Current Concepts in Antimicrobial Therapy Against Select Gram-Positive Organisms: Methicillin-Resistant *Staphylococcus aureus*, Penicillin-Resistant Pneumococci, and Vancomycin-Resistant Enterococci

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On completion of this article, the reader should be able to (1) compare current antibiotic options to treat infections caused by resistant gram-positive bacteria, differentiating them on the basis of adverse effect profile and evidence supporting their use in a clinical setting; (2) recognize the activity profile of each antibiotic against the resistant gram-positive organisms discussed in the article: methicillin-resistant Staphylococcus aureus*, penicillin-resistant* Streptococcus pneumoniae*, and vancomycin-resistant enterococci; and (3) use knowledge on current antibiotics to treat the infections caused by these organisms, considering potential to induce resistance.*

Gram-positive bacteria cause a broad spectrum of disease in immunocompetent and immunocompromised hosts. Despite increasing knowledge about resistance transmission patterns and new antibiotics, these organisms continue to cause significant morbidity and mortality, especially in the health care setting. Methicillin-resistant *Staphylococcus aureus* poses major problems worldwide as a cause of nosocomial infection and has emerged as a cause of community-acquired infections. This change in epidemiology affects choices of empirical antibiotics for skin and skin-structure infections and community-acquired pneumonia in many settings. Throughout the world, the treatment of community-acquired pneumonia and other respiratory tract infections caused by penicillin-resistant *Streptococcus pneumoniae* has been complicated by resistance to β-lactam and macrolide antibacterial drugs. Vancomycin-resistant enterococci are a major cause of infection in the hospital setting and remain resistant to treatment with most standard antibiotics. Treatment of diseases caused by resistant gram-positive bacteria requires appropriate use of available antibiotics and stewardship to prolong their effectiveness. In addition, appropriate and aggressive infection control efforts are vital to help prevent the spread of resistant pathogens.

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BSI = bloodstream infection; CA-MRSA = community-associated methicillin-resistant *Staphylococcus aureus*; CAP = community-acquired pneumonia; CLSI = Clinical Laboratory Standards Institute; CNS = central nervous system; FDA = Food and Drug Administration; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; PBP = penicillin-binding protein; PCV7 = pneumococcal conjugate vaccine 7; SSSI = skin and skin-structure infection; UTI = urinary tract infection; VAP = ventilator-associated pneumonia; VRE = vancomycin-resistant enterococci; VISA = vancomycin-intermediate *Staphylococcus aureus*

Staphylococcus aureus causes a broad spectrum of disease. Humans are colonized by this organism mainly in the nasopharynx and on the skin.[1] *S aureus* has the unique propensity to infect and destroy normal healthy tissue, causing skin and wound infections, bloodstream infection (BSI), pneumonia, osteomyelitis, endocarditis, lung abscess, and pyomyositis. Manifestations of *S aureus* central venous catheter–related infection include local infection at the site, thrombophlebitis and tunnel infections, and central venous catheter–related BSI.[2] These well-described health care–associated infections continue to challenge physicians globally.

Community-associated methicillin-resistant *S aureus* (CA-MRSA) has been described in patients with no previous contact with the health care environment. Unlike hospital-associated MRSA, many CA-MRSA strains are susceptible to gentamicin, tetracyclines, lincosamides, and trimethoprim-sulfamethoxazole.[1,3] Many of these infections are limited to superficial skin and skin-structure infections (SSSIs). However, CA-MRSA can cause severe systemic infections, including pneumonia and BSI.[4] In the United States, the first cases of severe CA-MRSA disease were 4 cases of fatal pneumonia reported to the Centers for Disease Control and Prevention in 1997-1999, all associated with a particular strain of CA-MRSA.[5] Several subsequent studies reported *S aureus* community-acquired pneumonia (CAP) with high mortality rates.[6,7] In a study of 3 different communities, more than two-thirds had SSSIs, followed by wound infection, urinary tract infection (UTI), sinus infection, and pneumonia as the most common manifestations of their CA-MRSA infection.[8] New challenges in treating

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infections caused by more resistant *S aureus* organisms include *S aureus* with heteroresistant vancomycin-intermediate *S aureus* (VISA), vancomycin-resistant *S aureus*, and MRSA resistant to linezolid and daptomycin.[9,10] In this article, we provide an overview on MRSA treatment.

METHICILLIN-RESISTANT *S AUREUS* SSSIs

The spectrum of MRSA SSSIs includes impetigo, folliculitis, cellulitis, erysipelas, staphylococcal scalded skin syndrome, toxic shock syndrome, furuncles, carbuncles, and deep skin abscesses.[11,12] In a study examining bacterial causes of SSSIs in 11 US emergency departments in 2004, CA-MRSA was the No. 1 cause of endemic SSSIs.[13]

No clear predictors of CA-MRSA exist, and local trends should be considered when selecting empirical therapy. However, some risk factors include a positive history of contact with CA-MRSA, crowding, contaminated personal objects, compromised skin integrity, and absence of cleanliness. Person to person transmission, among men who have sex with men and as the result of heterosexual contact, has been implicated in CA-MRSA epidemiologic trends.[14]

Although there are several strains of CA-MRSA in the United States, the predominant US strains include the USA300 and USA400 clones. The most common throughout the United States is the USA300 clone, except in Alaska.[15] In Europe the epidemiology is heterogeneous, but overall the most common clone is the *luskF-PV*-positive European ST80-MRSA-IV clone.[16] Community-acquired MRSA has unique virulence factors, including Panton-Valentin leukocidin, and is frequently associated with inadequate antibiotic therapy.[17-19]

AGENTS CURRENTLY AVAILABLE TO TREAT MRSA INFECTION

Some uncomplicated CA-MRSA SSSIs in immunocompetent hosts can be treated with incision and drainage, local debridement, and abscess drainage alone.[11] However, in patients with signs of systemic illness or comorbidities, empirical treatment of SSSIs should include antibacterial therapy. Unfortunately, clinical predictors of drug resistance are limited, so local rates of CA-MRSA must be considered when treating SSSIs. No large randomized controlled trials have compared oral antibiotics to treat SSSIs, although several ongoing National Institutes of Health studies should help address these questions.[20]

Observational studies demonstrate successful clinical outcomes with oral antibiotics, including trimethoprim-sulfamethoxazole, doxycycline, and clindamycin. Isolates that test resistant to erythromycin and are susceptible to clindamycin should be tested for inducible clindamycin resistance (via the D-test) because treatment failures have been reported.[21] Linezolid is not recommended to treat uncomplicated SSSIs because of the associated toxicity and cost.[22]

Treatment of SSSIs in patients with comorbidities or signs of systemic disease includes monotherapy with intravenous antibiotics in addition to prompt and thorough incision and drainage of abscesses, as well as debridement of wounds.[11] Table 1 lists the systemically available gram-positive antibiotics. Vancomycin may be used at a dosage of 10 to 15 mg/kg intravenously every 12 hours adjusted for renal function.[23] Other options include linezolid, 600 mg intravenously every 12 hours, with the limitations mentioned herein, including cost and toxicity. Daptomycin is another agent effective for therapy of SSSIs at a dosage of 4 mg/kg daily. New agents for SSSIs include telavancin, approved by the US Food and Drug Administration (FDA) in 2009 at the dosage of 10 mg/kg daily in patients with normal renal function, and ceftaroline, which was FDA approved in 2010 for treatment of acute bacterial SSSIs at the dosage of 600 mg intravenously every 12 hours in patients with normal renal function. High cost and risk of toxic effects limit use of these new drugs.[23,24] The mechanisms of resistance for MRSA are presented in Table 2.[25]

THERAPY FOR INVASIVE MRSA INFECTIONS

Vancomycin

Vancomycin remains first-line antimicrobial therapy for serious infections caused by MRSA, including complicated SSSIs, pneumonia, and BSI.[11] Available in multiple generic formulations, vancomycin is reasonably well tolerated, associated with a low incidence of adverse effects, and relatively inexpensive. However, despite being the criterion standard therapy, the susceptibility of MRSA to this antibiotic may be decreasing, and reports of clinical failure are increasing.[26,27]

Changes in MRSA vancomycin susceptibility have been observed over time. Increasing minimum inhibitory concentrations (MICs) seem to be related to vancomycin use.[28] As the MIC increases, the frequency of heteroresistant VISA also has been observed to increase.[29] Although most MRSA strains appear susceptible, subpopulations of strains may have VISA selected by vancomycin treatment.[30] Furthermore, increased vancomycin MIC has correlated with adverse clinical outcomes in some studies.[26,27] However, these data are limited in that they derive from retrospective studies, subset analyses, and variations among MIC testing methods.[31] In 2006, on the basis of clinical evidence suggesting reduced efficacy in the treatment of isolates with borderline susceptible MICs, the vanco-

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TABLE 1. **Agents for Infections Caused by Resistant Gram-Positive Organisms**

Drug	Class (mechanism of action)	Route of administration	Activity against			Common toxic effects
			MRSA	Resistant *Streptococcus pneumoniae*	VRE	
Vancomycin	Glycopeptide (cell wall synthesis inhibitor)	IV only	All	Yes	No	Renal, cranial nerve VIII, infusion-related reaction
Daptomycin	Lipoglycopeptide (cell membrane disruption, probably also acts at cell wall)	IV only	SSSI, BSI, SARIE, not pneumonia	No	Yes (*Enterococcus faecium* only)	Myopathy, eosinophilic pneumonia
Linezolid	Oxazolidonone (protein synthesis inhibitor)	IV or oral	SSSI, pneumonia, not BSI	No	Yes	Bone marrow suppression, lactic acidosis, peripheral neuropathy
Quinupristin-dalfupristin	Streptogramin (protein synthesis inhibitor)	IV only	Salvage	No	*E faecium*	Myalgias, arthralgias
Telavancin	Lipoglycopeptide (cell wall synthesis inhibitor)	IV only	SSSI, CAP	Yes	Yes	Renal, reproductive toxic effects
Tigecycline	Glycylcycline (protein synthesis inhibitor)	IV only	SSSI, CAP, not HAP/VAP or BSI	Yes	Yes	Nausea, vomiting
Ceftaroline	Cephalosporin (cell wall synthesis inhibitor)	IV only	SSSI, CAP	Yes	No	Allergy

BSI = bloodstream infection; CAP = community-acquired pneumonia; HAP/VAP = hospital-acquired pneumonia/ventilator-associated pneumonia; IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; SARIE = *Staphylococcus aureus* right-sided endocarditis; SSSI = skin and skin structure infection; VRE = vancomycin-resistant enterococci.

mycin breakpoints were lowered by the Clinical Laboratory Standards Institute (CLSI). The MRSA vancomycin MIC decreased from 4 μg/mL or less to 2 μg/mL or less for "susceptible," from 8 to 16 μg/mL to 4 to 8 μg/mL for "intermediate," and from 32 μg/mL or more to 16 μg/mL or more for the "resistant" designation.[32] Despite concerns about evolving resistance, most cases of invasive or severe infections caused by MRSA remain highly susceptible to vancomycin.[28,33,34] Nonetheless, recent guidelines suggest treating with higher doses of vancomycin with goal trough values of 15 to 20 μg/mL.[23] In patients who do not respond, follow-up cultures should be obtained and, when results are positive, repeat susceptibility testing performed to assess for increasing vancomycin MICs. Alternative antibiotics should be considered when the clinical response is suboptimal.[11]

Studies evaluating MRSA infections with reduced susceptibility to vancomycin (including VISA and heterogeneous VISA) suggest that prospective identification of these isolates may have limited value, but the importance of identifying these strains is critical in the context of clinical failure of vancomycin therapy.[35]

In a prospective, multinational cohort study evaluating the outcome of severe *S aureus* infections, higher MIC was associated with an increased mortality at 30 days. The remarkable finding of this study was that high vancomycin MIC was associated with worse outcomes in patients with methicillin-sensitive *Staphylococcus aureus* (MSSA) infections not treated with vancomycin. This finding suggests that other factors, presumably related to the bacteria or the host, may be implicated in the worse outcomes. This finding is aligned with current recommendations to consider changing from vancomycin therapy in light of clinical response, not MIC alone.[36,37]

The predictability of vancomycin nephrotoxicity has been demonstrated in a number of studies and is associated with higher vancomycin trough concentrations.[38] It has also been associated with underlying renal disease, longer duration of therapy, and use of other nephrotoxic medications.[39,40]

Teicoplanin

Teicoplanin is an antibiotic widely used outside the United States for the treatment of infections caused by gram-positive bacteria. It is chemically related to the group of glycopeptides, which also includes vancomycin.[41] This antibiotic demonstrates bactericidal activity against a broad spectrum of gram-positive organisms, including MRSA and methicillin-resistant coagulase-negative *Staphylococcus epidermidis*. It has a longer half-life, higher protein binding, higher bone uptake, and less potential for nephrotoxicity compared with vancomycin.[42]

In the United Kingdom, the most recent guidelines for the treatment of MRSA infections include teicoplanin as one of the glycopeptides of choice. Local epidemiology and the clinical setting would influence the choice of vancomycin vs teicoplanin. The pharmacokinetics of teicopla-

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TABLE 2. **Mechanism of Resistance in Selected Gram-Positive Pathogens**

Species	Resistance phenotype	Mechanism(s)
Streptococcus pneumoniae	β-Lactam	Low-affinity penicillin-binding proteins
	Fluoroquinolone	Mutant topoisomerases
Methicillin-resistant *Staphylococcus aureus*	Penicillin	β-Lactamase
	Oxacillin	Low-affinity penicillin binding proteins
	Clindamycin	Constitutive erm expression
	Vancomycin	Mechanism unclear
Enterococcus faecium	Ampicillin	Low-affinity penicillin-binding proteins
	Vancomycin	Altered peptidoglycan precursor
	Linezolid	Mutant ribosomal RNA genes
	Daptomycin	Mechanism unclear

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nin are unpredictable, and failures have been associated with low levels of the drug.[43]

Linezolid

Linezolid is a bacteriostatic, gram-positive antibiotic that inhibits protein synthesis at the 50S ribosome.[44] A synthetic oxazolidinone active against MRSA, penicillin-resistant *Streptococcus pneumoniae,* and vancomycin-resistant enterococci (VRE), linezolid is currently FDA approved for the treatment of complicated SSSIs and nosocomial pneumonia. Linezolid is administered at a dosage of 600 mg every 12 hours orally or intravenously, and dose adjustment is not necessary. Studies have shown higher clinical cure rates and reduced lengths of hospitalization in patients with complicated SSSIs treated with linezolid compared with vancomycin.[44] Higher survival rates were found in subset analyses of clinical trials comparing linezolid to vancomycin in the treatment of MRSA pneumonia.[45] One potential explanation for this effect is that linezolid achieves higher concentration levels in lung tissue.[46-48]

The role of linezolid in the treatment of MRSA BSI is unclear. Successful treatment of cases of BSI associated with pneumonia or SSSIs have been reported with linezolid.[49] However, on the basis of the results of a more recent open-label study of catheter-related BSI, linezolid is not recommended for the treatment of BSI.[11] An imbalance in deaths among linezolid-treated patients led to early termination of this European study. However, in the published analysis, this imbalance appears to have been driven by deaths among patients with gram-negative BSI or in whom no bacterial cause was elucidated.[50]

Linezolid is generally well tolerated. Bone marrow suppression is generally reversible with discontinuation of linezolid therapy. The association with serotonin toxicity and thrombocytopenia may limit its use.[51] Linezolid should be administered to patients receiving serotonin reuptake inhibitors with caution, and linezolid therapy should be discontinued if serotonin syndrome is suspected.[52] Patients with renal insufficiency have been found to be at a higher risk of developing thrombocytopenia.[53] The most common gastrointestinal adverse effects include nausea, vomiting, and diarrhea. Sporadic cases of lactic acidosis,[54] peripheral neuropathy, and optic neuritis have been reported.[55] Patients who receive therapy for more than 2 weeks should be monitored closely for myelosuppression and other less common toxic effects.

Linezolid-Resistant *S aureus*

Most strains of *S aureus* are susceptible to linezolid. Resistance surveillance data demonstrate that more than 99% of isolates are susceptible.[56] The first MRSA isolate resistant to linezolid was reported in 2001 in a patient treated for dialysis-associated peritonitis.[57] Since then, the emergence of linezolid-resistant *S aureus* has been reported in recent studies.[58] Appropriate monitoring for resistance should be considered during long courses of therapy. As in the case of vancomycin and daptomycin, clinical failure should prompt submission of specimens for culture, susceptibility testing, and MIC determination.[59]

Daptomycin

Daptomycin is a cyclic lipopeptide active in vitro against most resistant gram-positive bacteria. This bactericidal agent is thought to cause depolarization of the bacteria via calcium-dependent insertion to the cell membrane.[60] Daptomycin susceptibility may depend on its ability to penetrate through the cell wall to reach its target.[61] Heteroresistant VISA may have an increased daptomycin MIC, probably related to increased cell wall thickness.[62] Daptomycin was approved by the FDA for the treatment of serious MRSA infections, including SSSIs, MRSA, and MSSA BSI and right-sided endocarditis, on the basis of the results of prospective randomized clinical trials.[63,64] The daptomycin dosage is 4 mg/kg intravenously once daily for complicated SSSIs and 6 mg/kg intravenously once daily for *S aureus* BSIs, including right-sided endocarditis, in patients with normal renal function.[64] Daptomycin should not be used to treat pneumonia because it failed in clinical trials

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and was subsequently found to be inhibited by pulmonary surfactant.[65] Resistance developed in several daptomycin-treated patients in the *S aureus* BSI trial.[63] In these cases, clinical failure while receiving daptomycin was related to increased daptomycin MIC from 0.25 or 0.5 μg/mL to 2 or 4 μg/mL. The mechanism is not well understood.[9,63]

Daptomycin therapy is associated with myopathy. Creatine kinase levels should be monitored at baseline and weekly while the patient is undergoing therapy, more often in patients with symptoms of muscle pain or weakness and renal insufficiency or those who receive concomitant statin therapy. Daptomycin therapy should be discontinued for muscle pain or weakness or elevations in creatine kinase levels if the level is 5 to 10 times or more the upper normal limit.[64] Acute eosinophilic pneumonia has been reported with daptomycin therapy.[66] Although the mechanism of toxicity has not been proven, the release of inflammatory mediators after antigen presentation by macrophages or accumulation in the epithelium after daptomycin binding with surfactant has been implicated.[67] It is a diagnosis of exclusion, but physicians should have a low threshold for stopping therapy if daptomycin-induced acute eosinophilic pneumonia is suspected.[67]

Tigecycline

Tigecycline is a derivative of minocycline and the first drug approved in the class of glycylcyclines.[68] A modified side chain binds to the 30S ribosomal subunit, inhibiting protein translation in bacteria.[69,70] Tigecycline is active against various drug-resistant pathogens, including MRSA, VRE, and many extended β-lactamase, gram-negative bacteria. Tigecycline has a large volume of distribution and produces high concentrations in tissue. However, serum concentrations decrease rapidly after intravenous administration.[71] On the basis of these pharmacokinetic and pharmacodynamic properties, tigecycline should be used with caution in patients with suspected or proven BSI.[72] In the United States, this drug is approved for the treatment of complicated SSSIs due to MRSA and the treatment of complicated intra-abdominal infections caused by MSSA.[73] The approved tigecycline dosage is a 100-mg intravenous loading dose followed by a 50-mg dose given every 12 hours. Common adverse effects include nausea and vomiting.

In a large, randomized, double-blind clinical study of patients with hospital-acquired pneumonia comparing tigecycline with an imipenem-cilastatin regimen, cure rates were lower in the tigecycline ventilator-associated pneumonia (VAP) group (67.9%) compared with imipenem (78.2%), whereas in the non-VAP patients tigecycline was noninferior to imipenem. Mortality rates were also higher in the tigecycline group.[74] These results may be related to decreased tigecycline concentrations in these critically ill patients. On the basis of these trends and subsequent observations, the FDA recommends seeking alternatives to tigecycline to treat patients with severe infections.[75] A study is under way to evaluate the role of tigecycline at 2 higher dosages (75 or 100 mg every 12 hours) compared with imipenem-cilastatin in parallel in the treatment of hospital-acquired pneumonia.[76]

Quinupristin-Dalfopristin

Quinupristin-dalfopristin is a combination streptogramin agent that is FDA approved for the treatment of SSSIs due to MSSA, streptococci, and the treatment of VRE BSI. This combination antibiotic is bactericidal against *S aureus* via inhibition of protein synthesis. It was studied in patients with MRSA infections who were intolerant of other antibiotics. In an open-label, emergency use program, quinupristin-dalfopristin was successful in treatment of 66.7% of patients, most of whom had SSSIs and osteoarticular infections. Therapy failed in patients with endocarditis.[77] Dose-limiting adverse effects include joint pain, muscle pain, and severe pain at the site of infusion.[78]

Telavancin

Telavancin is a semisynthetic lipoglycopeptide that produces inhibition of cell wall synthesis and disruption of membrane barrier function.[79] It has a long half-life of 7 to 9 hours, allowing once-daily administration using 7.5 to 10 mg/kg daily. It is a rapidly bactericidal agent, active against MRSA. Telavancin was approved by the FDA in 2009 for the treatment of complicated SSSIs caused by gram-positive bacteria, including MRSA.[80] In clinical trials, telavancin was found to be noninferior to vancomycin, with cure rates of 88.3% and 87.1% in the treatment of complicated SSSIs.[81]

Telavancin was compared with vancomycin in large randomized studies in the treatment of hospital-acquired pneumonia due to gram-positive bacteria, particularly MRSA, and found to be noninferior to vancomycin based on clinical response.[82] The most common adverse effects include taste disturbances, nausea, headache, vomiting, constipation, insomnia, and foamy urine.[82] Telavancin therapy was associated with adverse fetal outcomes in animal studies, and the United States package insert includes a warning concerning the potential risk of abnormal fetal development.[83] Nephrotoxicity has been reported with elevation in the serum creatinine levels, which was more likely to occur in patients with underlying diseases that predisposed the patient to kidney dysfunction.[84]

Ceftaroline

Ceftaroline is a cephalosporin antibiotic with MRSA activity. Ceftaroline has high affinity for penicillin-binding protein (PBP) 2a, an MRSA-specific PBP, which correlates

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to its low MIC for MRSA. It demonstrates bactericidal, time-dependent killing in vitro and in vivo.[85,86] On the basis of randomized clinical trials, ceftaroline was approved by the FDA for SSSIs and CAP in 2010. The drug is dosed according to renal function and associated with toxic effects similar to other β-lactam antibiotics.[50,87] Recommended dosing is 600 mg intravenously every 12 hours or 400 mg intravenously every 12 hours for patients with moderate renal dysfunction.[88]

Activity against other pathogens, including coagulase-negative staphylococci, enterococci, β-hemolytic and viridans group streptococci, and some Enterobacteriaceae (*Escherichia coli, Klebsiella* spp, and *Proteus mirabilis*), makes ceftaroline a reasonable empirical antibiotic option in the treatment of SSSIs and CAP.[89]

Ceftaroline was compared with ceftriaxone for the treatment of CAP in 2 large randomized, double-blind multicenter studies. Of the patients treated with ceftaroline, 84.3% achieved clinical cure compared with 77.7% in the ceftriaxone group. Ceftaroline demonstrated a safety profile similar to ceftriaxone. *Staphylococcus aureus* was isolated in 55 (16.5%) of 333 patients treated with ceftaroline in these studies.[90]

Penicillin-Resistant Pneumococci

Streptococcus pneumoniae is one of the most common pathogens that causes CAP, otitis media, and meningitis.[91] Antimicrobial resistance among *S pneumoniae* has increased significantly in past decades. Penicillin susceptibility breakpoints were established in the late 1970s. Over time, studies in children and adults demonstrated more treatment failures in penicillin-treated patients found to have pneumococcal isolates from meningitis with higher penicillin MICs.[92] This observation was not seen among penicillin-treated patients with *S pneumoniae* infecting other areas of the body, including pneumonia and otitis media. However, the clinical impact of antimicrobial resistance remains unclear because of the lack of complete correlation between drug susceptibility data and treatment failure.[93] The CLSI recently reviewed the breakpoints of *S pneumoniae*.[94] Using the new meningitis penicillin breakpoint criteria (≥0.12 μg/mL), resistance prevalence was 34.8% in 2008, but it was found to be 12.3% using the old criteria (>2 μg/mL) for cerebrospinal fluid isolates.[95]

Risk factors associated with *S pneumoniae* resistance to penicillin include the presence of underlying immunosuppression and receipt of antibiotics within 3 months.[92] Resistance to β-lactam antibiotic drugs is mediated by alterations in PBPs, decreasing the affinity of the antibiotic to the *S pneumoniae*. Alterations in PBPs occur by transformation of genes that can be transferred not only by *S pneumoniae* species but also by other groups of streptococci.[96] Macrolide resistance occurs when there is a change in the ribosomal RNA though *erm(B)* or *mef(A)*. *Erm(B)* alters the site of macrolide binding through methylation, causing lack of recognition, whereas *mef(A)* encodes an efflux pump. Resistance to quinolones occurs by alteration of topoisomerases.[97] Multidrug resistance is usually spread through resistant genetic material with a small number of predominant clones.[98]

The impact of the pneumococcal conjugate vaccine 7 (PCV7) was evaluated using data from isolates collected in 2008 as part of the SENTRY surveillance program. The seroprevalence of PCV7 serotypes decreased from 68.5% before the vaccine to 29.3%. Most isolates with drug resistance before the vaccine were PCV7 serotypes; however, postvaccine noninvasive, nonvaccine serotypes were found to be increased and are more likely to acquire resistance over time.[99] The introduction of the 13-valent pneumococcal conjugate vaccine, licensed by the FDA for prevention of invasive pneumococcal disease caused by 13 pneumococcal serotypes, could further change the prevalence of isolates in the future.

AGENTS CURRENTLY AVAILABLE FOR TREATMENT OF RESISTANT *S PNEUMONIAE* INFECTION

Treatment of non–central nervous system (CNS) infection caused by antibacterial-resistant pneumococcal infection still relies on penicillins, aminopenicillins, and third-generation cephalosporins.[100] Some of the common mechanisms of resistance are listed in Table 2.[25] Meningitis is the exception because a combination of vancomycin and a third-generation cephalosporin is recommended due to concerns about emergence of penicillin or cefotaxime nonsusceptible pneumococcal isolates.[101]

There is no consensus on the use of combination therapy for resistant *S pneumoniae* pneumonia and associated BSI.[92] Macrolide monotherapy is not recommended as empirical treatment of CAP, especially in geographic areas with high rates of resistant *S pneumoniae* strains.[102] Treatment failure with fluoroquinolones has been reported.[103] Fluoroquinolones should be used only when local epidemiology suggests high rates of nonsusceptible *S pneumoniae* strains or in cases of allergy or intolerance to first-line antimicrobial therapy for CAP.[104] Although fluoroquinolones allow easy switch from parenteral to oral regimens and have excellent bioavailability, this class of drugs has several drawbacks, including broad-spectrum activity associated with "collateral damage," including disturbance of gastrointestinal flora, selection of resistance for multiple bacteria (eg, MRSA), drug interactions, and risk of *Clostridium difficile* infection.[105]

Resistance among pneumococci to fluoroquinolones is caused by quinolone resistance–determining regions in

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genes that encode subunits of topoisomerases.[106] During 2001-2002, *S pneumoniae* isolates were collected in the United States to determine susceptibility. Testing was performed on 1902 isolates. Although the rates of fluoroquinolone resistance remains low in the United States, 40% were found to have quinolone resistance–determining region mutations, and 35% of levofloxacin-nonsusceptible pneumococci were closely related to widespread pneumococcal clones that have spread antibiotic resistance among pneumococci strains in past decades. The authors suggest potential for a rapid increase in resistance associated with clonal dissemination and the wide use of quinolones worldwide.[103]

In a European study evaluating the outcome of patients treated for severe pneumococcal CAP, excluding penicillin-resistant pneumococci, the combination of levofloxacin with a β-lactam was associated with lower mortality rates than ofloxacin or ciprofloxacin. This study had many limitations, including recruitment over a long period and changes in standard antibiotic therapy in the intensive care unit during the study period.[107]

NEW OPTIONS FOR TREATMENT OF RESISTANT *S PNEUMONIAE* INFECTION

Ceftaroline

Ceftaroline binds to PBPs in *S pneumoniae*, interfering with cell wall synthesis.[108] In the international, multicenter, randomized, double-blind clinical trials comparing ceftaroline to ceftriaxone in the treatment of CAP, the cure rate for the ceftaroline group was 85.5% compared with 68.6% for ceftriaxone. However, few pneumococci with high MICs were isolated.[90] In the treatment of patients with multidrug-resistant *S pneumoniae* pneumonia, ceftaroline cure rates were numerically higher compared with ceftriaxone. However, the numbers were small, with cure rates of 4 of 4 patients in the ceftaroline group compared with 2 of 9 patients in the ceftriaxone group.[109]

Linezolid

In animal models, linezolid has shown efficacy in the treatment of pneumococcal pneumonia. The most important predictor of efficacy is the interval during which drug concentration exceeds the MIC.[110] The role of linezolid in the setting of CAP has been evaluated in several trials. In an open-label trial of 1700 patients comparing intravenous linezolid followed by oral linezolid with ceftriaxone followed by oral cefpodoxime, the linezolid-treated patients (n=272) had a cure rate of 91% compared with a clinical cure rate of 89% (n=225/254) in patients in the ceftriaxone-cefpodoxime group.[111] In a subgroup analysis examining the eradication of *S pneumoniae* and *S aureus*, a subset of 53 patients with blood cultures positive for *S pneumoniae* had a clinical cure rate of 93% (30 patients) in the linezolid group compared with 70% (23 patients) in the ceftriaxone-cefpodoxime group.[111]

Telavancin

Telavancin demonstrates in vitro activity against penicillin-nonsusceptible *S pneumoniae*.[112] In an animal model of meningitis, telavancin was found to be more efficacious than vancomycin plus ceftriaxone against a penicillin-resistant pneumococcal strain.[113] We hope that data from future clinical studies will define the role of telavancin in the treatment of clinical infections caused by penicillin-nonsusceptible *S pneumoniae*.

Tigecycline

Although not registered for the treatment of infections with penicillin-nonsusceptible *S pneumoniae*, tigecycline is active in vitro and might be considered as salvage therapy for these infections.[114] A study is currently under way to evaluate the role of tigecycline in the treatment of hospital-acquired pneumonia.[76]

Vancomycin-Resistant Enterococci

Enterococci are part of normal gastrointestinal tract flora and have relatively low virulence. Most clinical isolates are *Enterococcus faecalis* and *Enterococcus faecium* and are less commonly other enterococcal species. The CLSI defines vancomycin-susceptible enterococci as having a vancomycin MIC of 4 μg/mL or less and vancomycin-resistant enterococci as having an MIC of 32 μg/mL or more.[115] The first cluster of infections due to vancomycin-resistant enterococci was reported in 22 patients with end-stage renal disease.[116] Enterococcal BSIs continue to pose a problem in the hospital setting, causing nosocomial BSIs and post-surgical UTIs.[117] *E faecium*, which was much less common clinically than *E faecalis*, emerged as an important nosocomial infectious pathogen, with rates of vancomycin resistance of up to 60%.[117] Despite this problem there is a paucity of clinical data with the newer antibacterial agents, including linezolid, daptomycin, and tigecycline, in the treatment of this disease.[118,119] Moreover, even in the era of these newer agents, patients infected with VRE still need better tolerated alternatives.

Antibiotic resistance among enterococci is conferred through mutation and acquisition of genetic material from other species. *E faecium* often has acquired resistance to penicillin by increased expression of low-affinity PBP5 of mutations at this site.[120] *E faecalis* can have penicillin resistance, although it is less common, through a β-lactamase similar to the one found in *S aureus*.[121] One mechanism involves plasmid transfer among *E faecalis* isolates. Although there are 6 phenotypes of vancomycin resistance,

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2 can be harbored on plasmids (VanA and VanB).[42] The VanA phenotype is encoded by a gene located in a plasmid transferred to other isolates through conjugation. The VanA phenotype has a vancomycin MIC greater than 256 μg/mL and is teicoplanin resistant. The VanB phenotype codes for resistance to vancomycin and is also transferable to other enterococci; however, these isolates remain susceptible to teicoplanin.[122,123] The most common mechanisms of resistance in VRE are described in Table 2.[25]

In a large VRE surveillance program, most resistant isolates were *E faecium* (91%) and *E faecalis* (7.8%). These rates vary geographically, with a higher prevalence of the VanA phenotype in North America (76%) compared with Europe (40%).[124] In the health care setting, multiple factors drive the transmission of VRE, including selective pressure due to antibiotic use, the proportion of patients colonized with VRE vs susceptible enterococci, and adherence to prevention measures.[125-127]

Infection with VRE affects patients in intensive care units and those with intravascular or bladder catheter devices. Immunosuppressed patients, particularly recipients of liver and other solid organ transplants and hematopoietic stem cell transplants, remain vulnerable to VRE infections. Prolonged hospitalization, residence in long-term care facilities, and exposure to antibiotics are also implicated in VRE infections.[128]

Clinical outcome is worse and mortality rates higher in patients with VRE infections compared with those with infections caused by vancomycin-susceptible enterococci. One of the main challenges for physicians treating VRE is the intrinsic resistance to many antibiotics, including β-lactams, aminoglycosides, lincosamides, and trimethoprim-sulfamethoxazole.[129] Vancomycin-resistant *E faecalis* is usually susceptible to β-lactams.[130]

One of the most important decisions to make when presented with a positive microbiological report of VRE is to identify whether the isolate represents infection or colonization. Commonly, VRE isolates can be reported from superficial wounds, removed catheters, urine cultures, and abdominal drains. Positive blood cultures, as well as cultures of normally sterile sites, represent VRE infection. Catheters should be removed in the setting of VRE infection. Management and debridement of wounds and surgical management for source control should be performed as a first rule in the management of localized infections.[131]

AGENTS CURRENTLY AVAILABLE FOR TREATMENT OF VRE INFECTION

Infections due to VRE include urinary tract, wound infections, BSI, endocarditis, and meningitis. Efficacy data for agents used in the management of VRE infections are limited. Often based on anecdotal report, most of these drugs are not approved by the FDA for the treatment of VRE infections.[132] Tetracycline, doxycycline, oral novobiocin with ciprofloxacin, and doxycycline have been reported as effective in treating VRE infections. However, there are no clinical studies to support these therapies.[133]

For treatment of lower UTIs, nitrofurantoin may be effective because this agent is excreted into the urine.[134] Fosfomycin can be used for treatment of uncomplicated UTIs.[135] Invasive VRE infection, including BSI, endocarditis, and meningitis, warrants therapy with a bactericidal agent. Synergistic activity of a cell wall–active agent and aminoglycoside is used in the setting of endocarditis and/or critical illness. For serious enterococcal infections, including meningitis and endocarditis, treatment includes a cell wall–active agent and an aminoglycoside to produce a synergistic effect.[130,136]

Fosfomycin

Fosfomycin is a phosphonic acid derivate that was first isolated from cultures of *Streptomyces* species in 1969.[137] In the United States it is approved for the treatment of uncomplicated UTIs caused by *E coli* and *E faecalis*, but it is used widely intravenously, particularly in Europe. Fosfomycin has activity against gram-positive and gram-negative bacteria. Fosfomycin is active in vitro against *S aureus*, *S epidermidis*, *S pneumoniae*, and *E faecalis*,[138] as well as against a number of gram-negative organisms.[139] In a review of 1311 potentially relevant trials, 63 studies of fosfomycin for the treatment of infections caused by gram-positive and gram-negative bacteria were reviewed. The most common gram-positive organism was *S aureus*. Most patients received fosfomycin in combination with other antibiotics. The diversity and heterogeneity of the studies make it difficult to draw conclusions, but fosfomycin may be considered an antibiotic option for the treatment of infections caused by multidrug-resistant pathogens. Further studies should be performed to assess a possible role for intravenous fosfomycin.[140]

Quinupristin-Dalfopristin

Quinupristin-dalfopristin is a protein synthesis–inhibiting antibiotic that has potent in vitro activity against *E faecium* but poor activity against *E faecalis*.[141] In a large study of 396 patients with vancomycin-resistant *E faecium* infection, the overall efficacy of quinupristin-dalfopristin was 66%.[142] The most common sites of infection were intra-abdominal, BSI, UTI, catheter-related BSI, and SSSI.[142] Severe myalgias, arthralgias, and gastrointestinal adverse effects limit its use.[78]

Linezolid

Linezolid has potent in vitro and in vivo activity against vancomycin-resistant strains of *E faecium* and *E faecalis.* Initial data, obtained through compassionate use stud-

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ies, demonstrated resolution of infection in 63% to 81% of cases and led to FDA approval of linezolid in 2000.[143] Although linezolid has not been approved specifically for the treatment of enterococcal endocarditis, it has been used in this setting. In a large study of 796 patients who were treated for endocarditis, linezolid was used in patients who were intolerant to vancomycin or did not respond to it or were intolerant to quinupristin-dalfopristin therapy. Among these patients, 32 were re-treated, 59.9% had infection caused by VRE, and 19.4% had infection caused by MRSA. Overall, patients with vancomycin-resistant *E faecium* had a clinical cure rate of 81.4%, those with MRSA infection had a cure rate of 66.1%, and therapy failed in 12.8%.[144]

Daptomycin

Daptomycin is bactericidal in vitro against most gram-positive organisms, including VRE. Although daptomycin has not been approved for *E faecium* infections, it has been recommended for treatment based on in vitro data and few clinical studies.[145-147] Daptomycin MICs for *E faecium* are higher than for *E faecalis*. There are no FDA-approved daptomycin MIC breakpoints for *E faecium*, but the CLSI suggests that a daptomycin MIC greater than 4 μg/mL is nonsusceptible. The approved dosing is 4 mg/kg intravenously once daily for complicated SSSIs. For *S aureus* BSI, the approved dosage is 6 mg/kg intravenously daily. Some experts favor higher dosages of 8 mg/kg intravenously once daily.[148] Patients receiving daptomycin therapy should be monitored regularly for the development of myopathy with serum creatine kinase values measured at least weekly and careful monitoring for development of muscle pain or weakness.

Tigecycline

Tigecycline is approved for the treatment of complicated SSSIs and intra-abdominal infections, including those caused by vancomycin-susceptible *E faecalis.* On the basis of in vitro and animal data, VRE appears susceptible to tigecycline. Further studies are needed to define the role of tigecycline in the treatment of VRE infections.[75,149,150]

Published studies of antibacterial therapy for deep eye infections and CNS infections caused by resistant gram-positive bacteria are limited. Animal models suggest that daptomycin may have some advantages compared with vancomycin due to its bactericidal activity.[151] There are also some data examining linezolid in animal infection models. In a clinical study evaluating the possible role of linezolid in the treatment of acute postoperative endophthalmitis, 21 patients undergoing cataract surgery were included. Linezolid concentration intraocularly was measured after intravenous administration of 600 mg of linezolid. This study demonstrated acceptable aqueous humor concentrations of linezolid. We hope that further studies will help elucidate its role in acute postoperative endophthalmitis.[152]

In an open-label, prospective study evaluating linezolid in the management of neurosurgical infections, eradication of causative bacteria was documented in 2 patients with CNS infections and in 1 patient with staphylococcal bacteremia. The outcome for these 2 patients was favorable after 14 days of therapy. Twelve patients were treated prophylactically with linezolid, 1 of whom had a positive blood culture with *S epidermidis*.[153]

A study in Germany with 10 patients with poor response to other treatments demonstrated improvement in 6 patients with linezolid; however, some patients had abscesses and there were multiple organisms, including atypical mycobacteria.[154] Another study evaluated the use of linezolid for the management of nosocomial CNS infections; however, the study was limited because it was retrospective and the group was heterogenous, including differences in indwelling devices and intracranial collections in some patients.[155]

Although the data seem to be limited to case reports and small reports of CNS infections treated with linezolid, this antibiotic should be considered for the management of serious CNS infections that may not be responsive to other first-line antibiotics or in cases of failure to other antibiotics, but further clinical randomized prospective studies should be performed to clarify its role.

CONCLUSION

Resistant gram-positive bacteria cause significant morbidity and mortality. Methicillin-resistant *S aureus* continues to cause a variety of clinical syndromes worldwide. Vancomycin remains the mainstay treatment, but with the emergence of less susceptible strains other therapeutic options should be considered, depending on the clinical setting. Both MRSA BSI and endocarditis may be treated with daptomycin, but daptomycin should not be used for pneumonia. Linezolid is recommended for MRSA pneumonia and skin infection but not as first-line therapy for BSI. Tigecycline provides an alternative for MRSA SSSIs. Quinupristin-dalfopristin should be reserved for refractory cases of invasive MRSA because its use is limited by its adverse effects. Telavancin was approved for the treatment of SSSIs, but concerns of toxicity preclude its use in this indication; we hope to learn more about its potential role in VAP in the near term. Ceftaroline is the newest agent approved for MRSA SSSIs and CAP.

Penicillin-resistant pneumococcal strains vary in different countries and regions. Linezolid and telavancin have shown in vitro activity, but further studies are needed to clarify their role. These agents may be considered in the

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context of intolerance or resistance to β-lactams. β-Lactam antibiotics remain first-line therapy. However, knowledge of local epidemiology and resistance patterns may help inform empirical management of infections caused by these bacteria. Vancomycin plus a third-generation cephalosporin is recommended in the treatment of *S pneumoniae* CNS infection because of the concern of emergence of resistance. Ceftaroline represents a novel class of cephalosporins and may be a new option for treatment of penicillin-resistant *S pneumoniae.*

Vancomycin-resistant enterococci have emerged as concerning pathogens in the hospital setting with a high rate of BSI and other nosocomial infection. Nitrofurantoin and fosfomycin are options for the management of uncomplicated VRE UTI. Other agents, including tetracycline, novobiocin, and doxycycline, have been used to treat VRE infections, but supportive clinical trial data are lacking. Newer VRE therapies include quinupristin-dalfopristin, linezolid, and daptomycin. Quinupristin-dalfopristin and linezolid therapy are limited by tolerability and toxicity concerns; a paucity of efficacy data and uncertainty regarding optimal dose limit daptomycin use. We hope that new agents will be developed to address these challenges.

Improved knowledge of mechanisms of resistance continues to inform development of new antimicrobial therapies. These medicines are but one part of a comprehensive approach to the problem of antimicrobial resistance. Physicians must use existing antimicrobial drugs prudently and practice impeccable infection control in health care facilities if we are to control the spread of resistant bacteria.

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Questions About Current Concepts in Antimicrobial Therapy Against Select Gram-Positive Organisms

1. A 60-year-old man recently underwent hemodialysis for end-stage kidney disease associated with poorly controlled diabetes mellitus. He is evaluated in the hospital after development of fever during dialysis. The patient was hospitalized 3 months ago for placement of an atrioventricular fistula and receives dialysis through a Hickman catheter. On physical examination, his temperature is 39.3°C, blood pressure is 100/70 mm Hg, pulse rate is 100/min, and respiratory rate is 22/min. There is tenderness at the catheter insertion site and a new grade 3/6 holosystolic murmur that increases with inspiration, heard at the left lower sternal border. Multiple blood cultures reveal growth of methicillin-resistant *Staphylococcus aureus.* Transthoracic echocardiography reveals a 0.5-cm vegetation on the tricuspid valve and moderate tricuspid insufficiency. The patient has a history of documented urticaria, bronchospasm, and hypotension associated with vancomycin use.

In addition to removal of the catheter, which one of the following is the most appropriate treatment?
a. Vancomycin
b. Daptomycin
c. Linezolid
d. Ceftaroline
e. Tigecycline

2. A 55-year-old woman developed a fever during her third week of hospitalization in the cardiac care unit after she had a myocardial infarction and experienced cardiogenic shock. Initially, broad-spectrum antibiotics were prescribed, including vancomycin and cefepime; use of these agents was discontinued after 72 hours, when it was clear that her hypotension and shock were related to her cardiac status. The patient has been in acute renal failure, with a creatinine level ranging from 5.0 to 8.0 mg/dL in the past week. Soon after admission, her glomerular filtration rate was less than 10 mL/min. She is now febrile, with a temperature of 39.1°C. You are called by the microbiologist after blood cultures from the patient's central catheter yielded vancomycin-resistant *Enterococcus faecalis.*

Which one of the following would be the most appropriate treatment to initiate in this patient?
a. Start antibiotics only if cultures remain positive after removal of the catheter
b. Quinopristin-dalfopristin
c. Daptomycin
d. Linezolid
e. Ciprofloxacin

3. A 24-year-old male athlete is hospitalized after fever developed associated with an infected turf burn. He noticed some redness in the area 2 days ago but now has some purulent drainage and swelling. Cultures obtained from the drainage yielded *S aureus*, which is resistant to oxacillin but susceptible to vancomycin and linezolid.

Susceptibility testing of this strain will most likely show susceptibility to other antibiotics except for which one of the following?
a. Dicloxacillin
b. Linezolid
c. Trimethoprim-sulfamethoxazole
d. Tetracycline
e. Clindamycin

4. A 65-year-old woman with a medical history notable for diabetes mellitus and chronic obstructive pulmonary disease is admitted for symptoms consistent with possible exacerbation of chronic obstructive pulmonary disease and pneumonia. She has received azithromycin treatment many times in the past as an outpatient and again recently before this hospitalization. The patient is seeking treatment now because she is not improving with azithromycin therapy.

If the cause of her symptoms is Streptococcus pneumoniae*, resistance to macrolides is most likely caused by which one of the following*?
a. Alteration of topoisomerases
b. Presence of the *ermB* or *mefA* genes
c. Decreased permeability of the outer cell envelope
d. Plasmid acquisition
e. Presence of the *mecA* gene

5. *Which one of the following antibiotics is approved by the Food and Drug Administration for the management of methicillin-resistant* S aureus nosocomial pneumonia?
a. Linezolid
b. Daptomycin
c. Ceftarolin
d. Tigecycline
e. Telavancin

Correct answers:1. b, 2. d, 3. a, 4. b, 5. a

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