The Future of Antibiotics and Antibiotic Resistance

Brad Spellberg, M.D.
Associate Professor of Medicine, Associate Medical Director for Inpatient Services, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Los Angeles, California, United States

Summary
Society is facing two converging public health crises: inexorably rising antibiotic resistance combined with a collapse of the antibiotic research and development pipeline. To successfully confront these crises and develop countermeasures that have lasting effects, we must come to grips with their fundamental causes. A fallacy of human egocentrism is the notion that we invented antibiotics and that we cause antibiotic resistance to occur. There are partial truths to this fallacy, but the consequence of our incomplete recognition of the origins of antibiotics and resistance is that we have been led astray in our efforts to combat resistance and develop new ways to treat infections.

Current realities

Clinical resistance has been with us since the very first use of antibiotics in the 1930s. However, as resistance caught up with treatments, the pharmaceutical industry has historically provided a solution by developing the next generation of new antibiotics. This is no longer the case. Antibiotic resistance continues to skyrocket even as the antibiotic research and development pipeline collapses. As a result, untreatable infections, resistant to all antibiotics, are now being encountered in the United States and throughout the world. We are also seeing common community infections that used to be readily treatable with oral antibiotics (e.g., urinary tract infections and abdominal infections) now resistant to all oral antibiotics. These infections require hospitalization for intravenous therapy and may lead to serious or even fatal consequences after failing oral antibiotic therapy.

Slowing the spread of or reversing antibiotic resistance is not a new concept. As far back as 1945, Alexander Fleming, discoverer of penicillin, was perhaps the first person to call for society to stop overusing antibiotics to slow resistance. Since that time, the medical community and society have repeatedly and widely acknowledged the need to control antibiotic use. Despite this acknowledgment, we have not yet learned how to effectively protect antibiotics, as evidenced by the never-ending escalation of antibiotic use and resulting resistance. In 2009, in the U.S. alone, more than 3 million kilograms of antibiotics were administered to human patients. Furthermore, a staggering 13 million kilograms of antibiotics were administered to animals in the U.S. in 2010, the vast majority for promoting growth. We simply cannot confront resistance at a population level unless we stop exposing microbes in the environment to such a catastrophic selective pressure of antibiotics. Nor can we effectively deal with the threat of resistant infections without establishing better ways to prevent infections, slow resistance, and find new treatments for infections. It is time for disruptive, transformative tactics to be adopted, which requires us to understand the root cause of resistance.

Scientific opportunities and challenges

Humans did not invent antibiotics, and we do not create antibiotic resistance. Resistance is the result of bacterial adaptation to antibiotic exposure, likely dating back to the very invention of antibiotic synthesis by prokaryotes approximately 2 billion to 2.5 billion years ago. What are the fundamental implications of this reality? First, our use of antibiotics does not create resistance, but rather naturally selects out pre-existing resistant populations in nature. Second, it is safe to assume that in 2.5 billion years of evolution, prokaryotes have invented antibiotics that can attack every biochemical target that can be attacked, and thus have also developed resistance mechanisms to protect every one of those biochemical targets. Indeed, recent experimentation has confirmed the presence of resistance to essentially all antibiotic classes in bacteria isolated from the surface of the planet for 4 million years

that have never been exposed to human manufactured drugs. Remarkably, resistance was found even to synthetic drugs that do not exist in nature, including daptomycin, which did not exist until the 1980s. These results underscore a critical reality that we must confront: antibiotic resistance exists, widely disseminated in nature, to drugs that are yet to be invented. Thus, resistance is truly inevitable to any agent that we invent that has a goal of killing microbes.

Third, the implication of the above two principles is that it is not just "inappropriate" antibiotic use that drives resistance to antibiotics. Rather all antibiotic use, appropriate or not, drives resistance via natural selection of pre-existing resistant bacteria. However, the speed at which resistance spreads should be proportionate to the level of environmental contamination by human-manufactured antibiotics, as documented by multiple population-based studies. Thus, humans do not create resistance, but directly impact its spread.

Fourth and finally, there are no "new" targets against which we can develop new antibiotics. All targets are old targets from the perspective of the microbes. Since 1931, when Domagk and colleagues discovered that chemical red dyes can kill bacteria (we now know by attacking folate synthesis), the arc of antibiotic research and discovery has been to discover new ways to kill the microbes. This strategy has saved countless lives and prolonged the average lifespan of people all over the world by years or decades. But it has also driven the resistance that plagues us and threatens the very miracle of antibiotics. Merely continuing to find new ways to kill microbes is unlikely to serve as the basis of a successful, long-term therapeutic strategy. Ultimately, over centuries or millennia, we will run out of targets and resistance mechanisms will become so prevalent as to preclude effective deployment of microbicidal antibiotics.

To truly transform treatment of infections, it will be necessary to encourage scientific approaches that do not seek to kill microbes but rather seek to modify the nature of the interaction between microbe and host so that host injury does not occur. Such therapies could include alterations in expression or activity of virulence factors, disarming the pathogen and thereby preventing it from causing disease without seeking to kill it. As well, sequestration of host nutrients, such as trace metals or other vital factors microbes need to replicate and survive, could prevent microbial growth without attacking the pathogen directly. Rather, the therapeutic target is the host, and as such, will not drive microbial resistance to the treatment. There is also potential to more effectively restore normal microbial flora, and/or use probiotics to combat infections by habitat competition within the host. The most immediate example of this is the potential to treat and prevent relapses of *Clostridium difficile* using fecal transplant or probiotics. However, normal flora have the potential to compete with many other pathogens that exist in skin and mucosal surfaces that are normally colonized with microbes.

Policy issues

- Transform infection prevention by dissemination of new technologies and practices (including establishing payor mechanisms) to more effectively and comprehensively disinfect environmental surfaces, people, and food. For example, self-cleaning hospital rooms, or portable technologies that enable rapid disinfection of all surfaces in a hospital room, would enable a far more effective disinfection process than relying upon manual application of disinfectants by the lowest paid, least-invested employees in the hospital (i.e., the janitorial staff). Such technologies could include device-driven microaerosolization of Environmental Protection Agency (EPA)-approved disinfectants, application of hydrogen peroxide vapor, UV lights, or other technologies yet to be elaborated. Reimbursement for use of such technologies is critical to encourage their uptake and use in hospitals.

- Encourage development of new active or passive vaccines to prevent and treat infections. An ounce of prevention is worth a pound of cure: If we prevent infections from occurring in the first

place, there will be no need to use antibiotics, which will decrease selective pressure driving resistance. Furthermore, passive immune therapies can work adjunctively with antibiotic therapy to more effectively treat infections, which could result in shorter course therapies or less therapeutic failures, thereby reducing salvage antibiotic therapy (i.e., treatment with a second antibiotic).

- Transform the economics of antibiotic development by use of public-private partnerships, via grants and contracts and establishment of nonprofit companies focusing in this space. Public private partnerships can more effectively align which antibiotics are to be developed with areas of unmet medical need. For-profit development is primarily driven by market size, not unmet need, which explains the over-abundance of new antibiotics developed in the last decade to treat skin infections despite the absence of need for such new drugs.

- Establish a fundamental shift in regulatory approach to make easier, less expensive, and more timely development and approval of antibiotics using small studies of highly resistant pathogens, resulting in restrictive labeling and use post-marketing, combined with post-marketing safety surveillance (e.g., the Limited Population Antibiotic Drug (LPAD) proposal from the Infectious Diseases Society of America).

- Alter the regulatory approach so that labeling is granted for indications that reflect "appropriate use" of antibiotics, rather than granting indications that are perceived to result in more widespread use (and hence greater sales). Current U.S. Food and Drug Administration (FDA) approval processes encourage inappropriate use of antibiotics by enabling labeling of broad spectrum gram-negative-active antibiotics for common infections caused by much less resistant pathogens. Rather than preserving these critically needed new drugs for lethal highly resistant infections, they are routinely wasted on common infections for which many other antibiotic options exist.

- Slow the spread of resistance by encouraging widespread use of rapid molecular diagnostics to empower providers to withhold unnecessary antibiotics and stop empiric antibiotics (i.e., use of antibiotics in the absence of knowledge of what the pathogen is) as soon as possible.

- Eliminate antibiotics for growth-promoting purposes in animals.

*** A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Antimicrobial Resistance, convened by the Institute on Science for Global Policy (ISGP) March 19–22, 2013, at Baylor College of Medicine, Houston, Texas.*