DURATION OF ANTIMICROBIAL THERAPY

Debate continues regarding the duration of therapy for bacteremic *S. aureus* infections. Patients with "complicated" bacteremia are at increased risk of endocarditis and metastatic infections. Among the findings associated with an increased risk of complicated bacteremia are persistently positive blood cultures 96 h after institution of therapy, acquisition of the infection in the community, failure to remove a removable focus of infection (i.e., an intravascular catheter), and infection with cutaneous or embolic manifestations. For immunocompetent patients in whom short-course therapy is planned, transesophageal echocardiography to rule out endocarditis is warranted because neither clinical nor laboratory findings can reliably detect cardiac involvement. In addition, an aggressive radiologic investigation to identify potential metastatic collections is indicated. All symptomatic body sites must be carefully evaluated.

CHOICE OF ANTIMICROBIAL AGENTS

The choice of antimicrobial agents to treat both coagulase-positive and coagulase-negative staphylococcal infections has become increasingly problematic because of the prevalence of multidrug-resistant strains. Staphylococcal resistance to most antibiotic families, including β-lactams, aminoglycosides, fluoroquinolones, and (to a lesser extent) glycopeptides, has increased. This trend is more apparent with CoNS: >80% of nosocomial isolates are resistant to methicillin, and these methicillin-resistant strains are usually resistant to most other antibiotics as well. Because the selection of antimicrobial agents for *S. aureus* infections is similar to that for CoNS infections, treatment options for these pathogens are discussed together and are summarized in **Table 172-3**.

As a result of the widespread dissemination of plasmids containing the enzyme penicillinase, few strains of staphylococci (≤5%) remain susceptible to penicillin. However, penicillin remains the drug of choice against susceptible strains if the laboratory can reliably test for penicillin susceptibility. Penicillin-resistant isolates are treated with semisynthetic penicillinase-resistant penicillins (SPRPs), such as oxacillin or nafcillin. Methicillin, the first of the SPRPs, is now used infrequently. Cephalosporins are alternative therapeutic agents for these infections. Second- and third-generation cephalosporins do not offer a therapeutic advantage over first-generation cephalosporins for the treatment of staphylococcal infections. The carbapenems have excellent activity against methicillin-sensitive *S. aureus* but not against MRSA.

The isolation of MRSA was reported within 1 year of the introduction of methicillin. Since then, the prevalence of MRSA has steadily increased. In many hospitals, 40–50% of *S. aureus* isolates are now resistant to methicillin. Resistance to methicillin indicates resistance to all SPRPs as well as to all cephalosporins (except ceftaroline). Production of a novel penicillin-binding protein (PBP2a) is responsible for methicillin resistance. This protein is synthesized by the *mecA* gene, which (as stated above) is part of a large mobile genetic element—a pathogenicity or genomic island—called SCC*mec*. It is hypothesized that this genetic material was acquired via horizontal transfer from a related staphylococcal species, such as *Staphylococcus sciuri*. Phenotypic expression of methicillin resistance may be constitutive (i.e., expressed in all organisms in a population) or heterogeneous (i.e., displayed by only a proportion of the total organism population). Detection of methicillin resistance in the clinical microbiology laboratory can be difficult if the strain expresses heterogeneous resistance. Therefore, susceptibility studies are routinely performed at reduced temperatures (≤35°C for 24 h), with increased concentrations of salt in the medium to enhance the expression of resistance. In addition to PCR-based techniques, a number of rapid methods for the detection of methicillin resistance have been developed.

In light of decreasing susceptibility of MRSA isolates to vancomycin, both vancomycin and daptomycin are now recommended as the drugs of choice for the treatment of MRSA infections. Vancomycin is less effective than SPRPs for the treatment of infections due to methicillin-susceptible strains. Alternatives to SPRPs should be used only after careful consideration in patients with a history of serious β-lactam allergies.

Three types of staphylococcal resistance to vancomycin have emerged. (1) Minimal inhibitory concentration (MIC) "creep" refers to the incremental increase in vancomycin MICs that has been detected in various geographic areas. Studies suggest that infections due to *S. aureus* strains with vancomycin MICs of >1 μg/mL may not respond as well to vancomycin therapy as those due to strains with MICs of <1 μg/mL. Some authorities (e.g., *The Medical Letter*) have recommended choosing an alternative agent in this setting. (2) In 1997, an *S. aureus* strain with reduced susceptibility to vancomycin (vancomycin-intermediate *S. aureus* [VISA]) was reported from Japan. Subsequently, additional VISA clinical isolates were reported. These strains were all resistant to methicillin and many other antimicrobial agents. The VISA strains appear to evolve (under vancomycin selective pressure) from strains that are susceptible to vancomycin but are heterogeneous, with a small proportion of the bacterial population expressing the resistance phenotype. The mechanism of VISA resistance is in part due to an abnormally thick cell wall. Vancomycin is trapped by the abnormal peptidoglycan cross-linking and is unable to gain access to its target site. (3) In 2002, the first clinical isolate of fully vancomycin-resistant *S. aureus* was reported. Resistance in this and several additional clinical isolates was due to the presence of *vanA*, the gene responsible for expression of vancomycin resistance in enterococci. This observation suggested that resistance was acquired as a result of horizontal conjugal transfer from a vancomycin-resistant strain of *Enterococcus faecalis*. Several patients had both MRSA and vancomycin-resistant enterococci cultured from infection sites. The *vanA* gene is responsible for the synthesis of the dipeptide D-Ala-D-Lac in place of D-Ala-D-Ala. Vancomycin cannot bind to the altered peptide.

Daptomycin, a parenteral bactericidal agent with antistaphylococcal activity, is approved for the treatment of bacteremia (including right-sided endocarditis) and complicated skin infections. It is not effective in respiratory infections. This drug has a novel mechanism of action: it disrupts the cytoplasmic membrane. Staphylococcal resistance to daptomycin, sometimes developing during therapy, has been reported.

Linezolid—the first oxazolidinone—is bacteriostatic against staphylococci and offers the advantage of comparable bioavailability after oral or parenteral administration. Cross-resistance with other inhibitors of protein synthesis has not been detected. However, resistance to linezolid has been reported. Serious adverse reactions to linezolid include thrombocytopenia, occasional cases of neutropenia, and rare instances of peripheral and optic neuropathy.

Tedizolid, a second oxazolidinone released in 2014, is available as both oral and parenteral preparations. It has enhanced in vitro activity against antibiotic-resistant gram-positive bacteria, including staphylococci. Tedizolid is administered once a day.

Ceftaroline is a fifth-generation cephalosporin with bactericidal activity against MRSA (including strains with reduced susceptibility to vancomycin and daptomycin). It is approved for use in nosocomial pneumonias and for skin and soft tissue infections.

The parenteral streptogramin antibiotic quinupristin/dalfopristin displays bactericidal activity against all staphylococci, including VISA strains. This drug has been used successfully to treat serious MRSA infections. In cases of resistance to erythromycin or clindamycin, quinupristin/dalfopristin is bacteriostatic against staphylococci. There are limited data on the efficacy of either quinupristin/dalfopristin or linezolid for the treatment of infective endocarditis.

Telavancin is a parenteral lipoglycopeptide derivative of vancomycin that is approved for the treatment of complicated skin and soft tissue infections and for nosocomial pneumonia. The drug has two targets: the cell wall and the cell membrane. It remains active against VISA strains. Because of its nephrotoxicity, it should be avoided in patients with renal disease.

Dalbavancin is a long-acting, parenterally administered lipoglycopeptide that has been used to treat skin and soft tissue infections. Because of its long half-life, it can be administered on a weekly basis. There are limited data on its use in the treatment of invasive staphylococcal infections.