

Microbial Warfare: The Front Lines of Antibiotic Resistance

Mickie Stelck, CST

As surgical technologists, we are all aware of the need for hand washing and the rules of aseptic technique. But, we may not be aware of the extent of the problem of antibiotic resistance in the world today. Overuse and misuse of antibiotics has led the bacteria to a mutation evolution gone wild. “Organisms in 70 percent of hospital-acquired infections are resistant to at least one antibiotic. In 35 to 40 percent of infections, the organism is actually resistant to the drug considered by the physician as the usual first line therapy to treat that organism.”² The Centers for Disease Control estimates more than 2 million hospital-acquired infections each year in the United States, costing the country 90,000 lives and an estimated 4.5 billion a year. The rate of hospital-acquired infections has risen 36 percent in the last 20 years.² This astounding impact requires us to be as diligent as ever about practice of aseptic technique.

Education is a key issue, for the public as well as physicians. Antibiotics can't continue to be doled out for just any malady and, if prescribed, must be taken as ordered. Bacteria have been around for millions of years, and the evolutionary process will continue to allow them to thrive. As we examine the battleground, we need to consider how we are going to live with them now and how to prepare for the future.

HISTORY OF RESISTANCE

In 1928, Alexander Fleming realized that secretion of a mold was killing the *Staphylococcus aureus* (*S. aureus*) on a petri

dish thus discovering a revolutionary change in the fighting of bacterial infections—the first antibiotic.^{1,2} Antibiotics are defined as any “substance produced by microorganisms that inhibits or destroys pathogens during the disease process.” Many of these natural substances are now reproduced and manufactured in laboratories.⁴

Mass production of penicillin was not available until 1944, but even in 1943 during the second phase of clinical trials, scientists noted that the microbe was becoming resistant.^{1,2} The 1950s brought epidemics of resistant infections worldwide. As many as 50 percent of *S. aureus* strains were resistant to penicillin, but the trend was downplayed as not significant. In the 1960s, resistant strains of *Streptococcus pneumoniae* were found in Australia and New Guinea. By 1977, this bacteria was resistant to multiple antimicrobial drugs.² (Table 1)

In the mid-1970s, two more organisms became resistant to penicillin—*Haemophilus influenzae*, which causes respiratory infections, and *Neisseria gonorrhoeae*, responsible for the sexually transmitted disease gonorrhea. These bacteria not only turned drug resistant but fought back against the drugs that were being used to kill them. The source of the strain was found in servicemen and ultimately traced to Vietnamese prostitutes who had been given penicillin prophylactically.¹

By the late 1980s, a vancomycin-resistant strain of *E. faecium* appeared. In 1993, 14 percent of enterococcal isolates from patients in US intensive care units were resistant to vancomycin (Table 2) and 60 percent of *S. aureus* isolates in

Japan were resistant to methicillin. Just three years later, 35 percent of *S. aureus* isolates in the US were also resistant. By 1997, as many as 77 percent of *S. pneumoniae* cases in South Korea were resistant to penicillin.²

For decades, the medical community and drug companies ignored the rising problem of resistance. They were making huge profits and calling the shots. The market was seemingly flooded with drugs, and the cost of researching and developing a new product was high. Today, pharmaceutical companies can't keep up with the demand for new treatments.

MICROBIOLOGY

Bacteria are single-celled organisms that must be magnified 1000 times in order to be seen clearly. Although bacteria are found throughout our body as normal flora, when introduced into an abnormal area, they become pathogenic. Bacteria are controlled by a nucleoid, which contain a single chromosome of DNA. The cells are composed of a watery cytoplasm and contain particles that include ribosomes and mesosomes. Ribosomes synthesize essential proteins for the cell. Mesosomes handle cellular respiration—changing food to energy. The cytoplasm is surrounded by a cell membrane, which holds the cell together and regulates the flow of material into and out of the cell. The membrane is enclosed by a sturdy cell wall, a rigid structure that protects the cell and defines its shape. The cells use flagella for mobility. A by-product of a bacterium's metabolism is toxins.^{3,4} (Figure 1)

Bacteria (prokaryotic cells) reproduce using binary fission—the DNA replicates and then the cell divides in two equal parts. This process continues as long as nutrients, water and space are available or until waste products build up to a toxic level (affecting acidity). *E. coli*, *Vibrio cholerae*, *Staphylococcus* and *Streptococcus* all regenerate in about 20 minutes. Temperature, acidity, moisture and available nutrients can increase or decrease the growth rate of bacteria.^{3,4}

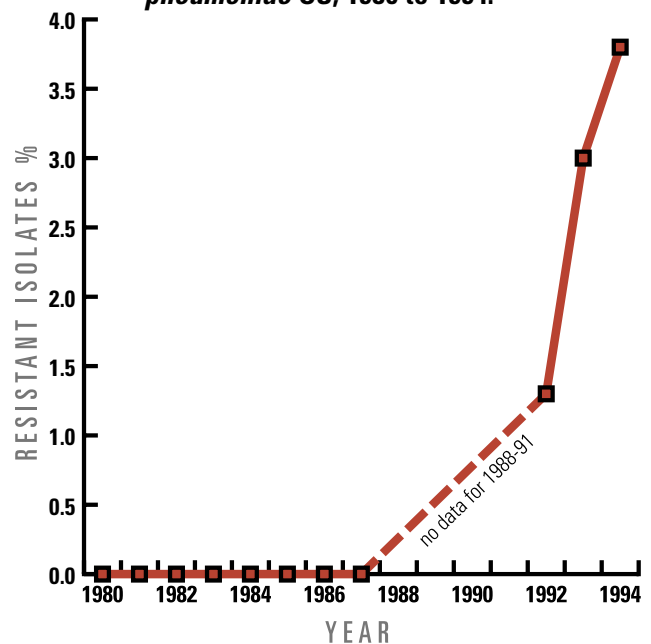
Bacteria may use oxygen, carbon, hydrogen, sulfur, phosphorus, nitrogen, or a combination of elements as nutrients. Organisms can be classified by their need of oxygen for survival. Aerobic organisms need the presence of oxygen to survive; anaerobic organisms thrive in the absence of oxygen. Some anaerobic organisms cannot survive at all when oxygen is present, so exposing them to oxygen will kill them.^{3,4}

Bacteria vary in size and shape: cocci are spherical, *Streptococci* form chains, and *Staphylococci* are grouped in clus-

ters. They are also classed either Gram-stain positive or negative indicating their shape and reaction. Gram-positive organisms stain purple or blue while Gram-negative organisms stain pink or red. This testing gives valuable information, which when used with susceptibility tests, can determine the best drug treatment.³

Bacterial cells are prokaryotic and human cells are eukaryotic. Antibiotics work effectively on bacterial pathogens

TABLE 1: Rate of high-level penicillin resistance among 6721 invasive isolates of *Streptococcus pneumoniae* US, 1980 to 1994.



Data from this CDC surveillance system were not reported from 1988 to 1991. (From: Butler JC, Hofmann J, Cetron MS, Elliott JA, Fracklam RR, Breiman RF. The continued emergence of drug-resistant *Streptococcus pneumoniae* in the United States: an update from the CDC Sentinel Surveillance System. *J Infect Dis.* 1996; 174:986-93.)

Courtesy of Pharmacia & Upjohn

without harming the person, because of the differences in the types of cells. For example, eukaryotic cells do not have cell walls so they aren't changed by the action of penicillin. Antibiotics are not effective on viruses because viruses are housed and reproduced within a human's eukaryotic cells. Most antiviral agents cannot effectively reach the source of the pathogen without harming the human cells.⁴

DESTRUCTION

Today, there are 160 antibiotics available, created from variations of 16 basic compounds.² These antibiotic compounds work in one of five different ways to destroy bacteria:

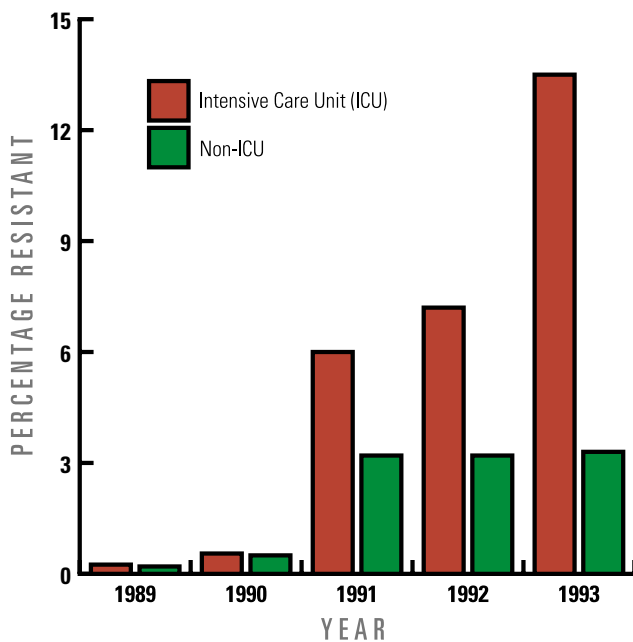
Drug resistance in an organism may occur by a single spontaneous genetic mutation or by a complex series of genetic changes that produce enzymes within the cell to inactivate an antibiotic family.

1. Disruption of cell wall synthesis. Bacteria use enzymes to build and maintain their cell walls. This process is interrupted when attacked with compounds such as penicillin, cephalosporins, teicoplanin and vancomycin. Susceptibility to treatment will vary considerably based on cell wall permeability and the type and concentration of the enzymes.²
2. Inhibition of bacterial protein synthesis. This group binds the bacteria's ribosomes and disrupts protein production thereby keeping the bacteria from functioning, growing or multiplying. This mechanism is effective for killing or inhibiting the growth of bacterial pathogens. Types include the tetracyclines, erythromycins and aminoglycosides.²

4. Inhibition of metabolic enzymes. Examples of this group include the sulfa drugs, which act by inhibiting the production of folic acid, an essential vitamin for cell metabolism, and rifamycin, which interferes with RNA polymerase, an enzyme needed for protein synthesis.²
5. Alteration of cell membrane permeability. These drugs create pores in the bacterial membrane that allow cell contents to spill out, destroying the bacteria. Types include the polymyxins.²

Antibiotics not only kill the harmful bacteria but also non-harmful bacteria in the body that helps us ward off infections.

TABLE 2: Resistance to the Antibiotic Vancomycin in *Enterococcal* Infections* in US Hospitals.



* *Enterococcal* infections affect the intestines and can be life-threatening primarily for the very old and sick.

Courtesy of Pharmacia & Upjohn

RESISTANCE

The bacteria that have developed resistance via genetic mutation are challenging these methods of destruction, and antibiotics are a large contributor to this behavior.²

Antibiotic resistance has been fueled by the inappropriate use of antibiotics. Doctors prescribe antibiotics for a cold or flu (20 percent of prescriptions) that is not of a bacterial origin.² (Table 3) It has been estimated that 50 percent of the antibiotic use is unnecessary in this country and the resistance of the organism has added \$4 billion to \$5 billion in costs in the United States.² Resistance also increases when patients don't finish the prescribed dose because they start to feel better. Another practice deemed unnecessary is the preoperative administration of antibiotics.¹ And, physicians often prescribe antibiotics for an infection without knowing what organism is causing the problem; therefore, the drug may not be appropriate or the dosage may not be adequate to eradicate all the organisms. In all these cases, bacteria that survive treatment will be the strongest. These bacteria, now exposed to the antibiotic, mutate to ensure survival, then pass these new characteristics on to the next generation. Over time, these bacteria may become resistant to several types of antibiotics, leading to the creation of superbacteria.^{1,2} (Table 4)

Other factors influence the mutation and spread of superbacteria. Increased global interaction allows organisms to travel with their hosts and spread around the world.

3. Interference with bacterial DNA. One drug, metronidazole, when metabolized in the cells, creates products that bind and disrupt the bacteria's DNA. Another group, the quinolones, binds an enzyme (DNA gyrase) and prevents protein synthesis. Effectiveness of this method depends on the antibiotic's ability to penetrate the cell wall.²

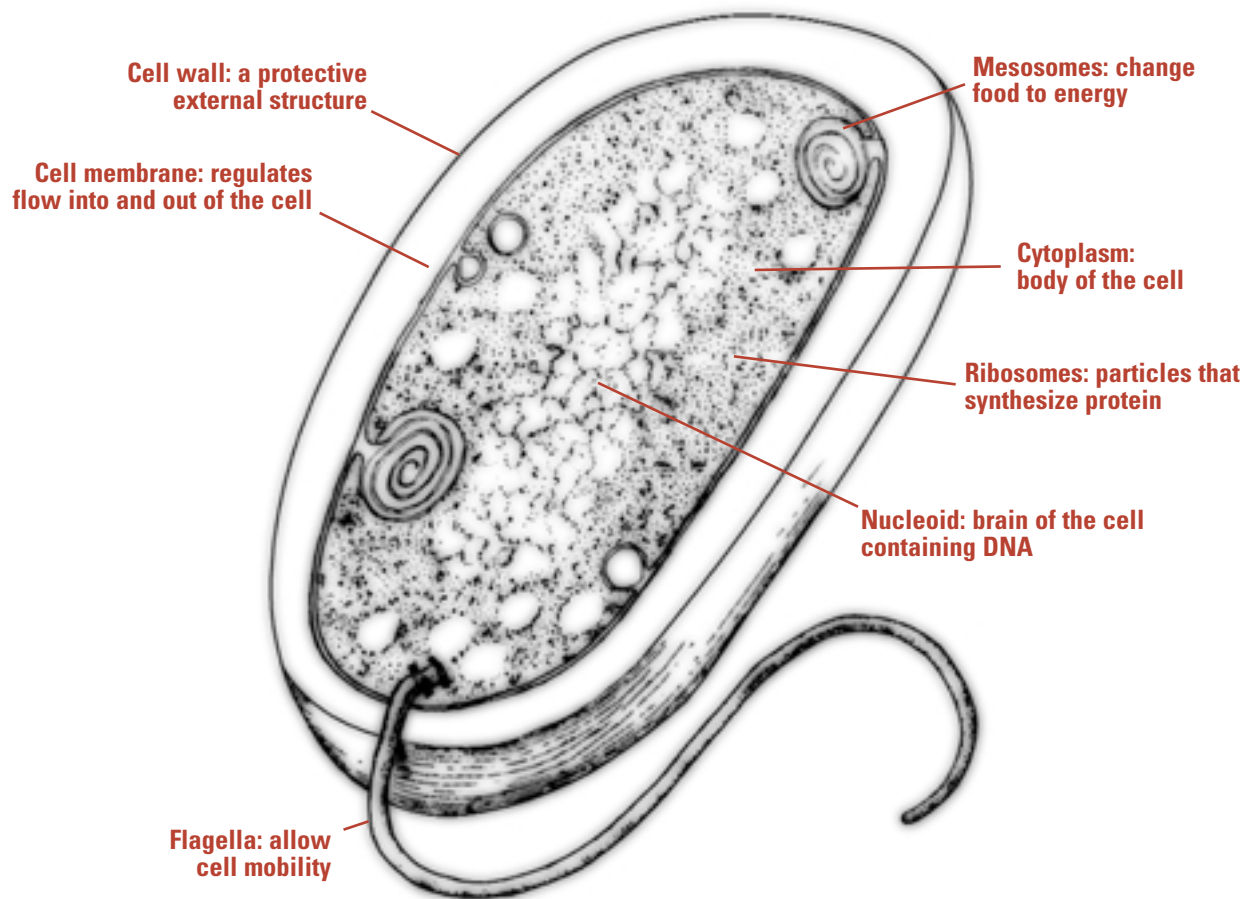


FIGURE 1: Bacterial cells are prokaryotic. They are different than human (eucaryotic) cells, because they have a cell wall and a simple nucleus.

Antimicrobial agents are not just used on humans to treat infection. They are also sprayed on fruit trees to fight disease, given to animals to promote growth and, most recently, incorporated into household soaps, cleaners, toys and toothpaste. These uses add up to 50 million pounds of drugs produced in the United States.¹

Bacterial resistance is achieved in one of four different ways:

1. Reduces cell wall permeability: This will keep the penicillins, gentamycin, neomycin and streptomycin from gaining access through the cell wall.
2. Alters drug target sites like penicillin-binding proteins.
3. Prevents the antibiotics from deactivating their enzymes.
4. Not allowing antibiotic access to antimicrobial targets such as enzymes.²

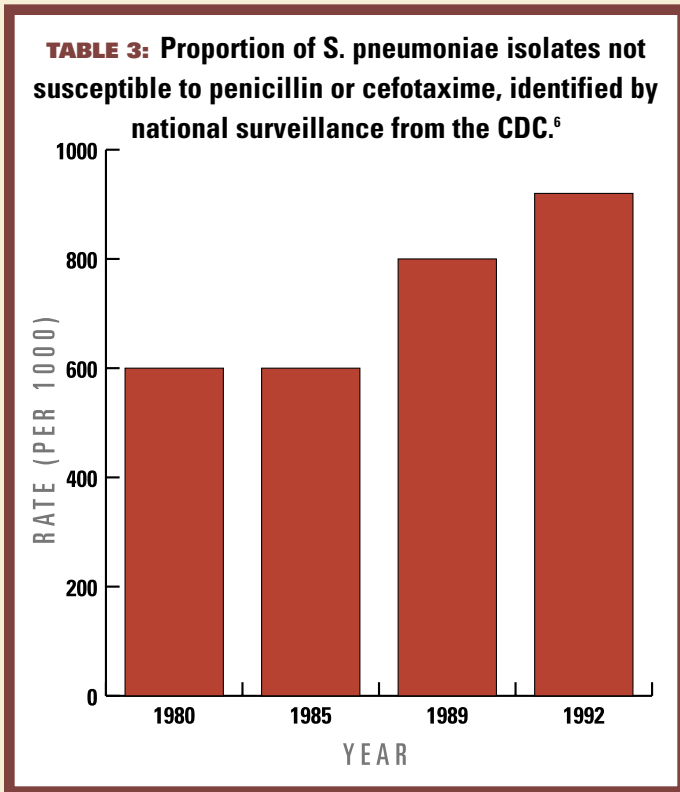
Drug resistance in an organism may occur by a single spontaneous genetic mutation or by a complex series of genetic changes that produce enzymes within the cell to inactivate an antibiotic family. The genes capable of creating bacteria that fight back against antibiotics occur naturally in other species of bacteria. Some researchers believe that bacteria under attack may access the natural antibiotic-resistant enzymes of other bacteria to get the genetic information needed to survive.²

SUPERBUGS

With bacteria mutating to the degree that they are attacking the drugs meant to attack them, new defenders are needed. Members of the bacteria family that have gained super status include *S. aureus*, *S. epidermidis*, *Streptococcus pneumoniae*, *Strep pyogenes* and *Enterococcus faecalis* and *E. faecium*. These

bacteria are all gram-positive and are the most common infection-causing agents.²

Staphylococcus aureus: This organism is present in boils and abscesses and, when penicillin was introduced in the 1940s, nearly every strain was susceptible to treatments. Through evolutionary changes 95 percent of *S. aureus* is now resistant, despite pharmaceutical products that are synthetic penicillin (ie methicillin, nafcillin and oxacillin). By the 1980s a strain of methicillin resistant *S. aureus* (MRSA) had emerged. MRSA is now a large problem in long-term care facilities and



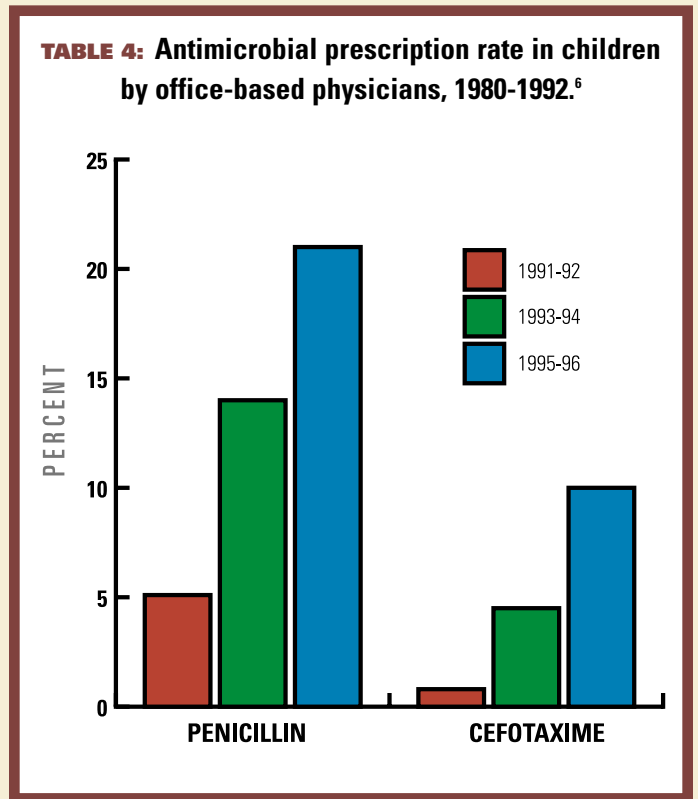
in US teaching hospitals in big cities. MRSA still shows sensitivity to vancomycin; however, there are now reports of *S. aureus* fighting vancomycin.^{2,5}

Another worrisome organism is *Staphylococcus epidermidis* (formerly *S. albus*), which is thought to cause bacterial endocarditis in the presence of intracardiac prostheses. With this bacteria, there is not only the potential of infection, but the organism may serve as a reservoir of resistant gene material for other bacteria by way of the plasmids.²

Streptococcal organisms are also posing resistance by the same means as staph organisms—by rapidly reproducing and incorporating DNA from other sources with their own. *S. pneumoniae* causes pneumonia, otitis media and is a leading

cause of meningitis. Since 1994, *S. pneumoniae* has developed a four-fold amount of penicillin resistance in the United States.

Enterococcus (E. coli) was not considered its own species until 1984, but now contains 12 significant strains, including *E. faecalis* and *E. faecium*. This organism spreads from person to person and is damaging when those infected and those susceptible are combined in an area such as a hospital. *E. coli* infections are also becoming vancomycin resistant (VRE). Normally found in the intestines as flora, *E. faecalis* is responsible for 80-90 percent of the enterococcus infections. *E. faecium* is the strain that is the most often vancomycin resistant (VRE).²




FIGHTING THE BATTLE

When bacteria fight back against the drugs meant to kill them, what happens? Several theories have been tried; one consisted of mixing susceptible strains of bacteria with resistant strains in hopes that a less resistant strain would be the end product. But nature provides for survival of the fittest and the resistance prevailed. Another theory that has been backed up by clinical studies has shown that by removing gentamicin for infections involving *E. coli*, the resistance level dropped. Yet another practice is to flood the gut with susceptibles, bacteria that have

been mixed with resistant strains, and flush out the resistants. A prototype of this theory is being done with baby chicks. By spraying them as they preen, the chicks ingest susceptible bacteria that will occupy the spaces that might otherwise be taken over by resistants including *Samonella*.¹

A newer form of antimicrobial called oxazolidinones was discovered in 1989. This agent seems to have success against the Gram-positives *S. aureus* and *S. epidermis*, *Strep pneumoniae*, *E. faecalis* and MRSA and VRE. Oxazolidinones are composed of a five-member heterocyclic ring system that works by inhibiting the bacteria's protein synthesis at an earlier stage of development. This prevents the cell from forming an outer wall thus making it more vulnerable to drugs.²

CONCLUSION

Overuse of antibiotics and antibacterial agents has caused an epidemic of bacterial resistance, yet awareness and change continues to be a slow process. Prescribing antibiotics either prophylactically, or in cases where it clearly is not indicated just to appease a patient or parent, is leading to a scenario where today's available drugs won't continue to be effective. Bacteria have the ability to mutate for their survival when they are attacked and will do so. Understanding the process of resistance and acting to discourage it will benefit all of us in the future. 

ABOUT THE AUTHOR

Mickie Stelck, CST, has 20 years' experience working for the Mayo Clinic in Rochester, Minn, at St Mary's Hospital. She specializes in bronchoscopy and urology has contributed many articles to the journal.

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MISPERCEPTION: A physician normally knows the causative organism before he/she selects an antibiotic to treat the infection.

REALITY: Many times physicians do not know the causative organism and therefore selecting an antibiotic can be very difficult.

MISPERCEPTION: All bacteria are harmful and should be eradicated from the body.

REALITY: Most bacteria live blamelessly and are a needed part of life. In fact, bacteria often protect us from disease because they compete with, and thus limit, the proliferation of pathogenic bacteria—the minority of species that can multiply aggressively and damage tissues or otherwise cause illness.

MISPERCEPTION: While resistance problems continue to increase, most antibiotics are still effective in fighting pathogenic bacteria.

REALITY: Two bacterial species commonly associated with nosocomial infections and capable of causing life-threatening illnesses (*Enterococcus faecalis* and *Pseudomonas aeruginosa*) already evade virtually every antibiotic available for approved use. Furthermore, many new antibiotics are structurally similar to existing antibiotics; they could easily encounter bacteria that already have defenses against them. The new oxazolidinone class, with the ability to attack pathogenic bacteria at a different part of the replication cycle than other antibiotics, may offer a new therapeutic option.

MISPERCEPTION: There is no way to determine an organism's sensitivity or resistance.

REALITY: There are many pre-existing factors that can influence whether bacteria in a person or in a community will become insensitive to an antibiotic. The main two forces are prevalence of resistance genes (which give rise to proteins that shield bacteria from an antibiotic's effect) and the extent of antibiotic use. In addition, laboratories can conduct in vitro susceptibility testing and resistance can be determined. However, physicians often have no choice but to treat patients with severe infections before they can test for resistance. Physicians sometimes cannot wait several days for lab results to be processed and therefore use commonly available antibiotics that may not have adequate coverage.

MISPERCEPTION: Antibiotics attack only pathogenic bacteria.

REALITY: When antibiotics attack disease-causing bacteria, they also affect benign bacteria in their path. They eliminate drug-susceptible "innocent" bystanders that could otherwise limit the expansion of pathogens and they may simultaneously encourage the growth of resistant bystanders.

MISPERCEPTION: Antibiotics are never used to treat a person with a viral infection.

REALITY: Sometimes physicians prescribe antibiotics for a person with a virus because of the possibility of also acquiring a bacterial infection during the virus-caused illness. Being ill places a person at risk for certain bacterial infections that are normally handled without any problem.

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