CME CREDIT

Antimicrobial resistance: An ecological approach to a growing threat

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ABSTRACT
Antibiotic resistance among pathogenic bacteria poses an increasing threat. To control it, we need a concerted effort from clinicians, patients, farmers, pharmaceutical companies, and public health officials.

"To regard any form of life merely as slave or foe will one day be considered poor philosophy, for all living things constitute an integral part of the cosmic order."[1]

—RENE DUBOS, MICROBIOLOGIST AND ENVIRONMENTALIST

Vancomycin-resistant *S aureus* may be unstoppable

IN COPING WITH the growing problem of antibiotic resistance, we physicians need to make a radical change in the way we think and act. Instead of confidently awaiting the next generation of antibiotics to conquer antibiotic resistance, physicians must take a humbler view (TABLE 1). We must:

- Prescribe fewer antibiotics.
- Prescribe antibiotics that target as narrow a range of bacteria as possible.
- Observe the oft-ignored basics of infection control, such as washing our hands carefully between patient visits and working to make sure the same standards are observed by all health care workers coming in contact with patients.

In addition, the medical community must begin to examine the consequences of the overuse of antibiotics in agriculture.

As Dubos noted in the quote above, bacteria are not simply foes to be vanquished, but a part of the natural world, capable of making deft adaptations to the drugs we use to fight them.

HOW BACTERIA ACQUIRE RESISTANCE

Although bacteria can acquire resistance through inherited mutations in their chromosomes, more often they do so through changes in their plasmids—circular, double-stranded DNA molecules outside the chromosomes (FIGURE 1).[2,3] This is particularly important because bacteria exchange plasmid genes through conjugation, allowing entire populations to quickly become resistant. In another mechanism, viral vectors can even transfer genetic material between entirely different species of bacteria. Thus, antibiotic resistance does not rely exclusively on evolution within a single clonal proliferation.

Bacteria can also lose resistance. In the absence of antibiotics, antibiotic-resistant bacteria are actually at a selective disadvantage, since they must expend energy and resources to manufacture the proteins that confer resistance. Over time, the prevalence of resistant bacteria declines after antibiotics are withdrawn. Indeed, several outbreaks of infections with resistant bacteria in hospital units were stopped only after all antibiotics were withdrawn.[4]

WHAT ORGANISMS ARE BECOMING RESISTANT?

Staphylococcus aureus

At least 30% of *S aureus* strains are now resistant to methicillin.[5] Ominously, a few cases of *S aureus* infections that were resistant to vancomycin have recently been reported.[6]

Since many strains already exist that are resistant to all antibiotics except vancomycin, vancomycin-resistant *S aureus* may be unstoppable.

How antibiotic use leads to resistance

ANTIBIOTICS KILL BACTERIA BY:

Damaging or inhibiting synthesis of the cell wall *(penicillins, cephalosporins, monobactams, carbapenems, bacitracin, vancomycin, cycloserine, fosfomycin)*

Damaging or inhibiting synthesis of the cell membrane *(polymyxins)*

Metabolizing or inhibiting synthesis of nucleic acids *(rifampin, nitrofurantoins, nitromidazoles)*

Inhibiting protein biosynthesis *(aminoglycosides, tetracyclines, chloramphenicol, erythromycin, clindamycin, spectinomycin, mupirocin, fusidic acid)*

Modifying energy metabolism *(sulfonamides, trimethoprim, dapsone, isoniazid)*

BACTERIA ACQUIRE RESISTANCE BY:

Receiving a plasmid bearing a resistance gene from another bacterium directly

Receiving a resistance gene from another bacterium by viral delivery

Mutating and passing on changes in chromosomal DNA

Scavenging DNA from dead bacteria

RESISTANT BACTERIA FOIL ANTIBIOTIC THERAPY BY:

Creating enzymes that destroy antibiotic molecules

Making the cell wall less permeable

Altering the binding site of the antibiotic

Creating a second, inactive site for the antibiotic

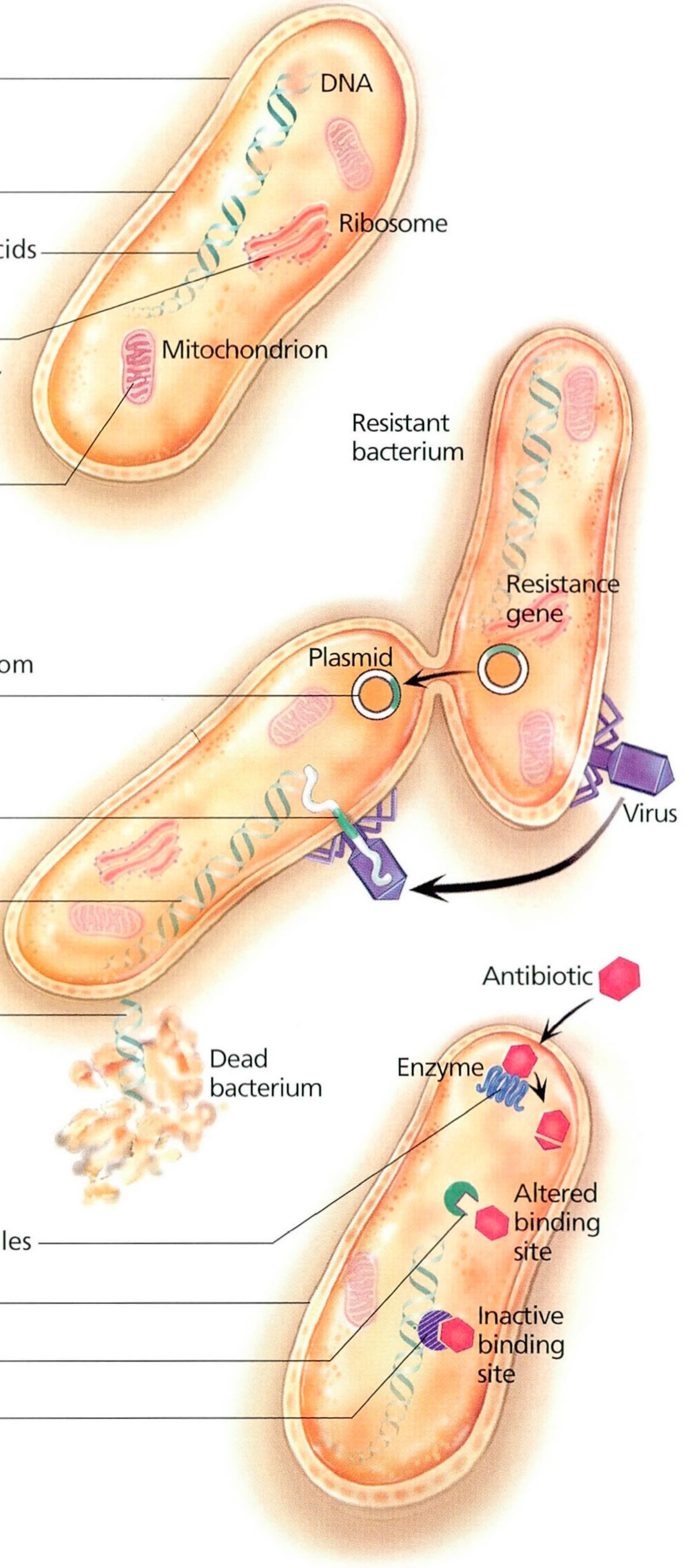

FIGURE 1

TABLE 1

What physicians and patients can do to slow the spread of antibiotic-resistant bacteria

Advice to physicians

Wash hands thoroughly between patient visits

Do not give antibiotics when not needed, even if patients ask for them

When possible, prescribe antibiotics that target only a narrow range of bacteria; computerized systems may help[16]

Isolate hospital patients with multidrug-resistant infections

Familiarize yourself with local data on antibiotic resistance

Advice to patients

Do not demand antibiotics

When given antibiotics, take them exactly as prescribed and complete the full course of treatment; do not hoard pills for later use

Wash fruit and vegetables thoroughly; avoid raw eggs and undercooked meat, especially in ground form

Use soaps and other products with antibacterial chemicals only when protecting a sick person whose defenses are weakened

SOURCE: ADAPTED FROM LEVY SB. THE CHALLENGE OF ANTIBIOTIC RESISTANCE. SCI AM MARCH 1998; 278(3):46–53.

Enterococcus faecalis, E faecium

Enterococci, which are already largely resistant to penicillin and aminoglycoside antibiotics, are acquiring resistance to vancomycin as well. Ten percent of cases of *E faecalis* infection were vancomycin-resistant in 1995, compared with only 0.3% in 1989.[7] Further, vancomycin-resistant enterococcal infections, formerly found only in intensive care units, are now seen in patients throughout the hospital.

No antimicrobial regimen is of established efficacy for vancomycin-resistant enterococcal infections. Chloramphenicol, fluoroquinolone, tetracycline, and rifampin may have some value for susceptible isolates, but these agents are not bactericidal. Experience is growing with using the streptogamin Synercid (quinupristin-dalfopristin) to treat vancomycin-resistant *E faecium*, but this agent is not active against *E faecalis*.

Examples of resistance in community-acquired organisms

Neisseria gonorrhoeae. Until 1992 almost all *N gonorrhoeae* strains were susceptible to fluoroquinolone antibiotics, including ciprofloxacin. However, in a series of cases of gonorrhea in men in Cleveland from 1992 to March 1994, 7.4% of isolates were resistant to ciprofloxacin.[8] Although quinolone-resistant *N gonorrhoeae* occur rarely in the United States, the prevalence could increase to the point that fluoroquinolones no longer reliably eradicate gonococcal infections.

Streptococcus pneumoniae. Of great concern is the emerging resistance to penicillin in *S pneumoniae*. Pneumococcal disease affects persons in all age groups, but particularly the elderly and very young. It is an important cause of otitis media in children. In a study at a day care center in Cleveland, 52 (21%) of 250 children were found to carry *S pneumoniae* strains that were resistant to multiple antibiotics.[9] Similarly, in 1997, approximately 20% of cases of community-acquired *S pneumoniae* pneumonia seen at the Cleveland Clinic were with strains that were resistant to penicillin.

WHY DO CLINICIANS OVERPRESCRIBE ANTIMICROBIAL DRUGS?

Antibiotics provide little or no benefit in treating colds, upper respiratory tract infections, or bronchitis.[10] Yet, these conditions accounted for an estimated 31% of prescriptions for antibiotics written by ambulatory care physicians.[11] According to a study by Gonzalves et al,[12] more than 50% of all patients who went to a physician with one of these conditions walked out with a prescription for an antibiotic.

One reason for using antibiotics in this situation is that patients ask for them, and overworked physicians acquiesce even though they know better. Education is needed for physicians, patients, and the public.[13] A public education campaign in Iceland succeeded in bringing down the rate of antibiotic use—and the rate of antibiotic-resistant bacteria.[14]

National recommendations led to a decrease in the use of erythromycin and of erythromycin resistance in group A streptococcal infections in Finland.[15]

In addition, physicians often prescribe antibiotics on incorrect assumptions that they are indicated:

- Prolonged cough occurs commonly in patients with viral respiratory infections, and does not necessarily indicate the need for antimicrobial therapy.
- A positive urine culture in a patient with a Foley catheter may be meaningless if the patient has no fever and feels well.
- Culturing skin in patients with decubitus ulcers and treating all organisms isolated is not necessary.
- Coagulase-negative staphylococcus isolated from one of two blood cultures probably represents a contaminant, and does not require treatment.

PREVENTING THE SPREAD OF ANTIBIOTIC-RESISTANT ORGANISMS

Increased use of antibiotics in the hospital is often associated with an increase of resistance among nosocomial pathogens, and efforts focused on reducing inappropriate use of antimicrobials are one important strategy. Recommendations for preventing the spread of vancomycin resistance published by the Hospital Infection Control Practices Advisory Committee (HICPAC) are one example of emphasis on prudent antimicrobial use and education.[7] In another direction, the use of a computerized antibiotic-management program has recently been shown to improve use of antimicrobial agents and improve the quality of care of hospitalized patients.[16]

It should not be forgotten, however, that handwashing remains the single most important prevention strategy that reduces the risk for health care workers transmitting potential pathogens from one patient to another.[17] Hands should be washed between patient contacts and after any contact with blood, body fluids, secretions, and contaminated equipment or fomites. Hands should also be washed after removing gloves. Use of a plain (nonantimicrobial) soap is adequate for routine handwashing.

AGRIBUSINESS: INAPPROPRIATE ANTIBIOTICS IN THE FEEDLOTS

Approximately 40% of antibiotic production goes into livestock feed as prophylaxis against infection. (A substantial portion also goes to spraying fruit trees.) Although effective in the short run, this practice is encouraging microbial resistance not only among the livestock, but among agricultural workers, persons living in the vicinity,[18] and people who consume the agricultural products.[19]

Approximately 6 billion broiler chickens are raised in the United States each year, and most are given antibiotics to improve their health and rate of growth. With the FDA licensing of fluoroquinolones for use in chickens, the level of drug-resistant *Campylobacter* in chickens and humans may be increasing.[20] Potential strategies to reduce the use of antibiotics fed to farm animals include the use of irradiation (to eliminate potential harmful bacteria after packaging for human consumption) and spraying newborn chickens with a mixture of beneficial microbes to colonize their gastrointestinal tracts and reduce or eliminate disease-causing bacteria.

CONCLUSIONS

Antimicrobial resistance is an emerging global problem, and prevention and control of the spread of antibiotic resistance among bacterial pathogens will require a coordinated, concerted effort from clinicians, patients, farmers, pharmaceutical companies, and public health officials. Appropriate antibiotic use in humans and animals is an essential component in programs to control resistance. In addition, in order to improve prescribing practices, more data is needed to determine appropriate duration of antimicrobial therapy for many types of infections where antimicrobial agents are indicated.

50% of patients with colds receive antibiotics

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