Microbiologists have known for decades that pathogens become resistant to antibiotics. Yet in his 1998 report, Stuart B. Levy, MD, wrote that approximately 80% of the 80 to 100 physicians attending one of his seminars admitted to prescribing—against their better judgment—antibiotics in response to patient pressure. Levy, who directs the Center for Adaptation Genetics and Drug Resistance, Tufts University School of Medicine in Boston, MA, and is president of the Alliance for the Prudent Use of Antibiotics, believes that medical technologists are the front line in the fight against antibiotic resistance.

### Why Resistance Has Increased

Many outpatient prescriptions are written for upper respiratory tract infections caused by viruses rather than bacteria, according to Tamar Barlam, MD, director of the Project on Antibiotic Resistance, Center for Science in the Public Interest, Washington, DC. “This is not appropriate,” she says. “Even when the infection is caused by bacteria, the minimum inhibitory concentration [the lowest concentration of drug that would inhibit growth of the test organism] of the drug may creep up."

—Tamar Barlam, MD, Director, Center for Science in the Public Interest

> Physicians understand the resistance problem, according to Barlam, but some may not have the confidence—especially when facing a patient—to treat an infection within a narrower therapeutic window or to not treat the infection at all. “Current diagnosis still depends on culture, which takes 24 to 72 hours to obtain a result, depending on the growth rate and how many strains must be isolated by subculturing,” she says.

But the problem is larger than physician behavior. Eugene D. Weinberg, PhD, professor of microbiology at Indiana University in Bloomington, IN, cites overuse by nonphysicians as a primary cause of bacterial resistance to antibiotics. “In developing nations, people have uncontrolled access to drugs,” he says. “For example, in many countries people can buy gentamicin over the counter. They may use very small quantities for incorrect time periods and for the wrong purposes. This facilitates stepwise resistance, which occurs when bacteria are exposed to small doses, then larger doses, acquiring resistance along the way, until a strain emerges that resists a huge dose.”

Another cause is the erroneous use of antibiotic drugs by patients. “Instead of taking the full course of antibiotic, some patients wait until they feel better and save the rest or give it to relatives,” says Weinberg. He adds that giving antimicrobial drugs to animals to enhance their growth also makes it easy for resistant strains to emerge, especially if the amount of antibiotic is not enough to inhibit bacterial growth. “Agriculture people are aware of this and are trying to shift to antibiotics not used in human medicine,” he says.
Salmonella ant genes move among gram-negative bacilli such as genes travel through a tube called a sex pilus. This is how resistant susceptible cells by conjugation, during which the resistant genes travel through a tube called a sex pilus. This is how resistant susceptible cells by conjugation, during which the resistant genes travel through a tube called a sex pilus. This is how resistant susceptible cells by conjugation, during which the resistant genes travel through a tube called a sex pilus. This is how resistant susceptible cells by conjugation, during which the resistant genes travel through a tube called a sex pilus.

Consequences of Increased Resistance

If the resistance gene is on a plasmid, it can spread to other species, according to Barlam. “Some plasmids can produce beta-lactamases,” she says. “These enzymes can be transferred via plasmids to many species or bacteria, allowing them, for example, to resist beta-lactam antibiotics such as penicillins and cephalosporins.” She adds that some antibiotics have even outlived their usefulness for some infections. “We used to give penicillin to every patient with gonorrhea,” she says, “and now we never use it for this purpose.”

Physicians often use multiple antibiotics to treat infections in hospitalized patients, notes Barlam. “This was also common before we had broad-spectrum antibiotics, especially when treating patients suspected of being infected with several types of bacteria,” she says. Now, according to Barlam, in addition to using broad-spectrum antibiotics, physicians use 2 to 3 antibiotics to slow the emergence of resistance or to optimize the probability of killing the bacteria.

Nosocomial Infections

Resistant strains of bacteria often become established in hospitals. “A hospital is a closed shop,” says Barlam. “Patients are confined, and they share hospital personnel, who are often not careful enough about infection control as they move from room to room with their equipment and materials.” According to Barlam, if a patient coming out of surgery takes many antibiotics, these drugs, coupled with those the patient was taking at the time of admission, further increase the chances that resistant strains will emerge. These bacteria, in turn, get into hospital sinks and other equipment and eventually to other patients, leading to outbreaks of bacteria not commonly found in the community.

Levy agrees that hospitals are breeding grounds for hard-to-treat bacteria. “Methicillin-resistant Staphylococcus aureus” is now more aptly called “multidrug-resistant S aureus” because we can’t kill it with any of 5 or 6 different drugs,” he says. “We treat S aureus infection with vancomycin, but now there are strains insensitive to this antibiotic as well. Vancomycin-resistant enterococcal infections are also difficult to treat, especially in immunocompromised patients.” He adds that quinupristin/dalfopristin (Synercid, Aventis Pharmaceuticals), a combination antibiotic, was developed specifically to treat methicillin-resistant S aureus infections as well as vancomycin-resistant Enterococcus faecium bacteremia.

Physicians Trying To Do Better

Weinberg believes that increasing antibiotic resistance has changed the way physicians use antibiotics. To prevent resistant strains from gaining a foothold, physicians combine drugs, as in

How Resistance Develops

Resistance may occur in a variety of ways, according to Weinberg. “One is mutation, a sudden heritable change in DNA that occurs spontaneously once in every million or billion cell divisions,” he says. “The mutation rate can be accelerated by exposure to radiation or mutagenic chemicals.” Weinberg cautions, however, that the primary way bacteria acquire resistance is not by mutation, but by picking up genes from other strains or species via plasmids. “These independent bodies within bacterial cells contain nonchromosomal DNA, which may include resistance genes,” he says. “Plasmids may leave resistant cells and enter susceptible cells by conjugation, during which the resistant genes travel through a tube called a sex pilus. This is how resistant genes move among gram-negative bacilli such as Salmonella and Shigella.” He adds that smaller plasmids—with only 1 or 2 drug-resistant genes—can be transferred without the sex pilus, such as in Neisseria gonorrhoeae. Other delivery vehicles include bacterial viruses, or phages (transduction), and transposons, DNA sequences that can move from one gene to another, from one plasmid to another, or to a bacteriophage.
treated tuberculosis or cancer, he explains. “If 2 antibiotics are used in combination, 1 of the pair can kill the 1-per-million mutant that resists the other drug,” he says, “providing that both drugs are at the disease site in adequate concentration. During the months of therapy for tuberculosis, for example, mutants can arise that, if the physician used a single drug, would cause the therapy to fail.” Physicians may also rotate drugs. “To treat malaria in Vietnam, physicians used one drug for a year, then switched to another when the resistant strains came in,” says Weinberg. He adds that a newer development is computer-assisted antibiotic prescribing, which has been shown to limit the emergence of resistant pathogens.

Nonantibiotic Approaches

According to the World Health Organization, vaccines offer a cost-effective alternative to antibiotics for treating infectious diseases. Research is focusing on developing vaccines against bacteria that cause pneumonia, middle ear infections, and infections of the urinary tract, all with a high rate of resistance. A variety of vaccines against pneumococci are under development, including a vaccine that has 23 of the most common pneumococci, as well as PNCRM7, a conjugate vaccine prepared from 7 common strains of Streptococcus pneumoniae.

Although experimental, the use of oral chelators (chemicals that sequester metal ions) to trap iron—which pathogens need to make DNA and get energy—has been tried as an adjunct to antibiotics, according to Weinberg. “The goal is to chelate microgram amounts of iron at the infection site and withhold it from the invading pathogens,” he says. “But the chelators used so far have had adverse effects associated with vision, hearing, or blood-cell formation, depending on the drug.”

As an example, Weinberg cites an iron chelator tried in Africa against malaria. “The chelator was used with quinine,” he says. “Because it was expensive and had to be injected, few patients, or the various African governments, could afford it, and the people had trouble mastering the injection technique.”

“Methicillin-resistant Staphylococcus aureus’ is now more aptly called ‘multidrug-resistant S aureus’ because we can’t kill it with any of 5 or 6 different drugs.”

—Stuart B. Levy, MD, Director, Center for Adaptation Genetics and Drug Resistance

In his 1998 report, Levy briefly describes chemical modifications that “give new life to existing antibiotics.” In his own laboratory, Levy is investigating derivatives of tetracycline designed to interfere with the “microbial pump” that bacteria use to remove tetracycline from their cellular interiors. “We hope to have them available to reduce the decline in the use of tetracyclines, which are good drugs,” says Levy.

Still another approach involves the use of cationic peptides, which bind to phospholipid bilayers in bacteria rather than to the proteins bacteria need to build cell walls. Cationic peptides cause channels to form in the cell membrane, allowing cytoplasm to leak and resulting in cell death.

Role of the Microbiology Laboratory

According to Levy, clinical microbiologists, technologists, and technicians are at the forefront of the fight against antibiotic resistance. “They are the first to detect, for example, a vancomycin-insensitive S aureus in the hospital,” he says. “They should immediately alert the hospital, because if they just report it, weeks could pass before the infection-control people become aware of it.”

Weinberg agrees. “Diagnostic laboratory professionals can play a key role in the selection of antimicrobial agents by physicians, but they must be tactful,” he says. “Antibiotic sensitivity tests must be tailored to the best agents, according to the organism, the site of infection, and any critical host factors [eg, neonate, pregnant woman, or elderly person].” He states that results should be reported by generic name and antibiotic class rather than by trade name and that laboratory personnel should be able to perform rapid qualitative sensitivity tests (which provide results in a few hours), standard quantitative tests (which provide results the next day), and assays for drug concentrations in plasma or spinal fluid, as for meningitis.

Conclusion

Barlam believes that physicians are starting to prescribe antibiotics more carefully, particularly in outpatient settings such as pediatric offices. “Studies show that educational programs of local groups and the Centers for Disease Control and Prevention have made a difference,” she says. “There is still a lot of misuse, though, particularly in hospitals where physicians must balance the desire to avoid antibiotic resistance against the needs of sicker patients and general concern for patients’ welfare.”

### Suggested Reading


Fred Wilson is Managing Editor of WilWrite, based in Syracuse, NY.