EMERGING INFECTIONS

I. THE PROBLEM: ANTIBIOTIC RESISTANT BACTERIA

Bacteria are emerging that will greatly challenge our treatment protocols. It is very likely that many of our most commonly used drugs will fail to halt a large number of common pathogens in the near future. One particular subset of emerging pathogens, antibiotic resistant bacteria, are an especially important threat. To deal with the challenge posed by these organisms, you will need to understand the reasons for the emergence of antibiotic resistance.

II. DEFINITION OF AN EMERGING PATHOGEN

A. A previously unknown organism that causes disease
   or
B. A previously identified organism that has recently acquired the capacity to cause disease
   or
C. A previously identified pathogen that has recently acquired the capacity to resist antibiotic treatment

III. CAUSES OF RESISTANCE:

A. WHY ARE WE SEEING EMERGING PATHOGENS NOW?

1. Human demographics and behavior
   sexual practices, longer life spans

2. Technology and industry
   misuse of antibiotics in livestock

3. Economic development and land use
   movement of populations, disruption of societies, poor sewage control

4. International travel and commerce
   there are no longer any effective barriers to the movements of people or things

5. Microbial adaptation and change
   bacteria have plastic genomes

6. Breakdown of public health measures
   public health is often not as high a priority as it needs to be. A low or nonexistent priority
   where it is needed the most.
B. MECHANISMS OF RESISTANCE ACQUISITION

For a resistant bacterium to become numerically significant in a host, it must have the chance to increase its numbers relative to the other bacteria that are present. This opportunity is often present in the clinic. The opportunity for resistance to arise is present when a patient is treated with antibiotics. In this environment, the antibiotic resistant pathogen has the selective advantage of being able to grow and divide where the antibiotic sensitive organism will be suppressed or killed.

In a healthy host in the absence of drug, a resistant strain of a pathogen might not reach a particularly high titer, as it will not necessarily have any growth advantage over non-resistant strains or the normal flora, nor any increased virulence. In the presence of the drug, however, much of the normal bacterial flora will be suppressed allowing the resistant organism to flourish.

Figure 4.1 Application of an antimicrobial drug can select for resistance. The striped bacteria are a pathogen and, in this example, are being treated with a drug. The letter R indicates bacteria that acquire resistance to the drug.
1. A spontaneous mutation resulting in resistance

2. Application of drug at a level sufficient to kill sensitive bacteria but insufficient to kill resistant (i.e. mutant) bacteria

3. Continued growth, not necessarily in the presence of drug

Why are sub-lethal doses of drug particularly effective in selecting for resistance? Because a mutation able to provide resistance to a reduced level of drug is a more likely event.

Figure 4.2 How does antimicrobial drug resistance arise?

Creation of a “gradient” of selective pressure throughout the patient:

1. Variation in drug concentration throughout the patient
2. Variation in tissue damage due to disease
3. Variation in levels of competitor bacteria

These conditions maximize the chance that selection for resistance will be successful

Figure 4.3. Conditions that promote selection of antimicrobial drug resistance.

In addition to the factors described above, a minor population of intrinsically resistant bacteria can reach high concentrations when a drug, to which they are resistant, is used to treat another organism in the same host. The drug removes the resistant bacteria’s competition.
Bacteria can transfer virulence factors to other strains and species in the hospital and in the patient. This can result in a previously non-pathogenic bacterium causing disease.

**Multi-drug resistant bacteria:**

This especially alarming type of resistance results in an organism that is resistant to several drugs. It can occur for several reasons, including the action of a multi-drug efflux system that can non-specifically export drugs that penetrate one or both membrane layers. This kind of mechanism is especially likely to arise when the organism encounters multiple drugs.

![Figure 4.4 Artist’s rendition of a multi-drug efflux system.](image)

The dynamics of bacterial growth and evolution in the clinic make it imperative for the physician to understand how to prescribe drugs so that they do not contribute to the emergence of antibiotic resistance.
Major errors in prescription:

a. Inappropriately prescribing (misdiagnosis)
b. Over-prescribing
c. Shortening the duration of treatment
d. Reducing the amount of drug

A reservoir of virulent organisms can arise during long term prophylaxis with an antibiotic that succeeds in suppressing the primary infection but which allows other resistant bacteria to become established.
Distinguishing between resistance, tolerance and persistence

**Resistance**
- Clear different MIC
- Due to mutations in population
- Higher concentration to produce the same effect

**Tolerance**
- MIC is the same and not informative
- Due to mutations in whole population
- Longer exposure to produce same effect

**Persistence**
- Generally MIC is the same, but subpopulation is not killed
- No mutations
- Biphasic killing
IV. SOLUTIONS: RESPONSES TO THE PROBLEM OF RESISTANT BACTERIA

1. ROLE OF THE PHYSICIAN
   a. Staying informed regarding new drugs and treatments
   b. Taking an activist role in developing policy when appropriate
   c. Educating patients about proper dispensing of antibiotics

2. PUBLIC POLICY
   a. Play a role where you feel you can make a difference. Remember that you are among the best informed on the issues and will be able to make valuable input
   b. Follow policy issues (i.e., via the CDC web site)

3. THE PHARMACEUTICAL INDUSTRY
   The pharmaceutical industry is a powerful force in the development of new drugs. The industry will be key in dealing with emerging diseases because it will be the leader in drug discovery. It will be important for physicians to follow the industry in order to understand new trends in treatment.
   a. The industry is enormous:
      $69 billion of goods were shipped in 1993
   b. It spends heavily on R&D:
      $13.8 billion was spent on R&D in 1994. R&D expenditures are growing at a rate of ~10%/yr. (based on 1993 figures) which is down from 16% (the rate between 1980 and 1992).
   c. It has made major contributions to drug discovery:
      The industry discovered almost 50% of all medicines identified between 1970 and 1992
d. The pharmaceutical industry faces some important challenges:
   i. Rising R&D costs. It takes, on average, 12 years and costs $359 million to bring a single new drug to market. These costs are recouped on only about 30% of drugs that go to market.
   ii. The drug marketplace has become more complex and lower profits are anticipated.
STUDY QUESTIONS

1. Drug resistant bacteria emerge in hospitals because:
   
   A. A more resistant bacterium is necessarily more virulent.
   
   B. Hospitals in developing countries and war-torn countries rarely have access to modern drugs.
   
   C. The heavy application of antibiotics in this environment gives a competitive advantage to resistant bacteria.
   
   D. Almost all locations all over the world are easily accessible to each other.

2. A key way physicians can help reduce the emergence of antibiotic resistant bacteria is to:
   
   A. Make sure that drugs are prescribed in a sufficient dosage and for the appropriate duration.
   
   B. Emphasize the use of rationally designed drugs.
   
   C. Ensure that already resistant bacteria do not exist in the patient’s body before treatment begins.
   
   D. Make certain that multi-drug resistance will not arise by iterative testing.