8.6.4 Staphylococci 991

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Geneva. 8.6.4 Staphylococci Kyle J. Popovich, Robert A. Weinstein, and Bala Hota ESSENTIALS Staphylococci are Gram-positive cocci that form clusters, but can occur singly, in pairs, chains, or tetrads. They are classically distin- guished from other Gram-positive cocci by presence of catalase, an enzyme that degrades hydrogen peroxide (H2O2). S. aureus is dis- tinguished from other coagulase-negative staphylococci, which are generally less virulent, by the presence of coagulase, an enzyme that coagulates plasma. Many toxins and regulatory elements enhance virulence in staphylococci. Epidemiology Colonization—staphylococci are skin commensals. About 20% of adults are persistently colonized by S. aureus, 60% are intermit- tently colonized, and 20% are never colonized. High-risk groups for S. aureus colonization include infants, insulin-dependent diabetics, intravenous drug users, HIV-infected patients, and renal dialysis patients. Methicillin-resistant S. aureus (MRSA)—risk factors for MRSA colon- ization and infection among hospitalized patients include antibiotic exposure, surgery, nursing home residence, or high MRSA ‘colon- ization pressure’ (i.e. frequent exposure to colonized or infected patients). However, MRSA is no longer only a hospital-related infec- tion, with community-associated MRSA affecting individuals without healthcare exposures. Clinical features S. aureus infection—clinical syndromes can be divided into three groups: (1) Illness due to release of toxins, leading to disease at sites often remote from infection—including (a) staphylococcal scalded skin syndrome—release of epidermolytic toxins leads to bullae and desquamation; (b) food-borne illness due to preformed toxin—a heat-stable superantigen toxin produces sudden vomiting and diarrhoea; (c) toxic shock syndrome—superantigen toxins cause multisystem organ dysfunction; may be menstrual (e.g. tampon- associated) or nonmenstrual. (2) Illness due to local tissue destruction and abscess formation—including (a) impetigo, folliculitis, and cel- lulitis; (b) furuncles and carbuncles; (c) mastitis; (d) pyomyositis; (e) septic bursitis; (f) septic arthritis; (g) osteomyelitis; (h) epidural ab- scess; (i) pneumonia; (j) urinary tract infection. (3) Hematogenous infection—including bacteraemia and endocarditis. Coagulase-negative staphylococci—most infections with these skin commensals are the consequence of medical interventions leading to foreign bodies (e.g. prosthetic joints or heart valves), indwelling intravascular catheters or grafts, or peritoneal catheters. Conditions

include endocarditis (5–8% of native valve infections, c.40% of pros- thetic valve infections), intravascular catheter infections (6–27% of vascular catheter infections), prosthetic joint infections (up to 38% of arthroplasty infections), peritoneal dialysis, catheter infections, and postoperative ocular infections. Diagnosis Diagnosis relies on characteristic clinical and epidemiological fea- tures, supported by positive cultures from the relevant clinical site, with identification (when appropriate) of exotoxin-positive strains. Outbreak and epidemiological investigations use molecular fingerprinting techniques to assess relatedness of staphylococci. Treatment Aside from supportive care, the mainstays of therapy are (1) prompt drainage of infected foci; and (2) antimicrobials—(a) coagulase- negative staphylococci—vancomycin is the mainstay of therapy because of the high rates of methicillin resistance; (b) S. aureus— antimicrobial choice should be based on the local prevalence of MRSA and the clinical severity of illness; a bactericidal agent, prefer- ably a β-lactam, is used whenever possible; oral agents active against MRSA include clindamycin, trimethoprim/sulfamethoxazole, doxy- cycline, minocycline, linezolid; glycopeptides (i.e. vancomycin or teicoplainin) have been the usual therapy of severe infections due to MRSA, but reduced susceptibility to vancomycin has been reported. Prevention Prevention of illness due to S. aureus, particularly MRSA, relies on proactive infection control measures, including (1) surveillance for MRSA colonization; (2) imposed grouping (cohorting) of infected and colonized patients; (3) barrier precautions (e.g. gowning and gloving by healthcare staff); (4) improved hand hygiene; (5) cleaning patients (e.g. with chlorhexidine); (6) improved environmental cleaning; (7) antimicrobial stewardship. Better strategies for treatment and salvage of infected cath- eters or methods for treatment of biofilm may improve treatment of coagulase-negative staphylococcal infections. No vaccines are available. Introduction and historical perspective Staphylococci are named for their microscopic appearance, the name coming from Greek words meaning ‘bunch of grapes’ and ‘berry’. First described in 1880 by Ogston as an important cause of abscesses in humans, staphylococci are among the most common causes of bacterial colonization and infection in the community and in hospitals.

section 8 Infectious diseases 992 Staphylococcus aureus, the pre-eminent human staphylococcus, has adapted efficiently to improvements in therapeutics. In the 1940s, shortly after the introduction of penicillin, penicillin-resistant S. aureus was noted in the United Kingdom and the United States of America, and by the end of the decade 50% of isolates were resistant. From 1940 to 1960, a particularly invasive clone of penicillin-resistant S. aureus, ‘phage type 80/81’, caused pandemic hospital infections. Following the introduction of methicillin, that strain faded from concern only to be replaced in subsequent dec- ades with endemic healthcare-associated methicillin-resistant S. au- reus (MRSA) that frequently was resistant to multiple antimicrobial classes. Most recently, reminiscent of the 1940 to 1960 experience, invasive strains of community-associated MRSA (CA-MRSA) have emerged rapidly in some communities among otherwise healthy in- dividuals. Coagulase-negative staphylococci infections, in contrast, are infecting implanted devices and occurring in association with healthcare, thereby filling a niche created by medical success. Microbiology and molecular genetics Staphylococci stain purple (‘positive’) with Gram’s stain and form grape-like clusters, but can occur singly, in pairs, in chains, or in tetrads. Of 32 staphylococcal species, 16 colonize or infect humans. Classically, staphylococci are distinguished from other Gram- positive cocci by the presence of catalase, an enzyme that degrades H_2O_2. S. aureus is distinguished from other staphylococci by the presence of coagulase, an enzyme that coagulates plasma. Most la- boratories use latex agglutination tests to detect coagulase; other as- says include the tube coagulase and free coagulase tests. Outbreak and epidemiological

investigations use molecular ‘finger printing’ techniques to assess relatedness of staphylococci, that is, bacteriophage typing, pulsed-field gel electrophoresis, multilocus sequence typing, or more recently, whole bacterial genome sequencing. In epidemiologic evaluations of MRSA, for example, limitations of methods such as pulsed-field gel electrophoresis have been the in- ability to differentiate between endemic MRSA strains. However, more recently whole genome sequencing which is highly discrim- inatory has been used as an epidemiologic tool in healthcare settings to improve our understanding of transmission of MRSA strains from one individual to another. In a study of an MRSA outbreak in a spe- cial care baby unit in the United Kingdom, whole genome sequencing allowed investigators to identify a staff member with MRSA carriage who likely allowed the outbreak to continue despite implementation of infection control measures. Whole genome sequencing was also ap- plied in an adult intensive care unit to investigate acquisitions of S. au- reus strains among patients. In this study, results of whole genome sequencing suggested that only 18.9% of S. aureus acquisitions could be explained by transmissions from other colonized patients. Validation of this work by integrating robust epidemiologic data with whole genome sequencing results is warranted. Future applications of this technology might be valuable for evaluating and directing infec- tion prevention strategies in outpatient and inpatient settings. Pathogenesis The infectiveness of staphylococci depends in part on bacterial fac- tors that promote growth, colonization, invasiveness (i.e. regulation and virulence determinants), and antibiotic resistance and in part on host susceptibility (e.g. presence of diabetes mellitus). Likely there is an important interplay of microbial, host, and epidemiologic factors that influence severity of illness for S. aureus infections. Regulation and virulence determinants Regulation determinants ‘autoregulate’ staphylococci based on en- vironmental conditions or host factors. The major S. aureus regu- latory gene is the accessory gene regulator (agr) that facilitates intercell communication. This and other systems might have roles in tissue destruction (through exoprotein production) and endocar- ditis (through adhesin regulation). Virulence determinants (e.g. peptidoglycan, lipoteichoic acids, protein toxins, and biofilm) enhance bacterial pathogenicity but can also activate patient protective mechanisms. Peptidoglycan, an important component of Gram-positive bacterial walls, and lipoteichoic acids, bound to the plasma membrane, are implicated in triggering the inflammatory response in humans that can enhance bacterial killing. Exoproteins and ‘superantigens’ (i.e. antigens that lead to nonspecific immune activation) can be released by S. aureus to cause a severe immune response or disease remote from infection, while local toxins, for example, Panton–Valentine leucocidin, may increase bacterial invasiveness. Biofilm, an extracellular complex of polysaccharides, enhances binding to foreign objects (e.g. intravas- cular catheters) and serves as a bacterial sanctuary from host de- fences and antimicrobials. Genome sequencing has been used to identify bacterial toxins that might be associated with worse clinical outcomes among in- dividuals with S. aureus infections. After adjusting for host factors, colonization with MRSA strains that carried the staphylococcal en- terotoxin P (sep) gene is a risk factor for subsequent development of MRSA infection. This highlights how integrating host and virulence data can improve our understanding of the pathogenesis of S. aureus infections. Antimicrobial resistance S. aureus resistance to β-lactams is mediated by β-lactamases (peni- cillin resistance) or, more commonly, by altered enzymes respon- sible for cell wall formation (methicillin resistance). Penicillinases propagate by plasmids or phage transfer; methicillin resistance re- sults from spread of a genomic island of DNA called the staphylo- coccal chromosomal cassette (SCC). The SCC carries the mecA gene (termed SCCmec). The product of mecA is penicillin-binding pro- tein 2a (PBP2a), which has low affinity for methicillin and enables cell wall synthesis in spite of active antibiotics. SCCmec type IV pri- marily is associated with CA-MRSA, while types I, II, and III are

associated primarily with hospital strains. Glycopeptides (i.e. vancomycin or teicoplanin) have been the usual therapy of severe infections due to MRSA. However, vancomycin re- sistance is emerging among MRSA. Two resistance patterns exist: (1) vancomycin- (or glycopeptide-) intermediate S. aureus (VISA or GISA) and (2) vancomycin-resistant S. aureus (VRSA). The VISA phenotype has vancomycin minimum inhibitory concentrations of 4–8 μg/ml, and is thought to arise from thickening of the cell wall, changes in agr function, and changes in cell metabolism that arise from subinhibitory exposure to vancomycin. VRSA have higher min- imum inhibitory concentrations (≥16 μg/ml) due to a gene (vanA) that has been passed from vancomycin-resistant Enterococcus faecalis to S. aureus. Clinical isolates of VRSA (13 so far) have been reported

8.6.4 Staphylococci 993 in the United States of America. Although new agents (linezolid and daptomycin) exist for therapy of MRSA and could be used for VISA/ VRSA, fledgling resistance has been reported. Outbreaks of linezolid-resistant MRSA have been identified, with the cfr gene believed to mediate resistance. One outbreak was felt to be associated with high usage of linezolid; the outbreak was con- trolled with antibiotic stewardship and enhanced infection control measures. Resistance to antimicrobials in the macrolide–lincosamide– streptogramin (MLS) group is not predictably concordant. Clindamycin resistance can be inducible, producing misleading sus- ceptibility phenotypes in automated testing that are erythromycin resistant and, seemingly but erroneously, clindamycin susceptible, or constitutive (readily detected resistance to erythromycin and clindamycin). The double-disc diffusion test, or D test, will detect inducible clindamycin resistance. Clindamycin therapy is unreliable in organisms with either inducible or constitutive resistance. Among the coagulase-negative staphylococci, 80% of isolates are resistant to methicillin due to the action of mecA. Laboratory testing of coagulase-negative staphylococci is complicated by heterotypic expression of methicillin resistance, which can lead to deceptively low methicillin minimum inhibitory concentrations. Polymerase chain reaction (PCR) testing for mecA or slide agglutination testing for PBP2a will reveal resistance; methicillin or oxacillin will not ef- fectively treat such strains. Epidemiology: S. aureus Colonization Among staphylococci, as a general rule, colonization precedes infec- tion. S. aureus colonizes multiple sites but predominately the anterior nares. Among adults, 20% are persistently colonized by S. aureus, 60% are intermittently colonized, and 20% are never colonized. Methicillin-susceptible S. aureus (MSSA) colonization prevalence rates are about 30% in the community; the prevalence of nasal col- onization with MRSA in the general community has increased from 0.8% in 2001–2002 to 1.5% in 2003–2004. Colonization outside the nares (e.g. throat, axilla, inguinal area, and peri-rectal area) can also occur with some individuals being colonized at multiple body sites. Colonization outside of the nares can have important implications for infection control, decolonization, and infection prevention. High-risk groups for S. aureus colonization include infants, insulin- dependent diabetics, intravenous drug users, HIV-positive patients, and patients undergoing either haemodialysis or peritoneal dialysis. Host factors promoting colonization may be antibiotic treatment and polymorphisms in host genes. Health care-associated MRSA Health care-associated MRSA infection causes significant morbidity and mortality, and has been associated with 29% longer stays and 36% greater hospital charges for patients with MRSA compared to MSSA bacteraemia. Among hospitalized patients, risk factors for MRSA colonization and infection include antibiotic exposure, sur- gery, nursing home residence, or high MRSA ‘colonization pressure’ (i.e. frequent exposure to colonized or infected patients). There is a large ‘resistance iceberg’ for MRSA; the ratio of infected-to-colonized patients might reach 1:3, which complicates control measures. The hands of healthcare workers probably represent a major vector for MRSA cross-transmission. Another

mechanism of staphylococcal transmission is bacterial shedding from nares of col- onized patients or staff, which can be enhanced by rhinitis. Spread via contaminated environmental surfaces might account for an add- itional 10–15% of MRSA transmissions in healthcare settings. Community-acquired MRSA (CA-MRSA) MRSA are no longer exclusively nosocomial pathogens. They have been affecting people without exposure to healthcare. Although CA-MRSA colonization rates have lagged behind those of MSSA, infection rates for those colonized with CA-MRSA are up to 10 times higher than rates for those colonized with MSSA. Worldwide, CA-MRSA infections have been mainly due to only a few pulsed-field gel electrophoresis types (e.g. USA300 strain). In the United States, USA300 is the predominant CA-MRSA strain and in some community settings is considered an endemic pathogen. CA- MRSA strains are now a common cause of skin and soft tissue infec- tions in ambulatory clinics and emergency rooms in the United States. In contrast to MRSA strains traditionally associated with hospitals, CA-MRSA strains are often characterized by an increased suscep- tibility to non-β-lactam antibiotics. However, a multidrug resistant strain of USA300 has been reported in the United States so continued monitoring of the local antibiogram is essential to inform empiric therapeutic decisions. In addition, the epidemiology of CA-MRSA has evolved with CA-MRSA strains now accounting for a significant proportion of healthcare-associated and nosocomial bacteraemias in several United States hospitals. Risk factors for infection or coloniza- tion with CA-MRSA include African American race, HIV infection, drug use, tattooing, and situations and environments associated with increased person-to-person contact such as military service, jails, homosexual contacts, sports activity, and children's day care. Potential reservoirs and sources for CA-MRSA include ani- mals (e.g. pigs, cattle, horses, chickens, and companion animals), prompting the terminology 'livestock-associated MRSA'. One study found that a novel strain of MRSA in the Netherlands was associ- ated with pig or cattle farmers. Another MRSA strain with an altered mecA gene has been identified in Europe among humans and dairy cows. The extent of transmission occurring between humans and animals, and how this contributes to spread of MRSA in the com- munity among humans, is unclear. Secular trends and morbidity Overall trends in hospitalizations for S. aureus infections sug- gest an increasing burden of illness. Trends fostering increases in- clude ageing of populations in western societies with increased comorbidities and use of prosthetic devices, such as joint replace- ments; the emergence of CA-MRSA, which is occurring in add- ition to, not in place of, community-associated MSSA; and use of broad-spectrum antibiotics. In the United States of America, it has been estimated that about 9 of every 1000 hospitalizations might be due to S. aureus, and about 43% of S. aureus admissions are due to MRSA. Mortality rates among patients infected with S. aureus are 15–34% in various studies. Clinical factors enhancing the likelihood of death include pneumonia, older age, diabetes, inadequate therapy, and failure to drain infected foci. With the spread of CA-MRSA into hospitals, the epidemiology and control of nosocomial MRSA may change. Recent studies in the United States have documented a decline in hospital-associated and healthcare-associated invasive MRSA

 infections over the past ten years. This decline is felt to reflect im- proved recognition of healthcare-associated infections as well as the institution of various infection control programmes in intensive care units. In contrast, the incidence of invasive CA-MRSA infections has remained relatively stable, suggesting that infection prevention strategies may need to be expanded to outpatient and community settings. In a population based matched cohort study in the United Kingdom from 1995-2015, investigators observed that a docu- mented penicillin allergy was associated with an increased risk of MRSA and Clostridium difficile infection, possibly due to in- creased exposure to alternative antibiotics (e.g., macrolides, fluoroquinolones,

clindamycin). The proportion of these pa- tients who actually had true penicillin allergies is not known. Nevertheless, this study highlights the importance of moving to- ward a more thorough evaluation of individuals who self-report penicillin allergies and how this effort could improve antibiotic stewardship efforts. Prevention: S. aureus General interventions Prevention of illness due to S. aureus, particularly MRSA, relies on proactive infection control measures. These include surveillance for MRSA colonization to detect the resistance iceberg, barrier precau- tions (use of gowning and gloving) for care of infected and colonized patients, imposed grouping (cohorting) of infected and colonized patients, isolation wards, improved hand hygiene, antimicrobial stewardship, cleaning patients with chlorhexidine, improved envir- onmental cleaning, and use of intensive care unit 'monitors' to pro- mote adherence to infection control measures. MRSA Studies of MRSA control suggest that multiple simultaneous inter- ventions can reduce colonization and infection rates. Highly pro- moted among packages or bundles of interventions are hospital admission surveillance nasal cultures for MRSA colonization. These are recommended in high-risk units or when other con- trol measures fail to reduce MRSA infection rates. The strongest support for decolonization comes from outbreak investigations, particularly in neonatal units, and from quasi experimental before- after trials. The relative roles of MRSA active surveillance, decolonization, and routine chlorhexidine bathing have been evaluated recently in more rigorous trials. A multicentre cluster-randomized study of daily bathing with chlorhexidine-impregnated washcloths in comparison to non-antimicrobial washcloths observed signifi- cant decreases in acquisition of multidrug resistant organisms and overall hospital-acquired bloodstream infections in the chlorhexidine bathing group. While the overall rate of MRSA acquisition was lower during the chlorhexidine study period, the decline did not reach statistical significance. A separate 43- hospital study examined three infection control strategies for preventing infections in the intensive care unit—(1) active de- tection and isolation of MRSA carriers, (2) active detection and isolation with targeted decolonization of MRSA carriers (using intranasal mupirocin for 5 days and daily chlorhexidine bathing), and (3) no active detection and isolation but implementation of universal decolonization (intranasal mupirocin for 5 days and daily chlorhexidine). Universal decolonization was associated with the greatest reduction in rates of MRSA clinical isolates as well as the largest decline in bloodstream infection from any pathogen. A subsequent decision-analysis model suggested that universal decolonization was more likely than the other two ap- proached to reduce infections and healthcare costs. Surveillance for development of resistance to decolonizing agents, especially mupirocin, would be important should this approach become widespread. Editorialists commenting on this article question the further need for active detection and isolation for controlling MRSA in an en- demic setting—an approach currently used in many hospitals—as well as advocate adopting more 'horizontal' infection control ap- proaches such as universal decolonization rather than 'vertical' or pathogen specific strategies. As another example of a horizontal infection control approach, a longitudinal study in Australia of the incidence of hospital-onset S. aureus bacteraemias from 2002–2013 observed a significant de- cline in the rate of both MRSA and MSSA during this time frame. The authors attribute this nationwide decline in the rate of S. aureus bacteraemia to the several infection prevention interventions that were instituted at the local and national level, and that the focus of efforts was on reducing all healthcare-associated infections, not just those due to MRSA. CA-MRSA Control of CA-MRSA presents distinct challenges. The feasibility of contact precautions or isolation of infected persons in the com- munity might be limited. Additionally, the role of fomites in trans- mission of CA-MRSA is unknown, and community environmental decontamination may be difficult. Current guidelines for people with CA-MRSA infections and their community contacts include proper dressings for infected areas, hand hygiene,

washing clothes contaminated with infected secretions, and avoiding contact sports while lesions exist. If infection is recurrent or spreading in specific settings, such as families, decolonizaton of carriers and potential family members may be warranted in conjunction with thorough environmental cleaning. Agents useful for decolonization Potential agents used for staphylococcal decolonization include topical agents (mupirocin, chlorhexidine, tea tree oil) or short courses of systemic antimicrobials. Mupirocin 2% is effective for decolonization but recolonization can occur and resistance can develop.. Tea tree oil, from the Ti (or Tea) tree (Melaleuca alterni- folia, Myrtaceae), has been effective for some colonized patients. Chlorhexidine gluconate has potent antibacterial effects for de- colonizing skin or as a nasal gel. Failure to control spread of spe- cific clones of MRSA due to efflux of chlorhexidine from resistant bacteria has been reported, but, resistant strains have been very rare in systematic studies. Some favour combining agents (e.g. mupirocin with chlorhexidine bathing with an oral MRSA anti- biotic) to target both nasal and extranasal colonization and prevent recurrent MRSA infections. Baths containing dilute bleach solu- tions have been advocated by paediatricians for interrupting cycles of MRSA skin infection in infants, and assiduous application of

8.6.4 Staphylococci 995 approved detergents/disinfectants or bleach can decontaminate the environment. Iodophors may be another option for the nasal treatment component of MRSA decolonization regimens; clinical trials of this alternative are currently under way. Clinical features: S. aureus Risk factors for infection Groups commonly at risk of colonization and infection include AIDS patients, intravenous drug users, and patients with diabetes mellitus. Multiple risk factors for S. aureus infection often co- exist. For example, haemodialysis and peritoneal dialysis patients are at increased colonization risk and have high-risk foreign bodies. Conditions that predispose specifically to tissue invasion include skin trauma, haematomas, burns, or chronic diseases (e.g. dermatitis or psoriasis); surgical wounds; indwelling vas- cular catheters; and postviral sequelae such as influenza-related mucosal damage. Rarer conditions associated with increased risks of staphylococcal infection include Chédiak–Higashi syn- drome and Job's syndrome. Clinical syndromes S. aureus infection syndromes can be divided into three groups: (1) illness due to release of toxins, leading to disease at sites often remote from infection; (2) illness due to local tissue destruction and abscess formation; and (3) haematogenous infection. Therapy for these syndromes is based on the use of active drugs at appro- priate dosages with appropriate concern for common side effects and toxicities. Toxin-related syndromes Staphylococcal scalded skin syndrome In 1878, staphylococcal scalded skin syndrome, or Ritter's dis- ease, was described in 297 children by the German physician Ritter von Rittershain. After release of epidermolytic toxins by S. aureus, patients develop bullae and desquamation. Though clin- ically impressive (Fig. 8.6.4.1a), this superficial desquamation can be distinguished clinically and histologically from deeper ex- foliative illnesses such as toxic epidermal necrolysis. In staphylo- coccal scalded skin syndrome, skin separation occurs within the epidermis, at the stratum granulosum, while in toxic epidermal necrolysis, separation occurs deeper, at the dermal–epidermal junction, leading to more severe skin loss. The absence of mucosal disease in staphylococcal scalded skin syndrome also distinguishes these syndromes. Staphylococcal scalded skin syndrome occurs more commonly in children (Fig. 8.6.4.1b). Disease may be generalized or local- ized (i.e. bullous impetigo), and the burden of S. aureus may be low. Nasal or mucosal colonization may cause disease. When cases occur in epidemics, such as in neonatal units, patients and healthcare workers should be screened for carriage. Diagnosis re- lies on the characteristic clinical and epidemiological features and is supported by identification of exotoxin-positive strains colon- izing or infecting clinical sites.

Treatment involves topical or sys- temic antibiotics for infected sites and supportive care for areas of skin/soft tissue destruction. Food-borne illness due to preformed toxin S. aureus can produce a heat-stable superantigen toxin that can per- sist even after cooking has eradicated the organism. Ingestion of toxin in contaminated, often unrefrigerated, food can result in epi- demic gastrointestinal disease. There is a short incubation of only 2–6 h, followed by sudden vomiting (82%), diarrhoea (68%), and occasionally fever (16%). The differential diagnosis includes other short-incubation toxin-mediated gastrointestinal pathogens such as Bacillus cereus and toxins (Chapter 8.6.7). Treatment involves sup- portive care, particularly rehydration. The illness is typically self- limited, lasting less than 12 h. Toxic shock syndrome Staphylococcal toxic shock syndrome is caused by systemic superantigen toxins released by S. aureus, resulting in multisystem organ dysfunction. Staphylococcal toxic shock is clinically similar to streptococcal toxic shock (high fever, mental confusion, erythroderma, diarrhoea, hypotension, and renal failure), but streptococcal toxic shock is typically associated with invasive infec- tion such as necrotizing fasciitis while staphylococcal toxic shock (a) (b) Fig. 8.6.4.1 Staphylococcal scalded skin syndrome: (a) in an adult;
(b) in a child. (a) copyright Professor S. J. Eykyn; (b) copyright Professor W. C. Noble.

 can be precipitated by clinically minor infections that are over- shadowed by the systemic effects of the toxin. Staphylococcal toxic shock occurs in two major forms, menstrual (e.g. tampon-associated) and nonmenstrual. In women with vaginal colonization by S. aureus, it is presumably the favourable micro- environment during menses that leads to increased production of toxin (TSST-1). Management of staphylococcal toxic shock relies on systemic antimicrobial therapy (Table 8.6.4.1), supportive care, and prompt drainage of infected/colonized foci. Common adjunctive ther- apies such as intravenous immunoglobulin to bind free toxin and antibacterials (especially clindamycin and potentially linezolid) with activity at the ribosome, which decreases bacterial protein (toxin) synthesis, have a theoretical rationale and some support from animal models; however, clinical data are limited. Illness due to local tissue invasion/destruction S. aureus and β-haemolytic streptococci cause approximately 80% of soft tissue infections. S. aureus is the aetiological agent of 37– 65% of native monoarticular joint infections in healthy adults and of 75% of joint infections in rheumatoid arthritis. Osteomyelitis, either of haematogenous or contiguous origin, is caused by S. au- reus or coagulase-negative staphylococci in more than 50% of cases. Any local infection can lead to secondary bacteraemia and haema- togenous seeding of distant sites. Impetigo, folliculitis, and cellulitis The most superficial S. aureus infections are impetigo, folliculitis, and cellulitis. Impetigo is limited to the epidermis, folliculitis to the hair follicles, and cellulitis to the dermis and/or the subcutaneous fat. Impetigo can appear as small round honey-crusted lesions on the skin, primarily on exposed areas (Fig. 8.6.4.2). Impetigo typic- ally is caused by streptococci; in the United Kingdom, S. aureus is an infrequent cause. However, bullous impetigo is a clinical variant (caused by S. aureus phage type 71), reported in up to 10% of impe- tigo cases. Initially, the lesions can be vesicles that enlarge into bullae containing clear or yellow fluid. Cellulitis is typically due to streptococci, but when associated with penetrating trauma, furuncles, or carbuncles S. aureus should be considered. Diagnosis depends on the clinical appearance and the presence of purulence that can be cultured. However, aspirates of cellulitic areas are positive in less than one-third of cases and bac- teraemia is rare. Treatment of impetigo (Table 8.6.4.2) should reflect local anti- biotic resistance patterns. Topical therapy (e.g. mupirocin or retapamulin) might be effective for limited disease, though EMRSA- 16, one of two predominant MRSA types in the United Kingdom, often shows high-level mupirocin

resistance. In settings of high topical fusidic acid use, resistance in S. aureus isolates has been reported. Systemic therapy should be used in patients with impetigo who have many lesions or who fail topical therapy. In areas where CA-MRSA prevalence exceeds 10%, initial therapy should be directed by local susceptibility patterns. Suspicion of more invasive infection, such as necrotizing fasciitis, should be high in cases of soft tissue infections with dis- proportionate pain, bullae, haemorrhagic or necrotic lesions, cutaneous anaesthesia, rapid progression of lesions, gas in the tissues, presence of risk factors, and when laboratory tests show elevated creatine kinase, acidosis, leucocytosis, or C-reactive pro- tein exceeding 13 mg/litre. Necrotizing infections should prompt inpatient antibiotic therapy assuming MRSA and urgent surgical consultation. Skin abscess furuncles and carbuncles Skin abscess is an infection within the dermis and deeper skin tis- sues. Furuncles and carbuncles are deep suppurative infections that Table 8.6.4.1 Therapy of toxic shock due to S. aureus Drug Dosage Duration/comment For penicillin-susceptible S. aureus: Duration based on focus of infection Adequate drainage is critical Data to support adjunctive use of immunoglobulin and/ or clindamycin are needed Penicillina 2–4 MU IV every 4 h Ampicillin 1–2 g IV every 4–6 h Ampicillin + sulbactam 1.5–3 g IV every 6 h For methicillin-susceptible S. aureus: Oxacillin/flucloxacillina 1–2 g IV every 4–6 h Cefazolin 1–2 g IV every 8 h For methicillin-resistant S. aureus (or β-lactam allergy): Vancomycina 15 mg/kg IV every 12 h Clindamycinb 600 mg IV every 8 h Daptomycin 6 mg/kg IV every 24 h Teicoplanin At least 400 mg IV BID Linezolidb 600 mg IV every 12 h Quinupristin/dalfopristin 7.5 mg/kg every 12 h Intravenous immunoglobulin Dosage not standardized BID, twice daily; IV, intravenously. Note: Dosing recommendations assume normal renal and hepatic function. a First-line agent. b These agents may be useful for reduction of protein synthesis and toxin production, but require further study. Fig. 8.6.4.2 Staphylococcal impetigo. Copyright Dr Renwick Vickers.

8.6.4 Staphylococci 997 occur in the dermis and originate at hair follicles. Infection can be limited to small lesions that appear as painful nodules, sometimes with necrotic centres (Fig. 8.6.4.3a). Confluence of furuncles leads to the formation of carbuncles (Fig. 8.6.4.3b). Several members of a family may be affected. Mild lesions cause limited systemic com- plaints, whereas fever, malaise, or symptoms and signs of sepsis can occur with extensive disease. Skin abscesses and furunculosis are caused increasingly by CA- MRSA. MRSA is now the most common pathogen identified in patients to presenting to emergency rooms with skin infections in the United States. Furthermore, most of these purulent skin infec- tions are due to the epidemic strain of CA-MRSA, USA300. The Panton–Valentine leucocidin toxin, which is associated with most USA300 strains, has been postulated to contribute to the increased virulence observed in some of these cases. However, others have suggested other virulence factors (e.g. α-toxin, ACME) are involved and the Panton–Valentine leucocidin toxin is merely an epidemio- logic marker of the CA-MRSA strain. CA-MRSA has been associ- ated with more fulminant infections, including necrotizing fasciitis, pneumonia, a sepsis-like picture, or even Waterhouse–Friderichsen syndrome occur. Drainage, spontaneously or surgically, is the mainstay of therapy. Early furuncles may be treated by application of moist heat to stimu- late drainage. While it was origianlly felt that for small abscesses in immunocompetent hosts, incision and drainage alone might be sufficient, more recent literature has suggested added benefit from post-drainage antibiotics. Lesions on the face, lesions with cellulitis (especially exceeding 5 cm in diameter), or the presence of systemic symptoms and/or signs (fever, chills, or haemodynamic changes) should lead to use of antistaphylococcal antibiotics (Table 8.6.4.3) in addition to drainage. Oral agents are sufficient in most cases, but in severe infections or for bacteraemia parenteral agents should be used. One designation that has

been suggested to guide empiric therapy in the outpatient setting is whether cellulitis is purulent or nonpurulent. Purulent cellulitis is purulent drainage associated with cellulitis; this clinical presentation is less consistent with infection solely due to β-haemolytic streptococci and instead should prompt empiric coverage for CA-MRSA. In contrast, nonpurulent cellulitis (i.e. no associated purulent drainage or abscess) should prompt em- piric therapy for β-haemolytic streptococci with CA-MRSA potentially being less of a concern if the patient is not systemically ill. However, in cases of nonpurulent ceullitis where the patient does not respond to β-lactam antibiotics or is systemically ill, empiric CA-MRSA coverage can be added. A recent multicentre randomized controlled trial in the United States compared trimethoprim-sulfamethoxazole versus clindamycin for the treatment of uncomplicated skin infections (cellulitis, abscess, or both) among children and adults. This study found no significant difference between treatment arms for uncom- plicated skin infections; further research is needed on the optimal therapy for individuals with underlying chronic illness or who are more severely ill. Systemic antibiotics given for skin and skin struc- ture infections might also reduce S. aureus colonization, reducing the risk of recurrent skin infections. However, some studies noted an increased risk of adverse effects with clindamycin in comparison to trimethoprim-sulfamethoxazole when used in this way. Table 8.6.4.2 Therapy of impetigo and mild soft tissue lesions caused by S. aureus Therapy Drug Dosage Duration Topical Mupirocin 2% ointment BID 5 days Retapamulin 1% ointment BID Fusidic acid 2% cream TID Oral For methicillin-susceptible S. aureus: Dicloxacillin or Flucloxacillina 250 mg PO QID 7 days Cefalexin 500 mg PO QID For methicillin-resistant S. aureus (or β-lactam allergy): Clindamycin (Erys, Clins, or D-test negative) 300–450 mg PO QID 7 days Trimethoprim/ sulfamethoxazole 1–2 double-strengthb tablets PO BID Doxycycline 100 mg PO BID Minocycline 100 mg PO BID Linezolid 600 mg po BID BID, twice daily; Clins, clindamycin-sensitive; D, double-disc diffusion; Erys, erythromycin-sensitive; PO, by mouth; QID, four times daily; TID, three times daily. a First-line agents. b 160 mg trimethoprim and 800 mg sulfamethoxazole in a double-strength tablet. Pustule Cellulitis (a) (b) Fig. 8.6.4.3 (a) Pustule/early furuncle with surrounding cellulitis due to S. aureus. (b) Coalescent furuncles (i.e. carbuncle, that required incision and drainage).

section 8 Infectious diseases 998 Mastitis Mastitis is most commonly caused by S. aureus, occurs in 1–3% of nursing mothers typically within 3 weeks of birth, and may lead to breast abscesses. Infection can appear as a painful nodule or a draining abscess. Therapy (Table 8.6.4.3) should include topical moist heat, oral antimicrobials with efficacy against S. aureus (and MRSA in endemic areas), and abscess incision and drainage. Pyomyositis Pyomyositis, or primary bacterial abscess of skeletal muscle, is most common in the tropics where ‘tropical pyomyositis’ can account for 1–4% of hospital admissions (Chapter 24.24.6). In nontropical areas the syndrome is uncommon. S. aureus is the cause in about 95% of tropical cases and about 70% of other cases. Associations are with muscle trauma (20–50% of cases), HIV infection, and possibly Toxocara canis infection. Symptoms develop subacutely over 2–3 weeks with variable de- grees of fever, muscle pain, swelling, and induration. Large lower extremity and trunk muscles are most commonly affected. Regional lymphadenopathy is typically absent. Diagnosis relies on clinical sus- picion, helpful radiographic findings (i.e. gas or soft tissue swelling on plain radiographs, abscess or muscle enlargement on ultrasound examination, inflammation, oedema, or focal abscess in muscles Table 8.6.4.3 Therapy of cellulitis, abscess, mastitis, furunculosis, and pyomyositis caused by S. aureus Therapy Drug Dosage Duration/comment Oral For methicillin-susceptible S. aureus: Flucloxacillin or dicloxacillina 500 mg PO QID 5 days for cellulitis For deeper infection duration

depends on proper drainage when necessary and clinical response With incision and drainage, lesions with <5 cm of cellulitis in immunocompetent patients may be cured without systemic antibiotics For deeper infection duration depends on proper drainage when necessary and clinical response Early change to oral therapy may be employed in stabilizing, nonbacteraemic patients May have a future role Cefalexin 500 mg PO QID For methicillin-resistant S. aureus (or β-lactam allergy): Clindamycin (Erys, Clins, or D-test negative) 300–450 mg PO QID Trimethoprim/sulfamethoxazole 1–2 double-strengthb
tablets PO BID Doxycycline 100 mg PO BID Minocycline 100 mg PO BID Linezolid 600 mg PO BID Tedizolid 200 mg po qday Erythromycinc 250 mg PO every 6 h or 500 mg PO every 12 h Parenteral For methicillin-susceptible S. aureus: Oxacillin/flucloxacillina 1–2 g IV every 4–6 h Cefazolin 1–2 g IV every 8 h For methicillin-resistant S. aureus (or β-lactam allergy): Vancomycina 15 mg IV every 12 h Erythromycinc 250 mg IV every 6 h or 500 mg IV every 12 h Clindamycin (Erys, Clins, or D-test negative) 600 mg IV every 8 h Linezolid 600 mg IV every 12 h Tedizolid 200 mg IV every 24 h Daptomycin 4 mg/kg IV every 24 h Quinupristin/dalfopristin 7.5 mg/kg every 12 h Tigecycline 100 mg initially, then 50 mg IV every 12 h Ceftaroline 600 mg IV q12 h Telavancin 10 mg/kg IV every 24 h Dalbavancin 1000 mg IV followed by 500 mg IV one week later Oritavancin 1200 mg IV as a single dose Note: Dosing recommendations assume normal renal and hepatic function. Trimethoprim-sulfamethoxazole and tetracyclines are felt to have poor β-haemolytic streptococci coverage; if coverage for β-haemolytic streptococci is needed, one should consider adding a β-lactam to doxycycline or trimethoprim-sulfamethoxazole therapy. a First-line agent. b 160 mg trimethoprim and 800 mg sulfamethoxazole in a double-strength tablet. c In many areas high rates of resistance should prevent empiric use of erythromycin.

8.6.4 Staphylococci 999 on MRI or computed tomography (CT)), and the results of aspir- ating the lesion. Antibacterial therapy for S. aureus (Table 8.6.4.3) and open or radiographically assisted percutaneous drainage of abscesses are essential parts of therapy. Septic bursitis Infection can occur in any of the approximately 160 bursae found in humans, but septic bursitis usually affects prepatellar or olecranon bursae, usually as a result of trauma. It is due to S. aureus in more than 80% of cases but is accompanied by bacteraemia in 8% or less. Diagnosis relies on clinical recognition of the characteristic findings of fever and pain, swelling, redness, and warmth in the area of an affected bursa. Leucocytes and S. aureus are found if there is enough bursal fluid to aspirate. Treatment of septic bursitis includes appropriate antimicrobials (Table 8.6.4.4) and, if possible, drainage. Treatment failures have been described when erythromycin is used as the sole agent. Localized infection with no systemic signs may be treated with oral therapy, since high antimicrobials levels are achieved in bursal fluid. Adequate drainage is important. Patients with systemic signs or symptoms or who are immunocompromised should receive paren- teral therapy. Patients who present within 7 days of developing symptoms might be treated successfully with antibiotics and aspiration every 1 to 3 days. In this situation, bursal fluid might become sterile within 4 days and therapy should be continued for an additional 5 days. Surgical intervention is needed only for patients whose fluid remains infected or cannot be aspirated because the bursa is deep, who have foreign or necrotic material in the bursal space, or who need explor- ation or removal of the bursa because of recurrences. Septic arthritis S. aureus is the most common cause of nonprosthetic monoarticular septic arthritis. The typical pathogenesis is haematogenous seeding, but traumatic direct inoculation can occur. Important differential diagnoses include gonococcal infection in adolescents and adults and urosepsis pathogens and crystal-induced arthropathies in older patients. Because joint destruction is rapid, prompt diagnosis through joint

aspiration is essential. The mainstays of therapy are antimicrobials (Table 8.6.4.4) and prompt joint drainage by serial aspiration; arthroscopy (preferred for knee, shoulder, and ankle) with irrigation, lysis of adhesions, and removal of purulent material; or open drainage (useful for hip or shoulder infections to protect blood supply to femoral or humeral heads, and in instances where repeated aspirates or arthroscopy fail). S. aureus can be a cause of infected prosthetic joints, which can have a more indolent atypical presentation. Osteomyelitis S. aureus osteomyelitis results from bacteraemia or contiguous spread from a soft tissue focus or chronic ulcer. Risk groups are pa- tients with diabetes mellitus, those with vascular disease or at risk Table 8.6.4.4 Therapy of septic bursitis and septic arthritis caused by S. aureus Therapy Drug Dosage Duration/comment Oral For methicillin-susceptible S. aureus: Flucloxacillin or dicloxacillina 500 mg PO QID For septic bursitis, continue therapy for 5 days after aspirates become sterile (with early change to oral therapy in non- bacteraemic patients). For septic arthritis, therapy should be continued for 4 weeks Cefalexin 500 mg PO QID For methicillin-resistant S. aureus (or β-lactam allergy): Clindamycin (Erys, Clins, or D-test negative) 300–450 mg PO QID Trimethoprim/sulfamethoxazole 1–2 double-strengthb tablets PO BID Doxycycline 100 mg PO BID Minocycline 100 mg PO BID Ciprofloxacin or levofloxacin 500 mg PO BID or 500 mg PO once daily With Rifampin 300 mg PO every 12 h Linezolid 600 mg PO BID Erythromycinc 250 mg PO every 6 h or 500 mg PO every 12 h Parenteral For methicillin-susceptible S. aureus: Oxacillin/flucloxacillina 1–2 g IV every 4–6 h Cefazolin 1–2 g IV every 8 h For methicillin-resistant S. aureus (or β-lactam allergy): Vancomycina 15 mg/kg IV every 12 h Linezolid 600 mg IV every 12 h BID, twice daily; Clins, clindamycin-sensitive; D, double-disc diffusion; Erys, erythromycin-sensitive; PO, by mouth; QID, four times daily; TID three times daily; IV, intravenously. Note: Dosing recommendations assume normal renal and hepatic function. a First-line agent. b 160 mg trimethoprim and 800 mg sulfamethoxazole in a double-strength tablet. c In many areas high rates of resistance should prevent empiric use of erythromycin.

section 8 Infectious diseases 1000 for haematogenous infection (i.e. haemodialysis), children, and eld- erly people. Diagnosis usually depends on radiographic studies. Plain radiographs may show evidence of periosteal reaction. However, the most sensitive test for osteomyelitis is MRI, which will dem- onstrate changes within bone and bone marrow. The most specific test is CT, which will reveal the presence of periosteal reaction or other bony changes not evident on plain radiographs. ‘Probing to bone’ in the case of a chronic ulcer is highly sensitive for a diag- nosis of osteomyelitis. The microbiological diagnosis of osteo- myelitis relies on positive blood or bone cultures; superficial wound or sinus track culture results are not reliable and might be misleading. Therapy for osteomyelitis includes drainage of pus (acute osteo- myelitis) or debridement of areas of avascular or ‘dead’ bone (se- questra in chronic osteomyelitis) and antibacterials with activity against the culture-proven pathogen(s). The duration of therapy sufficient to eradicate the organism and prevent relapse is based on common experience and usually is 4–6 weeks. Children with acute haematogenous S. aureus osteomyelitis can be treated with surgical drainage of purulent collections and short-course intra- venous therapy (e.g. 1 week) followed by oral therapy for 4–6 weeks as outpatients. Initial choice for therapy is based on the presence of MSSA or MRSA (Table 8.6.4.5); copathogens may require broader therapy. An open-label study showed that for diabetic foot infec- tions, linezolid performed as well as ampicillin–sulbactam for in- fected ulcers or osteomyelitis. A recent multicentre study in France examined the efficacy of a 6-week course of antibiotics in comparison to 12 weeks of therapy for the management of pyogenic vertebral osteomyelitis. The au- thors observed that 6 weeks of therapy was noninferior to the longer course of therapy. However, older age and infection with S. aureus were both significant risk factors for

treatment failure, independent of duration of therapy. The optimal duration of therapy for MRSA osteomyelitis is unclear although some suggest that longer courses of at least 8 weeks be used. Epidural abscess Epidural abscesses occur adjacent to vertebral osteomyelitis and are medical/surgical emergencies (Fig. 8.6.4.4). Enlarging epidural sites can compress the spinal cord or reduce vascular supply through thrombophlebitis. About 50% of cases follow haematogenous spread from known or occult trauma or from parenteral use of illicit drugs, while about 30% result from contiguous spread. S. aureus accounts Table 8.6.4.5 Therapy of osteomyelitis caused by S. aureus Therapy Drug Dosage Duration Parenteral For methicillin-susceptible S. aureus: 4–6 weeks IV Oxacillin/ flucloxacillina 1–2 g IV every 4–6 h Cefazolin 1–2 g IV every 8 h For methicillin-resistant S. aureus (or β-lactam allergy):b Vancomycina 15 mg/kg IV every 12 h Linezolid 600 mg IV every 12 h IV, intravenously. Note: Dosing recommendations assume normal renal and hepatic function. a First-line agent. b In 2011, the Infectious Disease Society of American came out with first guidelines for treatment of MRSA. Although the optimal duration of treatment of osteomyelitis due to MRSA has not been established, the guidelines suggest at least 8 weeks of therapy. Vertebral osteomyelitis and discitis Epidural abscess and cord compression Fig. 8.6.4.4 Epidural abscess and vertebral osteomyelitis due to S. aureus.

8.6.4 Staphylococci 1001 for more than 60% of cases. Risks for MRSA infection include recent healthcare exposure or rising CA-MRSA rates. Symptoms and physical findings progress at variable rates, some- times rapidly, through four stages: (1) back pain at the infected level, (2) pain radiating in the distribution of affected nerve roots, (3) motor weakness (including bladder and bowel dysfunction) and sensory deficit at the appropriate level, and (4) paralysis. The triad of back pain, fever, and neurological findings is highly suggestive of epidural abscess. MRI or CT scanning is most useful for evaluating epidural abscesses (Fig. 8.6.4.4). For diagnosis and therapy, a space-occupying lesion in the epidural space requires surgical evalu- ation and emergency laminectomy/decompression or drainage by interventional radiography. Preoperative neurological status predicts outcome. Broad empirical antimicrobial therapy should include coverage for MRSA (Table 8.6.4.6) and Gram-negative bacilli. If MSSA infection is diagnosed, β-lactams are preferred over glycopeptides. Pneumonia S. aureus pneumonia can result from haematogenous spread or direct inoculation following mucosal damage. S. aureus causes less than 10% of cases of community-acquired pneumonia but causes approximately 20–30% of cases of nosocomial pneu- monia. Case fatality of S. aureus pneumonia ranges from 8% to more than 30%. Risks for a more severe course include MRSA, acute respiratory distress syndrome, comorbidities, and renal dysfunction. S. aureus is a cause of postviral, particularly postinfluenza, pneu- monia. Patients may report a biphasic illness. CA-MRSA can cause a necrotizing pneumonia with more severe course. Additionally, S. aureus pneumonia might be associated with complications such as empyema, lung abscesses, and bronchopleural fistulae. Lung ab- scess must be differentiated radiographically from pneumatocele, a common and relatively benign complication of staphylococcal pneumonia. Diagnostic studies for patients with pneumonia in the pres- ence of staphylococcal bacteraemia or embolic-appearing le- sions on chest imaging (Fig. 8.6.4.5) should seek an intravascular source (e.g. endocarditis or infectious thrombophlebitis). Therapy (Table 8.6.4.7) should include use of an active drug for at least 8 days in less complicated cases or longer if pulmonary involve- ment is secondary to an intravascular infection, presence of MRSA, or complications such as emboli or empyema. Surgical drainage is indicated for empyema. Daptomycin should be avoided because of its poorer activity in pulmonary infections. Linezolid might emerge as a drug of choice for MRSA pneumonia based on its greater penetration due to smaller molecule size and putative clinical

benefit. A recent randomized controlled multicentre study examining vancomycin in comparison with linezolid for the treatment of hospital-acquired or healthcare-associated MRSA pneumonia found that the clinical response at the end of the study in the per-protocol patients was significantly better with linezolid than vancomycin. However, 60-day mortality was similar between the two arms. Furthermore, the rate of clinical success at the end of study was only 57.6% in the linezolid treated patients and 46.6% in the vancomycin-treated patients, underscoring the potential severity of MRSA pneumonia and the need for further research to improve therapy in this area. A recent meta-analysis of 22 studies evaluated the utility of MRSA nasal screening results in predicting MRSA pneumonia. Screening had a high specificity Table 8.6.4.6 Therapy of epidural abscess caused by S. aureus Therapy Drug Dosage Duration Parenteral For methicillin-susceptible S. aureus: ≥6 weeks IV Oxacillin/flucloxacillina 1–2 g IV every 4–6 h Cefazolin 1–2 g IV every 8 h For methicillin-resistant S. aureus (or β-lactam allergy): Vancomycina 15 mg/kg IV every 12 h Linezolid 600 mg IV every 12 h Daptomycin 6 mg/kg IV every 24 h IV, intravenously. Note: Dosing recommendations assume normal renal and hepatic function. a First-line agent. a b c Fig. 8.6.4.5 Pneumonia due to S. aureus, from septic pulmonary emboli. Note presence of (a) empyema, (b) nodular (including pleural-based) infiltrate, and (c) early cavitation of abscess. Table 8.6.4.7 Therapy of pneumonia due to S. aureus Drug Dosage Duration/comment For methicillin-susceptible S. aureus: 7–14 days for uncomplicated infection Requires longer courses if empyema, lung abscess, or bacteraemia present Oxacillin/flucloxacillina 1–2 g IV every 4 h Cefazolin 1–2 g IV every 8 h For methicillin-resistant S. aureus (or β-lactam allergy): Vancomycina 15 mg/kg IV every 12 h Linezolid 600 mg IV every 12 h IV, intravenously. Note: Dosing recommendations assume normal renal and hepatic function. a First-line agent.

section 8 Infectious diseases 1002 (90.3%) and high negative predictive value (96.5%) for excluding MRSA pneumonia. Urinary tract infections S. aureus urinary tract infections (UTIs) result from ascending in- fection in catheterized patients or haematogenous seeding, which might lead to renal carbuncles (abscesses). Staphylococcal UTIs should prompt consideration of sources of bacteraemia such as endovascular infection. Clinically, patients with renal abscesses have fever and flank pain, but urinary complaints may be ab- sent, and urinalyses and urine cultures might be negative. Renal ultrasonography or CT can show a range of findings from ‘lobar nephronia’ (renal phlegmon) to large multilocular abscesses. Treatment might require percutaneous or open drainage; anti- microbial therapy (Table 8.6.4.8) should reflect results of cultures. Haematogenous infections Bacteraemia S. aureus is among the most common causes of bacteraemia in hos- pitals and the community. It causes 18–27% of endocarditis cases (Fig. 8.6.4.6), is responsible for 13% of nosocomial bloodstream infections, and causes up to 78% of cases of intravascular catheter-related thrombophlebitis. Rates of community-associated S. aureus bacteraemia in the United States of America are estimated at 17/ 100 000 people, similar to rates of invasive Streptococcus pneumo- niae infection, with mortality of 10–20%, depending on underlying illnesses. In Oxfordshire, England, the incidence of nosocomial MRSA bacteraemia increased from 50/100 000 admissions in 1997 to 300/100 000 admissions in 2004, increasing the overall burden of S. aureus disease. S. aureus in blood should always be considered a true pathogen. Bacteraemia has traditionally been categorized as ‘healthcare- associated’ (i.e. onset more than 2 days after admission) and ‘community-associated’ (i.e. onset within 2 days of admission). Bacteraemia presenting within 2 days of hospitalization in indi- viduals with prior healthcare exposures (e.g. haemodialysis, re- cent prior hospitalization or surgery, or residence in a long-term care facility) has been categorized as ‘healthcare-associated, community-onset’. Complications of bacteraemia

include endo- carditis (itself a major cause of bacteraemia) and ‘metastatic’ seeding of distant sites, especially joints, bone, kidney, and skin (Fig. 8.6.4.7). An estimated 13% of nosocomial bacteraemias with S. aureus include endocarditis. Table 8.6.4.8 Therapy of urinary tract infection due to S. aureus Drug Dosage Duration/comment For methicillin-susceptible S. aureus: 7 days for ascending infection ≥ 14 days for renal abscess, bacteraemia, or complicated infection (duration is based on resolution of infected foci and/or use of drainage) Oxacillin/flucloxacillina 1–2 g IV every 4 h Cefazolin 1–2 g IV every 8 h For methicillin-resistant S. aureus
(or β-lactam allergy): Vancomycina 15 mg/kg IV every 12 h Linezolid 600 mg IV every 12 h IV, intravenously. Note: Dosing recommendations assume normal renal and hepatic function. a First-line agent. (a) (b) Fig. 8.6.4.6 S. aureus bacteraemia and infective endocarditis. (a) Meningococcal-like rash in a patient with S. aureus endocarditis of a bicuspid aortic valve and aortic root abscess. (b) Splenic abscess complicating S. aureus endocarditis. Copyright Professor S. J. Eykyn. Fig. 8.6.4.7 Seeding of MRSA to the skin in a Vietnamese patient. Copyright D. A. Warrell.

8.6.4 Staphylococci 1003 If MSSA is isolated from cultures, a penicillinase-resistant penicillin (flucloxacillin or nafcillin) should be used instead of vancomycin as these agents have better activity against MSSA. A cephalosporin, cefazolin, has also been widely used to treat MSSA infections because of its convenient dosing. There are limited data comparing these agents for treatment of MSSA infections. Recently, a retrospective case–control study comparing cefazolin to nafcillin for the treatment of MSSA bacteraemia observed that they had similar treatment failure rates, with cefazolin having fewer ad- verse drug effects. However, a limitation of this study is that there were few endocarditis cases and no meningitis cases, limiting the generalizability of these findings. One retrospective cohort study that compared treatment outcomes between cefazolin and oxacillin for the treatment of MSSA bacteraemia did not observe a higher rate of treatment failure with cefazolin, even for individuals with MSSA bacteraemia associated with endocarditis or deep-seated in- fection. In addition, rather than using vancomycin for therapy, pa- tients with MSSA bacteraemia and a reported penicillin allergy may benefit from an evaluation of the allergy and potentially treatment with cefazolin. However, there are data suggesting that some MSSA strains might have a bacterial ‘inoculum effect’; that is more antibiotic might be needed to treat a heavy bacterial load, as might be seen in deep- seated infections. Patients infected with strains demonstrating this effect might have worse outcomes when treated with cefazolin. However, this might be mitigated by possible geographic variation in the prevalence of such strains. Based on preliminary in vitro and clinical evidence, combin- ation therapy (vancomycin plus a beta-lactam antibiotic) has been used for initial treatment of S. aureus bacteraemia and might be associated with fewer treatment failures for MRSA, and earlier de- finitive therapy for MSSA, in comparison to therapy with vanco- mycin alone. The principles of therapy for S. aureus bacteraemia include evaluation for endocarditis; use of a parenteral agent; removal of infected foci (i.e. catheters or abscesses); and use of a bactericidal agent, preferably a β-lactam, whenever possible. Occasionally, uncomplicated bacteraemia with drainage of infected foci and no embolic sites might respond to only 14 days of therapy (Table 8.6.4.9); however, more often, prolonged bacteraemia, residual disease, undrained foci of infection, infected clots, or endocarditis all warrant longer therapy (at least 4 weeks). Several studies have shown that involvement of infectious diseases spe-cialists in the care of patients with S. aureus bacteraemia is associ- ated with better management and improved outcomes, including in-hospital mortality. A recent review of treatment modalities for S. aureus bacter- aemia suggests that given the significant potential complications associated with MRSA bacteraemia, modifications to therapy should be considered earlier into therapy—as early as

three to four days—if blood cultures have not yet cleared. This approach warrants controlled evaluation. The review also reiterates the im- portance of ensuring adequate source control as the cornerstone of therapy for MRSA bacteraemia. A multicenter, randomized, double-blind, placebo-controlled trial in the UK of 758 adults with S. aureus bacteraemia evaluated the benefit of adding rifampicin to standard antimicrobial therapy and found that rifampicin pro- vided no overall benefit. A multicenter, randomized, double-blind, placebo-controlled trial in the UK of 758 adults with S. aureus bacteremia evaluated the benefit of adding rifampicin to standard antimicrobial therapy and observed that adjunctive rifampicin provided no overall benefit. Several studies have now found that involvement of infectious disease providers in the care of patients with S. aureus bacter- emia is associated with improved management (e.g., obtaining an echocardiogram and repeating blood cultures) as well as with improved outcomes, including in-hospital mortality. In addition, Infectious Disease consultation can help improve antibiotic ad- justments, including de-escalation, and can optimize duration of therapy. Endocarditis (Chapter 16.9.2) Many features of endocarditis are nonspecific (fever, tachycardia, arthralgias and myalgias, wasting, and back pain). Finding a new cardiac (especially diastolic) murmur or septic emboli provides strong supportive evidence. Other suggestive findings include petechiae, Janeway's lesions, mycotic aneurysms of arterial ves- sels (with resultant pain, vascular leak, or adjacent deep venous thrombosis), discitis or osteomyelitis (particularly vertebral dis- ease), and neurological complications such as septic infarcts or mycotic cerebrovascular aneurysms. Conduction abnormalities (e.g. AV delay), might be noted in the presence of myocardial ab- scess. In the setting of right-sided endocarditis, septic pulmonary emboli are common. The presence of multiple positive blood cultures is a neces- sary criterion for diagnosis of endocarditis in the untreated pa- tient. Diagnosis is aided by specific criteria (e.g. modified Duke's criteria). Transthoracic echocardiography is indicated as a non-invasive method to evaluate the presence of cardiac vegetations in those with a low pretest probability of disease; individuals with nondiagnostic studies or worsening clinical course should

Table 8.6.4.9 Therapy of bacteraemia, without endocarditis, due to S. aureus

Drug	Dosage	Duration/ comment
For methicillin-susceptible S. aureus:		14 days with removable focus of infection Longer course of therapy for complicated infection
Oxacillin/flucloxacillina	1–2 g IV every 4–6 h	
Cefazolin	1–2 g IV every 8 h	
For methicillin-resistant S. aureus (or β-lactam allergy):		
Vancomycina	15 mg/kg IV every 12 h	
Daptomycina	6 mg/kg IV every 24 h	
Teicoplanin	At least 400 mg IV BID	
Linezolid	600 mg IV every 12 h	
Quinupristin/dalfopristin	7.5 mg/kg every 12 h	
Sodium fusidate	500 mg IV every 8 h	
Dalbavancin, oritavancin, telavancin		May have future role

BID, twice daily; IV, intravenously. Note: Dosing recommendations assume normal renal and hepatic function. a First-line agent.

 undergo transoesophageal echocardiogram. Patients with high clinical risk, despite nondiagnostic transoesophageal studies, should be restudied after 7–10 days. Recent evaluations have sug- gested that patients who fit a low-risk profile (e.g. no cardiac de- vice or prosthetic heart valve, quick clearance of blood cultures, and nosocomial onset of bacteraemia), can be evaluated ad- equately with transthoracic echocardiography, without recourse to transoesophageal echocardiogram. Therapy for staphylococcal endocarditis requires a bactericidal antibiotic (Tables 8.6.4.10–8.6.4.12). In general, therapy should last for 4 weeks (in uncomplicated disease) to 6 weeks or more (in the setting of metastatic infection, perivalvular abscess, or other complications). Combination therapies (agents given with either vancomycin or β-lactams) have not been demonstrated to improve outcomes in native valve endocarditis but are com- monly used. For example, the addition of gentamicin for 3–5 days shortens the duration of bacteraemia by

about 1 day, but does not influence outcome. Addition of rifampicin for bacteraemic pa- tients with putative failure of therapy (e.g. bacteraemia or fever persisting for more than 4–5 days) is a common strategy, but the recent ARREST trial casts doubt on this strategy. Rifampicin is still recommended as part of the standard treatment of prosthetic valve endocarditis. The average time to clearance of S. aureus from the bloodstream is 5 days of β-lactam or 1 week of vancomycin therapy. Prolonged bac- teraemia should prompt a closer evaluation of antibiotic minimum inhibitory concentrations (especially for vancomycin), a search for sequestered sites of infection or undrained foci, or a myocardial or valvular abscess. The 2011 Infectious Disease Society of America guidelines for the treatment of MRSA suggest a vancomycin trough concen- tration of 15–20 μg/ml for serious infections (e.g. bacteraemia, Table 8.6.4.11 Therapy of native valve right-sided endocarditis due to S. aureus Drug Dosage Duration/comment β-Lactams As for left-sided disease (Table 7.6.4.10) 4–6 weeks after negative cultures Vancomycina As for left-sided disease (Table 7.6.4.10) Daptomycina 6 mg/kg IV every 24 h Above therapies can be used with: Gentamicinb 1 mg/kg IV every 8 h 3–5 days at start of therapy, or combined therapy with β-lactam for MSSA infection Ciprofloxacin/ rifampicinb 750 mg/300 mg PO BID For use in patients with tricuspid valve endocarditis who can not/will not be admitted for intravenous therapy BID, twice daily; IV, intravenously; PO, by mouth. Note: Dosing recommendations assume normal renal and hepatic function. a First-line agent. b Use is indicated in only limited circumstances. Gentamicin therapy is optional and has not been shown to improve clinical outcomes. Table 8.6.4.12 Therapy of prosthetic valve endocarditis due to S. aureus Drug Dosage Duration/ comment For methicillin-susceptible S. aureus: Oxacillin/flucloxacillina 2 g IV every 4 h ≥6 weeks with Rifampicin 300 mg PO/IV every 8 h ≥6 weeks and Gentamicin 1 mg/kg IV every 8 h 3–5 days at start of therapy Cefazolin(second choice for MSSA) 1–2 g IV every 8 h For methicillin-resistant S. aureus (or β-lactam allergy): Vancomycina 15 mg/kg IV every 12 h with Rifampicin 300 mg PO/IV every 8 h ≥6 weeks and Gentamicin 1 mg/kg IV every 8 h 3–5 days at start of therapy IV, intravenously; PO, by mouth. Note: Dosing recommendations assume normal renal and hepatic function. a First-line agent. Table 8.6.4.10 Therapy of native valve left-sided endocarditis due to S. aureus Drug Dosage Duration/ comment For methicillin-susceptible S. aureus: 4–6 weeks after negative cultures Oxacillin/flucloxacillina 2 g IV every 4 h Cefazolin 1–2 g IV every 8 h For methicillin-resistant S. aureus (or β-lactam allergy): Vancomycina 15 mg/kg IV every 12 h Teicoplanina At least 400 mg IV BID Linezolid 600 mg IV every 12 h Quinupristin/dalfopristin 7.5 mg/kg every 12 h Daptomycin 6 mg/kg IV every 24 h Sodium fusidate 500 mg IV every 8 h Trimethoprim/ sulfamethoxazolec 320 mg/1600 mg IV every 12 h Above therapies can be used with: Gentamicinb (3–5 days at start of therapy) 1 mg/kg IV every 8 h BID, twice daily; IV, intravenously. Note: Dosing recommendations assume normal renal and hepatic function. a First-line agent. b Gentamicin therapy is optional, and has not been demonstrated to change clinical outcomes. c A recent study that compared trimethoprim-sulfamethoxazole to vancomycin for the treatment of severe infections due to MRSA observed that therapy with trimethoprim- sulfamethoxazole was associated with treatment failure; patients with left-sided endocarditis, meningitis, chronic haemodialysis, and prolonged neutropenia were excluded. This study used a fixed dose of trimethoprim-sulfamethoxazole for enrolled patients, which may be a limitation of the study.

8.6.4 Staphylococci 1005 infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe skin and soft tissue infections such as necrotizing fasciitis). Part of the impetus for higher trough levels comes from studies that have suggested that there is an increased chance of treatment failure with vancomycin as the minimum inhibitory concentra- tion for vancomycin increases to the

upper limit of the susceptible range. However, in a study of an Australian cohort of patients with S. aureus bacteraemia, elevated vancomycin minimum inhibitory concentration was associated with increased 30-day mortality but methicillin resistance and specific antibiotic selection were not, suggesting that vancomycin itself may be a marker for more difficult-to-treat strains but not the driver per se of worse out- comes in these patients. Increasing vancomycin dosing has not been demonstrated clearly to improve outcomes, although consensus supports in- creased trough levels of 15–20 μg/ml (requiring close monitoring of renal function) for serious infections. Although close moni- toring of renal function is recommended, the data establishing the causal link between serum vancomycin concentration and nephrotoxicity are limited since concomitant nephrotoxic agents might play a role in toxicity. Indications for surgical valve replace- ment include new congestive heart failure (associated with higher mortality), failure to clear the bloodstream, recurrent emboli, and myocardial or valvular abscess. As daptomycin has concentration-dependent bactericidal activity against Gram-positive organisms, some have suggested higher doses (e.g. 8 mg/kg per day or greater) might be effective for treatment of complicated Gram-positive infections. However, further evalu- ation of this is needed, in particular the safety and tolerability of higher doses. Clinical syndromes: Coagulase-negative staphylococci Coagulase-negative staphylococci are generally less virulent than S. aureus. Most infections with these organisms are the consequence of medical progress, related to foreign bodies (e.g. prosthetic joints or heart valves, indwelling intravascular cath- eters or grafts, or peritoneal catheters), and occur in associ- ation with healthcare. Syndromes caused by coagulase-negative staphylococci include endocarditis (5–8% of native valve in- fections, c.40% of prosthetic valve infections), intravascular catheter infections (6–27% of vascular catheter infections), prosthetic joint infections (up to 38% of arthroplasty infec- tions), peritoneal dialysis catheter infections, and postoperative ocular infections. Production of biofilm by coagulase-negative staphylococci aids infection of both intravascular and peri- toneal catheters. Therapy for infections with coagulase-negative staphylococci and side effects and toxicities are outlined in Tables 8.6.4.13 and 8.6.4.14. Bacteraemia and infected vascular catheters Clinical features and diagnosis Coagulase-negative staphylococci are the most commonly re- ported bacteria in positive blood cultures; however, unlike S. aureus, coagulase-negative staphylococci are frequently blood culture con- taminants. Typical rates of blood culture contamination by skin flora are approximately 2–3%; higher rates might be a sign of poor phle- botomy technique. Infected intravascular catheters are common sources of coagulase- negative staphylococcal bloodstream infections. However, given the association of S. epidermidis and contaminated blood cultures, a careful physical examination for signs of catheter infection is crit- ical to determine whether a single positive blood culture represents true infection and/or an infected catheter. Suggestive findings in- clude fever, erythema at or pus expressible from the site of catheter insertion, or tenderness. Methods to enhance the identification of true bloodstream infec- tion as opposed to contamination include proper skin preparation and obtaining at least two sets of blood cultures from sites separated by location and time. The use of quantitative catheter tip cultures (more than 15 colonies) or differential time to positivity (more than Table 8.6.4.13 Therapy for coagulase-negative staphylococcal infections Indication Drug Dosage Duration Bacteraemia (with prompt catheter removal) Vancomycina 15 mg/kg IV every 12 h 10–14 days Oxacillin/flucloxacillin (methicillin- susceptible S. epidermidis) 1–2 g IV every 4 h Bacteraemia (with attempted catheter salvage) Vancomycin catheter lock (for catheter salvage) 1–5 mg/ml vancomycin, mixed with 50–100 U heparin or normal saline, to fill catheter lumen (total 2–5 ml of solution) when catheter not in use 14 days Vancomycina 15 mg/kg IV every 12 h 10–14 days Oxacillin/flucloxacillin (methicillin- susceptible S. epidermidis) 1–2 g IV

every 4 h Prosthetic
valve endocarditis Vancomycina 15 mg/kg IV every 12 h ≥6 weeks with Rifampicina 300 mg PO/ IV every 8 h and Gentamicin 1 mg/kg IV every 8 h Oxacillin/flucloxacillin (methicillin- susceptible S. epidermidis) 1–2 g IV every 4 h Peritoneal dialysis- associated peritonitis Vancomycina 30–50 mg vancomycin per litre of dialysate given intraperitoneally 10–21 days Or Vancomycin 1 g IV once, then based on levels (keep trough

> 10–15 mcg/ml) 10–21 days IV, intravenously; PO, by mouth. Note: Dosing recommendations assume normal renal and hepatic function. a First-line agent.

section 8 Infectious diseases 1006 Table 8.6.4.14 Information on indications and toxicity for selected drugs Drug class Indications/use Side effects/toxicities Semisynthetic penicillins Flucloxacillin Oxacillin Drugs of choice in penicillin-resistant MSSA infection Interstitial nephritis (which limits methicillin use in adults) Nafcillin Not effective in MRSA infection Neutropenia (nafcillin) Dicloxacillin CA-MRSA may equal or exceed 50% prevalence in some areas Elevated transaminases (oxacillin, nafcillin) Range of prevalence of nosocomial MRSA is 2–70% Adequate incision and drainage of infected foci is critical First-generation cephalosporins Cefazolin Cefalexin Alternative agents for penicillin-resistant, MSSA infection 15% cross-reaction for penicillin-allergic patients Not effective in MRSA infection Hypersensitivity CA-MRSA may equal or exceed 50% prevalence in some areas Eosinophilia Range of prevalence of nosocomial MRSA is 2–70% Adequate incision and drainage of infected foci is critical Penicillins and aminopenicillins Penicillin Ampicillin Amoxicillin Ampicillin + sulbactam Amoxicillin + clavulanate Penicillin is the drug of choice in known penicillin-sensitive S. aureus infection Hypersensitivity Duration of therapy and indications similar to those of oxacillin Glycopeptides Vancomycin Teicoplanin Dalbavancin Oritavancin Telavancin Indicated for MRSA infections or MSSA infections in penicillin-allergic patients 3–11% of patients given vancomycin may develop anaphylactoid reaction (i.e. ‘red man’ or ‘red-neck’ syndrome) due to overly rapid infusion Indicated for coagulase-negative staphylococcal infections Nephrotoxicity with vancomycin (0–7% alone, 14–20 + % in conjunction with aminoglycoside) and teicoplanin (5%) MRSA that are vancomycin susceptible but have increased MIC may require higher doses Neutropenia with vancomycin (1–2%) Vancomycin trough levels should be 10–15 mg/litre and monitored
closely in the setting of renal dysfunction; ≥15 if vancomycin
MIC >1 mcg/ml Erythematous rash with teicoplanin (7%) Teicoplanin levels should be >10 mg/litre in bacteraemia and >20 mg/litre in endocarditis Lincosamide Clindamycin Indicated for nonsevere MRSA infections that are erythromycin and clindamycin susceptible or that are erythromycin resistant and double- disc diffusion (D) test is negative 20% of patients develop diarrhoea An option for nonsevere MSSA infections in penicillin-allergic patients Increased risk of Clostridium difficile-associated diarrhoea (10%) Tetracyclines Doxycycline Minocycline Tigecycline Not recommended in children aged <8 years Photosensitivity Bacteriostatic, not recommended for bacteraemia or severe infections Eosinophilia Recent review in osteomyelitis demonstrated success rate in over 80%; retained foreign body in osteomyelitis may lead to failure SLE-like reaction with minocycline Likely need additional agent for treatment of long duration (i.e. rifampicin or fluoroquinolone) to prevent emergence of resistance Pseudotumour cerebri or vestibular toxicity Potency/activity of drugs: tigecycline > minocycline > doxycycline > tetracycline Antianabolic

Dihydrofolate reductase inhibitors Trimethoprim/ sulfamethoxazole Higher failure rate as compared with vancomycin in MSSA
endocarditis seen in one study Hypersensitivity, may progress to erythema multiforme and/or Stevens–Johnson syndrome MRSA endocarditis success equivalent to vancomycin Macrocytic anaemia TMP/SMX resistance may be common among nosocomial MRSA
(up to 50%) but is generally uncommon among CA-MRSA (<10%) Photosensitivity Methaemoglobinaemia (rare) (continued)

8.6.4 Staphylococci 1007 2 h) for peripheral compared to catheter-drawn blood cultures helps assess whether a catheter is infected. Management of bacteraemia and catheter infection An approach for management of presumed infected catheters is to remove the catheter when the index of suspicion is high and/ or the patient is unstable, with insertion of a new catheter at an uninvolved site. When likelihood of infection is unclear and the patient is stable, the catheter can be changed over a guidewire and the tip cultured. Positive tip cultures should prompt removal of the replacement catheter and new catheter insertion at a different site. A negative culture might allow the replacement catheter to remain Drug class Indications/use Side effects/toxicities Fluoroquinolones Ciprofloxacin Levofloxacin Moxifloxacin Ofloxacin Should not be used as monotherapy due to rapid emergence of resistance Neurological (0.9–11% delirium and/or seizures) May possibly be used with other agents (e.g. TMP/SMX, rifampicin) Arthropathy, tendinitis, tendon rupture Ciprofloxacin or levofloxacin in combination with rifampicin may
be an option for patients with uncomplicated tricuspid valve endocarditis who cannot/will not be admitted; or those with
skin/soft tissue infection with CA-MRSA Hypoglycaemia Rifamycins Rifampicin Part of combination treatment of prosthetic valve endocarditis, or in setting of endovascular infection with a foreign body Gastrointestinal complaints Should be used with another agent given rapid acquisition of resistance Hepatitis Myeloid suppression Acute tubular necrosis or acute interstitial nephritis SLE-like syndrome Macrolides Erythromycin Clarithromycin Azithromycin May be used in penicillin-allergic patients for skin/soft tissue infections Gastrointestinal complaints (prokinetic) Should be used with caution based on local susceptibility to erythromycin in S. aureus and emergence of resistance QT prolongation in conjunction with other medications Oxazolidinones Linezolid Comparable indications to vancomycin; of use in therapy for MRSA
or VISA/VRSA Myelosuppression Data suggest better efficacy than vancomycin for pneumonia and skin/soft tissue infections with MRSA Serotonin syndrome Has been used for bacteraemia in small open-label trials Peripheral neuropathy Bacteriostatic Lactic acidosis (due to mitochondrial toxicity) Limited clinical experience Lipopeptides Daptomycin Bactericidal Myopathy, especially with higher doses or in the setting of renal insufficiency. Cases of eosinophilic pneumonia reported May have use in VISA/VRSA Resistance has been noted to develop on therapy Not indicated for treatment of pneumonia ‘Noninferior’ to vancomycin for right-sided endocarditis and uncomplicated bacteraemia with S. aureus and possibly better for MRSA Streptogramins Quinupristin/dalfopristin May have use in soft tissue infections, bacteraemia, or osteomyelitis in settings where other agents are not available/useful Phlebitis (30%)—limits general usefulness May have use in MRSA or VISA/VRSA infections Arthralgias (9.1%) Presence of inducible or constitutive clindamycin resistance (i.e. MLS resistance) may indicate elevated MICs for quinupristin/dalfopristin Myalgias (6.6%) Sodium fusidate Topical therapy for impetigo Thrombophlebitis (parenteral use) May be used parenterally in therapy of MRSA bacteraemia or endocarditis, depending on susceptibility Reversible jaundice (parenteral use) Should not be used in newborns Thrombocytopenia

(parenteral use) CA, community-acquired; MIC, minimum inhibitory concentration; MLS, macrolide–lincosamide–streptogramin, MRSA, methicillin-resistant S. aureus; MSSA, methicillin-susceptible S. aureus; SLE, systemic lupus erythematosus; TMP/SMX, trimethoprim/sulfamethoxazole, VISA/VRSA, vancomycin-intermediate/vancomycin-resistant S. aureus. Table 8.6.4.14 Continued

section 8 Infectious diseases 1008 in place, although its risk of subsequent infection is increased by the exchange process. Parenteral vancomycin is the mainstay of therapy for vascular catheters infected by methicillin-resistant coagulase-negative staphylococci, and should be continued for 7–14 days unless there is metastatic seeding requiring longer treatment. Antibiotic lock therapy (Table 8.6.4.13) might be useful in carefully selected pa- tients for 'line salvage'. The presence of tenderness along the course of a tunnelled catheter is highly predictive of failure of medical management and should lead to catheter removal. Endocarditis Multiple positive blood cultures with coagulase-negative staphylo- cocci might indicate the presence of infective endocarditis. More than 80% of patients with prosthetic valve infection have persistent fever, deep valve involvement (e.g. infection of the sewing ring or valve dysfunction, dehiscence, or abscess), and/or cardiac conduction abnormalities. Infections within the first 6–12 months fol- lowing surgery typically reflect acquisition of the organism in the perioperative period and may have a higher likelihood of complicated infection. Diagnosis of prosthetic valve infection should be sought aggressively when multiple positive cultures with coagulase- negative staphylococci have been obtained postoperatively soon after cardiac surgery. Physical examination usually shows fever and a new or worsening murmur or valve dysfunction. Evaluation includes serial blood cultures to document degree and persistence of bacteraemia, electrocardiography to search for conduction delay, and echocardiography or angiography for documentation of valve function. Therapy for prosthetic valve endocarditis should include parenteral vancomycin (for methicillin-resistant strains), gentamicin, and/or rifampicin (Table 8.6.4.13). Peritoneal dialysis-associated peritonitis Peritoneal dialysis catheter infection is characterized by abdom- inal pain, cloudy exchange fluid, and peritoneal fluid containing predominantly polymorphonuclear leucocytes (>100 leucocytes/ mm3). To improve diagnostic yield of peritoneal dialysate fluid cultures, 2–3 ml of fluid can be inoculated into thioglycolate broth or blood culture bottles. Therapy for catheter-associated S. epidermidis peritonitis depends on susceptibility results. For susceptible organisms, β-lactams, trimethoprim/sulfamethoxazole, and vancomycin have all been effective, and both parenteral and oral antibiotics have been used. However, if methicillin-resistant S. epidermidis is suspected, vancomycin therapy (Table 8.6.4.13) with moni- toring of serum levels may be indicated. Therapy can consist of either systemic or intraperitoneal antimicrobial administration. Intraperitoneal therapy is advantageous because it allows con- tinued ambulatory care and therapy directly to the site of infection. Catheter salvage is frequently possible, but relapses might require catheter removal. Other organisms S. saprophyticus is a common cause of UTIs (20% of UTIs in women 16–35 years old). S. lugdunensis S. lugdunensis is a coagulase-negative staphylococcus that can be a skin commensal but has also been reported to cause clin- ical disease such as soft tissue infections, endocarditis, including native valves, and bloodstream infection. The true incidence of infections due to S. lugdundensis is not clear given the lack of speciation of most coagulase-negative staphylococci in many laboratories; however, it should be considered a true pathogen if isolated, rather than a contaminant. S. lugdunensis infec- tions have been characterized by a clinical course more like that of S. aureus, with valve destruction a prominent part of the illness. In contrast to other forms of coagulase-negative staphylo- coccus, S. lugdunensis typically retains

susceptibility to a range of antibiotics. Likely developments in the near future Future directions in the management of S. aureus infections in- clude vaccine development, new antimicrobials, enhanced under- standing of epidemiology and control of nosocomial-associated and CA-MRSA, and evaluation and control of the emergence of VISA/VRSA. A bivalent vaccine containing S. aureus polysacchar- ides 5 and 8 briefly reduced risk of bacteraemia in haemodialysis recipients in a prospective study published in 2002. A novel vac- cine candidate against S. aureus was examined recently among in- dividuals undergoing cardiothoracic surgery. This vaccine did not reduce the rate of postoperative S. aureus infections in comparison to placebo and was associated with increased mortality among in- dividuals who did develop S. aureus infections; the study was halted by the independent data monitoring committee. An additional target for vaccine synthesis is the Panton–Valentine leucocidin toxin, which might provide protection against CA- MRSA. Another preventive measure might be screening for nasal or skin colonization with MRSA, with subsequent decolonization of colonized persons. However, populations that require screening (i.e. universal or targeted screening), actions to pursue among the col- onized, and efficacy and costs of such a programme are all variables that require further clarification. The promise of such a strategy might be control of MRSA and reduction of the costs and morbidity associated with MRSA infection. New glycopeptides (telavancin, oritavancin, and dalbavancin), new cephalosporins with activity against MRSA (ceftobiprole and ceftaroline), and existing agents with evolving indications (daptomycin, linezolid) might improve treatment options for MRSA and VISA/VRSA. Ceftaroline is approved in the United States for the treatment of complicated skin and soft structure in- fections as well as community-acquired pneumonia and may be a valuable treatment option for MRSA isolates with reduced sus- ceptibility to linezolid, daptomycin, and vancomycin. Despite its recent US FDA approval in 2010, resistance to ceftaroline has been reported. In the United States, the molecular mechanism of this resistance was determined using whole genome sequencing, highlighting ways this technology can be utilized to further study multidrug resistant organisms. Both oritavancin and dalbavancin are notable for their long half- life, allowing for less frequent dosing. One dose of oritavancin was found to be noninferior to a 7–10-day course of antibiotics for the treatment of acute skin and soft tissue infections due to Gram-positive

8.6.4 Staphylococci 1009 organisms. Dalbavancin can be dosed weekly and has been found to be noninferior to a regimen of vancomycin and linezolid for the treatment of acute bacterial skin and soft tissue infections. In 2014 in the United States, a new oxazolidinone drug, tedizolid, was ap- proved for the treatment of acute bacterial skin and skin structure infections; this drug has activity against MRSA. As with linezolid, tedizolid can be given orally or parenterally. In addition, tedizolid is given once daily and is active against linezolid-resistant S. aureus strains. It remains unclear if the risk of myelosuppression that is seen with linezolid will be lower with tedizolid in comparison to those who did not. Systemic antibiotics, e.g., clindamycin, given for skin and skin structure infections may also reduce S. aureus colonization, leading to downstream benefits of fewer recurrent skin infections. However, some studies have noted increased adverse effects of clindamycin in comparison to trimethoprim-sulfamethoxazole (e.g., diar- rhea, nausea) when used for treatment of skin and skin structure infections. Pneumonia section A recent meta-analysis of 22 studies evaluated the utility of MRSA nasal screening results in predicting MRSA pneumonia. They observed that MRSA nares screening had a high specificity (90.3%) and high negative predictive value (96.5%) for exclud ing MRSA pneumonia. Such a tool could guide antibiotic pre- scribing, e.g., no need for empiric MRSA coverage if nasal screen is negative. New drug In 2017, the FDA approved a new fluoroquinolone antibiotic, delafloaxin, for oral and parenteral therapy of adults with skin and skin structure infections, including those due to MRSA. Better strategies for treatment

and salvage of infected catheters with catheter coating (e.g. with chlorhexidine) or methods for treat- ment of biofilm might improve treatment of coagulase-negative staphylococci. FURTHER READING Baddour LM, et al. (2005). Infective endocarditis: diagnosis, anti- microbial therapy, and management of complications: a state- ment 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, 111, e394–434. Bai AD, et al. (2015). Impact of infectious disease consultation on quality of care, mortality, and length of stay in Staphylococcus aureus bacteremia: results from a large multicenter cohort study. Clin Infect Dis, 60, 1451–61. Blumenthal KG, et al. (2015). Improving clinical outcomes in patients with methicillin-sensitive Staphylococcus aureus bacteremia and reported penicillin allergy. Clin Infect Dis, 61, 741–9. Blumenthal KG, et al. (2018). Risk of meticillin resistant Staphylococcus aureus and Clostridium difficile in patients with a documented penicillin allergy: population based matched cohort study. BMJ, 361, k2400. Climo MW, et al. (2013). Effect of daily chlorhexidine bathing on hospital-acquired infection. N Engl J Med, 368, 533–42. Dantes R, et al. (2013). National burden of invasive methicillin- resistant Staphylococcus aureus infections, United States, 2011. JAMA Intern Med, 173, 1970–8. Darouiche RO (2006). Spinal epidural abscess. N Engl J Med, 355, 2012–20. Daum RS, et al. (2017). A pacebo-controlled trial of antibiotics for smaller skin abscesses. N Engl J Med, 376, 2545–55. Drees M, Boucher H (2006). New agents for Staphylococcus aureus endocarditis. Curr Opin Infect Dis, 19, 544–50. Edmond MB, Wenzel RP (2013). Screening inpatients for MRSA— case closed. N Engl J Med, 368, 2314–5. Elliott TS, et al. (2004). Guidelines for the antibiotic treatment of endocarditis in adults: report of the Working Party of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother, 54, 971–81. Fowler VG Jr, et al. (2005). Staphylococcus aureus endocarditis: a con- sequence of medical progress. JAMA, 293, 3012–21. Fowler VG, et al. (2013). Effect of an investigational vaccine for preventing Staphylococcus aureus infections after cardiothoracic surgery: a randomized trial. JAMA, 309, 1368–78. Gemmell CG, et al. (2006). Guidelines for the prophylaxis and treat- ment of methicillin-resistant Staphylococcus aureus (MRSA) infec- tions in the UK. J Antimicrob Chemother, 57, 589–608. Grundmann H, et al. (2006). Emergence and resurgence of meticillin- resistant Staphylococcus aureus as a public-health threat. Lancet, 368, 874–85. Heldman AW, et al. (1996). Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med, 101, 68–76. Hogan PG, et al. (2018). Impact of systemic antibiotics on Staphylococcus aureus colonization and recurrent skin infection. Clin Inf Dis, 66, 191–7. Holland TL, Arnold C, Fowler VG, Jr (2014). Clinical management of Staphylococcus aureus bacteremia: a review. JAMA, 312, 1330–41. Holland TL, Fowler VG, Jr (2011). Vancomycin minimum inhibitory concentration and outcome in patients with Staphylococcus aureus bacteremia: pearl or pellet? J Infect Dis, 204, 329–31. Holmes NE, et al. (2011). Antibiotic choice may not explain poorer outcomes in patients with Staphylococcus aureus bacteremia and high vancomycin minimum inhibitory concentrations. J Infect Dis, 204, 340–7. Huang SS, Datta R, Platt R (2006). Risk of acquiring antibiotic- resistant bacteria from prior room occupants. Arch Int Med, 166, 1945–51. Huang SS, et al. (2013). Targeted versus universal decolonization to prevent ICU infection. N Engl J Med, 368, 2255–65. Klevens RM, et al. (2006). Changes in the epidemiology of methicillin- resistant Staphylococcus aureus in intensive care units in US hos- pitals, 1992–2003. Clin Infect Dis, 42, 389–91.

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