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The Problem of Antimicrobial Resistance

Overview

Since antibiotics and other antimicrobial drugs first became widely used in the World War II era, they have saved countless lives and blunted serious complications of many feared diseases and infections. The success of antimicrobials against disease-causing microbes is among modern medicine's great achievements. After more than 50 years of widespread use, however, many antimicrobials are not as effective as they used to be.

Over time, some bacteria have developed ways to circumvent the effects of antibiotics. Widespread use of antibiotics is thought to have spurred evolutionarily adaptations that enable bacteria to survive these powerful drugs. Other microbes such as viruses, fungi, and parasites have developed resistance as well. Antimicrobial resistance provides a survival benefit to microbes and makes it harder to eliminate infections from the body. Ultimately, the increasing difficulty in fighting off microbes leads to an increased risk of acquiring infections in a hospital or other setting.

Diseases such as tuberculosis, gonorrhea, malaria, and childhood ear infections are now more difficult to treat than they were just a few decades ago. Drug resistance is an especially difficult problem for hospitals harboring critically ill patients who are less able to fight off infections without the help of antibiotics. Heavy use of antibiotics in these patients selects for changes in bacteria that bring about drug resistance. Unfortunately, this worsens the problem by producing bacteria with greater ability to survive even in the presence of our strongest antibiotics. These even stronger drug-resistant bacteria continue to prey on vulnerable hospital patients.

To help curb this problem, the Centers for Disease Control and Prevention (CDC) provides hospitals with prevention strategies and educational materials to reduce antibiotic resistance in health care settings. According to CDC statistics

- Nearly 2 million patients in the United States get an infection in the hospital each year
- About 90,000 of those patients die each year as a result of their infection, up from 13,300 patient deaths in 1992
- More than 70 percent of the bacteria that cause hospital-acquired infections are resistant to at least one of the antibiotics most commonly used to treat them
- People infected with antibiotic-resistant organisms are more likely to have longer hospital stays and require treatment with second- or third-choice medicines that may be less effective, more toxic, and more expensive

In short, antimicrobial resistance is driving up health care costs, increasing the severity

of disease, and increasing the death rates from certain infections.

ENVIRONMENT FORCES EVOLUTIONARY CHANGE

A key factor in the development of antibiotic resistance is the ability of infectious organisms to adapt quickly to new environmental conditions. Bacteria are single-celled organisms that, compared with higher life forms, have small numbers of genes. Therefore, even a single random genetic mutation can greatly affect their ability to cause disease. And because most microbes reproduce by dividing every few hours, bacteria can evolve rapidly. A mutation that helps a microbe survive exposure to an antibiotic will quickly become dominant throughout the microbial population. Microbes also often acquire genes from each other, including genes that confer resistance.

The advantage microbes gain from their innate adaptability is augmented by the widespread and sometimes inappropriate use of antibiotics. A physician, wishing to placate an insistent patient who has a virus or an as-yet undiagnosed condition, sometimes inappropriately prescribes antibiotics. Also, when a patient does not finish taking a prescription for antibiotics, some bacteria may remain. These bacterial survivors are more likely to develop resistance and spread. Hospitals also provide a fertile environment for antibiotic-resistant germs as close contact among sick patients and extensive use of antibiotics select for resistant bacteria. Scientists also believe that the practice of adding antibiotics to agricultural feed promotes drug resistance.

A GROWING PROBLEM

For all these reasons, antibiotic resistance has been a problem for nearly as long as we've been using antibiotics. Natural selection of penicillin-resistant strains in a bacterium known as *Staphylococcus aureus* began soon after penicillin was introduced in the 1940s. Today, antibiotic-resistant strains of *S. aureus* bacteria as well as various enterococci (bacteria that colonize the intestines) are common and pose a global health problem in hospitals. More and more hospital-acquired infections are resistant to the most powerful antibiotics available, such as vancomycin. These drugs are reserved to treat only the most stubborn infections to slow development of resistance to them.

There are multiple signs that the resistance problem is increasing.

- In 2003, epidemiologists reported in *The New England Journal of Medicine* that 5 to 10 percent of patients admitted to hospitals acquire an infection during their stay and that the risk for a hospital-acquired infection has risen steadily in recent decades.
- Increasing reliance on vancomycin has led to the emergence of vancomycin-resistant enterococci infections. According to CDC, prior to 1989, no U.S. hospital had reported any vancomycin-resistant enterococci but subsequently, such microbes have become common in U.S. hospitals.
- The first *S. aureus* infections resistant to vancomycin emerged in the United States in 2002, presenting physicians and patients with a serious problem. In July of that year, CDC reported that a Michigan patient with diabetes, vascular disease, and chronic kidney failure had developed the first *S. aureus* infection completely resistant to vancomycin. A similar case was reported in Pennsylvania in September 2002.

- In 2004, the third reported case of vancomycin-resistant *S. aureus* (VRSA) in the United States was reported in New York. This case highlighted the failure of several standard automated susceptibility tests to identify vancomycin resistance in that isolate and suggests that additional VRSA cases may have occurred nationwide but escaped detection. Since then, three additional cases of VRSA, all occurring in Michigan, have been reported to CDC.
- Strains of *S. aureus* resistant to methicillin are endemic in hospitals and are increasing in non-hospital settings such as locker rooms and day care centers. Since September 2000, outbreaks of methicillin-resistant *S. aureus* (MRSA) infections have been reported among high school football players and wrestlers in California, Indiana, and Pennsylvania, according to CDC. During the 2003 football season, an outbreak of MRSA occurred among members of a professional football team.
- A number of cases of community-associated MRSA have also been reported, including cases in patients without established risk factors.

NIAID RESEARCH

The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), funds research, drug development, and clinical trials to combat the problem of antimicrobial resistance. NIAID manages a research portfolio of grants specifically aimed at the problem of antibiotic resistance among common bacteria responsible for hospital-acquired infections. These grants fund

- Studies on the basic biology of resistant organisms
- Applied research on new diagnostic techniques, therapies, and preventive measures
- Studies of how bacteria develop and share resistance genes

Other NIAID-funded research projects seek to identify natural antimicrobial peptides (small pieces of protein molecules) that could help stave off resistant infections.

Under a new research initiative, Sepsis and CAP: Partnerships for Diagnostics Development, NIAID has funded multiple projects to support industry development of broad diagnostic technologies. The goal is early detection of septicemia, bacteremia, candidemia, and community-acquired pneumonia.

NIAID is sponsoring a trial to test the effectiveness of two infection control strategies for reducing MRSA and vancomycin-resistant enterococci colonization and infection in intensive care units. The Strategies to Reduce Transmission of Antimicrobial Resistant Bacteria in Intensive Care Units trial involves 20 hospitals collaborating with the NIH Clinical Center.

NIAID also supports the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA). NARSA is a multidisciplinary international cadre of scientists conducting basic and clinical research focused on combating antimicrobial resistant *S. aureus* and related staphylococcal bacterial infections. The network maintains a repository of antibiotic-resistant staphylococcus strains that scientists can request for use in their research. NARSA's Web site (www.narsa.net) offers scientific presentations and a discussion

forum to promote communication among researchers.

NIAID also supports a number of networks conducting clinical trials to evaluate new antimicrobial drugs and vaccines.

- The AIDS Clinical Trials Group evaluates drugs that combat the problem of HIV resistance to standard antiretroviral treatments.
- The Bacteriology and Mycology Study Group, a network of academic and private research institutes, conducts clinical trials to improve treatments for fungal infections, particularly in people with weakened immune systems.
- The Collaborative Antiviral Study Group, made up of researchers from approximately 50 institutions, evaluates experimental therapies for viral infections.
- NIAID's Vaccine and Treatment Evaluation Units are a network of seven U.S. institutions that conduct clinical research to speed development of new vaccines and therapies.

Other research projects at NIH or funded by NIH are seeking new, molecular-level knowledge on the interactions of microbes and human cells as well as the tricks microbes use to thwart antibiotics. Another avenue of research is sleuthing the genomes of drug-resistant bacteria for vulnerabilities that could be attacked with new or existing drugs.

ANTIMICROBIAL ADVANCES AND ACTIVITIES

NIAID-funded research grants and activities are yielding results that will help public health officials hold the line in our fight against drug-resistant microbes. Some examples follow.

NIAID-supported scientists followed the expression of virulence genes during *S. aureus* infection. They found that these genes are not expressed immediately upon infection, when low bacteria numbers would be overwhelmed by the host immune system. Instead, the bacteria monitor their cell number and density, waiting until there is a critical mass before expressing virulence genes. Experiments that interfered with self-monitoring also interfered with abscess formation, thus limiting pathogenicity. These results demonstrate that inhibiting expression of virulence genes for just a short time can have therapeutic value, but this value would only be significant if treatment were started early.

At The Institute for Genomic Research, NIAID is supporting development of proteomic profiling strategies to analyze surface proteins present in organisms such as *S. aureus* strains that are resistant to intermediate levels of vancomycin. These surface proteins play a role in virulence and survival in bacterial infections. Further research holds promise for elucidating mechanisms of virulence and antibiotic resistance.

NIAID-funded researchers have identified the molecular structure formed between a particular *S. aureus* protein and collagen, a ubiquitous eukaryotic structural protein. Understanding the mechanism by which *S. aureus* adheres to host structures helps to elucidate the infection process and could eventually lead to vaccines to thwart staphylococcal infections.

One of the negative impacts of using systemic antibiotics for localized infections is that the drug circulates throughout the body killing off both beneficial and detrimental microbes. This also unnecessarily subjects the native microflora to antibiotic selection. NIAID-supported scientists are using a form of buckminsterfullerene as a photosensitizer and combining that with visible light to generate reactive oxygen that kills off infecting bacteria at the site of infection.

PARTNERSHIPS AND INTERAGENCY COLLABORATIONS

In addition to sponsoring research, NIAID co-chairs the Federal government's Interagency Task Force on Antimicrobial Resistance. This task force is made up of representatives from NIAID, CDC, the Food and Drug Administration, the Agency for Healthcare Research and Quality, the Department of Agriculture, the Department of Defense, the Department of Veterans Affairs, the Environmental Protection Agency, the Centers for Medicare and Medicaid Services, and the Health Resources and Services Administration. The Task Force is working on implementing an antimicrobial resistance action plan that reflects a broad consensus of these agencies with input from a variety of constituents and collaborators. In short, antimicrobial resistance is driving up health care costs, increasing the severity of disease, and increasing the death rates from certain infections. Information is available online at <http://www.cdc.gov/drugresistance/index.htm>

NIAID also co-sponsors the Annual Conference on Antimicrobial Resistance with the Infectious Diseases Society of America and other government and nonprofit agencies. The conference updates attendees on the science, prevention, and control of antimicrobial resistance and provides a forum for discussing new methods of treatment and control.

NIAID contracted with the National Research Council, part of the National Academy of Sciences, to conduct two workshops on infectious disease therapeutics. One focused on potential new classes of antibiotics; the other explored the possibility of treating infectious diseases by modulating the immune system. Workshop participants assessed the current state of knowledge, identified approaches that have been successful in the past, and brainstormed about ways in which new areas of research could revolutionize the treatment of infectious diseases. The report is available at www.nap.edu/catalog/11471.html .

MORE INFORMATION

**National Institute of Allergy and Infectious Diseases
Division of Microbiology and Infectious Diseases**

www.niaid.nih.gov/dmid/antimicrob

National Library of Medicine

Medline Plus

8600 Rockville Pike

Bethesda, MD 20894

1-888-FIND-NLM (1-888-346-3656) or 301-594-5983

www.nlm.nih.gov/medlineplus/antibiotics.html

Centers for Disease Control and Prevention

1600 Clifton Road

Atlanta, GA 30333
1-800-311-3435 or 404-639-3534
www.cdc.gov/drugresistance/index.htm

CDC National Nosocomial Infections Surveillance System

www.cdc.gov/ncidod/dhqp/nnis.html

Food and Drug Administration

5600 Fishers Lane
Rockville MD 20857-0001
1-888-INFO-FDA (1-888-463-6332)
www.fda.gov/oc/opacom/hottopics/anti_resist.html

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Alexandria, VA 22314
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www.idsociety.org

NIAID is a component of the National Institutes of Health. NIAID supports basic and applied research to prevent, diagnose and treat infectious diseases such as HIV/AIDS and other sexually transmitted infections, influenza, tuberculosis, malaria and illness from potential agents of bioterrorism. NIAID also supports research on basic immunology, transplantation and immune-related disorders, including autoimmune diseases, asthma and allergies.

The National Institutes of Health (NIH)—The Nation’s Medical Research Agency—includes 27 Institutes and Centers and is a component of the U. S. Department of Health and Human Services. It is the primary federal agency for conducting and supporting basic, clinical and translational medical research, and it investigates the causes, treatments and cures for both common and rare diseases. For more information about NIH and its programs, visit <http://www.nih.gov>.

News releases, fact sheets and other NIAID-related materials are available on the NIAID Web site at <http://www.niaid.nih.gov>.



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