes by multilocus sequence typing. *J Clin Microbiol*. 2005;43:4751–4757.
73. Wang XM, Noble L, Kreiswirth BN, et al. Evaluation of a multilocus sequence typing system for *Staphylococcus epidermidis*. *J Med Microbiol*. 2003;52(Pt 11):989–998.
74. Thomas JC, Vargas MR, Miragaia M, et al. Improved multilocus sequence typing scheme for *Staphylococcus epidermidis*. *J Clin Microbiol*. 2007;45:616–619.
75. Tolo I, Thomas JC, Fischer RSB, et al. Do *Staphylococcus epidermidis* genetic clusters predict isolation sources? *J Clin Microbiol*. 2016;54:1711–1719.
76. Johansson A, Koskiniemi S, Gottfridsson P, et al. Multiple-locus variable-number tandem repeat analysis for typing of *Staphylococcus epidermidis*. *J Clin Microbiol*. 2006;44:260–265.
77. Francois P, Hochmann A, Huyghe A, et al. Rapid and high-throughput genotyping of *Staphylococcus epidermidis* isolates by automated multilocus variable-number of tandem repeats: a tool for real-time epidemiology. *J Microbiol Methods*. 2008;72:296–305.
78. Otto M. *Staphylococcus epidermidis*–the 'accidental' pathogen. *Nat Rev Microbiol*. 2009;7:555–567.
79. Rupp ME, Ulphani JS, Fey PD, et al. Characterization of *Staphylococcus epidermidis* polysaccharide intercellular adhesin/hemagglutinin in the pathogenesis of intravascular catheter-associated infection in a rat model. *Infect Immun*. 1999;67:2656–2659.
80. Rupp ME, Ulphani JS, Fey PD, et al. Characterization of the importance of polysaccharide intercellular adhesin/hemagglutinin of *Staphylococcus epidermidis* in the pathogenesis of biomaterial-based infection in a mouse foreign body infection model. *Infect Immun*. 1999;67:2627–2632.
81. Heilmann C, Schweitzer O, Gerke C, et al. Molecular basis of intercellular adhesion in the biofilm-forming *Staphylococcus epidermidis*. *Mol Microbiol*. 1996;20:1083–1091.
82. Kocianova S, Vuong C, Yao Y, et al. Key role of poly-gamma-DL-glutamic acid in immune evasion and virulence of *Staphylococcus epidermidis*. *J Clin Invest*. 2005;115:688–694.
83. Vuong C, Durr M, Carmody AB, et al. Regulated expression of pathogen-associated molecular pattern molecules in *Staphylococcus epidermidis*: quorum-sensing determines pro-inflammatory capacity and production of phenol-soluble modulins. *Cell Microbiol*. 2004;6:753–759.
84. Qin L, Da F, Fisher EL, et al. Toxin mediated sepsis caused by methicillin-resistant *Staphylococcus epidermidis*. *PLOS Path*. 2017;13:e1006153.
85. Moormeier DE, Bose JL, Horswill AR, et al. Temporal and stochastic control of *Staphylococcus aureus* biofilm development. *MBio*. 2014;5:e01341-14.
86. Resch A, Rosenstein R, Nerz C, et al. Differential gene expression profiling of *Staphylococcus aureus* cultivated under biofilm and planktonic conditions. *Appl Environ Microbiol*. 2005;71:2663–2676.
87. Yao Y, Sturdevant DE, Otto M. Genomewide analysis of gene expression in *Staphylococcus epidermidis* biofilms: insights into the pathophysiology of S. epidermidis biofilms and the role of phenol-soluble modulins in formation of biofilms. *J Infect Dis*. 2005;191:289–298.
88. Beenken KE, Dunman PM, McAleese F, et al. Global gene expression in *Staphylococcus aureus* biofilms. *J Bacteriol*. 2004;186:4665–4684.
89. Stewart PS, Franklin MJ. Physiological heterogeneity in biofilms. *Nat Rev Microbiol*. 2008;6:199–210.
90. Zhang YQ, Ren SX, Li HL, et al. Genome-based analysis of virulence genes in a non-biofilm-forming *Staphylococcus epidermidis* strain (ATCC 12228). *Mol Microbiol*. 2003;49:1577–1593.
91. Nilsson M, Bjerketorp J, Guss B, et al. A fibrinogen-binding protein of *Staphylococcus lugdunensis*. *FEMS Microbiol Lett*. 2004;241:87–93.
92. Hartford O, O'Brien L, Schofield K, et al. The fbe (SdrG) protein of *Staphylococcus epidermidis* HB promotes bacterial adherence to fibrinogen. *Microbiology*. 2001;147(Pt 9):2545–2552.
93. Gill SR, Fouts DE, Archer GL, et al. Insights on evolution of virulence and resistance from the complete genome analysis of an early methicillin-resistant *Staphylococcus aureus* strain and a biofilm-producing methicillin-resistant *Staphylococcus epidermidis* strain. *J Bacteriol*. 2005;187:2426–2438.
94. Bowden MG, Visai L, Longshaw CM, et al. Is the GehD lipase from *Staphylococcus epidermidis* a collagen binding adhesin? *J Biol Chem*. 2002;277:43017–43023.
95. Bowden MG, Heuck AP, Ponnuraj K, et al. Evidence for the "dock, lock, and latch" ligand binding mechanism of the staphylococcal microbial surface component recognizing adhesive matrix molecules (MSCRAMM) SdrG. *J Biol Chem*. 2008;283:638–647.
96. Heilmann C, Thumm G, Chhatwal GS, et al. Identification and characterization of a novel autolysin (aae) with adhesive properties from *Staphylococcus epidermidis*. *Microbiology*. 2003;149(Pt 10):2769–2778.
97. Heilmann C, Hussain M, Peters G, et al. Evidence for autolysin-mediated primary attachment of *Staphylococcus epidermidis* to a polystyrene surface. *Mol Microbiol*. 1997;24:1013–1024.
98. Rupp ME, Fey PD, Heilmann C, et al. Characterization of the importance of *Staphylococcus epidermidis* autolysin and polysaccharide intercellular adhesin in the pathogenesis of intravascular catheter-associated infection in a rat model. *J Infect Dis*. 2001;183:1038–1042.
99. Guo B, Zhao X, Shi Y, et al. Pathogenic implication of a fibrinogen-binding protein of *Staphylococcus epidermidis* in a rat model of intravascular-catheter-associated infection. *Infect Immun*. 2007;75:2991–2995.
100. Schaeffer CR, Woods KM, Longo GM, et al. Accumulation-associated protein enhances *Staphylococcus epidermidis* biofilm formation under dynamic conditions and is required for infection in a rat catheter model. *Infect Immun*. 2015;83:214–226.
101. Conlon BP, Geoghegan JA, Waters EM, et al. Role for the A domain of unprocessed accumulation-associated protein (aap) in the attachment phase of the *Staphylococcus epidermidis* biofilm phenotype. *J Bacteriol*. 2014;196:4268–4275.
102. Paharik AE, Kotasinska M, Both A, et al. The metalloprotease SepA governs processing of accumulation-associated protein and shapes intercellular adhesive surface properties in *Staphylococcus epidermidis*. *Mol Microbiol*. 2017;103:860–874.
103. Rice KC, Mann EE, Endres JL, et al. The cidA murein hydrolase regulator contributes to DNA release and biofilm development in *Staphylococcus aureus*. *Proc Natl Acad Sci USA*. 2007;104:8113–8118.
104. Schaeffer CR, Hoang TN, Sudbeck CM, et al. Versatility of biofilm matrix molecules in *Staphylococcus epidermidis* clinical isolates and importance of polysaccharide intercellular adhesin expression during high shear stress. *mSphere*. 2016;1:10.1128/mSphere.00165-16. eCollection 2016 Sep-Oct.
105. Izano EA, Amarante MA, Kher WB, et al. Differential roles of poly-N-acetylglucosamine surface polysaccharide and extracellular DNA in *Staphylococcus aureus* and *Staphylococcus epidermidis* biofilms. *Appl Environ Microbiol*. 2008;74:470–476.
106. Mack D, Fischer W, Krokotsch A, et al. The intercellular adhesin involved in biofilm accumulation of *Staphylococcus epidermidis* is a linear beta-1,6-linked glucosaminoglycan: purification and structural analysis. *J Bacteriol*. 1996;178:175–183.
107. Conlon KM, Humphreys H, O'Gara JP. Regulation of icaR gene expression in *Staphylococcus epidermidis*. *FEMS Microbiol Lett*. 2002;216:171–177.
108. Vuong C, Kocianova S, Voyich JM, et al. A crucial role for exopolysaccharide modification in bacterial biofilm formation, immune evasion, and virulence. *J Biol Chem*. 2004;279:54881–54886.
109. Gotz F. *Staphylococcus* and biofilms. *Mol Microbiol*. 2002;43:1367–1378.
110. Xu L, Li H, Vuong C, et al. Role of the luxS quorum-sensing system in biofilm formation and virulence of *Staphylococcus epidermidis*. *Infect Immun*. 2006;74:488–496.
111. Wang L, Li M, Dong D, et al. SarZ is a key regulator of biofilm formation and virulence in *Staphylococcus epidermidis*. *J Infect Dis*. 2008;197:1254–1262.
112. Vuong C, Kidder JB, Jacobson ER, et al. *Staphylococcus epidermidis* polysaccharide intercellular adhesin production significantly increases during tricarboxylic acid cycle stress. *J Bacteriol*. 2005;187:2967–2973.
113. Tormo MA, Marti M, Valle J, et al. SarA is an essential positive regulator of *Staphylococcus epidermidis* biofilm development. *J Bacteriol*. 2005;187:2348–2356.
114. Jefferson KK, Cramton SE, Gotz F, et al. Identification of a 5-nucleotide sequence that controls expression of the ica locus in *Staphylococcus aureus* and characterization of the DNA-binding properties of IcaR. *Mol Microbiol*. 2003;48:889–899.
115. Handke LD, Slater SR, Conlon KM, et al. SigmaB and SarA independently regulate polysaccharide intercellular adhesin production in *Staphylococcus epidermidis*. *Can J Microbiol*. 2007;53:82–91.
116. Conlon KM, Humphreys H, O'Gara JP. icaR encodes a transcriptional repressor involved in environmental regulation of ica operon expression and biofilm formation in *Staphylococcus epidermidis*. *J Bacteriol*. 2002;184:4400–4408.
117. McKenney D, Pouliot KL, Wang Y, et al. Broadly protective vaccine for *Staphylococcus aureus* based on an in vivo-expressed antigen. *Science*. 1999;284:1523–1527.
118. Kelly-Quintos C, Cavacini LA, Posner MR, et al. Characterization of the opsonic and protective activity against *Staphylococcus aureus* of fully human monoclonal antibodies specific for the bacterial surface polysaccharide poly-N-acetylglucosamine. *Infect Immun*. 2006;74:2742–2750.
119. Kropec A, Maira-Litran T, Jefferson KK, et al. Poly-N-acetylglucosamine production in *Staphylococcus aureus* is essential for virulence in murine models of systemic infection. *Infect Immun*. 2005;73:6868–6876.
120. Cerca N, Maira-Litran T, Jefferson KK, et al. Protection against *Escherichia coli* infection by antibody to the *Staphylococcus aureus* poly-N-acetylglucosamine surface polysaccharide. *Proc Natl Acad Sci USA*. 2007;104:7528–7533.
121. Rohde H, Burandt EC, Siemssen N, et al. Polysaccharide intercellular adhesin or protein factors in biofilm accumulation of *Staphylococcus epidermidis* and *Staphylococcus aureus* isolated from prosthetic hip and knee joint infections. *Biomaterials*. 2007;28:1711–1720.
122. Rohde H, Kalitzky M, Kroger N, et al. Detection of virulence-associated genes not useful for discriminating between invasive and commensal *Staphylococcus epidermidis* strains from a bone marrow transplant unit. *J Clin Microbiol*. 2004;42:5614–5619.
123. Cucarella C, Solano C, Valle J, et al. Bap, a *Staphylococcus aureus* surface protein involved in biofilm formation. *J Bacteriol*. 2001;183:2888–2896.
124. Christner M, Franke GC, Schommer NN, et al. The giant extracellular matrix-binding protein of *Staphylococcus epidermidis* mediates biofilm accumulation and attachment to fibronectin. *Mol Microbiol*. 2010;75:187–207.
125. Rogers KL, Rupp ME, Fey PD. The presence of icaADBC is detrimental to the colonization of human skin by *Staphylococcus epidermidis*. *Appl Environ Microbiol*. 2008;74:6155–6157.
126. Wang R, Braughton KR, Kretschmer D, et al. Identification of novel cytolytic peptides as key virulence determinants for community-associated MRSA. *Nat Med*. 2007;13:1510–1514.
127. Otto M, O'Mahoney DS, Guina T, et al. Activity of *Staphylococcus epidermidis* phenol-soluble modulin peptides expressed in *Staphylococcus carnosus*. *J Infect Dis*. 2004;190:748–755.
128. Cheung GY, Joo HS, Chatterjee SS, et al. Phenol-soluble modulins–critical determinants of staphylococcal virulence. *FEMS Microbiol Rev*. 2014;38:698–719.
129. Qin L, Da F, Fisher EL, et al. Toxin mediates sepsis caused by methicillin-resistant *Staphylococcus epidermidis*. *PLoS Pathog*. 2017;13:e1006153.
130. Mehlin C, Headley CM, Klebanoff SJ. An inflammatory polypeptide complex from *Staphylococcus epidermidis*: isolation and characterization. *J Exp Med*. 1999;189:907–918.
131. Little SF, Ivins BE. Molecular pathogenesis of *Bacillus anthracis* infection. *Microbes Infect*. 1999;1:131–139.
132. Vuong C, Voyich JM, Fischer ER, et al. Polysaccharide intercellular adhesin (PIA) protects *Staphylococcus epidermidis* against major components of the human innate immune system. *Cell Microbiol*. 2004;6:269–275.
133. Li M, Lai Y, Villaruz AE, et al. Gram-positive three-component antimicrobial peptide-sensing system. *Proc Natl Acad Sci USA*. 2007;104:9469–9474.
134. Kupke T, Gotz F. Expression, purification, and characterization of EpiC, an enzyme involved in the biosynthesis of the lantibiotic epidermin, and sequence analysis of *Staphylococcus epidermidis* epiC mutants. *J Bacteriol*. 1996;178:1335–1340.
135. Szabados F, Kleine B, Anders A, et al. *Staphylococcus saprophyticus* ATCC 15305 is internalized into human urinary bladder carcinoma cell line 5637. *FEMS Microbiol Lett*. 2008;285:163–169.

136. Kuroda M, Yamashita A, Hirakawa H, et al. Whole genome sequence of *Staphylococcus saprophyticus* reveals the pathogenesis of uncomplicated urinary tract infection. *Proc Natl Acad Sci USA*. 2005;102:13272–13277.
137. Hell W, Meyer HG, Gatermann SG. Cloning of aas, a gene encoding a *Staphylococcus saprophyticus* surface protein with adhesive and autolytic properties. *Mol Microbiol*. 1998;29:871–881.
138. Gatermann S, Marre R. Cloning and expression of *Staphylococcus saprophyticus* urease gene sequences in *Staphylococcus carnosus* and contribution of the enzyme to virulence. *Infect Immun*. 1989;57:2998–3002.
139. Nilsson M, Bjerketorp J, Wiebensjo A, et al. A von Willebrand factor-binding protein from *Staphylococcus lugdunensis*. *FEMS Microbiol Lett*. 2004;234:155–161.
140. Mitchell J, Tristan A, Foster TJ. Characterization of the fibrinogen-binding surface protein fbl of *Staphylococcus lugdunensis*. *Microbiology*. 2004;150(Pt 11):3831–3841.
141. Minhas T, Ludlam HA, Wilks M, et al. Detection by PCR and analysis of the distribution of a fibronectin-binding protein gene (fbn) among staphylococcal isolates. *J Med Microbiol*. 1995;42:96–101.
142. Barbier F, Lebeaux D, Hernandez D, et al. High prevalence of the arginine catabolic mobile element in carriage isolates of methicillin-resistant *Staphylococcus epidermidis*. *J Antimicrob Chemother*. 2011;66:29–36.
143. Neely AN, Maley MP. Survival of enterococci and staphylococci on hospital fabrics and plastic. *J Clin Microbiol*. 2000;38:724–726.
144. Sidhu MS, Heir E, Leegaard T, et al. Frequency of disinfectant resistance genes and genetic linkage with beta-lactamase transposon Tn552 among clinical staphylococci. *Antimicrob Agents Chemother*. 2002;46:2797–2803.
145. Frank DN, Feazel LM, Bessesen MT, et al. The human nasal microbiota and *Staphylococcus aureus* carriage. *PLoS ONE*. 2010;5:e10598.
146. Cogen AL, Yamasaki K, Sanchez KM, et al. Selective antimicrobial action is provided by phenol-soluble modulins derived from *Staphylococcus epidermidis*, a normal resident of the skin. *J Invest Dermatol*. 2010;130:192–200.
147. Ahlstrand E, Persson L, Tidefelt U, et al. Alteration of the colonization pattern of coagulase-negative staphylococci in patients undergoing treatment for hematological malignancy. *Eur J Clin Microbiol Infect Dis*. 2012;31:1679–1687.
148. Zingg W, Demartines N, Imhof A, et al. Rapid colonization with methicillin-resistant coagulase-negative staphylococci after surgery. *World J Surg*. 2009;33:2058–2062.
149. Huebner J, Pier GB, Maslow JN, et al. Endemic nosocomial transmission of *Staphylococcus epidermidis* bacteremia isolates in a neonatal intensive care unit over 10 years. *J Infect Dis*. 1994;169:526–531.
150. Krediet TG, Mascini EM, van Rooij E, et al. Molecular epidemiology of coagulase-negative staphylococci causing sepsis in a neonatal intensive care unit over an 11-year period. *J Clin Microbiol*. 2004;42:992–995.
151. Hira V, Sluijter M, Goessens WH, et al. Coagulase-negative staphylococcal skin carriage among neonatal intensive care unit personnel: from population to infection. *J Clin Microbiol*. 2010;48:3876–3881.
152. Agvald-Ohman C, Lund B, Edlund C. Multiresistant coagulase-negative staphylococci disseminate frequently between intubated patients in a multidisciplinary intensive care unit. *Crit Care*. 2004;8:R42–R47.
153. Widerstrom M, Monsen T, Karlsson C, et al. Molecular epidemiology of meticillin-resistant coagulase-negative staphylococci in a Swedish county hospital: evidence of intra- and interhospital clonal spread. *J Hosp Infect*. 2006;64:177–183.
154. Gordon RJ, Miragaia M, Weinberg AD, et al. *Staphylococcus epidermidis* colonization is highly clonal across US cardiac centers. *J Infect Dis*. 2012;205:1391–1398.
155. Widerstrom M, Monsen T, Karlsson C, et al. Clonality among multidrug-resistant hospital-associated *Staphylococcus epidermidis* in northern Europe. *Scand J Infect Dis*. 2009;41:642–649.
156. Li X, Arias CA, Aitken SL, et al. Clonal emergence of invasive multidrug-resistant *Staphylococcus epidermidis* deconvoluted via a combination of whole-genome sequencing and microbiome analyses. *Clin Infect Dis*. 2018;67:398–406.
157. Botelho AM, Nunes Z, Asensi MD, et al. Characterization of coagulase-negative staphylococci isolated from hospital indoor air and a comparative analysis between airborne and inpatient isolates of *Staphylococcus epidermidis*. *J Med Microbiol*. 2012;61(Pt 8):1136–1145.
158. Svensson K, Hellmark B, Soderquist B. Characterization of SCCmec elements in methicillin-resistant *Staphylococcus epidermidis* isolated from blood cultures from neonates during three decades. *APMIS*. 2011;119:885–893.
159. Hanssen AM, Kjeldsen G, Sollid JU. Local variants of staphylococcal cassette chromosome mec in sporadic methicillin-resistant *Staphylococcus aureus* and methicillin-resistant coagulase-negative staphylococci: evidence of horizontal gene transfer? *Antimicrob Agents Chemother*. 2004;48:285–296.
160. Schoenfelder SM, Lange C, Eckart M, et al. Success through diversity - how *Staphylococcus epidermidis* establishes as a nosocomial pathogen. *Int J Med Microbiol*. 2010;300:380–386.
161. Weinstein MP, Towns ML, Quartey SM, et al. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. *Clin Infect Dis*. 1997;24:584–602.
162. Hall KK, Lyman JA. Updated review of blood culture contamination. *Clin Microbiol Rev*. 2006;19:788–802.
163. Pien BC, Sundaram P, Raoof N, et al. The clinical and prognostic importance of positive blood cultures in adults. *Am J Med*. 2010;123:819–828.
164. Souvenir D, Anderson DE Jr, Palpant S, et al. Blood cultures positive for coagulase-negative staphylococci: antisepsis, pseudobacteremia, and therapy of patients. *J Clin Microbiol*. 1998;36:1923–1926.
165. Asaad AM, Ansar Qureshi M, Mujeeb Hasan S. Clinical significance of coagulase-negative staphylococci isolates from nosocomial bloodstream infections. *Infect Dis (Lond)*. 2016;48:356–360.
166. Elzi L, Babouee B, Vogeli N, et al. How to discriminate contamination from bloodstream infection due to coagulase-negative staphylococci: a prospective study with 654 patients. *Clin Microbiol Infect*. 2012;18:E355–E361.
167. Garcia-Vazquez E, Fernandez-Rufete A, Hernandez-Torres A, et al. When is coagulase-negative *Staphylococcus* bacteraemia clinically significant? *Scand J Infect Dis*. 2013;45:664–671.
168. van der Heijden YF, Miller G, Wright PW, et al. Clinical impact of blood cultures contaminated with coagulase-negative staphylococci at an academic medical center. *Infect Control Hosp Epidemiol*. 2011;32:623–625.
169. Beekmann SE, Diekema DJ, Doern GV. Determining the clinical significance of coagulase-negative staphylococci isolated from blood cultures. *Infect Control Hosp Epidemiol*. 2005;26:559–566.
170. Shafazand S, Weinacker AB. Blood cultures in the critical care unit: improving utilization and yield. *Chest*. 2002;122:1727–1736.
171. Rahkonen M, Luttinen S, Koskela M, et al. True bacteremias caused by coagulase negative *Staphylococcus* are difficult to distinguish from blood culture contaminants. *Eur J Clin Microbiol Infect Dis*. 2012;31:2639–2644.
172. Tokars JI. Predictive value of blood cultures positive for coagulase-negative staphylococci: implications for patient care and health care quality assurance. *Clin Infect Dis*. 2004;39:333–341.
173. Mirrett S, Weinstein MP, Reimer LG, et al. Relevance of the number of positive bottles in determining clinical significance of coagulase-negative staphylococci in blood cultures. *J Clin Microbiol*. 2001;39:3279–3281.
174. Leyssene D, Gardes S, Vilquin P, et al. Species-driven interpretation guidelines in case of a single-sampling strategy for blood culture. *Eur J Clin Microbiol Infect Dis*. 2011;30:1537–1541.
175. Seybold U, Reichardt C, Halvosa JS, et al. Clonal diversity in episodes with multiple coagulase-negative *Staphylococcus* bloodstream isolates suggesting frequent contamination. *Infection*. 2009;37:256–260.
176. Haimi-Cohen Y, Shafinoori S, Tucci V, et al. Use of incubation time to detection in BACTEC 9240 to distinguish coagulase-negative staphylococcal contamination from infection in pediatric blood cultures. *Pediatr Infect Dis J*. 2003;22:968–974.
177. Savithri MB, Iyer V, Jones M, et al. Epidemiology and significance of coagulase-negative staphylococci isolated in blood cultures from critically ill adult patients. *Crit Care Resusc*. 2011;13:103–107.
178. Schnell D, Lecuyer H, Geeraerts T, et al. Preliminary evaluation of a new clinical algorithm to interpret blood cultures growing coagulase-negative staphylococci. *Scand J Infect Dis*. 2013;45:562–566.
179. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1–45.
180. Raad I, Hanna HA, Alakech B, et al. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. *Ann Intern Med*. 2004;140:18–25.
181. Santolaya ME, Cofre J, Beresi V. C-reactive protein: a valuable aid for the management of febrile children with cancer and neutropenia. *Clin Infect Dis*. 1994;18:589–595.
182. Schuetz P, Mueller B, Trampuz A. Serum procalcitonin for discrimination of blood contamination from bloodstream infection due to coagulase-negative staphylococci. *Infection*. 2007;35:352–355.
183. Seo SK, Venkataraman L, DeGirolami PC, et al. Molecular typing of coagulase-negative staphylococci from blood cultures does not correlate with clinical criteria for true bacteremia. *Am J Med*. 2000;109:697–704.
184. Sharma M, Riederer K, Johnson LB, et al. Molecular analysis of coagulase-negative *Staphylococcus* isolates from blood cultures: prevalence of genotypic variation and polyclonal bacteremia. *Clin Infect Dis*. 2001;33:1317–1323.
185. Khatib R, Riederer KM, Clark JA, et al. Coagulase-negative staphylococci in multiple blood cultures: strain relatedness and determinants of same-strain bacteremia. *J Clin Microbiol*. 1995;33:816–820.
186. de Silva GD, Kantzanou M, Justice A, et al. The ica operon and biofilm production in coagulase-negative staphylococci associated with carriage and disease in a neonatal intensive care unit. *J Clin Microbiol*. 2002;40:382–388.
187. Papadimitriou-Olivgeri I, Giormezis N, Papadimitriou-Olivgeris M, et al. Number of positive blood cultures, biofilm formation, and adhesin genes in differentiating true coagulase-negative staphylococci bacteremia from contamination. *Eur J Clin Microbiol Infect Dis*. 2016;35:57–66.
188. Kitao T, Ishimaru M, Nishihara S. Detection of biofilm-producing and methicillin resistance genes in *Staphylococcus epidermidis* isolated from healthy humans and in blood culture tests. *J Infect Chemother*. 2010;16:170–173.
189. Spitalnic SJ, Woolard RH, Mermel LA. The significance of changing needles when inoculating blood cultures: a meta-analysis. *Clin Infect Dis*. 1995;21:1103–1106.
190. Rupp ME, Cavalieri RJ, Marolf C, et al. Reduction in blood culture contamination through use of initial specimen diversion device. *Clin Infect Dis*. 2017;65:201–205.
191. Chu VH, Woods CW, Miro JM, et al. Emergence of coagulase-negative staphylococci as a cause of native valve endocarditis. *Clin Infect Dis*. 2008;46:232–242.
192. Centers for Disease Control and Prevention (CDC). National and state healthcare associated infections progress report. https://www.cdc.gov/hai/pdfs/progress-report/hai-progress-report.pdf. Updated 2016. Accessed June 1, 2018.
193. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc*. 2006;81:1159–1171.
194. Dudeck MA, Edwards JR, Allen-Bridson K, et al. National healthcare safety network report, data summary for 2013, device-associated module. *Am J Infect Control*. 2015;43:206–221.
195. European Centre for Disease Prevention and Control. Healthcare-associated infections acquired in intensive care units- annual epidemiological report for 2015. https://ecdc.europa.eu/en/publications-data/healthcare-associated-infections-acquired-intensive-care-units-annual. Updated 2017. Accessed June 1, 2018.
195a. Rosenthal VD. Central line-associated bloodstream infections in limited resource countries: a review of the literature. *Clin Infect Dis*. 2009;49:1899–1907.
196. Fontela PS, Platt RW, Rocher I, et al. Epidemiology of central line-associated bloodstream infections in Quebec intensive care units: a 6-year review. *Am J Infect Control*. 2012;40:221–226.
197. Broekhuizen CA, Schultz MJ, van der Wal AC, et al. Tissue around catheters is a niche for bacteria associated with medical device infection. *Crit Care Med*. 2008;36:2395–2402.
198. Rodriguez-Aranda A, Alcazar JM, Sanz F, et al. Endoluminal colonization as a risk factor for coagulase-negative staphylococcal catheter-related bloodstream infections in haemodialysis patients. *Nephrol Dial Transplant*. 2011;26:948–955.
199. Hewlett AL, Rupp ME. Healthcare-associated infections related to the use of intravascular devices inserted for short-term vascular access. In: Mayhall CG, ed. *Hospital Epidemiology and Infection Control*. 4th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2012:241–247.
200. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. *N Engl J Med*. 1977;296:1305–1309.

201. Sherertz RJ, Heard SO, Raad II. Diagnosis of triple-lumen catheter infection: comparison of roll plate, sonication, and flushing methodologies. *J Clin Microbiol*. 1997;35: 641–646.
202. Lebeaux D, Larroque B, Gellen-Dautremer J, et al. Clinical outcome after a totally implantable venous access port-related infection in cancer patients: a prospective study and review of the literature. *Medicine (Baltimore)*. 2012;91:309–318.
203. Molina J, Penuela I, Lepe JA, et al. Mortality and hospital stay related to coagulase-negative staphylococci bacteremia in non-critical patients. *J Infect*. 2013;66:155–162.
204. O'Horo JC, Silva GL, Safdar N. Anti-infective locks for treatment of central line-associated bloodstream infection: a systematic review and meta-analysis. *Am J Nephrol*. 2011;34:415–422.
205. O'Grady NP, Alexander M, Burns LA, et al. Summary of recommendations: guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis*. 2011;52:1087–1099.
206. Snaterse M, Ruger W, Scholte Op Reimer WJ, et al. Antibiotic-based catheter lock solutions for prevention of catheter-related bloodstream infection: a systematic review of randomised controlled trials. *J Hosp Infect*. 2010;75:1–11.
207. Megged O, Shalit I, Yaniv I, et al. Outcome of antibiotic lock technique for persistent central venous catheter-associated coagulase-negative *Staphylococcus* bacteremia in children. *Eur J Clin Microbiol Infect Dis*. 2010;29:157–161.
208. Raad I, Davis S, Khan A, et al. Impact of central venous catheter removal on the recurrence of catheter-related coagulase-negative staphylococcal bacteremia. *Infect Control Hosp Epidemiol*. 1992;13:215–221.
209. Demitrovicova A, Hricak V, Karvay M, et al. Endocarditis due to coagulase-negative staphylococci: data from a 22-years national survey. *Scand J Infect Dis*. 2007;39:655–656.
210. Lalani T, Kanafani ZA, Chu VH, et al. Prosthetic valve endocarditis due to coagulase-negative staphylococci: findings from the international collaboration on endocarditis merged database. *Eur J Clin Microbiol Infect Dis*. 2006;25:365–368.
211. Wang A, Athan E, Pappas PA, et al. Contemporary clinical profile and outcome of prosthetic valve endocarditis. *JAMA*. 2007;297:1354–1361.
212. Lee JH, Burner KD, Fealey ME, et al. Prosthetic valve endocarditis: clinicopathological correlates in 122 surgical specimens from 116 patients (1985-2004). *Cardiovasc Pathol*. 2011;20:26–35.
213. Cahill TJ, Prendergast BD. Infective endocarditis. *Lancet*. 2016;387:882–893.
214. Amat-Santos IJ, Messika-Zeitoun D, Eltchaninoff H, et al. Infective endocarditis after transcatheter aortic valve implantation: results from a large multicenter registry. *Circulation*. 2015;131:1566–1574.
215. Karchmer AW, Archer GL, Dismukes WE. *Staphylococcus epidermidis* causing prosthetic valve endocarditis: microbiologic and clinical observations as guides to therapy. *Ann Intern Med*. 1983;98:447–455.
216. Iung B, Rouzet F, Brochet E, et al. Cardiac imaging of infective endocarditis, echo and beyond. *Curr Infect Dis Rep*. 2017;19:8. 017-0560-2.
217. Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation*. 2005;111:e394–e434.
218. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis. the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). *G Ital Cardiol (Rome)*. 2016;17:277–319.
219. Castonguay MC, Burner KD, Edwards WD, et al. Surgical pathology of native valve endocarditis in 310 specimens from 287 patients (1985-2004). *Cardiovasc Pathol*. 2013;22:19–27.
220. Vogkou CT, Vlachogiannis NI, Palaiodimos L, et al. The causative agents in infective endocarditis: a systematic review comprising 33,214 cases. *Eur J Clin Microbiol Infect Dis*. 2016;35:1227–1245.
221. Olmos C, Vilacosta I, Fernandez-Perez C, et al. The evolving nature of infective endocarditis in Spain: a population-based study (2003 to 2014). *J Am Coll Cardiol*. 2017;70:2795–2804.
222. Caputo GM, Archer GL, Calderwood SB, et al. Native valve endocarditis due to coagulase-negative staphylococci. clinical and microbiologic features. *Am J Med*. 1987;83:619–625.
223. Zaloudikova B, Nemcova E, Pol J, et al. Value of PCR in surgically treated patients with staphylococcal infective endocarditis: a 4-year retrospective study. *Eur J Clin Microbiol Infect Dis*. 2012;31:1187–1194.
224. Chambers ST. Diagnosis and management of staphylococcal infections of pacemakers and cardiac defibrillators. *Intern Med J*. 2005;35(suppl 2): S63–S71.
225. del Rio A, Anguera I, Miro JM, et al. Surgical treatment of pacemaker and defibrillator lead endocarditis: the impact of electrode lead extraction on outcome. *Chest*. 2003;124:1451–1459.
226. Chua JD, Wilkoff BL, Lee I, et al. Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. *Ann Intern Med*. 2000;133:604–608.
227. Gandelman G, Frishman WH, Wiese C, et al. Intravascular device infections: epidemiology, diagnosis, and management. *Cardiol Rev*. 2007;15:13–23.
228. Le KY, Sohail MR, Friedman PA, et al. Clinical features and outcomes of cardiovascular implantable electronic device infections due to staphylococcal species. *Am J Cardiol*. 2012;110:1143–1149.
229. Athan E, Chu VH, Tattevin P, et al. Clinical characteristics and outcome of infective endocarditis involving implantable cardiac devices. *JAMA*. 2012;307:1727–1735.
230. Madhavan M, Sohail MR, Friedman PA, et al. Outcomes in patients with cardiovascular implantable electronic devices and bacteremia caused by gram-positive cocci other than *Staphylococcus aureus*. *Circ Arrhythm Electrophysiol*. 2010;3:639–645.
231. Polewczyk A, Janion M, Podlaski R, et al. Clinical manifestations of lead-dependent infective endocarditis: analysis of 414 cases. *Eur J Clin Microbiol Infect Dis*. 2014;33:1601–1608.
232. Carrasco F, Anguita M, Ruiz M, et al. Clinical features and changes in epidemiology of infective endocarditis on pacemaker devices over a 27-year period (1987-2013). *Europace*. 2016;18:836–841.
233. Riaz T, Nienaber JJ, Baddour LM, et al. Cardiovascular implantable electronic device infections in left ventricular assist device recipients. *Pacing Clin Electrophysiol*. 2014;37:225–230.
234. Kusumoto FM, Schoenfeld MH, Wilkoff BL, et al. 2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction. *Heart Rhythm*. 2017;14:e503–e551.
235. Baddour LM, Bettmann MA, Bolger AF, et al. Nonvalvular cardiovascular device-related infections. *Circulation*. 2003;108:2015–2031.
236. Rohacek M, Weisser M, Kobza R, et al. Bacterial colonization and infection of electrophysiological cardiac devices detected with sonication and swab culture. *Circulation*. 2010;121:1691–1697.
237. Kleemann T, Becker T, Strauss M, et al. Prevalence of bacterial colonization of generator pockets in implantable cardioverter defibrillator patients without signs of infection undergoing generator replacement or lead revision. *Europace*. 2010;12:58–63.
238. Kratz JM, Toole JM. Pacemaker and internal cardioverter defibrillator lead extraction: a safe and effective surgical approach. *Ann Thorac Surg*. 2010;90:1411–1417.
239. Margey R, McCann H, Blake G, et al. Contemporary management of and outcomes from cardiac device related infections. *Europace*. 2010;12:64–70.
240. Perera GB, Fujitani RM, Kubaska SM. Aortic graft infection: update on management and treatment options. *Vasc Endovascular Surg*. 2006;40:1–10.
241. Stewart AH, Eyers PS, Earnshaw JJ. Prevention of infection in peripheral arterial reconstruction: a systematic review and meta-analysis. *J Vasc Surg*. 2007;46:148–155.
242. Leroy O, Meybeck A, Sarraz-Bournet B, et al. Vascular graft infections. *Curr Opin Infect Dis*. 2012;25:154–158.
243. Bergamini TM, Bandyk DF, Govostis D, et al. Identification of *Staphylococcus epidermidis* vascular graft infections: a comparison of culture techniques. *J Vasc Surg*. 1989;9:665–670.
244. Saleem BR, Meerwaldt R, Tielliu IF, et al. Conservative treatment of vascular prosthetic graft infection is associated with high mortality. *Am J Surg*. 2010;200:47–52.
245. Legout L, Delia P, Sarraz-Bournet B, et al. Factors predictive of treatment failure in staphylococcal prosthetic vascular graft infections: a prospective observational cohort study: impact of rifampin. *BMC Infect Dis*. 2014;14:228. 2334-14-228.
246. Batt M, Magne JL, Alric P, et al. In situ revascularization with silver-coated polyester grafts to treat aortic infection: early and midterm results. *J Vasc Surg*. 2003;38:983–989.
247. Trampuz A, Piper KE, Jacobson MJ, et al. Sonication of removed hip and knee prostheses for diagnosis of infection. *N Engl J Med*. 2007;357:654–663.
248. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. *N Engl J Med*. 2004;351:1645–1654.
249. Teterycz D, Ferry T, Lew D, et al. Outcome of orthopedic implant infections due to different staphylococci. *Int J Infect Dis*. 2010;14:e913–e918.
250. Steckelberg JM, Osmon DR. Prosthetic joint infections. In: Waldvogel FA, Bisno AL, eds. *Infections Associated With Indwelling Medical Devices*. 3rd ed. Washington, D.C: ASM Press; 2000:172–210.
251. Del Pozo JL, Patel R. Clinical practice. Infection associated with prosthetic joints. *N Engl J Med*. 2009;361:787–794.
252. Kwee TC, Kwee RM, Alavi A. FDG-PET for diagnosing prosthetic joint infection: systematic review and metaanalysis. *Eur J Nucl Med Mol Imaging*. 2008;35:2122–2132.
253. Atkins BL, Athanasou N, Deeks JJ, et al. Prospective evaluation of criteria for microbiological diagnosis of prosthetic-joint infection at revision arthroplasty. The OSIRIS collaborative study group. *J Clin Microbiol*. 1998;36:2932–2939.
254. Vergidis P, Greenwood-Quaintance KE, Sanchez-Sotelo J, et al. Implant sonication for the diagnosis of prosthetic elbow infection. *J Shoulder Elbow Surg*. 2011;20: 1275–1281.
255. Drago L, De Vecchi E, Cappelletti L, et al. Prolonging culture to 15 days improves bacterial detection in bone and joint infections. *Eur J Clin Microbiol Infect Dis*. 2015;34:1809–1813.
256. Metso L, Maki M, Tissari P, et al. Efficacy of a novel PCR- and microarray-based method in diagnosis of a prosthetic joint infection. *Acta Orthop*. 2014;85: 165–170.
257. Berbari EF, Marculescu C, Sia I, et al. Culture-negative prosthetic joint infection. *Clin Infect Dis*. 2007;45: 1113–1119.
258. Tande AJ, Osmon DR, Greenwood-Quaintance KE, et al. Clinical characteristics and outcomes of prosthetic joint infection caused by small colony variant staphylococci. *MBio*. 2014;5:e1910–e1914.
259. Jacobs AME, Benard M, Meis JF, et al. The unsuspected prosthetic joint infection : incidence and consequences of positive intra-operative cultures in presumed aseptic knee and hip revisions. *Bone Joint J*. 2017;99-B: 1482–1489.
260. Osmon DR, Berbari EF, Berendt AR, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56:e1–e25.
261. Singer J, Merz A, Frommelt L, et al. High rate of infection control with one-stage revision of septic knee prostheses excluding MRSA and MRSE. *Clin Orthop Relat Res*. 2012;470:1461–1471.
262. Cremniter J, Slassi A, Quincampoix JC, et al. Decreased susceptibility to teicoplanin and vancomycin in coagulase-negative staphylococci isolated from orthopedic-device-associated infections. *J Clin Microbiol*. 2010;48:1428–1431.
263. Allison DC, Holtom PD, Patzakis MJ, et al. Microbiology of bone and joint infections in injecting drug abusers. *Clin Orthop Relat Res*. 2010;468:2107–2112.
264. Aragon-Sanchez J, Lazaro-Martinez JL, Hernandez-Herrero MJ, et al. Clinical significance of the isolation of *Staphylococcus epidermidis* from bone biopsy in diabetic foot osteomyelitis. *Diabet Foot Ankle*. 2010;1:10.3402/dfa.v1i0.5418.
265. Oussedik SI, Haddad FS. The use of linezolid in the treatment of infected total joint arthroplasty. *J Arthroplasty*. 2008;23:273–278.
266. Rice DA, Mendez-Vigo L. Daptomycin in bone and joint infections: a review of the literature. *Arch Orthop Trauma Surg*. 2009;129:1495–1504.
267. Kaushal R, Hassoun A. Successful treatment of methicillin-resistant *Staphylococcus epidermidis* prosthetic joint infection with telavancin. *J Antimicrob Chemother*. 2012;67:2052–2053.
268. Norden CW. Prevention of bone and joint infections. *Am J Med*. 1985;78(6B):229–232.
269. Lidgren L. Joint prosthetic infections: a success story. *Acta Orthop Scand*. 2001;72:553–556.
270. Gastmeier P, Breier AC, Brandt C. Influence of laminar airflow on prosthetic joint infections: a systematic review. *J Hosp Infect*. 2012;81:73–78.
271. Laurent F, Bignon A, Goldnadel J, et al. A new concept of gentamicin loaded HAP/TCP bone substitute for prophylactic action: in vitro release validation. *J Mater Sci Mater Med*. 2008;19:947–951.
272. Conen A, Walti LN, Merlo A, et al. Characteristics and treatment outcome of cerebrospinal fluid shunt-associated infections in adults: a retrospective

analysis over an 11-year period. *Clin Infect Dis*. 2008;47:73–82.
273. Sorensen P, Ejlertsen T, Aaen D, et al. Bacterial contamination of surgeons gloves during shunt insertion: a pilot study. *Br J Neurosurg*. 2008;22:675–677.
274. Lozier AP, Sciacca RR, Romagnoli MF, et al. Ventriculostomy-related infections: a critical review of the literature. *Neurosurgery*. 2002;51:170–181, discussion 181–2.
275. Scheithauer S, Burgel U, Ryang YM, et al. Prospective surveillance of drain associated meningitis/ventriculitis in a neurosurgery and neurological intensive care unit. *J Neurol Neurosurg Psychiatry*. 2009;80:1381–1385.
276. Walti LN, Conen A, Coward J, et al. Characteristics of infections associated with external ventricular drains of cerebrospinal fluid. *J Infect*. 2013;66:424–431.
277. Arabi Y, Memish ZA, Balkhy HH, et al. Ventriculostomy-associated infections: incidence and risk factors. *Am J Infect Control*. 2005;33:137–143.
278. Gordon CL, Tokarz R, Briese T, et al. Evaluation of a multiplex polymerase chain reaction for early diagnosis of ventriculostomy-related infections. *J Neurosurg*. 2015;123:1586–1592.
279. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267–1284.
280. Ratilal B, Costa J, Sampaio C. Antibiotic prophylaxis for preventing meningitis in patients with basilar skull fractures. *Cochrane Database Syst Rev*. 2006;(1):CD004884.
281. Pirotte BJ, Lubansu A, Bruneau M, et al. Sterile surgical technique for shunt placement reduces the shunt infection rate in children: preliminary analysis of a prospective protocol in 115 consecutive procedures. *Childs Nerv Syst*. 2007;23:1251–1261.
282. Sciubba DM, Stuart RM, McGirt MJ, et al. Effect of antibiotic-impregnated shunt catheters in decreasing the incidence of shunt infection in the treatment of hydrocephalus. *J Neurosurg*. 2005;103(2 suppl):131–136.
283. Ritz R, Roser F, Morgalla M, et al. Do antibiotic-impregnated shunts in hydrocephalus therapy reduce the risk of infection? An observational study in 258 patients. *BMC Infect Dis*. 2007;7:38. 2334-7-38.
284. Konstantelias AA, Vardakas KZ, Polyzos KA, et al. Antimicrobial-impregnated and -coated shunt catheters for prevention of infections in patients with hydrocephalus: a systematic review and meta-analysis. *J Neurosurg*. 2015;122:1096–1112.
285. Klimo P Jr, Thompson CJ, Ragel BT, et al. Antibiotic-impregnated shunt systems versus standard shunt systems: a meta- and cost-savings analysis. *J Neurosurg Pediatr*. 2011;8:600–612.
286. Dawod J, Tager A, Darouiche RO, et al. Prevention and management of internal cerebrospinal fluid shunt infections. *J Hosp Infect*. 2016;93:323–328.
287. Stevens EA, Palavecino E, Sherertz RJ, et al. Effects of antibiotic-impregnated external ventricular drains on bacterial culture results: an in vitro analysis. *J Neurosurg*. 2010;113:86–92.
288. Mead PA, Safdieh JE, Nizza P, et al. Ommaya reservoir infections: a 16-year retrospective analysis. *J Infect*. 2014;68:225–230.
289. Weiner LM, Webb AK, Limbago B, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the national healthcare safety network at the centers for disease control and prevention, 2011-2014. *Infect Control Hosp Epidemiol*. 2016;37:1288–1301.
290. Berrios-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for disease control and prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surg*. 2017;152:784–791.
291. Kohler P, Sommerstein R, Schonrath F, et al. Effect of perioperative mupirocin and antiseptic body wash on infection rate and causative pathogens in patients undergoing cardiac surgery. *Am J Infect Control*. 2015;43:e33–e38.
292. Steingrimsson S, Thimour-Bergstrom L, Roman-Emanuel C, et al. Triclosan-coated sutures and sternal wound infections: a prospective randomized clinical trial. *Eur J Clin Microbiol Infect Dis*. 2015;34:2331–2338.
293. Vas S, Oreopoulos DG. Infections in patients undergoing peritoneal dialysis. *Infect Dis Clin North Am*. 2001;15:743–774.
294. Shin JH, Kim SH, Jeong HS, et al. Identification of coagulase-negative staphylococci isolated from continuous ambulatory peritoneal dialysis fluid using 16S ribosomal RNA, tuf, and SodA gene sequencing. *Perit Dial Int*. 2011;31:340–346.
295. Monsen T, Olofsson C, Ronnmark M, et al. Clonal spread of staphylococci among patients with peritonitis associated with continuous ambulatory peritoneal dialysis. *Kidney Int*. 2000;57:613–618.
296. de Lourdes Ribeiro de Souza da Cunha M, Montelli AC, Fioravante AM, et al. Predictive factors of outcome following staphylococcal peritonitis in continuous ambulatory peritoneal dialysis. *Clin Nephrol*. 2005;64:378–382.
297. Akoh JA. Peritoneal dialysis associated infections: an update on diagnosis and management. *World J Nephrol*. 2012;1:106–122.
298. Nessim SJ, Komenda P, Rigatto C, et al. Frequency and microbiology of peritonitis and exit-site infection among obese peritoneal dialysis patients. *Perit Dial Int*. 2013;33:167–174.
299. Barretti P, Montelli AC, Batalha JE, et al. The role of virulence factors in the outcome of staphylococcal peritonitis in CAPD patients. *BMC Infect Dis*. 2009;9:212. 2334-9-212.
300. Zelenitsky S, Barns L, Findlay I, et al. Analysis of microbiological trends in peritoneal dialysis-related peritonitis from 1991 to 1998. *Am J Kidney Dis*. 2000;36:1009–1013.
301. Burke M, Hawley CM, Badve SV, et al. Relapsing and recurrent peritoneal dialysis-associated peritonitis: a multicenter registry study. *Am J Kidney Dis*. 2011;58:429–436.
302. Bender FH, Bernardini J, Piraino B. Prevention of infectious complications in peritoneal dialysis: best demonstrated practices. *Kidney Int Suppl*. 2006;103:S44–S54.
303. Bonifati C, Pansini F, Torres DD, et al. Antimicrobial agents and catheter-related interventions to prevent peritonitis in peritoneal dialysis: using evidence in the context of clinical practice. *Int J Artif Organs*. 2006;29:41–49.
304. van Esch S, Krediet RT, Struijk DG. 32 years' experience of peritoneal dialysis-related peritonitis in a university hospital. *Perit Dial Int*. 2014;34:162–170.
305. de Kaspar HM, Kreidl KO, Singh K, et al. Comparison of preoperative conjunctival bacterial flora in patients undergoing glaucoma or cataract surgery. *J Glaucoma*. 2004;13:507–509.
306. Mollan SP, Gao A, Lockwood A, et al. Postcataract endophthalmitis: incidence and microbial isolates in a united kingdom region from 1996 through 2004. *J Cataract Refract Surg*. 2007;33:265–268.
307. Recchia FM, Busbee BG, Pearlman RB, et al. Changing trends in the microbiologic aspects of postcataract endophthalmitis. *Arch Ophthalmol*. 2005;123:341–346.
308. Passos RM, Cariello AJ, Yu MC, et al. Microbial keratitis in the elderly: a 32-year review. *Arq Bras Oftalmol*. 2010;73:315–319.
309. Li AL, Wykoff CC, Wang R, et al. Endophthalmitis after intravitreal injection: role of prophylactic topical ophthalmic antibiotics. *Retina*. 2016;36:1349–1356.
310. Gower EW, Keay LJ, Stare DE, et al. Characteristics of endophthalmitis after cataract surgery in the united states Medicare population. *Ophthalmology*. 2015;122:1625–1632.
311. Hanscom TA. Postoperative endophthalmitis. *Clin Infect Dis*. 2004;38:542–546.
312. Asbell PA, Sanfilippo CM, Pillar CM, et al. Antibiotic resistance among ocular pathogens in the united states: five-year results from the antibiotic resistance monitoring in ocular microorganisms (ARMOR) surveillance study. *JAMA Ophthalmol*. 2015;133:1445–1454.
313. Haider SA, Hassett P, Bron AJ. Intraocular vancomycin levels after intravitreal injection in post cataract extraction endophthalmitis. *Retina*. 2001;21:210–213.
314. Zhanel GG, Hisanaga TL, Laing NM, et al. Antibiotic resistance in outpatient urinary isolates: final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). *Int J Antimicrob Agents*. 2005;26:380–388.
315. Tambyah PA, Maki DG. The relationship between pyuria and infection in patients with indwelling urinary catheters: a prospective study of 761 patients. *Arch Intern Med*. 2000;160:673–677.
316. Ivanov IB, Gritsenko VA, Kuzmin MD. Phenotypic differences between coagulase-negative staphylococci isolated from seminal fluid of healthy men and men suffering from chronic prostatitis syndrome. *Int J Androl*. 2010;33:563–567.
317. Carson CC. Diagnosis, treatment and prevention of penile prosthesis infection. *Int J Impot Res*. 2003;15(suppl 5):S139–S146.
318. Darouiche RO. Treatment of infections associated with surgical implants. *N Engl J Med*. 2004;350:1422–1429.
319. Habous M, Farag M, Williamson B, et al. Conservative therapy is an effective option in patients with localized infection after penile implant surgery. *J Sex Med*. 2016;13:972–976.
320. Yeung LL, Grewal S, Bullock A, et al. A comparison of chlorhexidine-alcohol versus povidone-iodine for eliminating skin flora before genitourinary prosthetic surgery: a randomized controlled trial. *J Urol*. 2013;189:136–140.
321. Abouassaly R, Angermeier KW, Montague DK. Risk of infection with an antibiotic coated penile prosthesis at device replacement for mechanical failure. *J Urol*. 2006;176(6 Pt 1):2471–2473.
322. Dhabuwala C. In vitro assessment of antimicrobial properties of rifampin-coated titan((R)) coloplast penile implants and comparison with inhibizone((R)). *J Sex Med*. 2010;7:3516–3519.
323. Delgado S, Arroyo R, Jimenez E, et al. *Staphylococcus epidermidis* strains isolated from breast milk of women suffering infectious mastitis: potential virulence traits and resistance to antibiotics. *BMC Microbiol*. 2009;9:82. 2180-9-82.
324. Brown SL, Hefflin B, Woo EK, et al. Infections related to breast implants reported to the food and drug administration, 1977-1997. *J Long Term Eff Med Implants*. 2001;11:1–12.
325. Kjoller K, Holmich LR, Jacobsen PH, et al. Epidemiological investigation of local complications after cosmetic breast implant surgery in Denmark. *Ann Plast Surg*. 2002;48:229–237.
326. Cohen JB, Carroll C, Tenenbaum MM, et al. Breast implant-associated infections: the role of the national surgical quality improvement program and the local microbiome. *Plast Reconstr Surg*. 2015;136:921–929.
327. Pittet B, Montandon D, Pittet D. Infection in breast implants. *Lancet Infect Dis*. 2005;5:94–106.
328. Reischies FMJ, Krause R, Holzer J, et al. What can we learn from sonication results of breast implants? *PLoS ONE*. 2017;12:e0182267.
329. Rieger UM, Mesina J, Kalbermatten DF, et al. Bacterial biofilms and capsular contracture in patients with breast implants. *Br J Surg*. 2013;100:768–774.
330. Sampedro MF, Patel R. Infections associated with long-term prosthetic devices. *Infect Dis Clin North Am*. 2007;21:785–819, x.
331. Davidson LE, Boucher HW. Infections in immunocompromised patients. In: Crossley KB, Jefferson KK, Archer GL, et al, eds. *Staphylococci in Human Disease*. 2nd ed. Chichester, West Sussex. Hoboken, NJ: Wiley-Blackwell; 2009.
332. Sganga G, Spanu T, Bianco G, et al. Bacterial bloodstream infections in liver transplantation: etiologic agents and antimicrobial susceptibility profiles. *Transplant Proc*. 2012;44:1973–1976.
333. Taplitz RA, Kennedy EB, Flowers CR. Outpatient management of fever and neutropenia in adults treated for malignancy: American society of clinical oncology and Infectious Diseases Society of America clinical practice guideline update summary. *J Oncol Pract*. 2018;14:250–255.
334. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2011;52:e56–e93.
335. Centers for Disease Control and Prevention (CDC). The national healthcare safety network (NHSN) manual: Patient safety component. http://www.cdc.gov/nhsn/PDFs/pscManual/PSC-Manual-portfolio.pdf.
336. Costa SF, Barone AA, Miceli MH, et al. Colonization and molecular epidemiology of coagulase-negative staphylococcal bacteremia in cancer patients: a pilot study. *Am J Infect Control*. 2006;34:36–40.
337. Dong Y, Speer CP, Glaser K. Beyond sepsis: *Staphylococcus epidermidis* is an underestimated but significant contributor to neonatal morbidity. *Virulence*. 2018;9:621–633.
338. Blanchard AC, Quach C, Autmizguine J. Staphylococcal infections in infants: updates and current challenges. *Clin Perinatol*. 2015;42:119–132, ix.
339. Cortese F, Scicchitano P, Gesualdo M, et al. Early and late infections in newborns: where do we stand? A review. *Pediatr Neonatol*. 2016;57:265–273.
340. Hira V, Kornelisse RF, Sluijter M, et al. Colonization dynamics of antibiotic-resistant coagulase-negative staphylococci in neonates. *J Clin Microbiol*. 2013;51:595–597.
341. Soeorg H, Huik K, Parm U, et al. Genetic relatedness of coagulase-negative staphylococci from gastrointestinal tract and blood of preterm neonates with late-onset sepsis. *Pediatr Infect Dis J*. 2013;32:389–393.
342. Soeorg H, Huik K, Parm U, et al. Molecular epidemiology of *Staphylococcus epidermidis* in neonatal intensive care units. *APMIS*. 2017;125:63–73.
343. Patrick CH, John JF, Levkoff AH, et al. Relatedness of strains of methicillin-resistant coagulase-negative

Staphylococcus colonizing hospital personnel and producing bacteremias in a neonatal intensive care unit. *Pediatr Infect Dis J*. 1992;11:935–940.

344. Kaufman D, Fairchild KD. Clinical microbiology of bacterial and fungal sepsis in very-low-birth-weight infants. *Clin Microbiol Rev*. 2004;17:638–680. table of contents.
345. Strunk T, Richmond P, Simmer K, et al. Neonatal immune responses to coagulase-negative staphylococci. *Curr Opin Infect Dis*. 2007;20:370–375.
346. Freeman J, Goldmann DA, Smith NE, et al. Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. *N Engl J Med*. 1990;323:301–308.
347. Kordek A. Concentrations of procalcitonin and C-reactive protein, white blood cell count, and the immature-to-total neutrophil ratio in the blood of neonates with nosocomial infections: gram-negative bacilli vs coagulase-negative staphylococci. *Eur J Clin Microbiol Infect Dis*. 2011;30:455–457.
348. Dimitriou G, Fouzas S, Giormezis N, et al. Clinical and microbiological profile of persistent coagulase-negative staphylococcal bacteraemia in neonates. *Clin Microbiol Infect*. 2011;17:1684–1690.
349. Venkatesh MP, Placencia F, Weisman LE. Coagulase-negative staphylococcal infections in the neonate and child: an update. *Semin Pediatr Infect Dis*. 2006;17:120–127.
350. Borer A, Livshiz-Riven I, Golan A, et al. Hospital-acquired conjunctivitis in a neonatal intensive care unit: bacterial etiology and susceptibility patterns. *Am J Infect Control*. 2010;38:650–652.
351. Scheifele DW, Bjornson GL, Dyer RA, et al. Delta-like toxin produced by coagulase-negative staphylococci is associated with neonatal necrotizing enterocolitis. *Infect Immun*. 1987;55:2268–2273.
352. Tamma PD, Aucott SW, Milstone AM. Chlorhexidine use in the neonatal intensive care unit: results from a national survey. *Infect Control Hosp Epidemiol*. 2010;31:846–849.
353. Hocevar SN, Lessa FC, Gallagher L, et al. Infection prevention practices in neonatal intensive care units reporting to the national healthcare safety network. *Infect Control Hosp Epidemiol*. 2014;35:1126–1132.
354. Sathiyamurthy S, Banerjee J, Godambe SV. Antiseptic use in the neonatal intensive care unit - a dilemma in clinical practice: an evidence based review. *World J Clin Pediatr*. 2016;5:159–171.
355. Craft AP, Finer NN, Barrington KJ. Vancomycin for prophylaxis against sepsis in preterm neonates. *Cochrane Database Syst Rev*. 2000;(2):CD001971.
356. Garland JS, Alex CP, Henrickson KJ, et al. A vancomycin-heparin lock solution for prevention of nosocomial bloodstream infection in critically ill neonates with peripherally inserted central venous catheters: a prospective, randomized trial. *Pediatrics*. 2005;116:e198–e205.
357. Brusselaers N, Monstrey S, Snoeij T, et al. Morbidity and mortality of bloodstream infections in patients with severe burn injury. *Am J Crit Care*. 2010;19:e81–e87.
358. Patel BM, Paratz JD, Mallet A, et al. Characteristics of bloodstream infections in burn patients: an 11-year retrospective study. *Burns*. 2012;38:685–690.
359. Guggenheim M, Zbinden R, Handschin AE, et al. Changes in bacterial isolates from burn wounds and their antibiograms: a 20-year study (1986-2005). *Burns*. 2009;35:553–560.
360. Czekaj T, Ciszewski M, Szewczyk EM. *Staphylococcus haemolyticus* - an emerging threat in the twilight of the antibiotics age. *Microbiology*. 2015;161:2061–2068.
361. Hitzenbichler F, Simon M, Salzberger B, et al. Clinical significance of coagulase-negative staphylococci other than S. epidermidis blood stream isolates at a tertiary care hospital. *Infection*. 2017;45:179–186.
362. Raimundo O, Heussler H, Bruhn JB, et al. Molecular epidemiology of coagulase-negative staphylococcal bacteraemia in a newborn intensive care unit. *J Hosp Infect*. 2002;51:33–42.
363. Carretto E, Barbarini D, Couto I, et al. Identification of coagulase-negative staphylococci other than *Staphylococcus epidermidis* by automated ribotyping. *Clin Microbiol Infect*. 2005;11:177–184.
364. Shittu A, Lin J, Morrison D, et al. Isolation and molecular characterization of multiresistant *Staphylococcus sciuri* and *Staphylococcus haemolyticus* associated with skin and soft-tissue infections. *J Med Microbiol*. 2004;53(Pt 1):51–55.
365. Huang CR, Lu CH, Wu JJ, et al. Coagulase-negative staphylococcal meningitis in adults: clinical characteristics and therapeutic outcomes. *Infection*. 2005;33:56–60.
366. Ruzauskas M, Siugzdiniene R, Klimiene I, et al. Prevalence of methicillin-resistant *Staphylococcus haemolyticus* in companion animals: a cross-sectional study. *Ann Clin Microbiol Antimicrob*. 2014;13:56. 014-0056-y.
367. Da F, Joo HS, Cheung GYC, et al. Phenol-soluble modulin toxins of *Staphylococcus haemolyticus*. *Front Cell Infect Microbiol*. 2017;7:206.
368. Biavasco F, Vignaroli C, Varaldo PE. Glycopeptide resistance in coagulase-negative staphylococci. *Eur J Clin Microbiol Infect Dis*. 2000;19:403–417.
369. Takeuchi F, Watanabe S, Baba T, et al. Whole-genome sequencing of *Staphylococcus haemolyticus* uncovers the extreme plasticity of its genome and the evolution of human-colonizing staphylococcal species. *J Bacteriol*. 2005;187:7292–7308.
370. Mazzariol A, Lo Cascio G, Kocsis E, et al. Outbreak of linezolid-resistant *Staphylococcus haemolyticus* in an Italian intensive care unit. *Eur J Clin Microbiol Infect Dis*. 2012;31:523–527.
371. Chopra A, Gulati D, Woldenberg N, et al. Intracardiac lead endocarditis due to *Staphylococcus lugdunensis*. *Int J Infect Dis*. 2010;14(suppl 3):e291–e293.
372. Patel R, Piper KE, Rouse MS, et al. Frequency of isolation of *Staphylococcus lugdunensis* among staphylococcal isolates causing endocarditis: a 20-year experience. *J Clin Microbiol*. 2000;38:4262–4263.
373. Zinkernagel AS, Zinkernagel MS, Elzi MV, et al. Significance of *Staphylococcus lugdunensis* bacteremia: report of 28 cases and review of the literature. *Infection*. 2008;36:314–321.
374. Arias M, Tena D, Apellaniz M, et al. Skin and soft tissue infections caused by *Staphylococcus lugdunensis*: report of 20 cases. *Scand J Infect Dis*. 2010;42:879–884.
375. Non LR, Santos CA. The occurrence of infective endocarditis with *Staphylococcus lugdunensis* bacteremia: a retrospective cohort study and systematic review. *J Infect*. 2017;74:179–186.
376. Seng P, Traore M, Lavigne JP, et al. *Staphylococcus lugdunensis*: a neglected pathogen of infections involving fracture-fixation devices. *Int Orthop*. 2017;41:1085–1091.
377. Papapetropoulos N, Papapetropoulou M, Vantarakis A. Abscesses and wound infections due to *Staphylococcus lugdunensis*: report of 16 cases. *Infection*. 2013;41:525–528.
378. Lourtet-Hascoet J, Bicart-See A, Felice MP, et al. *Staphylococcus lugdunensis*, a serious pathogen in periprosthetic joint infections: comparison to *Staphylococcus aureus* and *Staphylococcus epidermidis*. *Int J Infect Dis*. 2016;51:56–61.
379. Argemi X, Riegel P, Lavigne T, et al. Implementation of matrix-assisted laser desorption ionization-time of flight mass spectrometry in routine clinical laboratories improves identification of coagulase-negative staphylococci and reveals the pathogenic role of *Staphylococcus lugdunensis*. *J Clin Microbiol*. 2015;53:2030–2036.
380. Bieber L, Kahlmeter G. *Staphylococcus lugdunensis* in several niches of the normal skin flora. *Clin Microbiol Infect*. 2010;16:385–388.
381. Fervenza FC, Contreras GE, Garratt KN, et al. *Staphylococcus lugdunensis* endocarditis: a complication of vasectomy? *Mayo Clin Proc*. 1999;74:1227–1230.
382. Giormezis N, Kolonitsiou F, Makri A, et al. Virulence factors among *Staphylococcus lugdunensis* are associated with infection sites and clonal spread. *Eur J Clin Microbiol Infect Dis*. 2015;34:773–778.
383. Hussain M, Steinbacher T, Peters G, et al. The adhesive properties of the *Staphylococcus lugdunensis* multifunctional autolysin AtlL and its role in biofilm formation and internalization. *Int J Med Microbiol*. 2015;305:129–139.
384. Argemi X, Prevost G, Riegel P, et al. Kinetics of biofilm formation by *Staphylococcus lugdunensis* strains in bone and joint infections. *Diagn Microbiol Infect Dis*. 2017;88:298–304.
385. Noguchi N, Goto K, Ro T, et al. Using the tannase gene to rapidly and simply identify *Staphylococcus lugdunensis*. *Diagn Microbiol Infect Dis*. 2010;66:120–123.
386. Ho PL, Leung SM, Chow KH, et al. Carriage niches and molecular epidemiology of *Staphylococcus lugdunensis* and methicillin-resistant S. lugdunensis among patients undergoing long-term renal replacement therapy. *Diagn Microbiol Infect Dis*. 2015;81:141–144.
387. Ravaioli S, Selan L, Visai L, et al. *Staphylococcus lugdunensis*, an aggressive coagulase-negative pathogen not to be underestimated. *Int J Artif Organs*. 2012;35:742–753.
388. May ER, Hnilica KA, Frank LA, et al. Isolation of *Staphylococcus schleiferi* from healthy dogs and dogs with otitis, pyoderma, or both. *J Am Vet Med Assoc*. 2005;227:928–931.
389. Rupp ME, Soper DE, Archer GL. Colonization of the female genital tract with *Staphylococcus saprophyticus*. *J Clin Microbiol*. 1992;30:2975–2979.
390. Raz R, Colodner R, Kunin CM. Who are you–*Staphylococcus saprophyticus*? *Clin Infect Dis*. 2005;40:896–898.
391. Latham RH, Running K, Stamm WE. Urinary tract infections in young adult women caused by *Staphylococcus saprophyticus*. *JAMA*. 1983;250:3063–3066.
392. Lo DS, Shieh HH, Barreira ER, et al. High frequency of *Staphylococcus saprophyticus* urinary tract infections among female adolescents. *Pediatr Infect Dis J*. 2015;34:1023–1025.
393. Mardh PA, Hovelius B. *Staphylococcus saprophyticus* infections. *Lancet*. 1977;2:875.
394. Widerstrom M, Wistrom J, Sjostedt A, et al. Coagulase-negative staphylococci: update on the molecular epidemiology and clinical presentation, with a focus on *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*. *Eur J Clin Microbiol Infect Dis*. 2012;31:7–20.
395. Paiva-Santos W, Barros EM, Sousa VS, et al. Identification of coagulase-negative *Staphylococcus saprophyticus* by polymerase chain reaction based on the heat-shock repressor encoding hrcA gene. *Diagn Microbiol Infect Dis*. 2016;86:253–256.
396. Peer MA, Nasir RA, Kakru DK, et al. Sepsis due to linezolid resistant *Staphylococcus cohnii* and *Staphylococcus kloosii*: first reports of linezolid resistance in coagulase negative staphylococci from india. *Indian J Med Microbiol*. 2011;29:60–62.
397. Mihaila L, Defrance G, Levesque E, et al. A dual outbreak of bloodstream infections with linezolid-resistant *Staphylococcus epidermidis* and *Staphylococcus pettenkoferi* in a liver intensive care unit. *Int J Antimicrob Agents*. 2012;40:472–474.
398. Vallianou N, Evangelopoulos A, Makri P, et al. Vertebral osteomyelitis and native valve endocarditis due to *Staphylococcus simulans:* a case report. *J Med Case Rep*. 2008;2:183. 1947-2-183.
399. Al Masalma M, Raoult D, Roux V. *Staphylococcus massiliensis* sp. nov., isolated from a human brain abscess. *Int J Syst Evol Microbiol*. 2010;60(Pt 5):1066–1072.
400. Rasigade JP, Raulin O, Picaud JC, et al. Methicillin-resistant *Staphylococcus capitis* with reduced vancomycin susceptibility causes late-onset sepsis in intensive care neonates. *PLoS ONE*. 2012;7:e31548.
401. Campoccia D, Montanaro L, Visai L, et al. Characterization of 26 *Staphylococcus warneri* isolates from orthopedic infections. *Int J Artif Organs*. 2010;33:575–581.
402. Oud L. Community-acquired meningitis due to *Staphylococcus capitis* in the absence of neurologic trauma, surgery, or implants. *Heart Lung*. 2011;40:467–471.
403. Pantucek R, Svec P, Dajcs JJ, et al. *Staphylococcus petrasii* sp. nov. including *S. petrasii* subsp. *petrasii* subsp. nov. and *S. petrasii* subsp. *croceilyticus* subsp. nov., isolated from human clinical specimens and human ear infections. *Syst Appl Microbiol*. 2013;36:90–95.
404. Han JI, Yang CH, Park HM. Prevalence and risk factors of *Staphylococcus* spp. carriage among dogs and their owners: a cross-sectional study. *Vet J*. 2016;212:15–21.
405. Somayaji R, Priyantha MA, Rubin JE, et al. Human infections due to *Staphylococcus pseudintermedius,* an emerging zoonosis of canine origin: report of 24 cases. *Diagn Microbiol Infect Dis*. 2016;85:471–476.
406. Wu MT, Burnham CA, Westblade LF, et al. Evaluation of oxacillin and cefoxitin disk and MIC breakpoints for prediction of methicillin resistance in human and veterinary isolates of *Staphylococcus intermedius* group. *J Clin Microbiol*. 2016;54:535–542.
407. McCann MT, Gilmore BF, Gorman SP. *Staphylococcus epidermidis* device-related infections: pathogenesis and clinical management. *J Pharm Pharmacol*. 2008;60:1551–1571.
408. Nuryastuti T, van der Mei HC, Busscher HJ, et al. Effect of cinnamon oil on icaA expression and biofilm formation by *Staphylococcus epidermidis*. *Appl Environ Microbiol*. 2009;75:6850–6855.
409. Hell E, Giske CG, Nelson A, et al. Human cathelicidin peptide LL37 inhibits both attachment capability and biofilm formation of *Staphylococcus epidermidis*. *Lett Appl Microbiol*. 2010;50:211–215.
410. Wang X, Yao X, Zhu Z, et al. Effect of berberine on *Staphylococcus epidermidis* biofilm formation. *Int J Antimicrob Agents*. 2009;34:60–66.
411. Lonn-Stensrud J, Landin MA, Benneche T, et al. Furanones, potential agents for preventing *Staphylococcus epidermidis* biofilm infections? *J Antimicrob Chemother*. 2009;63:309–316.
412. Sader HS, Biedenbach DJ, Paukner S, et al. Antimicrobial activity of the investigational pleuromutilin compound BC-3781 tested against gram-positive organisms commonly associated with acute bacterial skin and skin

structure infections. *Antimicrob Agents Chemother*. 2012;56:1619–1623.
413. Laverty G, McCloskey AP, Gorman SP, et al. Anti-biofilm activity of ultrashort cinnamic acid peptide derivatives against medical device-related pathogens. *J Pept Sci*. 2015;21:770–778.
414. Lohan S, Cameotra SS, Bisht GS. Systematic study of non-natural short cationic lipopeptides as novel broad-spectrum antimicrobial agents. *Chem Biol Drug Des*. 2013;82:557–566.
415. Siriwong S, Teethaisong Y, Thumanu K, et al. The synergy and mode of action of quercetin plus amoxicillin against amoxicillin-resistant *Staphylococcus epidermidis*. *BMC Pharmacol Toxicol*. 2016;17:39. 016-0083-8.
416. Mohamed MF, Hamed MI, Panitch A, et al. Targeting methicillin-resistant *Staphylococcus aureus* with short salt-resistant synthetic peptides. *Antimicrob Agents Chemother*. 2014;58:4113–4122.
417. Francolini I, Donelli G. Prevention and control of biofilm-based medical-device-related infections. *FEMS Immunol Med Microbiol*. 2010;59:227–238.
418. Van Mellaert L, Shahrooei M, Hofmans D, et al. Immunoprophylaxis and immunotherapy of *Staphylococcus epidermidis* infections: challenges and prospects. *Expert Rev Vaccines*. 2012;11:319–334.
419. Sbarra MS, Arciola CR, Di Poto A, et al. The photodynamic effect of tetra-substituted N-methyl-pyridyl-porphine combined with the action of vancomycin or host defense mechanisms disrupts *Staphylococcus epidermidis* biofilms. *Int J Artif Organs*. 2009;32:574–583.
420. Aswani V, Tremblay DM, Moineau S, et al. *Staphylococcus epidermidis* bacteriophages from the anterior nares of humans. *Appl Environ Microbiol*. 2011;77:7853–7855.
421. Kaplan JB. Therapeutic potential of biofilm-dispersing enzymes. *Int J Artif Organs*. 2009;32:545–554.
422. Todd DA, Parlet CP, Crosby HA, et al. Signal biosynthesis inhibition with ambuic acid as a strategy to target antibiotic-resistant infections. *Antimicrob Agents Chemother*. 2017;61:10.1128/AAC.00263-17. Print 2017 Aug.
423. Pihl M, Chavez de Paz LE, Schmidtchen A, et al. Effects of clinical isolates of pseudomonas aeruginosa on *Staphylococcus epidermidis* biofilm formation. *FEMS Immunol Med Microbiol*. 2010;59:504–512.
424. Harris LG, Bexfield A, Nigam Y, et al. Disruption of *Staphylococcus epidermidis* biofilms by medicinal maggot *Lucilia sericata* excretions/secretions. *Int J Artif Organs*. 2009;32:555–564.
425. Kaushal A, Gupta K, van Hoek ML. Characterization of *Cimex lectularius* (bedbug) defensin peptide and its antimicrobial activity against human skin microflora. *Biochem Biophys Res Commun*. 2016;470:955–960.

196 Classification of Streptococci

John P. Dekker and Kathryn L. Ruoff

Members of the genus *Streptococcus* are catalase-negative, gram-positive bacteria that form oval or coccoid cells arranged in pairs and chains. Streptococci are nutritionally fastidious and require complex media, preferably supplemented with blood, for optimal growth. They are homofermentative lactic acid bacteria, producing lactic acid without gas as the major end product of glucose metabolism. Although streptococci are referred to as facultative anaerobes, growing both aerobically and anaerobically, streptococci do not use oxygen metabolically. In addition, some strains are capnophilic, whereas others grow better under anaerobic conditions. This large and heterogeneous group of commensals of humans and animals harbors relatively avirulent normal microbiota organisms as well as some of the most impressive human pathogens.[1]

Early attempts to classify streptococci of clinical importance centered around their action on blood-containing agars[2] and antigens contained in their cell walls.[3] Some streptococci (β-hemolytic) can lyse blood cells and cause complete clearing of blood agar in the vicinity of their growth (Fig. 196.1). Other strains cause no change in blood agar (γ-hemolytic or nonhemolytic), whereas the remainder of the streptococci (α-hemolytic) reduce hemoglobin and cause a greenish discoloration of the agar (Fig. 196.2). Lancefield,[3] concentrating initially on virulent, β-hemolytic streptococci, found that they could be subdivided based on cell wall antigens. It was thought that β-hemolytic organisms with the same Lancefield antigen were closely related, but this correlation was not always valid for non–β-hemolytic strains. Other phenotypic traits of streptococci were also examined and catalogued throughout the 20th century, giving rise to various classification schemes. In 1937 Sherman[4] classified the streptococci into the pyogenic, viridans, enterococcal, and lactic divisions, based on phenotypic traits. Subsequent molecular studies generally upheld these basic divisions,[5] but revealed multiple genera among organisms traditionally thought to be streptococci.

By the mid-1980s, the enterococcal streptococci (Lancefield group D, bile esculin positive, and salt tolerant) had taken up residence in their own newly created *Enterococcus* genus, and the "dairy" or "lactic" streptococci (Lancefield group N, occasionally documented in human infection) were moved to the new *Lactococcus* genus. Ensuing studies of streptococci isolated from human and animal infections gave rise to updated classification schemes based on 16S ribosomal RNA sequences and other molecular information. These investigations also aided accurate differentiation of genera of streptococcal-like, catalase-negative, gram-positive cocci (e.g., *Leuconostoc, Pediococcus*, and numerous others) that had previously been unrecognized in clinical specimens. Many, but not all, β-hemolytic streptococci were found to be members of the pyogenic group, whereas the viridans streptococci were divided into groups of closely related species, one of which, the *Streptococcus mitis* species group, includes *Streptococcus pneumoniae*. Although the viridans strains, normal microbiota of the oral cavity and gastrointestinal tract, were traditionally characterized as α-hemolytic, it was realized that some members of this group also displayed β-hemolysis. Organisms considered to be nutritionally variant streptococci (also referred to as pyridoxal-dependent or satelliting streptococci) were reclassified in two new genera, *Abiotrophia* and *Granulicatella*.[1,6] It became apparent that the hemolytic reactions, Lancefield antigens, and other phenotypic characteristics relied on in the past were not always accurate predictors of genetic relatedness among strains. These characteristics are, however, still useful to clinical laboratorians for the presumptive identification of many commonly encountered streptococci. Table 196.1 summarizes currently described streptococcal species and species groups that are frequently isolated from humans. Streptococci normally associated with animals but infrequently isolated from human infection are presented in Table 196.2.

FIG. 196.1 Group A streptococci growing in pure culture on a sheep blood agar plate. Individual colonies are surrounded by zones of complete β-hemolysis. Subsurface hemolysis (agar stab) is caused in part by the action of streptolysin O, which is oxygen labile. The zone of inhibition around a low-potency bacitracin disk is a presumptive test for group A organisms.

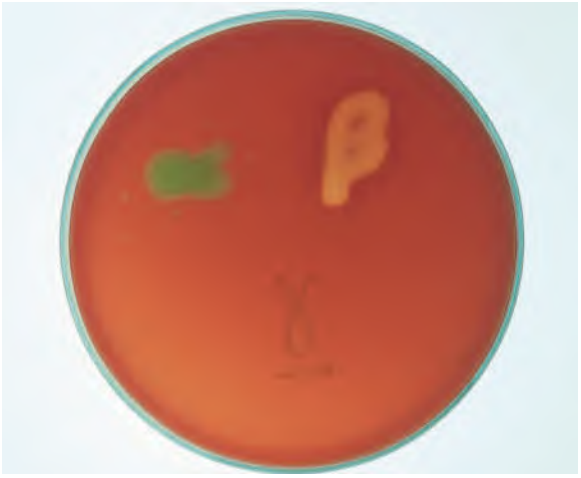

FIG. 196.2 Sheep blood agar plate with α-, β-, and γ-hemolytic streptococci.

TABLE 196.1 Classification of Streptococci Commonly Isolated From Humans

SPECIES	LANCEFIELD ANTIGEN(S)	HEMOLYTIC REACTION(S)	COMMENTS
S. pyogenes	A	β	Pyogenic; can be differentiated from β-hemolytic anginosus group strains with the group A antigen by the formation of relatively large colonies and other phenotypic traits; agent of pharyngitis and respiratory, skin, and other infections; can cause nonsuppurative sequelae (acute rheumatic fever, acute glomerulonephritis)
S. agalactiae	B	β, γ	Pyogenic; hemolytic reaction is weak; agent of chorioamnionitis, puerperal sepsis, neonatal sepsis and meningitis, and infections in nonpregnant adults
S. dysgalactiae subsp. *equisimilis*	C, G[b]	β	Pyogenic; formerly named *S. equisimilis;* can be differentiated from β-hemolytic *S. anginosus* group strains with the C or G antigen by the formation of relatively large colonies and other phenotypic traits; agent of respiratory and deep tissue infections, cellulitis, and septicemia
S. pneumoniae and the *S. mitis* spp. group	Not detected or not useful for differentiation	α	*S. pneumoniae,* an agent of respiratory infections, otitis media and meningitis, is a close relative of members of the *S. mitis* spp. group, a viridans streptococcal group. The nonpneumococcal *S. mitis* spp. group members include *S. mitis, S. oralis, S. sanguinis, S. gordonii,* and *S. pseudopneumoniae.* Some nonpneumococcal species produce extracellular polysaccharides[c] and play roles in subacute bacterial endocarditis and infections in neutropenic hosts
S. anginosus spp. group	A, C, F, G, or no detectable antigen	α, β, γ	Viridans streptococcal group composed of three species: *S. anginosus, S. constellatus,* and *S. intermedius;* two subspecies of *S. constellatus: S. constellatus* subsp. *constellatus* and *S. constellatus* subsp. *pharyngis,* have been described[7]; formerly known as *S. milleri;* β-hemolytic strains form small colonies compared with those of pyogenic β-hemolytic group A, C, and G streptococci and also differ in other phenotypic traits; agents of purulent infections
S. bovis spp. group	D	α, γ	Viridans streptococcal group formerly known as group D nonenterococcal streptococci; strains commonly isolated from humans are currently classified as *S. gallolyticus* subsp. *gallolyticus* (formerly *S. bovis* biotype I), *S. gallolyticus* subsp. *pasteurianus* (formerly *S. bovis* biotype II/2), *S. infantarius* subsp. *infantarius,* and *S. infantarius* subsp. *coli* (formerly *S. bovis* biotype II/1)[8]; some strains produce extracellular polysaccharides[c]; agents of endocarditis, meningitis; isolated from blood in patients with colonic cancer
S. mutans spp. group	Not useful for differentiation	α, γ, occasionally β	Viridans streptococcal group; *S. mutans* and *S. sobrinus* spp. are commonly isolated from humans; produce extracellular polysaccharides[c]; agents of dental caries and endocarditis
S. salivarius spp. group	Not useful for differentiation	α, γ	Viridans streptococcal group; *S. salivarius* and *S. vestibularis* spp. commonly isolated from humans; strains in the *S. salivarius* group may react with Lancefield group K antiserum and may produce extracellular polysaccharides[c]; infrequent opportunists in compromised hosts

[a]See reference 1 for additional information on streptococci mentioned in this table.
[b]Isolates with the group A antigen have also been described.
[c]Extracellular polysaccharides (dextran, levan) are thought to aid colonization and may play a role in virulence.

TABLE 196.2 Streptococci Primarily Isolated From Animals That May Occasionally Cause Human Infection

SPECIES	LANCEFIELD ANTIGEN(S)	HEMOLYTIC REACTION	COMMENTS
S. dysgalactiae subsp. *dysgalactiae*	C, L	α, β, γ	Pathogen of domesticated animals; participation in human infections not well documented
S. equi subsp. *equi*	C	β	Agent of equine strangles; participation in human infections not well documented
S. equi subsp. *zooepidemicus*	C	β	Agent of bovine mastitis and infection in other domesticated animals; implicated in outbreaks of nephritis in humans
S. porcinus	E, P, U, V	β	Swine are usual hosts; *S. porcinus*-like strains isolated from the human female genital tract are currently classified as *S. pseudoporcinus*[1]; may cross react with commercially available group B streptococcal grouping reagents
S. canis	G	β	Dogs and other animals are usual hosts; documented as an infrequent human pathogen
S. suis	R, S, T	α, β[b]	Swine are usual hosts; isolated infrequently from cases of human meningitis
S. iniae	No detectable antigen	β	Fish are usual hosts; isolated infrequently from cutaneous and systemic infection in humans

[a]See reference 1 for additional information on streptococci mentioned in this table.
[b]α-Hemolytic on sheep blood agar, but some strains may be β-hemolytic on horse blood agar.

References

1. Spellerberg B, Brandt C, et al. *Streptococcus.* In: Jorgensen JH, Carroll KC, Funke G, eds. *Manual of Clinical Microbiology.* 11th ed. Washington, DC: American Society for Microbiology; 2015:383–402.
2. Brown JH. *The Use of Blood Agar for the Study of Streptococci.* New York: Rockefeller Institute for Medical Research; 1919.
3. Lancefield RC. A serological differentiation of human and other groups of hemolytic streptococci. *J Exp Med.* 1933;57:571–595.
4. Sherman JM. The streptococci. *Bacteriol Rev.* 1937;1:3–97.
5. Bentley RW, Leigh JA, Collins MD. Intrageneric structure of *Streptococcus* based on comparative analysis of small-subunit rRNA sequences. *Int J Syst Bacteriol.* 1991;41:487–494.
6. Christensen JJ, Ruoff KL, et al. *Aerococcus, Abiotrophia,* and other aerobic catalase-negative, gram-positive cocci. In: Jorgensen JH, Carroll KC, Funke G, eds. *Manual of Clinical Microbiology.* 11th ed. Washington, DC: American Society for Microbiology; 2015:422–436.
7. Whiley RA, Hall LMC, Hardie JM, et al. A study of small-colony, β-haemolytic, Lancefield group C streptococci within the anginosus group: description of *Streptococcus constellatus* subsp. *pharyngis* subsp. nov., associated with the human throat and pharyngitis. *Int J Syst Bacteriol.* 1999;49:1443–1449.
8. Dekker JP, Lau AF. An update on the *Streptococcus bovis* group: classification, identification, and disease associations. *J Clin Microbiol.* 2016;54:1694–1699.

197 Streptococcus pyogenes

Amy E. Bryant and Dennis L. Stevens

SHORT VIEW SUMMARY

Definition

- *Streptococcus pyogenes* is an important global human pathogen that causes a wide variety of acute infections, such as soft tissue infections and pharyngitis; severe life-threatening infections, such as streptococcal toxic shock syndrome (strep TSS); and devastating postinfectious sequelae, such as rheumatic fever and glomerulonephritis.

Epidemiology

- The most common infection is streptococcal pharyngitis.
- Superficial skin and soft tissue infections include impetigo, erysipelas, and cellulitis.
- Severe life-threatening infections include scarlet fever, bacteremia, pneumonia, necrotizing fasciitis, myonecrosis, and streptococcal toxic shock syndrome.
- Postinfectious sequelae include acute rheumatic fever and poststreptococcal glomerulonephritis.

Microbiology

- *S. pyogenes* is a gram-positive, β-hemolytic *Streptococcus* that is catalase negative. More than 150 different strains have been identified based on different M-protein types. It is a group A *Streptococcus* based on its carbohydrate structure, according to Lancefield typing of β-hemolytic strains. Mucoid strains are rich in hyaluronic acid capsules, and numerous extracellular toxins are produced by most strains, which include streptolysin O (SLO; a cholesterol-dependent cytolysin), streptolysin S (SLS; a cell-associated hemolysin), nicotine adenine dinucleotidase (NADase; a metabolic toxin), fibrinogen-binding proteins, streptokinase (a fibrinolysin), numerous pyrogenic exotoxins that act as superantigens (e.g., streptococcal pyrogenic exotoxin A, [SpeA]), and a cysteine protease called streptococcal pyrogenic exotoxin B (SpeB).

Diagnosis

- Diagnosis of *S. pyogenes* pharyngitis is suspected based on specific clinical criteria and can be substantiated by rapid antigen tests or by bacteriologic culture.
- Similarly, impetigo, cellulitis, and erysipelas are suspected based on their clinical presentations. Cultures of impetiginous lesions will distinguish *Streptococcus* from *Staphylococcus aureus* as the cause. Cultures of lesions associated with cellulitis and erysipelas are useful only 20% of the time, and blood cultures are rarely positive.
- Invasive *S. pyogenes* is more difficult to diagnose early in the course, although blood cultures are positive in greater than 50% of cases. In the 50% of patients with necrotizing fasciitis associated with a portal of entry, such as surgical incision, postpartum sepsis, or insect bites, cultures of these sites are positive in most cases. In the 50% of patients with no portal of entry, infection begins deep in the fascia and muscle, and these patients often present with a history of previous nonpenetrating trauma, severe pain, and systemic toxicity. Classic signs of necrotizing infections are not apparent until late in the course, at a time when the patient has systemic shock and organ failure.
- Rheumatic fever is diagnosed based on clinical suspicion of patients with an antecedent pharyngitis who present with carditis, Sydenham chorea, migratory arthritis, and evidence that the pharyngitis was due to *S. pyogenes* by positive culture or rising anti-SLO titers and using the Jones criteria, which are reviewed elsewhere.
- Poststreptococcal glomerulonephritis is diagnosed based on evidence of renal failure with glomerular damage, as indicated by red blood cell casts and an antecedent streptococcal infection, which can be either pharyngitis or impetigo (see Chapter 200).

Therapy

- Penicillin remains the drug of choice for treatment of most streptococcal infections.
- Most cases of impetigo can be treated with topical bacitracin, mupirocin, or retapamulin, and only in severe cases or in epidemic situations is oral or parenteral administration of penicillin necessary.
- For severe cases of *S. pyogenes* infections, such as necrotizing fasciitis, myonecrosis, and strep TSS, the current recommendation includes the addition of clindamycin, which suppresses toxin production and in animal studies and limited human studies is superior to penicillin. Intensive care support, aggressive fluid resuscitation, ventilator support, and surgical intervention are commonly required.

Prevention

- Epidemics of streptococcal pharyngitis have been prevented in military recruits by the administration of monthly benzathine penicillin given intramuscularly.
- Rheumatic fever can be prevented by administration of penicillin within 9 days of the onset of streptococcal pharyngitis. Secondary prophylaxis should be considered in patients with rheumatic heart disease based on age, small children in the household, and exposure to cases of streptococcal infection.
- Improved living conditions, improved personal hygiene, and topical treatment of impetiginous lesions can prevent spread to susceptible individuals.
- Prevention of secondary cases should be considered in health care workers and family members with prolonged, intimate contact with patients with necrotizing fasciitis/strep TSS, particularly those who are immunocompromised, have varicella, have had recent surgery, or have recently given birth. The risk for secondary severe infection is low, but colonization and streptococcal pharyngitis can occur commonly. Oral penicillin for 7 to 10 days is reasonable, although no definitive studies have been done.

Streptococcus pyogenes (group A *Streptococcus;* [GAS]) is one of the most important bacterial pathogens of humans. This ubiquitous organism is the most frequent bacterial cause of acute pharyngitis, and it also gives rise to a variety of cutaneous and systemic infections. Its unique place in medical microbiology stems from its propensity to initiate two nonsuppurative sequelae: acute rheumatic fever and poststreptococcal glomerulonephritis. The former malady has been responsible for suffering, disability, and mortality in all parts of the world.

HISTORY

Streptococci were demonstrated in cases of erysipelas and wound infections by Billroth in 1874 and in the blood of a patient with puerperal sepsis by Pasteur in 1879. Fehleisen, in 1883, isolated chain-forming organisms in pure culture from erysipelas lesions and then demonstrated that these organisms could induce typical erysipelas in humans. Rosenbach applied the designation *Streptococcus pyogenes* to these organisms in 1884.

Initial progress toward a rational classification of streptococci dates from the description by Schötmuller in 1903 of the blood agar technique for differentiating hemolytic from nonhemolytic streptococci. In 1919 Brown[1] made a systematic study of patterns of hemolysis and introduced the terms α-, β-, and γ-hemolysis (see Chapter 196).

Rebecca Lancefield's classification of β-hemolytic streptococci into distinct serogroups in 1933 was a major turning point in our understanding of the epidemiology of streptococcal infections.[2] Most strains pathogenic for humans were found to belong to serogroup A *(S. pyogenes).* Systems of serotyping GAS were later developed on the basis of M-protein precipitin reactions (Lancefield) or T-protein agglutination reactions (Griffith). In addition, Lancefield established the critical role of M protein in streptococcal virulence and the type-specific nature of protective immunity to group A streptococcal infection. Studies by Dochez and collaborators and by George and Gladys Dick in the 1920s established the relationship of scarlet fever to hemolytic streptococcal infection. A few years later, Todd's description of the method for titration of anti–streptolysin O (ASO) in serum added still another important tool to the armamentarium available for study of the immunology and epidemiology of streptococcal disease. Such tools were used by a number of investigators, including Coburn, Collis, Rammelkamp, Stollerman, and Wannamaker, to establish the relationship of group A streptococcal infection to acute rheumatic fever and acute glomerulonephritis. Much of our knowledge of the detailed epidemiology of streptococcal infections and of acute rheumatic fever derives from the pioneering studies performed at Warren Air Force Base, Wyoming during 1949–51 by Rammelkamp, Wannamaker, and Denny.[3–5]

In 1981 the first superantigen was described from *Staphylococcus aureus* as a cause of staphylococcal toxic shock syndrome toxin 1 (TSST-1).[6] Later, pyrogenic exotoxins from GAS were shown to be superantigens as well (reviewed in Spaulding and colleagues[7]). These extracellular protein toxins have the ability to create a cytokine storm by simultaneously stimulating both T lymphocytes and macrophages (see discussion of virulence factors later).

In 1989 Stevens and colleagues[8] described 20 patients with streptococcal toxic shock syndrome (strep TSS) and implicated production of specific pyrogenic exotoxins associated with this condition.

DESCRIPTION OF THE PATHOGEN

GAS grow as spherical or ovoid cells 0.6 to 1.0 μm in diameter and occur as pairs or as short to moderate-length chains in clinical specimens. When growing in broth media enriched with serum or blood, long chains are frequently formed, and many strains produce capsules of hyaluronic acid. The organisms are gram positive, nonmotile, non–spore forming, catalase negative, and facultatively anaerobic. GAS are nutritionally fastidious and are usually cultivated in complex media, often supplemented with blood or serum.

When cultured on blood agar plates, *S. pyogenes* appears as white-to-gray colonies, 1 to 2 mm in diameter and surrounded by zones of complete (β) hemolysis. (Strains that fail to produce such hemolysis occur but are rare.) Strains that produce copious amounts of the hyaluronate capsular material appear mucoid, at times resembling a water drop on the plate. Less mucoid strains assume a crinkled, so-called matte appearance. Small opaque colonies of organisms that lack capsules and detectable M protein are termed *glossy.*

The complete genome sequences from several *S. pyogenes* serotypes have been reported, and this information is providing insight into the subtle genetic differences among streptococcal types that arm them to produce specific syndromes. Recent whole-genome studies have also revealed the phylogenic relatedness of GAS, including globally disseminated hypervirulent M-1 and M-3 strains.[9] A large number of somatic constituents and extracellular products of GAS have been identified. The most important of these are indicated in the following sections.

Somatic Constituents

The organism is enveloped in a hyaluronic acid capsule that serves as an accessory virulence factor in retarding phagocytosis by polymorphonuclear neutrophils (PMNs) and macrophages of the host.[10,11] Streptococcal strains vary greatly in their degree of encapsulation, and those with the most exuberant capsule production have a mucoid appearance when cultivated on blood agar plates. In certain heavily encapsulated group A streptococcal strains, the capsule may take precedence over M protein in mediating resistance to phagocytosis.[11] Group A streptococcal capsular hyaluronate is chemically similar to that found in human connective tissue. For this reason, it is a poor immunogen, and antibodies to group A streptococcal hyaluronic acid have not been demonstrated in humans.

The cell wall is a complex structure containing many different antigenic substances. The group-specific carbohydrate of group A strains is a dimer of rhamnose and *N*-acetylglucosamine in a ratio of approximately 2 : 1. The mucopeptide (peptidoglycan) layer provides rigidity to the cell wall; it is composed of polymers of repeating subunits of *N*-acetylglucosamine and *N*-acetylmuramic acid connected by amino-acid side chains.

M protein is the major somatic virulence factor of GAS. Strains rich in this protein are resistant to phagocytosis by PMNs, multiply rapidly in fresh human blood, and are capable of initiating disease. Strains that do not express M protein are avirulent.[12] GAS may be divided into serotypes on the basis of antigenic differences in M-protein molecules and more recently into genotypes on the basis of nucleotide differences in the *emm* gene encoding M protein. More than 150 such serotypes and more than 220 genotypes are currently recognized.[13] Acquired human immunity to streptococcal infection is based on the development of opsonic antibodies directed against the antiphagocytic moiety of M protein. Such immunity is type specific and quite durable, lasting for many years and perhaps indefinitely. Various vaccine strategies have targeted multiple individual M proteins with some success. Recently, however, convalescent serum samples from patients with skin and soft tissue infection demonstrated cross-reactive immune responses that align with M-protein clusters, suggesting that fewer individual M-types may be required for an effective vaccine against GAS.[14]

The M protein itself is a filamentous macromolecule that exists as a stable dimer with an α-helical coiled coil structure.[15] The molecule, which is anchored to the cell membrane, traverses and penetrates the cell wall. The more proximal portion of the molecule contains epitopes widely conserved among GAS, whereas the more distal portion contains type-specific epitopes.[16] This configuration localizes the type-specific moiety on the tips of fibrils protruding from the cell surface (Fig. 197.1). In the nonimmune host, M protein exerts its antiphagocytic effect by inhibiting activation of the alternative complement pathway on the cell surface.[17,18] Such inhibition appears to be mediated by the binding to the M-protein molecule of host proteins, among which are complement control proteins (factor H, a factor H–like protein, and human C4b-binding protein)[19–21] and fibrinogen.[22–24] The antiphagocytic effect is nullified in the presence of adequate concentrations of type-specific antibody. There is evidence that immunity caused by opsonic anti–M-type antibody may be strain and not type specific.[25,26] M proteins analogous to those of GAS are present in many strains of groups C[27] and G[28] streptococci.

Additional surface proteins related to M protein have now been identified. Although their structure is overall similar to that of M protein, they differ in the types of repeats and in their ability to interact with different human proteins. Genes encoding these proteins (e.g., *enn,*

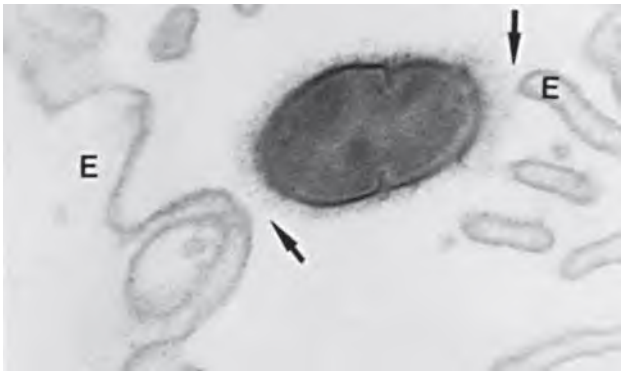

FIG. 197.1 Electron micrograph of group A streptococci. Surface fibrils contain type-specific, antiphagocytic epitopes of M protein. Lipoteichoic acid and fibronectin binding proteins facilitate adherence of streptococci to the membrane *(arrows)* of a human oral epithelial cell *(E)* (×67,500). *(From Beachey EH, Ofek I. Epithelial cell binding of group A streptococci by lipoteichoic acid on fimbriae denuded of M protein.* J Exp Med. *1976;143:759–771.)*

mrp, fcrA, arp, protH) have been designated as members of the *emm* gene superfamily. A number of the M-like proteins bind immunoglobulin (Ig)G or IgA at the non–antigen-binding site and appear to be cooperative with M protein in antiphagocytic effect.[29,30] Indeed, a notable function of the M-protein family is its ability to bind to a wide range of host proteins, including, among others, albumin, fibrinogen, and plasminogen. Still other antiopsonic surface proteins continue to be described.[31] For example, Mac, a secreted group A streptococcal protein with homology to a human β_2-integrin, binds to CD16 on the surface of human PMNs and inhibits phagocytosis and bacterial killing.[32] An additional surface protein, streptococcal heme-associated protein (Shp), has been found in M1 strains of GAS and likely has a role in transport of iron intracellularly. Antibody against Shp has been found in convalescent sera and has opsonic capability.[33] These observations underscore the extreme virtuosity with which the bacterium develops multiple mechanisms to evade phagocytic killing.

A protein antigen very closely associated with the M-protein molecule of GAS is the so-called serum opacity factor (OF). This factor is an α-lipoproteinase that is detected by its ability to opacify horse serum and that also has fibronectin-binding properties.[34] Strains of a minority of the currently identified M types elaborate this antigen.[35] OF itself is antigenic and type specific, that is, its ability to opacify serum can be specifically inhibited by antiserum raised against homologous but not heterologous M types. Type-specific and non–type-specific immune responses to streptococcal M protein are generally weaker after pharyngeal infection with OF-positive than with OF-negative types.[36] The former importance of this substance as an ancillary typing system for strains that could not be M serotyped has been obviated by the advent of *emm* genotyping. Of interest, antibody against OF has opsonic activity and has been shown to synergize with anti–M protein antibody in protecting mice against challenge with OF-positive strains.[37]

A number of somatic streptococcal constituents play critical roles in the first step of colonization, namely, adherence to the surface of human epithelial cells. At least 17 adhesin candidates have been described,[38] but the most extensively studied have been lipoteichoic acid (LTA), M protein, and fibronectin-binding proteins. Through hydrophobic interactions, LTA serves as a "first-step" adhesin, bringing the organisms into close contact with host cells and then allowing other adhesins to promote high-affinity binding.[39] Although M protein does not appear to promote adhesion to human buccal or tonsillar epithelial cells,[40,41] it does mediate adherence to skin keratinocytes via the attachment of the C repeat region to keratinocyte membrane cofactor CD46.[42,43] Group A streptococcal surface proteins that bind fibronectin have been studied extensively and are important in adherence to both throat and skin. These include protein F1 (PrtF1),[44] also known as SfbI (streptococcal fibronectin-binding protein I),[45] and related proteins known as SbfII,[46] FBP54,[47] protein F2,[48] and PFBB.[49]

Moreover, the expression of these adhesins has been reported to be environmentally regulated.[50] Expression of protein F1 is enhanced in an oxygen-rich environment, whereas that of M protein is greater at higher partial pressures of carbon dioxide.[51] Thus, teleologically, it might be postulated that the organism displays protein F1 on its surface when it seeks to adhere to the cutaneous surface but expresses M protein in the deeper tissues, where it is more likely to encounter phagocytic cells.

Extracellular Products

During the course of growth in vitro or in vivo, GAS elaborates numerous extracellular products, only a limited number of which have been well characterized. Two distinct hemolysins are recognized. SLO derives its name from its oxygen lability. It is reversibly inhibited by oxygen and irreversibly inhibited by cholesterol. In addition to its effect on erythrocytes, in high concentrations it is toxic to a variety of cells and cell fractions, including PMNs, platelets, endothelial cells, lysosomes, and isolated mammalian cardiomyocytes.[9,52] In subcytotoxic doses SLO stimulates hyperresponsiveness in these same cell types, including enhanced neutrophil degranulation, increased platelet activation and adhesion, induced synthesis of lipid mediators by endothelial cells and spontaneous, nonpaced and hyperaugmented contractions in cardiomyocytes.[53] SLO is produced by almost all strains of *S. pyogenes*, as well as many group C and G organisms, and is antigenic. Measurement of ASO antibodies in human sera is useful as an indicator of recent streptococcal infection.

Streptolysin S (SLS) is a hemolysin produced by streptococci growing in the presence of serum (hence the "S") or in the presence of a variety of other substances, such as serum albumin, α-lipoprotein, ribonucleic acid, or detergents such as Tween. SLS is nonantigenic, or at least no antibody to it has been detected that neutralizes its hemolytic activity. Like SLO, SLS can damage the membranes of PMNs, platelets, and subcellular organelles. Unlike SLO, it is not inactivated by oxygen, but it is thermolabile.[54,55] Most strains of *S. pyogenes* produce both hemolysins. Hemolysis on the surface of blood agar plates is primarily caused by SLS, whereas SLO exerts its hemolytic effect best in subsurface colonies, in pour plates, or in anaerobic cultures. An occasional strain may produce only one of the two hemolysins. Rarely, strains are encountered that lack both hemolysins.

Recently emerged, globally disseminated strains of hypervirulent GAS have been associated with production of nicotine adenine dinucleotidase (NADase), whereas older strains had the gene for this toxin but did not produce a functional enzyme.[56] Recent isolates have mutations in the SLO/NADase coregulator that result in enhanced coproduction of both virulence factors. It has been demonstrated that the binding of NADase to SLO stabilizes both toxins and enhances group A streptococcal virulence.[57]

Several extracellular products may theoretically serve to facilitate the liquefaction of pus and the spreading of streptococci through tissue planes characteristic of streptococcal cellulitis and necrotizing fasciitis. These include the following: (1) four antigenically distinct enzymes that participate in the degradation of deoxyribonucleic acid (DNases A, B, C, and D); (2) hyaluronidase, which enzymatically degrades hyaluronic acid found in the ground substance of connective tissue; (3) streptokinase, which promotes the dissolution of clots by catalyzing the conversion of plasminogen to plasmin; (4) streptococcal pyrogenic exotoxin B (SpeB), which is a potent protease; and (5) C5a peptidase, which specifically cleaves the human chemotaxis factor C5a at the PMN binding site.[58,59] SpeB also cleaves IgG bound to GAS, thus interfering with ingestion and killing by phagocytes.[60] The streptococcal pyrogenic exotoxins are a family of bacterial superantigens believed to be associated with strep TSS, necrotizing fasciitis, and other severe infections. This family includes the bacteriophage-encoded SpeA[61] and SpeC, historically known as the scarlatinal toxins because of their association with scarlet fever, as well as the cysteine protease SpeB; a number of additional pyrogenic exotoxins (e.g., mitogenic factor [MF, SpeF] and streptococcal superantigen [SSA]) have more recently been identified.[62] SSA and SpeC have been implicated in a recent upsurge of scarlet fever in China.[63] SpeB has also been implicated as a causative antigen in poststreptococcal glomerulonephritis, having been found in glomerular membranes in such patients.[64,65] Despite its many functions and its widespread distribution among clinical isolates of GAS[66] the role of SpeB in pathogenesis

remains controversial. One view is that SpeB is a key contributor to pathogenesis; alternatively, GAS may be under in vivo pressure to downregulate this toxin.

Superantigens are potent immunostimulators able to bind simultaneously to the class II major histocompatibility complex (MHC) and specific V-β regions of the T-cell receptor.[67] This binding results in clonal proliferation of these T cells. Superantigen activation of T cells leads to increased secretion of proinflammatory cytokines produced by both antigen-presenting cells and T lymphocytes. This issue is discussed in more detail later in the section "Streptococcal Toxic Shock Syndrome."

Emerging concepts regarding the molecular biology of streptococcal virulence, colonization, and tissue invasion have been reviewed.[62,68] Control of the expression of the heretofore-mentioned virulence factors over time and under diverse environmental circumstances depends on a complex system of genetic modulation. Of the known transcriptional regulators in *S. pyogenes,* the two most intensively studied are Mga[69] (multiple gene regulator) or Mry (regulator of M-protein expression) and a two-component regulatory system known as CsrRS[70] (capsule synthesis regulator) or, alternatively, CovRS[71] (control of virulence genes), which represses the synthesis of the capsule and several exotoxins.[72] The regulator of proteinase B (RopB) has been shown to have various polymorphisms that regulate the virulence of *S. pyogenes.*[73]

STREPTOCOCCAL PHARYNGITIS

Epidemiology

Streptococcal sore throat is among the most common bacterial infections of childhood. It is estimated that more than 600 million cases of streptococcal pharyngitis occur annually worldwide.[74] GAS are responsible for the great majority of such infections, but strains of other serogroups, especially groups C and G,[75] are occasionally involved. The disease occurs primarily among children 5 to 15 years of age, with the peak incidence occurring during the first few years of school. All age groups are susceptible, however, and severe epidemics are common in military training facilities. There is no gender predilection. The disease is ordinarily spread by direct person-to-person contact, most likely via droplets of saliva or nasal secretions. Crowding such as occurs in schools or barracks favors interpersonal spread of the organism (Fig. 197.2) and may also enhance its virulence by processes of natural selection analogous to those that occur during mouse passage in the laboratory. The effect of crowding in facilitating transmission may account in part for the increased incidence of streptococcal pharyngitis in northern latitudes during the colder months of the year. Explosive foodborne or waterborne outbreaks are also well documented. Contamination of dust, clothing, blankets, or other fomites does not appear to play a significant role in contagion.

GAS frequently colonize the throats of asymptomatic persons. Pharyngeal carriage rates among normal schoolchildren vary with geographic location and season of the year. Carriage rates as high as 15% to 20% have been noted in several studies. The carriage rate among adults is considerably lower.

Studies of experimentally induced human infections and of transmission in military barracks have shed considerable light on the variables involved in interpersonal spread. During the acute phase of tonsillopharyngeal infection, M-typeable GAS are frequently present in large numbers in the nose and throat. In untreated infections organisms may persist for many weeks, although the signs and symptoms of illness abate within a few days. During convalescence the organisms decrease in numbers and tend to disappear from the anterior nares sooner than from the throat. In addition, the M-protein content and virulence of persisting organisms gradually decline. The result of these qualitative and quantitative changes is that convalescent carriers are much less likely to transmit the organism to close contacts than acutely infected persons.

In patients who do not receive effective antibiotic therapy for acute streptococcal pharyngitis, type-specific antibodies are frequently detectable in the serum between 4 and 8 weeks after the infection. These opsonic antibodies protect against subsequent infection with organisms of the same M type, but the person remains susceptible to infection by heterologous types. Prompt and effective antibiotic therapy may ablate the type-specific immune response.

Clinical Manifestations

The usual incubation period of streptococcal pharyngitis is 2 to 4 days. The onset of illness is heralded by the rather abrupt onset of sore throat accompanied by malaise, feverishness, and headache. Nausea, vomiting, and abdominal pain are common in children. Prominent physical findings include redness, edema, and lymphoid hyperplasia of the posterior portion of the pharynx; enlarged, hyperemic tonsils; patchy discrete tonsillopharyngeal exudates (Fig. 197.3); enlarged, tender lymph nodes at the angles of the mandibles; and a temperature of 38.3°C (101°F) or higher. In the absence of these symptoms and signs, simple coryza, hoarseness, cough, or conjunctivitis does not suggest the presence of streptococcal infection. Laboratory findings include a positive throat culture for β-hemolytic streptococci and a total white blood cell (WBC) count usually exceeding 12,000/mm,[3] with increased numbers of PMNs. The test for C-reactive protein is usually positive.[76]

Not all patients with streptococcal pharyngitis have the full-blown syndrome just described. Endemically occurring infections in open populations manifest a wide spectrum of clinical severity. For example, only approximately 50% of such patients with sore throats and positive throat cultures have tonsillar or pharyngeal exudates. Patients who have undergone tonsillectomy tend to experience a milder clinical syndrome. In infants the response to streptococcal infection is much less sharply focalized to the lymphoid tissue of the faucial and posterior pharyngeal

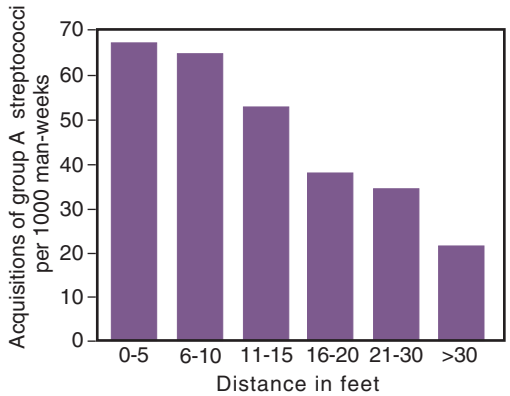

FIG. 197.2 Transmission of group A streptococci in a military barracks according to bed distance from the nearest carrier. *(From Wannamaker LW. The epidemiology of streptococcal infection. In: McCarty M, ed.* Streptococcal Infections. *New York: Columbia University Press; 1953:157–175.)*

FIG. 197.3 Streptococcal tonsillopharyngitis. Exudates *(arrows)* are present on the enlarged erythematous tonsils. *(From Nimishikavi S, Stead I. Images in clinical medicine: streptococcal pharyngitis.* N Engl J Med. *2005:352:e10.)*