ANTIBIOTIC RESISTANCE can be considered one of the most significant medical challenges of the 21st century, and it requires immediate attention. Response to resistance, either individually or globally, can take many approaches. However, the approach should be multifaceted because antibiotic resistance is no longer confined to nosocomial infections. Resistance in pathogens responsible for community-acquired mixed infections has increased dramatically over the last decade. This article reviews the different strategies that have been employed to respond to the changing epidemiology of community-acquired mixed infections and the considerations that must be given to resistant organisms. Real-life examples of programs employed in hospitals nationwide offer a clear view of the targets that need to be addressed to meet this formidable challenge. (Advanced Studies in Medicine 2002;2(4):117-125)

While antibiotics may be one of the most significant medical achievements of the 20th century, antibiotic resistance may prove to be the most significant medical challenge of the 21st century. Antibiotic resistance is not a new phenomenon, among the medical community or the general population. Leading magazines in broad readership populations such as Newsweek, Time, Sesame Street Parents, and Business Week have featured articles on “killer microbes” and the “end of the miracle drugs.” For physicians and health care providers, resistance was initially considered to be predominantly a nosocomial problem, but recent epidemiological data indicate that it is now becoming a community-acquired infectious disease (ID) issue, particularly with the emergence of drug-resistant pneumococcus. Organisms that initially were thought of as only nosocomial pathogens, eg, methicillin-resistant Staphylococcus aureus (MRSA), are now arising as community-acquired pathogens. The emergence of resistance in gram-positive organisms has been most prominent, or at least most stringently followed, in recent years. A recent surveillance study showed a roughly 20% to 80% increase since 1975 in the percentage of gram-positive pathogens resistant to antibiotics (Figure 1).

In developing a response to resistance, ID specialists need to consider where antibiotics are used and where the problems exist. Figure 2 shows the different areas of health care that use antibiotics and their interrelationships. Interestingly, most antibiotics are not used in tertiary care hospitals, as is commonly thought, but rather in community hospitals and, par-
ticularly, in the ambulatory setting. Other sources are daycare centers, nursing homes, and the animal industry. Any response must be global in nature in order to effect an impact on the emergence of resistance; the response cannot just focus on any single area where resistance may emerge. To date, this global approach has not been implemented.

**Efforts to Control Resistance**

Various efforts have been initiated to impact the emergence of resistance. Again, the problem is that most or almost all of the data in this area come from addressing resistance in the nosocomial setting. There are very few data dealing with the emergence of resistance in the ambulatory setting, particularly with the problem of antibiotic misuse or abuse.

**Improve Diagnostic Methods**

One of the big problems with antimicrobial use is our limited ability to diagnose the cause of infections to more accurately target the causative organism (Please also see “The Changing Epidemiology of Community-acquired Mixed Infections: A Focus on Community-acquired Pneumonia” by Dr. Richard P. Wenzel in this issue). We are at the beginning of the 21st century but are able to diagnose the cause of community-acquired pneumonia only 40% to 60% of the time.\(^5\)\(^6\)

**Infection Control Measures**

Several measures can be easily implemented in the ambulatory setting, the most important of which is handwashing. Both patients and physicians must wash their hands; this is a simple and well-tolerated practice that effectively controls the spread of infection. It is surprising at how willing patients are to take a 60-day course of antibiotics, but they seem unwilling to wash their hands regularly. Handwashing decreases the spread of infections and the spread of resistance.

In the hospital-based setting, active surveillance has been shown to be effective if it targets the correct population. An early surveillance study of MRSA examined clinical

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**Figure 1. Trends in Gram-Positive Resistance in the United States**

Data from references 2 and 3.

NPSP = nonpenicillin susceptible pneumococcus; VISA = vancomycin (glycopeptide) intermediate Staphylococcus aureus; VTSP = vancomycin tolerant Streptococcus pneumoniae; LISA = linezolid intermediate (and resistant) Staphylococcus aureus; MRSE = methicillin resistant Staphylococcus epidermidis; MRSA = methicillin resistant Staphylococcus aureus.

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**Figure 2. Environments Impacting on Antimicrobial Resistance**

Data from reference 4.
specimens from persons with MRSA. Once identified, the persons were isolated but the impact on prevalence was small, as shown in Table 1. In fact, there was an increase in MRSA prevalence in pneumonia, bloodstream infections, and surgical site infections. It appears that the failure of this effort was in not identifying people who were colonized with the organism.7

A more intensive program that identifies and isolates the people colonized with MRSA—before they have the chance to develop a clinical infection—was implemented at the University of Virginia in the early 1980s and shows more positive results. This program uses surveillance cultures for colonization, monthly prospective microbiologic surveys of high-risk patients, and the identification of previously infected or colonized patients at rehospitalization to identify individuals who should be placed in contact precautions. This type of enhanced surveillance resulted in a marked decrease in both the prevalence and the incidence of MRSA infections over a 12-month period (Figure 3).7,8

Furthermore, this program has led to a decrease in bloodstream infections with resistant organisms. Farr et al looked at the incidence of MRSA and vancomycin-resistant Enteroccci (VRE) bloodstream infections at the University of Virginia Health System and 6 other hospitals in the Virginia area. The results show that in a hospital with enhanced surveillance and identification and isolation of people who are colonized, significantly lower incidences of both MRSA and VRE bloodstream infections exist (Figure 4).9

The success of heightened surveillance and control measures has a significant economic as well as clinical impact. One study demonstrates $17,422 in excess costs for attributable hospital stays and total and variable direct costs, comparing MRSA with methicillin-sensitive S aureus infections. This translates into annual savings of $300,000 to $900,000 with control measures, based on data from the University of Virginia.10 VRE bloodstream infections cost approximately $27,190 more than similar infections caused by vancomycin-sensitive Enterococci. Therefore, this effort leads to significant cost savings by decreasing the number of both MRSA and VRE bloodstream infections.11

At our institution, a 50% decrease in MRSA and VRE bloodstream infections would lead to a cost savings of over $1 million.
Reduce Resistance Reservoirs in Healthcare Settings

Many of the current infections in healthcare settings result from interventions and the use of implantable devices, most notably intravascular catheters. However, implantable devices are not restricted to hospitals because indwelling intravascular devices are used ever increasingly in the homecare setting. How many people currently complete a course of intravenous antibiotics in the hospital? Rather, they complete them in skilled nursing facilities or at home with indwelling device. Increasingly, data show that new types of catheters, in which antiseptic or antibacterial substances are bonded to the catheter can decrease the incidence of bloodstream infections. The 3 new types of catheters currently on the market are the minocycline/rifampin catheter, the chlorhexidine/silver sulfadiazine catheter, and an ionized silver catheter. Darouiche et al recently compared the minocycline/rifampin and chlorhexidine/silver sulfadiazine catheters with the minocycline catheter, showing lower rates of infection. In this study, chlorhexidine/silver sulfadiazine coating was only on the external surface of the catheter. A catheter available with both internal and external coated surfaces is now available. A study is planned to compare this device with the minocycline/rifampin catheter, particularly because there is some concern about the emergence of rifampin resistance in gram-positive organisms with use of the latter catheter.

Benchmark Resistance and Antimicrobial Use

Benchmarking resistance and antibiotic use typically occur in a hospital-based setting, but what is the incidence of resistance in the community and how is it defined? Are susceptibilities in a hospital representative of the resistance pattern in a community? Benchmarking resistance in community-acquired settings and ascertaining any possible relationship between nosocomial resistance and community-acquired resistance require further study.

Develop New Drugs and Vaccines/Use the Vaccines We Have

Like antibiotics, the Haemophilus influenzae vaccine can be thought of as a modern medical miracle. Other effective vaccines include the 23-valent and pediatric conjugated pneumococcal vaccines. The pediatric vaccine is relatively new and the impact of its
Expanded use in children on the epidemiology of pneumococcal infection in adults will take several years to fully appreciate. Other important vaccines are *Neisseria meningitidis* conjugated vaccine to be available in 2 years and the *Staphylococcus aureus* vaccine that is now in phase III studies, as well as new vaccines targeting influenza virus. It will be interesting to see their impact on clinical disease in both the community and the hospital-based settings. However, despite the well-documented benefits of vaccination, use of available vaccines remains alarming low. Additionally, we have experienced insufficient supplies of influenza vaccine the past 2 years.

Another approach to the management of antimicrobial resistance is the development of new agents. There are nearly 30 new drugs under development with expanded in vitro activity against gram-positive organisms. However, the problem of emerging resistance in gram-negative organisms, such as those expressing extended-spectrum β-lactamases and resistance to fluoroquinolones, has not been addressed by the pharmaceutical industry. However, the development of new antibiotics alone is not the answer. As Dennis Maki pointed out, "The development of new antibiotics without having mechanisms to ensure their appropriate use is much like supplying your alcoholic patients with a finer brandy." Without appropriate early use, resistance will be seen rapidly after their introduction, as has been seen with all other antibiotics. Chen et al showed a 3-fold increase in pneumococci with reduced susceptibility to fluoroquinolones with a 6-fold increase in fluoroquinolone prescriptions per 100 persons over 10 years (Figure 5).

**Education and Antimicrobial Stewardship**

Unfortunately, education alone has been of little value in controlling antibiotic use. Even a simple program to educate health care professionals about the benefits of handwashing showed little, if any, improvement. However, the introduction of a new, increasingly accessible, alcohol-based waterless hand antiseptic improved compliance more than 2-fold. How can we harness this information for antibiotic use?

In the past, "antimicrobial stewardship" has fallen under the guise of various names including antibiotic control and antimicrobial management. The goals of antimicrobial stewardship are listed in Table 2. One of the most effective ways to improve antimicrobial use is to consider the decision to use antibiotics within a conceptual framework (Figure 6). Prescribing an antibiotic requires knowledge of antibiotics, infectious diseases, and the patient (eg, allergies, previous intolerance to any antibiotics). The physician's attitude is important, (eg, does the physician think that antimicrobial resistance is a problem?) Is the physician willing to release some control of his/her antibiotic prescribing in order to improve the use of antibiotics? In the ambulatory setting, the patient's attitude becomes more significant, as many patients demand antibiotics. So, defining the patient's understanding of and attitude towards resistance is important.

The availability of antibiotics varies by setting. In the ambulatory setting, availability is defined usually by what is in the supply closet. In the hospital-based setting, availability is dictated by the type of formula (open or closed, or any restrictions). The physicians and house staff play a key role in whether they use culture results and the results of other studies to help refine their antibiotic choices.

<table>
<thead>
<tr>
<th>Table 2. Goals of Antimicrobial Stewardship</th>
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<tr>
<td>▶ Promote quality health care</td>
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<td>▶ Improve antimicrobial use</td>
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<td>▶ Improve patient outcomes</td>
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<td>▶ Improve cure rates</td>
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<td>▶ Decrease failure rates</td>
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<td>▶ Decrease the number of adverse drug events</td>
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<td>▶ Decrease antimicrobial errors</td>
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<td>▶ Limit emergence of resistance</td>
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<td>▶ Improve institutional outcomes</td>
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Numerous interventions to improve the use of antibiotics have been described in the literature, but they can all be evaluated in the context of this conceptual framework. Education, as discussed previously, is not particularly effective due to lack of retention, or at least implementation. Formulary restrictions (ie, closed formularies) are of limited value. Several studies show that restricted formularies improve antibiotic use and can impact cost, but there are no studies to show an impact on resistance.17,18

Prior approval programs are effective in improving antibiotic use.19,20 Newer interventions include antibiotic streamlining and cycling or rotation. The rationale behind antibiotic cycling is to “keep the bug guessing,” but it is not clear that the resistant strain is actually extinguished and therefore may reemerge at a later time. There remain many questions with this strategy: What is the correct cycling duration? What antibiotics should be cycled? How many antibiotics should be cycled? When should cycling be implemented? Clearly, this is still an open area for research and very much a work in progress.

Computer-assisted programs are available, most notably the program developed at LDS Hospital in Utah. This antibiotic management program used local clinician-derived consensus guidelines in a decision-support program. The prescribing guidelines included in the program were for inpatient prophylactic, empiric, and therapeutic uses of antibiotics. Institution of this program resulted in improvement in both clinical and economic outcomes.21

At the University of Pennsylvania, our program impacts numerous areas and modes of communication and interaction to affect the physician's knowledge, attitude, and decision to use antibiotics, as well as the patient's attitude, and the availability of antibiotics. The participants include a program director and hospital epidemiologist working closely with infection control practitioners, the hospital director, ID faculty and fellows, the pharmacy and therapeutics committee, ID clinical pharmacists, and the director of clinical microbiology (Figure 7). In establishing our program, we developed guidelines for antibiotic use and

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**Figure 6. Conceptual Framework for Improving Antibiotic Use and Choice**

**Figure 7. The University of Pennsylvania Antimicrobial Stewardship Program**
empiric antimicrobial therapy. We established appro-
appropriate dosing and dosage intervals, based on disease
state and pharmacokinetics principles. We evaluated
agents for addition or deletion to the formulary, and
we have competitive bidding between therapeutic
equivalents. We instituted a restriction program, a
streamlining program, ongoing educational programs,
and continuous monitoring of antibiotic usage pat-
terns. We initially published our guidelines in hand-
book form, and they are also currently available at
http://www.uphs.upenn.edu/bugdrug/.

The University of Pennsylvania program has
achieved incredibly significant results in improving
appropriate antibiotic use, compared with the usual
practice group (87% vs 47%). The program was also
responsible for higher cure rates (64% vs 42%,
P = 0.007), decreased failure rates (15% vs 28%,
P = 0.03), and a trend towards decreased emergence
of resistance. Significant economic savings were rec-
ognized for the institution with a $300,000 savings
in antibiotic costs, $500,000 savings in infection-
associated costs, and $4.3 million savings in total
cost of hospitalization. The hospitalization savings
were primarily driven by decreased length of stay in
the intensive care unit.

Several other groups have shown that improved
antibiotic use can have an impact on emergence of
resistance. This has been shown for VRE, group A
streptococci, and Streptococcus pneumoniae.9 The
study involving S pneumoniae involved a multi-
pronged approach to improving use: a public cam-
paign, a physician education campaign, and an
effective increase in the cost of penicillin. The result
was a recovery of pneumococcal susceptibilities.24
Additional studies have shown a recovery of suscepti-
bility to β-lactam and quinolone antibiotics and
decreases in selected nosocomial infections with prior
approval programs.19,20

The Future of Infectious Diseases
and Antimicrobial Resistance

The future of this field, particularly for the ambu-
latory setting, appears to be heavily involved with
information technology. Several universities have post-
ed their guidelines on the Internet, the addresses of
which are shown at the end of this article. Some of
them are or will be available to download onto a hand-
held personal digital assistant (PDA). Interactive text-
books and more integrated systems such as TheraDoc,
developed by the LDS hospital group, can be used in any
hospital information system. Other companies such as
Allscripts Healthcare Solutions may also impact antimi-
crobial prescription through point-of-care decision tools.

The Centers for Disease Control and Prevention
have taken the initiative in educating the public on the
risks of antibiotic overuse and misuse. Their patient
information is available on their Web site (www.cdc.gov/drugresistance). However, the Internet
has proved to be, in some respects, a minefield for
attempts to control and/or improve antibiotic use among
the general public, especially in this age of bioterrorism
attacks with anthrax. Ciprofloxacin is available for pur-
chase online and the prices have risen exponentially in
the weeks following the discovery of anthrax-laced mail.
On the other hand, physicians are writing those pre-
scriptions, which precipitates significant issues with
respect to stockpiling antibiotics. It depletes the existing
pharmaceutical distribution networks, and, once
ciprofloxacin is in the household, the trigger to take the
antibiotic is more likely going to be the onset of sniffles
rather than an actual anthrax exposure. The misuse may
occur in mistaken administration to children and preg-
nant women, when the risk-to-benefit ratio does not
support administration. The incidence of adverse drug
events will probably increase and history shows us that
antibiotic misuse promotes antimicrobial resistance.

Conclusion

Antibiotic resistance has become an important
problem and it is the responsibility of the infectious
disease medical community to limit the emergence of
resistance using one or more proven strategies, includ-
ing infection control measures, surveillance and isola-
tion of colonized and infected persons, reducing
resistance reservoirs in all health care settings, bench-
marking antibiotic use, using the currently available
vaccines, and antimicrobial stewardship. With use of
these approaches, antibiotics can remain one of most
significant achievements of modern medicine.

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cillin-resistant Staphylococcus aureus—Minnesota and North


11. Stephenson J. Icelandic researchers are showing the way to bring down rates of antibiotic-resistant bacteria. JAMA. 1996;275:175.
Case Study

A 48-year-old woman with abdominal pain

HISTORY
Ms. Lucas is a 48-year-old woman with a history of hypertension controlled with a β-blocker who initially presented to the hospital in August 2001 with moderate midepigastrium pain associated with nausea and vomiting. The pain remained crampy and localized without radiation for approximately 2 hours. While in the emergency department, the pain localized to the right upper quadrant but did not increase in severity. There was no hematemesis, diarrhea, or hematochezia.

PHYSICAL EXAMINATION
The patient was a moderately obese African American woman who appeared uncomfortable. She was afebrile. Blood pressure was 150/100 mm Hg and her heart rate was 112/min. Lungs were clear to percussion and auscultation and the cardiac examination did not demonstrate a murmur or gallop. The patient's abdomen was soft with decreased bowel sounds. There was voluntary guarding in the right upper quadrant and the region was tender to palpation. There was no rebound tenderness and no masses were evident.

LABORATORY RESULTS
The patient had a normal white blood cell count and differential. Liver-associated enzymes and bilirubin were normal, as was an amylase and lipase. A right upper quadrant ultrasound demonstrated several nonobstructing gallstones and a dilated common bile duct. No stones were visible in the bile duct and there was no edema or fluid surrounding the gallbladder.

INTERVENTION
Ms. Lucas was admitted with a diagnosis of acute cholecystitis. It was also believed that she passed a gallstone. Therapy was instituted with ceftazidime and metronidazole, and symptoms subsided within 48 hours. The patient decided to postpone a cholecystectomy until after an upcoming trip to Europe. A PICC line was inserted and she was discharged to complete a 10-day course of ceftazidime and oral metronidazole.

FOLLOW-UP
Ms. Lucas completed the antibiotics without incident and the remainder of the summer and European vacation were uneventful. She modified her diet somewhat and did not experience any further right upper quadrant pain. On October 12, 2001, she developed mild upper respiratory symptoms characterized by cough, sore throat, and nonproductive cough, as well as diffuse myalgias. Her physician felt that the symptoms were due to a viral syndrome, but Ms. Lucas demanded a course of ciprofloxacin for possible inhalational anthrax because she drove through Trenton, NJ, 2 days prior to the onset of symptoms. After a 25-minute discussion, her doctor prescribed a 60-day course of ciprofloxacin at a dose of 500 mg twice daily.

Her symptoms improved in 2 days and she was confident she chose the correct course of therapy. As she approached the end of the course of ciprofloxacin, she developed severe right upper quadrant tenderness that radiated to her left shoulder. The pain was associated with fever, chills, nausea, and vomiting. Ultrasonography and a CT scan demonstrated findings consistent with emphysematous cholecystitis. Antimicrobial therapy was instituted with ceftazidime and metronidazole, and she was taken to the operating room the following morning. She remained febrile to 104°F. Blood cultures drawn at the time of admission, and cultures of bile and perihepatic fluid sent from the operating room, all grew Escherichia coli resistant to ampicillin, ampicillin/sulbactam, trimethoprim sulfamethoxazole, all upper-generation cephalosporins, piperacillin/tazobactam, ciprofloxacin, gentamicin, and tobramycin. The organism was susceptible to carbapenems and amikacin. Her post-operative course was complicated by a MRSA catheter-associated bacteremia.

DISCUSSION
Although antibiotics would not be advisable normally, she received ceftazidime and metronidazole because her physician was worried about anaerobes. Cultures are no longer typically done for anaerobes; we just treat them empirically. She received a PICC line and she returned home in good health, until she developed a viral syndrome. This is a very real problem that clinicians are going to face all winter long because people will want ciprofloxacin for their perceived anthrax infection. She ended up with a 60-day course of ciprofloxacin and returned with emphysematous cholecystitis. She was initially treated again with ceftazidime and metronidazole and eventually went to the operating room. All of her cultures grew E. coli that was resistant to ampicillin, sulbactam, trimethoprim sulfamethoxazole, cephalosporins, piperacillin/tazobactam, ciprofloxacin, gentamicin, and tobramycin. Her cultures were susceptible to cefepime, carbapenems, and amikacin. Clearly, this organism is expressing an extended-spectrum β-lactamase and has also developed quinolone resistance.

Cefepime would not be recommended, nor would any advanced-generation cephalosporin. The susceptibility results are misleading and may be attributed to inoculum effect. Additionally there are no clinical data to support using cefepime in the setting of an extended-spectrum β-lactamase. So, it comes down to using a carbapenem in this setting.

Interestingly, she also developed an MRSA catheter-associated bacteremia. It may have been related to her antibiotic use. There are some primarily epidemiological data that show a relationship between quinolone use and the emergence of MRSA.