Bacteria: Drug Resistance Spreads, but Few New Drugs Emerge

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That fighting bacteria is tough should come as no surprise. After all, bacteria outnumber humans by an estimated billion trillion to one and reproduce half-a-million times faster than we do. Evolution is on their side. Nonetheless, the speed with which resistant bacteria emerge to defeat even the most advanced antibiotics is stunning. And it is not just methicillin-resistant *Staphylococcus aureus* (MRSA), with its estimated annual toll of 100,000 deaths in the U.S., that causes concern. Multidrug resistant (MDR) *Pseudomonas*, *Acinetobater*, *Klebsiella*, and other organisms are infecting patients in increasing numbers just when the pipeline of drugs to fight them seems to be drying out. "Antibiotic resistance is a continually emerging and extremely serious global health crisis," says James Hughes, M.D., president-elect of the Infectious Diseases Society of America and professor of medicine and public health at Emory University. "We urgently need to develop an adequate and effective antibiotic armamentarium to deal with it."

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In the absence of such a resource, antibiotic resistance exacts a heavy toll from patients and society. In a resistant infection, physicians may need to rely on second- and third-line drugs that typically cost more but are less effective and more toxic than the standard treatment for the corresponding susceptible infection. Robert Weinstein, M.D., who heads the division of infectious diseases at Chicago's Stroger Hospital, estimates that a resistant bacterium on average doubles the cost of care and the risk of dying. Further, when such a patient gets care in a hospital setting, the bacteria may spread to others by unsanitized hands and medical devices such as ventilators and catheters. "While we are waiting for pharmacological bailouts, we can prevent 80% or more of hospital infections simply by using better asepsis," Weinstein says. The need for better hand and device hygiene is particularly dire in intensive care units, with their sick patients, intense pressure, and hectic pace. "The busier the environment, the more the lapses in hygiene," he says. "That's why the epicenter of antibiotic resistance is the ICU."

However, even if we adopted the best clinical practices—and even stopped using antibiotics altogether—resistance will not disappear. As users of antibiotics, humans lag far behind bacteria, fungi, and plants that have been fighting each other with and defending against these powerful chemicals for eons. A 2006 study of 500 spore-forming soil bacteria by a team led by McMaster University chemist Gerard Wright, Ph.D., found that *all* of the microbes were resistant to multiple drugs. The bugs resisted 7–8 compounds on average from a panel of 21. No drug escaped unresisted, not even synthetic antibiotics such as ciprofloxacin and others specifically designed to combat resistance. Other studies note that MDR is not a recent phenomenon; for instance, resistance to erythromycin is estimated to have originated 880 million years ago, while resistance to penicillin may date back almost two billion years, predating even the split of bacteria into Gram-positive and Gram-negative varieties. "Drug resistance is the natural and inevitable state for bacteria," says Wright. "We should think of it as a part of biological and chemical diversity, not as episodes in an ICU."

Resistance can be generic or specific. Most bacteria have efflux mechanisms that pump out antibiotics and other toxic molecules before they have had time to act. Gram-negative species possess a cell wall that blocks most drugs. The opportunistic water-dwelling pathogen *Pseudomonas*, in particular, has a notoriously impenetrable cell wall and membrane barrier as well as a devilishly effective set of efflux pumps. Other defense mechanisms respond to specific modes of attack. To neutralize β-lactam-based drugs such as penicillin that inhibit cell wall synthesis, bacteria have learned to make an astonishing variety of β-lactamases. To evade quinolones, ansamycins, and other RNA or DNA synthesis inhibitors, bacteria mutate to change the molecular target. The pinnacle of evasion may very well be resistance to glycopeptides such as vancomycin, which involves a delicate and precise orchestration of five genes to alter a cell wall component previously believed to be mutation-proof. "If you look at the different types of resistance, you see a gradient of complexity," says Wright. "It ranges from a single mutation that can detoxify an antibiotic to elaborate selection of gene clusters that can completely alter the molecular target."

Since bacteria routinely swap genes with one another, clinical pathogens under selective pressure from antibiotics quickly pick up resistance genes from the environmental "resistome." Overuse and misuse of antibiotics both in medicine and other settings such as animal farms and fishponds aggravates this problem. All of this has led to the present crisis, which couldn't come at a worse time for the medical community. The optimism of the 1945–1960 "Golden Era" of antibiotics, when most of the existing antibiotic drug classes were discovered, has faded; since then, very few new classes of antibiotics have reached the market, and most of the new approved drugs have been existing molecules tailored to combat resistance—an incremental approach that

offers at best temporary and partial relief. Ideally, new drugs should hit targets "that don't have an overlapping resistance spectrum with existing targets," says Michael Fischbach, Ph.D., of the University of California in San Francisco. "We need new scaffolds, not just fifth and sixth generation cephalosporin or penicillin."

Unfortunately, as pharmaceutical companies have found, this is easier said than done. Advances in sequencing bacterial genomes in the early 1990s led to premature hopes of finding new drug targets. A massive, costly effort by GlaxoSmithKline from 1995 to 2001 involving 70 high-throughput screens of nearly half-a-million compounds against more than 300 potential genomic targets yielded not a single usable drug. Similar efforts at other companies have also mostly failed. This repeated failure has driven most pharmaceutical companies away from antibiotic discovery, which has led to some unfair criticism of their priorities. "People say that Big Pharma lost interest in antibiotics because it is not economically attractive, but that's false" says Thomas Gootz, Ph.D., an antimicrobials consultant who retired last year after 25 years at Pfizer's antimicrobial research and development group. "The fact is that many companies made a huge effort, but it was very, very nonproductive in finding new leads."

There are many reasons for this failure. Many initially promising compounds turn out to have too narrow a spectrum to be clinically useful (and commercially viable). Other compounds show unacceptable toxicity for mammalian cells or lack drug-like properties. But the biggest problem is to get the drug into the target bacterium and keep it there. "In Gram-negative bacteria, you have to get the drug past two membranes with different sieving properties," says former Merck researcher Lynn Silver, Ph.D., now an antimicrobials commentator and consultant. "And even when you get it inside, you have the efflux pump to deal with." Silver notes that there are no rules for getting compounds into bacteria analogous to Lipinski's rules for predicting the drug-likeness of molecules. "In the absence of that, the best bet for Gram-negatives is to aim for targets outside the cell," she says. "If your target is located inside the cell in *Pseudomonas*, good luck."

To counteract influx barriers and efflux, antibiotics often need to be present in the blood at much higher levels than most other drugs. "We typically need micrograms per milliliter concentration inside the body, even if the drug has nanomolar potency against the target," says Molly Schmid, Ph.D., a molecular biologist at the Keck Graduate Institute of Applied Life Sciences, who has extensive industry experience in antimicrobials. "Finding a drug with an acceptable level of safety is challenging." The economics of antibiotic discovery are equally daunting. Unlike drugs for chronic conditions such as hypertension or diabetes, antibiotics are used only for short periods. Further, only a small fraction of infections involve resistant organisms, limiting the market for newer and often more expensive compounds. Finally, unlike most medications, the useful shelf-life of a new antibiotic may be limited to the few years it takes for resistance to become widespread. The combination of these factors may lead to poor return on investment. On top of that, the FDA has toughened its regulatory stance on antibiotics in recent years, according to industry experts. "Discovering any drug is hard, but discovering antibiotics is even harder," says Schmid. "The market and regulatory bars for new antibiotics are so high that if we discovered penicillin today, we almost certainly could not get it to the market."

Despite these obstacles, antibacterial research continues at many small companies. Lexington, Massachusetts-based Cubist has several compounds in its pipeline, including one that combines a β-lactamase inhibitor with a fifth generation cephalosporin. "Its spectrum, potency, and lack of resistance development is extraordinarily good against *Pseudomonas*," says Cubist's head of scientific affairs, Barry Eisenstein, M.D. Watertown, Massachusetts-based Tetraphase is using a new, fully synthetic method of generating tetracycline to develop new molecules of this class. "We're able to change the bulky tetracycline molecule at every position, something that was unheard of before," says Joyce Sutcliffe, Ph.D., the company's senior vice president for biology. "We can now unlock the full potential of this class of antibiotics."

Some in academia, such as Rockefeller Institute researcher Vincent Fischetti, Ph.D., are looking at alternatives to traditional antibiotics. "Bacteria laugh at us when we throw an antibiotic at them," he says. "Within a few months they've figured it out." Instead, he suggests that we learn from bacteriophages, long-term predators of bacteria that use a variety of lytic enzymes to break out of a cell they've infected and proliferated within. One such enzyme identified by Fischetti's group turns out to be very effective against anthrax and other Gram-positive microbes. "Phages have figured out by trial and error which are the substrates bacteria can't change," says Fischetti. "We can thus use nature against nature." Antivirulence—pacifying rather than killing bacteria—is another strategy. Tufts University researcher Naomi Balaban, Ph.D., has developed a compound that interferes with quorum sensing by bacteria and prevents them from forming biofilms. Stuart Levy, M.D., also from Tufts, whose pioneering work led to the discovery of the "mar" proteins in many bacteria that regulate genes involved in infection, now leads an effort at Boston-based Paratek to develop compounds that inhibit these proteins. "The cell can then sit there and live, but since it can't turn on these genes, it can't cause an infection," Levy says. "It's a whole novel paradigm: don't kill the bacteria, instead hold them in check and prevent an infection."

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