

What is Antimicrobial Resistance? Development, Measurement, and Spread

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Introduction

Antimicrobial drug resistance is resistance of microorganisms, especially bacteria, to antimicrobial drugs. Although it usually refers to an individual antimicrobial drug or drug class, multiple resistance can develop.

Why is Antimicrobial Drug Resistance Such a Concern?

Antimicrobial resistance is of concern in human medicine today for many reasons.

- For a long time, the solution to resistance was to develop another drug to overcome this resistance. About 10 years ago, pharmaceutical companies thought there was no value in developing new antibiotics since we had more than enough to deal with the problems being encountered.

- The emergence of AIDS, and consequently the emergence of totally new or resurgent “old” infections, has been one factor important for the resurgence of infectious disease as well as resistance problems.

- The practice of keeping infants in arms in day-care centers has increased the significance of some infectious diseases of children. For example, at any one time 5%-10% of children in day-care centers are (possibly now were) on broad-spectrum antibiotics for middle ear infections. Up to 50% of *Streptococcus pneumoniae* are now penicillin-resistant, a devastating problem for an organism which has for so long been exquisitely susceptible to penicillin.

- The “crisis” in antibiotic resistance has moved from the hospital, where it was known for so long, into the community (i.e., into general medical practice). This is due to the advent of day-care centers as well as budget cuts in hospitals which send patients home within day(s) of surgery.

- Modern treatments of cancer often involve severe immunosuppression, so that to prevent infection patients are placed on extremely “powerful” broad-spectrum antibiotics. These not only provide selection pressures for resistance, but also select for the intrinsically resistance “wimpy” pathogens.

- The progressive development of resistance of common human pathogens because of antibiotic use over decades. The crisis of antibiotic resistance in human medicine has led to questioning some practices of antibiotic use in animals. Veterinarians and others are re-examining their use of antibiotics to ensure they are prudent (i.e., optimize therapeutic efficacy while minimizing resistance).

Resistance of bacteria can be inherent or, much more importantly, acquired.

Intrinsic Resistance

Inherent, intrinsic, or constitutive resistance is the natural resistance of a bacterium to an antibiotic. A well-known example is the intrinsic resistance of *Enterococcus* species to commonly used antimicrobial drugs. Such resistance may become important in human medicine, since these bacteria may grow to large numbers on the surfaces of a patient treated with broad spectrum antimicrobial drugs to which these organisms are naturally resistant. If the patient also is severely immunocompromised (e.g., bone-marrow transplant patient) these intrinsically resistant bacteria, which may only be minor pathogens, can kill the patient.

Acquired Resistance

Acquired resistance is the development of resistance by bacteria which previously were susceptible. It can occur in many different ways and is particularly important since the genes for resistance may be transferable between very different bacteria in different ways.

A fundamental concept in biology, including pathogenic bacteriology, is the continuous process of natural selection, or “survival of the fittest”. Antimicrobial drugs exert tremendous pressures for the selection and maintenance of resistant bacteria. Their use in the last 50 years has altered bacterial infections seen in people, and to some extent in animals. The development of resistance is not inevitable, since some bacterial types don't have the genetic mechanisms to readily acquire resistance (particularly transferable resistance). Some bac-

terial species, however, have developed or acquired resistance almost hand-in-hand with the introduction of new antibiotics.

How Do Bacteria Become Resistant?

How bacteria acquire resistance gives us a fascinating glimpse into the basis of evolutionary or genetic change in bacteria. Although bacteria are categorized into "genera" and "species", they can acquire DNA across classes, families, genera and species. In some ways they can be thought of as part of a "giant microorganism" rather than distinct individuals.

Bacteria can acquire resistance through the normal process of mutation. Minor errors in DNA replication can lead to substitution of incorrect nucleotides and gradual corruption of the genetic message. This may lead to emergence of resistant bacteria, given the presence of antibiotic selection. It has been viewed as generally minor significance but is important for certain drug classes. For example, mutation is the method by which fluoroquinolone resistance develops. Bacteria can acquire (be transformed by) naked DNA which can recombine with homologous DNA to form new mosaic genes; if these genes involve those associated with susceptibility to an antimicrobial drug, the new mosaic genes may make the organism resistant. These resistant forms will emerge if there is antibiotic selection (e.g., day-care center). This is the basis of penicillin resistance in *Streptococcus pneumoniae*.

Bacteria can acquire transferable resistance in several ways: 1. By bacterial virus infection; 2. By plasmids. These are circular, self-replicating forms of DNA which often carry genes to make their host mate (conjugate) with non-plasmid-bearing bacteria or, if they lack these conjugative genes, can be piggy-backed into a new host with another conjugative plasmid; 3. By transposons. These are segments of DNA which can mobilize to insert in other parts of the DNA molecule without requiring homologous DNA ("illegitimate recombination"). Transposons ("jumping genes") can be simple or very complex, and are the basis of the progressive development of plasmids to encode multiple antibiotic resistance. Transposons are fundamental to the evolution of microorganisms, including the movement of virulence genes among bacteria.

One interesting additional mechanism of resistance transfer about which increasing information is available is the "integron". This term describes a class of mobile genetic elements distinct from transposons which contain a site-specific recombination site containing an integrase and a "captured" resistance gene or genes. Integrons, which are often found within plasmids, contain up to 8 different resistance genes which exist as individual "gene cassettes". Each, however,

contains a repeated (59-124 base pair) nucleotide element common to the cassettes, which is the element of DNA involved in site-specific recombination of the cassette into the integron.

Probably the major factor determining whether a certain bacterium becomes resistant is the ease of genetic change in that bacterium. Thus resistance is common in *Escherichia coli*, which seems to be a genetically labile organism, but uncommon in many gram-positive bacteria which don't seem to acquire exogenous DNA molecules well. For every rule, however, there will be an exception—we are dealing with the greatest survivors on the planet.

How is Resistance Measured?

Resistance is measured in the laboratory by determining *in vitro*, under rigidly standardized conditions, the minimum inhibitory concentration (MIC) of the test antibiotic against the microorganism. Results can be expressed quantitatively (MIC in g/ml) or qualitatively ("susceptible", "resistant", "intermediate", and recently in the United States, "flexible", to cover flexible professional labeling). Interpretive criteria for both quantitative and qualitative tests relate to achievable serum or tissue concentrations of drug based on pharmacokinetic parameters obtained for the drug and on the pharmacodynamic action of the antibiotic class tested.

In the United States, the National Council on Clinical Laboratory Standards^{1,2} subcommittee on Veterinary Antimicrobial Susceptibility Testing ("VAST") has made significant progress in standardizing methods for susceptibility testing of animal pathogens. It is indeed a vast (and necessarily rather slow) undertaking, which represents the first systematic steps to standardize in a veterinary context both the methods and the interpretive criteria.

The overall failure of veterinary medicine to have internationally agreed standards for antimicrobial drug testing relates to many factors, probably including consistent under-funding of diagnostic laboratories on a trans-national basis, chauvinism, and the lack of veterinary clinical bacteriologists. While there are some areas of excellence internationally, the lack of agreed standards (which also occurs in medicine) has meant that it is impossible to compare resistance trends across countries or continents, except on the crudest of bases. National efforts are under way in several countries, including the United States's National Antimicrobial Resistance Monitoring (NARM) program, but antimicrobial susceptibility testing of sentinel bacteria on a large scale is an expensive pastime. It is unfortunate that, if one wishes to assess resistance over time, trends emerging from diagnostic laboratories cannot be extrapolated to the general population of bacterial pathogens.

Resistance Spread

Resistance spreads by the transfer of resistant pathogens between animals, as well as by the transfer of resistance genes from both pathogens and nonpathogens to pathogens. Such transfer is difficult to control, but may be reduced by general hygiene approaches such as isolation of animals and their wastes. Optimizing the antimicrobial effect of the different drug classes and taking account of the most favorable pharmacodynamic action of the class also may reduce transfer of resistance. Resistance generally is maintained by antibiotic use. The phenomenon of multiple antibiotic resistance because of plasmids or integrons means that use of one antibiotic to which the organism is resistant may favor maintenance of multiple resistance genes.

The Future

The future for antimicrobial drugs is very bright.³ There are a number of new antimicrobial drugs in the

pipeline. Expectations from the many bacterial genome projects, both completed and underway, are that we should be able to identify new genes involved in fundamental metabolic processes or structures in bacteria which can be targets for totally new drug classes. New drug discovery can now be speeded by combinatorial chemistry approaches. Nevertheless, the crisis of resistance has focused us on the need to preserve and not to squander precious resources.

References

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