Antibiotic Resistance, Part 1: Gram-positive Pathogens

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ABSTRACT

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

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

INTRODUCTION

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

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

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

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

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

ANTIBIOTIC MECHANISM OF ACTION

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

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

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

[a] Refer to Tenover.[2]

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

MECHANISMS OF RESISTANCE

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

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