MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

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TB Drugs

- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Females doctor notes
- Grey: Males doctor notes

OBJECTIVES:

By the end of this lecture , you should be able to:

✓ Discuss the etiology of tuberculosis.

✓ Discuss the common route for transmission of the disease.

✓ Discusses the out line for treatment of tuberculosis.

✓ Discuss the drugs used in the first & second line Regarding :

- The mechanism of action
- Adverse effects
- Drug interactions
- Contraindications
- Discuss tuberculosis & pregnancy
- Discuss tuberculosis & breast feeding

Editing File

Tuberculosis

Etiology:

1

-**Mycobacterium tuberculosis**
, slow growing, an acid fast bacilli.

-Robert Koch was the first to isolate mammalian Mycobacterium tuberculosis with his staining technique in 1882.

Common sites of infections :

2

-Apical areas of lung, The mycobacteria survive & multiply within macrophages

- Renal parenchyma.

-Growing ends of bones.

"Can go out of the cell through blood monocyte , and target lymph node and other targets"

Route of transmission:

3

Mycobacterium tuberculosis transmit through the air:
- Coughs.
- Sneezes.

Treatment of TB:

4

-**Drugs combination** is important to prevent development of drug resistance.
-Periods of treatment (minimum 6 months).

Antimycobacterial drugs

Divided into 2 groups:

1st line

- Isoniazid (INH)
- Rifampin (RIF)
- Ethambutol
- Pyrazinamide
- Streptomycin (should not be the 1st line choice) used for severe cases only.

INH+RIF+ Ethambutol+ pyrazinamide Given for first 8 weeks, followed by **INH+RIF** for 18 weeks.

Never use a single drug therapy.

-**INH + RIF** combination given for 9 months will cure 95-98% of cases.

-Addition of **Pyrazinamide/Ethambutol** for this combination for the first 2 months allows total duration to be reduced to 6 months.

"If the hospital doesn't have all types of TB drugs we can use only INH and Rif but we will extend the period of the treatment to 9 months"

2nd line

- Ethionamide
- Flouro-quinolones (ciprofloxacin)
- Rifabutin
- Para-Aminosalicylic acid (PAS)

2nd line drug are more toxic than 1st line drugs, thus only used in these cases:

-Resistance to 1st line drugs.
-Contraindication to 1st line drugs.
-Failure of clinical response.
-Used in typical & atypical tuberculosis

1st line treatment

	Isoniazid (INH)	Rifampin (Rifampicin) (RIF)
Overview	-Bacteriostatic works on resting bacilli (slowly proliferating or not proliferating) -Bactericidal works on rapidly growing bacilli	Bactericidal
Site of action	intracellular & extracellular bacilli	
MOA	- **Inhibits** the synthesis of **mycolic acid**, an important component of mycobacterial cell wall. - Penetrates into macrophages.	Binds to bacterial **DNA- dependent RNA polymerase enzyme** & thus **inhibits RNA synthesis**.
Clinical uses	- Treatment of TB. - Treatment of Latent TB in patients with Positive tuberculin skin test. - Prophylaxis against active TB in individuals who are in great risk.	-Treatment of TB. -Prophylaxis. -Against other bacterial infection such as meningococcal & staphylococcal infections.
ADRs	-Peripheral neuritis. (pin & needles sensation in the feet) -Optic neuritis & atrophy (Pyridoxine should be given in both cases) INH is antagonist to Vitamin B6 as a result of that nerves are affected , so Vitamin B6 is prescribed with INH -Hepatitis (toxic metabolites) Hepatitis with INH, is age dependent; it is rare in persons younger than 20 years, risk increases with age & alcohol use. We should check liver function and enzymes before and during treatment	-Harmless red-orange discoloration of body secretions (saliva, sweat, urine, tears), Tell the patient about this effect can permanently stain contact lenses. -Hepatitis (less common compared to INH) -Flu-like syndrome -Hemolytic anemia
Drug-interaction	-**INH inhibits** cytochrome P450 **2C19** isoform (enzyme inhibitor) it prevents the metabolism of drugs that are metabolized by 2C19 which leads to accumulation of these drugs and then toxicity -Slow & fast acetylators. (acetylating is a process of metabolism by adding acetyl group to enhance excretion of the drug، some individuals are genetically fast or slow acetylators Fast acetylators → high toxic metabolites Slow acetylators → neuropathy)	-**RIF strongly induces** most cytochrome P450 isoforms **2C19,2C9,3A4**. -Clinically significant drug interactions: warfarin, methadone will be metabolized faster. therefore their activity is reduced

Vitamin B6 is essential for neurological functions, pyridoxine is the precursor for Vitamin B6, INH inhibit pyridoxine metabolism to its active form the metabolite Vitamin B6.

1st line treatment cont...

	Ethambutol	Pyrazinamide (PZA)	Streptomycin
Overview	Bacteriostatic		Bactericidal
Site of action	intracellular & extracellular bacilli	Intracellular Bacilli	extracellular bacilli.
MOA	Inhibits mycobacterial **arabinosyl transferase**; essential **enzyme** for mycobacterial cell wall synthesis ,thus disrupts the assembly of mycobacterial cell wall.	Pyrazinamide is converted to **pyrazinoic acid (the active form)** which disrupts mycobacterial cell membrane metabolism & transport functions. Pyrazinamide is converted to its active form by the bacteria	**Inhibitor of protein synthesis** by binding to **30S** ribosomal subunit (it is an aminoglycoside, this is their mechanism of action)
Clinical use	Treatment of TB in combination with other drugs	-Mycobacterial infections mainly in multidrug resistance cases. -It is important in short course (6 months) regimen. -Prophylaxis of TB .	Injectable drug used in severe, life-threatening form of T.B. as meningitis, disseminated disease. **Reminder: should be preserved for severe cases only, never used as a first option**
ADRs	-Impaired visual acuity. -Red-green color blindness. -it is **contraindicated** in children under 5 years old.	-Hepatotoxicity (common) -Hyperuricemia (gouty arthritis) -Drug fever & skin rash	-Ototoxicity (Vertigo & hearing loss) may be permanent. -Nephrotoxicity -Neuromuscular block Paralysis of the muscles (depolarizing)

Streptomycin is added to first line regimens because patients that have previously been treated for TB are more likely to have developed some drug resistance.

2nd line treatment

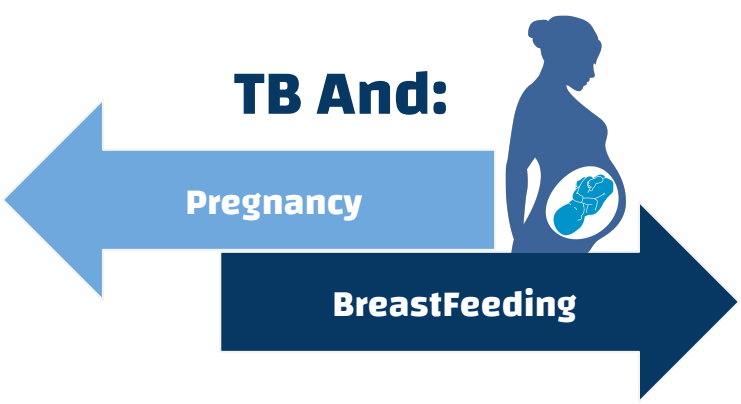
	Ethionamide	Flouro-quinolones (ciprofloxacin)	Rifabutin	Para-Aminosalicylic acid (PAS)
Over-view	-			Bacteriostatic
MOA	**Inhibit mycolic acid synthesis.** same MOA as INH	- *Fluoroquinolones are a class of antibiotics that includes Ciprofloxacin	-**RNA inhibitor**. -Cross resistance with rifampin is complete. if the patient is resistant to **rifampin** he can't take **rifabutin** because he will be resistant to it too, since both these drugs have the same MOA. -Enzyme inducer.	**Inhibits folic acid synthesis** thus slows bacterial cell growth & multiplication.
Clinical uses	2nd line treatment of TB (po). po = orally	Effective against multidrug-resistant tuberculosis.	-Effective in prevention & treatment of TB. -In prevention & treatment of atypical TB.	-As a 2nd line agent is used in the treatment of chronic pulmonary & other forms of TB. -Help to slow development of resistance to other drugs, especially INH & streptomycin.
ADRs	-Teratogenic. (deformities in the fetus) contraindication: pregnancy -poorly tolerated due to severe Gastric irritation & neurological manifestation.	-	- GIT intolerance. -Orange-red discoloration of body secretions.	-GIT upset. -Crystalluria (Cloudy urination)

-Untreated TB represents a great risk to the pregnant woman & her fetus than the treatment itself.

-First line **(INH, ethmabutol & rifampicin)** drugs are given for 9 months in normal doses.

-Streptomycin is not used. WHY? because it can cross the placenta

TB And:



It is not a contraindication to receive drugs, but caution is recommended.

QUIZ

MCQ:

1- Which of the following drugs has no harmful effect on the liver (no hepatotoxicity potential)

A-Isoniazid B-Pyrazinamide C-Ethambutol

2-Omar is a 53 year old man who visits your office with a month of productive cough, 8 kilograms of weight loss, and night sweats. You diagnose Omar with pulmonary tuberculosis (TB) and decide to initiate him on once-daily treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol. what counseling should you provide to counter potential medication adverse effects, so that he is more likely to adhere and complete therapy?

A-Advise him that he should not worry if his urine or tears turn red-orange color while on therapy
B-Tell him that his TB medications should only be taken at bedtime
C-Prescribe pyridoxine (vitamin B6) 50mg by mouth daily
D- Both A and C

3-Pyridoxine deficiency can occur due to treatment of which anti-TB drug?

A-Rifampicin B-Isoniazid C-Ethambutol

4-A 67-year-old man, recently diagnosed with pulmonary TB, is started on a treatment with antitubercular drugs. The man has been suffering from atrial fibrillation, and he is presently taking warfarin as one his drugs. At this point, which of the following changes in the therapeutic regimen of the patient would be most appropriate?

A-To increase the dose of warfarin
B-To reduce the dose of isoniazid
C-To increase the dose of rifampin
D-To stop pyrazinamide

5-A 45-year-old woman complained of blurred vision and inability to distinguish green objects from red objects. The woman, recently diagnosed with cavitary pulmonary tuberculosis, has been receiving a 4 drug combination regimen for two months. Which of the following drugs has most likely caused these adverse effects?

A-Isoniazid B-streptomycin C-Ethambutol

Q1-C Q2-D Q3-B Q4-A Q5-C

SAQ:

1-2.A 35-year-old male, formerly a heroin abuser, has been on methadone maintenance for the last 13 months. Two weeks ago, he had a positive tuberculosis skin test (PPD test), and a chest radiograph showed evidence of right upper lobe infection. He was started on standard four-drug antimycobacterial therapy. He has come to the emergency department complaining of “withdrawal symptoms.”

Q1.Which antimycobacterial drugs is likely to have caused this patient’s acute withdrawal reaction?
Q2.What is the mechanism of action of that drug?

Q3. A 42-year-old male HIV patient was recently diagnosed with active tuberculosis. Currently, he is on a stable HIV regimen consisting of two protease inhibitors and two nucleoside reverse transcriptase inhibitors (NRTIs).What is the most appropriate regimen to use for treatment of his tuberculosis?

Q4.Mention the indications of using the 2nd line drugs for TB ?

Q5.Why does the Streptomycin not used for treat a pregnant woman with TB?

Q1.Rifampin
Q2.Binds to bacterial DNA- dependent RNA polymerase enzyme & thus inhibits RNA synthesis.
Q3.Rifabutin - isoniazed - pyrazinamide - ethambutol
Q4.Resistance to the drugs of 1st line - Failure of clinical response - There is contraindication for first line drugs
Q5.Because it can pass the placenta easily and cause permanent damage in the ear and balance of the fetus

pharmacology

Team 438

GOOD LUCK

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Team 435