Macrolides

- All “macrolides” are based on a large, macrocyclic ring +2 sugars (except telithromycin)

Erythromycin  
Clarithromycin

Azithromycin  
Telithromycin  
(a ketolide)
Macrolides features

- Frequently used for community-acquired respiratory infections; also for skin, otitis media (ear)

- Alternative drug for *Strep.*, *Staph.*, *H. flu* infections for pen-allergic

- Erythromycin isolated 1952 from a soil microbe *Streptomyces erythreus*

- Later drugs (azithro-, clarithro-, telithro-) have broader spectra, especially Gm-, better acid stability and oral bioavailability

- Excellent tissue penetration, especially azithromycin and clarithromycin, but not to CNS

- Target the 50s large ribosomal subunit in bacteria, inhibit protein synthesis
  - Similar MOA to clindamycin and chloramphenical (shared binding site)
  - Bacteriostatic, except at very high concentration can be bactericidal
Macrolides MOA

30s

aminoglycosides
tetracyclines

50s

macrolides
chloramphenicol
lincosamides
streptogramins
linezolid

MACROLIDES: Bind to 50s subunit:
- Induce premature dissociation of peptidyl-tRNA from ribosome, hence premature termination
- Prevent addition of residues onto nascent polypeptide by blocking A to P translocation

figure by Stephen Douthwaite, University of Southern Denmark
General spectrum of activity

• Gram+
  • *S. pneumoniae*, *S. pyogenes*
  • *S. aureus*: MSSA but not MRSA

• Gram-
  • *H. influenzae* (not erythromycin), *M. cattarhalis*
  • Clarithromycin and azithromycin more potent than erythromycin

• “Atypicals” (not easily categorized by Gram stain technique)
  • *Mycoplasma pneumoniae* ("walking pneumonia"; a very persistent cough)
  • *Legionella pneumophila* (Legionare’s disease)
  • *Chlamydia trachomatis* (STD) and *Chlamydia* (aka *Chlamydophila*) *pneumoniae*
  • *Mycobacterium avian complex* (MAC): Clarithro- and azithro-
Distribution in the body

• Excellent tissue penetration
  • Tissue:blood ratio 10-100:1. Drug highly concentrated in tissue
  • Penetration into host cells too, so good for intracellular parasites such as Chlamydia

• Oral bioavailability
  • Erythromycin not acid stable (~25% orally bioavailable); take on empty stomach
  • Clarithromycin and azithromycin more stable (~50% orally bioavailable); OK w/ food
  • Telithromycin more stable (~57% orally bioavailable); OK w/ food
Erythromycin

- Not acid stable, poor oral bioavailability ~25%
- Short T<sub>1/2</sub>~1.5-2h
- Good Gm+ and reasonable Gm- activity
  - *Staph. aureus*, but not MRSA
  - *S. pyogenes*
  - *M. cattarhalis*
  - *N. menengitidis*
  - *Mycoplasma* (“walking pneumonia”)
  - *Chlamydia*
  - Not *Enterobacteriaceae*, cannot penetrate outer cell membrane
  - Not *Pseudomonas*

- Uses:
  - *URI, LRI*: mild to moderate
  - *Skin*: mild to moderate due to *S. pyogenes*
  - *Diphtheria*
  - *Amebiasis*
  - *N. gonorrhea*: for pen-allergic
  - *Leigonare’s disease*
Erythromycin

- GI discomfort, diarrhea (13-32%)
  - Induces peristalsis (gastroprokinetic); sometimes prescribed for this purpose. E.g. prior to endoscopy.

- Possible risk of QT elongation (time between Q and T waves in heart polarization), arrhythmias

- Drug interactions:
  - P-glycoprotein inhibitor: e.g. interacts with digoxin
  - CPY3A4 inhibitor: e.g. interacts with carbamazepine, cyclosporin
  - CYP1A2 inhibitor: e.g. interacts with theophylline and caffeine

- PO, IV, topical, opthalmic
Clarithromycin (Biaxin®)

- Acid stable; oral bioavailability ~50% (metallic taste); PO only
- 2-4x more potent than erythromycin
- $T_{1/2}$ ~3-7h
- Broader spectrum of coverage compared to erythromycin, more Gram-
- Macrolide of choice for treatment of:
  - *Mycobacterium avium complex* (MAC); common opportunist in AIDS
  - *H. pylori*
- Uses:
  - Pharyngitis/tonsilitis
  - Acute bacterial sinusitis
  - Bronchitis
  - CAP (community-acquired pneumo)
  - Otitis media
  - Skin
Clarithromycin (Biaxin ®)

- Metabolized in the liver. Some metabolites are even more active than parent compound.
  - More potent, longer half-life than the parent compound.

- Precautions:
  - Drug interactions.
    - E.g. many anti-retroviral drugs interact (not used with HIV patients)
  - QT prolongation. Careful with other drugs that can have QT prolongation
  - **Pregnancy category C** (risk cannot be ruled out), safety in children < 6 mo. not established. Teratogenic effects observed in animal models
  - Dizziness
Azithromycin (Zithromax®)

- Acid stable; oral bioavailability ~50%
- More potent than erythromycin; higher tissue conc (e.g. lungs) than clarithromycin
- $T_{1/2}$~days
- Better Gm- coverage than clarithromycin, but less Gm+ than clarithromycin
- Alternative to clarithromycin for MAC
- Macrolide of choice for:
  - *Chlamydia trachomatis*: 1gm single dose
  - *M. cat, H. flu*
  - *N. gonorrhea* (if patient is beta-lactam allergic); now used in combination w/ ceph.
  - *Legionella*
Azithromycin (Zithromax®)

- **Uses:** even for some tougher infections
  - Chronic obstructive pulmonary disease (COPD)
  - CAP
  - Bronchitis
  - Sinusitis
  - STD involving *Chlamydia*
  - Skin
  - *Otitis media*
  - *Mycobacterium avium complex* (MAC)
- **Does not appear to affect liver function or other drug metabolism to the extent of other macrolides**
- **Precautions:**
  - Do not take with antacids, impairs absorption
  - Rare hepatotoxicity
  - Potential arrhythmias. Caution with patients with heart conditions.
  - **Pregnancy category B**
• Binds more tightly to bacterial ribosome, and in more than one site

• Bugs that are erythromycin resistant (and clarith-, azith- too) may be still susceptible to telithromycin

• Does not induce expression of *erm* (erythromycin ribosome methylase) that methylate parts of ribosomal RNA to reduce binding of other macrolides

• Similar spectrum to azithromycin, also covers PRSP, but not MRSA

• Potentially fatal liver toxicity found after it was on the market. **Boxed warning**

• Aggravates myesthenia gravis: autoimmune disorder in which antibodies block nerve/muscle signaling. Potentially fatal.

• Pregnancy category C
Telithromycin (Ketek®)

- Inhibits liver enzymes: drug-interactions prevalent
- Blurred vision
- Prolonged QT interval: can produce ventricular arrhythmias; avoid in patients with congenital elongated QT, ongoing arrhythmic conditions, and those taking antiarrhythmic agents

- Acid stable, oral bioavailability ~57%; PO only
- Highest tissue penetration; even higher than azithromycin and clarithromycin
  - E.g. 200-400x above serum concentrations in some lung cells and macrophages
  - Drug stays above MIC for most respiratory pathogens
- Due to potentially severe adverse effects, telithromycin not to be used for mild cases or to treat bronchitis, sinusitis. Removed indications for those.
- NOW, only indicated use for CAP.
Macrolides Resistance

• Resistance is on the rise
  • E.g. between 1995 and 1999, *S. pneumo* resistance to macrolides rose from 10.6 to 20.4%

• Methylation of ribosome binding site via *erm* (erythromycin ribosomal methylation) enzymes
  • Affects erythro-, clarithro-, azithro-, but NOT telithromycin
  • *Erm* expression is inducible

• Active macrolide efflux pumps

• Esterases cleave the lactone ring

• Intrinsic *Enterobacteriacea* resistance due to outer membrane permeability
**Macrolide summary**

- Erythro-, Clarithro-, Azithro- commonly used for community-acquired respiratory infections

- Shut down protein synthesis by binding to bacterial 50s ribosomal subunit

- Newer macrolides (Az, Cl, Tel) are more acid stable and have a broader spectrum of coverage and greater potency than erythromycin.

- Variety of drug-interactions for Er, Cl, Tel but less so with Az

- Resistance due to change of target binding site (methylation of RNA) and efflux pumps in some bacteria

- Telithromycyn to be used with caution, numerous adverse effects
Aminoglycosides made of linked sugars. Decorated with many OH and NH$_2$ groups, which render these compounds positively charged and highly soluble at physiological pH.

- Not orally absorbed. All IV drugs.
- Interact with negatively charged lipopolysaccharide on Gram- cell wall.
• **Streptomycin**
  - Isolated in 1943 by Selman Waksman from *Streptomyces griseus*
  - Breakthrough drug for treatment of tuberculosis (*Mycobacterium tuberculosis*)

• **Gentamicin**
  - Isolated in 1963 from *Micromonospora purpurea* (“mycin” only if from *Strep.*)
  - Significant use in treatment of Gram- infections including *Pseudomonas*

• **Amikacin**
  - Semi-synthetic, derived from Kanamycin
  - Designed to overcome resistance due to modifying enzymes
Aminoglycoside properties

• Reserved for serious infections only
  • **Due to serious toxicity concerns**: ototoxicity, nephrotoxicity
  • Concentrations require monitoring

• IV only for systemic infections; majority passed unmodified in urine
  • If the patient is predisposed to renal dysfunction, important to monitor closely

• PO form for gut sterilization; none is absorbed into the blood, all goes through gut unmodified

• Does **not** cross blood-brain barrier into CNS

• Active against broad spectrum of Gram- aerobes and facultative anaerobes

• Weak coverage of Gram+ if used alone, but may be combined with another drug such as beta-lactams. E.g. possibly for enterococci such as *E. faecium*

• Poor coverage of obligate anaerobes
  • AG can transit through porins, but...
  • Anaerobes do not possess the transport machinery that would bring aminoglycosides into the cytosol
Aminoglycoside uses

• Reserved for serious infections only

• Empiric therapy of serious infections:
  • Septicemia, complicated RTI, UTI, intra-abdominal, osteomyelitis
  • Followed by switching to another less toxic antimicrobial once the pathogen is ID’d

• Prophylaxis for gastrointestinal (oral) or urogenital tract surgery
Aminoglycosides target the 30s ribosomal subunit: MOA

- Binds to 30s ribosomal subunit and interferes with protein synthesis in multiple ways
  - Single binding site for streptomycin; other AG have more than one binding site on 30s subunit, hence harder for sufficient mutations to arise to knock out all their inhibitory effect
- Outer membrane disruption (interacts w/ lipopolysaccharide) in Gram-negative bacteria leads to cell permeabilization and greater antibiotic uptake.
Aminoglycoside MOA: 1) protein synthesis disruption

- Binds to 30s ribosomal subunit and:
  - Interferes with initiation, ribosome locked at AUG start codon of mRNA (at higher concentrations)
  - Premature termination of translation
  - Incorporation of incorrect amino acid leading to nonsense proteins.

Figure 46-2. Effects of aminoglycosides on protein synthesis.
Interacts with Gram- outer membrane and makes it leaky. This leads to increased penetration of the drug. Also plays a role in increasing penetration of other drugs.

Bactericidal unlike most protein synthesis inhibitors. This is probably due to the activity against the membrane.
Aminoglycoside MOA

- **Bactericidal**

- **Concentration-dependent killing**: increasing concentrations increases rate and extent of bacterial death
  - How best to reach and maintain necessary therapeutic concentrations in balance with toxicities, which also are concentration dependent?
  - Consolidated or single daily dose approach.

- **Strong post-antibiotic effect (PAE)**:
  - Persistent inhibition of bacterial growth even after systemic drug is cleared
  - PAE gets stronger for higher concentrations, up to a point
  - Seen with aminoglycosides in Gram- bacteria
  - *Staph.* but not other Gram+ bacteria
  - Also white blood cells show enhanced phagocytosis and bacterial killing after exposure to aminoglycosides.
• Concentration-dependent killing: Want to hit a certain optimal peak concentration, which can be hard to achieve with traditional, multi-dosing. More likely to hit those optimal concentrations w/ “consolidated” dose.

• Possible benefits:
  • Reduced toxicity (nephro only; does not reduce ototoxicity):
    • Assume aminoglycoside renal and inner ear uptake can be saturated
    • Do not want to have the trough concentrations stay elevated due to increased chance of nephrotoxicity
  • Lower cost

• Not necessarily effective for treatment of all bacteria (e.g. Gram+ don’t show PAE)
Synergy

- Often combined with cell-wall inhibitor:
  - Can help for Gram+ treatments (AG alone not effective)
  - Beta-lactam + aminoglycoside: e.g. ampicillin + gentamicin
  - Vancomycin + aminoglycoside
  - Cell-wall disruptors may increase permeability of aminoglycoside into cell

- Examples:
  - Infective endocarditis: Staph, Strep viridans, Enterococci
  - Pseudomonas (Gram-): high intrinsic resistance to mono-therapies

- But beta-lactams and aminoglycosides in vitro at high concentrations can interact, undergo chemical reaction, and inactivate each other
  - Do not mix in the same solution
  - This effect varies based on pairing of beta-lactam and aminoglycoside
Spectrum and usage

• Gram- aerobes:
  • *Pseudomonas aeruginosa* (tobramycin)
  • *Acinetobacter spp.*
  • *Enterobacteriaceae*:
    • *Klebsiella, Proteus, Enterobacter, Serratia, Providencia...*
  • *Haemophilus influenzae*
  • *Etc.*

• Gram+ aerobes: usually used in combination with a beta-lactam or vancomycin
  • *Streptococcus*
  • *Staphylococcus*

• Mycobacteria
  • *M. tuberculosis*
  • *MAC*

• Not much activity against anaerobes
  • Believed that anaerobes lack the ability to actively take up AG into their cytosol
Specific Aminoglycoside properties

**Gentamycin** (IV/IM, opthalmic, topical)
- The “go-to” aminoglycoside for Gram- aerobic infections
- Associated with ototoxicity, especially affecting vestibular system

**Tobramycin** (IV/IM, opthalmic, topical)
- Greater potency compared to Gentamycin against *Pseudomonas*
- Less ototoxicity than Gentamycin, but auditory loss possible

**Kanamycin** (IV/IM, PO)
- Can be used for intestinal infections or as sterilizing prophylaxis of the gut, often combined with cell-wall disruptor (beta-lactam, vanco)
- Can be profoundly ototoxic, less impact on vestibular system

**Amikacin** (IV/IM)
- Less susceptible to enzymatic inactivation by resistance factors
- Powerful agent, reserved for cases that are resistant to Gentamycin/Tobramycin, so as not to foster resistance
- Somewhat less toxic to vestibular system than gentamycin
- If a bacteria is resistant to Amikacin, it is likely to be resistant to all the other aminoglycosides as well
Resistance

• Compared to other antibiotics, resistance to aminoglycosides is rare

• Primarily mediated by enzymatic modification of the OH and NH$_2$ groups
  • Phosphorylation
  • Acetylation
  • Adenylation
  •Encoded on plasmids, transposons

• *Pseudomonas*
  • Efflux pump removal of drug from cytosol

• Modified ribosomal binding site
  • Methylation of 16s ribosomal RNA
  • Single mod can knock out streptomycin binding since it has a single binding site; other AG have more than one, harder to evolve resistance
Resistance

**Gentamicin**: multiple sites available for enzymatic modification

**Amikacin**: side chain modification made Amikacin more resistant to enzyme modification

Toxicity: Nephrotoxicity

- Usually reversible
- More common than ototoxicity, 5-20% of patients
- Aminoglycoside accumulates in proximal tubules of renal cortex, kills the cells
  - Tubular cell degeneration can lead to sloughing of cells and fine sediment in urine
Toxicity: Ototoxicity

- **Irreversible**
- Less common than nephrotoxicity; toxicities do not appear to be correlated
- Aminoglycoside accumulates in inner ear and leads to destruction of cochlear hair cells
  - Produces reactive radicals that kill the hair cells
- **Vestibular toxicity**: imbalance, vertigo, tinnitus, nystagmus (involuntary eye movement)
  - More frequently seen with gentamicin
- **Auditory toxicity**: high frequency hearing loss
  - More common with amikacin, kanamycin (particularly damaging)
- Emergence unpredictable, could be after a single dose; can appear weeks after therapy is completed (continue monitoring)
  - AG accumulate in inner ear fluids and are cleared slowly, hence latency
  - Possibly a genetic factor: mutation on ribosomal RNA in mitochondria that enables AG to bind to human ribosomes; leading to disruption of mitochondrial protein synthesis
Toxicity: Neuromuscular blockage

- Rare
- Myasthenia gravis
  - Drug induces auto-immune response that leads to blockage of neuromuscular communication
    - Antibodies block acetylcholine receptors at neuromuscular junctions
- Fatigue, weakness
Aminoglycoside summary

• Reserved for serious infections in a nosocomial setting only

• Possibility of oto- and nephro-toxicity
  • If the patient is predisposed to renal dysfunction, important to monitor closely

• Gram- aerobes and facultative anaerobes are the primary targets; broad spectral coverage

• Weak coverage of Gram+ if used alone, but often combined with another drug such as beta-lactams

• Multiple mechanisms of action:
  • Protein synthesis disruption at more than one stage
  • Membrane disruption in Gram- bacteria leading to increased drug penetration and cell trauma