Antimicrobial Agents

By:Prof. Dr. Rafal K. Farhan

Antibiotics

- Substances produced by various species of microorganisms: bacteria, fungi, actinomycetes- to suppress the growth of other microorganisms and to destroy them.

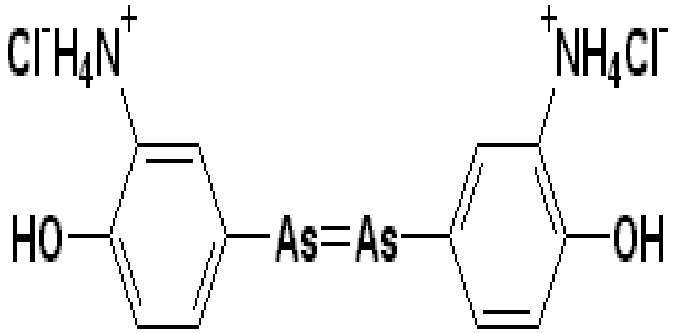
Today the term antibiotics extends to include synthetic antibacterial agents: sulfonamides and quinolones.

Where do antibiotics come from?

- Several species of fungi including *Penicillium* and *Cephalosporium*
  - E.g. penicillin, cephalosporin
  - Species of actinomycetes, Gram positive filamentous bacteria
    - Many from species of *Streptomyces*
  - Also from *Bacillus*, Gram positive spore formers
  - A few from myxobacteria, Gram negative bacteria
  - New sources explored: plants, herps, fish

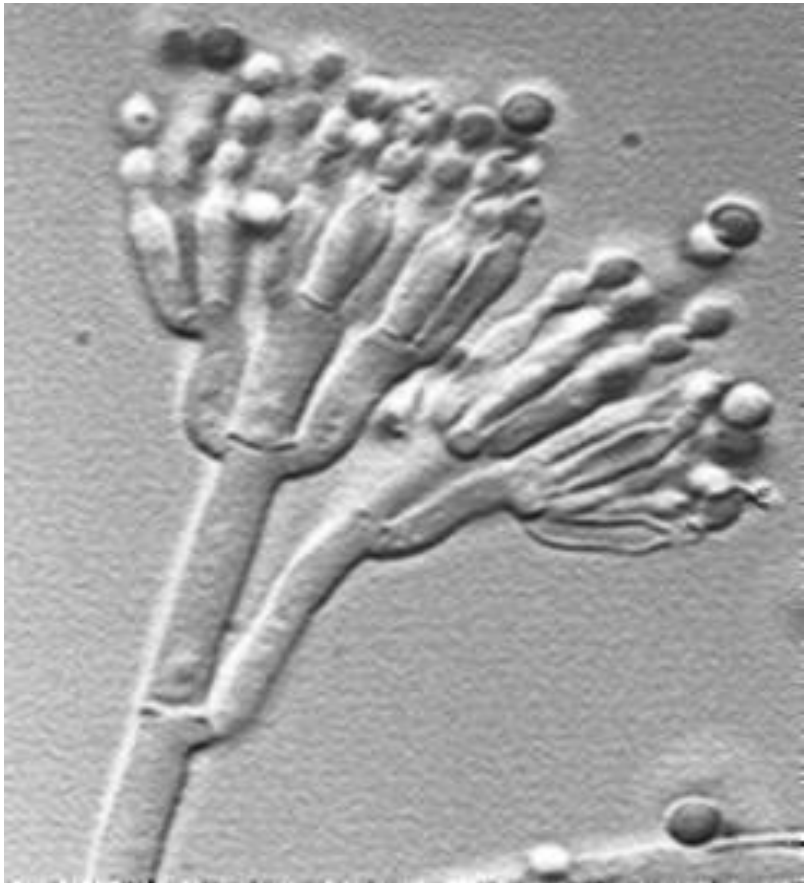
History of Antimicrobial Therapy

- 1909 Paul Ehrlich
  - Differential staining of tissue, bacteria
  - Search for magic bullet that would attack bacterial structures, not ours.
  - Developed salvarsan, used against syphilis.

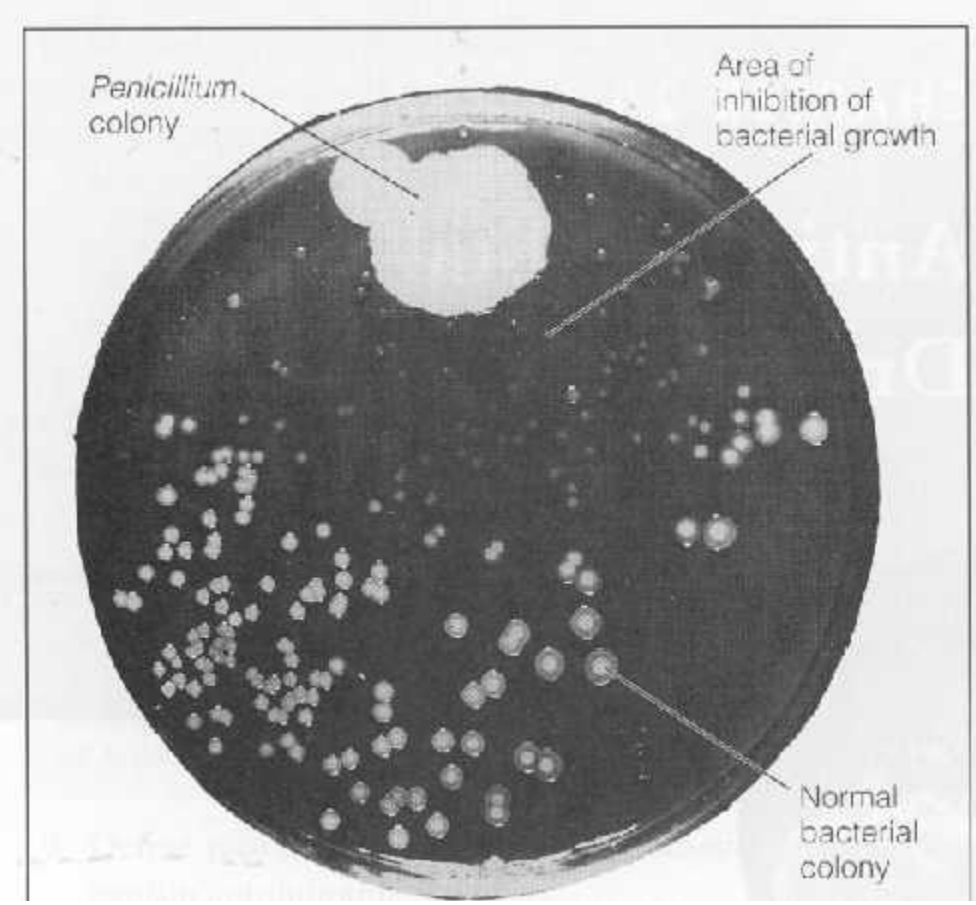


- 1929 Penicillin discovered by Alexander Fleming
- 1940 Florey and Chain mass produce penicillin for war time use, becomes available to the public.
- 1935 Sulfa drugs discovered
- 1944 Streptomycin discovered by Waksman from *Streptomyces griseus*

Sir Alexander Fleming



Fleming's Petri Dish



Historical distinctions

- Antibiotics: substances produced by organisms that have inhibitory effects on other organisms.
  - Penicillin, streptomycin
- Synthetic drugs: produced in a lab.
  - Salvarsan, sulfa drugs
- Nowadays, most antimicrobials are semi-synthetic
  - Distinction between "antibiotics" and "synthetic drugs" slowly being abandoned.

Penicillins

- **Penicillins contain a β-lactam ring which inhibits the formation of peptidoglycan crosslinks in bacterial cell walls (especially in Gram-possitive organisms)**
- **Penicillins are bactericidal but can act only on dividing cells**
- **They are not toxic to animal cells which have no cell wall**

Cephalosporins

- They also owe their activity to β-lactam ring and are bactericidal.
- Produced from a fungus *Cephalosporium acremonium.*
- Good alternatives to penicillins when a broad - spectrum drug is required
- should not be used as first choice unless the organism is known to be sensitive

Cephalosporins

- BACTERICIDAL- modify cell wall synthesis
- Interfere at the final step of peptidoglycan synthesis (Transpeptidation)
- CLASSIFICATION- first generation are early compounds
- Second generation- resistant to β-lactamases
- Third generation- resistant to β-lactamases & increased spectrum of activity
- Fourth generation- increased spectrum of activity

Vancomycin

- This interferes with bacterial cell wall formation and is not absorbed after oral administration and must be given parenterally.
- It is excreted by the kidney.
- It is used i.v. to treat serious or resistant *Staph. aureus* infections and for prophylaxis of endocarditis in penicillin-allergic people.

Aminoglycosides (bactericidal)

streptomycin, kanamycin, gentamicin, tobramycin, amikacin, netilmicin, neomycin (topical)

- **Mode of action** - The aminoglycosides irreversibly bind to the 16S ribosomal RNA and freeze the 30S initiation complex (30S-mRNA-tRNA) so that no further initiation can occur. They also slow down protein synthesis that has already initiated and induce misreading of the mRNA. By binding to the 16 S r-RNA the aminoglycosides increase the affinity of the A site for t-RNA regardless of the anticodon specificity. May also destabilize bacterial membranes.
- **Spectrum of Activity** -Many gram-negative and some gram-positive bacteria
- **Resistance** - Common
- **Synergy** - The aminoglycosides synergize with β-lactam antibiotics. The β-lactams inhibit cell wall synthesis and thereby increase the permeability of the aminoglycosides.

Aminoglycosides

Examples

- *Gentamicin* is the most commonly used, covering Gram-negative aerobes, e.g. Enteric organisms *(E.coli, Klebsiella, S. faecalis, Pseudomonas and Proteus spp.)*
- It is also used in antibiotic combination against *Staphylococcus aureus*.
- It is not active against aerobic *Streptococci*.

Macrolides (bacteriostatic)

erythromycin, clarithromycin, azithromycin, spiramycin

- **Mode of action -** The macrolides inhibit translocation by binding to 50 S ribosomal subunit

- **Spectrum of activity -** Gram-positive bacteria, *Mycoplasma, Legionella (intracellular bacterias)*

- **Resistance - Common**

Chloramphenicol, Lincomycin, Clindamycin (bacteriostatic)

- **Mode of action** - These antimicrobials bind to the 50S ribosome and inhibit peptidyl transferase activity.

- **Spectrum of activity** - Chloramphenicol - Broad range; Lincomycin and clindamycin - Restricted range

- **Resistance** - Common

- **Adverse effects** - Chloramphenicol is toxic (bone marrow suppression) but is used in the treatment of bacterial meningitis.

Clindamycin

- Clindamycin, although chemically distinct, is similar to erythromycin in mode of action and spectrum.
- It is rapidly absorbed and penetrates most tissues well, except CNS.
- It is particularly useful systematically for *S. aureus* (e.g.osteomyelitis as it penetrates bone well) and anaerobic infections.

Chloramphenicol

- This inhibits bacterial protein synthesis.
- It is well absorbed and widely distributed , including to the CNS.
- It is metabolized by glucoronidation in the liver.
- Although an effective broad-spectrum antibiotics, its uses are limited by its serious toxicity.

Tetracyclines (bacteriostatic)

tetracycline, minocycline and doxycycline

- **Mode of action -** The tetracyclines reversibly bind to the 30S ribosome and inhibit binding of aminoacyl-t-RNA to the acceptor site on the 70S ribosome.
- **Spectrum of activity -** Broad spectrum; Useful against intracellular bacteria
- **Resistance -** Common
- **Adverse effects -** Destruction of normal intestinal flora resulting in increased secondary infections; staining and impairment of the structure of bone and teeth.

Tetracyclines

Examples and clinical pharmacokinetics

- *Tetracycline, oxytetracycline* have short half-lives.
- *Doxycycline* has a longer half-life and can be given once per day.
- These drugs are only portly absorbed.
- They bind avidly to heavy metal ions and so absorption is greatly reduced if taken with food, milk, antacids or iron tablets.

Trimethoprim, Methotrexate,
(bacteriostatic)

- **Mode of action -** These antimicrobials binds to dihydrofolate reductase and inhibit formation of tetrahydrofolic acid.
- **Spectrum of activity -** Broad range activity against gram-positive and gram-negative bacteria; used primarily in urinary tract and *Nocardia* infections.
- **Resistance -** Common
- **Combination therapy -** These antimicrobials are used in combination with the sulfonamides; this combination blocks two distinct steps in folic acid metabolism and prevents the emergence of resistant strains.

Sulfonamides and trimethoprim

Mode of action

- Folate is metabolized by enzyme dihydrofolate reductase to the active tetrahydrofolic acid.
- *Trimethoprim* inhibits this enzyme in bacteria and to a lesser degree in animal s, as the animal enzyme is far less sensitive than that in bacteria.

Quinolones

- The quinolones are effective but expensive antibiotics.
- With increased use, resistance to these drugs is becoming more common.

Quinolones

Examples and clinical pharmacokinetics

- *Nalidixic acid*, the first quinolone, is used as a urinary antiseptic and for lower urinary tract infections, as it has no systemic antibacterial effect.
- *Ciprofloxacin* is a fluoroquinolone with a broad spectrum against Gram-negative bacilli and *Pseudomonas*,

Metronidazole

- Metronidazole binds to DNA and blocks replication.

Pharmacokinetics

- It is well absorbed after oral or rectal administration and can be also given i.v.
- It is widely distributed in the body (including into abscess cavities)
- It is metabolized by the liver.

Nitrofurantoin

- This is used as a urinary antiseptic and to treat Gram-negative infections in the lower urinary tract. It is also used against *Trypanosoma* infections.
- It is taken orally and is well absorbed and is excreted unchanged in the urine.

Fucidin

- Fucidin is active only against *Staphylococcus aureus* (by inhibiting bacterial protein synthesis) and is not affected β-lactamase.
- It is usually only used with flucloxacillin to reduce the development of resistance.
- It is well absorbed and widely distributed, including to bone
- It can be given orally or parenterally.
- It is metabolized in the liver.

Antibiotics for leprosy

- Leprosy is caused by infection with *Mycobacteria leprae.*
- A mixture of drugs are used to treat leprosy, depending on the type and severity of the infection and the local resistance patterns.

Antibiotics for leprosy

- *Rifampicin* is used, which is related to the sulphoamides.
- Rifampicin and Rifamycin block synthesis of m-RNA.
- Its adverse effects include haemolysis, gastrointestinal upsets and rashes.

Spectrum

- When specific testing is not done or delayed, antibiotic with a broad spectrum is administered
  - Broad spectrum antibiotics can penetrate Gram – outer membranes, resist inactivation, etc.
  - Shotgun: better chance of inhibiting pathogen
- Death of normal microbiota results in overgrowth of resistant bacteria (endogenous infection; "superinfection") or allows invasion by outside opportunists.

Drug administration

- Antibiotics administered oral, i.v., i.m.,i.p
  - Same caveats apply, i.e. acid instability, delayed absorption with food for oral
  - i.v. gives higher, quicker concentrations, reaches more compartments with sufficient dose quickly

Combination therapy

- Some valuable reasons why combination therapy is used
  - Synergistic effects between two drugs
  - Polymicrobial infections, e.g. abdominal injuries
  - Avoid Antagonistic effects.