Antibiotic classification and mechanisms of action

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Outline

• Definition
• Antibiotic development challenges
• Key terminologies
• Antibiotic classes
• Mechanisms of action of key antibiotics
• Highlights on new antibiotics
Definition

a substance produced by one microorganism that selectively kills or inhibits the growth of another.
<table>
<thead>
<tr>
<th>Illness</th>
<th>Usual Cause</th>
<th>Antibiotic Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold/Runny Nose</td>
<td>✔️</td>
<td>NO</td>
</tr>
<tr>
<td>Bronchitis/Chest Cold (in otherwise healthy children and adults)</td>
<td>✔️</td>
<td>NO</td>
</tr>
<tr>
<td>Whooping Cough</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Flu</td>
<td>✔️</td>
<td>NO</td>
</tr>
<tr>
<td>Strep Throat</td>
<td>✔️</td>
<td>Yes</td>
</tr>
<tr>
<td>Sore Throat (except strep)</td>
<td>✔️</td>
<td>NO</td>
</tr>
<tr>
<td>Fluid in the Middle Ear (otitis media with effusion)</td>
<td>✔️</td>
<td>NO</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>✔️</td>
<td>Yes</td>
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</tbody>
</table>
Challenges of antibiotic development

• the global antibiotic resistance pandemic heralds a post antibiotic era as bad as the pre antibiotic era.
• there is also a decline in the development of new antibiotic classes as pharmaceutical companies direct their effort and funding to chronic illnesses with a potential for long term revenue
• between 1998 and 2003 only 9 new antibiotics compared to 16 new ones between 1983 and 1987.
• following 911, drug companies are directing their efforts to drugs and vaccines for fighting bioterrorism,
History of antibiotic development

1928: Alexander Fleming noted mould of the genus penicillium contaminating one of his cultures preventing the growth of bacteria.
1935: Domagk, sulphonamide – synthetic dye
1941: clinical trials of penicillin- Florey and Chain
ANTIBIOTIC DISCOVERY TIMELINE

Decades without identifying antibiotics that go on to be used for the treatment of patients has put our defence against bacteria at risk. This timeline pinpoints the year that the antibiotics were first discovered.
Bacteriostatic vs bactericidal activity

- Bactericidal - kill susceptible bacteria; bacteriostatic - inhibit growth of bacteria, hosts immune responses necessary to eradicate bacteria
- Not absolute terms: action depends on in vitro growth conditions, bacterial density, test duration
- Bactericidal action necessary in endocarditis, meningitis, osteomyelitis, neutropenia – host immune system not adequate in these sites and consequences of incomplete killing grave
- Disadvantage of bactericidal: rapid bacterial lysis in meningitis with overwhelming inflammatory response with increased mortality
- Advantage of bacteriostatic: clindamycin in staph TSS effective in inhibiting TSST-1 production without excessive inflammatory response
DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW

**Key:**
- Green Circle: Commonly act as bacteriostatic agents, restricting growth & reproduction
- Yellow Circle: Commonly act as bactericidal agents, causing bacterial cell death

### β-LACTAMS
- Used in the NHS
- Contains a β-lactam ring
- Examples: Penicillins (e.g., penicillin G), cephalosporins (e.g., cephalaxin)
- Mode of action: Inhibits the synthesis of proteins by bacteria, leading to cell death

### AMINOGLYCOSIDES
- Family of over 20 antibiotics
- Contains an aminoglycoside substructure
- Examples: Streptomycin, neomycin, amikacin
- Mode of action: Inhibits the synthesis of proteins by bacteria, leading to cell death

### CHLORAMPHENICOL
- Commonly used in low-income countries
- Distinct individual compound
- Mode of action: Inhibits the synthesis of proteins by bacteria, leading to cell death
- Resistance evolves rapidly

### GLYCOPETIDES
- Common drugs of last resort
- Consists of carbapenem or linked to a peptide formed of amino acid
- Examples: Vancomycin, teicoplanin
- Mode of action: Inhibits the synthesis of proteins by bacteria, leading to cell death

### QUINOLONES
- Resistance evolves rapidly
- All contain a quinolone ring with a 3-aminocarboxylic acid group attached
- Examples: Ciprofloxacin, levofloxacin, norfloxacin
- Mode of action: Inhibits the synthesis of proteins by bacteria, leading to cell death

### OXAZOLIDINONES
- Potent antibiotics commonly used as drugs of last resort
- All contain 2-oxazolidine group anywhere in their structure
- Examples: Linezolid, telavancin
- Mode of action: Inhibits bacterial cell wall biosynthesis

### DISCOVERY
- 1930: First commercial antibiotics were sulphonamides
- 1940: Tetracyclines becoming less popular due to development of resistance
- 1950: Macrolides as second most prescribed antibiotics in the NHS
- 1960: Ansamycins can also demonstrate antiviral activity
- 1970: Streptogramins - two groups of antibiotics that act synergistically
- 1980: Lipopeptides - instances of resistance rare

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Mechanisms of action

• antibiotics act by disrupting various molecular targets within bacteria and cell surface, preventing growth or initiating killing.
• 3 broad mechanisms:
  • Disrupt bacterial cell envelope
  • Block production of new proteins
  • Inhibit DNA replication
<table>
<thead>
<tr>
<th>GROUP</th>
<th>EXAMPLES</th>
<th>MOA</th>
<th>PROPERTIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactams</td>
<td>Penicillins</td>
<td>Inhibit cell wall synthesis</td>
<td>Bactericidal Time dependent Long PAE on g+ve (carbapenems also g -ve)</td>
</tr>
<tr>
<td></td>
<td>Cephalosporins</td>
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<td>Carbapenems</td>
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<td>Monobactams</td>
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<tr>
<td>Glycopeptides</td>
<td>Vancomycin</td>
<td>Inhibit cell wall synthesis</td>
<td>Time dependent PAE</td>
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<td></td>
<td>Teichoplanin</td>
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<td></td>
<td>Telavancin</td>
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<tr>
<td>Macrolides and ketolides</td>
<td>Azithromycin</td>
<td>Inhibit protein synthesis</td>
<td>Bacteriostatic Time and concentration dependent Long PAE</td>
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<tr>
<td></td>
<td>Telithromycin</td>
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<tr>
<td></td>
<td>Erythromycin</td>
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<td></td>
<td>Clarithromycin</td>
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<tr>
<td>Aminoglycosides</td>
<td>Gentamicin</td>
<td>Inhibit protein synthesis</td>
<td>Bactericidal Concentration dependent PAE</td>
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<tr>
<td></td>
<td>Amikacin</td>
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<td></td>
<td>Tobramycin</td>
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<td></td>
<td>Netilmicin</td>
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<td>Streptomycin</td>
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<tr>
<td>Tetracyclines and Glycylcyclines</td>
<td>Tetracycline&lt;br&gt;Tigecycline&lt;br&gt;Doxycycline&lt;br&gt;Minocycline</td>
<td>Inhibit protein synthesis</td>
<td>Bacteriostatic&lt;br&gt;Time dependent&lt;br&gt;Long PAE</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Ciprofloxacin&lt;br&gt;Norfloxacin&lt;br&gt;Levofloxacin&lt;br&gt;moxifloxacin</td>
<td>Inhibit DNA gyrase</td>
<td>Bactericidal&lt;br&gt;Conc. dependent&lt;br&gt;Long PAE</td>
</tr>
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<td>Bactericidal&lt;br&gt;Conc. dependent&lt;br&gt;Long PAE</td>
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<tr>
<td>Lincosamides</td>
<td>clindamycin</td>
<td>Inhibits protein synthesis</td>
<td>Bactericidal/ static&lt;br&gt;Conc. dependent&lt;br&gt;Long PAE</td>
</tr>
<tr>
<td>Streptogramins</td>
<td>Quinupristin/dalfopristin</td>
<td>Inhibits protein synthesis</td>
<td>Bactericidal&lt;br&gt;PAE&lt;br&gt;Conc. dependent</td>
</tr>
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<tr>
<td>oxalidinones</td>
<td>linezolid</td>
<td>Inhibits protein synthesis</td>
<td>Bacteriostatic Time dependent PAE</td>
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<tr>
<td>lipopeptides</td>
<td>daptomycin</td>
<td>Destroys cell membrane structure</td>
<td>Bactericidal Conc.dependent Long PAE</td>
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<tr>
<td>polymixins</td>
<td>Colistin Polymixin B</td>
<td>Destroys cell membrane structure</td>
<td>Bactericidal Conc.dependent Long PAE</td>
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<tr>
<td>ansamycins</td>
<td>rifampicin</td>
<td>Inhibits protein synthesis</td>
<td>Bactericidal Long PAE</td>
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<tr>
<td>chloramphenicol</td>
<td></td>
<td>Inhibits protein synthesis</td>
<td>Bacteriostatic</td>
</tr>
<tr>
<td>Sulfa drugs</td>
<td>Sulfamethoxazole-trimethoprim</td>
<td>Inhibits DNA synthesis</td>
<td>Bactericidal Conc.dependent</td>
</tr>
</tbody>
</table>
Structure of the bacterial cell wall

- Rigid peptidoglycan layer – alternating amino sugars (NAG and NAM) crosslinked by peptide chains
- Transpeptidation is the final stage in cross linking of the linear glycan chains.
Cell wall synthesis inhibitors: \( \beta \) lactam antibiotics

- the \( \beta \) lactam ring mimics the D-alanyl-D alanine portion of the peptide chain that is normally bound by pbps that assemble the peptidoglycan layer

- This prevents cross linking of the glycan strands leading to bacterial lysis
Beta lactams

penicillins
Natural penicillins
Penicillin G
Penicillin V
Benzathine P
Procaine P
Penicillinase R
Methicillin
Nafcillin
Cloxacillin
aminopenicillins
Amoxycillin
ampicillin
Extended spectrum
Ticarcillin
Piperacillin
carbenicillin

cephalosporins

1st gen
Cefadroxil
Cephalexin
Cephradine
cefazolin

2nd gen
Cefaclor
Cefamandole
Cefuroxime
cefoxitin

3rd gen
Cefotaxime
Ceftazidime
ceftriaxone

4th gen
cefepine

5th gen
Ceftaroline
ceftobiprole

carbapenems
Imipenem
Meropenem
Ertapenem

monobactams
aztreonam
Spectrum of activity: Penicillins

**Natural penicillins**
G+ve bacteria: streptococci, L. monocytogenes, some anaerobes, some spirochaetes, G-ve: N. meningitidis, some H. Infl

**Penicillinase R**
S. aureus, S. Epidermidis

**Aminopenicillins**
Similar to natural penicillins with additional G-ve: E. coli, P. Mirabilis, S. enterica, Shigella spp.

**Aminopenicillin/ B lactamase Inhibitors**
Sulbactam and clavulanate inactivate the B lactamases and broaden aminopenicillin activity:
Some S. Aureus, many enterobacteriaceae, clostridia except difficile, Bacteroides spp

**Extended spectrum**
p. aeruginosa
Spectrum of activity: Cephalosporins

- Each successive generation has broader activity against aerobic G-ve.
- Limited activity against anaerobes
- Lack activity against L. Monocytogenes and enterococci
- **1st gen**: good cover for aerobic G+ve cocci(staph/strep), some G-ve.
- **2nd gen**: increased activity against aerobic G-ve and facultative(E.coli,P.mirabilis,H.infl,B.fragilis

- **3rd gen**: in addition, activity against B burgdorferi, greater activity against aerobic G-ve than 2nd gen, shortlived activity against enterobacteriaceae, no activity against p.aeroginosa except ceftazidime
- **4th and 5th gen**: good antipseudomonal and antistaph cover, also enterobacteriaceae
Carbapenems

• Very broad spectrum (G+ve and –ves, anaerobes) due to:
  • Small molecules with charge characteristics that allow them to use porins in the OM of G-ve bacteria to access the PBPs
  • Resistant to B lactamases
  • Affinity to broad range of PBPs
Monobactams

- Aztreonam
- Single Beta lactam ring
- Very good G-ve cover (Neisseria, Haemophilus spp. Intermediate on P. aeruginosa), poor activity on G+ves, anaerobes
- No cross reaction in Beta lactam allergy
Cell wall synthesis inhibitors: Vancomycin

- like beta lactams, binds to the D-alanyl-D-alanine portion of the peptidoglycan layer preventing the pbps from adding them to the peptidoglycan layer
- Effective against nearly all aerobic and anaerobic G+ves including C. difficile, no activity on G-ves
- Emerging R against enterococci
Antibiotics that inhibit protein synthesis

Antibiotics that inhibit protein synthesis

- **Tetracycline**
  - Tetracycline
  - Oxytetracycline
  - Demeclocycline
  - Minocycline
  - Doxycycline

- **Aminoglycosides**
  - Streptomycin
  - Neomycin
  - Gentamicin
  - Amikacin
  - Tobramycin

- **Macrolides**
  - Erythromycin
  - Clarithromycin
  - Azithromycin
  - Roxithromycin
  - Spiramycin

- **Others**
  - Chloramphenicol
  - Oxalidinones
  - Ketolides
  - Lincosamides
  - Streptogramins
Protein synthesis in ribosomes

- Ribosomes in bacteria – 70s (50s & 30s); eukaryotes 80s
mechanisms of protein synthesis inhibitors

• Interact with various components of the bacterial ribosome and inhibit its function.
Aminoglycosides

★ positive charge allows them to bind to the negatively charged outer membrane with formation of transient holes through which antibiotic molecules move.
★ penetrate the inner cytoplasmic membrane and bind the 30S subunit of the bacterial ribosome inhibiting synthesis of new proteins from mRNA
★ Good activity against aerobic G- ves, no activity on anaerobes
Macrolides

• bind tightly to the 50s subunit preventing exit of the newly synthesized peptide and hence blocking protein production.
• Active against a broad variety of bacteria: some G+ves, G-ves, atypicalcs, some mycobacteria and spirochaetes
Tetracyclines and Glycylcyclines

• interact with the 30s subunit of the bacterial ribosome and prevent binding by tRNA molecules blocking protein synthesis
• Active against some aerobic G+ves, some aerobic G-ves, atypicals and spirochaetes
Chloramphenicol

- Binds the 50s subunit of the ribosome blocking the binding of tRNA loaded with an amino acid
- Less limited use in resource rich due to toxicity concerns-reversible dose dependent BM suppression
- Broad spectrum: aerobic G+ves, aerobic G-ves, anaerobes and atypicals
Clindamycin

- Lincosamide antibiotic
- Bind to the 50s subunit of the bacterial ribosome and inhibit protein synthesis
- Active against aerobic G+ves and anaerobes
- No activity on aerobic G-ves
- Associated with C. Difficile colitis
Streptogramins

- quinupristin/dalfopristin are two macrocyclic compounds each of which binds to the 50s subunit of the bacterial ribosome to inhibit protein synthesis
- Work synergistically against G+ves including MRSA, penicillin R strep pneumo, some VRE
Linezolid

- oxazolidinones
- bind to the 50s subunit of the ribosome preventing association with the 30s subunit
- also inhibits protein synthesis by preventing formation of the first peptide bond
- Activity against aerobic G+ves including MRSA, VRE but not approved for penicillin R sterp pneumo
Antimetabolites: Sulfa drugs

- Trimethoprim-sulfamethoxazole and dapsone
- Inhibitors of folic acid synthesis (bacteria cannot use preformed folic acid)
- TMP inhibits bacterial growth by preventing the synthesis of tetrahydrofolate
- Sulfonamides and sulphones - PABA analogues, competitive inhibition of dihydropteric acid
- Broad variety of aerobic G+ve and G-ve susceptible. No activity on atypicals and anaerobes
Inhibitios of DNA synthesis: Quinolones

- All except nalidixic acid have fluorine added to enhance potency
- Bind to the A sub-unit of DNA gyrase, prevent supercoiling of DNA
- Broad variety: G+ve, G-ve, atypicals and mycobacteria
Inhibitors of RNA synthesis: Rifamycins

- Inhibit bacterial RNA polymerase
- Activity against staph, N. Meningitidis and H. Influenza
- Used in combination treatment for mycobacterial infections
Metronidazole

- Small molecule that can passively diffuse into bacteria.
- Has a nitro group that must be reduced (accept electrons) for it to be active.
- Anaerobic bacteria can donate electrons to this nitro group enabling it to form free radicals that lead to breaks in DNA molecules and subsequent cell death.
- Active against G+ve and –ve anaerobes including C. Difficile and microaerophilic H. pylori
Tigecycline

- Structurally related to minocycline
- Binds 30s preventing entry of tRNA similar to TTCs
- Has an additional N,N,-dimethylglycylamido group that increases affinity for the ribosomal target – broader spectrum, less R
Lipopeptides

• Daptomycin
• lipid portion inserts into the bacterial cytoplasmic membrane forming an ion conducting channel that allows ions to escape from the bacterium leading to cell death
• Active against aerobic G+ves, also MRSA, penicillin R S.pneumo, some VRE
• No activity against G-ves, poor activity in lungs
Lipoglycopeptide: telavancin

- New antibiotic for vancomycin R organisms
- Dual mechanism of action: cell wall synthesis inhibition – binds to the terminalacyl-d-alanyl-d-alanine chains preventing cross-linking; disrupts cell membrane as well
Video links

https://www.youtube.com/watch?v=qBdYnRhdWcQ  beta lactams

https://www.youtube.com/watch?v=oC21vLFtsjo&index=21&list=PLljUvnIqppbeM4w36nCziqnNZGwLzrPru  macrolides

https://www.youtube.com/watch?v=IkKZ_gxAOXI  quinolones
Thank you for your time!