

Antibiotic Resistance

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Introduction:

- The first antibiotic
 - Discovered in 1929 by Sir Alexander Fleming
- World War II
 - Penicillin used to treat staphylococci and streptococci (1946)
- How effective was penicillin?
 - Resistance to penicillin recognized almost immediately
 - 80% of all strains of staphylococcus aureus
 - Streptococcus pyogenes (Group A strep) still treated with penicillin
 - Interestingly, penicillin has never been effective against Gram-negatives (Salmonella, shingella, bordetella pertussis, Yersinia pestis, Pseudomonas) - why?
- Late 1940s and early 1950's

Antibiotic therapy

- Effective chemotherapy depends on selective toxicity
 - Good against pathogen, does not affect host
- Exploit pathogen processes not seen in humans
 - Cell wall, metabolism, etc.
- Knowledge of likely microorganism is crucial...
 - Site
 - Organism
 - Allergy to host?
- Other considerations
 - Route of administration
- Monitoring therapy
- Adverse effects
 - GI-tract, skin, haemopoietic system, renal system, liver

Acquired Resistance

- Three major mechanisms of resistance
 - Alteration in drug target

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- Production of inactivating enzymes
- Decreased uptake of antibiotic

Antibiotic Resistance

- Resistance occurs when a susceptible microorganism is no longer inhibited by an antibiotic agent
- Many reasons why this can happen
 - Intrinsic - a predictable form of resistance based on the mechanisms of action of the antibiotic and characteristics of microorganism
 - Acquired - new or added (driven by two genetic processes in bacteria... mutation and selection (vertical evolution); and exchange of genetic material (horizontal evolution)
 - Alteration in drug target
 - Production of inactivating enzymes
 - Decreased antibiotic uptake

Genetics of Antibiotic Resistance:

- Genes can be encoded by the bacterial chromosome or other entities (plasmid_
- Genes may confer resistance by:
 - Exchange of genetic material
 - Conjugation (plasmid): cell-to-cell contact and pili to transfer DNA molecules in the form of plasmids
 - Mechanism of horizontal gene transfer
 - Transformation: uptake of free or naked DNA from the environment
 - Transduction: transfer of genetic material among bacterial cells using a bacteriophage
 - Transposition: mobilizes antibiotic resistance genes from one DNA molecule to another
 - Conjugative transposons and integrons make this possible
 - Chromosomal alteration or activation: mutation of a chromosomal gene involved with:
 - Encoding the target site of the antibiotic
 - Controlling alternative pathways or efflux mechanism
 - Controlling cell permeability
- Multiple Antibiotic Resistant (Mar)
 - Discovered in 1980's
 - Chromosomal locus
 - May be widely distributed among different bacteria

- Activation of the mar locus, resulting in bacteria that have a Mar phenotype, may be a clinically important form of multiple drug resistance

The chromosome: role in antibiotic resistance

- Mutations lead to
 - Change it site of antibiotic target (but protein for bacterial still works fine!)
 - Regulatory genes
 - Turn on alternative path
 - Turn on efflux mechanisms
 - Change cell permeability

Post-antibiotic era: is it possible?

- With current overuse of antibiotics, we are forcing bacteria to change (evolve) in order to survive
- How is this achieved/helped by us?

Decreasing antimicrobial resistance?

- Withhold antibiotics
 - Self-limited viral infections (i.e., the "common cold")
- Use narrowest spectrum antimicrobial agents
- Base decision about broadness of empiric antibiotic coverage on severity of illness
 - Clinically stable and not at risk for significant morbidity... may be appropriate to wait culture results and MIC testing
- Prevention of infection
 - Hygiene, hand-washing
 - Education
 - Helps to achieve therapeutic and preventative goals
 - When are antibiotics needed?
 - How to take them?
 - Proper duration
 - Earlier detection of therapeutic failure
 - Good for patients with antibiotic-resistant pathogens