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Antimicrobial Resistance

Patricia M. Dowling

Take Home Message

- ✓ *Antibiotics* and *antimicrobials* are products that kill or inhibit the growth of bacteria and other microorganisms. The term *antibiotic* specifically refers to drugs that are produced by bacteria themselves, whereas *antimicrobial* refers to any drug or product with such activity and is technically a more correct term for the products we use in animal agriculture.
- ✓ Bacterial resistance to antimicrobials is a serious and costly problem in human and veterinary medicine.
- ✓ Bacteria are able to exchange genetic information and conserve resistance genes.
- ✓ Antimicrobials should only be used within the confines of a valid veterinarian-client-patient relationship (VCPR).[a]
- ✓ Producers and veterinarians should continually update their knowledge of disease prevention methods, drug resistance trends and new drug therapies to ensure the prudent use of antimicrobials.
- ✓ Everyone using antimicrobials should be educated in their proper use, including administration, handling, storage, disposal and record-keeping.

Consequences of Antimicrobial Resistance

In both humans and animals, illness and death rates increase with antimicrobial resistance because effective therapy for specific infections is delayed or unavailable. When resistance emerges to the *drug of choice* for a specific infection, it may take days for susceptibility testing to identify an appropriate therapy(**1**). Serious illness and death may also result when the only effective antimicrobials are too expensive for all patients to afford, or when these drugs cannot be feasibly administered to all infected patients. All people and animals have populations of normal bacteria in and on their bodies. A more subtle effect of resistance on the incidence of disease occurs when a person or animal receives an antimicrobial to which a potentially infective or colonizing bacteria in this population is already resistant. By killing off competing bacteria, the antimicrobial drug alters the normal bacterial population to favour the resistant bacteria that may cause disease, persist in the host longer, or spread more widely to others.

Individuals and society must pay for the higher cost of the newer antimicrobials needed to combat resistant bacteria. In human medicine, some of these treatments cost more than $500 a day for medications alone. In contrast, older forms of penicillin cost less than $1 a day. A Centers for Disease Control study concluded that the likelihood of hospitalization and the length of hospital stay were typically twice as long for patients with a drug-resistant bacterial isolate compared to patients with a drug-sensitive isolate of the same species. It is costly, time-consuming and complex to treat a patient with an antibiotic-resistant infection and to control the spread of resistant isolates (**2**).

Emergence of Antimicrobial Resistance

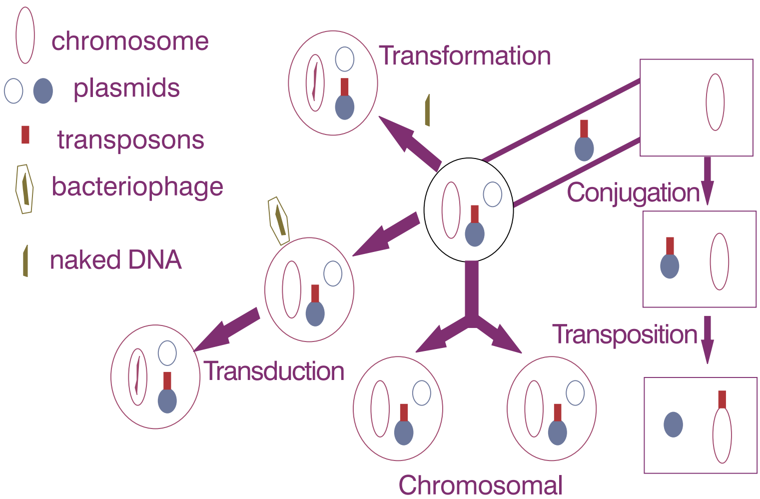
Bacteria are able to evolve rapidly because they are genetically versatile. All bacteria possess an inherent flexibility that enables them, sooner or later, to evolve genes that render them resistant to antimicrobials. Unlike mammals, bacteria can incorporate DNA from different species and even different genera into their own genetic make-up. Bacteria also multiply very rapidly. Under ideal conditions, they can double their number in less than 20 minutes. During the more than 50 years since antimicrobials were developed, bacteria have evolved through as many generations as humans have during the last 25 million years. If even one bacteria in a billion is able to survive exposure to an antimicrobial by becoming resistant, then its descendants will quickly reproduce. The use of antimicrobials in humans and animals over the last five decades encouraged the multiplication and spread of resistant strains (**3**).

Mechanisms of Antimicrobial Resistance

The two major forms of antimicrobial resistance are mutational and transmissible (see **Figure 1**). Mutational resistance occurs from chromosomal mutations in the bacterial DNA that are then transmitted to progeny during replication. This form of resistance is slow and step-wise, and usually requires long exposure to an antimicrobial to become clinically significant. Clinical resistance to fluoroquinolone antimicrobials occurs from chromosomal mutations.

Transmissible resistance requires genetic exchange between bacteria and can rapidly spread resistance genes. Most of the problems with bacteria becoming resistant to commonly used antimicrobials occurs because of transmissible resistance. Bacteria can exchange or transmit antimicrobial resistance genes by four different mechanisms: transformation, transduction, conjugation and transposition (**4**).

Figure 1. Bacterial Mechanisms for the Exchange or Transmission of Antimicrobial Resistance Genes.



- Transformation occurs when bacteria pick up and use naked DNA from the environment. The DNA may have come from a nearby bacterium that for some reason has ruptured. Once in a new cell, the naked DNA becomes part of the bacteria's chromosome or a plasmid (see below) and begins to function.
- Transduction is a genetic exchange between bacteria by a bacterial virus - a bacteriophage, or 'phage' for short. Phages infect bacteria the same way that animal viruses infect animal cells.
- Conjugation is the transfer of one or more plasmids from one bacteria to another via a pilus that temporarily connects one bacteria to another. All bacteria contain the majority of their genetic information on a single chromosome, but bacteria also carry small circles of accessory DNA, called plasmids. Plasmids carry as few as 3 and as many as 300 genes. A single bacteria may carry from one to 1000 copies of a single plasmid and can simultaneously harbour many different plasmids. The cell containing the plasmid transfers it to the recipient while retaining a copy. Some plasmids have broad host ranges and can be exchanged between bacterial species (e.g., from an *E. coli* to a *Salmonella*).
- Transposition is the transfer of DNA sequences in either the same or between independently replicating DNA strands. Thus transposable DNA can 'jump' onto plasmids or the chromosome of a new strand of DNA.

Population Genetics of Antimicrobial Resistance

The efficient mechanisms of gene transfer in bacterial populations, in the presence of a background of antimicrobial usage, results in the emergence of antimicrobial resistant bacteria. Any kind of antimicrobial use selects for resistant bacteria, and increases the reservoir of resistance genes. Many of the plasmids responsible for antimicrobial resistance carry genes that code for resistance to more than one drug. From gastrointestinal bacteria, it is common to isolate plasmids that determine resistance to five or more antimicrobials. Consequently, even when a particular antimicrobial is not used, the plasmid that encodes resistance to that antimicrobial can be favoured by the use of other antimicrobials for which that plasmid also codes for resistance. In addition to the antimicrobial-associated linkage selection, resistance plasmids can carry genes for resistance to ultraviolet light, mercury and other heavy metals, fermentation of carbon energy sources and virulence. Associated linkage selection for these other plasmid encoded characteristics contributes to the persistence of plasmid-mediated antimicrobial resistance even when antimicrobials are not used at all (**5**)!

Plasmids may carry genes conferring virulence (or pathogenicity) as well as ones that determine antimicrobial resistance. Plasmids are known to code for toxins that cause diarrhea, factors that promote bacterial adhesion and components that allow bacteria to penetrate cells and multiply. Plasmids may contain genes coding for both resistance and for virulence. Hence, even if selective pressure of antimicrobial use is removed, plasmid mediated resistance is unlikely to disappear if the virulence factor conveys a survival advantage to the organism. Currently, drug-resistant strains of bacteria are not universally more or less virulent than susceptible strains (**6**).

Antimicrobial Use in Veterinary Medicine

Animal agriculture uses antimicrobials for therapy of disease, prophylaxis (disease prevention) and growth promotion. The National Academy of Sciences/Institute of Medicine estimates that nearly half of the total annual production of antimicrobials is used in food animals. Nearly 80% of poultry, 75% of swine, 60% of feedlot cattle, and 75% of dairy calves in the United States are fed antimicrobials at some time. There is a growing concern regarding animal health, antimicrobial resistance and food production. In the media, animal feedlots are blamed as reservoirs for resistant organisms. But antimicrobial use by the food industry is not limited to farm animal production. Antimicrobials are also used in fisheries and in crop agriculture, as a means of limiting disease in trees and plants.

Since any kind of antimicrobial use selects for resistance genes, the question for human medicine is to what extent has the antimicrobial resistance problem in humans been influenced by the use of antimicrobials in agriculture and veterinary medicine? This question can be answered in part by looking at the bacterial infections that affect only humans: gonococci, meningococci, *H. influenzae* and pneumococci. The resistance problems in these organisms is solely due to the misuse of antimicrobials in human medicine. For the bacterial pathogens that are common to both humans and animals, the answer is not as clear. Although it has been shown that resistant bacteria can move from farm animals to humans in close contact and that these bacteria can establish themselves for a certain period of time as part of the human flora, it is not clear that this uniformly or inevitably results in human clinical disease. Evidence indicates that such colonization requires exposure to large numbers of bacteria and is maybe temporary, unless the person is receiving concurrent antimicrobials. Even though the colonization of bacteria of food animal origin may be brief, the human flora may acquire plasmids or R factors from the animal strains.

The importance of human-to-human transmission of pathogens of food animal origin is typically underemphasized by the media. More isolations of *Salmonella* in cases of food-borne illness occur in urban than rural areas. Despite media hype, currently there is little evidence to show that resistance genes, originating in animal bacteria, are being transferred to human pathogens, and are resulting in untreatable infections. Humans are frequently prescribed antimicrobials, which directly influences the development of resistant flora. These resistant strains may be transmitted to close contacts who are not receiving antimicrobials. This makes it very difficult to differentiate between the contributions to antimicrobial resistance of antibiotic growth promotants in animals and the direct administration to people. It continues to be debatable whether a significant decrease in resistance in human pathogens would result if antimicrobials were withdrawn from veterinary use (**7**).

A Global Perspective

The possibility that use in animal agriculture is contributing to the problem of antimicrobial resistance in human patients and the potential for even greater public health problems in the future has become a global issue. Antimicrobial use has the potential to become a non-tariff trade barrier. Recently, the World Health Organization called for withdrawal of growth promoters from agricultural use if these drugs were important to human medicine. In Europe, some national and international regulatory agencies are advocating the 'precautionary principle', in that drugs are not approved unless there is a reasonable certainty of no harm.

This principle is particularly appealing to regulatory agencies as it is sufficiently ill-defined for them to invoke it in cases, such as growth promoter use, where political pressure by consumer or other groups means that they would have to make unpopular political decisions in continuing to license such products. The global effects of this approach rather than a scientific, rational approach are devastating to the animal health industry. Already, a number of food animal antimicrobials have been banned in Europe.

In the United States, the Food and Drug Administration (FDA) is developing a framework for evaluating and assuring the human safety of the microbial effects of antimicrobial drugs intended for use in food-producing animals. FDA believes it is necessary to evaluate two separate, but related aspects:

- the rate and extent of development of antimicrobial drug resistant enteric bacteria formed in the animal's intestinal tract following exposure to the antimicrobial new animal drug (resistance), and;
- changes in the number of enteric bacteria in the animal's intestinal tract that cause human illness (pathogen load).

This framework document will allow for approval and withdrawal of drug approval based on changes in antimicrobial susceptibility. At the current time in Canada, the Bureau of Veterinary Drugs has no mandate to consider antimicrobial resistance when approving food animal drugs. Because of the current global concerns, Health Canada has convened the Advisory Committee on Non-human Uses of Antimicrobials and Their Impact on Resistance and Human Health. This expert committee, in conjunction with the Canadian Food Inspection Agency and other stakeholder groups, will develop comprehensive policies aimed at identifying and managing risks associated with the use of antimicrobials in food production.

How Producers and Veterinarians Can Limit Antimicrobial Resistance

Infectious diseases of feedlot cattle are sufficiently complicated that accurate diagnosis and optimal treatment requires input from a trained animal health professional. Because of the seriousness of antimicrobial resistance problem, the Canadian Veterinary Medical Association has recently developed prudent use guidelines (**8**) and believes that a veterinarian should be involved in any situation requiring antimicrobials, whether the products used are available 'over-the-counter' or by prescription. This relationship, known as a Veterinarian-Client-Patient Relationship (see sidebar, next page), insures that good medical treatment and follow up are provided. Producers and veterinarians should use antimicrobials only when medically indicated, not 'just in case' of an infection. Veterinarians are trained to make such decisions based on clinical signs, history, necropsy examinations and laboratory testing. They should use or prescribe an antimicrobial with the narrowest possible spectrum of activity, so as not to alter or cause resistance genes in normal bacterial populations. Prophylactic and growth promoting antimicrobials should only be used when demonstrated to be of benefit to animal health and welfare, not as a substitute for good management or sterile surgical techniques. Producers and veterinarians should continually update their knowledge of disease prevention methods, drug resistance trends and new drug therapies.

Producers must follow the label or prescription directions for the full treatment regimen. Underdosing or shortening treatment encourages resistance development. Everyone involved must be trained in handling and administering antimicrobials properly and in appropriate record keeping. Leftover drugs should not be stockpiled for later use without guidance. Veterinarians and producers should practice good infection control methods. As treated animals may shed resistant bacteria into the environment, efforts should be made to minimize premise contamination.

References

1. Cohen, M.L. (1992) Epidemiology of drug resistance: implications for a post-antimicrobial era. Science, 257:1050-1055.
2. Amyes, S.G.B., Gemmell, C.G. (1992) Antibiotic resistance in bacteria. Journal of Medical Microbiology, 36:4-29.
3. Krause, R.M. (1992) The origin of plagues: old and new. Science, 257:1073-1078.
4. Murray, B.E. (1991) New aspects of antimicrobial resistance and the resulting therapeutic dilemmas. The Journal of Infectious Diseases, 163:1185-1194.
5. Kayser, F.H. (1993) Evolution of resistance in microorganisms of human origin. Veterinary Microbiology, 35:257-267.
6. Cohen, M.L. (1992) Epidemiology of drug resistance: implications for a post-antimicrobial era. Science, 257:1050-1055.
7. National Research Council. The Use of Drugs In Food Animals. National Academy Press, Washington DC, 1999.
8. CVMA Guidelines on The Prudent Use of Antimicrobial Drugs in Animals, 1999.

[a]A Veterinarian/Client/Patient Relationship (VCPR) exists when all of the following conditions have been met:

- The veterinarian has assumed the responsibility for making clinical judgments regarding the health of the animal(s) and the need for medical treatment, and the client has agreed to follow the veterinarian's instructions.
- The veterinarian has sufficient knowledge of the animal(s) to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s). This means that the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of an examination of the animal(s) or by medically appropriate and timely visits to the premises where the animal(s) are kept.
- The veterinarian is readily available for follow-up evaluation, or has arranged for emergency coverage, in the event of adverse reactions or failure of the treatment regimen.