Antibiotic Resistance, Part 1: Gram-positive Pathogens

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ABSTRACT

Antibiotics have been instrumental in reducing mortality and morbidity associated with bacterial infections. However, antibiotic resistance has been increasing at an alarming rate due to overuse and inappropriate utilization. The emergence of resistance in Streptococcus pneumoniae, Staphylococcus aureus and enterococci is of concern. The increasing incidence of resistance in these pathogens has led to increased morbidity, mortality and health care costs. Understanding mechanisms of resistance and current patterns of resistance found in gram-positive organisms is important when prescribing antimicrobials in patients. A collaborative effort to promote the appropriate prescribing of antimicrobial agents must be undertaken to preserve currently available antibiotics.

Keywords: antibiotic, antimicrobial, gram positive, pathogens, resistance

INTRODUCTION

Since the discovery of penicillin in the 1940s, antibiotics have been instrumental in reducing morbidity and mortality associated with microbial infections. However, just as antibiotics seemed to have gained the upper hand against bacteria, resistance developed, which further illustrates the ongoing struggle between humans and microorganisms causing infection and disease.[1,2] Unfortunately, antibiotic resistance is no longer limited to a single microorganism or antibiotic and continued inappropriate use is leading to increased antibiotic-resistant organisms.

According to a 2013 report by the Centers for Disease Control and Prevention (CDC), antibiotic resistance is a global problem occurring at an alarming rate.[3] At health-care institutions, resistant bacteria, such as staphylococci, enterococci, *Pseudomonas* spp, and *Klebisella pneumoniae*, are more common and pose challenges for clinicians.[2] Bacterial resistance leads to decreased antibiotic effectiveness or failure, which can have serious consequences, especially in critically ill patients.[2] Most deaths related to resistance occur in health-care facilities.[3] The Centers for Disease Control and Prevention further estimates that more than 2 million individuals per year in the United States are infected with antibiotic-resistant bacteria, resulting in at least 23,000 deaths. In 2008, the cost of resistant infections was estimated to be as high as $20 billion in direct health-care costs to upwards of $35 billion, including costs associated with lost productivity.[3]

Antibiotic use drives resistance and is the single most important cause of resistance.[3] Extensive and inappropriate use of antibiotics leads to decreased efficacy. Improper prescribing of antibiotics in patients with viral infections and overuse of broad-spectrum antibiotics has resulted in the emergence of resistance. Unfortunately, as many as half of all prescribed antibiotics are not needed or are prescribed at inappropriate doses.[3] Current practices are creating an environment in which once easily treatable bacteria are more difficult, and in some instances almost impossible, to treat.

Over the last few decades, development of new antibiotics has continued to diminish. There are numerous reasons for this dismal reality. First and foremost, antibiotics are typically used for short

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durations and are less profitable when compared with medications used for chronic diseases.[1,4] Second, there is difficulty in developing new antibiotics when resistance is unpredictable. Finally, manufacturers of new antibiotics are faced with various regulatory and approval obstacles. Unfortunately, this has led to decreased research and development of such agents in a time when it is imperative that newer agents be developed.[1,4]

ANTIBIOTIC MECHANISM OF ACTION

To understand how bacterial resistance develops, a review of current antimicrobial mechanisms of action is presented in Table 1. Antimicrobials can be classified by their mechanism of action as either inhibiting or interfering with: (1) cell wall synthesis; (2) protein synthesis; (3) nucleic acid synthesis; (4) a metabolic pathway; or (5) the bacterial membrane structure.[2]

Table 1. Mechanism of Action of Antimicrobial Agents[a]

β-lactams: Inhibit synthesis by interfering with enzymes required for the synthesis of the peptidoglycan layer:
Penicillins
Cephalosporins
Carbapenems
Monobactams
Glycopeptides: Inhibit synthesis by binding to terminal D-alanine residues preventing cross-linking required for cell wall synthesis:
Vancomycin
Telavancin
Teicoplanin (not available in US)
Inhibition of 30s ribosomal subunit:
Aminoglycosides
Tetracyclines
Tigecycline
Inhibition of 50s ribosomal subunit:
Macrolides
Clindamycin
Chloramphenicol
Linezolid
Quinuprisin-dalfopristin
Inhibition of DNA synthesis (DNA gyrase and topoisomerase):
Fluoroquinolones
Inhibition of RNA synthesis:
Rifampin
Inhibition of Metabolic Pathway
Sulfonamides
Folic acid analogs
Increase bacterial membrane permeability:
Polymyxins
Causes membrane depolarization:
Daptomycin

[a] Refer to Tenover.[2]

Beta-lactams (β-lactams) and glycopeptides inhibit cell wall synthesis. β-lactams (penicillins, cephalosporins, carbapenems, monobactams) interfere with enzymes that build and maintain the peptidoglycan layer. Glycopeptides (vancomycin, telavancin, and teicoplanin) inhibit cross-linking steps of cell wall synthesis by binding to terminal D-alanine residues in the peptidoglycan chain. Macrolides, tetracyclines, aminoglycosides, streptogramins, and oxazolidinones bind to ribosomal subunits in bacteria and inhibit bacterial growth. Fluoroquinolones inhibit either DNA-gyrase and/or DNA-topoisomerase, causing relaxation of supercoiled DNA, resulting in breakage of the DNA. Sulfonamides and trimethoprim block crucial pathways required for folic acid synthesis, which in turn inhibits DNA synthesis. Daptomycin and polymyxins cause disruption of bacterial membrane structures. Daptomycin incorporates into the bacterial cell wall causing membrane depolarization and eventual cell death. Polymyxins increase cell membrane permeability by causing leakage of intracellular components.[2]

MECHANISMS OF RESISTANCE

Selective pressures exerted by antibiotics result in evolutionary changes (mutations) and favor bacteria that are able to resist antibiotic effects. These bacterial populations increase in size and are capable of transferring their resistance genes to new generations (progeny) or to other bacteria. Resistance mechanisms can be described as intrinsic or acquired. Intrinsic resistance is an innate characteristic of bacteria that renders it naturally resistant to an antimicrobial.[5] Acquired resistance is the ability of bacteria to develop resistance via spontaneous mutations or through acquisition of genetic material from other bacteria.[2,5,6]

Chromosomally mediated resistance occurs through spontaneous mutations that can be transferred to the bacteria's progeny (referred to as vertical transmission). Many bacteria also contain mobile genetic elements known as plasmids. Plasmids are extra-chromosomal elements that participate in genetic exchange of genes among bacteria.

Plasmid-mediated resistance often results in high-level resistance among various species of bacteria and can be passed via vertical or horizontal transmission (transfer of resistance genes to other organisms). Genetic exchange of resistant material between bacteria can occur through conjugation, transformation, transduction, or transposons.[2,6]

Mechanisms of resistance include: (1) altering or eradicating target binding sites to which the antibiotic binds; (2) efflux pumps that decrease intracellular antibiotic concentrations; (3) enzymes that inactivate or alter the antibiotic; and (4) decreasing or altering porin channels limiting drug entry.[2,6]

Bacteria can alter the target site of the antibiotic, rendering it ineffective. Examples include alteration of ribosomal target sites (macrolides, lincosamides, streptogramins, tetracyclines, aminoglycosides), cell wall precursor targets (glycopeptides), and target enzymes, such as penicillin-binding proteins (PBPs), DNA-gyrase, and DNA-topoisomerase. Efflux pumps result in decreased accumulation of the antibiotic in the cell. Bacteria may contain enzymes that inactivate the antibiotic. Examples of such enzymes include β-lactamase- and aminoglycoside-modifying enzymes. β-lactamases are common mechanisms of resistance in both gram-positive and gram-negative bacteria. β-lactamases hydrolyze the β-lactam ring and render it ineffective. Examples of β-lactamases include penicillinases, cephalosporinases, and carbapenemases. Bacteria can also alter permeability of their membranes. Gram-negative bacteria have an outer membrane that contains porins, which are protein channels through which antibiotics pass through to reach their target sites. Mutations can occur that result in alterations or loss of specific porin channels, thus reducing antibiotic concentrations.[6] Resistance mechanisms are discussed further in each featured bacterial section and are summarized in Table 2. Table 2 also lists which antibiotics to consider avoiding based on the mechanism of resistance.

Table 3 shows risk factors for acquisition of resistant pathogens.

GRAM-POSITIVE PATHOGENS

Streptococcus pneumoniae

Streptococcus pneumoniae (*S pneumoniae*) is a gram-positive cocci that occurs in pairs (diplococci) or short chains. *S pneumoniae* is commonly found in the nasopharynx and may be recovered throughout the year in adults and children. *S pneumoniae* are a common cause of community-acquired pneumonia (CAP), otitis media, sinusitis, bronchitis, and meningitis.[7,8]

Resistance. Prior to the emergence of resistant *S pneumoniae*, patients could effectively be treated with penicillins, cephalosporins, and macrolides. However, in the early 1990s, reports of penicillin-nonsusceptible *S pneumoniae* (PNSP) began to surface within the US.[7] PNSP includes both intermediately resistant and resistant strains. By the late 1990s, increasing resistance to penicillin and cephalosporins as well as resistance to other antibiotics, such as macrolides, fluoroquinolones, and trimethoprim-sulfamethoxazole (TMP-SMX), was observed.[7]

Table 2. Mechanisms of Resistance by Organism and Antibiotics to Consider Avoiding if Resistance is Suspected[2,6-8,13,15,16,24]

Bacteria	Mechanism of Resistance	Antibiotics to Generally Avoid if Resistance is Suspected (by Mechanism of Resistance)
S pneumoniae	Alteration of PBPs	Standard-dose penicillins, first-/second-/oral third-generation cephalosporins
	Efflux pumps	Macrolides
	Ribosomal modification	Macrolides, clindamycin, quinupristin/dalfopristin
S aureus	Alteration of PBP	Penicillins, cephalosporins,[a] carbapenems
Enterococcus	Alteration of PBPs	β-lactams
	β-lactamase	β-lactams
	Aminoglycoside-modifying enzymes	Gentamicin and/or streptomycin
	VanA/VanB	Vancomycin

PBP = penicillin-building protein.
[a] Exception is ceftaroline.

Table 3. Risk Factors Associated With Resistance and Specific Risk Factors by Pathogen[7,10-13,17,18,22,25-27]

General risk factors
ICU admission
Critically ill
Current or recent hospitalization
Health-care exposure
Immunosuppressed
Long-term care resident
Older age
Recent antibiotic exposure
S pneumoniae
Asplenia
Day-care attendance
Exposure to children who attend day-care
Comorbidities
High alcohol intake
Smoking
S aureus
HA-MRSA
Indwelling line or catheter
Surgical wounds
Chronic liver/lung/vascular disease
Hemodialysis
Malignancy
Intravenous drug use
ICU admission
Previous MRSA isolation
Exposure to patient with risk factors
CA-MRSA
Younger healthier patients[a]
Household contacts of MRSA SSTI patients
Emergency department patients[b]
Urban underserved communities[c]
Indigenous population[d]
Incarcerated populations
Cystic fibrosis
Military personnel
Men who have sex with men
HIV patients
Veterinarians/livestock handlers/pet owners
Enterococcus spp
VRE
Critically ill (including transplant recipients and malignancy)
Poor infection control measures
Close proximity to VRE-colonized or -infected patients
Prior exposure to agents that promote VRE colonization, including:
Third-generation cephalosporins
Clindamycin
Metronidazole
Quinolones
Vancomycin
Broad-spectrum antibiotics

CA/HA-MRSA = community-acquired/health-care–acquired methicillin-resistant *Staphylococcus aureus*; ICU = intensive care unit; VRE = vancomycin-resistant enterococcus.

[a] Neonates, children, and athletes.

[b] Underserved and underinsured.

[c] Intravenous drug use, homelessness, and poverty.

[d] Native Americans, First Nation, Australian Aboriginal, Pacific Islander, and Alaskan Natives.

S pneumoniae resistance to β-lactams occurs via the alteration of PBPs. The level of resistance (intermediate versus resistant) depends on the extent of the alterations of the PBPs. Altered PBPs lead to decreased binding affinity of the β-lactam agent to *S pneumoniae*.[7,8] *S pneumoniae* strains with reduced penicillin susceptibility usually have decreased susceptibility to other β-lactam agents (primarily first-, second-, and oral third-generation cephalosporins, although intravenous third-generation cephalosporins may also have decreased susceptibility). Cross-resistance is common with other antibiotics, including macrolides, clindamycin, TMP-SMX, and tetracyclines, and these agents should not be used against PNSP unless susceptibility results demonstrate activity.[7,9]

Macrolide resistance to *S pneumoniae* occurs primarily via active drug efflux, but methylation of the ribosomal target site may also occur. *S pneumoniae* that have acquired active drug efflux are resistant to macrolides whereas ribosomal methylation confers resistance to macrolides, lincosamides (eg, clindamycin), and streptogramins (eg, quiniupristin-dalfopristin).[7] Resistance of *S pneumoniae* to fluoroquinolones occurs through alteration of topoisomerase through mutations in the parC and gyrA genes.[7,8]

The prevalence of *S pneumoniae* resistance to penicillin, macrolides, and fluoroquinolones varies by geographic region in the US, with southern regions having higher rates of resistance compared with other regions. During 2005-2007, the prevalence of PNSP was approximately 9% in the northwest and 25% in the southeast region. Macrolide resistance, during 2005-2007, was 20% to 30% whereas fluoroquinolone resistance has remained low in the US.[10] The introduction of the pneumococcal

vaccines has been efficacious in decreasing the common serotypes causing disease, including known resistant serotypes.[8]

Treatment. Despite the emergence of resistant *S pneumoniae*, the relationship between drug resistance and outcomes does not always result in treatment failures. Treatment failures in patients with penicillin-resistant *S pneumoniae* have been reported with meningitis, otitis media, and pneumonia. In some studies, high-level penicillin resistance has been shown to adversely affect clinical outcomes (increased complications and mortality) in patients with pneumonia. However, in other infections, the penicillin minimum inhibitory concentration (MIC) does not appear to correlate with clinical outcome. The same is true for macrolide and fluoroquinolone resistance as well; resistant MICs do not accurately predict outcomes for all infection types. Possible explanations for this discordant therapy include pharmacokinetic/pharmacodynamics parameters of the antibiotics, or that the more resistant strains may be less virulent than susceptible strains.[9]

In general, oral β-lactam antibiotics should not be used to treat penicillin-nonsusceptible pneumococcus because the duration of the antibiotic concentration exceeding the MIC is too short. β-lactam agents exhibit time-dependent pharmacokinetics and levels need to exceed the MIC for more than 40% to 50% of the dosing interval for the antibiotic to be efficacious. However, amoxicillin has better pharmacokinetic and pharmacodynamic properties than other oral β-lactams and may be considered for use in such infections. The rationale for using high-dose amoxicillin is that the resulting high serum concentrations exceed the MIC for greater than 40% to 50% of the dosing interval.[7,9,10]

Amoxicillin, cefotaxime, and ceftriaxone are the most active β-lactam antibiotics against *S pneumoniae*. The addition of a β-lactamase inhibitor (clavulanate, sulbactam, or tazobactam) does not improve the efficacy of the parent β-lactam antibiotic (amoxicillin, ampicillin, or piperacillin).[9] Ampicillin, amoxicillin, and third-generation cephalosporins are recommended first line for the treatment of non-central nervous system pneumococcal infections. Combination therapy using vancomycin and a third-generation cephalosporin is indicated when treating meningitis, due to the possibility of PNSP.[8]

The Infectious Disease Society of America adult CAP guidelines recommend high-dose amoxicillin (1 g three times daily) plus a macrolide for patients at risk for PNSP.[11] In addition, the acute bacterial rhinosinusitis guidelines also recommend high-dose amoxicillin-clavulanate (2 g twice daily or 90 mg/kg/day in divided doses) in patients at risk for PNSP.[10] The American Association of Pediatrics otitis media guidelines also recommend high-dose amoxicillin (90 mg/kg/day in divided doses, maximum dose of 4 g/day). They state that high-dose amoxicillin will achieve antibiotic concentrations in the middle ear that exceed the MIC of all intermediately resistant strains and most (but not all) high-level strains of pneumococcus.[12]

Use of macrolides as empirical monotherapy for adult CAP is not recommended in areas with high resistance rates of *S pneumoniae* or in patients who have comorbidities, risk factors for resistant pathogens (including recent antibiotic use), or if admitted to the hospital. Fluoroquinolones are indicated in cases of intolerance to recommended first-line antimicrobials, allergy, or in areas of high rates of nonsusceptible *S pneumoniae* strains.[8,11] Antimicrobial agents effective against penicillin-resistant *S pneumoniae* include vancomycin, ceftaroline, linezolid, telavancin, tigecycline, and quinupristin/dalfopristin.[8] Table 4 lists empiric management options for the resistant pathogens assessed in this article.

Staphylococcus aureus

Staphylococcus aureus (*S aureus*) is a gram-positive cocci that occurs in grapelike clusters. *S aureus* is found as normal skin and mucosal (including the anterior nares, in which ~30% of healthy noninstitutionalized individuals are colonized) flora in humans. It is a common pathogen involved in community and nosocomial infections. *S aureus* can cause illnesses ranging from skin infections, such as folliculitis, impetigo, carbuncles, and cellulites, to life-threatening conditions, such as pneumonia, osteomyelitis, endocarditis, bacteremia, and sepsis. It is a virulent pathogen associated with significant morbidity and mortality.[13]

Resistance. *S aureus* has the ability to adapt to changing conditions. The emergence of *S aureus* resistance to penicillin occurred soon after penicillin was introduced in the mid-1940s via production of a β-lactamase, penicillinase. Penicillinase-producing *S aureus* hydrolyzes penicillin and other penicillinase-susceptible agents conferring resistance to penicillin, amoxicillin, and ampicillin. Today, more than 90% of clinical isolates of *Staphylococcus* produce penicillinase.[13,14]

Penicillinase-stable β-lactams (methicillin, which is no longer available in the US, and nafcillin) became available in the late 1950s and, shortly thereafter, methicillin-resistant *S aureus* was described. Methicillin resistance is mediated by penicillin-binding protein 2A (PBP-2A), encoded by the staphylococcal chromosomal cassette mecA (SCCmec) gene, resulting in low affinity for most β-lactam antibiotics.[13-15] The SCCmec is a mobile element that carries β-lactam resistance.[13] This confers resistance to all β-lactams, except one cephalosporin (ceftaroline).[15,16] This resistance is referred to as methicillin-resistant *S aureus* (MRSA). The prevalence of MRSA varies. In high-risk settings, such as intensive care units, the MRSA rate may be as high as 60%.[13] MRSA was initially described in the hospital and health-care setting (health-care–acquired or associated MRSA or HA-MRSA), but it has now emerged as a community-associated pathogen. Community-associated MRSA (CA-MRSA) was first described in the late 1990s.[14,16,17]

Differences exist between HA-MRSA and CA-MRSA. HA-MRSA strains generally contain SCCmec types I, II, or III. These are large cassettes and confer resistance to β-lactams as well as many non–β-lactam antimicrobial agents. In contrast, CA-MRSA strains generally contain SCCmec type IV or V. These cassettes are smaller and confer resistance to β-lactams antibiotics as well; however, resistance to non–β-lactam antibiotics is less common. CA-MRSA strains frequently carry the genes for PVL toxin, whereas HA-MRSA rarely carry these genes. PVL is a protein or leukocidin that has been demonstrated to lyse the membrane of human neutrophils as well as cause tissue necrosis.[13,17,18]

Ribosomal modification and drug efflux are mechanisms of resistance in *S aureus* against macrolides and clindamycin. Quinolone resistance is also common and occurs via overexpression of an efflux pump and as mutations in topoisomerase IV and gyrase. Glycopeptide resistance has also been documented although with much less prevalence than MRSA.[13-16] Vancomycin intermediate *S aureus* (VISA) is defined by intermediate resistance associated with increased vancomycin MIC (MIC 4 to 8 μg/mL). VISA strains appear to synthesize excessive D-alanine–D-alanine, resulting in thickened cell walls that prevent vancomycin from reaching its target site. This may occur as a result of selective pressure associated with vancomycin exposure.[15] Vancomycin-resistant *S aureus* (VRSA) is defined by resistance to vancomycin as shown by high MICs (>16 μg/mL).[14,19] VRSA strains appear to

Table 4. Management of Suspected Resistant Pathogens: Empiric Antimicrobial Therapy Options[2,6-8,13,15,16,22,24,26,27]

Bacteria	Empiric Antibiotic Options
S pneumoniae	
• Nonmeningeal	High-dose amoxicillin, third-generation cephalosporins, fluoroquinolones (second-line alternatives ceftaroline, linezolid, telavancin, tigeycycline)
• Meningeal (ie, meningitis)	Vancomycin plus third-generation cephalosporin
S aureus	
• HA-MRSA	Vancomycin, daptomycin, linezolid, ceftaroline, tigecycline, telavancin
• CA-MRSA	
Mild-moderate	TMP-SMX, doxycycline, minocycline, clindamycin[a]
Severe	Vancomycin, daptomycin, linezolid, ceftaroline, tigecycline, telavancin
Enterococcus spp	
• β-lactam resistant	Vancomycin with or without gentamicin or streptomycin
• Vancomycin resistant	Daptomycin, linezolid, quinupristin/dalfopristin, tigecycline (uncomplicated UTI—fosfomycin, nitrofurantoin)

CA/HA-MRSA = community-acquired/health-care–acquired methicillin-resistant *S aureus*; TMP-SMX = trimethoprim-sulfamethoxasole; UTI = urinary tract infection.
[a] If the isolate is erythromycin-resistant, perform D test (disk diffusion procedure) to determine if inducible resistance to clindamycin.

have acquired the VanA gene, which is present in vancomycin-resistant enterococcus (VRE). Of the few documented VRSA infections, the majority of patients have had coinfections with VRE, thus it is likely that the vanA gene was transferred.[15,16,19]

HA-MRSA

S aureus is a common cause of health-care–associated infections. HA-MRSA is commonly implicated in bacteremia, pneumonia, sepsis, endocarditis, and other invasive infections. Up to 65% of health-care–associated *S aureus* infections are methicillin-resistant. Until recently, there were an estimated 94,000 cases of invasive MRSA infections annually with an associated mortality of greater than 18,000 per year.[20] There has been a downward trend (likely a result of prudent antibiotic use) in invasive MRSA infections, including bacteremias, with an estimated 30,800 fewer infections and 9,000 fewer deaths in 2011 compared with 2005.[21]

Treatment. HA-MRSA is multidrug resistant, meaning that it is resistant to more than one antimicrobial agent. Penicillins, cephalosporins (except ceftaroline), and carbapenems are not effective against HA-MRSA.[13,16,22] In addition, HA-MRSA is resistant to macrolides, clindamycin, and, frequently, to quinolones, tetracyclines, TMP-SMX, and aminoglycosides. For many years, vancomycin was the only effective antibiotic for serious HA-MRSA infections. In the last several years, new anti-MRSA agents have been introduced, including daptomycin, linezolid, quinupristin-dalfopristin, tigecycline, telavancin, and ceftaroline.[13,16,22] Ceftaroline, unlike other β-lactam agents, has high-affinity binding for PBP2a. VISA and VRSA strains have also been reported, but with significantly less prevalence than MRSA. VISA and VRSA strains may be treated with the aforementioned anti-MRSA agents, although data supporting their effectiveness are limited.[13,15,16]

CA-MRSA

CA-MRSA is defined as any MRSA infection diagnosed in an outpatient or within 48 hours of hospitalization if the patient lacks risk factors for HA-MRSA. Disease recurrence is common after treatment of CA-MRSA. The necrotizing nature of CA-MRSA has been associated with mortality and significant morbidity; severe invasive disease has a high mortality rate.[17,18,23]

CA-MRSA is predominantly associated with purulent SSTIs; however, severe clinical syndromes, such as necrotizing pneumonia and severe sepsis, can occur.[17,18,23] Due to the PVL toxin, CA-MRSA infections are associated with tissue necrosis and abscess formation.[14,17,18] Uncomplicated SSTIs secondary to CA-MRSA often present as abscesses resembling spider bites containing purulent material with or without surrounding erythema.[17,18,22] The SSTIs caused by CA-MRSA range from impetigo, abscesses, cellulitis, boils, and folliculitis, to necrotizing fasciitis.

Treatment. CA-MRSA strains are also resistant to β-lactam antimicrobial agents, but tend to be more susceptible to non–β-lactam antimicrobial agents than HA-MRSA, due to the smaller SCCmec cassettes. Non–β-lactam agents that tend to have activity against CA-MRSA include TMP-SMX, tetracyclines (minocycline or doxycycline), and clindamycin. The majority of CA-MRSA strains are resistant to erythromycin and a D test should be performed to ensure there is not inducible resistance to clindamycin. Fluoroquinolones may demonstrate activity against MRSA; however, resistance has emerged and use may be limited by this concern, as well as the fact that quinolones cover a broad spectrum of pathogens. The treatment of severe, invasive CA-MRSA is similar to the treatment of HA-MRSA. Rifampin has excellent *S aureus* coverage, but it should never be used alone, due to the emergence of resistance with monotherapy. Empiric therapy for uncomplicated SSTIs should be chosen based on local antimicrobial susceptibility data, but should generally involve TMP-SMX, doxycycline, minocycline, or clindamycin.[15-18,22,23]

Enterococcus

Enterococci are gram-positive bacteria that grow as single cells, pairs, or short chains. They are normal flora of the gastrointestinal (GI) tract. Most clinical infections are caused by *Enterococcus faecalis* (*E faecalis*) and *Enterococcus faecium* (*E faecium*), with *E faecalis* being the most prevalent. Enterococci are responsible for a variety of infections, including urinary tract infections, SSTIs, wound infections, intra-abdominal

infections, catheter-related infections, bacteremia, and endocarditis.[24] Enterococci are not as virulent as *S aureus* but they are intrinsically resistant to many antibiotics and have acquired resistance to virtually all antimicrobials, including vancomycin.[24,25]

Resistance to ampicillin/amoxicillin, penicillin, and vancomycin is more common with *E faecium* than with *E faecalis*.[24] The incidence of resistant enterococci has continued to increase since its initial observation in the mid-1980s. Resistant enterococci are more prevalent in patients who are hospitalized or reside in long-term care facilities.[24-26] Approximately 30% of enterococcal health-care infections are vancomycin-resistant. The majority of the vancomycin-resistant strains are *E faecium*.[3]

Resistance. Enterococci are intrinsically resistant to a number of antibiotics. Intrinsically they exhibit low levels of resistance to penicillins, carbapenems, aminoglycosides, lincosamides, and TMP-SMX. Enterococci exhibit relative resistance to β-lactams via production of a low-affinity PBP, known as PBP5, resulting in reduced affinity for β-lactam agents. PBP5 allows bacteria to continue to synthesize cell wall components in the presence of moderate concentrations of β-lactam agents. Enterococci demonstrate tolerance to cell wall active antibiotics, meaning that penicillins and vancomycin inhibit, but do not kill, at clinically achievable concentrations. The most potent antimicrobial activity is observed with amoxicillin, ampicillin, penicillin G, and piperacillin/tazobactam. Enterococci are intrinsically resistant to cephalosporins and should not be used. In addition, TMP-SMX and fluoroquinolones have little to no activity against these pathogens and should not be used for therapy.[16,24-26]

Enterococci, particularly *E faecium*, also have acquired resistance to β-lactams via overproduction of PBPs, resulting in decreased effectiveness of β-lactam agents. β-lactamase production by enterococci has also been reported. Enterococci that have acquired these mechanisms of resistance are considered resistant to β-lactam agents.[16,24,25]

High-level aminoglycoside resistance is acquired via acquisition of an aminoglycoside-modifying enzyme. This confers high-level resistance against all aminoglycosides and negates the synergistic and bactericidal effect of a combination of a β-lactam and aminoglycoside.[24] This also presents a challenge to clinicians because bactericidal activity is preferred for the majority of serious infections.

Vancomycin resistance has also emerged in enterococci (VRE). VRE was first observed in the US in the mid-1980s. This resistance is particularly problematic because vancomycin has become the preferred agent due to the increasing resistance to β-lactams. The genes that encode vancomycin resistance result in an altered target with reduced binding of vancomycin. Subsequently, there is decreased inhibition of cell wall synthesis. Six different phenotypes of glycopeptide resistance exist. The most common phenotypes in the US are VanA and VanB. These resistance genes are easily transferred and are a source of concern for vancomycin resistance in other organisms. The VanA resistance phenotype is the most common and results in high-level resistance to vancomycin (and teicoplanin, which is not available in the US). The VanB-resistance phenotype confers variable resistance to vancomycin (and remains susceptible to teicoplanin).[16,24,25]

Resistance to daptomycin has been documented and may occur during daptomycin therapy. Linezolid resistance has also been reported and appears to involve mutations in the 23S rRNA (a binding site for linezolid). Tigecycline resistance has been reported as well.[24,25]

Treatment. Penicillin, ampicillin, or amoxicillin remain the agents of choice for susceptible enterococci. In the case of increased β-lactam resistance, vancomycin is generally the antimicrobial agent of choice. Monotherapy, with either a β-lactam or vancomycin, is not bactericidal against enterococci. The addition of an aminoglycoside, gentamicin, or streptomycin to ampicillin, penicillin, or vancomycin results in a synergistic and bactericidal effect.[16,24,26] These combinations are required for serious infections (bacteremia, endocarditis, and osteomyelitis).

VRE may be treated with daptomycin, linezolid, quinupristin/dalfopristin (lacks activity against *E faecalis*), or tigecycline. However, limited data exist for the treatment of VRE infections with these antibiotics. Clinicians should monitor for worsening signs of infection as resistance can emerge during therapy.[16,24] Nitrofurantoin and fosfomycin are options for enterococcal urinary tract infections

(including ampicillin- and vancomycin-resistant strains).[16,27] Cephalosporins, fluoroquinolones, and TMP-SMX are not recommended for the treatment of enterococcal infections.[24]

SUMMARY

Antimicrobial resistance among gram-positive bacteria presents a challenge to clinicians treating community-acquired and nosocomial-acquired infections. Resistance has occurred in part due to increased use, as well as misuse, of antibiotics. As a result, antimicrobial agents are less effective in eradicating bacterial infections, leading to increased morbidity, mortality, and health-care costs. Strategies should be implemented to prevent and limit the emergence of resistant pathogens. Efforts to promote the prudent use of antimicrobial agents should be emphasized. All members of the health-care team can participate in reducing the presence of resistant pathogens. JNP

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