Inhibitors of Microbial Protein Synthesis

Why antimicrobials selectively inhibit bacterial protein synthesis?

Basis for the selective toxicity

Ribosomal subunits

Nucleic acids

Chemical composition and functional specificities

Antibiotics targets the bacterial ribosomes

Bacterial ribosomes

Smaller -- 70 S

Subunits

50 S, 30 S

Mammalian ribosomes

Larger -- 80 S

60 S, 40 S

Mammalian mitochondrial ribosomes resembles the bacterial ribosomes

High levels of antibiotic may cause toxic effects ------- Chloramphenicol & Tetracyclines

Protein synthesis inhibitors

Broad spectrum

Tetracyclines

Chloramphenicol

Moderate Spectrum

Macrolides /ketolides

Protein synthesis inhibitors

Narrow psectrum

Lincosamide (Clindamycin)

Linezolid

Streptogramins ---- Quinopristin/daflopristin

Aerobic G-Ve Bacilli

Aminoglycosides &

Spectinomycins

Step 1 – charged tRNA (aa + tRNA) binds to the acceptor site of the ribosomal–mRNA complex --- Tetracycline

Step 2 – transpeptidation – binds the aa to growing aa chain ----- chloramphenicol & Macrolides

Step 3 – uncharged tRNA is released

Step 4 – Translocation ---- new tRNA shift to the peptidyl site

Mechanism of action
Target site 30 S
Tetracyclines - Glycylcylines
Aminoglycosides
Target site 50 S
Macrolides /ketolides - Chloramphenicol
Clindamycin - Linezolid
Streptogramins --- Quinopristin/daflopristin
CHLORAMPHENICOL

Classification and Pharmacokinetics
Chloramphenicol has a simple and distinctive structure, and no other antimicrobials have been discovered in this chemical class.
It is effective orally as well as parenterally
distributed throughout all tissues; it readily crosses the placental and blood-brain barriers.
The drug undergoes enterohepatic cycling, and a small fraction of the dose is excreted in die urine unchanged.

Antimicrobial Activity
Chloramphenicol has a wide spectrum of antimicrobial activity and is usually bacteriostatic.
Some strains of
Haemophilus influenzae,
Neisseria -meningitidis,
Bacteroides are highly susceptible,.
Resistance to chloramphenicol, which is plasmid mediated, occurs through the formation of acetyltransferases that inactivate the drug.

Clinical Uses
Salmonella species
pneumococcal and meningococcal meningitis in beta-lactam-sensitive persons.
rickettsial diseases
anaerobes such as *Bacteroides fragilis.*
The drug is commonly used as a topical antimicrobial agent
Toxicity
Gastrointestinal disturbances

These may occur from
direct irritation

and from" super-infections, especially candidiasis.

Bone marrow—

Inhibition of red cell maturation leads to a decrease in circulating erythrocytes. This action is dose dependent and reversible. Aplastic anemia is a rare idiosyncratic reaction (approximately 1 case in 25,000-40,000 patients treated). It is' usually irreversible and may be fatal.

Gray baby syndrome

Gray baby syndrome (also termed Gray or Grey syndrome) is a rare but serious side effect that occurs in newborn infants (especially premature babies) following the accumulation of antibiotic chloramphenicol.

This syndrome occurs in infants and is characterized by

- decreased red blood cells,
- cyanosis
- cardiovascular collapse.

Gray baby syndrome

Loss of appetite
Vomiting
Ashen gray color of the skin
Hypotension (low blood pressure)
Cyanosis (blue discolouration of lips and skin)
Hypothermia
Cardiovascular collapse
Hypotonia
Abdominal distension
Irregular respiration
Increased blood lactate

Pathophysiology

Two pathophysiologic mechanisms

This condition is due to a lack of glucuronidation reactions occurring in the baby, thus leading to an accumulation of toxic chloramphenicol metabolites.The UDP- glucoryl transferase enzyme system of infants, especially premature infants, is immature and incapable of metabolizing the excessive drug load.

Insufficient renal excretion of the unconjugated drug.

leads to increased blood concentrations of the drug, causing blockade of the electron transport in the liver, myocardium, and skeletal muscles, resulting in the above symptoms.

Prevention
The condition can be prevented by using chloramphenicol at the recommended doses and monitoring blood levels
or alternatively, third generation cephalosporins can be effectively substituted for the drug, without the associated toxicity
Treatment
chloramphenicol therapy should be stopped immediately.
Exchange transfusion may be required to remove the drug.
Drug interactions

Chloramphenicol, inhibits hepatic drug-metabolizing enzymes, increasing the elimination half-lives of drugs including

Phenytoin
Tolbutamide
Warfarin

TETRACYCLINES

The tetracyclines are a group of closely related compounds that, as the name implies, consist of four fused rings with a system of conjugated double bonds.

Mechanism of action
Nonresistant strains concentrate the tetracyclines intracellularly.
The drug binds reversibly to the 30S subunit of the bacterial ribosome, thereby blocking access of the amino acyl-tRNA to the mRNA-ribosome complex at the acceptor site.
By this mechanism, bacterial protein synthesis is inhibited

Antibacterial spectrum
Resistance
naturally occurring resistance ("R") factor[2] confers an inability of the organism to accumulate the drug, thus producing resistance.
Mg^{2+}-dependent, active efflux of the drug, mediated by the plasmid-encoded resistance protein
enzymatic inactivation of the drug
production of bacterial proteins that prevent tetracyclines from binding to the ribosome

Pharmacokinetics

Absorption
All tetracyclines are adequately but incompletely absorbed after oral ingestion
taking these drugs concomitantly with dairy foods in the diet decreases absorption due to the formation of nonabsorbable chelates of the tetracyclines with calcium ions.
Nonabsorbable chelates are also formed with other divalent and trivalent cations (for example, those found in magnesium and aluminum antacids and in iron preparations).
Doxycycline and *minocycline* are almost totally absorbed on oral administration.
Distribution
Concentrate in the liver, kidney, spleen, and skin, and they bind to tissues undergoing calcification (for example, teeth and bones) or to tumors that have a high calcium content (for example, gastric carcinoma).
Penetration into most body fluids is adequate.
Although all tetracyclines enter the cerebrospinal fluid (CSF), levels are insufficient for therapeutic efficacy, except for *minocycline.*
Minocycline enters the brain in the absence of inflammation and also appears in tears and saliva.
All tetracyclines cross the placental barrier, and concentrate in fetal bones and dentition.
Fate
in the liver they are, in part, metabolized and conjugated to form soluble glucuronides.
Excreted in the urine by glomerular filtration.

Unlike other tetracyclines, doxycycline can be employed for treating infections in renally compromised patients, because it is preferentially excreted via the bile into the feces.

Clinical Uses
Primary Uses
infections caused by *Mycoplasma pneumoniae* (in adults), chlamydiae, rickettsiae, vibrios, and some spirochetes.
Doxycycline is currently an alternative to macrolides in the initial treatment of community-acquired pneumonia.
Secondary Uses
Tetracyclines are alternative drugs in
syphilis.
respiratory infections
Leptospirosis
acne.
Adverse effects

Gastric discomfort:
Effects on calcified tissues
Fatal hepatotoxicity
Phototoxicity
Vestibular problems
Pseudotumor cerebri:
Superinfections:
Selective Clinical Uses
TETRACYCLINE ----gastrointestinal ulcers caused by *Helicobacter pylori* in Lyme disease (doxycycline)
MINOCYCLINE ----in the meningococcal carrier state.
DOXYCYCLINE ------

- Lyme disease,
- amebiasis
- prevention of malaria

DEMECLOCYCLINE inhibits the renal actions of antidiuretic hormone (ADH) and is used in the management of patients with ADH-secreting tumors

Gastric discomfort
Epigastric distress commonly results from irritation of the gastric mucosa,
responsible for noncompliance in patients treated with these drugs.
The discomfort can be controlled if the drug is taken with foods other than dairy products.

Effects on calcified tissues
Deposition in the bone and primary dentition occurs during calcification in growing children.
This causes discoloration and hypoplasia of the teeth
temporary stunting of growth.

Fatal hepatotoxicity
This side effect has been known to occur in pregnant women who received high doses of tetracyclines, especially if they were experiencing pyelonephritis.

Phototoxicity
Phototoxicity, such as severe sunburn, occurs when a patient receiving a tetracycline is exposed to sun or ultra-violet rays.
This toxicity is encountered most frequently with *tetracycline, doxycycline,* and *demeclocycline*
Vestibular problems

These side effects (for example, dizziness, nausea, and vomiting) occur particularly with *minocycline,* which concentrates in the endolymph'of the ear and affects function. *Doxycycline* may also cause vestibular effects.

Pseudotumor cerebri
Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults. Although discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur.

Superinfections
Overgrowths of Candida (for example, in the vagina)
or of resistant staphylococci (in the intestine) may occur.
Pseudomembranous colitis due to an overgrowth of Clostridium difficile has also been reported.

Contraindications
Renally impaired patients should not be treated with any of the tetracyclines except *doxycycline.*

The tetracyclines should not be employed in pregnant or breast-feeding women or in children under eight years of age.

GLYCYLCYCLINES

Tigecycline is the first available member of a this new class of antimicrobial agents
Tigecycline, a derivative of *minocycline,* is structurally similar to the tetracyclines and has a broad-spectrum activity against multi-drug resistant gram-positive pathogens, some gram-negative organisms, and anaerobic organisms.
Mechanism of action
Tigecycline exhibits bacteriostatic action by reversibly binding to the 30S ribosomal subunit and inhibiting protein translation
Antibacterial spectrum
Exhibits expanded broad-spectrum activity
methicillin-resistant staphylococci,
multidrug-resistant Streptococcus pneumoniae
susceptible strains of streptococcal species
vancomycin-resistant enterococci,
extended-spectrum β-lactamase producing gram-negative bacteria,

is not active against Proteus. Providencia, and Pseudomonas species.

Resistance
Efflux
Ribosomal protection

Pharmacokinetics
extensively distributed throughout plasma and body tissue.
does not undergo significant liver metabolism
primarily eliminated via biliary/fecal excretion.
No dose adjustment is necessary for patients who are renally impaired. However, dose adjustment is needed in severe hepatic dysfunction.

Adverse effects
Tigecycline is well tolerated,
nausea and vomiting.
photosensitivity,
pseudotumor cerebri
discoloration of permanent teeth when used during tooth development
fetal harm when administered to a pregnant woman.

Drug interactions
it has been found to inhibit the clearance of *warfarin so,* anticoagulation be monitored closely when *tigecycilne* is coadministered with *warfarin.*
another method of contraception is suggested when *tigecycline* and oral contraceptives are co-administered, because the oral contraceptives may become less effective.

MACROLIDES

Macrolides
Erythromycin, Clarithromycin, Azithromycin,
Ketolides ----- Telithromycin
Macrocyclic lactone ring +
one or more deoxy sugar
Erythromycin --- Prototype, derived from *streptomyces erythreus*
Semi-synthetic derivatives
Clarthromycin - a methylated form of erythromycin
Azithromycin - have a large lactone ring

Clarithromycin
Spectrum & clinical uses similar to erythromycin
Also has activity against Mycobacterium leprae, Toxoplasma gondii, & H influenzae
Activity against intracellular pathogens is higher than that of erythromycin --- Chlamydia, legionella, moraxella, ureaplasma
Clarithromycin
Spectrum & clinical uses similar to erythromycin
Mycobactrium-avium-intracellular complex --- Prophylaxis & treatment
A component of H pylori eradication therapy
Azithromycin
Spectrum similar to erythromycin
Far more active against --- H. influenzae, Morexella catarrhalis, & Neisseria
Preferred therapy for urethritis caused by chlamydia trachomatis
Active against – M avium complex, & T gondii
Azithromycin --- Long $t_{1/2}$
single dose --- urogenital infection caused by C trachomatis
4 day course --- in community acquired pneumonia
Tissue concentration exceed plasma concentration by 10- 100 fold
Free of drug interactions that occur with ery & clarithromycin
Resistance
↓ permeability or active influx
Production of Plasmid associated erythromycin esterase --- (by Eterobacteriaceae) that hydrolyze macrolides
MLS-type B resistance --- methylase production --- Macrolide-Lincosamide-Streptogramins
Ribosomal protection --- modification of the ribosomal binding site --- by chromosomal mutation or by macrolide inducible or constitutive methylase
Cross Resistance
Complete Cross resistance – Erythromycin, Clarithromycin, & Azithromycin
Telithromycin can be effective against macrolide-resistant organisms
Macrolides --- Distribution
Distributed to all body tissues except the CSF
Diffuse into prostatic fluid
Accumulate in macrophages
All 4 drugs concentrate in liver
Inflammation allows far greater penetration

Azithromycin --- Distribution
The level achieved in tissue and macrophages are considerably higher than those in the plasma ----The drug is concentrated in neutrophils, macrophages, & fibroblasts
largest volume of distribution

Widely distributed (extensive tissue distribution), except CSF
Longest half life (3 days) -- once daily dose

Macrolides --- contraindications
Hepatic dysfunction --- Erythromycin, Azithromycin & telithromycin accumulate in the liver
Telithromycin may cause
- Severe hepatotoxicity
- Prolongs the QT interval
- To be used with caution in Renal failure
- Contraindicated in myasthenia gravis

Fidaxomicin
is a narrow-spectrum macrolide antibiotic
selectively active against gram-positive aerobes and anaerobes.
Given orally, systemic absorption is minimal.
Fidaxomicin has proved to be as effective as vancomycin for the treatment of C difficile colitis, possibly with lower relapse rate.

Telithromycin
A "Ketolide" --contain a 3-keto group
Ketolides spectrum very similar to macrolides
Active against many macrolide resistant gram positive strains
- Neutralizes the most common resistance mechanism (methylase-mediated & efflux mediated)

Telithromycin is given orally once daily
eliminated in the bile and the urine.

<u>ADVERSE EFFECTS</u>
- Hepatic dysfunction
- Prolongation of the QTc interval.
- The drug is an inhibitor of the CYP3A4 drug-metabolizing system.

Clindamycin

Clindamycin
Lincomycin ---- elaborated by *streptomyces lincolnensis*
Clindamycin is chlorine substitute derivative of lincomycin
Clindamycin - spectrum
Anaerobic bacteria --- bacteroides fragilis & other anaerobes, both G+ve & G-ve
Streptococci, pneumococci, Staphylococci including some MRSA
Pneumocystis Jiroveci

Clindamycin uses - Anaerobic infection

Bacteriodes fragilis & other anaerobes that often participate in mixed infection

Clidamycin, sometimes in combination with aminoglycosides or cephalosporin ---

Penetrating wounds of the abdomen & gut,

infection originating in female genital tract e.g., septic abortion & pelvic abscess

Aspiration pneumonia

Clindamycin uses

Prophylaxis of endocarditis in valvular heart disease before dental procedure in patients allergic to penicillin

Backup drug against G (+) cocci ---- Skin & soft tissue infections caused by Streptococci, Pneomococci, Staphylococci ------ community acquired strains of MRSA

Clindamycin uses

AIDS related pneumocystis jiroveci infection Clidamycin + Primaquine --- pneumocystis jiroveci pneumonia (an alternative to trimethoprim – sulfamethoxazole)

Clidamycin + Pyrimethamine --- toxoplasmosis of brain

Clindamycin - resistance

Clostridium difficle is always resistant

Enterococci are resistant

G-Ve aerobic species (susceptible to erythromycin) are intrinsically resistant because of poor permeability of the outer membrane

Clindamycin – resistance mechanisms

Same as for erythromycin. Cross resistance has been described

MLS-type B resistance --- methylase production --- macrolide-lincosamide-streptogramins

Ribosomal protection --- modification of the ribosomal binding site (Mutation of ribosomal receptors) --- by chromosomal mutation or by macrolide inducible or constitutive methylase

Clindamycin --- Adverse effects
GIT irritation, skin rashes, neutropenia
Impaired liver function(with or without jaundice)
Pseudomembranous colitis
Caused by over growth (superinfection) of *C difficle*, which elaborates necrotizing toxins
Serious & Potentially fatal
Treated by oral metronidazole or vancomycin (if does not respond to metronidazole)
Oxazolidinones
Linezolid
A synthetic oxazolidinone

Linezolid

23 S ribosomal RNA of the 50S ribosomal subunit
Unique site on 50 S near the interface with the 30S subunit
Inhibit initiation by blocking formation of the tRNA-ribosome-mRNA tertiary complex (70 S)

Antimicrobial activity
Aerobic G(+) pathogens – PRSP, MRSA and enterococci (both E faecalis and Vancomycin sensitive & resistant E faecium)
G (+ rods) --- Corynebacteria, L monocytogen
Anaerobic organisms – C Perfringens
Nocardia SP, &
Also active against M tuberculosis --- Achieves good intracellular concentration
Antibiotic Spectrum
A bacteriostatic agent except for streptococci & C. Perfringens, for which it is bactericidal

Linezolid ---

Use usually restricted to serious infections where other antibiotics have failed
Multi drug resistant G+ve Cocci
Resistant to penicillins
MSRA & PRSP
Resitant to vancomycin
VRE – (Enterococci -- faecium & faecalis)
Linezolid --- Clinical uses
Pneumonia -- Nosocomial or Community acquired
Septicemia, Skin & soft tissue infections
Antibiotic --- Resistance

G-ve organisms are not susceptible
Resistance develop due to mutation of the linezolid binding site on 50 S subunit ribosomal RNA
Cross resistance does not occur with other protein synthesis inhibitors

Linezolid
Oral & parenteral formulation
100% bioavailable after oral administration
t ½ --- 4-6 hours
Neither an inducer nor inhibitor of CYP450

Adverse effects --- Linezolid
Myelosuppression --- (when used > 2 weeks) -- inhibition of mitochondrial protein synthesis
Reversible Thrombocytopenia in 3 %
Anemia & neutropenia
GIT upset – N & D
Headache & rash
Optic and peripheral neuropathy ---- Irreversible after prolong use --- ATT
Lactic acidosis
Adverse effects
Early oxazolidinones -- Non selective inhibition of MAO
Linezolid do not inhibit MAO. However patients are advised not to take tyramine-containing foods
Interaction with dopaminergic or serotonrgic agents ----------Serotonin syndrome when co-administered with serotonergic drugs --- SSRI
Reversible enhancement of the pressor effects of pseudoephedrine or phenylpropanolamine
Streptogramins
Quinupristin/Dalfopristin

Quinupristin/Dalfopristin –
30:70 ratio

Derived from *streptomycete* and then chemically modified
Reserved for the treatment of infections caused by
Staphylococci or
Vancomycin-resistant enterococcus faecium
Streptogramins
Each component binds to a separate site on the 50S bacterial ribosome & synergistically interrupt protein synthesis
Constrict the exit channel on the ribosome through which nascent polypeptides are extruded

Inhibit tRNA synthetase activity --- ↓ in free tRNA within the cell
Antibacterial spectrum -- G+ve cocci including
Multidrug resistant strains of strepococci --- Penicillin resistant S pneumococci (PRSP)
Methicillin resistant staphylococci (MRSA)
Vancomycin resistant staphylococci (VRSA)
Vancomycin resistant Enterococcus faecium (VRE).
Antibacterial spectrum
Rapidly bactericidal for most organisms except Enterococcus faecium which is killed slowly
Not effective against enterococcus faecalis --- Primary resistance via efflux transport mechanism
A long postbiotic effect
Resistance
E faecalis is intrinsically resistant
An active efflux pump can ↓ level of drug in the bacteria
Modification of quinopristine binding site (MLS-B type)
Enzymatic inactivation of dafloprístin---Plasmid associated acetyltransferase inactivates dafloprestin
Streptogramins are incompatible with a saline solution
Given in 5% dextrose
Penetrates macrophages & polymorphs
    Effective against intracellular organisms
    Levels in CSF are low
Metabolized in the liver and excreted via bile
    Urinary secretion is secondary
Adverse effects & drug interactions
Venous irritation
Arthralgia-myalgia syndrome
Hyperbilirubinaemia
        In 25 % of patients
        Result from competition with the antibiotic for excretion