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Subject: Pharmacolgy-III (BP 602T)
Unit: III
Topic: Anti TB Drugs

Classification Of ATT Drugs

FIRST line drugs[HRZSE]

- F Field defects causing drug i.e. Ethambutol [E]
- I Isoniazid (INH) [H]
- R Rifampicin [R]
- S Streptomycin [S]
- T Twice a day given drug i.e. Pyrazinamide [Z] (All other first line antituberculars are given once a day)

SECOND line drugs

- S Salicylates like Para-amino salicylate
- E Ethionamide
- C Cycloserine
- O Old drug: Thiacetazone
- N Newer Drugs:
  Quinolones e.g. Ciprofloxacin, Levofloxacin, gatifloxacin and Moxifloxacin Macrolides e.g. Clarithromycin, Azithromycin
- D Drugs rarely used: Aminoglycosides e.g. Capreomycin, Kanamycin, Amikacin
- Rifabeutin

Standard Regimen And Dosing Frequency For TB Patients

Category of Treatment	Type of Patient	Regimen*
Category I	New sputum smear-positive Seriously ill** new sputum smear-negative Seriously ill** new extra-pulmonary	2H3R3Z3E3+ 4H3R3
Category II	Sputum smear-positive Relapse Sputum smear-positive Failure Sputum smear-positive Treatment After Default, Others***	2H3R3Z3E3S3 + 1H3R3Z3E3 + 5H3R3E3
Category III	New Sputum smear-negative, not seriously ill New Extra-pulmonary, not seriously ill	2H3R3Z3 + 4H3R3

Dosing frequency		Comments
Intensive phase	Continuation phase	
Daily	Daily	Optimal
Daily	3 times per week	Acceptable alternative for any new TB patient receiving directly observed therapy

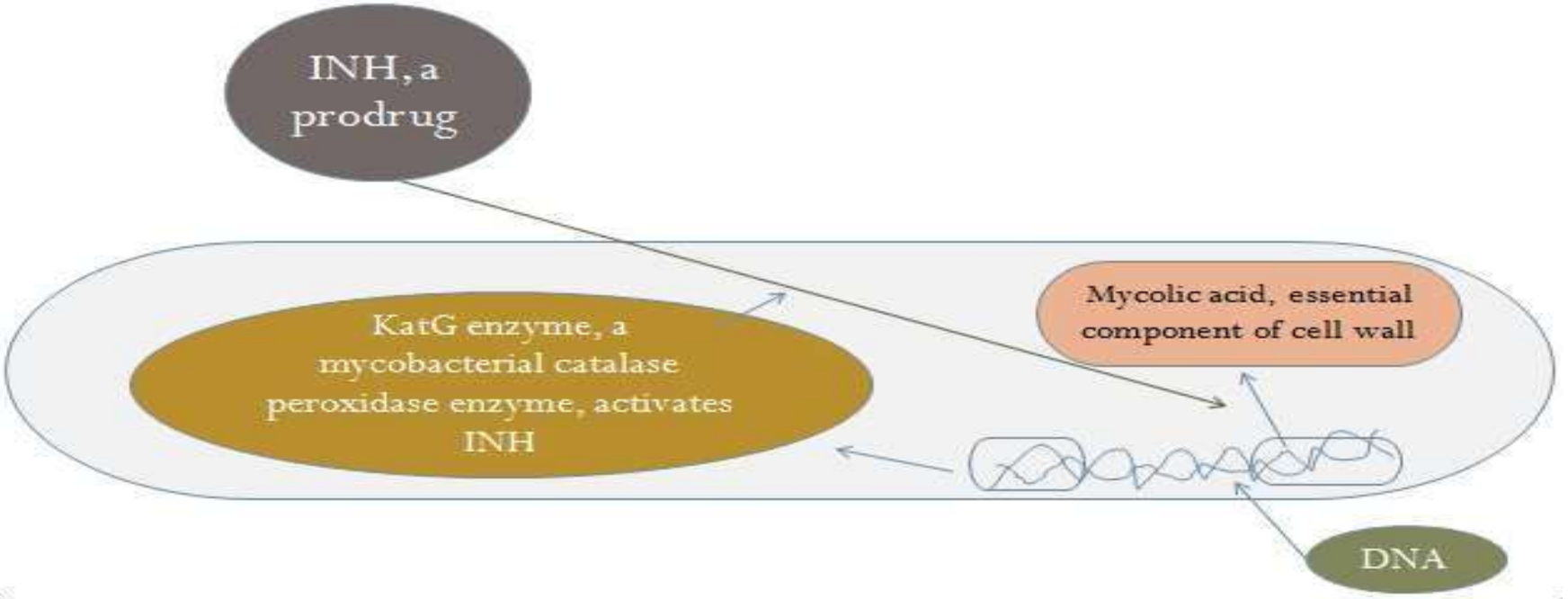
Recommended Doses Of First-line Anti-tuberculosis Drugs For Adults

Drug	Recommended dose			
	Daily		3 times per week	
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and range (mg/kg body weight)	Daily maximum (mg)
Isoniazid	5 (4–6)	300	10 (8–12)	900
Rifampicin	10 (8–12)	600	10 (8–12)	600
Pyrazinamide	25 (20–30)	–	35 (30–40)	–
Ethambutol	15 (15–20)	–	30 (25–35)	–
Streptomycin[a]	15 (12–18)		15 (12–18)	1000

ISONIAZID

MECHANISM

The activated form of isoniazid - forms a covalent complex with an inh-A (Acyl carrier protein -AcpM) and KasA, a ß-ketoacyl carrier protein synthetase, which blocks mycolic acid synthesis and kills the cell.



PHARMACOKINETICS

Absorption

- Rapid and complete; rate can be slowed with food
- Peak Plasma Time: 1-2 hr

Distribution

- All body tissues and fluids including CSF; crosses placenta; enters breast milk
- Protein Bound: 10-15%

Metabolism

- Hepatic (fast, slow acetylators)

Elimination

- Half-life elimination: fast acetylators: 30-100 min; slow acetylators: 2-5 hr; may be prolonged with hepatic or severe renal impairment
- Excretion: Urine (75-95%); feces

Mechanism of resistance:

- Resistance can emerge rapidly if the drug is used alone.
- Resistance can occur due to either
  1. High-level resistance is associated with deletion in the katG gene that codes for a catalase peroxidase involved in the bioactivation of INH.
  2. Low-level resistance occurs via deletions in the inhA gene that encodes —target enzyme‖ an acyl carrier protein reductase.

Pregnancy & Lactation

Pregnancy Category: C

Lactation: distributed into milk but safe for nursing infants

Oral Administration

Food may decrease the absorption and peak plasma concentrations of isoniazid.

Contraindications & Cautions

Black Box Warnings

- Severe and sometimes fatal hepatitis may occur within the first 3 months of treatment and months after treatment. Risk is related to age and increased with daily alcohol consumption.
- Patients should be instructed about signs and symptoms of hepatitis.

Contraindications

- Previous INH hepatic injury or reaction; acute liver damage
- Hypersensitivity

Cautions

- Alcohol or illicit injectable drug use, severe renal impairment, chronic liver damage.
- Use w/ other anti-TB agents
- Give pyridoxine (B6) concurrently for pregnant women, malnourished pts or those with neuropathic diathesis
- Alcohol use, renal or hepatic dysfunction will affect serum levels

Adverse Effects

- **>10%:** Mild incr LFTs (10-20%), Peripheral neuropathy (dose-related incidence, 10-20% incidence with 10 mg/kg/d), Loss of appetite, Nausea, Vomiting, Stomach pain, Weakness.
- **1-10%:** Dizziness, Slurred speech, Lethargy, Progressive liver damage (increases with age; 2.3% in pts > 50 yrs), Hyperreflexia.
- **<1%:** Agranulocytosis, Anemia, Megaloblastic anemia, Thrombocytopenia, SLE, Seizure.

Monitoring Parameters:

- LFTs
- ophthalmologic exam

DRUG INTERACTIONS:

- INH can increase CBZ concentrations and cause CBZ toxicity. This interaction occurs more often with INH doses at >/=200 mg/day
- INH and ethionamide may cause a temporary increase in serum concentrations of INH.
- Aluminum salts, decrease the absorption of INH by a reducing gastric emptying. Administration of INH 1 hour before antacids is recommended.
- INH may inhibit valproic acid hepatic metabolism. Elevated valproic acid concentrations and hepatotoxicity.
- INH is known to inhibit the hepatic metabolism of drugs that undergo oxidation including warfarin at the dose of 600mg/d

RIFAMPICIN

Rifampin is a semisynthetic derivative of rifamycin, an antibiotic produced by Streptomyces mediterranei.

It is active against gram positive and gram negative cocci, some enteric bacteria, mycobacteria and chlamydia.

Mechanism

- Rifampin binds to the β subunit of bacterial DNA–dependent RNA polymerase and thereby inhibits RNA synthesis.

Resistance results from any one of several possible point mutations in repoB, the gene for the β subunit of RNA polymerase.

Pharmacokinetics

Absorption

- PO well absorbed; food may delay absorption
- Peak plasma time: 2-4 hr

Distribution

- Highly lipophilic; crosses blood-brain barrier well, with or without inflammation
- Protein bound: 80%

Metabolism

- Metabolized by liver; undergoes enterohepatic recirculation

Elimination

- Half-life: 3-4 hr (prolonged in hepatic impairment); in end-stage renal disease, 1.8-11 hr
- Excretion: Feces (60-65%) and urine (~30%) as unchanged drug

Pregnancy & Lactation:

Pregnancy category: C

Lactation: Drug enters breast milk

Contraindications & Cautions

Contraindications

- Hypersensitivity to rifamycins
- Concomitant administration of live bacterial vaccines
- Contraindicated in patients receiving ritonavir-boosted saquinavir, because of increased risk of severe hepatocellular toxicity

Precautions

- May decrease the effectiveness of oral contraceptive pills (OCPs)
- Discontinue therapy if patient develops any signs of hepatocellular damage, including hyperbilirubinemia

- Use with caution in patients with history of alcoholism and patients receiving additional medications that may cause hepatotoxicity
- Rifampin has enzyme-inducing properties that can enhance metabolism of endogenous substrates, including adrenal hormones, thyroid hormones, and vitamin D

Monitoring Parameters

- CBC
- LFTs
- platelet count
- serum creatinine

ADRS:

- **1-10%:** Elevated liver function test (LFT) results (up to 14%), Rash (1-5%), Epigastric distress (1-2%), Anorexia (1-2%), Nausea (1-2%), Vomiting (1-2%), Diarrhea (1-2%), Cramps (1-2%), Pseudomembranous colitis (1-2%), Pancreatitis (1-2%)

Drug Interactions:

- Drugs that induce hepatic microsomal enzymes, particularly those drugs that increase CYP2C9 or CYP2C19 metabolism, can accelerate phenytoin clearance, reduce the plasma concentrations and also possibly the efficacy of phenobarbital.
- Reduce the plasma concentrations and possibly the efficacy of chloramphenicol, dosages may need to be adjusted while the patient is receiving rifampin.
- Reduce the plasma concentrations and possibly the efficacy of oral sulfonylureas. Oral sulfonylurea dosages may need to be adjusted while the patient is receiving rifampin.

Pyrazinamide

Mechanism of Action

Pyrazinamide's exact mechanism of action is not known. Susceptible strains release pyrazinamidase, which converts PZA to pyrazinoic acid (POA). POA decreases the pH below that which retards the growth of *M. tuberculosis* and inhibiting the fatty acid synthesis .Studies indicate that PZA is most effective in the initial stages of treatment, which may be the result of diminished organism populations in macrophages early in therapy.

Pharmacokinetics

- Absorption: well absorbed
- Distribution: widely into body tissues and fluids including liver, lung, and CSF
- Relative diffusion from blood into CSF: adequate with or without inflammation
- CSF: blood level ratio: inflamed meninges: 100%
- Protein binding: 50%
- Metabolism: hepatic
- Half-life elimination: 9-10 hr
- Time to peak, serum concentration: within 2 hr
- Excretion: urine (4% as unchanged drug)

Pregnancy & Lactation

- Pregnancy Category: C
- Lactation: enters breast milk

Adverse Effects

- **1-10%:** Malaise, Nausea, Vomiting , Anorexia, Arthralgia, Myalgia
- **<1%:**
  Fever, Rash, Itching, Acne, Photosensitivity, Gout, Dysuria, Porphyri a, Thrombocytopenia, Hepatotoxicity, Interstitial nephritis.

Interactions

- PZA can increase serum uric acid levels and precipitate gout attacks the dosages of antigout agents, including
  allopurinol, colchicine, probenecid , and sulfinpyrazone may need to be adjusted.
- PZA is associated with dose-related hepatoxicity. Daily use of ethanol while receiving pyrazinamide increases the risk of drug-induced hepatitis.

Liver-function tests should be conducted prior to and every 2—4 weeks during treatment in patients who consume ethanol routinely

Ethambutol

Mechanism

Ethambutol inhibits mycobacterial arabinosyl transferases. Arabinosyl transferases are involved in the polymerization reaction of arabinoglycan, an essential component of the mycobacterial cell wall.

- Resistance to ethambutol is due to mutations resulting in overexpression of Emb gene products or within the emb B structural gene.

Pharmacokinetics

Absorption

- Bioavailability: ~80%
- Peak Plasma Time: 2-4 hr

Distribution

- Widely throughout body; concentrated in kidneys, lungs, saliva, and red blood cells

- CSF: blood level ratio: 0% (normal meninges); 25% (inflamed meninges)
- Protein binding: 20-30%

Metabolism

- Hepatic (20%) to inactive metabolite

Elimination

- Half-life elimination: 2.5-3.6 hr; 7-15 hr (end-stage renal disease)
- Excretion: ~50% urine; ~50% feces as unchanged drug.

Pregnancy & Lactation

- Pregnancy Category: B
- Lactation: enters breast milk; use with caution

Contraindications

- Optic neuritis
- Hypersensitivity

Monitoring Parameters

- Ophthalmologic exam
- Platelet count
- Serum creatinine/BUN
- Serum uric acid

ADRS

- Acute gout or hyperuricemia, Abdominal pain, Anaphylaxis, Confusion, disorientation, Fever, Headache, LFT abnormalities, Malaise, Nausea
- Optic neuritis; symptoms may include decreased acuity, color blindness or visual defects (usually reversible with discontinuation)
- Peripheral neuritis
- Rash

Drug Interactions

- Aluminum hydroxide can reduce the rate or extent of ethambutol absorption. At least 4 hours should elapse between doses of aluminum hydroxide-containing antacids and ethambutol.

- Ethambutol may interfere with the development of an immune response following Bacillus Calmette-Guerin vaccine, BCG. The vaccine is a live vaccine and is sensitive to commonly used antituberculosis agents (e.g., isoniazid, ethambutol, rifampin)

Streptomycin

Streptomycin was isolated from a strain of Streptomyces griseus.

Mechanism of action:

Irreversibly inhibits bacterial protein synthesis. Protein synthesis is inhibited in at least three ways:

1. Interference with the initiation complex of peptide formation.
2. Misreading of mRNA, which causes incorporation of incorrect aminoacids into the peptide, resulting in a nonfunctional or toxic protein.
3. Breakup of polysomes into nonfunctional monosomes.

Pharmacokinetics

- Absorption: IM: well absorbed; not absorbed from gut
- Distribution: To extracellular fluid including serum, abscesses, ascitic, pericardial, pleural, synovial, lymphatic, & peritoneal fluids; crosses placenta; small amounts enter breast milk
- Protein Bound: 34%
- Half-life elimination: newborns: 4-10 hr; adults: 2-4.7 hr, prolonged with renal impairment
- Peak Plasma Time: within 1 hr
- Excretion: urine (90% as unchanged drug); feces, saliva, sweat, & tears (<1%)

Adverse Effects

Hypotension, Neurotoxicity, Drowsiness, Drug fever, Skin rash, Nausea, Vomiting, Eosinophilia , Arthralgia, Tremor, Ototoxicity (auditory, vestibular), Nephrotoxicity.

Monitoring Parameters

- audiometry
- serum creatinine/BUN

Drug Interactions

- Streptomycin may interfere with the development of an immune response following administration of BCG vaccine.
- Loop diuretics may cause volume depletion and allow for the concentration of aminoglycosides within the nephron; concurrent therapy has been considered a risk-factor for aminoglycoside-induced nephrotoxicity.

SECOND LINE DRUGS
Para amino salicylic acid

Mechanism of action

Aminosalicylic acid is a folate synthesis antagonist that is active almost exclusively against mycobacterium tuberculosis.

It is structurally similar to p-amino benzoic acid(PABA) and the sulfonamides.

Pharmacokinetics

Absorption

- T_{max} is about 6 h

Distribution

- About 50% to 60% is protein bound.

Elimination

- 80% is excreted in the urine with at least 50% excreted in acetylated form.
- The $t_{1/2}$ of free aminosalicylic acid is 26.4 min.

Dose: 4g 3 times daily, children < 15yrs: 200-300mg/kg daily in 2-4 divided doses.

Adverse Reactions

GI

- Nausea; vomiting; diarrhea; abdominal pain.

Metabolic

- Goiter with or without myxedema.

Miscellaneous

- Hypersensitivity (eg, fever, skin eruptions, leukopenia, thrombocytopenia, hemolytic anemia, jaundice, hepatitis, encephalopathy, Loffler syndrome, vasculitis).

Drug Interactions

Pregnancy

- Category C .

Lactation

- Excreted in breast milk.

Contraindications

- Severe hypersensitivity to aminosalicylate sodium and its congeners.

Precautions:

Renal Function Impairment

Drug and its acetyl metabolite may accumulate

- **Digoxin-** May reduce oral absorption and serum levels of digoxin.
- **Rifampin-** May decrease absorption of rifampin.
- **Vitamin B_{12}** May decrease GI absorption of oral vitaminB_{12}.

Hepatic Function- Use with caution.

CHF

- Use with caution because of high sodium content (55 mg of sodium per 500 mg tablet).

Crystalluria

- Maintain urine at neutral or alkaline pH to avoid crystalluria.

Ethionamide

Mechanism of Action:

Ethionamide, like pyrazinamide, is a nicotinic acid derivative related to isoniazid. It is thought that ethionamide undergoes intracellular modification and acts in a similar fashion to isoniazid.

Pharmacokinetics:

- Absorption: completely absorbed following oral administration
- Bioavailability approximately 100%.
- Volume of distribution 93.5 L.

- Protein binding :Approximately 30% bound to proteins.
- Metabolism: Hepatic . Metabolized to the active metabolite sulfoxide, and several inactive metabolites.

The sulfoxide metabolite has been demonstrated to have antimicrobial activity against Mycobacterium tuberculosis.

- Route of elimination: Less than 1% of the oral dose is excreted as ethionamide in urine.
- Half life2 to 3 hours

Dose:

Tuberculosis:

- 15-20 mg/kg/day PO Max: 1000 mg/day

Renal Impairment

- CrCl <10 mL/min: decrease dose 50%

Administration

- Part of multi-drug regimen; not first-line treatment
- Take with food

Monitor:

- baseline & periodic LFTs, TFTs, glucose

Interactions

Significant - Monitor Closely

- cycloserine
- isoniazid
- magnesium oxide/anhydrous citric acid

ADRS

>10%

- Disorder of gastrointestinal tract (50%)

Frequency Not Defined

- Postural hypotension
- Dizziness
- Drowsiness
- Headache
- Peripheral neuropathy
- Psychosis

Contraindications & Cautions

Contraindications

- Hypersensitivity to ethionamide
- Severe hepatic dysfunction

Cautions

- Diabetes mellitus, thyroid disease, hepatic impairment

Pregnancy & Lactation

- Pregnancy Category: C
- Lactation: excretion in milk unknown; use with caution

CYCLOSERINE

Cycloserine is an antibiotic produced by streptomyces orchidaceus.

Mechanism of action:

- It inhibits the incorporation of D- alanine into peptidoglycan pentapeptide by inhibiting alanine racemase, which converts L-alanine to D- alanine, and D- alanyl-D –alanine ligase (finally inhibits mycobacterial cell wall synthesis).
- Cycloserine used exclusively to treat tuberculosis caused by mycobacterium tuberculosis resistant to first line agents

Dosing and uses

Active Tuberculosis

- Initial: 250 mg PO BID
- Maintenance: 500 mg -1 g/day in 2 divided doses for 18-24 months; not to exceed 1 g/day

Renal Impairment

- CrCl 50-80 mL/min: Give q12-16hr
- CrCl 10-49 mL/min: Give q24-36hr
- CrCl <10 mL/min: Contraindicated

Administration

- Part of multi-drug regimen; not first-line treatment

Pharmacokinetics

- Distribution: CSF concentration equal to that in plasma
- Metabolism: liver
- Excretion: urine

INTERACTIONS

Significant - Monitor Closely

- ethionamide
- isoniazid
- magnesium oxide/anhydrous citric acid

ADR

Frequency Not Defined

- Confusion
- Dizziness
- Headache
- Somnolence
- Seizure
- Psychosis

Contraindications & Cautions

Contraindications

- Hypersensitivity
- Alcohol use
- Renal dysfunction, severe
- History of seizure disorder, mental depression, severe anxiety or psychosis

Cautions

- Alcoholism, anemia, impaired hepatic/renal function

Pregnancy & Lactation

- Pregnancy Category: C
- Lactation: enters breast milk; safe

Thioacetazone

Mechanism of action: Bacteriostatic- inhibits cyclopropanaton of cell wall mycolic acids.

Uses: It continues to be used as a convenient low cost drug to prevent emergence of isoniazid resistance, streptomycin & ethambutol.

Dose: 150mg OD in adults; 2.5mg/kg in children; it is frequently combine with isoniazid

T1/2: 12 hrs

ADR: hepatitis, exfoliative dermatitis, SJS, bone marrow depression rarely

Common: Abdominal discomfort, loose motions, rashes, mild anemia, anorexia.

Azithromycin

Mechanism of Action

Binds to 50S ribosomal subunit of susceptible microorganisms and blocks dissociation of peptidyl t-RNA from ribosomes, causing RNA-dependent protein synthesis to arrest; does not affect nucleic acid synthesis

Absorption

- Rapidly absorbed
- Bioavailability: 37%; variable effect with food
- Peak plasma time: 2.3-4 hr

Distribution

- Extensively distributed into skin, lungs, sputum, tonsils, and cervix; penetrates cerebrospinal fluid (CSF) poorly
- Protein bound: 7-50% (concentration dependent)
- Vd: PO, 33.3 L/kg; IV, 31.1 L/kg

Metabolism

- Metabolized in liver

Elimination

- Half-life: Immediate release, ~70 hr; extended release, 59 hr
- Excretion: Feces (50% as unchanged drug), urine (5-12%)

Dose

Mycobacterium Avium Complex Infection

Prevention

- 1.2 g PO once weekly; may be combined with rifabutin 300 mg once daily

Treatment

- 250 mg PO once daily in combination with ethambutol 25 mg/kg/day for 2 months 15 mg/kg/day plus rifabutin 300 mg/day or rifampin 600 mg/day

Interactions

Contraindicated

- pimozide

Serious - Use Alternative

- BCG- vaccine live
- Digoxin
- Fondaparinux
- heparin
- Ondansetron
- quinidine
- typhoid vaccine live
- warfarin

ADRS

>10%: Diarrhea (52.8%), Nausea (32.6%), Abdominal pain (27%), Loose stool (19.1%)

1-10%: Cramping (2-10%), Vaginitis (2-10%), Dyspepsia (9%), Flatulence (9%), Vomiting (6.7%), Malaise (1.1%)

<1%: Agitation, Allergic reaction, Anemia, Anorexia, Candidiasis, Chest pain, Conjunctivitis, Constipation, Dermatitis (fungal), Dizziness, Eczema

Contraindication

- hypersensitivity
- Cholestatic jaundice or hepatic impairment

Cautions

- Bacterial or fungal overgrowth may result from prolonged use
- Prolonged QT interval: Cases of torsades de pointes have been reported.
- Renal impairment (CrCl <10 mL/min)
- Use with caution in patients with myasthenia gravis (exacerbation may occur)

Administration

IV Preparation

- Dilute 500-mg vial in 4.8 mL of SWI (100mg/mL)
- Dilute further in NS to 1 mg/mL (500 mL) or 2 mg/mL (250 mL)

IV Administration

- 1 mg/mL solution: Infuse over 3 hours
- 2 mg/mL solution: Infuse over 1 hour

Pregnancy & Lactation

- Pregnancy category: B
- Lactation: Unknown whether drug is excreted into breast milk; use with caution

Clarithromycin

Mechanism of Action

Semisynthetic macrolide antibiotic that reversibly binds to P site of 50S ribosomal subunit of susceptible organisms and may inhibit RNA-dependent protein synthesis by stimulating dissociation of peptidyl t-RNA from ribosomes, thereby inhibiting bacterial growth

Pharmacokinetics

- **Absorption**
- Highly stable in presence of gastric acid (unlike erythromycin); food delays but does not affect extent of absorption
- Bioavailability: 50%
- Peak plasma time: 2-3 hr

Distribution

- Distributed widely into most body tissues except central nervous system (CNS)
- Protein bound: 42-50%

Metabolism

- Partially metabolized by CYP3A4
- Metabolites: 14-OH clarithromycin (active)

Elimination

- Half-life: Immediate release, 3-7 hr; active metabolite, 5-9 hr
- Renal clearance: Approximates normal glomerular filtration rate (GFR)
- Excretion: Urine (30-55%)

Dosing & Uses

Mycobacterial Infection

- Prophylaxis and treatment
- 500 mg PO q12hr for 7-14 days

Dosing Modifications

- Renal impairment (CrCl <30 mL/min): Reduce normal dose by 50%

ADR

- **>10%:** Gastrointestinal (GI) effects, general (13%)
- **1-10%:** Abnormal taste (adults, 3-7%, Diarrhea (3-6%), Nausea (adults, 3-6%), Vomiting (adults, 1%; children, 6%), Elevated BUN; 4%, Abdominal pain (adults, 2%; children, 3%), Rash (children, 3%), Dyspepsia (2%), Headache (2%), Elevated prothrombin time (PT; 1%)
- **<1%:** Anaphylaxis, Anxiety, Clostridium difficile colitis, Dizziness, Dyspnea, Elevated liver function tests

Contraindications

- hypersensitivity
- Coadministration with pimozide, cisapride, ergotamine, and dihydroergotamine
- History of cholestatic jaundice or hepatic dysfunction associated with previous use of clarithromycin
- History of QT prolongation
- Coadministration with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin, simvastatin), due to the increased risk of myopathy, including rhabdomyolysis

Cautions

- Severe renal impairment
- Elderly patients may be more susceptible to drug-associated QT prolongation
- Discontinue immediately if severe hypersensitivity reactions occur
- Clostridium difficile associated diarrhea reported with use of nearly all antibacterial agents, including clarithromycin
- Exacerbation of myasthenia gravis or new onset of symptoms reported

Hepatic dysfunction

- Increased liver enzyme activity and hepatocellular or cholestatic hepatitis, with or without jaundice, have been reported; this may be severe and is usually reversible

Pregnancy & Lactation

- Pregnancy category: C
- Lactation: Drug is excreted in breast milk; use with caution

AMIKACIN

Mechanism of Action

Irreversibly binds to 30S subunit of bacterial ribosomes; blocks recognition step in protein synthesis; causes growth inhibition. For gram-negative bacterial coverage of infections resistant to gentamicin and tobramycin

Pharmacokinetics

- Absorption: IM: May be delayed in bedridden patient
- Vd: 0.25-0.4 L/kg, primarily into extracellular fluid (highly hydrophilic); penetrates blood-brain barrier when meninges inflamed; crosses placenta.
- Excretion: urine (94-98%)
- Half-Life: 2-3 hr
- Peak Plasma Time: IM: 45-120 min
- Protein Binding: 0-11%

Dosing

15 mg/kg/day divided IV/IM q8-12hr

Renal Impairment/Elderly

- CrCl >90 mL/min & <60 years old: q8hr
- CrCl 60-90 mL/min OR >60 years old: q12hr
- CrCl 25-60 mL/min: q24hr
- CrCl 10-25 mL/min: q48hr
- CrCl <10 mL/min: q72hr

Interactions

Contraindicated

- amphotericin b deoxycholate
- cidofovir
- neomycin

Serious - Use Alternative

- Atracurium
- **BCG-** vaccine live
- Bumetanide
- cyclosporine
- ethacrynic acid
- Furosemide

ADR

- **1-10%**
- Neurotoxicity
- Nephrotoxicity (if trough >10mg/L)
- Ototoxicity
- **<1%:** Hypotension, Headache, Drug fever, Rash, Nausea, Vomiting, Eosinophilia, Tremor, Arthralgia

Contraindications

- Documented hypersensitivity

Cautions

- Renal impairment
- Risk of neurotoxicity, ototoxicity, nephrotoxicity - risk of ototoxicity increase with concurrent loop diuretics

Pregnancy & Lactation

- Pregnancy Category: D
- Lactation: excretion in milk unknown/not recommended**IV Preparation**
- Dilute 500 mg to 100 or 200 mL sterile diluent (usu NS or D5W)

IV/IM Administration

- IM: give undiluted to upper outer quadrant of buttocks
- IV: infuse over 30-60 min in adults and children and 1-2 hr in infants

KANAMYCIN

Mechanism of Action

Bactericidal and believed to inhibit protein synthesis by binding to 30 S ribosomal subunit.

Pharmacokinetics

- Metabolism: unknown
- Excretion: urine

Dosing & Uses

- IV Administration: 5-7.5 mg/kg/dose divided q8-12hr; not to exceed 15 mg/kg/day divided q6-12hr; administer slowly
- IM Administration: 5-7.5 mg/kg/dose divided q8-12hr; not to exceed 15 mg/kg/day IM divided q12hr at equally divided intervals;
- **Renal Impairment**
- CrCl 50-80 mL/min: give 60-90% of usual dose or give q8-12hr
- CrCl 10-50 mL/min: give 30-70% of usual dose or give q12hr
- CrCl <10 mL/min: give 20-30% of usual dose or give q24-48hr

ADR

Agranulocytosis, Anorexia, Diarrhea, Dyspnea, Elevated BUN, Enterocolitis, Headache, Incr salivation, Muscle cramps, Nausea, Nephrotoxicity, Neurotoxicity, Ototoxicity, Pruritus.

Contraindications

- Documented hypersensitivity

Cautions

- Auditory toxicity more common with kanamycin than with streptomycin and capreomycin;
- monthly audiometry is recommended while patients are being treated with this drug;
- renal toxicity occurs at a frequency similar to that of capreomycin; regular monitoring of serum creatinine recommended
- Renal impairment
- Myasthenia gravis
- Nephrotoxic agents

Pregnancy & Lactation

- Pregnancy Category: D
- Lactation: usually compatible

ADMINISTRATION

- **IV Preparation**
- For adults, IV infusions are prepared by adding 500 mg of kanamycin to 100-200 mL of usual IV infusion fluid such as NS or D5W or by adding 1 g of the drug to 200-400 mL of diluent
- **IV/IM Administration**
- Administer by deep IM injection, or IV infusion
- May administer by intraperitoneal instillation, irrigation, or inhalation
- Infuse over 30-60 min

RIFABUTIN

Mechanism of Action

Inhibits DNA-dependent RNA polymerase

Pharmacokinetics

Absorption: readily, 53%

Distribution: body tissues including the lungs, liver, spleen, eyes, & kidneys

- Vd: 9.32 L/kg
- Protein Bound: 85%
- Bioavailability: absolute: HIV: 20%
- Half-Life, 45 hr (range: 16-69 hr)
- Peak Plasma Time: 2-4 hr

Metabolism: hepatic CYP3A4 to active and inactive metabolites

Excretion

- Urine: 10% as unchanged drug, 53% as metabolites
- Feces: 10% as unchanged drug, 30% as metabolites

Prophylaxis

- Indicated for prefention of disseminated Mycobacterium avium complex (MAC) disease in paitents with advanced HIV infection: 300 mg PO qDay
- Patients with N/V diathesis: 150 mg PO BID with food

Active TB (off-label)

- 5 mg/kg PO qD or 2-3x/week + other antitubercular agents, no more than 300 mg/dose

Renal Impairment

- CrCl<30mL/min dose should be reduced by 50%

Interactions

- artemether
- Clarithromycin

ADR:

>10%: Discoloration of urine (30%), Neutropenia (25%), Leukopenia (17%), Rash (11%)

1-10%: Incr AST/ALT (7-9%), Thrombocytopenia (5%), Abdominal pain (4%), Diarrhea (3%), Eructation (3%), Headache (3%), Nausea/vomiting (3%), Anorexia (2%), Flatulence (2%)

Contraindications & Cautions

Contraindications

- Hypersensitivity to rifamycins
- Concomitant live bacterial vaccines

Cautions

- Monitor hematologic status
- Eye pain, redness, loss of vision may indicate inflammatory ocular condition
- May have brown-orange color of urine, feces, saliva, sputum, perspiration, tears, & skin
- Pregnancy Category: B

Fluoroquinolones

Ciprofloxacin, Levofloxacin, gatifloxacin, moxifloxacin can inhibit strains M tuberculosis. They are also active against atypical mycobacteria.

Moxifloxacin is the most active against M tuberculosis.

Mechanism of action:

They inhibit bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA Gyrase) and topoisomerase IV.

- Inhibition of DNA Gyrase prevents the relaxation of supercoiled DNA that is required for normal transcription and replication.
- Inhibition of topoisomerase IV interferes with separation of replicated chromosomal DNA into the daughter cells during cell division.

Pharmacokinetics

Rapidly absorbed orally- but food delays absorption,

BA: C- 60-80%, L- 100%, G- 96%

PPB: C- 20-35%, L- 15%, G- 20%

Vd: C- 3-4%, L-8%,

Half life: C- 3-5hrs, L-8hrs, G-8hrs

High tissue penetration: lungs, sputum, muscle, prostate but low in CSF

Excreted primarily in urine, urinary and biliary concentrations are 10-50 times more than plasma

Dosage

- Ciprofloxacin 750mg BD,PO
- Levofloxacin 500mg OD.PO
- Moxifloxacin 400mg OD. PO

Adverse effects

Nausea, vomiting,diarrhoea(most common).

Headache, dizziness, insomnia, skin rash, photosensitivity.

Damage growing cartilage and cause an arthropathy. Tendinitis,tendon rupture.

Interactions

- All fluoroquinolones interact with aluminum- or magnesium-containing antacids and products containing calcium, iron, or zinc. Concomitant use invariably results in marked reduction of oral absorption of the antimicrobial and decreased the bioavailability of these drugs by up to 98% when given within 2 hours of antibiotic administration.

- Fluoroquinolones are administered with food, peak concentration times are usually slightly delayed, and maximum plasma concentrations (Cmax) are decreased 8-16%.
- Reductions in renal and total systemic clearance caused by probenecid are 24% for levofloxacin, 50% for ciprofloxacin, and 42% for gatifloxacin.
- Significantly interact with theophylline-ciprofloxacin decreased theophylline clearance by 25-30%, and increased theophylline plasma concentrations by up to 308%.