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The Rise of Antibiotic-Resistant Infections

by Ricki Lewis, Ph.D.

When penicillin became widely available during the second world war, it was a medical miracle, rapidly vanquishing the biggest wartime killer--infected wounds. Discovered initially by a French medical student, Ernest Duchesne, in 1896, and then rediscovered by Scottish physician Alexander Fleming in 1928, the product of the soil mold *Penicillium* crippled many types of disease-causing bacteria. But just four years after drug companies began mass-producing penicillin in 1943, microbes began appearing that could resist it.

The first bug to battle penicillin was *Staphylococcus aureus*. This bacterium is often a harmless passenger in the human body, but it can cause illness, such as pneumonia or toxic shock syndrome, when it overgrows or produces a toxin.

In 1967, another type of penicillin-resistant pneumonia, caused by *Streptococcus pneumoniae* and called pneumococcus, surfaced in a remote village in Papua New Guinea. At about the same time, American military personnel in southeast Asia were acquiring penicillin-resistant gonorrhea from prostitutes. By 1976, when the soldiers had come home, they brought the new strain of gonorrhea with them, and physicians had to find new drugs to treat it. In 1983, a hospital-acquired intestinal infection caused by the bacterium *Enterococcus faecium* joined the list of bugs that outwit penicillin.

Antibiotic resistance spreads fast. Between 1979 and 1987, for example, only 0.02 percent of pneumococcus strains infecting a large number of patients surveyed by the national Centers for Disease Control and Prevention were penicillin-resistant. CDC's survey included 13 hospitals in 12 states. Today, 6.6 percent of pneumococcus strains are resistant, according to a report in the June 15, 1994, *Journal of the American Medical Association* by Robert F. Breiman, M.D., and colleagues at CDC. The agency also reports that in 1992, 13,300 hospital patients died of bacterial infections that were resistant to antibiotic treatment.

Why has this happened?

"There was complacency in the 1980s. The perception was that we had licked the bacterial infection problem. Drug companies weren't working on new agents. They were concentrating on other areas, such as viral infections," says Michael Blum, M.D., medical officer in the Food and Drug Administration's division of anti-infective drug products. "In the meantime, resistance increased to a number of commonly used antibiotics, possibly related to overuse of antibiotics. In the 1990s, we've come to a point for certain infections that we don't have agents available."

According to a report in the April 28, 1994, *New England Journal of Medicine*, researchers have identified bacteria in patient samples that resist all currently available antibiotic drugs.

Survival of the Fittest

The increased prevalence of antibiotic resistance is an outcome of evolution. Any population of organisms, bacteria included, naturally includes variants with unusual traits--in this case, the ability to withstand an antibiotic's attack on a microbe. When a person takes an antibiotic, the drug kills the defenseless bacteria, leaving behind--or "selecting," in biological terms--those that can resist it. These renegade bacteria then multiply, increasing their numbers a millionfold in a day, becoming the predominant microorganism.

The antibiotic does not technically cause the resistance, but allows it to happen by creating a situation where an already existing variant can flourish. "Whenever antibiotics are used, there is selective pressure for resistance to occur. It builds upon itself. More and more organisms develop resistance to more and more drugs," says Joe Cranston, Ph.D., director of the department of drug policy and standards at the American Medical Association in Chicago.

A patient can develop a drug-resistant infection either by contracting a resistant bug to begin with, or by having a resistant microbe emerge in the body once antibiotic treatment begins. Drug-resistant infections increase risk of death, and are often associated with prolonged hospital stays, and sometimes complications. These might necessitate removing part of a ravaged lung, or replacing a damaged heart valve.

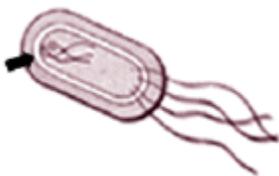
Bacterial Weaponry

Disease-causing microbes thwart antibiotics by interfering with their mechanism of action. For example, penicillin kills bacteria by attaching to their cell walls, then destroying a key part of the wall. The wall falls apart, and the bacterium dies. Resistant microbes, however, either alter their cell walls so penicillin can't bind or produce enzymes that dismantle the antibiotic.

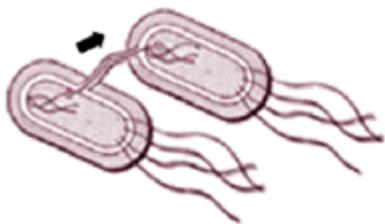
In another scenario, erythromycin attacks ribosomes, structures within a cell that enable it to make proteins. Resistant bacteria have slightly altered ribosomes to which the drug cannot bind. The ribosomal route is also how bacteria become resistant to the antibiotics tetracycline, streptomycin and gentamicin.

How Antibiotic Resistance Happens

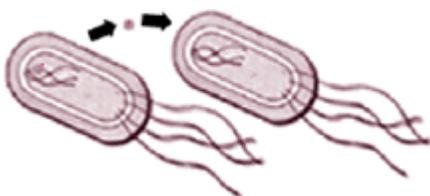
Antibiotic resistance results from gene action. Bacteria acquire genes conferring resistance in any of three ways.



In spontaneous DNA mutation, bacterial DNA (genetic material) may mutate (change) spontaneously (indicated by starburst). Drug-resistant tuberculosis arises this way.



In a form of microbial sex called transformation, one bacterium may take up DNA from another bacterium. Pencillin-resistant gonorrhea results from transformation.



Most frightening, however, is resistance acquired from a small circle of DNA called a plasmid, that can flit from one type of bacterium to another. A single plasmid can provide a slew of different resistances. In 1968, 12,500 people in Guatemala died in an epidemic of *Shigella* diarrhea. The microbe harbored a plasmid carrying resistances to four antibiotics!

A Vicious Cycle: More Infections and Antibiotic Overuse

Though bacterial antibiotic resistance is a natural phenomenon, societal factors also contribute to the problem. These factors include increased infection transmission, coupled with inappropriate antibiotic use.

More people are contracting infections. Sinusitis among adults is on the rise, as are ear infections in children. A report by CDC's Linda F. McCaig and James M. Hughes, M.D., in the Jan. 18, 1995, *Journal of the American Medical Association*, tracks antibiotic use in treating common illnesses. The report cites nearly 6 million antibiotic prescriptions for sinusitis in 1985, and nearly 13 million in 1992. Similarly, for middle ear infections, the numbers are 15 million prescriptions in 1985, and 23.6 million in 1992.

Causes for the increase in reported infections are diverse. Some studies correlate the doubling in doctor's office visits for ear infections for preschoolers between 1975 and 1990 to increased use of day-care facilities. Homelessness contributes to the spread of infection. Ironically, advances in modern medicine have made more people predisposed to infection. People on chemotherapy and transplant recipients taking drugs to suppress their immune function are at greater risk of infection.

"There are the number of immunocompromised patients, who wouldn't have survived in earlier times," says Cranston. "Radical procedures produce patients who are in difficult shape in the hospital, and are prone to nosocomial [hospital-acquired] infections. Also, the general aging of patients who live longer, get sicker, and die slower contributes to the problem," he adds.

Though some people clearly need to be treated with antibiotics, many experts are concerned about the inappropriate use of these powerful drugs. "Many consumers have an expectation that when they're ill, antibiotics are the answer. They put pressure on the physician to prescribe them. Most of the time the illness is viral, and antibiotics are not the answer. This large burden of antibiotics is certainly selecting resistant bacteria," says Blum.

Another much-publicized concern is use of antibiotics in livestock, where the drugs are used in well animals to prevent disease, and the animals are later slaughtered for food. "If an animal gets a bacterial

infection, growth is slowed and it doesn't put on weight as fast," says Joe Madden, Ph.D., strategic manager of microbiology at FDA's Center for Food Safety and Applied Nutrition. In addition, antibiotics are sometimes administered at low levels in feed for long durations to increase the rate of weight gain and improve the efficiency of converting animal feed to units of animal production.

FDA's Center for Veterinary Medicine limits the amount of antibiotic residue in poultry and other meats, and the U.S. Department of Agriculture monitors meats for drug residues. According to Margaret Miller, Ph.D., deputy division director at the Center for Veterinary Medicine, the residue limits for antimicrobial animal drugs are set low enough to ensure that the residues themselves do not select resistant bacteria in (human) gut flora.

FDA is investigating whether bacteria resistant to quinolone antibiotics can emerge in food animals and cause disease in humans. Although thorough cooking sharply reduces the likelihood of antibiotic-resistant bacteria surviving in a meat meal to infect a human, it could happen. Pathogens resistant to drugs other than fluoroquinolones have sporadically been reported to survive in a meat meal to infect a human. In 1983, for example, 18 people in four midwestern states developed multi-drug-resistant Salmonella food poisoning after eating beef from cows fed antibiotics. Eleven of the people were hospitalized, and one died.

A study conducted by Alain Cometta, M.D., and his colleagues at the Centre Hospitalier Universitaire Vaudois in Lausanne, Switzerland, and reported in the April 28, 1994, *New England Journal of Medicine*, showed that increase in antibiotic resistance parallels increase in antibiotic use in humans. They examined a large group of cancer patients given antibiotics called fluoroquinolones to prevent infection. The patients' white blood cell counts were very low as a result of their cancer treatment, leaving them open to infection.

Between 1983 and 1993, the percentage of such patients receiving antibiotics rose from 1.4 to 45. During those years, the researchers isolated *Escherichia coli* bacteria annually from the patients, and tested the microbes for resistance to five types of fluoroquinolones. Between 1983 and 1990, all 92 *E. coli* strains tested were easily killed by the antibiotics. But from 1991 to 1993, 11 of 40 tested strains (28 percent) were resistant to all five drugs.

Towards Solving the Problem

Antibiotic resistance is inevitable, say scientists, but there are measures we can take to slow it. Efforts are under way on several fronts--improving infection control, developing new antibiotics, and using drugs more appropriately.

Barbara E. Murray, M.D., of the University of Texas Medical School at Houston writes in the April 28, 1994, *New England Journal of Medicine* that simple improvements in public health measures can go a long way towards preventing infection. Such approaches include more frequent hand washing by health-care workers, quick identification and isolation of patients with drug-resistant infections, and improving sewage systems and water purity in developing nations.

Drug manufacturers are once again becoming interested in developing new antibiotics. These efforts have been spurred both by the appearance of new bacterial illnesses, such as Lyme disease and Legionnaire's disease, and resurgences of old foes, such as tuberculosis, due to drug resistance.

FDA is doing all it can to speed development and availability of new antibiotic drugs. "We can't identify new agents--that's the job of the pharmaceutical industry. But once they have identified a promising new

drug for resistant infections, what we can do is to meet with the company very early and help design the development plan and clinical trials," says Blum.

In addition, drugs in development can be used for patients with multi-drug-resistant infections on an "emergency IND (compassionate use)" basis, if the physician requests this of FDA, Blum adds. This is done for people with AIDS or cancer, for example.

No one really has a good idea of the extent of antibiotic resistance, because it hasn't been monitored in a coordinated fashion. "Each hospital monitors its own resistance, but there is no good national system to test for antibiotic resistance," says Blum.

This may soon change. CDC is encouraging local health officials to track resistance data, and the World Health Organization has initiated a global computer database for physicians to report outbreaks of drug-resistant bacterial infections.

Experts agree that antibiotics should be restricted to patients who can truly benefit from them--that is, people with bacterial infections. Already this is being done in the hospital setting, where the routine use of antibiotics to prevent infection in certain surgical patients is being reexamined.

"We have known since way back in the antibiotic era that these drugs have been used inappropriately in surgical prophylaxis [preventing infections in surgical patients]. But there is more success [in limiting antibiotic use] in hospital settings, where guidelines are established, than in the more typical outpatient settings," says Cranston.

Murray points out an example of antibiotic prophylaxis in the outpatient setting--children with recurrent ear infections given extended antibiotic prescriptions to prevent future infections. (See "Protecting Little Pitchers' Ears" in the December 1994 FDA Consumer.)

Another problem with antibiotic use is that patients often stop taking the drug too soon, because symptoms improve. However, this merely encourages resistant microbes to proliferate. The infection returns a few weeks later, and this time a different drug must be used to treat it.

Targeting TB

Stephen Weis and colleagues at the University of North Texas Health Science Center in Fort Worth reported in the April 28, 1994, *New England Journal of Medicine* on research they conducted in Tarrant County, Texas, that vividly illustrates how helping patients to take the full course of their medication can actually lower resistance rates. The subject--tuberculosis.

TB is an infection that has experienced spectacular ups and downs. Drugs were developed to treat it, complacency set in that it was beaten, and the disease resurged because patients stopped their medication too soon and infected others. Today, one in seven new TB cases is resistant to the two drugs most commonly used to treat it (isoniazid and rifampin), and 5 percent of these patients die.

In the Texas study, 407 patients from 1980 to 1986 were allowed to take their medication on their own. From 1986 until the end of 1992, 581 patients were closely followed, with nurses observing them take their pills. By the end of the study, the relapse rate--which reflects antibiotic resistance--fell from 20.9 to 5.5 percent. This trend is especially significant, the researchers note, because it occurred as risk factors for spreading TB--including AIDS, intravenous drug use, and homelessness--were increasing. The conclusion: Resistance can be slowed if patients take medications correctly.

Narrowing the Spectrum

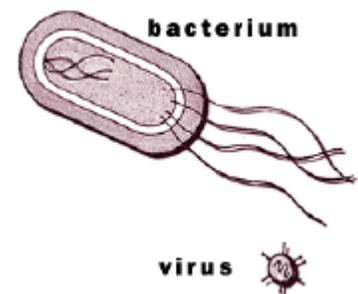
Appropriate prescribing also means that physicians use "narrow spectrum" antibiotics--those that target only a few bacterial types--whenever possible, so that resistances can be restricted. The only national survey of antibiotic prescribing practices of office physicians, conducted by the National Center for Health Statistics, finds that the number of prescriptions has not risen appreciably from 1980 to 1992, but there has been a shift to using costlier, broader spectrum agents. This prescribing trend heightens the resistance problem, write McCaig and Hughes, because more diverse bacteria are being exposed to antibiotics.

One way FDA can help physicians choose narrower spectrum antibiotics is to ensure that labeling keeps up with evolving bacterial resistances. Blum hopes that the surveillance information on emerging antibiotic resistances from CDC will enable FDA to require that product labels be updated with the most current surveillance information.

Many of us have come to take antibiotics for granted. A child develops strep throat or an ear infection, and soon a bottle of "pink medicine" makes everything better. An adult suffers a sinus headache, and antibiotic pills quickly control it. But infections can and do still kill. Because of a complex combination of factors, serious infections may be on the rise. While awaiting the next "wonder drug," we must appreciate, and use correctly, the ones that we already have.

Big Difference

If this bacterium could be shown four times bigger, it would be the right relative size to the virus beneath it. (Both are microscopic and are shown many times larger than life.)



Although bacteria are single-celled organisms, viruses are far simpler, consisting of one type of biochemical (a nucleic acid, such as DNA or RNA) wrapped in another (protein). Most biologists do not consider viruses to be living things, but instead, infectious particles. Antibiotic drugs attack bacteria, *not* viruses.

The Greatest Fear--Vancomycin Resistance

When microbes began resisting penicillin, medical researchers fought back with chemical cousins, such as methicillin and oxacillin. By 1953, the antibiotic armamentarium included chloramphenicol, neomycin, terramycin, tetracycline, and cephalosporins. But today, researchers fear that we may be nearing an end to the seemingly endless flow of antimicrobial drugs.

At the center of current concern is the antibiotic vancomycin, which for many infections is literally the drug of "last resort," says Michael Blum, M.D., medical officer in FDA's division of anti-infective drug products. Some hospital-acquired staph infections are resistant to all antibiotics except vancomycin.

Now vancomycin resistance has turned up in another common hospital bug, enterococcus. And since bacteria swap resistance genes like teenagers swap T-shirts, it is only a matter of time, many

microbiologists believe, until vancomycin-resistant staph infections appear. "Staph aureus may pick up vancomycin resistance from enterococci, which are found in the normal human gut," says Madden. And the speed with which vancomycin resistance has spread through enterococci has prompted researchers to use the word "crisis" when discussing the possibility of vancomycin-resistant staph.

Vancomycin-resistant enterococci were first reported in England and France in 1987, and appeared in one New York City hospital in 1989. By 1991, 38 hospitals in the United States reported the bug. By 1993, 14 percent of patients with enterococcus in intensive-care units in some hospitals had vancomycin-resistant strains, a 20-fold increase from 1987. A frightening report came in 1992, when a British researcher observed a transfer of a vancomycin-resistant gene from enterococcus to Staph aureus in the laboratory. Alarmed, the researcher immediately destroyed the bacteria.

Ricki Lewis is a geneticist and textbook author.

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