

PROGRAM BRIEF

CERTs Research: Infectious Disease

AHRQ's mission is to improve the quality, safety, efficiency, and effectiveness of health care by:

- Using evidence to improve health care.
- Improving health care outcomes through research.
- Transforming research into practice.

Background

The mission of the Centers for Education and Research on Therapeutics (CERTs) is to conduct research and provide education that will advance the best use of therapeutics (drugs, medical devices, and biological products). The CERTs seek to increase awareness of the benefits and risks of new, existing, and combined uses of therapeutics, thereby improving the effectiveness and safety of their use.

The program is administered as a cooperative agreement by the Agency for Healthcare Research and Quality (AHRQ), in consultation with the U.S. Food and Drug Administration (FDA). The CERTs receive funds from both public and private sources, with AHRQ providing core financial support. The CERTs network currently comprises 11 research centers (see box, next page), a Coordinating Center, a Steering Committee, and numerous partnerships with public and private organizations. Each CERTs center focuses its educational and research

efforts on therapies in a particular population, therapeutic area, or topic.

CERTs Research on Infectious Disease

Science has made great progress in controlling or even eliminating many infectious diseases; however, we remain vulnerable to newly recognized and resurgent organisms. Every day it seems the media announce a new threat to the public. While antibiotics and other antimicrobials have played an important role in the fight against infectious diseases, some microorganisms have developed resistance to the drugs used against them. In addition, factors such as population crowding, easy worldwide travel, large-scale agriculture, and the threat of bioterrorism have raised concerns about the spread of infectious agents.

Since the inception of the program, CERTs researchers have tackled a variety of important questions related to infectious diseases, resulting in dozens of published research studies. These researchers have examined diverse areas such as the overuse and misuse of



Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

CERTs Research Centers

Arizona CERT at The Critical Path Institute (C-Path), Tucson, AZ

Detection and prevention of adverse drug interactions

Duke University Medical Center, Durham, NC

Therapies for disorders of the heart and blood vessels

HMO Research Network, Boston, MA

Use, safety, and effectiveness studies of therapeutics, using health plans that serve defined populations

Rutgers, The State University of New Jersey,*

New Brunswick, NJ

Therapies for mental health

University of Alabama at Birmingham, Birmingham, AL

Therapies for musculoskeletal disorders

University of Iowa,*

Iowa City, IA

Therapies for older adults and the effects of aging

University of North Carolina at Chapel Hill,

Chapel Hill, NC

Therapies for children

University of Pennsylvania School of Medicine,

Philadelphia, PA

Therapies for infection; reduction in antibiotic resistance

University of Texas MD Anderson Cancer Center and Baylor College of Medicine,*

Houston, TX

Risk and health communication; patient, consumer, and professional education; health decisionmaking and decision support; therapeutic adherence

Vanderbilt University Medical Center,

Nashville, TN

Prescription drug use in Medicaid and veteran populations

Weill Medical College of Cornell University,*

New York, NY

Therapeutic medical devices

*New center as of April 2006.

antibiotics, infection prevention and its associated costs, side effects of commonly used anti-infectives, physician prescribing patterns, and factors affecting patient adherence to treatment regimens, just to name a few. In addition, the CERTs program has conducted several studies aimed at understanding and improving our Nation's bioterrorism preparedness.

The CERTs research efforts fall into three main categories: advancing knowledge, informing patients and providers, and improving the system. Here are a few of the program highlights related to infectious disease.

Advancing Knowledge

Understanding the dangers of antibiotic resistance

Antibiotics constitute an essential weapon in the arsenal against infectious diseases, and yet the widespread use of these drugs can undermine their effectiveness. The more broadly antibiotics are used, the more likely it is that resistant strains of microorganisms will emerge.

In order to understand the possible consequences of antibiotic resistance, researchers studied a group of patients who had taken antibiotics for an extended period of time—patients treated for acne. Researchers wanted to know if those who had taken antibiotics long term suffered a higher incidence of upper respiratory tract infections than those who had not.

Although upper respiratory tract infections are generally viral in nature and of limited clinical consequence, they have significant public health implications. Previous studies have shown that more than 200 million episodes occur per year in the United States, and that the economy suffers a loss of more than \$25 billion in annual revenue due to them.

The General Practice Research Database (GPRD) houses information on patients in the United Kingdom who are assigned to some of the National Health Service's general practitioners who maintain their clinical records electronically. Using GPRD data, the CERTs team identified more than 118,000 people diagnosed with acne. Of these, 72 percent received some type of antibiotic treatment for more than 6 weeks, while 28 percent did not. The study found that patients receiving antibiotics were twice as likely to develop an upper respiratory tract infection as were patients who did not use antibiotics.¹

While these results are not proof that the antibiotics caused the increased infections, there are theories to explain the connection. Perhaps antibiotics change the bacterial flora at the back of the throat, making people more vulnerable to infections. Or perhaps the antibiotics lead to changes in the immune system—changes that could make patients more vulnerable to upper respiratory tract infections. Until physicians have more information with concrete guidelines to follow, research in this area should continue.

Finding ways to reduce postoperative infections in children

Children with life-threatening congenital heart disease often face surgery within the first few weeks of life. After surgery, a chest infection, also called mediastinitis, can develop. While this complication is rare, it is serious and can be fatal. A CERTs research team designed a study to find out how often this problem occurs and to find ways to reduce the risk of developing this infection.

CERTs researchers found the attack rate of mediastinitis to be about 1.4 percent, which was similar to the rate found in previous studies of adults. However, one-third of the infections were due to gram-negative bacilli (GNB), a higher percentage than previously found in

children. Researchers believe the higher number of GNB infections was due, at least in part, to the fact that the study included infants—a group often exposed to GNB immediately before or after birth. Additionally, researchers found that when physicians delayed surgically closing the patient's sternum (sometimes done due to swelling after surgery), there was an even greater risk of GNB infection. These results were alarming to the investigators because GNB are some of the most antibiotic-resistant strains of bacteria.²

Exposing the dangers of the antibiotic erythromycin

Erythromycin has been on the market for 50 years and is commonly prescribed to treat conditions such as strep throat, certain types of pneumonia, and other infections. While it is generally accepted as safe and effective, some reports have associated its use with serious arrhythmias (irregular heartbeats) and sudden cardiac death. Because previous reports focused on the intravenous form of erythromycin, many have presumed that the oral form of the drug was not associated with serious arrhythmias. CERTs researchers designed a study to test this theory and to find out whether taking certain medications in addition to erythromycin could increase the risk of sudden cardiac death.

CERTs researchers reviewed the electronic records of 4,404 Medicaid patients from Tennessee who died of sudden cardiac death from 1988 through 1993. The researchers confirmed 1,476 cases and then studied Medicaid's records of each patient's medication use.

The research team found an association between the use of erythromycin and the risk of sudden death from cardiac arrest with both the oral and intravenous forms of erythromycin. Even more concerning, they found an increased risk associated with taking erythromycin in combination with

medications that inhibit a specific type of enzyme in the body known as CYP3A. The risk of death for people using both erythromycin and a CYP3A inhibitor was five times as high as the risk for those who were not using any of the antibiotic drugs from the study or a CYP3A inhibitor.

Commonly used medications that inhibit the CYP3A enzyme include the antibiotic clarithromycin (Biaxin); certain antifungal drugs used to treat toenail fungus and yeast infections, such as fluconazole (Diflucan), ketoconazole (Nizoral), and itraconazole (Sporanox); and calcium channel blockers prescribed for high blood pressure such as verapamil (Verelan) and diltiazem (Cardizem).

Because CYP3A inhibitors slow down erythromycin's breakdown in the body, its concentration in the bloodstream is significantly increased. At high levels, it traps salt inside muscle cells and can interrupt normal heart muscle contraction, triggering serious heart rhythms or even sudden death. With safer antibiotics, such as amoxicillin, readily available, researchers recommend that physicians avoid prescribing erythromycin in conjunction with CYP3A inhibitors.³

This study illustrates that it is important for patients to keep a list of medications that they can share with all their doctors. It also shows the need for continuing research on the safety of older medicines, including how they interact with newer drugs.

Finding risk factors associated with resistant urinary tract infections in children

The research community has limited data on the extent of antibiotic resistance in bacteria that cause urinary tract infections (UTIs) in children. This information is needed to help optimize the use of antibiotics for such infections. A CERTs study has investigated recent changes in the frequency of different

types of bacteria that cause UTIs, the extent of antibiotic resistance, the association of ethnicity with resistance, and experience-based therapy in pediatric UTIs.

During the study period, CERTs investigators found that isolates of *Escherichia coli* (the most common bacteria causing UTIs) obtained from Hispanic children were less likely to be pan-susceptible (or treatable by a variety of antibiotics) than were isolates from other children. Bacteria from Hispanic children were more likely to exhibit poor susceptibility to TMP-SMX, an antimicrobial combination commonly used for UTI treatment, as well as resistance to two or more drugs. The choice of empirical therapy varied during the study period, and higher resistance rates in Hispanic children may correlate with a greater risk of a poor response to initial antibiotic therapy. CERTs investigators are conducting additional research to characterize further associated risk factors for resistance and to optimize experience-based therapy in these children.

Informing Patients and Providers

Education campaign works to decrease antibiotic prescriptions in children

The use of antibiotics in children greatly increased between the mid 1970s and early 1990s. Unfortunately, with this trend, rates of bacterial resistance also increased. Public health officials grew increasingly worried for a number of reasons—rising rates of resistant organisms were making a number of antibiotics less useful, and pharmaceutical companies were doing only limited research to develop new antibiotics.

In 1999, 10 Federal agencies and departments, led by the Department of Health and Human Services, formed a

task force to tackle the problem of antimicrobial resistance. Cochaired by the Centers for Disease Control and Prevention, the FDA, and the National Institutes of Health, the task force issued a plan of action in 2001.

To better understand the latest antibiotic-prescription patterns, CERTs researchers designed a study to look for prescribing changes between 1996 and 2000. The study found that antibiotic prescriptions for children ages 3 months to 18 years dropped significantly between 1996 and 2000, suggesting that the combination of public health campaigns and attention by the lay press and other groups was effective in shaping public attitudes toward these drugs.

Although such educational campaigns are beneficial, public health officials warn that antimicrobial resistance continues to be a serious threat. Researchers agree that intensive educational efforts must continue.⁴

Published guidelines decrease dangerous drug combinations in HIV patients

The biggest news and greatest benefit to people with human immunodeficiency virus (HIV) came in the winter of 1995-96 with the introduction of protease inhibitors, a new class of drugs. Patients started taking protease inhibitors in combination with other drugs, and the number who became ill from opportunistic infections or died from AIDS dropped by about 70 percent in the United States.

Unfortunately, protease inhibitors can cause elevated levels of cholesterol, putting patients at risk of heart disease, so sometimes they are given prescriptions for lipid-lowering medications such as statins. However, some statin drugs interact with protease inhibitors and increase the risk of dangerous side effects.

CERTs researchers examined the use of protease inhibitors and statins in a large group of HIV patients to determine how often physicians prescribed dangerous combinations of these drugs. Specifically, researchers wanted to see if health care providers changed their prescribing habits after the publication of preliminary guidelines for combining these drugs.

The study found that the number of dangerous combinations prescribed decreased significantly after the release of the preliminary guidelines but still remained relatively high. CERTs researchers believe that continued education will help physicians reduce the use of dangerous combinations of protease inhibitors and statins.⁵

Improving the System

Drug used to prevent infection in preterm infants does not reduce costs

The Medicaid program provides care for approximately 46 million people. In most States, it is the fastest growing category of spending and has already surpassed education as the largest portion of the State budget. With these cost increases, there is increased public scrutiny—each potential medical treatment must be weighed against its cost and benefit.

CERTs researchers designed a cost analysis of palivizumab, an expensive antibody preparation used by the North Carolina Medicaid Program to prevent a serious viral infection of the lung in premature infants. In 2003 the program spent more than \$12 million on palivizumab.

The study compared costs related to this infection in two groups of infants born 5 to 8 weeks prematurely. One group received palivizumab as a preventive measure, while the other group did not. Although the group receiving the drug had fewer hospitalizations during this period, the study found that the cost of palivizumab outweighed the money saved from treating fewer infections.



Medicaid programs across the United States may want to reconsider the criteria used to determine which infants should receive this product and look for less expensive ways of reducing the number of babies at high risk of this infection.⁶

Bioterrorism concerns place demands on the health care system

The 2001 anthrax attacks occurred over the course of several weeks beginning on September 18, 2001. Letters containing anthrax bacteria, mailed to several news media offices and two U.S. Senators, killed five people. In the days that followed, many Americans who feared anthrax exposure requested prophylactic doses of antimicrobials.

To understand better how such a situation affects our health care system, CERTs researchers surveyed emergency physicians in Pennsylvania to find out whether they had received patient requests for antimicrobials because of the fear of anthrax exposure and, if so, whether they had prescribed them.

A majority of the respondents received requests for antimicrobials, and one-quarter prescribed them due to a request. Although antimicrobials are an important tool for treating anthrax exposure, prescribing them inappropriately is a public health concern. Overuse of antimicrobials can have serious consequences, ranging from potential adverse effects on individual patients to the increased risk of drug resistance, depletion of supplies, and increased costs to insurers and patients.

This study demonstrated gaps in our current understanding of how to handle public demands for medications after

perceived exposure to biological agents. The study respondents suggest that improving public communication to reduce fear could help.

This study underscores the importance of a strong working relationship between public health officials and health care providers in responding to demands for treatment of possible exposure after a bioterrorist incident.⁷

Looking to the Future

The CERTs program conducts research and develops educational projects that study and report the efficacy, safety, and use of various medical therapies. The studies highlighted in this Program Brief demonstrate our progress in the area of infectious disease, but additional research is needed.

For More Information

The CERTs welcome input about the types of research and education needed to better address costs, effectiveness, and safety issues related to the use of therapeutics. More information on the CERTs program is available at www.certs.hhs.gov.

References

1. Margolis DJ, Bowe WP, Hoffstad O, et al. Antibiotic treatment of acne may be associated with upper respiratory tract infections. *Arch Dermatol* 2005;141:1132-6.
2. Long CB, Shah SS, Lautenbach E, et al. Postoperative mediastinitis in children: epidemiology, microbiology and risk factors for Gram-negative pathogens. *Pediatr Infect Dis J* 2005;24:315-9.

3. Ray WA, Murray KT, Meredith S, et al. Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004;351:1089-96.
4. Finkelstein JA, Stille C, Nordin J, et al. Reduction in antibiotic use among US children, 1996-2000. *Pediatrics* 2003;112:620-7.
5. Hulgán T, Sterling TR, Daugherty J, et al. Prescribing of contraindicated protease inhibitor and statin combinations among HIV-infected persons. *J Acquir Immune Defic Syndr* 2005;38:277-82.
6. Wegner S, Vann JJ, Liu G, et al. Direct cost analyses of palivizumab treatment in a cohort of at-risk children: evidence from the North Carolina Medicaid Program. *Pediatrics* 2004;114:1612-9.
7. M'ikanatha NM, Julian KG, Kunselman AR, et al. Patients' request for and emergency physicians' prescription of antimicrobial prophylaxis for anthrax during the 2001 bioterrorism-related outbreak. *BMC Public Health* 2005;5:2.



www.ahrq.gov

AHRQ Pub. No. 07-P008
May 2007