Done by: Noor Marzooq & Zeina Yassin

Tuberculosis Overview and Principles of Therapy

- **Treatment Challenges**: Management of TB has become difficult due to the development of multidrug-resistant mycobacteria (resistant to at least isoniazid and rifampin). This is primarily caused by noncompliance, incorrect drug selection, or ineffective serum concentrations.
- **AIDS Impact**: HIV/AIDS has increased the incidence of TB to **170** times that of the general population.
- **Combination Therapy**: Required to overcome resistance and target different populations of bacilli:
    - **Intracellular (Macrophages)**: Targeted by isoniazid, rifampin, and pyrazinamide.
    - **Extracellular (Cavities)**: Targeted by isoniazid, streptomycin, ethambutol, and fluoroquinolones.
    - **Resting (Caseating Granulomas)**: Targeted by pyrazinamide; (isoniazid and rifampin may also be effective).
- **Treatment Duration**:

  A)**Initial intensive phase** : the **first 2 months** (either isoniazid, rifampin, pyrazinamide and ethambutol OR isoniazid, pyrazinamide, rifapentine, and moxifloxacin until susceptibility of the clinical isolate has been determined.)

  B)**The continuation phase** : additional **4 months** with isoniazid and rifampin OR an additional **2 months** of rifapentine, moxifloxacin, and isoniazid.

  *Neither ethambutol nor other drugs adds substantially to the overall activity of the regimen and **can't reduce** treatment duration, but the fourth drug is included in the traditional regimen in case the isolate proves to be resistant to isoniazid, rifampin, or both

  *Addition of pyrazinamide will shorten duration of therapy from 9 to 6 months.
- **IMP NOTES**:

*** Isoniazid and rifampin** are the most active drugs and will cure >95% of cases caused by susceptible strains.

*An initial intensive phase of treatment is recommended in the first 2 months due to the prevalence of resistant strains

*Therapy is usually initiated with a four-drug regimen of either isoniazid, rifampin, pyrazinamide and ethambutol OR isoniazid, pyrazinamide, rifapentine, and moxifloxacin until susceptibility of the clinical isolate has been determined.

Regimen	Months
Isoniazid + Rifampin + Pyrazinamide	6
Isoniazid + Rifampin	9
Rifampin + Ethambutol + Pyrazinamide	6
Isoniazid + Pyrazinamide + Rifapentine + Moxifloxacin	4
Rifampin + Ethambutol	12
Isoniazid + Ethambutol	18

First-Line Antimycobacterial Drugs:

Isoniazid, Rifampin, Ethambutol, Pyrazinamide.

Isoniazid

Category	Details
General	The most active drug for TB; structurally similar to pyridoxine (Vitamin B6). Bactericidal for actively growing bacilli.
Mechanism	A prodrug activated by mycobacterial catalase-peroxidase. Inhibits mycolic acid synthesis, essential for the cell wall.
Resistance	Mutation in genes involved in mycolic acid synthesis.
Pharmacokinetics (penetrates into macrophages & active against intra- and extracellular mycobacteria.)	Readily absorbed from GIT ,Peak concentration decreases when given with a fatty meal , Al3+ interferes with its absorption , Diffuses readily into all body fluids and tissues including CNS and penetrates caseous material. Metabolized by N-acetyltransferase (Rapid vs. Slow Acetylators). Plasma concentration in RA is 1/3rd – ½ of that in SA **t½ < 1 hour in RA and < 3 hours in SA Daily, there are no therapeutic consequences in RA, once weekiy, or in malabsorption, the concentration may be subtherapeutic **No dose adjustment is needed in renal failure, but dose adjustment should be directed by plasma concentration for patients with severe hepatic insufficiency.
Adverse Effects (related to dose & duration)	**Allergic: (**fever ,skin rash , Drug induced lupus syndrome) **Hepatitis**: Major toxic effect (1-3%). Clinically: loss of appetite, nausea, vomiting, jaundice and right upper quadrant pain. Histologically:hepatocellular necrosis. The drug should be discontinued promptly and not reused again. (The risk increases with age, alcohol use, pregnancy and the postpartum period. Transient elevation of aminotransferases in 10-20% of patients, usually asymptomatic **Peripheral Neuropathy**: (10-20%) due to pyridoxine deficiency. especially at high doses (>300 mg/day). More likely in SAs, malnutrition, alcoholism, diabetes, AIDS & uremia. Due to relative pyridoxine deficiency because of reduced formation of pyridoxal phosphate, and increased excretion ** Can be prevented by coadministration of vitamin B6 (10 mg/day) **CNS**: Psychosis, seizures. Memory loss. **can be prevented by vitamin B6 Others: Tinnitus, GIT irritation, pyridoxine deficiency anemia and hemolysis in G6PD deficiency.
Interactions	Reduces metabolism of phenytoin, carbamazepine, benzodiazepines, and warfarin.

Rifampin

Category	Details
Mechanism	Inhibits bacterial DNA-dependent RNA polymerase; bactericidalor both intra- & extracellular. Does not affect human RNA polymerase.
Resistance	mutation of the RNA polymerase resulting in reduced affinity for rifampin.
Activity	Active against *M. tuberculosis*, *M. leprae*, Gram positive bacteria: Staphylococcus aureus Gram negative bacteria: E. coli, Proteus, Klebsiella, Brucella . Neisseria meningitidis , Haemophilus influenzae , Chlamydia
Pharmacokinetics	-Well absorbed after oral administration, and delayed by co-administration of aminosalicylic acid. -eliminated in bile and undergoes enterohepatic cycling & is excreted as deacylated metabolites in feces. -readily penetrates most tissues and phagocytic cells and into abscesses and lung cavities. ** It is highly plasma protein bound -Adequate CSF concentrations are only achieved in the presence of meningeal inflammation. -Dosage adjustment in renal and hepatic insufficiency is not necessary.
Enzyme Induction	Strongly induces enzymes, increasing metabolism of digitoxin, quinidine, propranolol, verapamil, cyclosporine, warfarin, theophylline, sulphonylureas, oral contraceptives, steroids, narcotics, zidovudine, protease inhibitors, ketoconazole.
Therapeutic Uses:	Mycobacterial infections:TB & Leprosy,Alternative to isoniazid prophylaxis for patients who are unable to take it (close contacts of an active TB case), Prophylaxis against meningitis due to Neisseria meningitidis and Haemophilus influenzae in persons in contact with active cases , Elimination of meningococcal carrier state, & staphylococcal carrier state. In combination with other agents, it is used for serious staphylococcal infections, such as osteomyelitis and prosthetic valve endocarditis. , In combination with ceftriaxone or vancomycin for highly penicillin-resistant strains of pneumococci. ,Brucellosis.
Adverse Effects	harmless orange color to urine, sweat, tears, contact lenses, sputum, and other secretions ,Allergic reactions: rash, thrombocytopenia & interstitial nephritis, Cholestatic jaundice and occasionally hepatitis, light chain proteinuria. Superinfections , Elevation of hepatic enzymes (potentiates isoniazid hepatotoxicity by increasing enzyme activity responsible for conversion of monoacetylhydrazine into a hepatotoxic intermediate). **less than twice weekly, it produce a flu-like syndrome characterized by fever, chills, myalgia ,Anemia, thrombocytopenia , Acute renal tubular necrosis. & GIT irritation.

Pyrazinamide

Category	Details
Mechanism	Prodrug converted to pyrazinoic acid (POA) by **pyrazinamidase.** a.POA disrupts the cell membrane and lowers intracellular pH. b.disruption in the energy production and nutrient uptake (This interference weakens the cell and contributes to its eventual death) c.inhibition of fatty acid synthase which reduces the synthesis of fatty acids d.lowers the intracellular pH(acidic environment detrimental bacterial survival.) e.interfere with the bacterial stress response
Resistance	Mutation that impairs conversion of the drug into its active form. Impairment of drug uptake by macrophages.
Pharmacokinetics	-Well absorbed from GIT. -Taken up by macrophages and exerts its activity against mycobacteria residing within the acidic environment of lysosomes. -Distributed in body tissues including inflamed meninges -Eliminated by hepatic metabolism & excreted by glomerular filtration.
Adverse Effects	**Hepatotoxicity:** the major limiting adverse effect, dose-dependant, common **(**1-5% of patients). **Photosensitivity** **Joint pain** **Hyperuricemia >** acute gouty arthritis because of inhibition of uric acid excretion leading to arthritis**.** **GIT irritation:** notorious nausea and vomiting **Allergic** (drug fever)

Ethambutol

Category	Details
Mechanism	Inhibits arabinosyl transferase, preventing cell wall polymerization; bacteriostatic.
Resistance	Overexpression of the gene of an enzyme needed for formation of arabinoglycan
Pharmacokinetics	-Well absorbed orally -Crosses BBB when the meninges are inflamed. -Excreted 20% in feces and 50% in urine. - Accumulates in renal failure -The dose reduced by 50% when CLcr < 10 mL/min, or administered 3 times weekly instead of daily.in urine; requires dose adjustment in renal failure.
Adverse Effects	**-Hypersensitivity reactions.** **-Retrobulbar neuritis:** loss of vision, visual field defects and red-green color blindness. **a. most serious adverse reaction.**

Category	Details
	b. the drug is contraindicated in children too young to permit vision assessment. c. dose-related, more likely at high doses (25 mg/kg/day) or if continued for several months. **-GIT irritation.** **-Peripheral neuritis.** **-Confusion, disorientation, headache.** **-Hyperuricemia > acute gouty arthritis.**

Second-Line and Alternative Drugs:

Indications: 1. Resistance of drugs of first choice. 2. Failure of response to conventional therapy. 3. Treatment-limiting adverse drug reactions. 4. expert guidance is available to deal with the adverse effects.

Ethionamide, Aminosalicylic acid, Cycloserine, Capreomycin, Amikacin, Kanamycin, Streptomycin, Ciprofloxacin, levofloxacin, Linezolid, Clofazimine, Rifabutin & Rifapentine.

Drug	Mechanism	Adverse Effects	Indications & Specific Clinical Notes
Ethionamide	Similar to Isoniazid (inhibits mycolic acid).	Intense gastric irritation (poorly tolerated); Peripheral neuropathy(Prevented by pyridoxine) Convulsions ,Olfactory and visual disturbances Hepatotoxicity.	Bacteriostatic; Cross-resistance with Isoniazid exists.
Capreomycin	Peptide; inhibits protein synthesis.	Nephrotoxicity; Ototoxicity (auditory and vestibular); Local pain/ sterile abscess.	Administered IM; used when there is resistance or failure of first-line drugs.
Cycloserine	D-alanine analog; inhibits cell wall synthesis.(inhibits many gram positive and gram negative bacteria)	Serious peripheral neuropathy &CNS dysfunction (convulsions, psychosis, depression);Ameliorated by 150 mg/day pyridoxine	Widely distributed to tissues, including CNS. Eliminated by the kidney (dose should be reduced by 50% if CLcr <50 mL/min, or used 3 times weekly Requires therapeutic drug monitoring (peak 20-40 mg/L); 2-4 hours after the dose

Drug	Mechanism	Adverse Effects	Indications & Specific Clinical Notes
Rifabutin	Rifamycin derivative; similar to Rifampin. ***Rifapentine is similar to rifampin	-Similar to Rifampin (cross-resistance occurs).	-Less potent inducer of drug metabolizing enzymes.so it is preferred over rifampin for TB in HIV infected patients who are receiving concomitant antiretroviral therapy (protease inhibitors or nucleoside reverse transcriptase inhibitors).
Bedaquiline	Inhibits mycobacterial (adenosine 5′-triphosphate)ATP synthase.	**Hepatotoxicity; Cardiac toxicity** (QTc prolongation).	Associated with increased mortality due to QTc effects.
Pretomanid	-Requires selective activation in mycobacteria by reduction -Blocks mycolic acid synthesis and thus cell wall.	**Neuropathy**, headache, acne, anemia, gastrointestinal symptoms, elevat ed liver enzymes, rash, hyperamylasemia. -**QT prolongation** -**Others**: pancreatitis, elevated creatine phosphokinase, electrolyte disturbances, and seizures.	Metabolized in part by CYP3A4; excreted in urine and feces.

Summary of Overlapping Adverse Effects

Adverse Effect	Isoniazid	Rifampin	Pyrazinamide	Ethambutol	Ethionamide
Hepatotoxicity	Yes	Yes	Yes	No	Yes
GIT Irritation	Yes	Yes	Yes	Yes	Yes
Peripheral Neuropathy	Yes	No	No	Yes	Yes
Hyperuricemia / Gout	No	No	Yes	Yes	No
CNS Effects/Toxicity	Yes	No	No	Yes	Yes

﴿أَوَلَيْسَ ٱلَّذِي خَلَقَ ٱلسَّمَٰوَٰتِ وَٱلْأَرْضَ بِقَٰدِرٍ عَلَىٰٓ أَن يَخْلُقَ مِثْلَهُم ۚ بَلَىٰ وَهُوَ ٱلْخَلَّٰقُ ٱلْعَلِيمُ * إِنَّمَآ أَمْرُهُۥٓ إِذَآ أَرَادَ شَيْـًٔا أَن يَقُولَ لَهُۥ كُن فَيَكُونُ * فَسُبْحَٰنَ ٱلَّذِي بِيَدِهِۦ مَلَكُوتُ كُلِّ شَيْءٍ وَإِلَيْهِ تُرْجَعُونَ﴾
(سورة يس)

اللهم اجعل أجر هذا العمل صدقة جارية عن روح **عمر عطيه عوده المرابي**

اللَّهُمَّ اغْفِرْ له وَارْحَمْهُ، وَاعْفُ عنْه وَعَافِهِ، وَأَكْرِمْ نُزُلَهُ، وَوَسِّعْ مُدْخَلَهُ، وَ اغْسِلْهُ بمَاءٍ وَثَلْجٍ وَبَرَدٍ، وَنَقِهِ مِنَ الخَطَايَا كما يُنَقّى الثَّوْبُ الأبْيَضُ مِنَ الدَّنَسِ.

اللَّهُمَّ أبدله داراً خيراً من داره، وأهلاً خيراً من أهله، وأدخله الجنّة، وأعذه من عذاب القبر ومن عذاب النّار.

اللهمّ يمّن كتابه، ويسّر حسابه، وثقل بالحسنات ميزانه، وثبّت على الصراط أقدامه، وأسكنه في أعلى الجنات، بجوار حبيبك محمد صلّى الله عليه وسلم.

اللهم اغفر لحينا وميتنا وشاهدنا وغائبنا وصغيرنا وكبيرنا وذكرِنا وأنثانا اللهم من أحييته منا فأحيِه على الإسلام ومن توفيته منا فتوفه على الإيمان اللهم لا تحرمنا أجره ولا تضلنا بعده.

اللهم اغفر له وارفع درجته في المهديين، واخلفه في عقبه في الغابرين، واغفر لنا وله يا رب العالمين، وافسح له في قبره، ونوّر له فيه.

اللَّهُمَّ أنزل على أهله الصّبر والسلوان وارضهم بقضائك.

اللهم لا تفجعنا بأنفسنا ولا أهلنا ولا أحبتنا، اللهم أعوذ بك من فواجع الأقدار ومن مصائب الدنيا وتقلب حوادثها، اللهم إنا نخاف الفقد فلا تحملنا ما لا طاقة لنا به.