

## LEARNING OBJECTIVES

- Outline the epidemiology of antimicrobial resistance and common mechanisms of resistance
- Describe factors that contribute to antimicrobial resistance
- Recognize the clinical impact of resistance
- Describe interventions aimed at reducing resistance and the effectiveness of these strategies

# Antibiotic resistance: The ongoing challenge for effective drug therapy

The abilities to evolve and exchange DNA are unique survival tactics used by bacteria. Overcoming these mechanisms is a clinical challenge for the 21st century.

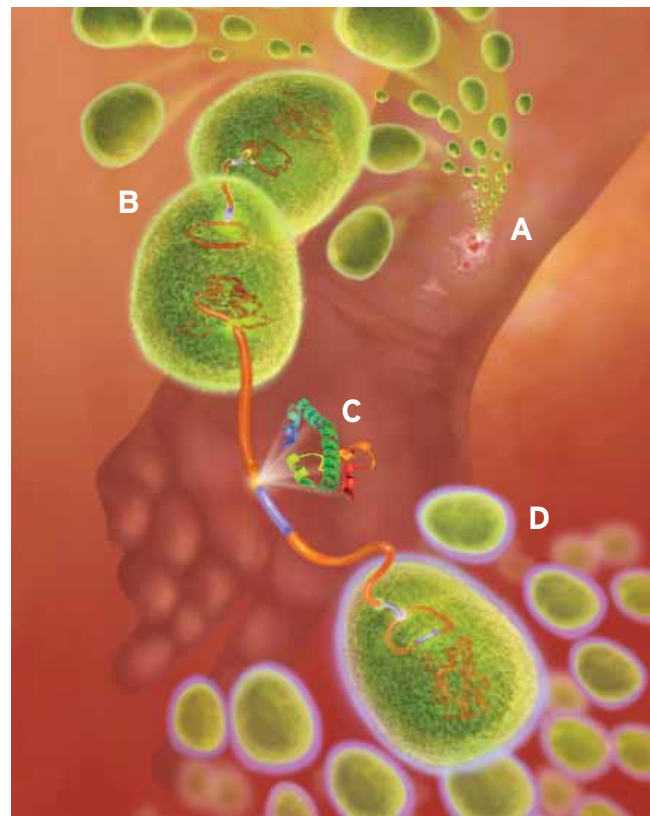
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*Antibiotic resistance is an increasingly common problem that complicates the treatment of both community-acquired and nosocomial infections. A series of three articles reviews this serious health threat, explains why the challenge is never-ending, and offers possible solutions. In this article, the author discusses the factors that contribute to antimicrobial resistance and the mechanisms that bacteria use to achieve resistance. The second and third installments of this series will appear in the April and May issues, respectively.*

**A**ntibiotic resistance is the ability of bacteria to oppose the inhibitory (bacteriostatic) or killing (bacteriocidal) effects of antibiotics. Antibiotic resistance has increased dramatically in the past 15 years and presents a threat to the successful treatment of bacterial infections. Antimicrobial resistance increases morbidity, mortality, length of hospital stay, and health care costs. These adverse outcomes may be the result of the ineffectiveness of antibiotics or a delay in therapy caused by antimicrobial resistance.<sup>1</sup>

In 1928, Alexander Fleming isolated penicillin from the fungus *Penicillium notatum*. However, biochemists were not able to isolate, purify, and manufacture penicillin until 11 years later. The pharmaceutical industry rose to the challenge of identifying molds, testing the chemicals produced, and, eventually, mass producing antibiotics. Antibiotics saved many lives and transformed medicine.

By 1943, penicillin was widely available and demand for the drug grew. Antibiotics were seen as miracle drugs, and patients developed a generalized expectation for a rapid cure. Even minor illnesses, previously handled by the body's own defenses, were treated with these miracle drugs. Unfortu-



A hidden threat to antibiotic effectiveness is demonstrated by methicillin-resistant *Staphylococcus aureus* infection (A). DNA are transferred from the plasmid of one bacterium to another (B), and resistance information can be relayed to the DNA of nonresistant bacteria (C). The result is indirect exposure to antibiotics that increases antimicrobial resistance (D).

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nately, widespread use of antibiotics led to a selection of resistant bacteria.<sup>2</sup> Interestingly, Alexander Fleming predicted this event in 1945.

*“But I would like to sound one note of warning.... It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.”<sup>3</sup>*

### EPIDEMIOLOGIC FACTORS

Bacteria adapt to the presence of antibacterial agents in their environment in order to survive. Therefore, resistant *Staphylococcus aureus* emerged soon after penicillin was in wide use.<sup>4</sup> Sulfonamides, a class of synthetic antimicrobial drugs, were introduced in the 1930s, and resistance to sulfa in *Streptococcus pyogenes* (group A beta-hemolytic streptococci [GABHS]) rapidly emerged.<sup>5</sup>

Drug-resistant strains initially appeared in hospitals, where utilization of antibiotics was greatest. However, resistant bacteria also became a serious problem in the community as well, in particular the appearance of ampicillin-resistant *Haemophilus influenzae* and *Neisseria gonorrhoeae* (see Table 1, page 20). Multidrug-resistant (MDR) bacteria were detected in the late 1950s and early 1960s. Enteric gram-negative bacilli—*Escherichia coli*, shigella, and salmonella—were the first MDR bacteria identified.<sup>2</sup>

The origins of bacterial resistance are important when considering the causes of and the means for curtailing resistance. Scientists believe that bacteria probably contain a low level of genetic resistance for protection against exposure of naturally occurring antibiotics produced by other microorganisms in the environment.<sup>6</sup> Resistant bacterial genes increased in number and became more diverse when man-made antibiotics were used to treat and prevent disease.

In addition to rapidly multiplying, bacteria continuously exchange genetic material, thereby acquiring resistant genes from other microbes. Genes for antibiotic resistance are found within the bacterial chromosomal DNA, but many genes that confer antibiotic resistance are found on mobile genetic elements such as plasmids. *Plasmids* are naturally occurring, circular, self-replicating strands of DNA that exist outside of the bacterial chromosome. Bacteria can transfer their plasmids to other bacteria, including those of different

taxonomic groups. When a bacterium containing a plasmid with a resistant gene (or genes) transfers this plasmid, the recipient bacterium now also has resistance. The process of transfer continues, and an exponential increase in resistant strains occurs as bacteria multiply. Resistance also can be acquired by mutation or by acquisition of new DNA. Spontaneous mutation occurs much less frequently than does acquisition of resistant plasmids; therefore, plasmid-mediated resistance is a more significant clinical problem. In addition to plasmids, bacteria acquire foreign DNA with resistant genes from bacteriophages, naked sequences of DNA, and transposable genetic elements.

Antibiotic usage did not create resistant genes but has led to an increased number of resistant genes and resistant bacteria.<sup>7</sup> Common bacteria now have combinations of genes that enable resistance to multiple antibiotics. These resistant bacteria have a selective advantage. Antibiotics are also used to treat infectious diseases in animals and plants; this widespread use further expands the environment in which bacteria are exposed to antibiotics. Additional factors that contribute to the development of resistance include unnecessary antibiotic use in people, incorrect dosing regimens, and failure to complete antibiotic treatment courses; exposure to antimicrobial soaps and solutions is also a possible factor.<sup>8</sup>

### MECHANISMS OF RESISTANCE

A randomized, controlled trial published in 2007 demonstrated the rapid buildup of resistance following antibiotic administration.<sup>9</sup> The study investigated the effect of antibiotic exposure on oral streptococcal flora in 224 healthy persons who were given azithromycin, clarithromycin, or a placebo. Pharyngeal cultures were obtained at spaced intervals during 180 days of antibiotic administration. The proportion of macrolide-resistant streptococci was significantly increased in persons given either of the macrolides compared with the proportion in persons given the placebo at all points studied. The highest number of resistant organisms was seen 1 day after the drug course was completed. Resistance at this point was approximately 50%; 6 months later, the percentage of sensitive streptococci had still not returned to baseline. This study demonstrated that antibiotic administration affects not only the intended pathogen but also the normal flora. This

### KEY POINTS

- Bacteria multiply rapidly and continually exchange genetic material, which allows them to acquire resistant genes from other microbes. Genes for antibiotic resistance can be found within the bacterial chromosomal DNA, but many genes that confer antibiotic resistance are found on mobile genetic elements such as plasmids.
- The main mechanisms of antibiotic resistance are enzymatic inactivation, decreased uptake, increased removal, and alteration of target sites. These mechanisms are not mutually exclusive, and resistant bacteria most likely use multiple mechanisms concurrently.
- Antibiotic sensitivity patterns vary geographically in the United States; therefore, empiric therapy should be based on local summary tables, or antibiograms. A typical antibiogram displays the total number of bacterial isolates tested against a range of antimicrobials and includes the percentage of bacterial isolates susceptible to or resistant to each antimicrobial agent tested.
- The goal is to administer sufficient antibiotic to eradicate the pathogen and prevent recurrence, but not so much antibiotic that resistance develops from exposure after the pathogen is eliminated. Unfortunately, this ideal duration is often not known. The trend is for shorter courses of antibiotic with duration of therapy based on the time the patient takes to achieve clinical stability.

commensal flora can then act as a reservoir of resistance and pass resistant genes to potentially pathogenic bacteria.<sup>9</sup>

Antibiotic exposure allows bacteria to develop novel mechanisms for overcoming the effects of antimicrobials. The main mechanisms of antibiotic resistance are enzymatic inactivation, decreased uptake, increased removal, and alteration of target sites.<sup>10</sup> These mechanisms are not mutually exclusive, and resistant bacteria most likely use multiple mechanisms concurrently.<sup>11</sup>

**Enzymatic inactivation** Some bacteria produce enzymes that are able to inactivate or destroy a particular antibiotic. For example, beta-lactamases are bacterial enzymes that split the beta-lactam ring of penicillin antibiotics, cephalosporins, carbapenems, and monobactams. Narrow-active enzymes are active against only a specific antibiotic; extended-spectrum beta-lactamases are resistant to multiple antibiotics.<sup>10</sup>

**Antibiotic uptake reduction** Genetic mutations decrease membrane and cell wall permeability to antibiotics. These mutations occur frequently in gram-negative bacteria and resistance to beta-lactam antibiotics, aminoglycosides, chloramphenicol, and tetracycline may be partially attributed to the decreased uptake.<sup>10</sup>

**Increased antibiotic removal** Active drug efflux pumps transport antibiotics away from bacteria. Multidrug efflux pumps prohibit the effectiveness of tetracycline and the macrolides.<sup>10</sup>

**Alteration of bacterial target sites** A change in the ribosomal binding site (or sites) results in the inability of antibiotics to interfere with bacterial cell growth. This mechanism is used for resistance to a wide range of antimicrobial agents including beta-lactams, macrolides, tetracyclines, fluoroquinolones, aminoglycosides, sulfonamide, and vancomycin.<sup>10</sup>

**CLINICAL CONSIDERATIONS**

The rise in antibiotic resistance by many human pathogens has implications for clinical practice and poses challenges for the health care provider. Choosing empiric therapy is

“The trend is for shorter courses of antibiotic with duration of therapy based on the time the patient takes to achieve clinical stability.”

increasingly difficult as pathogens that once were controlled by certain antibiotics are now resistant to these therapies. In order to effectively treat infectious diseases in the future, clinicians must actively limit the emergence of antibiotic resistance and its spread. Evaluation and treatment methods may need to be changed, such as using diagnostic tests to accurately identify pathogens, administering an effective narrow-spectrum antibiotic when possible, and maintaining treatment for an appropriate amount of time. Patient education is also crucial.

**TABLE 1. Drug-resistant bacteria**

Community-acquired
<i>Escherichia coli</i> (resistant to extended-spectrum beta-lactamases, may be health care-associated)
<i>Haemophilus influenzae</i>
Methicillin-resistant <i>Staphylococcus aureus</i>
<i>Mycobacterium tuberculosis</i>
<i>Neisseria gonorrhoeae</i>
Penicillin-resistant pneumococci
Salmonella
Shigella
Hospital-acquired
<i>Enterobacter</i> species
<i>Klebsiella</i> species
Methicillin-resistant <i>S aureus</i>
<i>Pseudomonas</i> species
Vancomycin-intermediate <i>S aureus</i>
Vancomycin-resistant enterococci
Vancomycin-resistant <i>S aureus</i>

When treating a patient with a potentially infectious disease, the clinician needs to ask, “Is this an infection that requires an antibiotic?” Many infections are viral in origin, and antibiotics are not indicated. Rapid antigen-based diagnostic tests can make the decision process more accurate. In patients with pharyngitis who meet the criteria for testing, a negative result on a rapid antigen test for GABHS indicates that an antibiotic is not warranted; however, the patient’s pain needs to be treated. Likewise, rapid antigen tests used to diagnose influenza can eliminate unnecessary antibiotics.

Usually the most likely causative bacteria for the site of the infection are taken into account, and empiric antibiotic therapy is initiated with an agent that covers those pathogens. The ideal is to use as narrow spectrum an antibiotic as possible; however, if the patient is very ill or the source is unclear, a broad-spectrum antibiotic is administered. If culture and sensitivity testing (C&S) yields the cause, the antibiotic can be changed when the results are known. This practice is termed *streamlining*. In this era of resistance, an increased use of cultures is appropriate. C&S of purulent wounds is now recommended by the CDC for routine infection management in individual patients to determine local resistance rates of methicillin-resistant *Staphylococcus aureus* (MRSA) and to monitor trends in susceptibility.<sup>12</sup>

Antibiotic sensitivity patterns vary geographically in the United States; therefore, empiric therapy should be based on local summary tables, known as *antibiograms*. Most hospitals report cumulative susceptibility testing in these tables. A typical antibiogram displays the total number of bacterial isolates

tested against a range of antimicrobials and includes the percentage of bacterial isolates susceptible to or resistant to each antimicrobial agent tested. These antibiograms should be used by clinicians both in hospital and in community practice to optimize initial antibiotic choices and improve patient outcomes.

Initial antibiotic choice should also take into consideration the patient's risk for less common or resistant pathogens based on the person's medical and travel history. Prior infection and recent antibiotic use (past 3-6 months) should be assessed because these factors increase the likelihood of resistance. Selecting appropriate antibiotic therapy can be critical, especially in severely ill patients. A prospective study of infected patients in an ICU showed that the mortality rate in patients who received inappropriate antimicrobial therapy was considerably higher than in patients who received appropriate therapy (52.1% versus 12.2%, relative risk of 4.26).<sup>13</sup> Prior antibiotic administration was found to be the most important risk factor associated with inadequate therapy.

The longer the duration of antimicrobial treatment, the more likely it is that colonization with resistant organisms will occur.<sup>14</sup> The goal is to administer sufficient antibiotic to eradicate the pathogen and prevent recurrence, but not so much antibiotic that resistance develops from exposure after the pathogen is eliminated. Unfortunately, this ideal duration is often not known. The trend is for shorter courses of antibiotic with duration of therapy based on the time the patient takes to achieve clinical stability. The Infectious Diseases Society of America (IDSA) and American Thoracic Society updated their joint guidelines for treating community-acquired pneumonia (CAP). The updated guidelines recommend 5 days of antibiotic treatment for patients with CAP who are stable and afebrile for 48 to 72 hours.<sup>15</sup> More studies are needed to identify drug concentrations, dosages, and schedules for suppression of mutations that lead to antimicrobial resistance in bacteria.

Another intervention may be probiotics, which inhibit growth of pathogenic bacteria in the intestinal tract. Probiotics are live, nonpathogenic bacteria or yeasts that colonize a host. Probiotics alter intestinal mucus production and increase barrier function and otherwise augment the intestinal immune system.<sup>16</sup> In a randomized double-blind trial, infants attending day care were fed a formula supplemented with probiotics. Study findings showed that the infants had fewer days with fever, fewer clinic visits, fewer day-care absences, and fewer antibiotic prescriptions.<sup>17</sup> However, infectious complications of specific probiotics have occurred in patients who were highly immunosuppressed or critically ill.<sup>18</sup>

#### STRATEGIES TO CURB RESISTANCE

Addressing the growing problem of antibiotic resistance requires cooperation between multiple groups including clinicians, the public, health care agencies, health administrations, and the pharmaceutical industry. As discussed earlier, clinicians must avoid prescribing antibiotics for nonbacterial illnesses. Local resistance patterns, diagnostic techniques, and updated treatment guidelines must be applied when adminis-

tering antimicrobials. Optimal administration of all available vaccines to children and adults offers protection against infection and infectious complications and reduces the need for antibiotics. Infection control practices must be consistently followed, in particular, strict adherence to hand-washing practices between each patient contact.

**Patient education** is an important factor in changing the attitudes and behaviors that increase the risk of antibiotic resistance. Patients should be instructed to complete the full course of prescribed antibiotics, even if symptoms resolve before they have taken all of the medication, and they must be strongly advised against taking antibiotics that were prescribed for another person. The CDC, the Alliance for Prudent Use of Antibiotics (APUA), and other groups have published educational brochures for the public and for health care providers. The CDC educational programs include the Get Smart program, which focuses on outpatients,<sup>19</sup> and the 12-step Campaign to Prevent Antimicrobial Resistance in Healthcare Settings.<sup>20</sup>

Educational interventions have been shown to reduce antibiotic prescription levels. The Knox County Health Department in Tennessee led a year-long campaign aimed at reduc-

**“Revival of susceptible bacteria can occur if there is no selective advantage for the resistant strains in the environment.”**

ing unnecessary antibiotic administration to children after very high levels (more than 50%) of antibiotic resistance to invasive *Streptococcus pneumoniae* were documented. Educational efforts were directed toward health care practitioners, the parents of young children, and the public. Antibiotic prescriptions for children living in Knox County and in a control county declined 19% and 8%, respectively, yielding an 11% intervention-attributable decline ( $P < .001$ ).<sup>21</sup>

Hospitals and other health care institutions often employ a comprehensive program for antimicrobial management and resistance control. In 2007, the IDSA, with the Society for Healthcare Epidemiology of America, released guidelines for developing institutional programs that enhance antimicrobial stewardship—the appropriate selection, dosing, route, and duration of antimicrobial therapy. The two core components of these guidelines are (1) prospective audit of antimicrobial use with intervention and feedback to the prescriber and (2) formulary restriction and preauthorization. In addition, eight supplemental activities are offered that can be used based on local needs.<sup>22</sup>

**Antimicrobial resistance** is a global problem. The APUA, which has members in more than 90 countries, provides a model for improving antibiotic use.<sup>23</sup> Strong national surveillance systems are necessary for international surveillance of

antimicrobial resistance. The World Health Organization is working with member countries to strengthen their surveillance systems and to build a repository of information about resistance in key pathogens.<sup>24</sup>

New antibiotics have been developed to treat drug-resistant infections such as MDR gram-positive bacteria, MRSA, and hospital-acquired pneumonia, as well as diabetic foot infections, intra-abdominal infections, and skin and soft tissue infections. Judicious use of these drugs is required to maintain efficacy and prevent further resistance.<sup>25</sup> Continuing drug development is needed, particularly for resistant gram-negative bacteria.

**“When antibiotics are warranted, a narrow-spectrum agent should be prescribed at an optimal dose for an appropriate treatment duration.”**

#### CAN RESISTANCE BE REVERSED?

Revival of susceptible bacteria can occur if there is no selective advantage, such as the presence of an antibiotic, for the resistant strains in the environment. A Finnish study documented a reduction in macrolide resistance among group A streptococci that correlated with a decrease in the administration of macrolide antibiotics.<sup>26</sup> Group A streptococci resistance to macrolides had increased to 13% from approximately 5% between 1988 and 1990. In response to this finding, national guidelines were issued that recommended reducing the use of these agents. Finnish physicians were educated on alternative drugs. Between 1991 and 1992, macrolide antibiotic use declined from 2.40 defined daily doses per 1,000 inhabitants per day to 1.38; macrolide antibiotic use remained at this lower level to the end of the study period in 1996. Resistance among group A streptococci decreased to 8.6% from 16.5%. In addition to correlating antibiotic use and bacterial resistance, this study demonstrated the success of educational intervention programs and the ability to extend the effective life span of antibiotics.<sup>26</sup>

#### CONCLUSION

The development of effective antibiotics was one of the major medical advances of the last century. However, bacterial resistance that inhibits our ability to treat infectious diseases developed in response to antibiotic use. Health care providers should use antibiotics less often and more wisely to reduce the risk of antibiotic resistance. When antibiotic therapy is warranted, a narrow-spectrum agent should be prescribed at an optimal dose for an appropriate duration. Subinhibitory concentration of antibiotics for even a short period is likely to induce resistance in the pathogens as well as normal flora. Further research is needed to determine the best-practice antimicrobial regimens and to develop new antibiotics. **JAAPA**

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#### DRUGS MENTIONED

Azithromycin (Zithromax)  
Chloramphenicol (Chloromycetin Injection)  
Clarithromycin (Biaxin)  
Penicillin  
Tetracycline (Bristaclycline, Sumycin)  
Vancomycin (Vancocin)

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