

Antibiotic Resistance

Introduction

Since the first introduction of antibiotics, there has been an almost inevitable emergence of antibiotic-resistant bacteria, regardless of the mechanism of antimicrobial activity. No sooner is a new agent introduced than the bacteria develops a means to resist it. At present we are faced with certain bacterial pathogens that are resistant to all currently available antimicrobial agents. While new antimicrobial agents are regularly developed, there have been a very limited number of new agents introduced with novel mechanisms of action. As a result, resistance often emerges in rapid order to agents that are modifications of other currently available antibiotics. This lecture will discuss the emergence of antimicrobial resistance as well as describe different resistance mechanisms, means of bacterial and gene dissemination and finally the epidemiology of antimicrobial resistance in the community and the hospital.

The consequences of the emergence of antimicrobial resistant bacteria include an increase in morbidity and mortality. The use of less effective *e.g.*, bacteriostatic rather than bactericidal drugs, may be necessary. Hospitalization may be prolonged or the patient may be isolated as a result of his particular infection. Finally, the drugs may be more expensive or more toxic.

Molecular Genetics of Antimicrobial Resistance

Bacteria become resistant to antibiotics in one of three ways:

- 1) The development of point mutations in one of the target genes (micro evolutionary change). An example of this is the alterations in the beta-lactamase gene extending its spectrum of activity against different beta-lactam antibiotics.
- 2) Macro evolutionary changes include the rearrangement of genes as might occur with the acquisition of antibiotic resistance bearing plasmids or transposons.
- 3) The final way is to acquire DNA from an exogenous source. For example naturally transformable species such as neisseria can acquire DNA from the environment. It is believed that this is the way neisseria species acquired antibiotic-resistant genes (*e.g.*, penicillin).

Terminology:

Cross-resistance – a single resistance mechanism confers resistance to an entire class of antibiotics. An example is the aminoglycoside-modifying enzymes which may confer resistance to several members of the aminoglycoside family.

Cross resistance can also occur across different classes of agents - a result of either overlapping drug targets as is the case with macrolides and lincosamides or if there is a drug efflux pump with a broad range of activity (*i.e.* capable of exporting different classes of drugs).

Co-resistance refers to the presence of resistance to more than one class of antibiotics in the same bacterial strain as might occur on a plasmid.

Co-selection is the selection of multiple antibiotic resistance genes when one of these genes is selected. The most elegant example of this is the integron which is a cassette of antibiotic-resistance genes that are under the control of a single promoter. As a result, these genes are expressed in a coordinate manner, although the most downstream gene may not be as efficiently expressed as the gene next to the promoter. These cassettes are now found in both Gram positive and negative bacteria. Since they are a form of transposon they can become a part of the bacterial chromosome or plasmid and can then be transmitted among different strains.

Mechanisms of Antimicrobial Resistance

- 1) Enzymatic modification: Bacteria elaborate enzymes that are capable of modifying or destroying the antibiotic before it reaches its target. Beta-lactamases elaborated by both gram positive and negative bacteria hydrolyze the amide bond of the beta-lactamic nucleus destroying the antimicrobial activity of the beta-lactamic agent. These enzymes have differing specificities that make them either relatively selective or broad ranging in their target. These enzymes may be constitutively expressed or induced to express on exposure to a beta-lactam.
- 2) Decreased accumulation of antibiotic: Penicillin is unable to penetrate the outer membrane of Gram negative bacteria and as a result is ineffective against Gram negative bacteria
- 3) Alteration of the drug target: Modification of the cellular target for an antibiotic is another mechanism of resistance. Vancomycin lost activity against enterococci when the cell wall precursor that it bound was modified so that vancomycin was no longer able to attach to the site.

Methods for the dissemination of antimicrobial resistance genes

The world is a small place when microbial pathogens are concerned!!

- 1) Clonal spread of a resistant strain: Under the selective pressure of antibiotics a strain carrying antimicrobial resistance genes may be preferentially selected and transferred within a population.
- 2) Plasmid transfer: Plasmids carrying one or multiple antibiotic resistance genes can be transferred among different bacterial strains or species by conjugation or transduction.
- 3) Free DNA: Naturally transformable species such as the pneumococcus can acquire native DNA from the environment. Recombination events can then integrate this genetic material into the chromosome. This is believed to be the means by which pneumococci acquired penicillin resistance.
- 4) Bacteriophage: Transduction may be a means of transfer of both antimicrobial resistance genes as well as genes conferring virulence.

The Epidemiology of Transmission of Antimicrobial Resistance Mechanisms

The transmission of resistance genes within the community has become an increasingly common event. Children attending day care, adults in nursing home facilities, as well as patients recently discharged from hospitals all act as reservoirs, serving as potential vectors of spread of resistant bacteria. The increasing use of antimicrobials within the community provides selective pressure for the preservation of these isolates.

Another reservoir of antimicrobial resistance genes is animals raised on farms where antibiotics are used as growth factors. The quantity of antibiotics used in healthy animals (cattle, chickens *etc.*) far exceeds the quantity used for therapy of bacterial infections in humans. Recent outbreaks have highlighted the spread of antibiotic-resistant bacteria either via food (quinolone resistant salmonella) or from direct exposure to animals (methicillin-resistant *S. aureus* among pig farmers).

Finally, international travel allows subjects visiting foreign countries to acquire the uniquely resistant strains in a particular locale and to transport these strains back to the United States. There has been global dissemination of a number of unique bacterial clones in this manner including methicillin resistant staphylococci and penicillin resistant pneumococci.

In the hospital setting, the proximity of patients to each other, their immunocompromised status, their exposure to numerous healthcare workers and the frequent need for broad-spectrum antibiotics set the stage for the emergence of the most resistant strains. Without careful infection control procedures these virulent, resistant strains can be transferred from patient to patient.

Methods to Reduce the Spread of Antimicrobial Resistant Bacteria

- 1) Eliminate the use of antibiotics in animal feed
- 2) Observe strict infection control policies in the hospital setting
- 3) Reduce the inappropriate prescribing of antibiotics in the community (*e.g.*, for the treatment of upper respiratory tract infections)
- 4) Antibiotic restriction policies in the hospital setting