The History of Medicine

- 2000 BC – Here, eat this root.
- AD 1000 – That root is heathen. Here, say this prayer.
- 1850 – That prayer is superstition. Here, drink this potion.
- 1920 – That potion is snake oil. Here, swallow this pill.
- 1945 – That pill is ineffective. Here, take this penicillin.
- 1955 – Oops… bugs mutated. Here, take this tetracycline.
- 1960–1999 – 39 more “oops”… Here, take this more powerful antibiotic.
- 2000 – The bugs have won! Here, eat this root.

—Anonymous

Society’s ongoing struggle against infectious disease.
Brief history of antimicrobials

- Antimicrobials are “magic bullets” *sensu* Ehrlich

- First modern antimicrobial was **Salvarsan**, an arsenic-based magic bullet discovered by the German infectious disease specialist Paul Ehrlich. Used to treat syphilis

- Quinine became widely used as an antimalarial after it was isolated in 1820 from the bark of the cinchona tree

- Sulfonamides were introduced in the 1930s. They are synthetic antimicrobials that block folic acid production in bacteria
Brief history of antimicrobials

• The first **antibiotic** (in the original sense of the word) was **penicillin**

• The term “antibiotic” originally was used to denote formulations derived from living organisms but is now used for partially or wholly synthetic antimicrobials too

• The French physician Ernest Duchesne first noted that certain moulds kill bacteria, but his work was forgotten

• Alexander Fleming rediscovered that *Penicillium* kills bacteria in 1928
Brief history of antimicrobials

Alexander Fleming

- Working on cultures of Staphylococcus
- Contamination with mold
- Noticed colonies growing near mold looked odd
- Found that mold was secreting substance that was killing bacteria
**Figure 20.1**

- **Penicillium colony**
- **Area of inhibition of bacterial growth**
- **Normal bacterial colony**
Brief history of antimicrobials

• Fleming was convinced that the observation could never lead to therapeutic agents

• Florey and Chain resurrected the work, isolated penicillin, and by WWII were treating millions with antibiotics

• The age of antibiotics changed the landscape of modern medicine and antibiotics are one of the key medical interventions that have impacted human health
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- **Mechanism of action include:**
  - Inhibition of cell wall synthesis
  - Inhibition of protein synthesis
  - Inhibition of nucleic acid synthesis
  - Inhibition of metabolic pathways
  - Interference with cell membrane integrity
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- Inhibition of Cell wall synthesis
  - Bacteria cell wall unique in construction
    - Contains peptidoglycan
  - Antimicrobials that interfere with the synthesis of cell wall do not interfere with eukaryotic cell
    - Due to the lack of cell wall in animal cells and differences in cell wall in plant cells
  - These drugs have very high therapeutic index
    - Low toxicity with high effectiveness
  - Antimicrobials of this class include
    - β lactam drugs
    - Vancomycin
    - Bacitracin
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- **Penicillins and cephalosporins**
  - Part of group of drugs called β-lactams
    - Have shared chemical structure called β-lactam ring
  - Competitively inhibits function of penicillin-binding proteins
    - Inhibits peptide bridge formation between glycan molecules
    - This causes the cell wall to develop weak points at the growth sites and become fragile.
The weakness in the cell wall causes the cell to lyze.
The weakness in the cell wall causes the cell to lyse.

Penicillins and cephalosporins are considered bactericidal.

Penicillins are more effective against Gram+ bacteria. This is because Gram + bacteria have penicillin binding proteins on their walls.
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- The cephalosporins
  - Chemical structures make them resistant to inactivation by certain β-lactamases
  - Tend to have low affinity to penicillin-binding proteins of Gram + bacteria, therefore, are most effective against Gram - bacteria.
  - Chemically modified to produce family of related compounds
    - First, second, third and fourth generation cephalosporins
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- **Vancomycin**
  - Inhibits formation of glycan chains
    - Inhibits formation of peptidoglycans and cell wall construction
    - Does not cross lipid membrane of Gram -
      - Gram - organisms innately resistant
  - Important in treating infections caused by penicillin resistant Gram + organisms
  - Must be given intravenously due to poor absorption from intestinal tract
  - Acquired resistance most often due to alterations in side chain of NAM molecule
    - Prevents binding of vancomycin to NAM component of glycan
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- **Bacitracin**
  - Interferes with transport of peptidoglycan precursors across cytoplasmic membrane
  - Toxicity limits use to topical applications
  - Common ingredient in non-prescription first-aid ointments
Biosynthesis of Peptidoglycan

- Synthesize precursors in cytoplasm
- Transport of precursors across cell membrane
- Addition of precursors to peptidoglycan
- Cross-linking of peptidoglycan chains
Biosynthesis of Peptidoglycan

1. Synthesize precursors in cytoplasm
2. Transport of precursors across cell membrane
3. Addition of precursors to peptidoglycan
4. Cross-linking of peptidoglycan chains

NAG, NAM, peptide
Biosynthesis of Peptidoglycan

- **NAG**
- **NAM**
- **peptide**

1. **Synthesize precursors in cytoplasm**
   - Cycloserine
2. **Transport of precursors across cell membrane**
   - Bacitracin
3. **Addition of precursors to peptidoglycan**
   - Glycopeptides
4. **Cross-linking of peptidoglycan chains**
   - β-Lactams Glycopeptides
Biosynthesis of Peptidoglycan

- Synthesize precursors in cytoplasm
  - Cycloserine

- Transport of precursors across cell membrane
  - Bacitracin

- Addition of precursors to peptidoglycan
  - Glycopeptides

- Cross-linking of peptidoglycan chains
  - β-lactams, glycopeptides
Action of β-lactams
Effect of penicillin on a bacterium
Protein synthesis inhibitors
Protein synthesis inhibitors (PSI): Aminoglycosides

Aminoglycosides, eg. Streptomycin, Gentamicin, Amikacin

NB. The only protein synthesis inhibitors that are bactericidal

Inhibit initiation

Cause misreading of mRNA
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- **Aminoglycosides**
  - Irreversibly binds to 30S ribosomal subunit
    - Causes distortion and malfunction of ribosome
    - Blocks initiation translation
      - Causes misreading of mRNA
  - Not effective against anaerobes, enterococci and streptococci
  - Often used in synergistic combination with β-lactam drugs
    - Allows aminoglycosides to enter cells that are often resistant
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- Examples of aminoglycosides include
  - Gentamicin, streptomycin and tobramycin
- Side effects with extended use include
  - Ototoxicity
  - Nephrotoxicity
PSI: Tetracyclines
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- **Tetracyclins**
  - Reversibly bind 30S ribosomal subunit
    - Blocks attachment of tRNA to ribosome
    - Prevents continuation of protein synthesis
  - Effective against certain Gram + and Gram -
  - Newer tetracyclines such as doxycycline have longer half-life
    - Allows for less frequent dosing
  - Resistance due to decreased accumulation by bacterial cells
  - Can cause discoloration of teeth if taken as young
PSI: Chloramphenicol, macrolides and lincosamides

Inhibit peptidyl transferase

Chloramphenicol
Macrolides
Lincosamides

Inhibit translocation

Macrolides
Lincosamides
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- **Macrolids**
  - Reversibly binds to 50S ribosome
    - Prevents continuation of protein synthesis
  - Effective against variety of Gram + organisms and those responsible for atypical pneumonia
  - Often drug of choice for patients allergic to penicillin
  - Macrolids include
    - Erythromycin, clarithromycin and azithromycin
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- Resistance can occur via modification of RNA target
  - Other mechanisms of resistance include production of enzyme that chemically modifies drug as well as alterations that result in decreased uptake of drug
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- **Chloramphenicol**
  - Binds to 50S ribosomal subunit
    - Prevents peptide bonds from forming and blocking protein synthesis
  - Effective against a wide variety of organisms
  - Generally used as drug of last resort for life-threatening infections
  - Rare but lethal side effect is aplastic anemia
Protein synthesis inhibitors

- **Chloramphenicol**
- **Macrolides, lincosamides**
- **Tetracyclines**
- **Aminoglycoside**

Diagram showing the interaction of different protein synthesis inhibitors with the ribosome, indicating their effect on translation. The ribosome is depicted as a 70S complex, with the nascent polypeptide chain and mRNA orientation marked."
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- Inhibition of nucleic acid synthesis
  - These include
    - Fluoroquinolones
    - Rifamycins
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- Fluoroquinolones
  - Inhibit action of topoisomerase DNA gyrase
    - Topoisomerase maintains supercoiling of DNA
  - Effective against Gram + and Gram -
  - Examples include
    - Ciprofloxacin and ofloxacin
  - Resistance due to alteration of DNA gyrase
Rifamycins
- Block prokaryotic RNA polymerase
  - Block initiation of transcription
- Rifampin most widely used rifamycins
- Effective against many Gram + and some Gram - as well as members of genus *Mycobacterium*
- Primarily used to treat tuberculosis and Hansen’s disease as well as preventing meningitis after exposure to *N. meningitidis*
- Resistance due to mutation coding RNA polymerase
  - Resistance develops rapidly
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- Inhibition of metabolic pathways
  - Relatively few
  - Most useful are folate inhibitors
    - Mode of actions to inhibit the production of folic acid
  - Antimicrobials in this class include
    - Sulfonamides
    - Trimethoprim

Diagram:
- Para-aminobenzoic acid (PABA)
- Sulfanilamide
- Antimicrobials in this class include:
  - Sulfonamides
  - Trimethoprim

Note: The diagram illustrates the mechanism of action of sulfonamides and trimethoprim, showing how they inhibit the production of folic acid.
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- **Sulfonamides**
  - Group of related compounds
    - Collectively called sulfa drugs
  - Inhibit growth of Gram + and Gram - organisms
    - Through competitive inhibition of enzyme that aids in production of folic acid
  - Structurally similar to para-aminobenzoic acid
    - Substrate in folic acid pathway
  - Human cells lack specific enzyme in folic acid pathway
    - Basis for selective toxicity
  - Resistance due to plasmid
    - Plasmid codes for enzyme that has lower affinity to drug
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- **Trimethoprim**
  - Inhibits folic acid production
    - Interferes with activity of enzyme following enzyme inhibited by sulfonamides
  - Often used synergistically with sulfonamide
  - Most common mechanism of resistance is plasmid encoded alternative enzyme
    - Genes encoding resistant to sulfonamide and trimethoprim are often carried on same plasmid
MECHANISMS OF ACTION OF ANTIBACTERIAL DRUGS

- Interference with cell membrane integrity
  - Few damage cell membrane
    - Polymixin B most common
      - Common ingredient in first-aid skin ointments
  - Binds membrane of Gram - cells
    - Alters permeability
      - Leads to leakage of cell and cell death
    - Also bind eukaryotic cells but to lesser extent
      - Limits use to topical application
12/30/13

Dr. Shyamal Kr Paul, Antimicrobial agents/ resistance
RESISTANCE TO ANTIMICROBIAL DRUGS
The most important problem associated with infectious disease today is the rapid development of resistance to antibiotics.

It will force us to change the way we view disease and the way we treat patients.
OVERVIEW

Antibiotic Resistance

- Evolution of Antibiotic Resistance
- Mechanisms for Acquiring Resistance
- MRSA, VRSA, VRE, and Other Pathogens
- Contributing Factors and Possible Solutions
Antibiotics’ use has not been without consequence. There are several factors in the development of antibiotic resistance:
- Considerable potential for rapid spontaneous mutation
- Some of these mutations are for antibiotic resistance
- These mutations are selected for certain antibiotics.
Bacterial cells that have developed resistance are not killed off.

- They continue to divide
- Resulting in a completely resistant population.

Mutation and evolutionary pressure cause a rapid increase in resistance to antibiotics.
..DEVELOPMENT OF RESISTANCE

$P_S$ penicillin-sensitive
$P_R$ penicillin-resistant

penicillin is added; sensitive organisms are killed

resistant $P_R$ cells multiply

Figure 20.1 Microbiology: A Clinical Approach (© Garland Science)
Modern technology and sociology can further aggravate the development of resistant strains.

- **Travelers** carry resistant bacteria.
  - They travel with several or many other people.
- Other people are infected with the resistant bacteria.
  - These people continue traveling and infecting.
- The process is repeated and the resistant bacteria spread.
DEVELOPMENT OF RESISTANCE: Living Conditions

- There are more large cities in the world today.
  - Large numbers of people in relatively small areas
  - Passing antibiotic-resistant pathogens is easier.
  - Many large urban populations have poor sanitation.
DEVELOPMENT OF RESISTANCE: Food

- Food is also a source of infection that could affect the development of resistance.
  - More meals are prepared outside the home.
  - Contamination goes unnoticed until infection has started.
    - Outbreaks of *Escherichia coli O157* in spinach and lettuce in the US.
  - As the number of foodborne infections increases, so does the use of antibiotics.
    - Causes an increase in the development of resistance.
An important social change is the increase in the number of people who are immunocompromised.

- Necessitates increased use of antibiotics
- Fosters development of resistance

DEVELOPMENT OF RESISTANCE:

Immunocompromised Patients
Emerging and re-emerging diseases are another source for resistance.

- Emerging diseases have not been seen before.
- Re-emerging are caused by organisms resistant to treatment.
## DEVELOPMENT OF RESISTANCE: ..Emerging and Re-emerging Bacterial Diseases

<table>
<thead>
<tr>
<th>Year</th>
<th>Agent</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td><em>Bartonella henselae</em></td>
<td>Cat-scratch disease; bacillary angiomatosis</td>
</tr>
<tr>
<td>1992</td>
<td><em>Vibrio cholerae</em> O139</td>
<td>New strain, epidemic cholera</td>
</tr>
<tr>
<td>1989</td>
<td><em>Ehrlichia chaffeensis</em></td>
<td>Human ehrlichiosis</td>
</tr>
<tr>
<td>1983</td>
<td><em>Helicobacter pylori</em></td>
<td>Peptic ulcer disease</td>
</tr>
<tr>
<td>1982</td>
<td><em>Borrelia burgdorferi</em></td>
<td>Lyme disease</td>
</tr>
<tr>
<td>1981</td>
<td>Toxin-producing strains of <em>Staphylococcus aureus</em></td>
<td>Toxic shock syndrome</td>
</tr>
<tr>
<td>1977</td>
<td><em>Campylobacter jejuni</em></td>
<td>Enteric pathogen, global distribution</td>
</tr>
</tbody>
</table>
The clinical success of antibiotics led to:
- Increasing efforts to discover new antibiotics.
- Modification of existing drugs.
- Development of antibiotics with broader spectra.

Effort is now targeted towards overcoming strains resistant to current antibiotics.
...EVOLUTION OF RESISTANCE TO ANTIBIOTIC

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Year Deployed</th>
<th>Resistance Observed</th>
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<tr>
<td>Sulfonamides</td>
<td>1930s</td>
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<tr>
<td>Penicillin</td>
<td>1943</td>
<td>1946</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1943</td>
<td>1959</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>1947</td>
<td>1959</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>1948</td>
<td>1953</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>1952</td>
<td>1988</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1956</td>
<td>1988</td>
</tr>
<tr>
<td>Methicillin</td>
<td>1960</td>
<td>1961</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>1961</td>
<td>1973</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>1960s</td>
<td>late 1960s</td>
</tr>
</tbody>
</table>

Table 20.2 Microbiology: A Clinical Approach (© Garland Science)
Resistance develops at different rates.

- Several groups of antibiotics were used for many years before resistance was seen.
- Resistance to penicillin was seen in only three years.
- Some semi-synthetic forms of penicillin (ampicillin) had a relatively long time before resistance developed.
- Other semi-synthetic forms (methicillin) lasted only a year before resistance developed.
  - Short interval is directly related to increased use.
The therapeutic life span of a drug is based on how quickly resistance develops. The more an antibiotic is used, the more quickly resistance occurs.
..EVOLUTION OF ANTIBIOTIC RESISTANCE: Rate of Development

<table>
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Table 20.2 Microbiology: A Clinical Approach (© Garland Science)
The most important contributing factor for resistance is overuse.

- A good example is prescribing antibiotics that don’t kill viruses for the common cold.
- These antibiotics do destroy the normal flora.
- Opportunistic pathogens that are resistant survive and can take hold.
Hospitals are ideal reservoirs for the acquisition of resistance.
- A population of people with compromised health
- A high concentration of organisms, many of which are extremely pathogenic
- Large amounts of different antibiotics are constantly in use

Increased use of antibiotics leads to resistance.
- Hospital is a place where resistance can develop rapidly.
Resistance can be transferred by bacteria swapping genes.

- This can be easily accomplished in a hospital setting.
- Health care workers who don’t follow infection control protocols aid in increasing resistance.
Plasmids containing genes for resistance can integrate into the chromosome. Here they form resistance islands. Resistance genes accumulate and are stably maintained.
Microorganisms producing antibiotic substances have autoprotective mechanisms.

- Transmembrane proteins pump out the freshly produced antibiotic so that it does not accumulate.
  - If it did, it would kill the organism producing it.

Genes that code for these pumps are closely linked to genes that code for antibiotic substances.

- When genes for antibiotic production are turned on so are the pump genes.
MECHANISMS FOR ACQUIRING RESISTANCE

- Bacteria use several mechanisms to become antibiotic-resistant:
  - Inactivation of the antibiotic
  - Efflux pumping of the antibiotic
  - Modification of the antibiotic target
  - Alteration of the pathway
INACTIVATION OF ANTIBIOTIC

- **Inactivation** involves enzymatic breakdown of antibiotic molecules.
- A good example is **β-lactamase**:
  - Secreted into the bacterial periplasmic space
  - Attacks the antibiotic as it approaches its target
  - There are more than 190 forms of β-lactamase.
  - E.g. of lactamase activity in *E.coli* and *S. aureus*
MECHANISMS FOR ACQUIRING RESISTANCE

(a) drug inactivation

Active penicillin → penicillinase → inactive penicillin

an enzyme (in this case penicillinase) cleaves a portion of the antibiotic molecule and renders it inactive

(b) decreased permeability/change in shape of receptor

Drug receptor → microbial cell

mutations can alter the receptor that transports the drug, so that the drug cannot enter the cell

(c) activation of drug pumps

Drug pump → microbial cell

specialized membrane proteins are activated and continually pump the drug out of the cell

(d) use of alternative metabolic pathway

Drug acts to block pathway

A → B → C → D → product

alternative pathway

A → B → E → F

some drugs block the usual metabolic pathway, organisms can circumvent this by using an alternative, unblocked pathway that produces the required product

Figure 20.2 Microbiology: A Clinical Approach (© Garland Science)
EFFLUX PUMPING OF ANTIBIOTIC

- Efflux pumping is an active transport mechanism.
  - It requires ATP.
- Efflux pumps are found in:
  - The bacterial plasma membrane
  - The outer layer of gram-negative organisms
- Pumping keeps the concentration of antibiotic below levels that would destroy the cell
- Genes that code for efflux pumps are located on plasmids and transposons.
- Transposons are sequences of DNA that can move or transpose move themselves to new positions within the genome of a single cell. Transposones:
  - Readily acquired by nonresistant bacteria
  - Transforms them into resistant bacteria
Some bacteria reduce the permeability of their membranes as a way of keeping antibiotics out.
- They turn off production of porin and other membrane channel proteins.
- Seen in resistance to streptomycin, tetracycline, and sulfa drugs.
MODIFICATION OF ANTIBIOTIC TARGET

- Bacteria can modify the antibiotic’s target to escape its activity.
- Bacteria must change structure of the target but the modified target must still be able to function. This can be achieved in two ways:
  - Mutation of the gene coding for the target protein
  - Importing a gene that codes for a modified target
- E.g. with MRSA (methicillin-resistant - S. aureus), similar to PBP (penicillin-binding-protein)
Bacteria have PBPs in their plasma membranes. These proteins are targets for penicillin. 

MRSA has acquired a gene (*mec A*) that codes for a different PBP. 
- It has a different three-dimensional structure. 
- MRSA less sensitive to penicillins.
MRSA is resistant to all β-lactam antibiotics, cephalosporins, and carbapenems. It is a very dangerous pathogen particularly in burn patients.

Streptococcus pneumoniae also modifies PBP.
- It can make as many as five different types of PBP.
- It does this by rearranging, or shuffling, the genes.
  - Referred to as genetic plasticity
  - Permits increased resistance
MODIFICATION OF TARGET RIBOSOMES

- Bacterial ribosomes are a primary target for antibiotics
  - Different antibiotics affect them in different ways.
- Resistance can be the result of modification of ribosomal RNA so it is no longer sensitive.
- Some organisms use target modification in conjunction with efflux pumps.
  - Resistance is even more effective.
Some drugs competitively inhibit metabolic pathways.

Bacteria can overcome this method by using an alternative pathway.

Approximately 7% of the total *S. aureus* genome is genes for antibiotic resistance.

*Bacillus subtilis*, a nonpathogenic organism, has none.
Several specific resistance genes of MRSA have been identified. They are associated with different resistance mechanisms.

- β-lactamase resistance
- Erythromycin resistance
- Production of aminoglycosides
- Operation of efflux pumps
Bacteria that are part of the normal flora are becoming more dangerous due to resistance.

- *E. coli* is part of the normal flora of the large intestine.
- It has become more involved with urinary tract infections.
- Antibiotic-resistant infections are now being seen throughout the world.
MRSA, VRSA, VRE, AND OTHER PATHOGENS

Several antibiotic-resistant bacteria are considered clinically dangerous.

- MRSA (Methicillin-Resistant) and VRSA (Vancomycin-resistant \textit{S. aureus} are very virulent in humans and are referred as \textit{professional pathogens}. (Refer Table 20.3 pg 472)

- MRSA and VRSA contain many resistance genes.
  - Three or four resistance islands on the chromosome
  - 26-28 additional gene clusters on plasmids which can move to other bacterial cells.
  - VRE-Vancomycin enterococcus e.g \textit{E. faecalis} contributes to 90% of all vancomycin resistant bacteria
CONTRIBUTING FACTORS AND POSSIBLE SOLUTIONS

- Variety of factors involved in the development of drug resistance
- An underestimated factor is the success of so many antibiotics.
  - They are very effective at killing microorganisms.
  - Doctors and patients have become dependent on them.
CONTRIBUTING FACTORS AND POSSIBLE SOLUTIONS

- The doctor-patient-drug relationship leads to resistance.
  - Most clearly seen in the case of common viral infections.
  - Patients expect to have antibiotics have prescribed.
  - There is overprescription of antibiotics that are not required.
  - Patients who feel better and stop using the drug make the problem worse.
CONTRIBUTING FACTORS AND POSSIBLE SOLUTIONS

- Overuse of broad-spectrum antibiotics (cephalosporins) leads to the rise of resistance.
  - It permits the superinfection effect.
    - Pathogens occupy areas where normal microbes have been killed.
    - Antibiotics have essentially compromised the patient.
CONTRIBUTING FACTORS AND POSSIBLE SOLUTIONS

- Clostridium difficile is a superinfection pathogen.
  - Establishes itself in the intestinal tract as part of a superinfection
  - It is very resistant to antibiotics.
  - Patients with this infection are difficult to treat
Destruction of normal flora allows pathogenic pathogens to dominate.

(a) infection through fecal-oral route

(b) drug circulates

(c) super-infection

Figure 20.3 Microbiology: A Clinical Approach (© Garland Science)
The potential for global antibiotic resistance is real due to:

- Overuse of antibiotics
- Improper adherence to hospital infection control protocols
- Difficulty finding new antibiotics
- Ease of worldwide travel

There are ways to lengthen the useful life of antibiotics.
Guidelines for extending the useful life of antimicrobial drugs

<table>
<thead>
<tr>
<th>Point</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Optimal use of all antibacterial drugs</td>
</tr>
<tr>
<td>2</td>
<td>Selective removal, control, or restriction of classes of antibacterial agents</td>
</tr>
<tr>
<td>3</td>
<td>Use of antibacterial drugs in rotation or cyclic patterns</td>
</tr>
<tr>
<td>4</td>
<td>Use of combination antibacterial therapy to slow the emergence of resistance</td>
</tr>
<tr>
<td>5</td>
<td>Evaluation of routes of resistance</td>
</tr>
<tr>
<td>6</td>
<td>Implementation of global changes</td>
</tr>
</tbody>
</table>

Table 20.5 Microbiology: A Clinical Approach (© Garland Science)
Probably the most widely used testing method is the disk-diffusion method, also known as the Kirby-Bauer test.
Susceptibility of Bacterial to Antimicrobial Drug

- **Conventional disc diffusion method**
  - Kirby-Bauer disc diffusion routinely used to qualitatively determine susceptibility
  - Standard concentration of strain uniformly spread of standard media
  - Discs impregnated with specific concentration of antibiotic placed on plate and incubated

- Clear zone of inhibition around disc reflects susceptibility
  - Based on size of zone organism can be described as susceptible or resistant
EFFECTS OF COMBINATIONS OF DRUGS

- Sometimes the chemotherapeutic effects of two drugs given simultaneously is greater than the effect of either given alone.

- This is called synergism. For example, penicillin and streptomycin in the treatment of bacterial endocarditis. Damage to bacterial cell walls by penicillin makes it easier for streptomycin to enter.
EFFECTS OF COMBINATIONS OF DRUGS

- Other combinations of drugs can be antagonistic.
- For example, the simultaneous use of penicillin and tetracycline is often less effective than when wither drugs is used alone. By stopping the growth of the bacteria, the bacteriostatic drug tetracycline interferes with the action of penicillin, which requires bacterial growth.
EFFECTS OF COMBINATIONS OF DRUGS

- Combinations of antimicrobial drugs should be used only for:
  1. To prevent or minimize the emergence of resistant strains.
  2. To take advantage of the synergistic effect.
  3. To lessen the toxicity of individual drugs.