Antimicrobial Resistance: A Plan of Action for Community Practice

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Antibiotic resistance was once confined primarily to hospitals but is becoming increasingly prevalent in family practice settings, making daily therapeutic decisions more challenging. Recent reports of pediatric deaths and illnesses in communities in the United States have raised concerns about the implications and future of antibiotic resistance. Because 20 percent to 50 percent of antibiotic prescriptions in community settings are believed to be unnecessary, primary care physicians must adjust their prescribing behaviors to ensure that the crisis does not worsen. Clinicians should not accommodate patient demands for unnecessary antibiotics and should take steps to educate patients about the prudent use of these drugs. Prescriptions for targeted-spectrum antibiotics, when appropriate, can help preserve the normal susceptible flora. Antimicrobials intended for the treatment of bacterial infections should not be used to manage viral illnesses. Local resistance trends may be used to guide prescribing decisions. (Am Fam Physician 2001;63:1087-96,1097-8.)

A patient information handout on antibiotic resistance, written by the authors of this article, is provided on page 1097.

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Since their introduction in the 1940s, antibiotics have been the primary treatment for bacterial infections. Although antibiotics were once hailed as "miracle drugs" without adverse consequences, widespread and often inappropriate use has contributed to the emergence of bacteria that are resistant to not just one, but multiple antibiotics.

Most concerns about resistance have focused primarily on hospitals and the developing world, seemingly with limited relevance to family physicians in the United States; however, the problem is now increasing at an alarming rate in the outpatient setting. In fact, various forms of antimicrobial resistance now pervade all communities and all health care settings, including the physician's office and the home care environment. As a result, family physicians are confronted with new diagnostic challenges, complicated therapeutic choices, rising treatment costs and an increased risk of patient morbidity and mortality. Compounding this public health crisis is the fact that few novel agents are being developed for use in the future.

See editorial on page 1034.

The growing sense of urgency surrounding the problem of antibiotic resistance was heightened recently by alarming reports of community-onset infections caused by strains of methicillin-resistant *Staphylococcus aureus* (MRSA) in Minnesota and North Dakota.[1] Although MRSA infections were once confined to patients in hospitals and long-term care facilities (as well as intravenous drug users), they were recently implicated as the cause of four pediatric deaths in the community over a two-year period, raising concerns that this pathogen may spread to settings such as schools and day care facilities.[1]

National medical organizations, including the Infectious Diseases Society of America (IDSA), have identified antibiotic resistance as a major concern. As the problem worsens, physicians must evaluate the ways in which they may be contributing to antibiotic resistance and ways in which changes in their prescribing patterns can help manage it. Physicians have

Of all antibiotic prescriptions given in community settings, 20 percent to 50 percent are believed to be unnecessary.

recognized the disturbing trends in resistance and are beginning to discuss solutions in meetings such as the Summit on Antimicrobial Resistance, sponsored by the Alliance for the Prudent Use of Antibiotics (APUA), which was convened in San Francisco before the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in September 1999.

Scope of the Problem

Millions of times each year physicians, regardless of specialty, prescribe antibiotics inappropriately. From 20 percent to 50 percent of antibiotic prescriptions in community settings are believed to be unnecessary *(Table 1)*.[2,3] One recent report[4] attributed these prescribing patterns to unreasonable patient expectations or demands, inadequate time to explain to patients (or parents) why antibiotics are unnecessary and misdiagnosis of nonbacterial infections. Another study[5] found that even when physicians know that the use of antibiotics has marginal, if any, efficacy in particular circumstances (e.g., viral infections), antibiotics may be prescribed so that physicians can maintain good relationships with their patients; these physicians are frequently torn between scientific evidence and requests from their patients *(Table 2)*.[2]

One recent study[6] of parents found that they would be satisfied with a medical visit even if antibiotics were not prescribed, provided the physician explained why this decision was made. But a survey of primary care physicians in Massachusetts, conducted by APUA in collaboration with the Massachusetts Department of Public Health and the Massachusetts Infectious Diseases Society, found that the most common factors leading to increased antibiotic prescribing in outpatient settings are patient requests for these drugs and the physician's diagnostic uncertainty. In addition, when physicians were asked why they often prescribe broad-spectrum antibiotics if a targeted-spectrum agent would be effective, they cited diagnostic and treatment uncertainty as the primary reasons (unpublished data from APUA, retrieved August 1998, from: http://www.apua.org).

TABLE 1
Estimated Annual Human Antibiotic Use in the United States

Site of use	*Amount*	*Uses considered necessary (%)*	*Resistant pathogens*
Hospital	190 million defined daily doses annually	25 to 45	Staphylococci, enterococci, gram-negative rods
Community	145 million courses annually (110 million outpatient, 35 million emergency department)	20 to 50	Pneumococci, gonococci, group A streptococci, streptococci, *Escherichia coli*, *Mycobacterium tuberculosis*

Adapted with permission from Harrison PF, Lederberg J, eds. Antimicrobial resistance: issues and options. Workshop Report. Forum on Emerging Infections, Division of Health Sciences Policy, Institute of Medicine. Washington, D.C.: National Academy Press, 1998:40-1, and U.S. Congress, Office of Technology Assessment. Impacts of Antibiotic-Resistant Bacteria, OTA-H-629. Washington, D.C.: US Government Printing Office, September 1995.

TABLE 2
Factors Responsible for Inappropriate Antibiotic Use

Patient-parent factors
Anxiety
Misconceptions about:
- What antimicrobials do
- Fever requiring antibiotics
- Belief in healing power of physician
- Economic concern for patients (missing work)

Physician-provider factors
Real or perceived patient-parent pressure
Economic concern for self (e.g., loss of clientele)
Litigation concerns
Physician fallibility:
- Inadequate knowledge
- Cognitive dissonance (i.e., knowledge but failure to act on it)

Managed care factors
Cost-saving pressures to substitute therapy for diagnostic tests
Productivity incentives, reduced appointment time per patient, less explanation time
Monitoring of rates of return visits to obtain prescription for antibiotic
Responsiveness to patient complaints about "inadequate antibiotic use"

Industry factors
Misleading or erroneous advertising
Promotion by retailers

Adapted with permission from Harrison PF, Lederberg J, eds. Antimicrobial resistance: issues and options. Workshop report. Forum on Emerging Infections, Division of Health Sciences Policy, Institute of Medicine. Washington, D.C.: National Academy Press, 1998:46.

Because of the overuse of antibiotics, organisms that were susceptible to a number of agents even 10 years ago are now much more difficult to manage. In the multinational SENTRY antimicrobial resistance surveillance program, 1,047 respiratory tract isolates of *Streptococcus pneumoniae* were obtained and analyzed in 1997.[7] The percentages of penicillin-intermediate strains and strains resistant to penicillin were 28 percent and 16 percent, respectively, in the United States; among 31 centers in the United States and Canada where 19 or more isolates were collected, the combined incidence of intermediate plus highly resistant strains ranged from 24 percent to 68 percent.[7]

The Centers for Disease Control and Prevention (CDC) maintains its own population-based surveillance system for *S. pneumoniae* within its Active Bacterial Core Surveillance program. It collects information on the susceptibility patterns of invasive strains of this organism.[8] In a recent report of 1997 surveillance data, the prevalence of *S. pneumoniae* not susceptible to penicillin varied among geographic regions and among hospitals within those regions. Overall, 25 percent of isolates were not susceptible to penicillin: 11.4 percent exhibited intermediate susceptibility and 13.6 percent were resistant. The highest proportion of nonsusceptible *S. pneumoniae* was found in Tennessee (38.3 percent).[8]

In the SENTRY surveillance program, 92 percent of community-acquired respiratory tract isolates of *Moraxella catarrhalis* produced beta lactamase compared with 34 percent of isolates of *Haemophilus influenzae*; this beta-lactamase production results in amoxicillin resistance.[9] Some strains of three bacterial species—*Enterococcus faecalis*, *Mycobacterium tuberculosis* and *Pseudomonas aeruginosa*—are resistant to almost every antibiotic now available.[10]

The problem of resistance is complicated by the widespread use of antibiotics in animals, which has implications for the treat-

Although antibiotics may be effective in the treatment of acute exacerbations of chronic bronchitis, antibiotic therapy is not generally indicated for cases of acute uncomplicated bronchitis.

ment of human illness. For example, in low dosages, these compounds are used as growth enhancers in animal feed for cattle and poultry. Although the mechanism by which antibiotics promote animal growth is not well understood, more than 40 percent of antibiotics manufactured in the United States are used in animals, mostly in feed but also to treat or prevent infections.[10] This type of use creates the circumstances for selecting resistant bacteria in animals that may, in turn, be passed to the human population at large.[10,11] A panel of World Health Organization consultants has recommended the gradual discontinuation of antibiotics as growth promoters in animals.[12]

Appropriate Prescribing

For many of the leading illnesses diagnosed by office-based physicians, prescribing patterns must be adjusted to minimize antibiotic resistance. The following diseases commonly treated in family practice settings are representative of areas in which increased caution may be advisable in administering antimicrobial agents.

RESPIRATORY TRACT INFECTIONS

Research has failed to document a prophylactic or therapeutic benefit from antibiotic therapy in viral upper respiratory tract infections. Nevertheless, one study[13] concluded that office visits for colds, upper respiratory tract infections and bronchitis accounted for about 2 million antibiotic prescriptions in 1992; 51 percent of patients with colds, 52 percent with upper respiratory tract infections and 66 percent with bronchitis received antibiotic treatment. Another study[14] found that 60 percent of patients with an uncomplicated common cold received a prescription for an antibiotic.

In many cases of uncomplicated upper respiratory tract infection, patients have mild sinusitis-like symptoms (e.g., facial pressure, colored nasal discharge) and believe they need antibiotics. As a result, they ask physicians for these drugs, although there is no real need for them. In most such patients, symptoms resolve spontaneously in seven to 10 days, although symptomatic management with nasal decongestants, hydration and antipyretics may be warranted. One recent study[15] concluded that antibiotics did not improve the clinical course of maxillary sinusitis in patients presenting to general practices and that initial treatment could be limited to symptomatic management. The increasing problem of antibiotic-resistant *Haemophilus influenzae* and *S. pneumoniae* has provided further support for avoiding inappropriate antibiotic use in managing sinusitis.[16]

Nevertheless, the use of antibiotics is indicated in patients with bacterial sinusitis. Criteria for identifying the presence of infectious sinusitis have been developed that include five independent predictors of this infection: purulent nasal secretions, history of colored nasal discharge, maxillary toothache, abnormal transillumination and poor response to

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nasal decongestants or antihistamines.[17,18] In patients with combinations of these signs and symptoms, the use of antibiotics is a reasonable choice.

Because most cases of pharyngitis are viral in nature,[19] they can be treated with acetaminophen for pain and fever relief. Antimicrobial therapy is indicated, however, for symptomatic group A streptococcal pharyngitis, once the presence of a bacterial pathogen in the throat is confirmed through appropriate diagnostic testing.[20] Even so, antibiotic therapy can be postponed safely for up to nine days after symptom onset.[20]

When antibiotics are indicated for treatment of pharyngitis, penicillin should be considered first[19]; it offers proven efficacy, safety, targeted spectrum and low cost.[20] There is no evidence that group A streptococci are resistant to beta-lactam antibiotics, but high rates of resistance to macrolides (often prescribed for patients who are allergic to penicillin) have been documented in several areas.[19]

Antibiotics have not been shown to be useful in the treatment of acute uncomplicated bronchitis.[21] Most cases of acute bronchitis are viral in nature, and the illness tends to be self-limiting and benign.[22,23] A review of randomized, placebo-controlled trials of antibiotic use in acute bronchitis concluded that, in the majority of patients, treatment should be largely symptomatic and directed at the control of cough.[21] Some studies have shown that bronchodilators such as inhaled albuterol are more effective than antibiotics like erythromycin in treating acute bronchitis.[23] Researchers have stressed the importance of reducing risk factors (e.g., cigarette smoking) that contribute to the onset of bronchitis.[21]

It is reasonable to consider prescribing antibiotics for the treatment of acute exacerbations of chronic bronchitis. A meta-analysis[24] of randomized, placebo-controlled trials found a small but statistically significant improvement associated with antibiotic use in treating acute exacerbations of chronic bronchitis.

Interventions to reduce antibiotic use for respiratory infections have proved effective. For example, a study of primary care practices belonging to a group-model health maintenance organization evaluated the effects of a multidimensional intervention on antibiotic use for uncomplicated acute bronchitis in adults. The intervention program included office-based and household patient education materials, plus clinician intervention incorporating education and practice profiling. This program produced a substantial decrease in antibiotic prescribing rates (from 74 percent to 48 percent) when the full intervention was employed.[25]

Vaccines are available for the prevention of influenza and pneumococcal disease. In the United States, immunoprophylaxis with the influenza vaccine is seen as the primary option for reducing the impact of influenza.[26] A study[27] of healthy working adults found that vaccination against influenza resulted in a lower incidence of upper respiratory infections and fewer work days missed. Use of the vaccine lowers the prevalence of influenza and also reduces the inappropriate prescribing of antibiotics for managing such infections.

To further minimize the imprudent use of antibiotics for treatment of influenza, diagnostic techniques should be considered. Several office laboratory tests are available for the rapid diagnosis of influenza, all of which can detect both A and B infections.[28] If influenza is identified, one of the new antiviral drugs for influenza may be prescribed.[28]

Patients at risk for pneumonia are candidates for immunization with the 23-valent pneumococcal vaccine. The U.S. Food and Drug Administration recently approved the labeling of a new conjugate heptavalent pneumococcal vaccine for use in infants and children.[29]

ACUTE OTITIS MEDIA

Acute otitis media is one of the most common indications for the use of antibiotics in outpatient settings in the United States.[30] Overuse of antibiotics has produced selective

pressure promoting an increased proportion of infections caused by multidrug-resistant strains of *S. pneumoniae*.[31]

About 80 percent of cases of acute otitis media in children resolve in seven to 14 days without treatment and with observation alone, compared with about 95 percent of patients receiving antibiotic therapy.[30] Thus, antibiotics have a modest but significant impact on this condition.[32] One current set of guidelines states that "antimicrobials are indicated for treatment of acute otitis media; however, diagnosis requires documented middle ear effusion and signs or symptoms of acute local or systemic illness."[30] According to the same guidelines, "uncomplicated [acute otitis media] may be treated with a five- to seven-day course of antimicrobials in certain patients."[30] On the other hand, antibiotics are not indicated for the initial treatment of otitis media with effusion in the absence of signs or symptoms of acute infection or for persistent effusion after the treatment of acute otitis media.[29]

When antibiotic therapy is used, high-dose amoxicillin (in a dosage of 80 to 90 mg per kg per day) is the treatment of choice in most communities. If pain, fever and an inflamed tympanic membrane persist, resistance may be present. In such a case, the use of a second-line drug, such as high-dose amoxicillin–clavulanate potassium (Augmentin), cefuroxime axetil (Ceftin) or intramuscular ceftriaxone (Rocephin) should be considered.[33]

"Watchful waiting," or the withholding of antibiotic therapy from all but the sickest children, is popular in some European countries as a way of managing acute otitis media in children older than two years. The proponents of this approach in Europe initially use analgesics for symptomatic management and prescribe antibiotics only when signs or symptoms persist after observation for one to three days.[33,34] In the United States, a review article of recent consensus reports concluded that physicians could consider observation alone for children older than two years when they are afebrile and free of notable ear pain or signs of middle ear pus or inflammation.[33]

UNCOMPLICATED URINARY TRACT INFECTIONS

Urinary tract infections account for about 7 million physician visits each year and are among the most common problems for which young women seek medical care.[35] In a recent study[36] of the prevalence of antimicrobial resistance associated with acute uncomplicated cystitis in women who visited a health maintenance organization, resistance to trimethoprim and trimethoprim-sulfamethoxazole increased from 9 percent in 1992 to 18 percent in 1996 among *Escherichia coli* and from 8 percent to 16 percent among all isolates combined. The prevalence of resistance to ampicillin and cephalothin also rose significantly, although resistance to nitrofurantoin and ciprofloxacin remained low.[36] In other surveys of young women with acute cystitis, 11 percent to 18 percent of causative strains were resistant to trimethoprim-sulfamethoxazole, and 28 to 33 percent were resistant to ampicillin. Resistance to nitrofurantoin and fluoroquinolones was very low in these surveys.[37]

According to the current practice guidelines of IDSA, a three-day regimen of trimethoprim-sulfamethoxazole is considered standard therapy for acute uncomplicated cystitis.[38] Alternatives to trimethoprim-sulfamethoxazole should be considered in areas where the prevalence of resistance is 10 percent to 20 percent or more.[38] In mild uncomplicated cystitis, it is reasonable to use a targeted-spectrum agent, such as a seven-day course of nitrofurantoin (Macrodantin) or a single dose of fosfomycin (Monurol). A three-day regimen of a fluoroquinolone is also acceptable treatment for uncomplicated cystitis.

To control costs and curtail antibiotic resistance, however, IDSA recommends that fluoroquinolones not be used universally as first-line agents for acute uncomplicated cystitis but considered only in areas with high levels of resistance to trimethoprim-sulfamethoxazole.[38] Increasing concerns over resistance

associated with the use of fluoroquinolones should discourage an over-reliance on their use. The development of surveillance systems that identify regional resistance trends can help in optimizing drug choices.

A patient's presenting symptoms and signs and the results of a urinalysis can be used to diagnose cystitis.[35] Cultures are not routinely indicated for acute uncomplicated cystitis.[37] However, if there is suspicion of complicated cystitis or pyelonephritis, a urine culture should be obtained, and a seven- to 14-day course of a fluoroquinolone is the recommended first-line empiric regimen.

Meeting the Resistance Challenge

Once antibiotic resistance emerges, it may develop rapidly and usually declines slowly, if at all *(Table 3)*.[12] Family physicians, however, are pivotal players in determining whether resistance in the United States will worsen or be brought under control. Good day-to-day decisions in patient care, including the appropriately restrained use of antibiotics, can prevent the selection of resistant strains.

At the Summit on Antimicrobial Resistance, co-chaired by the authors of this article, family physicians met with leaders in the infectious diseases community to evaluate the problem and determine the need for action by every clinician. This group of opinion leaders and front-line physicians recommended the following key steps to preserve the power of antibiotics in community practice.

• Do not accommodate patient demands for unneeded antibiotics.[10] Although patients (or parents) often request antibiotics so they can go back to work (or return their children to school), resist those requests when they are ill-advised. Recognize that there is support for not using antibiotics when their use is unwarranted. Explain to patients and parents that the emergence of resistance through the misuse of antibiotics has important public health implications. At the same time, make it clear that antimicrobial agents put the user at greater risk for a resistant pathogen (and carriage of resistant organisms) than a person who did not take these drugs.

When given accurate information, patients tend to be satisfied with reassurance that symptomatic treatment alone is appropriate.

• Educate your patients on the prudent use of antibiotics and the importance of preventive measures (such as use of the pneumococcal vaccine). Explain when antibiotic use is appropriate and when it is not; patients must understand that there is not "a pill for every ill."[39] These educational efforts can even be conducted during routine office visits.

In a study[40] of more than 700 patients with sore throats who were seen in general practices in England, the prescribing of antibiotics strengthened the patient's belief in these drugs and increased the likelihood of subsequent clinic visits. However, patient expectations about the need for antibiotics can be made

TABLE 3
Lessons Learned About Antibiotic Resistance

Given enough antibiotic and time, resistance will appear. For example, the penicillin-resistant *Streptococcus pneumoniae* took 25 years to become a clinical problem; fluoroquinolone-resistant Enterobacteriaceae took 10 years to emerge clinically.
Resistance is progressive, moving from low to intermediate to high levels.
Organisms that are resistant to one antibiotic will likely become resistant to others. For example, tetracycline resistance in *Neisseria gonorrhoeae* first appeared among strains with existing resistance to penicillin.
Once selected, drug resistance will not disappear, although it may decline slowly. This gradual decrease in resistance is associated with poorly reversible genetic and environmental factors. No counterselective steps against resistant bacteria now exist.
When antibiotics are used by any patient, this use affects other people by changing the microbiology in both the immediate and the extended environment.

Information from Levy SB. Multidrug resistance—a sign of the times [Editorial]. N Engl J Med 1998;338:1376-8.

Prescription Pad

Name: _____ Date: _____

Diagnosis: ❑ Cold or flu ❑ Middle ear fluid (otitis media with effusion)
❑ Cough ❑ Viral sore throat
❑ Other:

℞

You have been diagnosed as having an illness caused by a virus. Antibiotic treatment does not cure viral infections. If given when not needed, antibiotics can be harmful. The treatments prescribed below will help you feel better while your body's own defenses are defeating the virus.

General instructions:

❑ Increase fluids.

❑ Use cool mist vaporizer or saline nasal spray to relieve congestion.

❑ Soothe throat with ice chips or sore throat spray; lozenges for older children and adults.

Specific medicines:

❑ Fever or aches: _____

❑ Congestion: _____

❑ Cough: _____

❑ Ear pain: _____

❑ _____ : _____

❑ _____ : _____

Use medicines as directed by your doctor or the package instructions. Stop the medicine when the symptoms get better.

Follow-up:

❑ If not improved in _____ days, if new symptoms occur or if you have other concerns, please call or return to the office for a recheck.

❑ Other: _____

Signed: _____

FIGURE 1. This "prescription pad" may be used to explain to patients why it is necessary for physicians to be cautious when prescribing antibiotics.

Reprinted from Centers for Disease Control and Prevention, retrieved from: http://www.cdc.gov/ncidod/antibioticresistance/files/viralprescriptionpad.pdf.

more realistic through education. When given accurate information, patients tend to be satisfied when reassured that symptomatic treatment alone is appropriate in their case.

• Before using antibiotics, make use of diagnostic methods, when appropriate, to identify the causative pathogen so that a drug targeted at the microbe can be chosen.[39]

• To help preserve the normal susceptible flora in patients and slow the build-up of antibiotic resistance in patients and in the community, select targeted-spectrum antibiotics when appropriate.[10]

• Do not prescribe antibiotics for viral infections, including the common cold.[41,42] In the management of otitis media, amoxicillin should remain the agent of choice.[33,43]

• Recognize the importance of relieving symptoms experienced by patients. When appropriate, prescribe decongestants, cough medicine or antipyretics. The patients will be appreciative and perhaps less demanding of antibiotics. The CDC has developed "prescription pads" that help physicians explain to their patients why an antibiotic is not being prescribed and recommend symptomatic treatments *(Figure 1)*.[44,45]

• Make sure patients understand that, when they are prescribed an antibiotic, they must complete the full course of therapy even after their symptoms have resolved to ensure that all pathogenic bacteria are destroyed.[42] Patients should be instructed not to keep leftover antibiotics in the medicine cabinet for future use by family members.

• Use shorter courses of antibiotics when supported by clinical data.

• Adopt optimal hygiene practices and encourage your patients to do the same to reduce infection risks. Washing hands thoroughly with soap and water between patient visits is one of the best defenses against the spread of antibiotic resistance.[10,43] Waterless hand-cleaning products, now used by personnel in many hospitals, are another increasingly popular hygienic option.

• Remain abreast of the latest available data

TABLE 4
Resources for Information About Antibiotic Resistance

Alliance for the Prudent Use of Antibiotics
75 Kneeland St.
Boston, MA 02111-1901
Telephone: 617-636-0966
Fax: 617-636-3999
Web address: www.apua.org

Infectious Diseases Society of America
99 Canal Center Plaza, Ste. 210
Alexandria, VA 22314
Telephone: 703-299-0200
Fax: 703-299-0204
Web address: www.idsociety.org

Centers for Disease Control and Prevention
Web address: www.cdc.gov/ncidod/dbmd/antibioticresistance/

World Health Organization
Web address: www.who.int/emc/amr.html

on local resistance trends and adjust your prescribing habits accordingly. Support public health agencies in your area in their efforts to implement sophisticated surveillance and reporting systems using state-of-the-art information technology.[10,12]

Final Comment

Although managing antibiotic resistance is a major challenge, family physicians have an important role to play in their own communities. Even though the problem of antibiotic resistance is global, family physicians can make a difference by becoming better stewards of antibiotics in their own practices, thereby protecting the health of their patients while addressing the resistance crisis in the community. For more information, contact the resources listed in *Table 4*.

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