Antibiotics Resistance
Introduction to Antibiotics Resistance

- Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it.
- Penicillin G: first introduced, only 3% of bacteria resistant, now, over 90% are resistant.
- Many bacterial pathogens are currently resistance to many antibiotics with some organisms are currently resistance to every known antibiotics.
- WHO’s 2014 report on global surveillance of antimicrobial resistance reveals that antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world, and is putting at risk the ability to treat common infections in the community and hospitals.
Antibiotic introduced

- Erythromycin 1953
- Gentamicin 1967
- Imipemen and Ceftazidine 1985
- Linezolid 2000
- Ceftaroline 2010

Penicillin 1943
- Tetracycline 1950
- Methicillin 1960
- Vancomycin 1972
- Levofloxacin 1996
- Daptomicin 2003
- Ceftaroline resistant staph

1959 Tetracycline resistant shigella
1962 Methicillin resistant staph
1965 Penicillin resistant pneumococcus
1979 Gentamicin resistant enterococcus
1988 Vancomycin resistant enterococcus
1996 Levofloxacin resistant pneumococcus
2000 XDR (Extensively Drug Resistant) Tuberculosis
2001 Linezolid resistant staph
2004 pan-drug resistant Acinetobacter And Pseudomonas

Antibiotic resistance identified
The Development of a Resistant Strain of Bacteria
Natural & Acquired Resistance

1. Natural resistance
   - Intrinsic resistance: some species naturally insensitive
   - Chromosomic genetic support
   - Affect almost all species strains
   - Existed before antibiotic use (*Enterobacter* sp. - amoxicillin)

2. Acquired resistance (mutation)
   - Spontaneous mutation: happen as cells replicate
   - Gene transfer: usually spread through conjugative transfer of R plasmid
   - Affects a fraction of strains
   - Increased with antibiotic use (extended spectrum beta-lactamase producing *E. coli*)
Mechanisms of Resistance

1. Production of enzyme that destroys or deactivates drug
2. Pump antimicrobial drug out of the cell before it can act
3. Slow or prevent entry of drug into the cell
4. Alter target of drug so it binds less effectively
5. Alter their metabolic chemistry
(a) **drug inactivation**

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**

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

(c) **activation of drug pumps**

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

(d) **use of alternative metabolic pathway**

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)
1. Enzymatic Inactivation

- **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* (Extended spectrum beta-lactamases - ESBL)

![Diagram of β-lactamase activity]
2. Efflux Pumping

- 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.
3. Decrease Permeability

- 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.
4. Modification of Antibiotics Targets

- 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
- Bacteria have penicillin-binding-protein (PBPs) in their plasma membranes. These proteins are targets for penicillin.
- MRSA (methicillin-resistant - *S. aureus*) has acquired a gene (*mecA*) 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
- *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
- 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
5. Alteration of Pathway

- Some drugs competitively inhibit metabolic pathways.
- Bacteria can overcome this method by using an alternative pathway.
- Some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by sulfonamides, instead, like mammalian cells, they turn to using preformed folic acid.
Contributing Factors to Resistance

- Misuse and overuse of antibiotics
- Modern live: travelers carry resistant bacteria
- 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
- Food is also a source of infection that could affect the development of resistance.
- An important social change is the increase in the number of people who are immunocompromised.
Emerging and re-emerging diseases are another source for resistance.

Hospitals are ideal reservoirs for the acquisition of resistance.

Destruction of normal flora allows pathogenic pathogens to dominate
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Impact of Antibiotics Resistance

- Infections caused by resistance organisms result in prolonged illness, disability or death
- Antimicrobial resistance reduces the effectiveness of treatment; thus patients remain infectious for a longer time, increasing the risk of spreading resistant microorganisms to others
- AMR increases the costs of health care
- AMR jeopardizes health care gains to society
- AMR has the potential to threaten health security, and damage trade and economies
Slowing the emergence and spread of antimicrobial resistance

1. Responsibilities of Physicians: must work to identify microbe and prescribe suitable antimicrobials, must educate patients
2. Responsibilities of Patients: need to carefully follow instructions
3. Educate Public: must understand appropriateness and limitations of antibiotics; antibiotics not effective against viruses
4. Global Impacts: organism that is resistant can quickly travel to another country, in some countries antibiotics available on non-prescription basis
Approaches to Antibiotic Therapy To Prevent Resistance

- Use antimicrobials only when necessary
- Maintain high concentration of drug in patient for sufficient time
- Use antimicrobial agents in combination
- Develop new variations of existing drugs
  Second-generation drugs
  Third-generation drugs
- Search for new antibiotics, semi-synthetics, and synthetics
- Design drugs complementary to the shape of microbial proteins to inhibit them
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<td>1</td>
<td>Optimal use of all antibacterial drugs</td>
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<td>2</td>
<td>Selective removal, control, or restriction of classes of antibacterial agents</td>
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<td>3</td>
<td>Use of antibacterial drugs in rotation or cyclic patterns</td>
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<td>Use of combination antibacterial therapy to slow the emergence of resistance</td>
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<td>Evaluation of routes of resistance</td>
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Determination of Drug Efficacy

- Drug efficacy determined based on clinical and laboratory parameters
- Drug efficacy can be measured by susceptibility testing
  - Including:
    1. Kirby-Bauer Method (diffusion test)
    2. Broth dilution test
    3. The E test
    4. Automatic (Vitek, Vitek 2)
Kirby-Bauer Method for Determining Drug Susceptibility

1. Bacteria spread on surface of agar plate
2. 12 disks, each with different antimicrobial drug, placed on agar plate
3. Incubated- drugs diffuse outward and kill susceptible bacteria
4. Zone of inhibition around each disk
5. Compare size of different antibiotics
Dilution Test

Sub-culture to agar medium

MIC = 8 ug/ml
MBC = 16 ug/ml
An E test combines aspects of Kirby-Bauer and MIC tests.
Thank you....