Antimicrobial resistance in bacterial pathogens

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One of the most challenging aspects of infectious diseases is the recent emergence of several bacterial pathogens that are resistant to conventional antibiotic therapy. In some cases, no viable options for treatment are available. This article provides an overview of the factors contributing to the emergence of resistance, the mechanisms involved in the development of resistance, and some specific issues related to certain pathogens.

An increasing problem in the practice of infectious diseases is the emergence of multiple bacterial species that are resistant to currently available antimicrobial agents. Many factors are responsible for the emergence of resistant organisms. These factors generally fall into 2 categories—indiscriminate antibiotic use and an increasing at-risk population. Antibiotic use in animal husbandry and agriculture, public pressure on physicians for antibiotic treatment of viral illnesses, and inappropriate antibiotic use contribute to the selection of antibiotic-resistant genes among essentially all bacterial pathogens. Likewise, the increase in immunosuppressed patients (e.g., due to acquired immunodeficiency syndrome, transplantation, or chemotherapy) and the increasing longevity of patients with chronic debilitating illnesses (i.e., those necessitating repeated hospitalization and rounds of antibiotic courses) increase relative susceptibility. In addition, congregate facilities, such as hospitals, nursing homes, and day care centers, serve as reservoirs for multidrug-resistant bacteria (1).

MECHANISMS OF RESISTANCE

Acquired resistance, as opposed to intrinsic resistance, is the result of a change in the bacterial genome so that a drug that originally was effective in vivo is no longer active. General mechanisms of resistance fall into 1 of 4 categories: 1) decreased intracellular drug concentration, 2) drug inactivation, 3) target modification, or 4) target bypass. Intracellular drug concentration can be minimized by increased efflux of an antibiotic from a bacterial cell, such as Escherichia coli’s tetracycline efflux system or Staphylococcus aureus’ efflux system for fluoroquinolones. Decreased permeability of the bacterial outer membrane can result in lessened intracellular antibiotic concentration, such as the alterations in outer membrane porin proteins of Pseudomonas aeruginosa conferring resistance to β-lactam agents, imipenem and possibly fluoroquinolones and aminoglycosides. An additional mechanism contributing to diminished intracellular drug concentration is decreased uptake by the bacterial cytoplasmic membrane, as seen in some aminoglycoside-resistant staphylococcal species (2).

Induction of inactivating enzymes is the predominant mechanism of bacterial resistance to several major antibiotic classes. Examples of this phenomenon include b-lactamase
production, production of aminoglycoside- or macrolide-modifying enzymes, and elaboration of chloramphenicol-inactivating enzymes.

Target modification, a prominent mechanism of resistance, is used by a large number of bacterial species against a wide array of antibiotic agents. Modification may range from a single mutation, to a multisequence event, to major alterations achieved by the incorporation of foreign DNA. Modification of penicillin-binding proteins is the mechanism of resistance used by penicillin-resistant pneumococcus, Neisseria meningitidis, and Enterococcus fecium, and by methicillin-resistant S. aureus. Modification of the genes for DNA gyrase confers fluoroquinolone resistance, and various ribosomal alterations contribute to macrolide, tetracycline, rifampin, and mupirocin resistance.

The most elaborate mechanism of resistance results in the development of alternate metabolic pathways, resulting in primary target bypass. Examples of this mechanism include enterococcal and staphylococcal vancomycin resistance and various bacterial pathogens’ resistance to the folate antagonists.

Specific pathogens

Antibiotic-resistant pneumococci

Streptococcus pneumoniae is a major cause of morbidity and mortality worldwide. Once exquisitely sensitive to penicillin, highly antibiotic-resistant pneumococci began surfacing in reports from South Africa in the late 1970s (3). Degrees of resistance are defined by the minimum inhibitory concentration (MIC) of penicillin required for bacteriostasis. A pneumococcal strain is “sensitive” if the penicillin MIC is <0.1 mg/mL, “intermediate” if the MIC is 0.1 to 1 mg/mL, and “highly resistant” if the MIC is >2 mg/mL (2). In the USA, highly penicillin-resistant strains are estimated to occur in approximately 30% of pneumococcal isolates. Factors associated with colonization and infection with highly resistant pneumococci include age <6 years, participation in day care, contact with a child carrier, previous antibiotic treatment, immunosuppression, presence of debilitating disease, and certain pneumococcal serotypes (1). Penicillin resistance is conferred by alteration in the genes encoding for the pneumococcus’ 5 high-molecular-weight penicillin-binding proteins (2, 3). This generally also will confer resistance to the first- and second-generation cephalosporins, but many isolates are susceptible to the third- and fourth-generation cephalosporins. Most are sensitive to imipenem as well. Many are also resistant to erythromycin, the other macrolides, tetracyclines, and trimethoprim-sulfamethoxazole. Resistance to chloramphenicol, rifampin, and clindamycin has been described but is rare in the USA (2, 4). The penicillin-resistant pneumococci remain universally sensitive to vancomycin, and although S. pneumoniae has intrinsic resistance to many of the older fluoroquinolones, some of the newer agents, including levofloxacin, have excellent activity against penicillin-resistant strains. In addition, appropriate use of the pneumococcal vaccine may prevent many cases of invasive pneumococcal disease (1).

Vancomycin-resistant enterococci

Emergence of vancomycin-resistant enterococci (VRE) as nosocomial pathogens in the 1990s has served to heighten awareness of the threat posed by multidrug-resistant bacteria.
Incidence of VRE isolates reported by the National Nosocomial Infections System increased from <1% in 1989 to 8% by 1993. Overall, enterococci are the second most common cause of nosocomial infection in the USA (1, 2). The organisms are very hardy, surviving on hospital environmental surfaces as well as on the hands and in the gastrointestinal tract of health care personnel. Enterococci are intrinsically resistant to a number of commonly used antibiotics, including semisynthetic penicillins, all cephalosporins, and clindamycin, and are tolerant to penicillin and vancomycin alone. Until the emergence of multidrug-resistant enterococci, a bactericidal effect was generally achieved by the combination of a penicillin or vancomycin plus an aminoglycoside.

Although low-level ampicillin resistance occurs in the community, high-level penicillin, aminoglycoside, and glycopeptide (vancomycin and teicoplanin) resistance usually is seen in the hospital setting. The increase in glycopeptide resistance follows the marked increase in vancomycin use as methicillin-resistant S. aureus (MRSA) became established in the 1980s. In addition, the overuse of oral vancomycin for pseudomembranous enterocolitis is thought to have markedly increased the development of enterococcal vancomycin resistance (3). Risk factors for VRE colonization and infection include prior broad-spectrum antibiotic therapy, particularly intravenous or oral vancomycin use; prolonged hospitalization, particularly in the intensive care unit; end-stage renal disease; and immunosuppression (5).

The primary method of enterococcal resistance to penicillin involves alteration of the penicillin-binding proteins on the bacterial cell surface, thus producing less affinity for the penicillins. Less frequently, enterococci may produce ß-lactamases as well. Either ribosomal alterations or production of aminoglycoside-modifying enzymes confers high-level aminoglycoside resistance. Glycopeptide resistance is the most mechanistically complex. Glycopeptides work by interfering with cell wall synthesis by blocking a target on a cell wall constituent precursor. Resistance ultimately results in continued cell wall synthesis along an alternate pathway, bypassing the precursor molecule (2).

Currently, there are no Food and Drug Administration-approved alternatives for the treatment of multidrug-resistant enterococci. Occasionally, multidrug-resistant enterococci may be bacteriostatically susceptible to tetracycline, chloramphenicol, fluoroquinolones, novobiocin, and rifampin. Two experimental antibiotics, dalfopristin–quinupristin (Synercid) and linezolid, are available on a compassionate basis. Unlike MRSA, there is no evidence that the carrier state can be eliminated (1). Strict infection control measures, including contact isolation as well as restriction of vancomycin use, are crucial in containing the spread of VRE.

**Methicillin-resistant staphylococci**

Use of the semisynthetic penicillins against staphylococci in the 1960s was rapidly followed by the first outbreaks of MRSA. Current estimates of MRSA in large teaching hospitals approach 40% of S. aureus isolates (2). The majority of staphylococci are also resistant to erythromycin, tetracycline, and clindamycin. Resistance to the fluoroquinolones and mupirocin is becoming increasingly common (6). Methicillin resistance is controlled by a single genetic mutation (mecA gene) that is shared by both coagulase-positive and coagulase-negative staphylococci, resulting in the overproduction of a single, low-affinity,
Management of MRSA infections include strict infection control policies, including contact isolation. In contrast to VRE, there is evidence that oral/topical antibiotics can eliminate the carrier state (1). Methicillin-resistant staphylococci infections generally are treated with intravenous vancomycin. Alternatives may include fluoroquinolones plus rifampin, trimethoprim-sulfamethoxazole, or minocycline. Although vancomycin resistance among staphylococci has been described in vitro for several years, the recent isolation of vancomycin-resistant S. aureus from a hospitalized patient is an ominous sign.

**Multidrug-resistant gram-negative bacilli**

Enteric gram-negative rods (GNRs) began to emerge as major pathogens in the 1950s and 1960s. Subsequently, new classes of \(\beta\)-lactams were introduced to contain these organisms. However, the GNRs have developed increasingly more sophisticated mechanisms of resistance to overcome newer agents. The predominant mechanism of resistance of the GNRs hinges on the production of \(\beta\)-lactamase (1). Many GNRs produce \(\beta\)-lactamase that renders the extended spectrum penicillins and even third-generation cephalosporins inactive; however, new patterns of \(\beta\)-lactam resistance are emerging. Resistance to the \(\beta\)-lactamase inhibitors (sulbactam, clavulanate, tazobactam) has been described (2). This is accomplished via a variety of mechanisms, including overproduction of \(\beta\)-lactamase, by bacterial outer membrane permeability changes, or by \(\beta\)-lactamase mutations that render the enzyme immune to \(\beta\)-lactamase inhibitors. Although most of these GNRs were initially susceptible to imipenem, imipenemases in Stenotrophomonas maltophilia, Pseudomonas cepacia, and other gram-negative rods have been reported. Furthermore, outer membrane permeability changes as well as \(\beta\)-lactamase overproduction have also contributed to imipenem resistance. Additionally, aminoglycoside resistance secondary to production of aminoglycoside-modifying enzymes, trimethoprim-sulfamethoxazole resistance, and fluoroquinolone resistance are increasingly problematic (2).

**CONTROL MEASURES**

Infection control measures are critical in controlling the spread of antibiotic resistance among microorganisms. Goals of infection control include optimal use of antibiotic therapy, including appropriate perioperative prophylaxis, minimal effective duration of treatment, and limiting the use of vancomycin and broad-spectrum antimicrobials to appropriate clinical scenarios. In addition, development of an epidemiological plan to detect and report organisms is of primary importance. Perhaps the most important goal is to increase adherence to basic infection control policies and procedures. These include isolating colonized or infected patients, grouping patients and staff, using gloves and gowns appropriately, providing single-patient-use noncritical equipment, disinfecting the environment properly, and fully incorporating the most current laboratory techniques to detect antibiotic-resistant organisms. Finally, the single most important and effective infection control technique is, as it was in Simmelweiss’ time, the simple act of handwashing.
References


