GRAM-POSITIVE INFECTIONS

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Learning Objectives

1. Classify the different mechanisms of antibiotic drug resistance among *Streptococcus pneumoniae*, *Staphylococcus* species, and *Enterococcus* species and how they impact the spread of bacterial resistance.
2. Differentiate among the common gene mutations that confer antibiotic drug resistance in *Streptococcus* species, *Staphylococcus* species, and *Enterococcus* species.
3. Identify risk factors that increase chances of an infection with drug-resistant gram-positive organisms.
4. Understand the different pharmacodynamic parameters for antimicrobial drugs used against *S. pneumoniae* and devise treatment strategies to maximize antibiotic drug efficacy.
5. Describe methods to decrease the infection risk with drug-resistant gram-positive organisms.
6. Compare and contrast the available antimicrobial therapy for a patient with an infection caused by a drug-resistant *S. pneumoniae*.
7. Design an appropriate treatment regimen for a patient with an infection caused by antibiotic-resistant staphylococcal species.
8. Given a patient with an infection caused by a drug-resistant *Enterococcus* species, develop an appropriate treatment plan.
9. Distinguish among the available methods to prevent emergence and spread of gram-positive resistance.

Introduction

Background

There are several classic gram-positive species that cause disease in humans. The most common organisms include the *Streptococcus*, *Staphylococcus*, *Enterococcus*, *Bacillus*, *Clostridium*, *Corynebacterium*, and *Listeria* species. Species of the *Streptococcus*, *Staphylococcus*, and *Enterococcus* genera have become more problematic throughout the past 20 years. Species of these genera, more than the other gram-positive species, have developed resistance to several antibiotic drugs through various mechanisms. Resistance by these species is particularly worrisome because of the increased frequency of involvement of these pathogens in infections. *Streptococcus pneumoniae* is the most common pathogen in community-acquired pneumonia (CAP), sinusitis, otitis media, and meningitis. *Enterococcus* and *Staphylococcus* species are among the most common pathogens in nosocomial bloodstream, wound, and intravascular catheter-related infections. Furthermore, infections caused by antibiotic-resistant pathogens compared to antibiotic-susceptible isolates of the same species result in higher use of medical care, prolonged hospital stays, and increased mortality. In an intensive care unit population, mortality was twice as high when antibiotic drugs lacking in vitro activity were administered compared with antimicrobial drugs with activity against the offending organism.

Antimicrobial efficacy is assessed differently from drugs used to treat other disease states. It would be expected that insulin will be as active at lowering blood sugar in a patient with diabetes in 50 years as it is today. In the future, there may be more effective drugs for treating patients with diabetes, but insulin would still be an option. This is not true for antibiotic drugs. Antimicrobial drugs used today may have reduced potency or no effect in the future. Through evolution, microorganisms have developed several methods to protect themselves against the increasing armamentarium of new antibiotic drugs. It also has become apparent that when an antimicrobial drug is discovered, some microbes develop the ability to survive doses of that drug that were initially lethal.

Abbreviations

Abbreviations in this Chapter

CAP	Community-acquired pneumonia
DNA	Deoxyribonucleic acid
MIC	Minimum inhibitory concentration
MLS_B	Macrolide-lincosamide-streptogramin type B
MRSA	Methicillin-resistant *Staphylococcus aureus*
PBP	Penicillin-binding protein
RNA	Ribonucleic acid
VISA	Vancomycin-intermediate *Staphylococcus aureus*
VRE	Vancomycin-resistant *Enterococcus*
VRSA	Vancomycin-resistant *Staphylococcus aureus*

History of Resistance

Resistance has occurred clinically with every antimicrobial drug class that has been used. Throughout the past 30 years, glycopeptides have become the antibiotic drug of last resort for gram-positive infections, especially those due to methicillin-resistant *Staphylococcus aureus* (MRSA). However, the recent emergence of organisms resistant to glycopeptides, such as vancomycin-resistant *Enterococcus* (VRE), vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *Staphylococcus aureus* (VRSA), and vancomycin-tolerant *S. pneumoniae*, has created a tremendous urgency to understand the resistance mechanisms and explore new opportunities for drug development and design.

Microbiology

All bacteria are prokaryotes, single-cell organisms that do not contain a nuclear membrane or other membrane-enclosed organelles. Most bacteria are protected by a peptidoglycan-containing cell wall. The peptidoglycan is a heteropolymer consisting of a sugar backbone and repeating *N*-acetylglucosamine and *N*-acetylmuramic acid molecules. Gram-positive bacteria have a cell wall made up of a thick layer of peptidoglycan surrounding a phospholipid bilayer, the cell membrane. Infectivity of a gram-positive pathogen depends on both virulence of the organism and susceptibility of the host.

Resistance Mechanisms

Practitioners should have a comprehensive understanding of the mechanism of action of antimicrobial drugs. This information, combined with the complex mechanisms of bacterial resistance, is necessary to provide appropriate drug therapy. Antibiotic drug resistance is multifaceted, and knowing resistance methods will allow predictions that provide optimal therapeutic outcomes. Antibiotic drug choices should be based on resistance profiles, and cross-resistance with other antimicrobial drug classes must be considered. For example, it can be possible to determine if macrolide resistance in pneumococci is mediated by an efflux or a target-site mutation based on cross-resistance to other antimicrobial drug classes. Having this information allows the selection of the best antimicrobial drug for that resistance type. Furthermore, knowledge of genetics in every aspect of medicine is becoming increasingly important. Infectious diseases is no exception, and future drug development and design likely will be guided by genetics not only of the host, but also the infecting organism. The most common resistance mechanisms in gram-positive bacteria are discussed in detail and are summarized in Table 1-1. In addition, a diagram summarizing the possible sites in gram-positive bacteria for drug resistance to occur is illustrated in Figure 1-1.

Mechanisms of β-Lactam Resistance

β-Lactam Resistance in *Streptococcus pneumoniae*

β-Lactam drugs inhibit cell wall synthesis by binding to one or more of the penicillin-binding proteins (PBPs), thus inhibiting the final transpeptidation step of peptidolgylcan synthesis in the cell wall, resulting in cell lysis. Resistance to β-lactams in *S. pneumoniae* occurs from stepwise mutations in one or more of the five major PBPs in the cytoplasmic membrane. In *S. pneumoniae*, PBPs 1 (1a and 1b) and 2 (2a, 2b, and 2x) are essential for cell viability and mutations in these PBPs are involved in resistance to β-lactam antibiotic drugs. Individual amino acid changes in PBP result in only low levels of resistance to penicillins and cephalosporins. However, *S. pneumoniae* has developed considerable high-level resistance to β-lactams by transformation and homologous recombination made possible by several distinctive factors. *Streptococcus pneumoniae* is naturally competent to take up foreign deoxyribonucleic acid (DNA) by a process called transformation. If the imported foreign DNA has similar homology to genes on the pneumococcal chromosome, then *S. pneumoniae* can recombine it into its own chromosomal DNA, creating mosaic genes containing segments of both original host and imported DNA. In addition, other species genetically related to *S. pneumoniae*, such as *Streptococcus viridans*, have PBPs with low affinity for penicillin. Furthermore, *S. viridans* are normally located in the upper respiratory tract, a common site of carriage or colonization of *S. pneumoniae*. This close proximity allows for the exchange of genetic information between *S. pneumoniae* and genetically related species.

Multiple changes in PBPs are necessary for *S. pneumoniae* to have high-level penicillin resistance. Clinical isolates with reduced susceptibility to penicillins have mosaic genes encoding for modified PBP 2x, 2b, and 1a. In addition, high-level resistance to oxacillin requires low-affinity forms of PBP 2x and 2b, and cephalosporin-resistance requires mutations in PBP 2x and 1a. With the overlap of PBPs involved, it is apparent that cross-resistance to other groups of β-lactam antibiotic drugs can occur.

The production of β-lactamase, an enzyme that degrades penicillins and other β-lactam drugs, has not been described as a mechanism of β-lactam resistance in *S. pneumoniae*.

Currently, penicillin resistance in *S. pneumoniae* only occurs with mosaic gene changes in the PBPs.

β-Lactam Resistance in *Staphylococcus* Species

In the history of clinical practice, β-lactams have been recognized as the most useful antistaphylococcal drugs available. However, not long after penicillin was introduced into clinical practice, resistance was observed. This resistance is mediated by the production of β-lactamases, which inactivates the antibiotic drug by hydrolyzing the β-lactam ring. The resistance determinant responsible for β-lactamase production is carried on small plasmids or transposons. Today, more than 90% of all *Staphylococcus* species produce β-lactamases and are resistant to penicillin and ampicillin. The production of staphylococcal β-lactamases has prompted the commercial development of β-lactamase-resistant semisynthetic penicillins, such as methicillin and oxacillin. These drugs have remained active; however, methicillin and oxacillin resistance also has developed.

Methicillin resistance occurs when the additional chromosomal DNA, *mec*, is incorporated into the genome. The *mec* DNA contains *mecA*, the structural gene for PBP 2a. This makes PBP 2a have a lower binding affinity for β-lactams, conferring resistance to all β-lactam antibiotic drugs, including nafcillin; oxacillin; β-lactam/β-lactamase inhibitors, such as ampicillin-sulbactam, cephalosporins, and carbapenems. Furthermore, the *mec*-associated DNA contains transposons and insertion elements, providing a mechanism for the considerable variability found within the *mec* regions. Through genetic studies, it has been determined that the *mec* DNA is polymorphic, allowing variation in the number of base pairs, genetic organization, number of insertion sequences, and resistant determinants. Therefore, *mecA* and its associated DNA can allow for integration of other determinants, including genes for resistance to fluoroquinolones, aminoglycosides, tetracyclines, macrolides, and trimethoprim-sulfamethoxazole.

Currently, a difference exists between MRSA strains that are nosocomial or institution-acquired compared to strains that are community-associated. In general, institution-associated MRSA strains tend to be resistant to several antimicrobial drug classes, whereas community-associated isolates tend to be susceptible to several antibiotic drugs, including trimethoprim-sulfamethoxazole, doxycycline, and clindamycin. One theory for this difference is that the community-associated MRSA arose as a consequence of horizontal transfer of the methicillin resistance determinant into a fully susceptible *Staphylococcus* isolate. This is further supported because different SCCmec alleles are observed in community-associated MRSA compared to institution-acquired MRSA strains.

The insertion of *mec* DNA into the chromosome of staphylococci appears to be a rare event, and most clinical MRSA strains are the result of clonal spread. It appears that the original source of *mec* DNA is most likely from coagulase-negative staphylococci. Similar to high-level penicillin resistance in pneumococci, the infrequency of genetic events that produce new resistant clones has not been an obstacle to the persistence and spreading of MRSA worldwide. Methicillin resistance is widespread, particularly in tertiary referral centers, and is now more commonly observed in the community setting.

β-Lactam Resistance in *Enterococcus* Species

Enterococci have both intrinsic and acquired resistance. Intrinsic resistance in enterococci is because of the physiology of the organism, which does not allow antibiotic drugs to exert their activity. Enterococci are intrinsically resistant to several β-lactam antibiotic drugs because of a reduced affinity of PBPs. In general, the decreased affinity with PBPs is greater with *Enterococcus faecium* compared to *Enterococcus faecalis*, although *E. faecalis* is relatively resistant to penicillin compared to *Streptococcus* species. About 90% of all isolates of *E. faecalis* are inhibited by ampicillin concentrations ranging from 1 mcg/ml to 2 mcg/ml or less. In contrast, *E. faecium* is much more resistant to penicillins because of the presence of a low-affinity PBP designated PBP5. This PBP can synthesize cell wall material even in the presence of penicillin. More low-affinity PBP5 is produced as the resistance level increases. However, once resistance increases to a high level (minimum inhibitory concentration [MIC] greater than 64 mcg/ml for resistance to vancomycin), less PBP5 is produced. In addition, point mutations in the *pbp5* gene are possibly responsible for the differences observed in binding intensities.

As previously discussed, *E. faecalis* species are more susceptible to penicillins than *E. faecium*. However, *E. faecalis* strains with higher penicillin resistance have been encountered and are the result of increased production of PBP5 and decreased binding of penicillin to PBP1 and PBP6. *Enterococcus faecalis* strains are not susceptible to antistaphylococcal penicillins, but are susceptible to ampicillin, amoxicillin, and piperacillin. Enterococcal PBPs have a low affinity for all cephalosporins antibiotic drugs despite being targets for penicillin antibiotic drugs. The low affinity of enterococcal PBPs to cephalosporins is an intrinsic resistance and is not the result of any type of mutational event. Despite the additional resistance mechanisms that *E. faecalis* has acquired over time, penicillins can still be a treatment option. However, the use of penicillins typically is not an option against *E. faecium*, and the use of vancomycin has become primary therapy for these infections. Unfortunately, glycopeptide resistance also has developed.

Mechanisms of Glycopeptide Resistance

Glycopeptide Resistance in *S. pneumoniae*

Vancomycin, a glycopeptide, inhibits synthesis of peptidoglycan polymers by binding with D-alanyl-D-alanine precursors, thus inhibiting cell wall synthesis. Pneumococcal resistance with vancomycin has not been encountered; however, clinical isolates that can survive but not reproduce in the presence of vancomycin (vancomycin-tolerant strains) have been identified. Investigations have suggested that tolerance may be a precursor to the development of vancomycin resistance. Studies also have demonstrated that the loss of function of *vnc*S, a histidine kinase portion of a two-component system, resulted not only in vancomycin tolerance, but tolerance to β-lactams, cephalosporins, aminoglycosides, and quinolones. These findings suggest that signal transduction through *vnc*S

Abbreviations

Table 1-1. Summary of Antibiotic-resistant Mechanisms in Gram-positive Pathogens

Organism	Resistance Determinant (or Mechanism)	Antibiotics Affected	Notes
Streptococcus pneumoniae			
	Alteration in PBPs	Penicillins and cephalosporins	Mutations occur in PBPs 1 (1a and 1b) and 2 (2a, 2b, and 2x). Typically, the more mutations, the higher the level of resistance
	May involve *vncS*, a two-component system	Vancomycin	The mechanism of vancomycin tolerance is not clearly defined
	Presence of *ermB* gene	Macrolides, streptogramins, and clindamycin	Methylation of the 23S rRNA moiety encoded by the *ermB* gene generally results in high-level macrolide resistance, and also can result in cross-resistance with streptogramins and lincosamide antibiotic drugs
	Presence of *mefA* gene	Macrolides	Efflux-mediated resistance encoded by *mefA* gene. Typically, is a low-level resistance to macrolides
	Stepwise mutations in the *parC* and/or *gyrA* genes	Fluoroquinolones	Chromosomal mutations in the quinolone resistance-determining region in the *gyrA* and *parC* genes
	Mutations in *pmrA* gene	Fluoroquinolones	Efflux-mediated resistance in a membrane-associated pump
	Single mutation in *rpoB* gene	Rifampin	A single-point mutation can confer high-level rifampin resistance
	Conjugative transposon Tn*1545*	Tetracyclines, chloramphenicol, and macrolides	This transposon or a related transposon may carry one or more of the determinants responsible for resistance
***Staphylococcus* species**			
	β-Lactamases	Penicillins	More than 90% of *Staphylococcus aureus* produce β-lactamases. The *mec*-associated DNA is polymorphic and allows integration of other resistance determinants
	mecA gene and its *mec*-associated DNA	β-Lactam antibiotic drugs, antistaphylococcal penicillins (methicillin, nafcillin, and oxacillin)	
	Thickening of the cell wall with the pentapeptide D-Ala-D-Ala termini	Vancomycin	This mechanism of resistance is observed in VISA and heteroresistant-VRSA stains and is not fully understood
	vanA gene	Vancomycin	Likely the result of genetic transfer of *vanA* gene from *Enterococcus faecalis* strain. Only two clinical cases reported
	Stepwise mutations in the *parC* and *gyrA* genes	Fluoroquinolones	Chromosomal mutations in the quinolone resistance-determining region in the *gyrA* and *parC* genes
	Mutations in norA	Fluoroquinolones	Efflux-mediated resistance in a membrane-associated pump

Table 1-1. Summary of Antibiotic-resistant Mechanisms in Gram-positive Pathogens (Continued)

Organism	Resistance Determinant (or mechanism)	Antibiotics Affected	Notes
***Staphylococcus* species** (continued)	Presence of *ermB* gene	Macrolides, streptogramins, and clindamycin	Methylation of the 23S rRNA moiety encoded by the *ermB* gene generally results in high-level macrolide resistance. It also can result in cross-resistance with streptogramins and lincosamide antibiotics
	Single mutation in *rpoB* gene	Rifampin	A single-point mutation can confer high-level rifampin resistance
	Enzymatic inactivation of AGs	AG	Encoding genes found on plasmids and transposons
	Expression of *ileS2* gene	Mupirocin	Encodes for an isoleucyl tRNA synthetase with decreased affinity for mupirocin
	Mutation in domain V of the 23S rRNA gene	Linezolid	Reported in a few clinical strains after long-term use of linezolid
	Conjugative transposon Tn*1545*	Tetracyclines, chloramphenicol, and macrolides	This transposon or a related transposon may carry one or more of the resistance determinants responsible for resistance
***Enterococcus* species**	Decreased affinity in PBP5	β-Lactam antibiotic drugs	Enterococci have intrinsic resistance to β-lactam antibiotic drugs. *Enteroccus faecalis* is more susceptible to penicillins than *Enterococcus faecium*
	Plasmid mediated transfer of *vanA* gene	Vancomycin	Several other *van* genes also have been identified. Results in the production of abnormal peptidoglycan precursors ending in D-Ala-D-Lac rather than D-Ala-D-Ala
	Stepwise mutations in the *parC* and *gyrA* genes	Fluoroquinolones	Chromosomal mutations in the quinolone resistance-determining region in the *gyrA* and *parC* genes
	Presence of *ermB* gene	Macrolides, streptogramins, and clindamycin	Methylation of the 23S rRNA moiety encoded by the *ermB* gene generally results in high-level macrolide resistance. Can also result in cross-resistance with streptogramins and lincosamide antibiotic drugs
	Single mutation in *rpoB* gene	Rifampin	A single-point mutation can confer high-level rifampin resistance
	Production of 5'-acetyltransferase	AG	Enterococci are intrinsically resistant to low levels of AG. *Enterococcus faecium* produces this enzyme leading to high-level resistance to all AGs except gentamicin and streptomycin
	Ribosomal mutation	Aminoglycoside	This mechanism produces high-level resistance and also affects gentamicin and streptomycin
	Conjugative transposon Tn*1545*	Tetracyclines, chloramphenicol, and macrolides	This transposon or a related transposon may carry one or more of the determinants responsible for resistance

AG = aminoglycoside; DNA = deoxyribonucleic acid; PBP = penicillin-binding protein; rRNA = ribosomal ribonucleic acid; tRNA = transfer ribonucleic acid; VISA = vancomycin-intermediate *Staphylococcus aureus*; VRSA = vancomycin-resistant *Staphylococcus aureus*.

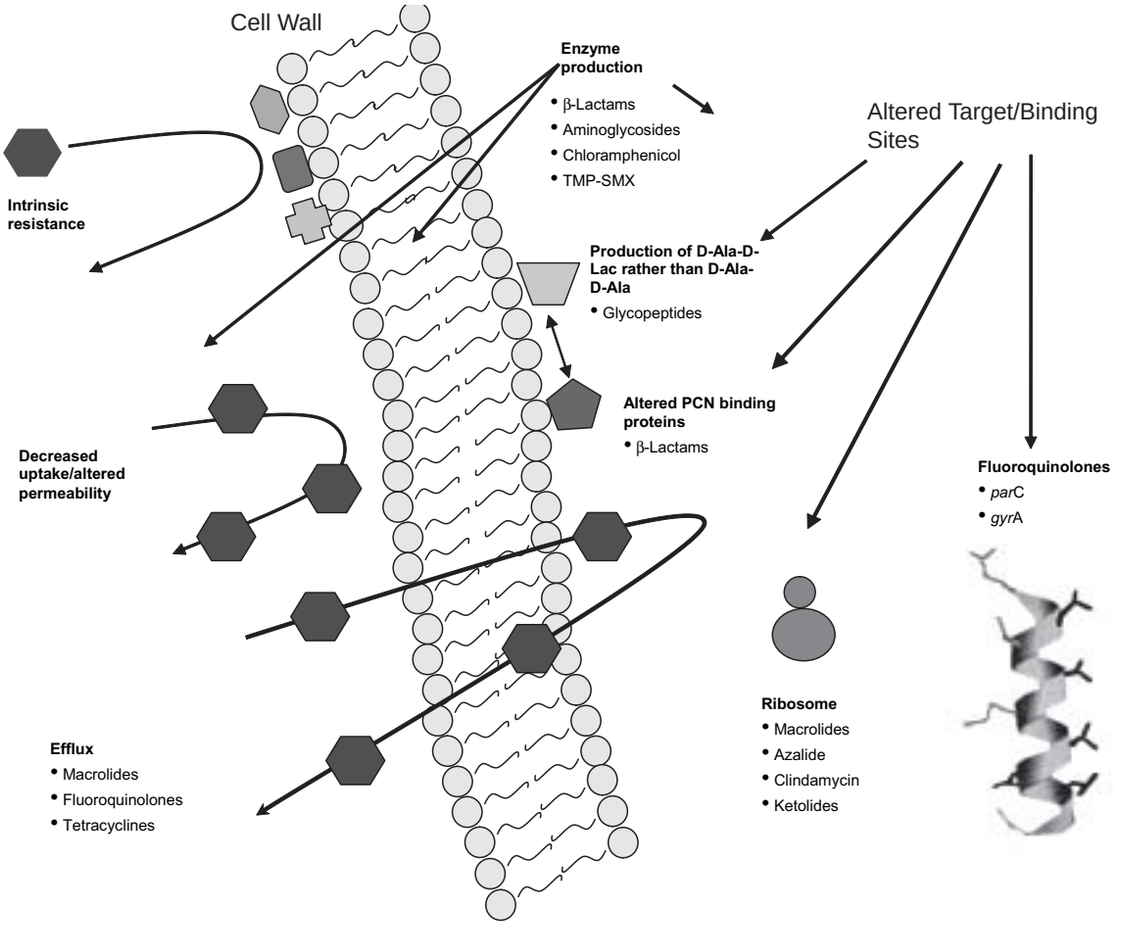

Figure 1-1. Summary of different mechanisms of antimicrobial resistance.
PCN = penicillin; TMP-SMX = trimethoprim-sulfamethoxazole.

may be necessary for cell death in *S. pneumoniae* after antimicrobial exposure. In addition, this mechanism of tolerance appears to be different than vancomycin resistance observed in other bacterial species. Furthermore, tolerance cannot be detected by routine antimicrobial susceptibility testing, making surveillance more difficult. Of interest, tolerance to penicillin and vancomycin has been found in clinical isolates of *S. pneumoniae* serotype 9V. This serotype also has been linked to multidrug resistance.

Glycopeptide Resistance in *Staphylococcus* Species

Glycopeptides were fully active against *Staphylococcus* species until 1997, when the first report of an *S. aureus* strain with reduced susceptibility to vancomycin was described in Japan. Since then, there have been additional reports of *S. aureus* strains with resistance to vancomycin. In the United States, the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical and Laboratory Standards) has established breakpoints for activity of vancomycin against *S. aureus* isolates. *Staphylococcus aureus* isolates with vancomycin MIC of 4 mcg/ml or less are considered susceptible; isolates with vancomycin MICs of 8–16 mcg/ml are intermediate; and strains having a vancomycin MIC of 32 mcg/ml or more are resistant. Isolates that are intermediate and resistant to the glycopeptides vancomycin and teicoplanin are called glycopeptide-intermediate *S. aureus* and glycopeptide-resistant *S. aureus*, respectively. However, because teicoplanin is not available in the United States, these strains are referred to as VISA and VRSA. In addition to VISA and VRSA isolates, heterogeneous VISA strains also have been identified. Heterogeneous VISA refers to *S. aureus* strains that are considered susceptible to vancomycin, except that they contain subpopulations of organisms for which the MIC of vancomycin is in the intermediate range. Heterogeneous VISA strains appear to be the step that precedes the development of intermediate-level resistance in *S. aureus*. Vancomycin-intermediate *S. aureus* infections usually emerge after long treatment courses with vancomycin. However, reports of VISA strains in patients without previous glycopeptide exposure have been observed, which suggests possible clonal spread of VISA.

Vancomycin-intermediate *S. aureus* strains are associated with the production of a thicker cell wall with the pentapeptide D-Ala-D-Ala termini, the binding site for glycopeptides. Glycopeptides can still bind to their target site, but activity is limited to the periphery of the cell wall. An excess of PBP2 also is associated with the increase in glycopeptide MIC. Thickening of the cell wall in these

VISA strains appears to be inducible by vancomycin; nonetheless, this mechanism for vancomycin resistance is not fully elucidated. Other changes in peptidoglycan structure and regulation of cell wall synthesis also probably contribute to decreased glycopeptide susceptibility. Treatment experience with these infections is limited, and antibiotic drug therapy should be based on in vitro susceptibility patterns.

Three VRSA clinical isolates have been identified. Resistance to glycopeptides is rare; but based on historical emergence of resistance, it may not remain rare for long. Currently, high-level vancomycin and teicoplanin resistance in staphylococci is the result of acquisition of the *vanA* gene from *E. faecalis* and is defined as requiring 32 mcg/ml or more of vancomycin to inhibit growth (discussed in greater detail in *Enterococcus* Species section). From initial clinical reports of patients infected with VRSA strains, patients also were infected with VRE. Acquisition of the *vanA* gene was most likely a result of genetic transfer of genes, possibly through a plasmid or transposon.

Glycopeptide Resistance in *Enterococcus* Species

Several classes of glycopeptide-resistant enterococci exist, including VanA, VanB, VanC, and VanD. The VanA phenotype, described in strains of *E. faecalis* or *E. faecium*, has inducible high levels of resistance to vancomycin (MIC of more than 64 mcg/ml) and teicoplanin (more than 8 mcg/ml). VanA resistance is plasmid-mediated and involves transposon Tn*1546*. This transposon contains seven genes involved in glycopeptide resistance, including a two-component regulatory system that mediates inducibility of glycopeptide resistance. Expression of these genes result in the synthesis of abnormal peptidoglycan precursors ending in D-Ala-D-Lac rather than D-Ala-D-Ala. Both vancomycin and teicoplanin bind to D-Ala-D-Lac with much lower affinity than to the D-Ala-D-Ala peptidoglycan precursor. VanB strains of the same species have lower levels of resistance to vancomycin; however, they still remain susceptible to teicoplanin. The mechanism of VanB glycopeptide resistance is similar to that described for VanA. VanB resistance involves a two-component system that is inducible by vancomycin, but not by teicoplanin. VanC class includes the intrinsically VRE species: *Enterococcus gallinarum*, *Enterococcus casseliflavus*, and *Enterococcus flavescens*. These isolates are resistant to vancomycin (MIC less than 64 mcg/ml), but are susceptible to teicoplanin. VanD is another phenotype with constitutive expression resulting in modest levels of vancomycin (MIC 64–128 mcg/ml) and teicoplanin (MIC 4 mcg/ml) resistance, and has been described in several isolates of *E. faecium*. VanE, VanF, and VanG phenotypes, although less common, also have been described.

Mechanisms of Macrolide Resistance

Macrolides exert their activity by binding to the ribosomal ribonucleic acid (RNA) of the 50S ribosomal subunit, thus preventing the extension of nascent polypeptide chains. Resistance to macrolides in pneumococcal, staphylococcal, and enterococcal strains is attributed to a target site mutation. Methylation of the 23S ribosomal RNA moiety by a methyltransferase enzyme which is encoded by *erm* genes results in a conformation change at the macrolide ribosomal binding site. Consequently, high-level macrolide resistance (i.e., erythromycin MIC 64 mcg/ml or more) is observed, and cross-resistance with lincosamides, such as clindamycin and streptogramin B, can occur because of overlapping binding sites. This resistance typically is referred to as the macrolide-lincosamide-streptogramin type B (MLS_B) phenotype. In addition, rare mutation in the 23 ribosomal RNA or ribosomal proteins L4 or L22 in *S. pneumoniae* also may alter the target site and result in resistance to macrolides, lincosamides, streptogramins, and in some cases, to ketolides.

Another common type of macrolide resistance that occurs in pneumococci and less commonly in *Staphylococcus* and *Enterococcus* species is active drug efflux mediated by an efflux pump encoded by the *mef* genes. Resistance is noted to occur among 14- and 15-member macrolides in strains with the *mef* gene mutations; however, no resistance is observed with clindamycin or streptogramins. Macrolide efflux resistance is a low- to mid-level resistance, whereas *erm*-mediated resistance results in higher level macrolide resistance. In general, in North America, macrolide resistance in *S. pneumoniae* is because of mutations in the *mefA* gene, resulting in efflux-mediated resistance. However, the opposite is true for Europe, Asia, and South Africa, where the target site ribosomal methylation is the predominant form of macrolide resistance. Macrolide resistance with enterococci and streptococci is most commonly *erm*-mediated.

The structurally related ketolide, telithromycin, is active against *S. pneumoniae* isolates expressing the *mefA* gene. It also typically retains activity against strains expressing the *ermB* gene; however, activity with telithromycin can be limited when the *ermB* expression is constitutive. The greater activity of telithromycin compared to macrolides is a result of increased affinity to the ribosomal binding site.

Mechanisms of Fluoroquinolone Resistance

Fluoroquinolones inhibit two enzymes necessary for replication of bacterial DNA, including DNA gyrase (encoded by *gyrA* and *gyrB*) and topoisomerase IV (encoded by *parC* and *parE*). Inhibition of these enzymes prevents

Vancomycin-resistant *Staphylococcus aureus*—Pennsylvania, 2002. MMWR Morb Mortal Wkly Rep 2002;51:902.

Staphylococcus aureus resistant to vancomycin–United States, 2002. MMWR Morb Mortal Wkly Rep 2002;51:565–7.

Vancomycin-resistant *Staphylococcus aureus*—New York, 2004. MMWR Morb Mortal Wkly Rep 2004;53:322–3.

Chang S, Sievert DM, Hageman JC, et al. Infection with vancomycin-resistant *Staphylococcus aureus* containing the *vanA* resistance gene. N Engl J Med 2003;348:1342–7.

Whitener CJ, Park SY, Browne FA et al. Vancomycin-resistant *Staphylococcus aureus* in the absence of vancomycin exposure. Clin Infect Dis 2004;38:1049–55.

DNA supercoiling and relaxation, thereby causing bacterial cell death. Two distinct methods of fluoroquinolone resistance occur. In *S. pneumoniae*, *Staphylococcus*, and *Enterococcus* species, stepwise accumulation of chromosomal mutations occur in the quinolone-resistance-determining regions, including mainly *gyrA* or *parC* genes. The second mechanism of fluoroquinolone resistance is the active efflux of fluoroquinolones mediated by the membrane-associated protein multidrug transporter, such as pmrA (pneumococcal multidrug resistance) or NorA, in *S. pneumoniae* and *Staphylococcus* species, respectively. Efflux-mediated resistance typically results in low-level fluoroquinolone resistance. However, efflux resistance may confer added resistance when combined with mutations in the *parC* or *gyrA* genes.

After specific mutations in genes of the quinolone-resistance-determining regions, decreased binding and activity of the fluoroquinolone occurs. In general, a first-step mutant (one mutation in either *gyrA* or *parC*) will be associated with a 4–8-fold elevation in the MIC for all fluoroquinolones. Different fluoroquinolones demonstrate stronger or weaker affinity to these enzyme-binding sites and preferentially target one or both enzymes. For example, in pneumococci, first- and second-generation fluoroquinolones (i.e., norfloxacin and ciprofloxacin) bind primarily to DNA gyrase or DNA topoisomerase IV, whereas the third-generation fluoroquinolones (i.e., moxifloxacin and gatifloxacin) typically bind strongly to both DNA gyrase and DNA topoisomerase IV. Thus, a single-point mutation in DNA gyrase and DNA topoisomerase IV typically affects first- and second-generation fluoroquinolones to a greater extent clinically than third-generation fluoroquinolones.

Spontaneous mutations can arise in the quinolone-resistance-determining regions when bacterial densities reach about 1×10^6 to 1×10^9 colony-forming units/ml. Therefore, when the first-step mutants reach this similar bacterial density, another mutation may occur, resulting in a second-step mutation. Clinically, bacterial densities similar to these concentrations could be achieved in most patients with pneumonia or other serious infections.

Mechanism of Rifampin Resistance

Rifampin inhibits transcription by attaching to the β-subunit of RNA polymerase. Rifampin resistance in *S. pneumoniae*, *Staphylococcus*, and *Enterococcus* species occurs after a single mutation in the *rpoB* gene, resulting in an alteration to the RNA polymerase β-subunit, thereby decreasing the ability of rifampin to bind to its target site. The ability of a single spontaneous mutation to confer high-level rifampin resistance limits the clinical usefulness of this drug; therefore, rifampin typically is used in combination therapy with other antimicrobial drugs.

Mechanisms of Aminoglycoside Resistance

Aminoglycosides irreversibly bind to the 30S subunit of the bacterial ribosome and prevent protein synthesis. These drugs are bactericidal and are used with β-lactam antibiotic drugs for potential synergy primarily against staphylococcal and enterococcal species. Resistance occurs by enzymatic inactivation of the aminoglycosides. These modifying enzymes are of exogenous origin, and their encoding genes are found on plasmids and transposons.

Enterococci are intrinsically resistant to low concentrations of aminoglycoside antibiotic drugs and do not allow penetration through the cell envelope. Despite this low-level intrinsic resistance, aminoglycosides can be combined with β-lactam antibiotic drugs for synergy. This combination typically works well for infections caused by *E. faecalis*. However, *E. faecium* produces low levels of aminoglycoside 5'-acetyltransferase, a chromosomally encoded enzyme that leads to high MICs for all the aminoglycosides, excluding gentamicin and streptomycin. Therefore, antimicrobial therapy for *E. faecium* is limited to high doses of the β-lactam antibiotic drugs with antienterococcal activity combined with gentamicin or streptomycin for potential synergistic activity. In addition, high-level aminoglycoside resistance in both *E. faecium* and *E. faecalis* also has occurred after a ribosomal mutation, which prevents their use even in combination with β-lactam antibiotic drugs.

Mechanism of Mupirocin Resistance in *Staphylococcus* Species

Mupirocin has become an important drug for topical use to decrease nasal colonization by MRSA. It binds to staphylococcal isoleucyl transfer RNA synthetase, resulting in inhibition of protein and RNA synthesis. Low-level resistance typically is not detected clinically and is caused by mutations in the chromosome encoding isoleucyl transfer RNA synthetase. High-level resistance is because of the acquisition of the *ileS2* gene, a gene that encodes for an isoleucyl transfer RNA synthetase with decreased affinity for mupirocin. Mupirocin resistance usually is observed in oxacillin- or methicillin-resistant isolates. About 3–4% of MRSA and methicillin-resistant *Staphylococcus epidermidis* strains are mupirocin-resistant.

Mechanism of Linezolid Resistance

Linezolid inhibits bacterial protein synthesis by binding to domain V of the 23S ribosomal RNA subunit of the 50S ribosomal subunit. Initially, it was thought that selection of linezolid resistance would be difficult because four to six copies of the gene that encodes the target site of linezolid are present in *Staphylococcus* and *Enterococcus* species. However, a few reports of linezolid resistance in *Staphylococcus* and *Enterococcus* species have been reported. The mechanism for resistance is a mutation in domain V of the 23S ribosomal RNA gene which appears in all copies of the gene. The few clinical cases of linezolid resistance in MRSA and *Enterococcus* species have resulted after extended linezolid use. Surveillance susceptibility testing also has identified linezolid-resistant *Staphylococcus* and *Enterococcus* isolates. Although the number of clinical isolates with linezolid resistance is still small (currently less than 20), there is concern for potential increased resistance rates. Evidence also exists of nosocomial spread of a linezolid-resistant *E. faecium* isolate despite appropriate infection-control measures. No clinical reports of pneumococcal isolates with linezolid resistance have been reported, but in vitro resistant isolates have been described.

Mechanism of Lincosamide Resistance

Clindamycin reversibly binds to the 50S ribosomal subunit, preventing peptide bond formation; thus, inhibiting protein synthesis. *Enterococcus faecalis* typically is resistant to clindamycin; however, some strains of *E. faecium* are susceptible. The MLS_B phenotype discussed in the Mechanisms of Macrolide section also confers resistance to clindamycin. Therefore, any *S. pneumoniae*, *Staphylococcus*, or *Enterococcus* species expressing the MLS_B phenotype will be resistant to clindamycin. In addition, an enzymatic modification mediated by the *linB* gene also has been described in *E. faecium* strains. Of interest, all *E. faecium* strains that expressed the *linB* gene also contained the *ermB* gene. Furthermore, the *linB* gene also can be transferred to *E. faecalis* by conjugation.

Mechanism of Streptogramin Resistance

Enterococcus faecalis are intrinsically resistant to the streptogramin B and streptogramin A combination quinupristin-dalfopristin. As previously discussed, the MLS_B resistance phenotype results from the expression of the *erm* genes and is encountered in enterococci, staphylococci, and pneumococci. In general, bacteria with the MLS_B resistance phenotype are not susceptible to streptogramin B; however, the combination of the two streptogramins typically results in maintenance of inhibitory activity against strains of *E. faecium*. The *vgbA* gene present in *S. aureus*, mediating production of a streptogramin B hydrolase, also has been identified. The *vgbA* gene also has been reported in *E. faecium*. In addition, streptogramin A compounds are susceptible to acetylation mediated by the *vatA* gene also observed in *E. faecium*. With more time, the impact of this resistance will be better understood.

Multiple Antibiotic Drug Resistance

Numerous multidrug-resistant pneumococcal serotypes have been identified. The most prevalent is the serotype 23F Spanish clone. This serotype has been reported in many countries and on all continents except Australia. Isolates of this clone typically are resistant to several antimicrobial drugs, including penicillin, tetracycline, trimethoprim-sulfamethoxazole, chloramphenicol, and macrolides. This clone has acquired at least five distinct capsular type variants, including 3, 6B, 9V, 14, and 19F. Resistance by pneumococci, enterococci, and staphylococci to tetracyclines, chloramphenicol, and macrolides also can result from the acquisition of the highly mobile conjugative transposon Tn*1545* or a related transposon that may carry one or more of these and other resistance determinants. Conjugative transposon Tn*1545* also has been linked to vancomycin tolerance in *Enterococcus* species.

Streptococcus pneumoniae Infections

During the past 20 years, resistance to many of the different classes of antibiotic drugs commonly used to treat pneumococcal infection has globally spread. Currently, no country is free of penicillin-resistant pneumococci, and rates of multidrug-resistant strains are on the rise. In the United States, the prevalence of penicillin-nonsusceptible *S. pneumoniae* among clinical isolates has increased from about 4% in the late 1980s to 32–43% currently. All *S. pneumoniae* organisms with a MIC equal to or greater than that defined for the intermediate category, MIC more than 0.12 mcg/ml, of resistance are classified as penicillin-nonsusceptible *S. pneumoniae*. Furthermore, among penicillin-nonsusceptible *S. pneumoniae*, 18–33% have high-level penicillin resistance (MIC more than 2 mcg/ml). There is regional variation in resistance rates in the United States as well as certain areas of the world. In general, foreign countries in Southeastern Asia have the highest rates of penicillin resistance, followed by Spain and France.

The etiology of the dramatic increase in penicillin nonsusceptible clinical isolates, primarily observed in the past 15 years, remains to be explained. Inappropriate use and overuse of antimicrobial drugs appear to be plausible explanations; however, they are unlikely to be the only reasons. Moreover, not only has there been an increase in the frequency of infections caused by penicillin-resistant pneumococci, but there has been a rise in the prevalence of pneumococcal infections with high levels of penicillin-resistance and multidrug resistance. Isolates that are penicillin nonsusceptible also have a greater likelihood of being resistant to other antimicrobial drug classes, including other β-lactams, macrolides, tetracyclines, and sulfa drugs (see Table 1-2).

Epidemiology

Streptococcus pneumoniae is one of the leading causes of pneumonia, sinusitis, otitis media, meningitis, and bacteremia. Infection with *S. pneumoniae* is a major cause of morbidity and mortality worldwide, and is a particular concern among the immunocompromised, young, and elderly populations. Pneumococci are considered part of the normal flora of the human upper respiratory tract and typically are cultured in 5–10% of healthy adults and 40–50% of healthy children younger than 2 years of age. Asymptomatic carriage rates fluctuate throughout the year and typically peak during winter months. Typically, colonization with a given serotype may continue for a year or more. In general, duration of carriage decreases with age and tends to be longer in children than adults. In addition, invasive disease is more frequent among infants attending, than not attending, day care and among children with other siblings than without siblings. Outbreaks of pneumococcal disease are rare, but do occur among individuals living in close contact such as day care centers, military training centers, and nursing homes.

Risk Factors for Resistant Pneumococcal Infections

Host defense systems, such as antibody and complement production, phagocytic cells, specifically polymorphonuclear cells, are necessary to prevent pneumococcal disease. Therefore, conditions that predispose individuals to infection with pneumococci include a decreased ability to form antibodies, multiple myeloma, human immunodeficiency virus infection, or

Table 1-2. United States Cross-resistance Rates for *Streptococcus pneumoniae*. Alexander Project 1998–2000, TRUST study 1998–2002, and PROTEK 2001–2002

	Percent Resistant		
Antimicrobial	Pen-S	Pen-I	Pen-R
Amoxicillin	0[a]	0[a]/0.1[c]	21.3[a]/32.5[c]
Ceftriaxone/Cefuroxime	0[b,d]	0.3[b,d] /33[c,e]	1.3[b,d]/99.9[c,e]
Macrolides			
Erythromycin	7.1[a]	49.8[a]/49.8[c]	72.4[a] /80.6[c]
Azithromycin	5.6[b]	51[b]/49.8[c]	76.3[b]/80.4[c]
Doxycycline	5.3[a]	36.2[a] /22.8[c,f]	53.2[a] /47.4[c,f]
TMP-SMX	13.9[a]/6.3[b]	51.9[a]/51.9[b]/52[c]	89.7[a]/87.3[b]/91.1[c]
Levofloxacin	0.4[b]	1.0[b]/0.2[c]	1.3[b]/2.2[c]

[a]Jacobs MR, Felmingham D, Appelbaum PC, Gruneberg RN. The Alexander Project 1998–2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. J Antimicrob Chemother 2003;52:229–46.
[b]Karlowsky JA, Thornsberry C, Critchley IA, et al. Susceptibilities to levofloxacin in *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* clinical isolates from children: results from 2000–2001 and 2001–2002 TRUST studies in the United States. Antimicrob Agents Chemother 2003;47:1790–7.
[c]Brown SD, Rybak MJ. Antimicrobial susceptibility of *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* collected from patients across the USA, in 2001–2002, as part of the PROTEKT US study. J Antimicrob Chemother 2004;54(suppl 1):i7–15.
[d] Nonmeningeal breakpoints were used for ceftriaxone.
[e] Cefuroxime.
[f]Tetracycline.
Penicillin Breakpoints: Pen-S (penicillin susceptible); MIC = ≤ 0.06 mcg/ml; Pen-I (penicillin intermediate) = 0.12–1 mcg/ml; Pen-R (penicillin resistant), MIC = ≥ 2 mcg/ml.
MIC = minimum inhibitory concentration; TMP-SMX = trimethoprim-sulfamethoxazole.

abnormalities with the complement system. In addition, because the spleen is the principal organ that clears pneumococci from the blood, individuals in whom the spleen has been removed or does not function normally have a greater risk of pneumococcal bacteremia and meningitis.

The greatest risk factor for infection with antibiotic-resistant pneumococci is colonization with these strains. Those with an increased risk of colonization with resistant *S. pneumoniae* include individuals with recent antibiotic drug use, young age, living in a geographic region that has high antibiotic drug usage in children, and exposure to children. Children in day care centers are among the most common people to be colonized with resistant pneumococci.

Pathophysiology

Streptococcus pneumoniae typically resides in the nasopharynx and is transmitted from one individual to another by extensive, close contact. Several factors determine the ability of a colonizing strain to break through mucosal defenses and cause disease. These factors potentially include simultaneous viral infection which causes local inflammation, impairment of macrophage function, dysfunction of ciliated epithelia, and impaired mucociliary transport. The viral-bacterial relationship has been well characterized in acute otitis media, where inflammation and congestion of the eustachian tube after a viral infection allows for an obstruction to occur and results in failure to clear secretions from the middle ear. Trapped bacteria from the nasopharynx multiply and invade the submucosa, resulting in additional inflammation. A similar course of events is recognized in the progress of acute sinusitis.

Other properties, most notably the polysaccharide capsule, make *S. pneumoniae* a pathogen in pneumonia and meningitis. Most clinical isolates of *S. pneumoniae* are encased in a capsule made up of repeating oligosaccharides. These polysaccharides that make up the capsule are covalently bound to the cell wall. The capsule allows *S. pneumoniae* to cause disease because it protects the organism against ingestion and killing by host phagocytic cells, particularly in an immunologically naïve host. More than 90 serotypes of *S. pneumoniae* have been identified on the basis of antigenic differences in their capsular polysaccharides. *Streptococcus pneumoniae* serotypes have been classified according to antigenic similarities. Certain serotypes have been linked to the global spread of multidrug-resistant clones, including 23F, 6B, and 9/14 clones. Many of these strains not only are penicillin nonsusceptible, but also often resistant to tetracyclines, macrolides, chloramphenicol, and trimethoprim-sulfamethoxazole. Regardless of the *S. pneumoniae* serotype, resistance has developed to almost all of the classes of antimicrobial drugs used to treat patients with these infections.

Pharmacodynamic Considerations

Optimal antibiotic drug use requires choosing the best drug for a pneumococcal infection. Recently, there has been much interest in establishing pharmacodynamic parameters for the antibiotic drugs active against *S. pneumoniae*. Pharmacodynamic parameters describe the relationship between drug concentrations, dose, and clinical effects in a patient. In general, there are three parameters that determine the best way to dose anti-infective drugs. These pharmacodynamic parameters are: time above the MIC (percentage of time in the dosing interval where serum concentrations exceed the MIC); maximum serum concentration divided by MIC (maximal serum concentration to MIC ratio); and the area under the curve divided by the MIC (area under the concentration curve to MIC ratio). Pharmacodynamic data derived from in vitro models, animal models, and patient data allow comparisons of available antimicrobial drugs to predict the most efficacious treatment regimens and limit the selection of

resistant mutants. If antimicrobial drug use is not fully maximized, it could theoretically result in suboptimal dosing regimens that could provide an environment favorable for drug-resistant pneumococci. This may lead to infection or colonization with resistant isolates that also can lead to the spread of resistant clones. Therefore, using local susceptibility patterns with pharmacodynamics provides a better tool against treatment of drug-resistant pneumococci. The pharmacodynamics of the most commonly used antimicrobial drugs for pneumococcal infections are discussed in greater detail in the next section.

β-Lactams

The stepwise accumulation of PBP mutations implies that penicillin and β-lactam resistance is not an all-or-none occurrence; rather it is concentration-dependent. It has been difficult to assess the true clinical impact of penicillin and β-lactam resistance. Treatment failures with β-lactam use have been documented for meningitis; however, there is minimal evidence that the emergence of resistant pneumococci has resulted in clinical failures among patients with respiratory tract infections. Furthermore, because β-lactam resistance is a concentration-dependent phenomenon, it is possible that β-lactam concentrations that are achieved in certain tissues, such as lungs and inner ears, may be sufficient to treat pneumococcal infections.

Because there appeared to be discordance between clinical outcomes in pneumonia patients infected with penicillin-resistant *S. pneumoniae* strains and in vitro susceptibility, there was concern that the Clinical and Laboratory Standards Institute breakpoints were not appropriate for pneumococcal pneumonia. When susceptibility breakpoints for *S. pneumoniae* initially were established by the Clinical and Laboratory Standards Institute, they were based on concentrations of penicillin achievable in the cerebrospinal fluid. These concentrations were intended to prevent clinical failure in meningitis treatment caused by penicillin-intermediate isolates. However, recently, the pharmacodynamic parameters of β-lactam drugs were evaluated with pneumococcal strains that appeared nonsusceptible in vitro to determine if adequate concentrations could be achieved to treat patients with pneumococcal pneumonia.

Based on animal studies, the pharmacodynamic parameter that most often correlated with clinical efficacy with β-lactam drugs was the time the serum concentration remained above the MIC. In general, the greatest bactericidal effect with β-lactams was observed when serum concentrations were 4 times greater than the MIC, and higher drug concentrations did not provide any added benefit. Furthermore, antibiotic drug concentrations did not need to be above the MIC for the entire dosing interval. Free drug concentrations of penicillins and cephalosporins above the MIC for greater than 40% and 50% of the dosing interval, respectively, were adequate for bactericidal activity.

Subsequently, based on pharmacodynamic parameters and animal studies, the Clinical and Laboratory Standards Institute has modified the interpretive breakpoints for amoxicillin, cefotaxime, and ceftriaxone for nonmeningeal pneumococcal infections, such as CAP, sinusitis, and otitis media. With these new breakpoints, about 90% of all nonmeningitis *S. pneumoniae* isolates are considered susceptible to amoxicillin. Now, amoxicillin, amoxicillin-clavulanate, ceftriaxone, and cefotaxime have become the β-lactams of choice for empiric treatment of CAP, sinusitis, and otitis media.

Macrolides and Ketolides

Pharmacodynamic parameters are not well established for macrolides. Time above the MIC for greater than 40% of the dosing interval is the pharmacodynamic parameter that is best correlated with clinical efficacy with clarithromycin and erythromycin. In contrast, an area under the concentration curve to MIC ratio greater than 25 may be the best predictor of clinical success with azithromycin.

Telithromycin recently was made available for treating respiratory tract infections. It inhibits bacterial protein synthesis by binding to two sites on the 50S ribosomal subunit. The area under the curve to MIC ratio for telithromycin correlated with efficacy against *S. pneumoniae* in animals. Animal models have determined that the area under the concentration curve to MIC ratio should be between 50 and 200. However, more clinical data are needed to confirm this.

Fluoroquinolones

From in vitro and in vivo pharmacodynamic models, area under the concentration curve to MIC ratio and to a lesser extent maximal serum concentration to MIC ratio correlate best with clinical effect of fluoroquinolones. In vitro models suggest that area under the concentration curve to MIC ratios should be 25–40 to predict optimal fluoroquinolone activity against *S. pneumoniae*. In addition, limited clinical studies suggest area under the concentration curve to MIC ratios of 30 or more correlated with successful clinical outcomes. The more potent newer fluoroquinolones, such as moxifloxacin and gatifloxacin, achieve higher area under the concentration curve to MIC ratios compared to levofloxacin. However, levofloxacin 750 mg results in a pharmacodynamic profile similar to the newer fluoroquinolones.

Overall, in vitro pharmacodynamic parameters for β-lactams, macrolides, and fluoroquinolones have been studied against *S. pneumoniae* isolates. Evaluation of pharmacodynamics allows a greater understanding of how drug concentrations correlate to effect and potentially, clinical efficacy and, therefore, may guide optimal dosing. Although established pharmacodynamic parameters for antimicrobial drugs are not fully elucidated for all drug classes, these preliminary data may provide a powerful tool in clinical decisions for treating gram-positive infections.

Therapy Choices for *Streptococcus pneumoniae*

In all relevant clinical decisions, empiric therapy is based on the most common organisms that cause infection at that site and typical susceptibility patterns for a given community. The most common infections caused by *S. pneumoniae* include CAP, meningitis, sinusitis, and otitis media. When making decisions for empiric therapy, local rates of drug resistance and risk factors for penicillin-nonsusceptible *S. pneumoniae* must be

Table 1-3. Guideline for Treatment of Acute Otitis Media in Children

Initial therapy	High-dose amoxicillin (80–90 mg/kg/day divided in two dosages) High-dose amoxicillin-clavulanate (90/6.4 mg/kg/day divided in two dosages)[a]
NOT type 1 hypersensitivity to penicillin	Cefdinir (14 mg/kg/day in one or two dosages) Cefpodoxime (10 mg/kg/day, once daily) Cefuroxime (30 mg/kg/day in two dosages)
Type 1 hypersensitivity to penicillin	Azithromycin (10 mg/kg/day on day 1 then 5 mg/kg/day for 4 days) Clarithromycin (15 mg/kg/day divided in two dosages) Erythromycin-sulfisoxazole (50 mg/kg/day of erythromycin) Cotrimoxazole (6–10 mg/kg/day of trimethoprim)

[a]Use in patients with severe illness (moderate to severe otalgia or fever of 39ºC or higher) or if β-lactamase *Haemophilus influenza* or *Moraxella catarrhalis* is a concern.
Adapted with permission from the American Academy of Pediatrics. American Academy of Pediatrics and American Academy of Family Physicians. Diagnosis and management of acute otitis media. Pediatrics 2004;113:1451–65.

considered. This is particularly true when treating sinusitis and otitis media, in which therapy usually is empiric and susceptibility testing is not often conducted. Therefore, trends in susceptibility of *S. pneumoniae* observed in a given community or institution must be considered to select appropriate drug therapy. Clinical guidelines are available for pneumonia, sinusitis, and otitis media providing a good foundation for therapy choices, but local susceptibility trends also must be considered to make educated decisions. Furthermore, if cultures are obtained and susceptibility testing is done, broad-spectrum empiric choices must be streamlined when those data are made available.

Otitis Media

The most common bacterial pathogen in otitis media is *S. pneumoniae*, occurring in about 25–50% of children. Based on the new nonmeningitis susceptibility breakpoints from the Clinical and Laboratory Standards Institute, more than 95% of all *S. pneumoniae* isolates are susceptible to amoxicillin. Therefore, the American Academy of Pediatrics and American Academy of Family Physicians 2004 guidelines for diagnosing and managing acute otitis media include high-dose amoxicillin (80–90 mg/kg/day) as first-line therapy for children with otitis media. High doses of amoxicillin typically result in middle ear fluid levels that exceed the MIC of penicillin-nonsusceptible *S. pneumoniae*. This is not true for conventional dosing of amoxicillin (45 mg/kg/day) which is no longer recommended for treating otitis media. In patients unable to take amoxicillin, oral cephalosporins, macrolides, or trimethoprim-sulfamethoxazole can be used, depending on local resistance patterns. Length of therapy for acute otitis media typically is 7–10 days with the exception of azithromycin, which is 5 days. Infection caused by a resistant pathogen is not an indication for longer treatment unless the initial antibiotic drug choice was ineffective. First-line treatment options for otitis media are summarized in Table 1-3.

Therapy choices become more complex if infection fails to respond to the initial antibiotic drugs within 48–72 hours. In general, the patient is stabilized and possibly may get somewhat worse the first day of therapy; however, by the second day, the patient should be improving. If the patient does not improve after 2 days of therapy, failure of therapy secondary to infection with a resistant *S. pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis* species should be considered. The initial treatment must be considered when choosing an alternative regimen. If a patient failed high-dose amoxicillin initially, neither trimethoprim-sulfamethoxazole nor erythromycin-sulfisoxazole should be selected because of the high cross-resistance that is observed with penicillin-nonsusceptible *S. pneumoniae* strains against sulfa drugs (see Table 1-2). In addition, if high-dose amoxicillin was used with no clinical improvement, amoxicillin-clavulanate will provide no additional benefit for pneumococci. In *S. pneumoniae*, resistance to β-lactam drugs occurs through alterations in the PBPs and not through the production of β-lactamases. If amoxicillin-clavulanate was used initially with no response, an oral second-generation cephalosporin or intramuscular ceftriaxone is advocated for use. Fluoroquinolones are not recommended to treat otitis media because of its associated risk of impaired bone and joint development in children. Although human data do not appear to support the concern for quinolone-induced arthropathy, quinolone use in children should be reserved for life-threatening situations when other drugs are not possible options.

Sinusitis

Guidelines published in 2004 by the American Academy of Otolaryngology Head and Neck Surgery, the American Academy of Otolaryngic Allergy, and the American Rhinologic Society include high-dose amoxicillin or high-dose amoxicillin-clavulanate as first-line therapy for sinusitis in children and adults. Treatment guidelines are summarized in Table 1-4 and provide therapy recommendations for adults and children. *Streptococcus pneumoniae* is the cause of bacterial sinusitis in about 33% of all cases. With sinusitis, cultures often are not obtained and drug therapy is approached empirically. Because serious complications can be associated with pneumococcal sinus infections, empiric therapy must always include coverage for *S. pneumoniae*. Treatment guidelines for adults and children categorize sinus infections into two groups: those with mild disease and no previous antibiotic drugs in the preceding 4–6 weeks, and individuals with mild disease having previous antibiotic drug exposure or those with moderate disease. Recent antibiotic drug exposure is a risk for infections caused by resistant pathogens, most commonly resistant *S. pneumoniae*. Antibiotic drugs

recommended to be avoided among patients who had received antimicrobial drugs in the previous 4–6 weeks include trimethoprim-sulfamethoxazole, doxycycline, azithromycin, clarithromycin, and erythromycin. Although these drugs can be used, the risk of infection with resistant isolates is much higher.

For patients with mild sinus disease and no previous antibiotic drug exposure, the American Academy of Otolaryngology Head and Neck Surgery guidelines recommend amoxicillin or amoxicillin-clavulanate, or oral cephalosporins, including cefpodoxime, cefuroxime, or cefdinir as initial recommendations for adults and children. However, in children, high-dose amoxicillin and amoxicillin-clavulanate should be used first. Trimethoprim-sulfamethoxazole, azithromycin, clarithromycin, or erythromycin can be considered if a history of immediate type I reactions to β-lactams exists. In addition, doxycycline or telithromycin can be considered for treatment in adults.

Among adults and children with mild sinus disease with previous antibiotic drug exposure or moderate disease, high-dose amoxicillin clavulanate or cephalosporins are recommended. In addition, combination therapy can be considered, including amoxicillin or clindamycin plus cefixime, or high-dose amoxicillin or clindamycin plus rifampin. The respiratory fluoroquinolones, including gatifloxacin, levofloxacin, and moxifloxacin can be used for adult patients with previous antibiotic drug exposure, but clinical consequences of fluoroquinolone use should be considered. The newer fluoroquinolones have been associated with the promotion of resistant organisms, most commonly commensal gram-negative species of the gastrointestinal tract and MRSA.

Antimicrobial drug resistance should be considered if the infection does not respond to initial antibiotic drug therapy within 72 hours. When reevaluating therapy for sinusitis, the limitations of coverage, most notably with resistant pneumococci, should be considered. The length of antibiotic drug therapy among patients who respond to the initial antimicrobial drug choice for mild sinusitis disease ranges from 5 to 10 days. Five-day therapy can be used if telithromycin or azithromycin are used. Infection caused by a resistant pathogen is not an indication for longer treatment unless the initial antibiotic drug choice was ineffective.

Table 1-4. Guidelines for Sinusitis Therapy

Mild Disease	Moderate Disease or Mild Disease and Exposure to Antibiotic Drugs in the Past 4–6 Weeks
Adults	
Amoxicillin-clavulanate	Fluoroquinolone (moxifloxacin, gatifloxacin, and levofloxacin)
Amoxicillin	High-dose amoxicillin-clavulanate
Cefpodoxime	Ceftriaxone
Cefuroxime	Combination Therapy:
Cefdinir	High-dose amoxicillin or clindamycin plus cefixime
Doxycycline[a]	High-dose amoxicillin or clindamycin plus rifampin
Azithromycin[a]	
Clarithromycin[a]	
Erythromycin[a]	
Telithromycin[a]	
Children	
High-dose amoxicillin-clavulanate	High-dose amoxicillin-clavulanate
Amoxicillin	Cefpodoxime
Cefpodoxime	Cefuroxime
Cefuroxime	Cefdinir
Cefdinir	Ceftriaxone
Cotrimoxazole[a]	Cotrimoxazole
Azithromycin[a]	Azithromycin[a]
Clarithromycin[a]	Clarithromycin[a]
Erythromycin[a]	Erythromycin[a]
	Combination Therapy:
	High-dose amoxicillin or clindamycin plus cefixime
	High-dose amoxicillin or clindamycin plus rifampin

[a]May be considered for patients with β-lactam allergies but have a higher risk of treatment failure.

Adapted with permission from the American Academy of Otolaryngology—Head and Neck Surgery Foundation, Inc. Anon JB, Jacobs MR, Poole MD, et al. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg 2004;130:1–45.

Community-acquired Pneumonia

As with otitis media and sinusitis, the most common bacterial cause of CAP is *S. pneumoniae*. The Infectious Diseases Society of America published guidelines in December 2003, and its recommended empiric therapy is summarized in Table 1-5. With the Clinical and Laboratory Standards Institute changes in susceptibility breakpoints for nonmeningitis pneumococcal strains, amoxicillin, amoxicillin-clavulanate, ceftriaxone, and cefotaxime have become the preferred drugs for pneumococcal pneumonia and should be included in the initial treatment regimen. However, in an outpatient setting in a community with relatively low resistance rates, doxycycline or a macrolide can still be used. Once a patient has been exposed to previous antibiotic drug therapy, doxycycline or a macrolide alone are not appropriate choices because risk of resistance to these drugs is much higher than with other antimicrobial drug classes. However, azithromycin or clarithromycin could be combined with high-dose amoxicillin or high-dose amoxicillin-clavulanate.

The use of fluoroquinolones for CAP has been highly debated. Previous guidelines from the American Thoracic Society and Centers of Disease Control and Prevention have attempted to restrict the use of the fluoroquinolones when the likelihood of drug-resistant *S. pneumoniae* was low. However, the newest guidelines from the Infectious Diseases Society of America include these drugs as first-line drugs in patients with antibiotic drug exposure in the preceding 3 months, or patients with underlying comorbidities. Despite these recommendations, there is still concern about the overuse of fluoroquinolone antimicrobial drugs and the potential emergence of more resistance with subsequent use. Increased prevalence of MRSA and resistant gram-negative organisms has been associated with fluoroquinolone use. Although fluoroquinolone resistance rates currently are low

in *S. pneumoniae*, it is possible that pneumococci could become resistant to fluoroquinolones in a fate similar to that observed with β-lactam antibiotic drugs.

Among hospitalized patients living in areas with higher rates of pneumococci resistance to cephalosporins, vancomycin must be included in the empiric regimen of severely ill patients with CAP. Because vancomycin-tolerant pneumococci and other vancomycin-resistant gram-positive organisms have emerged, prudent use of vancomycin is warranted. Vancomycin should only be used when truly necessary, and should be removed as soon as susceptibility testing allows for selection of another drug.

Another option for treating of β-lactam-resistant pneumococcal CAP includes linezolid, an oxazolidinone antibiotic drug. A small study comparing ceftriaxone to linezolid for CAP resulted in comparable cure rates for pneumococcal pneumonia in the two treatment groups. However, among patients with CAP and concurrent bacteremia, cure rates were higher with linezolid compared to the cephalosporin-treated group. Because of limited data, linezolid would not be indicated as first-line empiric therapy for CAP. In addition, side effects with linezolid, such as thrombocytopenia and leucopenia, make linezolid use less desirable compared to the cephalosporins, which have a

Table 1-5. Infectious Diseases Society of America Guidelines for the Treatment of Community-Acquired Pneumonia

Patient Variable	Preferred Treatment Options
Outpatient	
Previously healthy	
No recent antibiotic drug therapy	A macrolide[a] or doxycycline
Recent antibiotic drug therapy[b]	A respiratory fluoroquinolone[c] alone, an advanced macrolide[d] plus high-dose amoxicillin[e], or an advanced macrolide plus high-dose amoxicillin-clavulanate[f]
Comorbidities[g]	
No recent antibiotic drug therapy	An advanced macrolide[d] or a respiratory fluoroquinolone[c]
Recent antibiotic drug therapy	A respiratory fluoroquinolone[c] alone or an advanced macrolide plus a β-lactam[h]
Suspected aspiration with infection	Amoxicillin-clavulanate or clindamycin
Influenza with bacterial superinfection	A β-lactam[h] or a respiratory fluoroquinolone[c]
Inpatient	
Medical ward	
No recent antibiotic drug therapy	A respiratory fluoroquinolone[c] alone or an advanced macrolide plus a β-lactam[h]
Recent antibiotic drug therapy	An advanced macrolide[d] plus a β-lactam[i] or a respiratory fluoroquinolone[c] alone (will depend on recent antibiotic drug therapy regimen)
Intensive care unit	
No concern of *Pseudomonas* infection	A β-lactam[i] plus either an advanced macrolide[d] or a respiratory fluoroquinolone[c]
No *Pseudomonas*, but β-lactam allergy	A respiratory fluoroquinolone[c], with or without clindamycin
Concern of *Pseudomonas* infection[j]	Either 1) and antipseudomonal agent[k] plus ciprofloxacin, or 2) an antipseudomonal agent[k] plus an aminoglycoside[l] plus a respiratory fluoroquinolone[c] or a macrolide
Pseudomonas and β-lactam allergy	Either 1) aztreonam plus levofloxacin[m], or 2) aztreonam plus moxifloxacin or gatifloxacin, with or without an aminoglycoside
Nursing home	
Receiving treatment in nursing home	A respiratory fluoroquinolone[c] alone or amoxicillin-clavulanate plus an advanced macrolide[d]
Hospitalized	Same as for medical ward and ICU

[a]Erythromycin, azithromycin, and clarithromycin.
[b]Any antibiotic drug therapy in the past 3 months, excluding the current episode of infection. Previous antibiotic drug therapy is a risk factor for drug-resistant *Streptococcus pneumoniae* and possibly for infection with gram-negative bacilli. Depending on the class of antibiotics recently given, one of the suggested options may be selected. Recent use of fluoroquinolone should dictate selection of a nonfluoroquinolone regimen, and vice versa.
[c]Moxifloxacin, gatifloxacin, levofloxacin, or gemifloxacin (only available oral).
[d]Azithromycin or clarithromycin.
[e]Dosage 1 g orally 3 times/day.
[f]Dosage 2 g orally 2 times/day.
[g]Chronic obstructive pulmonary disease, diabetes, renal or congestive heart failure, or malignancy.
[h]High-dose amoxicillin, high-dose amoxicillin-clavulanate, cefpodoxime, cefprozil, or cefuroxime.
[i]Cefotaxime, ceftriaxone, ampicillin-sulbactam, and ertapenem (limited experience with ertapenem).
[j]Risk factors for *Pseudomonas* infection include severe structural lung disease, and recent antibiotic drug therapy or stay in hospital (especially in the ICU). For patients with CAP in the ICU, coverage for *S. pneumoniae* and *Legionella* species must always be assured.
[k]Piperacillin, piperacillin-tazobactam, imipenem, meropenem, or cefepime.
[l]Data suggest that elderly patients receiving aminoglycosides have worse outcomes.
[m]Dosage for hospitalized patients is 750 mg/day.
CAP = community-acquired pneumonia; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit.
Reprinted with permission from the University of Chicago Press. Mandell LA, Bartlett JG, Dowell SF, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003;37:1405–33.

San Pedro GS, Cammarata SK, Oliphant TH, Todisco T; Linezolid Community-Acquired Pneumonia Study Group. Linezolid versus ceftriaxone/cefpodoxime in patients hospitalized for the treatment of Streptococcus pneumoniae pneumonia. Scand J Infect Dis 2002;34:720–8.

relatively low side effect profile. More clinical data are available for treating bacteremia with cephalosporins compared to linezolid, and there is a much greater comfort using drugs that are well known, safe, and proven efficacious to treat a life-threatening infection. Also, linezolid's cost is much higher compared to the cephalosporins. Switching to linezolid or fluoroquinolones if traditional therapy with cephalosporins or vancomycin is not effective for CAP may be a more reasonable clinical decision.

Telithromycin is a newly approved oral ketolide indicated for CAP and sinusitis. Because it is available only in an oral dose form, use is limited to treating CAP in the outpatient setting or when intravenous therapy is switched to oral therapy in the hospital. The mechanism of action of ketolides is similar to that of macrolides; however, ketolides have a higher affinity for the target binding sites on the 23S ribosomal RNA of the 50S ribosomal subunit, which accounts for its more potent in vitro activity against *S. pneumoniae*. Ketolides have concentration-dependent killing and their activity is not modified against *S. pneumoniae* isolates with *erm* or *mef* resistant determinants. Telithromycin would be a good choice for therapy if macrolide resistance is high in the community. One of the major advantages of telithromycin is that it may decrease fluoroquinolone use, which has been linked to increased selection of MRSA and resistant gram-negative organisms. Telithromycin appears to be well tolerated; however, it is metabolized by the cytochrome P450 enzyme system, increasing the potential for drug interactions. The drug can cause cardiovascular side effects such as bundle branch block and QTc prolongation. Therefore, use with antiarrhythmics or other drugs that alter QTc should be done cautiously.

Therapy duration for pneumonia depends on the causative pathogen as well as the host response. Among hospitalized patients, pneumococcal pneumonia typically is treated until the patient is afebrile for 72 hours. In the outpatient setting, CAP typically is empirically treated for 7–14 days, depending on the suspected pathogen and the chosen antibiotic drug. If the patient responds to the initial antibiotic drug selection, length of therapy does not need to be increased for recovery of a resistant pathogen. Shorter therapies with the fluoroquinolones and ketolides also are treatment options

Meningitis

In contrast to sinusitis, otitis media, and CAP, *S. pneumoniae* meningitis has a much higher morbidity and mortality rate. Pneumococcal meningitis can be the result of hematogenous spread from another site, including the lower airways or more commonly, from a site near the central nervous system, such as the middle ear or paranasal sinuses. Once the pneumococci reach the central nervous system, a severe inflammatory process occurs which can become worse after antimicrobial drugs are administered. Despite appropriate antibiotic drug treatment, serious neurological sequelae, such as seizures, frequently are encountered. Furthermore, neurological complications are more frequent in pneumococcal meningitis compared with meningitis from other bacterial causes.

In general, cefotaxime or ceftriaxone are the preferred cephalosporins for empiric treatment of suspected or diagnosed pneumococcal meningitis, primarily because they achieve adequate concentrations in the cerebrospinal fluid. These drugs have been the most extensively evaluated cephalosporins for treating meningitis. However, depending on geographical location, some surveillance studies have documented that about 20% of pneumococcal strains are resistant to cephalosporins. If cephalosporin resistance is a concern, then vancomycin should be added to the initial empiric regimen. In vitro and animal data have demonstrated synergy when cefotaxime or ceftriaxone and vancomycin are used together. The combination of cefotaxime or ceftriaxone with rifampin also has been advocated as an empiric treatment option for pneumococcal meningitis, which is believed to be effective because rifampin crosses the blood-brain barrier well. However, clinical data regarding the combination of cephalosporins with rifampin for empiric therapy are lacking. If this combination is chosen, higher doses of the cephalosporin also should be administered to ensure its cerebrospinal fluid concentrations are not subtherapeutic. A situation where rifampin was the only drug present in the cerebrospinal fluid even for a short time period could result in rapid development of rifampin resistance similar to rifampin monotherapy.

If a patient has a β-lactam allergy, vancomycin could be considered as an alternative. However, vancomycin monotherapy typically is not indicated because it has poor penetration into the central nervous system, and it has a tendency to kill pneumococci slower than penicillins and cephalosporins. Rifampin can be added to vancomycin; however, clinical data supporting this practice are limited. If vancomycin is used for pneumococcal meningitis, theoretically maximum vancomycin doses should be administered to ensure adequate concentrations in the central nervous system. In addition, serum trough levels should be monitored for appropriateness. Because spinal fluid concentrations are about 10–20% of those observed in the serum, theoretically, serum trough levels should not fall below 15–20 mcg/ml to maintain adequate concentrations in the central nervous system. In general, the MIC that inhibits growth of 90% of a bacterial strain vancomycin against most gram-positive clinical isolates is 1–2 mcg/ml. Therefore, vancomycin concentrations in the central nervous system would be at or slightly above the MIC of the organism if serum vancomycin trough concentrations were between 15 mcg/ml and 20 mcg/ml. Intraventricular or intrathecal administration of vancomycin could be considered to obtain higher cerebrospinal fluid concentrations if necessary.

Although clinical studies are lacking, animal data support the use of fluoroquinolones for pneumococcal meningitis.

Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267–84.

In addition, in vitro and animal data show synergy with combined use of fluoroquinolones and β-lactams, such as ceftriaxone and meropenem. The newer fluoroquinolones, including moxifloxacin, gatifloxacin, and levofloxacin, achieve cerebrospinal fluid concentrations of about 25–45% the observed serum concentrations. In patients with true β-lactam allergies and allergies to vancomycin, a fluoroquinolone could be a possible choice. Because of the life-threatening nature of bacterial meningitis, especially pneumococcal meningitis, clinical studies are difficult to coordinate and implement in this patient population. Eventually, studies evaluating efficacy of fluoroquinolone use for pneumococcal meningitis will become available; however, it is likely that these studies will be case reports and small clinical trials. Until these data are available, fluoroquinolone use in meningitis should not be advocated as first-line therapy.

Because pneumococcal meningitis is life-threatening, empiric antibiotic drug therapy must be delivered as soon as possible, and drug resistance must be assumed until susceptibility testing proves otherwise. The guidelines by the American Academy of Pediatrics addressing meningitis were published mainly to address antimicrobial drug resistance in *S. pneumoniae*. Although these guidelines were established for children based on literature from the pediatric population, they can be extrapolated to the adult population. Because of the life-threatening nature of meningitis, vancomycin should be used for empiric therapy if an infection risk with cephalosporin-resistant pneumococci exists. However, vancomycin should be removed from the drug regimen as soon as possible to prevent selection of resistant gram-positive organisms. No matter what empiric regimen is chosen, once antibiotic susceptibilities are known, drug therapy should be tailored. Duration of antibiotic drug therapy for pneumococcal meningitis is 10–14 days. If appropriate empiric therapy was initiated and the patient responded, therapy does not need to be extended even if a resistant isolate is the causative pathogen for meningitis.

Antibiotic Drugs to Treat Vancomycin-tolerant *Streptococcus pneumoniae* Infections

Currently, vancomycin tolerance has not been a significant clinical issue and only limited cases have been reported. Clinical data are lacking for treatment recommendations for vancomycin-tolerant *S. pneumoniae* infections. Linezolid, moxifloxacin, and rifampin combined with vancomycin all appear to have in vitro activity against vancomycin-tolerant pneumococci. A clinical cure has been reported in a 10-month-old child with vancomycin-tolerant *S. pneumoniae* meningitis treated with the combination of ceftriaxone, vancomycin, and rifampin.

Preventing the Emergence of Antibiotic-resistant Pneumococci

Emergence of drug-resistant pneumococci has been blamed on the misuse and overuse of antibiotic drugs, most notably for respiratory infections. It is imperative in both the hospital and community settings to limit the antibiotic drug use to prevent a favorable environment for selection and emergence of resistant pathogens. If vancomycin must be used because of concern of resistance, it must be discontinued as soon as the susceptibility results warrant.

Risk factors can be reduced to decrease the incidence of infections caused by *S. pneumoniae*. Risk factor reduction has been most extensively studied in children with otitis media, and would likely decrease the risk of sinusitis, CAP, and meningitis in children as well. Day care center attendance is associated with increased colonization of penicillin-nonsusceptible *S. pneumoniae* and can increase the risk of developing otitis media. Children in day care centers are much more likely than children not in day care centers to be colonized with drug-resistant strains of *S. pneumoniae*. The greater the number of children a child comes into contact with, the more likely that child will be colonized with drug-resistant pneumococci. Similar to hospitals and nursing homes, day care facilities are colonized with drug-resistant gram-positive organisms. Breastfeeding for the first 6 months of life, avoiding bottle feeding an infant in the supine position (bottle propping), reducing or eliminating pacifier use after 6 months of life, and eliminating passive exposure to tobacco smoke have reduced the incidence of acute otitis media in young children. Among children older than 2 years of age, administering the influenza vaccine decreased the risk of otitis media during the respiratory season by greater than 30%. Administering the influenza vaccine decreases the risk of not only influenza, but also secondary bacterial respiratory tract infections. The pneumococcal conjugate vaccine provides a small benefit in preventing acute otitis media. However, administering the pneumococcal conjugate vaccine in elderly individuals has been successful for preventing CAP and meningitis. Influenza vaccination in adults also would decrease the chance of developing secondary respiratory tract infections, most common with *S. pneumoniae*.

Staphylococcal Infections

Similar to *S. pneumoniae*, resistance in *S. aureus* and *S. epidermidis* has occurred against several classes of antibiotic drugs. Shortly after the introduction of penicillin, staphylococcal species became able to produce β-lactamases. Resistance to macrolides, tetracyclines, and chloramphenicol also arose after exposure to these drugs. The prevalence of methicillin-resistant *S. aureus* and *S. epidermidis* has increased since first being described about 25 years ago. More concerning is the emergence of VISA and VRSA, limiting the antimicrobial drug arsenal to even fewer drugs. Currently, 20–59% of all *Staphylococcus* species recovered in the intensive care unit are methicillin-resistant. Although methicillin resistance in *S. epidermidis* is common, the majority of the research and surveillance work has been done with *S. aureus*. Therefore, this chapter focuses on *S. aureus*.

American Academy of Pediatrics: Committee on Infectious Diseases. Therapy for children with invasive pneumococcal infections. Pediatrics 1997;99:289–99.

Abbreviations

Epidemiology

Staphylococci are among the most common bacteria causing human disease. Humans are the natural reservoir for *S. aureus* and *S. epidermidis*. Asymptomatic carriage is common, and about 10–40% of individuals are colonized with *S. aureus* in the anterior nares, and *S. epidermidis* is normal bacterial flora in all humans. *Staphylococcus* species are normal inhabitants of the upper respiratory tract, skin, intestine, and vagina. Individuals with insulin-dependent diabetes, intravenous drug use, dermatological conditions, long-term intravenous catheters, or who work in health care have an increased likelihood of being colonized with *S. aureus*. Coagulase-positive strains, including *S. aureus*, typically cause more severe infections and coagulase-negative strains, including *S. epidermidis*, historically are associated with nosocomial infections. Staphylococci, harbored by either an asymptomatic carrier or a person with disease, can be spread by direct contact, expulsion from the respiratory tract, or transport on inanimate surfaces. Staphylococci can produce disease in almost every tissue and organ of the body and often cause invasive infection in patients whose host defensive mechanisms have been compromised.

Risk Factors for Resistant Staphylococcal Infections

With the initial surge of MRSA in the 1980–1990s, several risk factors for infection with this organism were identified. These include prior hospitalization, admission to an intensive care unit or burn unit, invasive procedures and devices, skin lesions, increased age hemodialysis, insulin-dependent diabetes, intravenous drug abuse, and previous antimicrobial drug treatments. Colonization of the nares by MRSA also has been determined to increase the risk for MRSA infection. Furthermore, anyone with close contact to individuals with these risk factors would be at risk for colonization and potentially causing the spread of resistant clones. Traditionally, all MRSA cases were acquired in hospitals or other health care facilities. However, there is a trend of increasing MRSA from the community setting. Community-associated MRSA is more commonly associated with skin and soft tissue infections rather than invasive diseases, which traditionally is observed with nosocomial strains. Individuals with community-associated MRSA tend to be younger than those infected with nosocomial strains, and typically do not have risk factors that are associated with MRSA.

Although limited cases of VISA have been reported, risk factors for these infections have been identified. These risk factors include prolonged vancomycin use, hemodialysis dependence, and indwelling foreign bodies. In addition, isolation of a MRSA from a culture in the previous 2–3 months has been linked to recovery of *S. aureus* isolates with reduced susceptibility to vancomycin. This suggests that individuals infected or colonized with MRSA are at risk of infection with *S. aureus* strains with decreased susceptibility to vancomycin.

Risk factors that have been associated with heterogeneous VISA bacteremia include infections with a high bacterial burden, such as endocarditis, failure of vancomycin therapy, long fever duration, slow time until clearance of bacteremia, and long length of hospital stay. In addition, low vancomycin trough levels less than 10 mcg/ml during the first week of therapy were associated with recovery of heterogeneous VISA.

Because only three VRSA cases have been reported, risk factors for VRSA are less well defined. All patients with VRSA had a history of recurrent MRSA infections and a prior or current infection or colonization with VRE. Two of these patients also had received vancomycin.

Pathophysiology

Staphylococcus species cause disease with their capability to proliferate and spread extensively throughout tissues. In addition, staphylococci have the ability to produce many extracellular substances, including exotoxins and several other enzymes considered to be helpful in tissue invasiveness. Often, toxin genes are carried on plasmids, and, in some cases, genes responsible for pathogenicity reside on both a plasmid and the host chromosome. Recently, virulence factors for community-associated MRSA have been identified. In contrast to institution-associated MRSA, community-associated MRSA strains possess the gene for Panton-Valentine leukocidin, a cytotoxic virulence factor associated with skin and soft tissue infections and more serious infections, such as necrotizing pneumonia. *Staphylococcus aureus* also produce and grow in a biofilm, making treatment of these infections difficult. Antibiotic drugs often cannot penetrate organisms in the lower layers of the biofilm. Endocarditis and catheter infections caused by *S. aureus* often resemble growth observed in biofilm production. Because these infections are difficult to treat, endocarditis often requires surgical intervention and long-term antibiotic drug therapy and catheter-related infections often require removal of the catheter to eliminate the source of infection.

Considerations in Treatment and Treatment Options

In contrast to *S. pneumoniae*, fewer clinical data are available for treating resistant staphylococcal infections. The most common infections caused by *Staphylococcus* species are skin and soft tissue infections and these are discussed in greater detail in the Superficial Skin Infections chapter. Guidelines are available for managing endocarditis and catheter infection, in which *Staphylococcus* species are among the most common pathogens, but limited information regarding antibiotic drug resistance is available. Furthermore, only a few antibiotic drugs are available for resistant staphylococcal infection, and comparison trials between treatment groups have been small in size.

β-Lactam-resistant Staphylococcal Species

The majority of staphylococcal species produce β-lactamases; however, if an infection is caused by a

Charles PG, Ward PB, Johnson PD, Howden BP, Grayson ML. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus*. Clin Infect Dis 2004;38:448–51.

penicillinase-negative strain, penicillin G is the preferred antibiotic drug to use. If a serious staphylococcal infection is treated empirically and MRSA is not a concern, β-lactamase resistance should be assumed and therapy with oxacillin, nafcillin, clindamycin, or a cephalosporin such as cefazolin should be initiated and continued until susceptibility testing indicates otherwise. For less severe staphylococcal infections in an outpatient setting, oral therapy with dicloxacillin, amoxicillin-clavulanate, clindamycin, trimethoprim-sulfamethoxazole, or minocycline can be initiated based on local susceptibly patterns. In general, fluoroquinolones are not recommended for staphylococcal infections because of the potential for the development of resistance.

Methicillin-resistant *Staphylococcus aureus*

Glycopeptides have been the first-line therapy for treating MRSA since the emergence of methicillin-resistant staphylococci. However, clinical data are now available supporting linezolid use for treating infections caused by MRSA. An open-labeled, randomized trial compared vancomycin with linezolid in hospitalized patients with suspected or proven MRSA. Patients with pneumonia, skin and soft tissue infections, urinary tract infections, or bacteremia were included. S*taphylococcus aureus* was isolated from 53% of the patients and 93% of those isolates were MRSA. There was no difference in cure rates or microbiological success between the two treatments among patients with MRSA. A similar study compared linezolid with teicoplanin and demonstrated no difference in clinical and microbiological success between the two drugs for treating suspected or proven gram-positive infections in the intensive care population. The majority of pathogens recovered in this study was MRSA. Another study demonstrated that patients with nosocomial ventilator-associated MRSA pneumonia treated with linezolid had a higher clinical cure rate and hospital survival compared to standard-dose vancomycin. A concern of this study was that vancomycin doses may not have been high enough; vancomycin trough concentrations were 5–10 mcg/ml. Although there are no well-designed clinical trials to support the practice of maintaining vancomycin trough levels higher than 10 mcg/ml, many practitioners advocate this practice based on theoretical considerations. Because vancomycin is a time-dependent drug, higher trough concentrations ensure that adequate drug concentrations are maintained at the infection site. This is particularly true for infections in the lung, a site that has low vancomycin concentrations. Linezolid has an advantage over vancomycin because it has an intravenous and oral formulation, and with the recent increase in community-associated MRSA infections, it is more convenient for outpatient therapy for MRSA. However, the cost of linezolid is much higher than vancomycin; therefore, if intravenous therapy is necessary, vancomycin would be the less expensive choice. Switching patients from vancomycin in the hospital setting to oral linezolid for outpatient use also would be an option.

Susceptibility testing for MRSA should be performed to determine if any other antibiotic drugs, such as clindamycin, minocycline, or trimethoprim-sulfamethoxazole, still remain active. Many community-associated MRSA strains still remain susceptible to these antimicrobial drugs. Older data demonstrated that trimethoprim-sulfamethoxazole is as effective as vancomycin for MRSA. In a randomized trial comparing vancomycin to trimethoprim-sulfamethoxazole, all 47 patients with MRSA were cured regardless of the antibiotic drug regimen. Toxicity rates were similar between trimethoprim-sulfamethoxazole and vancomycin treated groups. Trimethoprim-sulfamethoxazole is inexpensive and the oral form has good bioavailability. Some drug interactions and patient intolerance with trimethoprim-sulfamethoxazole may prevent its use; however, for MRSA infections that are not life-threatening, trimethoprim-sulfamethoxazole or trimethoprim-sulfamethoxazole combined with rifampin is a convenient and less expensive oral alternative to vancomycin or linezolid therapy.

Rifampin or aminoglycosides, most commonly gentamicin, have been combined with vancomycin for potential synergistic activity against MRSA. However, some in vitro data have demonstrated antagonism with both these combinations. If available, synergy studies should be performed before using these combination therapies in patients. It is unclear how in vitro antagonism observed with combination therapy in some MRSA isolates correlates with clinical outcomes. There would be no indication to use combination therapy if in vitro antagonism was noted. Preliminary in vitro data demonstrated synergy with fluoroquinolones combined with glycopeptides against MRSA. More studies are needed to confirm these results. Currently, because of limited clinical data, the combination of fluoroquinolones with vancomycin would not be advocated.

Vancomycin-intermediate *S. aureus* and Vancomycin-resistant *S. aureus*

Inadequate clinical data are available to provide recommendations for antibiotic drug therapy for infections because of VISA and VRSA strains. High-dose monotherapy with vancomycin may be a possible option for patients infected with VISA strains. In vitro data suggest that high vancomycin doses may result in bactericidal activity against these isolates. Therefore, higher trough concentrations of 15–20 mcg/ml may be desired if vancomycin therapy is selected. When making therapy choices, it also is important to consider the infection site before choosing vancomycin to treat these strains. Vancomycin does not have good central nervous system penetration, and its concentrations in the lung tend to be much lower than the blood and tissues. Therefore, intravenous vancomycin may not be a good choice for

Kollef MH, Rello J, Cammarata SK, Croos-Dabrera RV, Wunderink RG. Clinical cure and survival in Gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin. Intensive Care Med 2004;30:388–94.

Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. Ann Intern Med 1992;117:390–8.

meningitis or pneumonia with a VISA strain regardless of the dose. Furthermore, vancomycin concentrations at the infection site theoretically will have to be much higher because the MIC is elevated. In many cases, these concentrations are not clinically achievable, or are limited because of drug toxicity.

Trimethoprim-sulfamethoxazole and tetracycline have in vitro activity against all of the VISA isolates recovered in the United States. These antibiotic drugs have been included in several combinations for treating VISA infections. Of the VRSA strains identified to date, two were resistant to tetracycline, but all three were sensitive to trimethoprim-sulfamethoxazole. Both patients had a microbiological cure after treatment with combination therapy, including trimethoprim-sulfamethoxazole.

Limited data are available on linezolid use for treating VISA, but case reports indicated that it may have a role. Successful outcomes have been documented with monotherapy and combination therapy of infections caused by VISA and heterogeneous VISA strains. A successful microbiological cure using combination therapy, including linezolid, was documented, suggesting that it may have a role in treating VRSA infections. Additional clinical data with linezolid monotherapy and combinations with other antibiotic drugs, such as rifampin and trimethoprim-sulfamethoxazole, are needed to determine their role in treating VISA and VRSA infections.

In vitro susceptibility has been reported with dalfopristin and quinupristin for treating VRSA strains. However, some susceptibility studies with VISA isolates have not demonstrated in vitro activity. Additional clinical data are necessary to determine if this streptogramin combination will have a role in treating VISA and VRSA infections.

Daptomycin is the newest drug available for treating infections caused by resistant gram-positive organisms. Limited in vitro data with daptomycin against each VISA and VRSA strain have demonstrated bactericidal activity. In addition, the combination of daptomycin and an aminoglycoside demonstrated in vitro synergistic effect against a VISA strain.

As previously discussed, some VISA strains are susceptible to trimethoprim-sulfamethoxazole, chloramphenicol, gentamicin, rifampin, or tetracycline. In addition, in vitro data suggest that VISA strains may be more susceptible than MRSA to β-lactam antibiotic drugs. In vitro and animal studies with VISA isolates demonstrated synergy with β-lactam antibiotic drugs, such as nafcillin, combined with vancomycin, suggesting the combination may be effective although each drug alone does not appear to be active based on susceptibility tests. Because clinical data in treating these resistant strains are limited at this time, combination therapy based on susceptibility patterns will most likely be used against these strains. If available, synergy testing should be used to help make therapy decisions.

Prevention of Repeat MRSA Infections in Colonized Patients

When a patient is known to be colonized with MRSA, measures should be taken to prevent further infections with that strain. The use of vancomycin lock solutions has been advocated for patients requiring long-term catheter use to prevent catheter-associated bacteremias. Antibiotic lock technique involves the filling of a catheter lumen with high concentrations of antibiotic drugs for 12–24 hours between uses of the catheter. The goal of this therapy is to decontaminate the intraluminal surface of the catheter. Although the studies have been small, they support this practice in high-risk patients. However, in theory, a more effective way to prevent recurrent MRSA infections would be to eliminate the source of infection by removal of the catheter for possible eradication of the carrier state. Among individuals with MRSA colonization, intranasal application of mupirocin and octenidine dihydrochloride body wash for 5 days may successfully eradicate MRSA colonization. Use of chlorhexidine washes also have been used to eliminate MRSA colonization. Among MRSA-colonized patients who received intranasal mupirocin, 61% successfully remained decolonized at 90 days. Decolonization is expected to prevent spread from patient to patient or from patient to health care provider. More clinical studies are needed to determine whether these methods of decolonization would effectively control an outbreak situation in a hospital or lower the MRSA infection rate of hospitalized patients. It is safe to assume that decolonization in high-risk patients would prevent infection with MRSA. Routine surveillance cultures in patients successfully decolonized of MRSA may be warranted to ensure that recolonization does not occur.

Enterococcal Infections

Enterococci are the third most common pathogen recovered in nosocomial infections in intensive care units. Enterococcal species are recovered in about 9% of all bloodstream infections and 12% of urinary tract infections. More than 25% of all enterococcal isolates recovered from patients in the intensive care unit are resistant to vancomycin. The most recent study evaluating intensive care unit pathogens during 2000–2002 found that less than 5% and 76% of *E. faecalis* and *E. faecium* isolates, respectively, were resistant to vancomycin. More concerning is the rapid rise in VRE isolates that has been observed in the past 2 decades. Vancomycin-resistant *Enterococcus* was first reported in the United States in 1987, and now 25% of all enterococcal isolates are resistant to vancomycin. Fortunately, in the United States, VRE is almost exclusively found in the health care setting. In general, patients who became infected with VRE were first colonized while in a health care setting and then became susceptible to infection. In contrast, VRE in Europe is not

Rohr U, Mueller C, Wilhelm M, Muhr G, Gatermann S. Methicillin-resistant *Staphylococcus aureus* whole-body decolonization among hospitalized patients with variable site colonization by using mupirocin in combination with octenidine dihydrochloride. J Hosp Infect 2003;54:305–9.

Mody L, Kauffman CA, McNeil SA, Galecki AT, Bradley SF. Mupirocin-based decolonization of *Staphylococcus aureus* carriers in residents of 2 long-term care facilities: a randomized, double-blind, placebo-controlled trial. Clin Infect Dis 2003;37:1467–74.

limited to the health care setting. Avoparcin, a glycopeptide, had been used in the animal industry in some European countries and has been linked to the emergence of VRE in the community setting.

In clinical medicine, enterococci have been recognized as a species that often are resistant to inhibition or killing by antibiotic drugs commonly used to treat other gram-positive infections, most notably vancomycin. Enterococci often are antibiotic-resistant opportunistic pathogens that are recovered from patients who received multiple courses of antimicrobial drugs and were hospitalized for long time periods. *Enterococcus faecalis* and *E. faecium* are the two species most often associated with human disease.

Epidemiology

Enterococci are normal inhabitants of the gastrointestinal tract and can cause a broad variety of diseases. Common infections include endocarditis, bacteremia, urinary tract, wound, intra-abdominal, and skin and soft tissue infections. Rarely do enterococcal strains cause meningitis, pneumonia, otitis, sinusitis, or septic arthritis. Typically, antibiotic-resistant enterococci, most commonly VRE, are clonally spread in health care settings, resulting in gastrointestinal tract colonization. Vancomycin-resistant *Enterococcus* intestinal colonization is asymptomatic and can persist for long time periods, serving as a reservoir for transmission of VRE to other patients and health care providers. Colonization with VRE or other drug-resistant enterococci is a precursor to infection.

Risk Factors for VRE

Many patients may be colonized with VRE; however, only a small percentage of these patients develop documented VRE infections. Every colonized patient has the risk of spreading VRE directly through health care providers or through fomite transmission if appropriate infection control measures are not followed. Chances of becoming colonized with VRE increase the closer a patient is to another individual with VRE. In addition, the transmission risk is high if the bacterial burden of the colonized individual is high, such as a patient receiving antibiotic drugs that allowed selection of VRE. There are data to support that exposure to certain antimicrobial drugs may increase the risk of VRE colonization. Exposure to metronidazole, clindamycin, second- or third-generation cephalosporins, and aminoglycosides may increase risk of colonization with VRE. It is possible that using an antimicrobial drug with anti-anaerobic activity with no activity against enterococci allows for overgrowth of enterococcal species. Also, the longer the patient is in the hospital, the greater the chance of becoming colonized with VRE. Health care workers and their family members also have a risk of becoming colonized. Colonized health care workers are at risk of spreading resistant enterococci to patients in their care.

Most VRE-colonized patients will remain colonized for a prolonged period. Patients colonized with VRE have the greatest infection risk if they have underlying comorbidities or immunosuppression. Widespread colonization of VRE in health care settings in the United States emphasizes the need for increased detection of patients with VRE and greater control measures to prevent further spread of these organisms.

Pathophysiology

Several factors may play a role in pathogenesis of enterococcal infections. Results from one animal study demonstrated that mice treated with broad-spectrum antibiotic drugs allowed enterococci to translocate across a histologically normal intestinal epithelium. The mechanism of this translocation is not fully understood; however, it is well documented that broad-spectrum antibiotic drug use, most frequently cephalosporins, increases the risk of enterococcal infection, possibly by allowing translocation to occur. Enterococci also may produce extracellular products such as cytolysin and coccolysin. Cytolysin typically is encoded by large transmissible plasmids and has the ability to lyse eukaryotic cells. Coccolysin is an enzyme capable of hydrolyzing and inactivating human endothelin. Coccolysin may contribute to the pathogenicity of enterococcal disease through preventing vasoconstriction as a result of endothelin inactivation.

Therapy Choices for Clinical Infections

Limited data are available on antimicrobial drug therapy with enterococcal infections, particularly vancomycin-resistant species. Ampicillin or penicillin is the preferred antimicrobial drug to treat enterococcal infections if the causative organism is susceptible to these drugs. These drugs typically are bacteriostatic and, therefore, usually are combined with an aminoglycoside such as gentamicin or streptomycin to treat serious life-threatening infections such as endocarditis and meningitis. Because of the risk of resistance to ampicillin, vancomycin is commonly used empirically for enterococcal infection and also is combined with an aminoglycoside, gentamicin or streptomycin for potential synergistic activity. Historically, streptomycin was difficult to obtain and measuring serum drug concentrations could only be done by a few laboratories. Although streptomycin is now easier to obtain and more companies are able the measure serum concentrations, gentamicin has become the more commonly used aminoglycoside for these infections. Combination therapy typically is advocated because of the intrinsic resistance of enterococci with cell wall-active antimicrobial drugs. Two-drug combination therapy is used to treat enterococcal endocarditis and meningitis; however, uncertainty exists regarding combination therapy for bacteremia. Although clinical, controlled trial data are not available, many practitioners also will use combination therapy to treat bacteremia.

Fosfomycin, tetracyclines, and nitrofurantoin have activity against VRE urinary tract infections, but they are not options for systemic infections. These drugs achieve adequate concentrations in the urine, but not in the blood. Some success has been reported with fluoroquinolones for treating enterococcal urinary tract infections and prostatitis. However, because of spread of fluoroquinolone-resistant enterococcal isolates, few strains remain susceptible to fluoroquinolones and, therefore, are not recommended for systemic infections.

Therapy choices for antibiotic-resistant enterococci are limited. Quinupristin-dalfopristin, linezolid, and

daptomycin are among the newer drugs that are included as options for treating VRE infections. Quinupristin-dalfopristin is bacteriostatic against *E. faecium*, but has no activity against *E. faecalis*. Linezolid also is bacteriostatic and also does not have activity against both *E. faecium* and *E. faecalis*. Unfortunately, a few reports of resistance with linezolid have been observed in *E. faecium* strains. Two cases of linezolid resistance have occurred in vancomycin-resistant *E. faecium* isolates after exposure to linezolid. Both individuals had indwelling catheters and were treated with linezolid for more than 4 weeks. However, recently, a few linezolid- and vancomycin-resistant *E. faecium* isolates were reported without any exposure to linezolid therapy.

A prospective, randomized trial of 40 patients with cancer compared linezolid to quinupristin-dalfopristin for treating vancomycin-resistant *E. faecium*. Comparable clinical response rates were observed for the two treatment groups. Of interest, relapse rates were 2-fold higher among patients who received linezolid compared with those who received quinupristin-dalfopristin (21% vs. 10%, respectively). This study size was too small to determine if the difference in relapse rate was significant. However, investigators hypothesized that the lower relapse rate with quinupristin-dalfopristin could have been because of less vancomycin-resistant *E. faecium* bacterial burden in the gastrointestinal tract, because 75% of the drug is eliminated through the hepatobiliary/fecal route. In contrast, less than 10% of linezolid or its inactive metabolites are excreted through the hepatobiliary/fecal route.

Limited clinical data are available for daptomycin in enterococcal infections. In vitro data demonstrated bactericidal activity of daptomycin against VRE strains. In animal pyelonephritis models, daptomycin was effective against both vancomycin-susceptible and VRE species. About 78% of daptomycin is excreted as unchanged drug in the urinary tract. The increased urinary concentrations of daptomycin likely lead to its successful outcomes in treating urinary tract infections caused by *Enterococcus* species. Daptomycin also was used successfully to treat a patient with linezolid-resistant VRE bacteremia. Clinical studies are being conducted to evaluate daptomycin use for urinary tract infections, endocarditis, and bacteremia. Initial animal studies evaluating daptomycin in an endocarditis infection model demonstrated a poor outcome, which was attributed to the high protein binding of the drug. When these clinical studies are completed, the role of daptomycin for enterococcal infections will become clearer.

Imipenem still remains active against some VRE strains. Chloramphenicol also may be an option; however, resistance to this drug also has emerged.

Combination Therapy

Because there is such a lack of clinical data regarding the treatment of VRE infections, combination therapy is appealing. Both quinupristin-dalfopristin and linezolid are bacteriostatic against VRE. Bactericidal drugs or synergistic combinations of antimicrobial drugs may be more desirable, particularly to treat patients with neutropenia. A compassionate-use trial of quinupristin-dalfopristin combined with minocycline, a combination that was synergistic against VRE isolates in vitro, was conducted in 56 oncology patients. Among patients with hematological malignancies, response rates with quinupristin-dalfopristin ranged from 43% to 44%. The response rate with combination therapy of quinupristin-dalfopristin plus minocycline was 69%. In patients with prolonged neutropenia, the combination of quinupristin-dalfopristin and minocycline may provide a synergistic response and improve outcomes. Although comparative studies need to confirm this finding, this may be an effective treatment option for patients with neutropenia with severe VRE infection.

In vitro synergy has been described for daptomycin plus rifampin and daptomycin plus ampicillin. In addition, the combination of nitrofurantoin plus rifampin has been effective to cure long-term prostatitis in a liver transplant recipient. It is likely that more combinations will be evaluated to find effective drug therapy to treat enterococcal infections.

Prevention of Emergence and Spread of VRE

As with MRSA, preventing emergence of VRE requires prudent antibiotic drug use. Minimizing antibiotic drug exposure, particularly vancomycin, prevents selection of resistant strains to overgrow and become the primary flora. Preventing the spread of VRE to other individuals requires screening for VRE and isolating patients who are colonized or infected. In addition, appropriate standard precautions such as using masks, gloves, gowns, and effective environment decontamination should prevent further spread of these strains.

Goals of Therapy for Gram-positive Infections

The main treatment goal with gram-positive bacterial infections includes eradication of the bacterial pathogen. Therapeutic goals include resolution of signs and symptoms of infection without toxicity or side effects from the chosen antimicrobial regimen. In a few clinical situations, it is possible to sterilize the infection site; however, the patient may not fully improve clinically. Antibiotic drugs may cure many infections, but the host's immune system also plays a role in treatment. Severely immunocompromised patients typically make up the population that may not respond or respond slower to a given antibiotic drug therapy. The best attempt to produce a therapeutic success includes obtaining cultures and susceptibility testing of the recovered organism. More important is choosing appropriate empiric antibiotic coverage when an infection is suspected. Maintaining current antibiograms of a given institution or community allows for more informed decisions based on recent trends. This is particularly important in the immunocompromised population where the initial antibiotic

Raad I, Hachem R, Hanna H, et al. Treatment of vancomycin-resistant enterococcal infections in the immunocompromised host: quinupristin-dalfopristin in combination with minocycline. Antimicrob Agents Chemother 2001;45:3202–4.

drug choice may be critical for the patient's survival. Knowledge of increased resistance with a given pathogen allows practitioners to change empiric regimens and likely prevent therapeutic failures.

Clinical Overview of Drugs for Gram-positive Infections

β-Lactams

The β-lactams include a large variety of drugs, including the penicillins, cephalosporins, monobactams, and carbapenems. The β-lactams have historically been first-line therapy for pneumococcal, enterococcal, and staphylococcal infections. However, because of antimicrobial resistance, β-lactam antibiotic drugs have a lesser role as initial empiric therapy for gram-positive infections. Nonetheless, if the gram-positive pathogens are determined to be susceptible to a β-lactam antibiotic drug and the patient does not have any contraindication that prevents their use, β-lactams still remain the treatment of choice for pneumococcal, enterococcal, and staphylococcal infections in these clinical situations. β-Lactams are most commonly used for susceptible *S. pneumoniae* infections, with amoxicillin being the first-line therapy for otitis media and sinusitis. Third-generation cephalosporins, most frequently ceftriaxone and cefuroxime, are most commonly used for pneumococcal meningitis and pneumonia requiring intravenous therapy. Ampicillin combined with an aminoglycoside is the preferred therapy for most susceptible enterococcal infections and nafcillin or oxacillin for susceptible staphylococcal infections. In most clinical settings, vancomycin typically is used empirically for both staphylococcal and enterococcal infections until susceptibilities are known.

β-Lactam antibiotic drugs typically are well tolerated and have limited side effects. The most common adverse effects include rash, and gastrointestinal side effects such as abdominal pain, nausea, and diarrhea. Less common adverse effects include anemia, thrombocytopenia, eosinophilia, leucopenia, interstitial nephritis, pseudomembranous colitis, hepatotoxicity, seizures, and hypokalemia. Although not common, the hematological effects, seizures, and pseudomembranous colitis can prevent usage of a β-lactam antibiotic drug and warrant switching to a different class of antibiotic drugs.

Glycopeptides

Vancomycin has become first-line empiric therapy for serious infections suspected to be caused by a *Staphylococcus* or *Enterococcus* species. If cephalosporin resistance is a concern when treating suspected *S. pneumoniae* meningitis, vancomycin often is added to the treatment regimen. In each of these clinical scenarios, resistance is assumed until otherwise proven. Once susceptibility results are known, vancomycin therapy should be changed to other antibiotic drugs based on the susceptibility profile.

Adverse reactions with vancomycin are similar to those observed with the β-lactam antibiotic drugs. Vancomycin also causes an infusion-related adverse effect called Red Man syndrome, which is characterized by sudden and/or profound hypotension with or without a macropapular rash on the face, neck, chest, and less commonly the extremities. The mechanism of this reaction is not fully understood; however, histamine is thought to be involved. This reaction may be mistaken for an allergic or anaphylactic reaction, and often is managed by administration of fluids, antihistamines, hydrocortisone, and slowing of the rate of the intravenous infusion. Typically, Red Man syndrome is not a contraindication to vancomycin therapy. Interstitial nephritis is an uncommon side effect with vancomycin; however, if it is serious, therapy may need to be changed to another antibiotic drug.

There is no clinical evidence that states maintaining vancomycin serum concentrations in a specific range will decrease nephrotoxicity compared to empiric dosing. In addition, there is no correlation between serum peak concentrations of vancomycin and clinical efficacy. Vancomycin is time-dependent and concentrations at the infection site should exceed the MIC of the organism, which is about 2 mcg/ml. Vancomycin dosing should be based on the patient's weight, age, and renal function. Trough concentrations can be obtained to guide therapy in a few clinical cases. For example, monitoring trough concentrations in patients with impaired or rapidly changing renal function or those with infections at sites that have lower vancomycin concentrations such as osteomyelitis, endocarditis, or meningitis, may be helpful to maximize therapy. Vancomycin trough concentrations also are useful for monitoring patients receiving higher than normal doses such as obese or burn patients. If trough concentrations are obtained, target concentrations should range between 10 mcg/ml and 20 mcg/ml and randomly obtained serum concentrations less than 15 mcg/ml are indicative for redosing vancomycin.

Macrolides and Ketolides

Available macrolides for treating gram-positive infections include azithromycin, clarithromycin, erythromycin, and dirithromycin. The only available ketolide in the United States is telithromycin. The most frequent use of macrolides is for treating macrolide-susceptible *S. pneumoniae* infections. Telithromycin has activity against many macrolide-resistant pneumococci and, thus, may have a prominent role in empiric therapy particularly in environments where macrolide resistance rates are high. With the exception of azithromycin and erythromycin, this group of antibiotic drugs is available only in oral dose forms. Because of widespread resistance, macrolides typically are not useful for treating infections caused by *Enterococcus* and *Staphylococcus* species.

Macrolides and telithromycin are well tolerated, and the most common adverse events include gastrointestinal effects, headache, and hypersensitivity. Torsade de pointes has been observed in patients with a history of cardiac arrhythmias or concomitant administration of other drugs that can cause arrhythmias. In addition, telithromycin and macrolides have the potential to prolong the QT interval and

should be used cautiously when coadministered with other drugs that are associated with QT prolongation.

Fluoroquinolones

The most commonly used fluoroquinolones for gram-positive infections include the newer respiratory drugs, such as levofloxacin, moxifloxacin, gatifloxacin, and gemifloxacin. Although indicated for the use of infections caused by *Staphylococcus* and *Enterococcus* species, the rapid development of resistance with fluoroquinolones may limit their clinical use for treating these gram-positive infections. Suspected pneumococcal sinusitis, bronchitis, and CAP are the leading gram-positive infections treated with fluoroquinolones. Use of fluoroquinolones should be minimized to prevent the emergence of fluoroquinolone resistance in pneumococci as well as resistance in gram-negative organisms. The development of fluoroquinolone resistance in gram-positive isolates requires stepwise mutations in the quinolone-resistance determining region and exposure to fluoroquinolones may allow for selection of resistant isolates. Increased use of ciprofloxacin has been linked to providing a favorable environment for the selection of fluoroquinolone-resistant pneumococci.

Limited side effects and ease of administration of the fluoroquinolones has led to the increased use of this class of antibiotic drugs. The newer fluoroquinolones only require once-daily dosing, and all but gemifloxacin have an intravenous and oral formulation. Also, gastrointestinal side effects tend to be less than reported with some of the β-lactam drugs. Fluoroquinolones are not recommended for use in children and during pregnancy because of the theoretical risk of quinolone-induced arthropathy.

Tetracyclines

Tetracyclines, including doxycycline, tetracycline, and minocycline primarily are useful for the empiric treatment of sinusitis and bronchitis in patients without underlying comorbidities or risk of infection with resistant pneumococci. Doxycycline also is effective for treating CAP in patients with low risk of infection with antibiotic-resistant pneumococci. Tetracyclines also may be treatment options for enterococcal urinary tract infections. Because absorption is variable, tetracyclines typically are not indicated for more serious infections. Recently, with the emergence of community-associated MRSA infections, doxycycline and minocycline have gained popularity for treating skin and soft tissue infections.

Tetracyclines are well tolerated and the most common adverse effects include rash and gastrointestinal side effects. Because of the risk of discoloration of teeth, tetracyclines are not indicated for use in children with developing teeth. In addition, tetracyclines are contraindicated in pregnancy.

Sulfa Drugs

The most commonly used sulfa drug is sulfamethoxazole combined with trimethoprim as cotrimoxazole. Trimethoprim-sulfamethoxazole can be used empirically for sinusitis and bronchitis caused by pneumococci if local susceptibility patterns show low rates of sulfa resistance. However, average sulfa resistance rates range from 30% to 50%, thus preventing widespread use of this drug for pneumococcal infections. Trimethoprim-sulfamethoxazole can be effectively used for enterococcal urinary tract infections, but it typically is not used for systemic enterococcal infection.

More recently, trimethoprim-sulfamethoxazole has gained increased consideration for treating skin and soft tissue infections caused by community-associated MRSA isolates. More than 95% of community-associated MRSA isolates demonstrate in vitro susceptibility to trimethoprim-sulfamethoxazole. An advantage of trimethoprim-sulfamethoxazole is the availability of an oral and intravenous dosage form. The most common adverse effects include rash and gastrointestinal side effects.

Clindamycin

Clindamycin is effective for treating suspected pneumococcal infections. Use should be based on local susceptibility patterns and avoided if resistance rates are high. Clindamycin also is an effective antistaphylococcal antibiotic drug and is active against many of the community-associated MRSA isolates. However, isolates of the MLS_B phenotype with inducible clindamycin resistance have been described; therefore, clindamycin should be used cautiously if staphylococcal MLS_B-mediated resistance is common in a given community or institution. In vitro inducible MLS_B-mediated resistance also can be detected through the use of a double-disk diffusion assay. Clindamycin typically is not used for enterococcal infections. Clindamycin usually is well tolerated, but it has a higher incidence of gastrointestinal side effects as well as increased risk of pseudomembranous colitis compared to many other antibiotic drugs. Advantages of clindamycin include the availability of an oral and intravenous formulation and good penetration to all sites of infection.

Linezolid

The current principal use for linezolid is for treating serious infections caused by MRSA and VRE. Linezolid administration should be reserved for vancomycin treatment failures or for patients intolerant to vancomycin because of the lack of evidence to demonstrate better clinical efficacy with linezolid compared to vancomycin. In addition, vancomycin is less expensive and has a better toxicity profile. Linezolid has an advantage over vancomycin for treating MRSA because it has an intravenous preparation and an oral tablet that has excellent bioavailability. There are some data from small trials that suggest linezolid may be better than vancomycin for MRSA surgical site infections and empiric therapy for suspected gram-positive ventilator-associated pneumonia. However, these trials are small, and larger trials are necessary to further evaluate the comparative efficacy of linezolid and vancomycin. Linezolid also has activity against pneumococci; however, less expensive antibiotic drugs with more clinical data should be used first.

Therapy may be limited with linezolid because of the risk of myelosuppression, most commonly thrombocytopenia, which requires weekly monitoring. This also may prevent use in patients with underlying myelosuppression. In addition, the preliminary reports of emergence of resistance

in *Staphylococcus* and *Enterococcus* species after use of linezolid may limit its clinical use. Linezolid is a reversible, nonselective inhibitor of monoamine oxidase, and combination therapy with monoamine oxidase inhibitors, including the selective serotonin reuptake inhibitors, may result in central nervous system toxicity or serotonin syndrome. Ideally, concomitant administration should be avoided and therapy with either drug should be separated by 2 weeks.

Streptogramins

Quinupristin-dalfopristin is the only available streptogramin product in the United States. The main use for quinupristin-dalfopristin is for treating infections caused by vancomycin-resistant *E. faecium* and MRSA infections not responding to vancomycin. Quinupristin-dalfopristin is not active against *E. faecalis*; therefore, it should not be used empirically for suspected enterococcal infections. If a patient is intolerant to vancomycin or is myelosuppressed such that linezolid is contraindicated, quinupristin-dalfopristin can be considered. Adverse events are common with quinupristin-dalfopristin and include infusion site reactions, such as inflammation and pain, and myalgias and arthralgia in as high as 50% of patients. Because of the adverse events with this drug, linezolid and daptomycin typically are preferred.

Daptomycin

At this time, the main role for daptomycin is for treating VRE infections and staphylococcal infections where the patient was intolerant to vancomycin or vancomycin failed. Because this is a new drug, limited clinical data are available comparing daptomycin to other antimicrobial drugs. Daptomycin has in vitro activity against penicillin-resistant pneumococci and MRSA; however, there are no clinical data demonstrating superior efficacy of daptomycin compared to other available antimicrobial drugs. In addition, the need for weekly monitoring of creatine phosphokinase enzyme levels and the increased cost compared with other antimicrobial drugs further limits its clinical use for pneumococcal and staphylococcal infections. Daptomycin is only available in an intravenous preparation which further restricts its use.

Infection Control

The majority of infections caused by the strains of resistant *Staphylococcus* and *Enterococcus* species discussed thus far are nosocomial and, therefore, are preventable. An exception to nosocomial spread of resistant strains would include community-associated MRSA and the rare acquisition of a new resistant strain. However, these infections also can be preventable with appropriate infection control. Guidelines are available from the Society for Healthcare Epidemiology of America for preventing the spread of multidrug-resistant strains of *S. aureus* and *Enterococcus* species. In addition, the Centers for Disease Control and Prevention developed a 12-step campaign to prevent antimicrobial resistance among hospitalized adults (Table 1-6). This campaign is not limited to gram-positive pathogens, but all of the concepts are applicable for preventing antimicrobial resistance in gram-positive pathogens. Step one, for example, stresses the importance of patients at high risk for infections with *S. pneumoniae* to receive the pneumococcal vaccine. Current recommendations from the Centers for Disease Control and Prevention Advisory Committee on Immunization Practice suggest providing the pneumococcal polysaccharide vaccine to all adults older than 65 years of age and people 2–64 years of age with chronic illnesses who are at higher risk of pneumococcal disease. In addition, the influenza vaccine is recommended; by decreasing the risk of influenza, the risk of a secondary infection also will be minimized.

The second step focuses on preventing catheter-related blood stream infections, of which *Staphylococcus* and *Enterococcus* species are the pathogens in more than 60% of all cases. Catheters and other invasive devices are the most common exogenous cause of hospital-acquired infections. The longer these devices stay in place, the more likely an infection will occur. Therefore, removal of these devices as soon as they are no longer necessary is imperative. If catheters must remain in place, proper handling techniques to minimize infection risk should be followed. Peripheral catheters should be replaced every 24–48 hours and the catheter site should be evaluated daily to assess for infection.

Inadequate or inappropriate antimicrobial treatment among patients in the intensive care unit increases the risk of hospital mortality. Therefore, pathogens that cause infections should be targeted by administering appropriate antimicrobial drug therapy in the correct regimen at the appropriate timing, dosage, route, and duration. Empiric antimicrobial drug choices should be based on local antibiograms, and therapy must be tailored based on identified pathogens and susceptibility results once available. If uncertainty exists regarding therapy, infectious diseases experts can be consulted to guide practitioners to appropriate therapy.

Other methods can be incorporated in practice to improve appropriate antimicrobial drug use. Standardized antimicrobial order forms, formulary restrictions, prior approval to start or continue therapy, pharmacy substitution or switch programs, multidisciplinary drug use evaluations, prescriber education, provider or unit performance feedback, and computerized decision support or online ordering systems, are methods that may improve antibiotic drug use.

A major cause of antimicrobial overuse is the initiation of therapy for contaminated cultures or from positive cultures because of colonization. Correct techniques must be used to obtain and process cultures, and patient risk factors and clinical evidence of infection must be considered when interpreting culture results. A positive culture result is not an indication for antimicrobial therapy. If questions arise about a culture potentially being contaminated or reflecting colonization, cultures should be repeated and infectious disease experts consulted.

Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115:462–74.

Abbreviations

Antibiotic drug use promotes emergence, selection, and spread of resistant pathogens. Inappropriate therapy with vancomycin has been particularly problematic when dealing with gram-positive pathogens. Regarding gram-positive infections, vancomycin use is indicated to treat serious infections caused by β-lactam-resistant pathogens or for individuals with severe allergies to β-lactam antibiotic drugs. In addition, prophylaxis for surgical procedures in patients colonized with MRSA or methicillin-resistant *S. epidermidis* also would be appropriate. Inappropriate use of vancomycin would include treatment of gram-positive infections susceptible to β-lactam antibiotic drugs, continued treatment of presumed infections without positive cultures, treatment of contaminated blood cultures, empiric therapy for neutropenic fever without suspicion for gram-positive infection, routine prophylaxis, and eradication of MRSA colonization.

Continuing antibiotic drugs longer than necessary after an infection is cleared can promote the emergence of resistant organisms. Shorter courses of drug therapy often can be as efficacious as longer regimens. Recent clinical data support shorter antibiotic regimens for ventilator-associated pneumonia and CAP. Furthermore, if cultures are negative and infection is not likely, the unnecessary antibiotic drugs should be discontinued because they can promote antibiotic drug resistance.

Most of the resistant gram-positive pathogens are acquired through person-to-person contact or by means of contaminated vectors. To prevent the spread of these organisms, standard precautions that apply to all patients and health care professionals should be followed. These precautions involve a common sense approach and include the use of gloves when touching any body fluids and washing hands with soap and water or alcohol-based antimicrobial hand rubs before and after wearing gloves. When used appropriately, alcohol-based hand rubs have been equally or more effective than handwashing with soap and water. Masks, eye protection, and gowns should be worn if there is any risk of contamination from body fluids. Furthermore, contact precautions with patients colonized or infected with any resistant organism, such are VRE or MRSA, should be enforced. These patients can be placed in a regular room, but it must be private. They should have dedicated noncritical equipment such as stethoscopes and thermometers. Furthermore, all surfaces should be thoroughly disinfected after that patient leaves the hospital room. If these infection control measures are followed, the emergence and spread of antibiotic-resistant organisms should be reduced.

Pharmacists' Role in Managing Gram-positive Infections

The main role a pharmacist can play in managing gram-positive infections is to implement actions that minimize the potential for the emergence and spread of drug-resistant organisms. These actions should emphasize reducing

Table 1-6. Centers for Disease Control and Prevention Campaign to Prevent Antimicrobial Resistance in Health Care Settings: 12 Steps to Prevent Antimicrobial Resistance Among Hospitalized Adults

Step 1	Vaccinate • Give influenza/pneumococcal vaccine to at-risk patients before discharge • Get influenza vaccine annually
Step 2	Get the catheters out • Use catheters only when essential • Use correct catheter • Use proper insertion and catheter-care protocols • Remove catheters when they are no longer essential
Step 3	Target the pathogen • Culture the patient • Target empiric therapy to likely pathogens and local antibiogram • Target definitive therapy to known pathogens and antimicrobial susceptibility test results
Step 4	Access the experts • Consult infectious diseases experts for patients with serious infections
Step 5	Practice antimicrobial control • Engage in local antimicrobial control efforts
Step 6	Use local data • Know your antibiogram • Know your patient population
Step 7	Treat infection, not contamination • Use proper antisepsis for blood and other cultures • Culture the blood, not the skin or catheter hub • Use proper methods to obtain and process all cultures
Step 8	Treat infection, not colonization • Treat pneumonia, not the tracheal aspirate • Treat bacteremia, not the catheter tip or hub • Treat urinary tract infection, not the indwelling catheter
Step 9	Know when to say "no" to vancomycin • Treat infection, not contaminant or colonization • Fever in a patient with an intravenous catheter is not a routine indication for vancomycin
Step 10	Stop antimicrobial treatment: • When infection is cured • When cultures are negative and infection is unlikely • When infection is not diagnosed
Step 11	Isolate the pathogen • Use standard infection control precautions • Contain infectious body fluids (follow airborne, droplet, and contact precautions) • When in doubt, consult infection control experts
Step 12	Break the chain of contagion • Stay at home when you are sick • Keep hands clean • Set and example

http://www.cdc.gov/drugresistance/healthcare/patients.htm. Accessed March 17, 2005.

inappropriate drug use and preventing drug-resistant pathogens. Practice guidelines to assist physicians in choosing appropriate prophylactic or empiric regimens can be established and implemented by pharmacists. Data also should be collected comparing antibiotic usage patterns with resistance patterns that are observed in a given hospital. Summaries of these data can be useful when implementing policy changes to alter prescribing habits. In addition, this information can be used for developing formularies or antibiotic drug use restriction policies, such as time limits for empiric or prophylactic therapy or policing of broad-spectrum antibiotic drugs for inappropriate indications. Also, pharmacists can ensure that antibiotic drugs are changed based on susceptibility results and ensure that therapy is appropriately individualized by adjusting dosage, drug class, or administration route. In an outpatient setting, pharmacists can promote the prudent use of antibiotic drugs for treating otitis media, sinusitis, and pneumonia. Furthermore, they can educate patients about the importance of compliance with antibiotic drug therapy to prevent subtherapeutic concentrations of antimicrobial drugs that provide an environment favorable for resistant organisms.

In the past decade, vancomycin commonly has been used for empiric treatment of resistant pneumococci. Vancomycin often is included as first-line empiric therapy for meningitis and pneumonia in hospitalized patients. In some institutions, patients with skin and soft tissue infection or suspected catheter infection often are at high risk of infection with a MRSA or methicillin-resistant *S. epidermidis* and vancomycin must be included in the empiric regimen. It is important that pharmacists help keep vancomycin as a viable option for treating gram-positive infections by preventing inappropriate use of this drug and discontinuing therapy when vancomycin is no longer necessary.

Active surveillance is essential to identify the reservoir for spread of MRSA and VRE infections. Countries that advocate a rigorous national approach to hospital infection control practices for VRE and MRSA have maintained lower rates of resistance in these organisms. Although there have been no reports of antibiotic control practices eradicating antibiotic-resistant organisms in health care facilities, efforts should be made to limit the use of inappropriate antibiotic drugs. Pharmacists can have a role in developing, implementing, and providing education about these infection control policies. Furthermore, once a patient is determined to be colonized with a resistant gram-positive organism, isolation of that patient and the use of standard precautions to prevent the spread of that strain are necessary.

Pharmacists must use isolation and barrier precautions to prevent the spread of gram-positive organisms, including the use of gloves and gowns when in contact with individuals colonized with these organisms. Hand hygiene by health care providers is essential in preventing nosocomial spread of these organisms. Data support the use of alcohol-based rubbing solutions, making compliance with hand hygiene easier. Health care providers also must be careful about handling environmental objects that also may be a source of colonization of resistant gram-positive organisms.

Conclusion

Infections with common gram-positive organisms have become more problematic to treat because of the growing trend of antibiotic drug resistance. As a result of widespread resistance to most common gram-positive pathogens, *S. pneumoniae*, *Staphylococcus* species, and *Enterococcus* species, antimicrobial resistance must be a consideration before initiating empiric antibiotic therapy.

With newly emerging resistant organisms, it is imperative that antibiotic drugs are used prudently. It is essential that antibiotic drugs are used only when necessary, so that unnecessary use does not result in the emergence of new antibiotic-resistant strains that are difficult or impossible to treat. Patients who are infected with MRSA, VISA, and VRE in the health care setting must be identified early and isolated to prevent the spread of resistant strains. If resistance to each of the major antimicrobial drug classes continue to elevate with these gram-positive pathogens, it is conceivable that adequate antimicrobial therapy for some strains will no longer be available.

Annotated Bibliography

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   Because *Streptococcus pneumoniae* is the most common pathogen in community-acquired pneumonia (CAP), it is necessary to consider antibiotic-resistant *S. pneumoniae* when making an empiric antibiotic drug choice. These guidelines from the Infectious Diseases Society of America provide a consensus based on the literature and offer recommendations for CAP therapy. Furthermore, the new breakpoints from the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical and Laboratory Standards) for cefotaxime and ceftriaxone for *S. pneumoniae* are reflected in these guidelines. In addition, because of the developing resistance to antibiotic drugs and new antimicrobial drugs, the committee that established these guidelines says new guidelines should be available every few years. Therefore, updated guidelines for CAP will be available on a regular basis. In addition, the next version will reflect a joint effort between the Infectious Diseases Society of America and the American Thoracic Society.

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principles when recommending drug therapy choices for treating sinusitis. In addition, the most common serotypes involved in sinusitis and resistance mechanisms among *S. pneumoniae* are summarized.

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   This paper reviews the problem of vancomycin-resistant *Enterococcus* (VRE) in health care institutions and hospitals. It includes a historical perspective summarizing all the factors associated with or leading up to the emergence and spread of antibiotic-resistant strains of enterococci. The authors provide an overview of the genetic changes that have occurred to confer drug resistance in enterococci and describe the mechanisms that pneumococci have developed to inactivate current antimicrobial drugs. Transmission methods and risk factors for acquiring VRE infections are summarized. In addition, techniques to prevent the emergence and spread of drug-resistant pneumococci are highlighted. Special emphasis is placed on coordinating surveillance programs for VRE in hospitals and methods for successfully screening patients are outlined.

4. American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatrics 2004;113:1451–65.

   These guidelines are a joint effort of the American Academy of Pediatrics and the American Academy of Family Physicians and provide recommendations for children 2–12 years of age for treating acute otitis media. Recommendations are provided for confirming the diagnosis of otitis media and evaluating if antibiotic drug therapy is necessary. Drug therapy recommendations are provided with special emphasis on resistant pneumococci. In addition, therapy failure is addressed. Special information regarding unsuccessful therapy and how to modify drug choices based on drug resistance with *S. pneumoniae* are covered. Furthermore, because otitis media can reoccur often in some children, suggestions based on review of the literature are provided to decrease the risk factors associated with recurrent acute otitis media.

5. Muto CA, Jernigan JA, Ostrowsky BE, et al. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and *enterococcus*. Infect Control Hosp Epidemiol 2003;24:362–86.

   This is an overview of infection control to prevent the emergence and spread of drug-resistant *Staphylococcus aureus* and *Enterococcus* infections. The authors included the published literature from 1966 to 2002 and relevant abstracts from unpublished studies. They discuss the genetic alterations that occur with drug resistance and also evaluate methicillin-resistant *Staphylococcus aureus* (MRSA) and VRE infections and the impact of clonal spread. In addition, mechanisms of transmission of drug-resistant strains are discussed, including the role of contaminated health care workers hands, clothes, equipment, and the environment. Methods to prevent the spread of antibiotic-resistant pathogens are addressed, and the authors provide recommendations based on findings from the literature. These recommendations include the use of active surveillance cultures to identify the reservoir for spread and the need for contact precautions to prevent spread, as well as the role of barrier precautions. In addition, the role of antibiotic control and antibiotic stewardship is covered. Cost-effectiveness in preventing MRSA and VRE infections also is presented. Finally, the authors discuss the need for educational programs directed at health care providers that stress the importance of antibiotic-resistant pathogens, and also offer methods to aid in education.

Abbreviations

Abbreviations

Please start new PSAP-V answer sheet before continuing.

SELF-ASSESSMENT QUESTIONS

Questions 1 and 2 pertain to the following case.
C.N. is a 41-year-old woman who has been in the surgical intensive care unit for 9 days after a motor vehicle accident. She had multiple bone fractures and a head injury. She was intubated and has had an intracranial pressure monitoring device since the accident. A urinary catheter, triple lumen catheter, central venous catheter, peripheral venous catheter, and a chest tube have all been placed. The patient was in critical but stable condition. Yesterday, her temperature increased to 104ºF and blood, urine, cerebrospinal fluid, and nasotracheal cultures were obtained. Until the temperature spike, C.N. had received several short courses of cefazolin for surgical prophylaxis. When she became febrile, the primary team changed the antibiotic drugs from cefazolin to ceftriaxone and levofloxacin. Today, preliminary cultures revealed *Staphylococcus aureus* in the nasotracheal and cerebrospinal fluid cultures and an *Enterococcus* species in the blood and urine. The patient has no known drug allergies.

1. Based on the available patient information, which one of the following choices should be included in the empiric antibiotic drug therapy that would treat both *S. aureus* and the *Enterococcus* species?
   A. Oxacillin.
   B. Daptomycin.
   C. Vancomycin.
   D. Quinupristin-dalfopristin.

2. Often, patients such as C.N. develop infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Which one of the following is the best explanation for the acquisition of the methicillin resistance determinant in *S. aureus*?
   A. Exposure to β-lactam antibiotic drugs allows for selection after a spontaneous mutation.
   B. *Staphylococcus aureus* growth in a biofilm in indwelling catheters allowing a favorable environment for spontaneous mutations to occur.
   C. Acquisition of an isolate with chromosomally encoded alteration to penicillin-binding protein (PBP) 2A called *mec* deoxyribonucleic acid (DNA).
   D. The acquisition of vanA or vanB determinants from enterococci.

Questions 3 and 4 pertain to the following case.
T.C. is a 64-year-old man who has been in the intensive care unit for 6 weeks with a complicated history of a bowel perforation. Since admission, he has had multiple abdominal surgeries and he has received several courses of antibiotic drugs, including cefotetan, meropenem, vancomycin, and levofloxacin. His surgical wound cultures have grown MRSA on two separate occasions 3 weeks apart, in addition to *Escherichia coli*. He has received vancomycin therapy continuously for the past 4 weeks. Yesterday, he again went to surgery and an intraoperative abdominal culture was obtained that was confirmed positive today for vancomycin-resistant *Enterococcus faecium*.

3. Which one of the following options is the best for empirically treating the *E. faecium* infection in T.C.?
   A. Vancomycin plus gentamicin.
   B. Linezolid.
   C. Moxifloxacin.
   D. Ampicillin plus gentamicin.

4. Which one of the following risk factors is the most likely reason that T.C. developed an infection with vancomycin-resistant *Enterococcus* (VRE)?
   A. Infection with MRSA.
   B. Bowel perforation.
   C. Vancomycin use.
   D. Multiple abdominal surgeries.

Questions 5–7 pertain to the following case.
J.D. is an 80-year-old man with a history of seizures, congestive heart failure, hypertension, chronic obstructive

pulmonary disease, and alcoholism. He went to the clinic with complaints of shortness of breath and generalized weakness. His temperature was 103°F and blood pressure was 140/80 mm Hg when sitting and 105/78 mm Hg when standing. Physical examination revealed decreased breath sounds, rales, and egophony. In addition, nasal flaring and dry mucus membranes were noted. J.D. had completed 5 days of azithromycin 2 days before this clinic visit for similar respiratory symptoms with little improvement. The physician decided to admit J.D. to the university hospital. Sputum Gram's stain and blood cultures were obtained. Several hours later, the Gram's stain from the sputum culture identified gram-positive diplococci and *Streptococcus pneumoniae* pneumonia was suspected.

5. Based on the available patient information, which one of the following is the best recommendation for empiric treatment of community-acquired pneumonia (CAP) in J.D.?
   A. Doxycycline.
   B. Gatifloxacin.
   C. Gatifloxacin plus azithromycin.
   D. Piperacillin-tazobactam plus gentamicin.

Two days later, the susceptibility test results for the *S. pneumoniae* strain became available and it was resistant to penicillin and erythromycin. In addition, J.D. improved dramatically and he was ready to be discharged from the hospital. The attending physician on the health care team just returned from a seminar discussing pharmacodynamics, and he was convinced that concentration-dependent drugs are more effective than time-dependent drugs for treating pneumococcal CAP. Although you disagree with his conclusion, he still wants your recommendation for an orally available antibiotic drug that is concentration-dependent.

6. Which one of the following classes of antibiotic drugs has an oral dose form that has concentration-dependent activity that can be used to treat *S. pneumoniae* CAP?
   A. Macrolides.
   B. Fluoroquinolones.
   C. β-Lactams.
   D. Tetracyclines.

7. *Streptococcus pneumoniae* antibiotic resistance, similar to what is present in the pneumococcal strain causing J.D.'s pneumonia, has increased dramatically in the past 15 years. Which one of the following is the most important reason for the increased resistance that has been observed with *S. pneumoniae*?
   A. Inappropriate antibiotic drug use.
   B. More children attending day care centers in the past 15 years.
   C. Antibiotic-resistant strains are more virulent.
   D. Clonal spread of drug-resistant strains.

Questions 8–10 pertain to the following case.
J.W. is a 32-year-old woman with chronic idiopathic intestinal pseudo-obstruction requiring chronic total parenteral nutrition for more than 10 years. She has a history of recurrent MRSA bacteremia and MRSA colonization. She was admitted again with fever, chills, and abdominal pain. The blood Gram's stain showed gram-positive cocci in clusters. Vancomycin therapy was initiated. J.W. has poor venous access because of the frequent need for central catheters in the past, and now the medical team is reluctant to remove the catheter for fear of losing intravenous access. Two days later, the culture is confirmed to be MRSA and she continues to be bacteremic despite vancomycin therapy. The *S. aureus* strain is susceptible to vancomycin and linezolid.

8. Based on the available information, which one of the following choices is the best choice to treat J.W.'s catheter-related bacteremia?
   A. Remove the catheter and continue vancomycin.
   B. Keep the catheter in place and start vancomycin and linezolid.
   C. Keep the catheter in place and start linezolid.
   D. Remove the catheter and start vancomycin and linezolid.

9. J.W.'s therapy was successful, and now the team wants to prevent recurrence of the MRSA catheter-related infection. Which one of the following is the most effective method to prevent future catheter-related infections with resistant gram-positive organisms?
   A. All health care providers in contact with J.W. should wash their hands and remove any contaminated clothing.
   B. Screen J.W. for VRE.
   C. Use vancomycin solutions to flush J.W.'s catheter after each use.
   D. Do whole-body MRSA decolonization in J.W.

10. Which one of the following is the factor most likely to increase J.W.'s the risk of developing a vancomycin-resistant *Staphylococcus aureus* (VRSA) infection?
    A. Colonization with VRE.
    B. Long-term vancomycin use.
    C. Continuous need for intravenous catheter.
    D. Chronic idiopathic intestinal pseudo-obstruction.

Questions 11–13 pertain to the following case.
S.W. is a 12-month-old girl who was taken to University Family Medicine Clinic 2 days ago with a fever, irritability, and pulling on her ears. She had bilateral middle ear effusions, and amoxicillin (45 mg/kg/day in two dosages) was prescribed because of success in treating previous episodes of otitis media at 6 and 12 months of age. A tympanocentesis was performed when S.W. was 8 months old and *S. pneumoniae*, susceptible to all antibiotic drugs, was cultured from the inner ear. Today, she goes to the clinic with little improvement in her symptoms and her left ear is full of purulent material and is actively draining. The right ear still shows an effusion and and otitis media caused by *S. pneumoniae* with reduced susceptibility to penicillin suspected.

11. Which one of the following antibiotic drugs is the best therapy to treat *S. pneumoniae* otitis media?
    A. High-dose amoxicillin (95 mg/kg/day).
    B. Trimethoprim-sulfamethoxazole.
    C. Azithromycin.
    D. Amoxicillin-clavulanate.

12. Macrolide resistance in *S. pneumoniae* commonly occurs in children such as S.W. If the *S. pneumoniae* isolate in S.W. were macrolide-resistant, which one of the following gene mutations is the most likely explanation to confer macrolide resistance in S.W.?
    A. Efflux-mediated mutation encoded by *ermB*.
    B. Efflux-mediated resistance encoded by *mefA*.
    C. Efflux-mediated resistance by pmrA.
    D. Target site mutation in the PBP2A.

13. Several recommendations can be given to S.W.'s parents to try to decrease the risk factors for addition infections with *S. pneumoniae*. Which one of the following is the most helpful at reducing the risk of future otitis media infections?
    A. Bottle feed in the supine position (bottle propping).
    B. Administer the influenza vaccine.
    C. Put the child in a day care center.
    D. Use a pacifier in this patient.

Questions 14 and 15 pertain to the following case.
L.B. is 72-year-old woman who was found with an altered level of consciousness by family members and admitted to the hospital. The family member who last spoke to L.B. 2 days earlier stated that she was complaining of a severe headache. The patient has a history of hypertension, congestive heart failure, and diabetes. Cerebrospinal fluid was obtained and the Gram's stain showed gram-positive cocci. Vancomycin and ceftriaxone therapy was initiated. After 2 days of therapy, there was little improvement in L.B.'s condition. She was nonresponsive and remained febrile. Cerebrospinal fluid culture was confirmed to be *S. pneumoniae*, and the following susceptibility results were made available to the team.

Penicillin-intermediate	Vancomycin-susceptible
Erythromycin-resistant	Clindamycin-resistant
Trimethoprim-sulfamethoxazole-resistant	Cefotaxime-susceptible
Tetracycline-resistant	Levofloxacin-susceptible
Quinupristin-dalfopristin-resistant	

14. Based on the available information, which one of the following is appropriate therapy for L.B. at this time?
    A. Vancomycin and ceftriaxone.
    B. Ceftriaxone.
    C. Levofloxacin.
    D. High-dose ampicillin.

15. Based on the previously discussed susceptibility results, which one of the following gene mutations is most likely present in the *S. pneumoniae* strain that is causing L.B.'s meningitis?
    A. *mefA*.
    B. *gyrA*.
    C. *ermB*.
    D. *rpoB*.

16. J.C. is a 21-year-old man who was admitted to the hospital with abscesses on his face, forearm, and medial thigh. These abscesses are purulent and he has substantial swelling in the affected areas. The patient has a 12-year history of diabetes, is an intravenous drug abuser with methamphetamine and cocaine, and is homeless. His diabetes has been poorly controlled and his hemoglobin A1c is 13%. One month before this admission, he was seen in the emergency department for an infected pimple on his right chin which caused significant facial pain and swelling. J.C. was successfully treated with a 10-day course of oral amoxicillin-clavulanate. Based on this history, which one of the following antibiotic drugs should be included in the initial empiric regimen for this hospital admission?
    A. Ampicillin-sulbactam.
    B. Cefazolin.
    C. Oxacillin.
    D. Vancomycin.

17. Which one of the following statements best characterizes the differences observed between community- and institution-associated MRSA infections?
    A. Patients infected with community-associated MRSA strains typically are older and have several underlying medical conditions compared to institution-associated strains.
    B. Community-associated MRSA is a result of spread of institution-associated strains.
    C. Institution-associated strains are more virulent than community-associated MRSA strains.
    D. Community-associated MRSA isolates typically are more likely to be susceptible to multiple antimicrobial drug classes compared to institution-associated strains.

Questions 18–20 pertain to the following case.
J.J. is a 26-year-old woman with a history of recurrent urinary tract infections. She is a transplant intensive care unit nurse at the university hospital. Three weeks ago, she became sexually active again and within a week she had symptoms of a urinary tract infection. She reported urgency, painful urination, and frequency of urination. She was afebrile. She called her physician and he prescribed trimethoprim-sulfamethoxazole, which had worked in the past with similar episodes. She took the drug for 7 days with slight improvement in symptoms, but never resolution. Two days after she finished the trimethoprim-sulfamethoxazole, she had worsening symptoms and again

called her physician. At that time, he had her come to the office for a urinalysis and urine culture. He then prescribed levofloxacin, pending the culture results. The identification and susceptibility results from her urine culture are:

Organism: *Enterococcus faecium*

Ampicillin-resistant	Nitrofurantoin-susceptible
Ciprofloxacin-resistant	Vancomycin-resistant
Trimethoprim-sulfamethoxazole-resistant	Linezolid-susceptible

18. Which one of the following antibiotic drugs should J.J. receive to treat her *E. faecium* urinary tract infection?
    A. Continue levofloxacin.
    B. Nitrofurantoin.
    C. Linezolid.
    D. Amoxicillin-clavulanate.

19. Colonization with vancomycin-resistant *E. faecium* typically occurs before infection with that organism. Therefore, which one of the following methods is the most probable method by which J.J. became colonized with vancomycin-resistant *E. faecium*?
    A. Exposure to trimethoprim-sulfamethoxazole allowed for selection of VRE.
    B. The acquisition of vanA resistance determinant from *S. aureus*.
    C. Person-to-person spread.
    D. Chromosomally encoded alteration to PBP5 from a plasmid in *Staphylococcus aureus*.

20. Ideally, J.J. would not want to harm any of the critically ill patients she cares for in the transplant intensive care unit. If J.J. continued to care for patients, which one of the following precautions is the most successful at preventing the spread of vancomycin-resistant *E. faecium* to her patients?
    A. Not to care for patients receiving vancomycin.
    B. Good hand hygiene.
    C. Wearing gown.
    D. Wearing a mask.

21. S.B. is a 59-year-old woman with end-stage renal failure on hemodialysis. She has had multiple catheter infections and the most recent was 5 weeks ago caused by MRSA (vancomycin minimum inhibitory concentration [MIC] = 0.5 mcg/ml). S.B. improved after receiving vancomycin and gentamicin for 3 weeks. For the past 2 weeks, she also received vancomycin after dialysis for prophylaxis of infection. Three days ago, S.B. became febrile. Blood cultures were obtained and were identified to be MRSA. Vancomycin and gentamicin were again started. S.B. has experienced little improvement, she is still febrile, and this morning she became hypotensive and was transferred to the intensive care unit. Her blood Gram's stain shows gram-positive cocci in clusters. Susceptibility results are:

Organism: *Staphylococcus aureus*

Trimethoprim-sulfamethoxazole-susceptible	Quinupristin-dalfopristin-susceptible
Penicillin-resistant	Rifampin-susceptible
Erythromycin-resistant	Gentamicin-resistant
Vancomycin MIC = 4 mcg/ml	Daptomycin-susceptible
Oxacillin-resistant	Clindamycin-resistant

Based on the available information, which one of the following choices is the best option for treating this MRSA strain with reduced susceptibility to vancomycin?
    A. Vancomycin and gentamicin.
    B. Trimethoprim-sulfamethoxazole.
    C. Continue vancomycin monotherapy.
    D. Rifampin.

22. G.K. is a 20-year-old, 140-kg man who was admitted to the intensive care unit 5 weeks ago after a motor vehicle accident. He had multiple injuries and has remained in a coma since admission. He has been intubated and had several courses of antibiotic drugs, including ceftriaxone, levofloxacin, and imipenem, for a nosocomial pneumonia in which no pathogen was identified. Seven days ago, G.K. also became bacteremic and MRSA grew from multiple blood cultures. An echocardiogram of the heart ruled out endocarditis. Vancomycin and gentamicin therapy was initiated. Serum drug concentrations were obtained and the gentamicin concentrations were in the desired range; however, the initial vancomycin trough concentration was 3.4 mcg/ml. Despite subsequent dosage increases, the vancomycin trough concentrations for the past week have remained less than 7 mcg/ml. The vancomycin dose was again increased and this morning the trough concentration was 12 mcg/ml. Despite drug therapy, G.K. has remained febrile and his blood cultures continue to grow gram-positive cocci in clusters. Heterogeneous vancomycin-intermediate *Staphylococcus aureus* (VISA) or VISA is suspected. The *S. aureus* strain is being sent to another laboratory for confirmation of resistance. Until the susceptibility results are available, which one of the following is the best treatment option for G.K.?
    A. High-dose vancomycin (trough concentrations more than 10 mcg/ml).
    B. Vancomycin and rifampin.
    C. Quinupristin-dalfopristin.
    D. Linezolid.

23. G.S. is a 55-year-old woman who is neutropenic and had an allogenic bone marrow transplantation 10 days ago. She developed a fever 2 days ago. Blood and

urine cultures were obtained. Cefepime was empirically started. Yesterday, the Gram's stain revealed gram-positive cocci in the urine. Vancomycin was then added to the empiric therapy. Today, the urine culture revealed *E. faecium*, which was resistant to vancomycin. This morning, G.S. became hypotensive and was transferred to the intensive care unit. Urosepsis from vancomycin-resistant *E. faecium* is suspected. Which one of the following antibiotic drugs is the best therapy for G.S.?

A. Linezolid.
B. Quinupristin-dalfopristin.
C. Nitrofurantoin.
D. Chloramphenicol.

24. W.B. is a 36-year-old woman who has worked full-time at a day care center for the past 4 years. She had a sinus infection for 10 days, and azithromycin was started 3 days ago. She has a history of about one to two pneumococcal sinus infections every year since she started working at the day care center, and azithromycin has always been effective for treating the previous sinus infections. However, there has been no improvement in her symptoms with this infection and macrolide-resistant pneumococcal sinusitis is suspected. Which one of the following antibiotic drugs is the best choice for W.B. to treat macrolide-resistant pneumococcal sinusitis?

A. Levofloxacin.
B. Cefixime.
C. Doxycycline.
D. Telithromycin.

Abbreviations