Antibacterial therapy 1

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Principles and terms
Different categories of antibiotics
Spectrum of activity and mechanism of action
Resistances
New Antibiotics...? Oh... I got to evolve again!!!
Antibacterial therapy

What is an Antibiotics?

Egyptians 1500BC: Honey for wounds

Alexander Fleming and Louis Pasteur
Antibacterial therapy

2000 B.C. - "Here, eat this root."

1000 B.C. - "That root is heathen, say this prayer."

1850 A.D. - "That prayer is superstition, drink this potion."

1940 A.D. - "That potion is snake oil, swallow this pill."

1985 A.D. - "That pill is ineffective, take this antibiotic."

2000 A.D. - "That antibiotic is useless and artificial. Here, eat this root."

~Author Unknown
The Bright side
Yet .... even life savers may take life

(remember! Antibiotics are DANGEROUS DRUGS!!)
Antibiotics are DANGEROUS DRUGS
C deathicille (difficile)

A UK Consultant Microbiologists nightmare!
Antibacterial therapy

- **Antibiotics:** natural products derived from soil bacteria and fungi
  
  Examples:
  
  Penicillin from penicillin notatum mould
  
- **Semisynthetic agents:**
  
  Natural compounds that have been chemically modified to increase its activity and improve pharmacokinetics
  
  Examples:
  
  Amoxycillin, Ampicillin, Cephalosporins and Carbapenems, Rifampicin
Antibacterial therapy

Synthetic chemicals:
Trimethoprim and linezolid, quinolones are examples

➢ Antibiotics are loosely applied to all antibacterial agent

Terms related to antibiotics use:
Selective toxicity
Static vs cidal (MIC vs MLC)
Synergism
Broad vs narrow spectrum
Empirical use?
Synergism: Meaning and example
Spectrum of activity
Basic principles:

Selective toxicity:
Kill or inhibit the growth of microorganism without harming human tissue.

Antibiotic susceptibility testing
Bactericidal versus bacteriostatic **FIGURE 1**
Bactericidal: MLC
Bacteriostatic: MIC

Some infections such as infective endocarditis or immunocompromised patients > Bactericidal is a must
MIC

Determination of MIC

Tetracycline (g/ml)
MIC = 2 g/ml

Disk Diffusion Test

Str
Tet
Ery
Chl
Amp
Antibacterial therapy Figure 1

![Graph showing the effect of antibiotics on bacterial growth](image)
Antibacterial therapy

Bacteriostatic allows for natural immunity to deal with the microbe
- Antibodies, Phagocytosis etc

Bactericidial may lead to release of toxins and microbial contents leading to subsequent illness and inflammatory responses.
Antibacterial therapy/

Indications for use / to avoid abuse:

1. Treat infections empirically / culture sensitivity.

2. Prophylaxis/ limited situation.

Abuse:

Side effects
Resistance
Cost-effectiveness
Antibacterial therapy/

Route of administration:

Nature of infection

Bioavailability and therapeutic index or window

Tissue penetration, excretion, pharmacokinetics

Precautions:

> History of hypersensitivity

>Glandular fever (Epstein-Barr virus infection), cytomegalovirus infection greatly increase the risk of developing a penicillin-induced rash

> Impaired liver and kidney functions

> Pregnancy, breastfeeding and children
Antibacterial therapy
Target of antibacterial agents: Figure 2:

Cell wall: Peptidoglycan?

Protein synthesis: Ribosome 70S versus 80S

Folate synthesis:
Bacteria manufacture its own folates while human obtain it in food

Nucleic acid synthesis

Other sites such as bacterial cell membrane
Antibacterial therapy Figure 2: Antibiotics target
Antibacterial therapy/Inhibition of cell wall synthesis

Most bacteria possess a cell wall to protect from osmotic pressures.

Microbe divides – needs to create a new cell wall
- Interrupt this leads to new microbes being susceptible to external influences
- Cell ruptures → Microbe death

Beta lactam agents and glycopeptides
The cell wall of gram-positive and gram-negative bacteria.

Penicillin binding proteins = trans- and carboxypeptidases

of repeating units of N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) are responsible for cross-linking these peptide side chains.
Antibacterial therapy/Inhibition of cell wall synthesis

Fig. 5.1 Formation of bacterial cell wall peptidoglycan, showing the sites of action of inhibitors in the process.
**Beta lactam agents**

Penicillins, cephalosporins, monobactams, carbapenems and beta lactamase inhibitors

Bind penicillin binding proteins preventing cross linking

Beta lactamases are enzymes produced by bacteria that break the antibiotic beta lactam ring > resistance
Site of penicillinase action.
Breakage of the $\beta$ lactam ring.
**Beta lactam agents**

Penicillins:

E.g Benzylpenicillin and penicillin G

Narrow spectrum

Short acting

Resistance by beta lactamases

Synthetic penicillins:

Penicillin V

Flucloxacillin and methicillin: Inactivated by S. aureus beta lactamase

However, MRSA developed. MRSA?

Ampicillin and amoxicillin: G+ and G-

**Amoxicillin+Clavulinic Acid** (B-lactamase inhibitor) compound)/ Broad Spectrum.. Penicillinase-R
Beta lactam agents

Monobactam/ Aztreonam used mostly against serious aerobic and Facultative G-ve infection.

Carbapenem / imipenem & meropenem.. Broad Spectrum G- G+ aerobic anaerobic.., Penicillinase-R.

Cephalosporins:

Broader spectrum

Less hypersensitivity reactions

5 Different generations
Inhibition Cell Wall-3

1\textsuperscript{st} (1960) \textit{Cephalexin, Cephradine}, \underline{spectrum G+}.

2\textsuperscript{nd} (70s) \textit{Cefoxitin, Cefuroxime}, \underline{Broad spectrum}.

3\textsuperscript{rd} (80s) \textit{Ceftriaxone, Cefotaxime}.. \underline{mainly G-ve Enteric bacteria}.

4\textsuperscript{th} (1990s) \textit{Cefepime}.. \underline{mainly G-ve, GPC and pseudomonas}

5\textsuperscript{th} generation 2000s: \textit{ceftaroline} ...MRSA
Glycopeptides

Vancomycin and teicoplanin

Large molecules that are unable to penetrate the outer membrane of Gram-negative bacteria.

The spectrum is consequently restricted to Gram-positive organisms.

Gram-positive cocci with multiple resistance to other drugs such as Enterococci and staphylococci, including MRSA, that exhibit resistance or reduced sensitivity to glycopeptides are being reported more frequently.
Antibacterial therapy/disruption of microbial cell membrane

Essentially, affect cell membrane transportation in and out

Increases permeability of membrane
  - External influences have greater effect
  - Microbe death

Examples: Polymyxin, Colistin

*These agents are more toxic systemically than those agents that inhibit cell wall synthesis.*
The End