Pharmacology - RS

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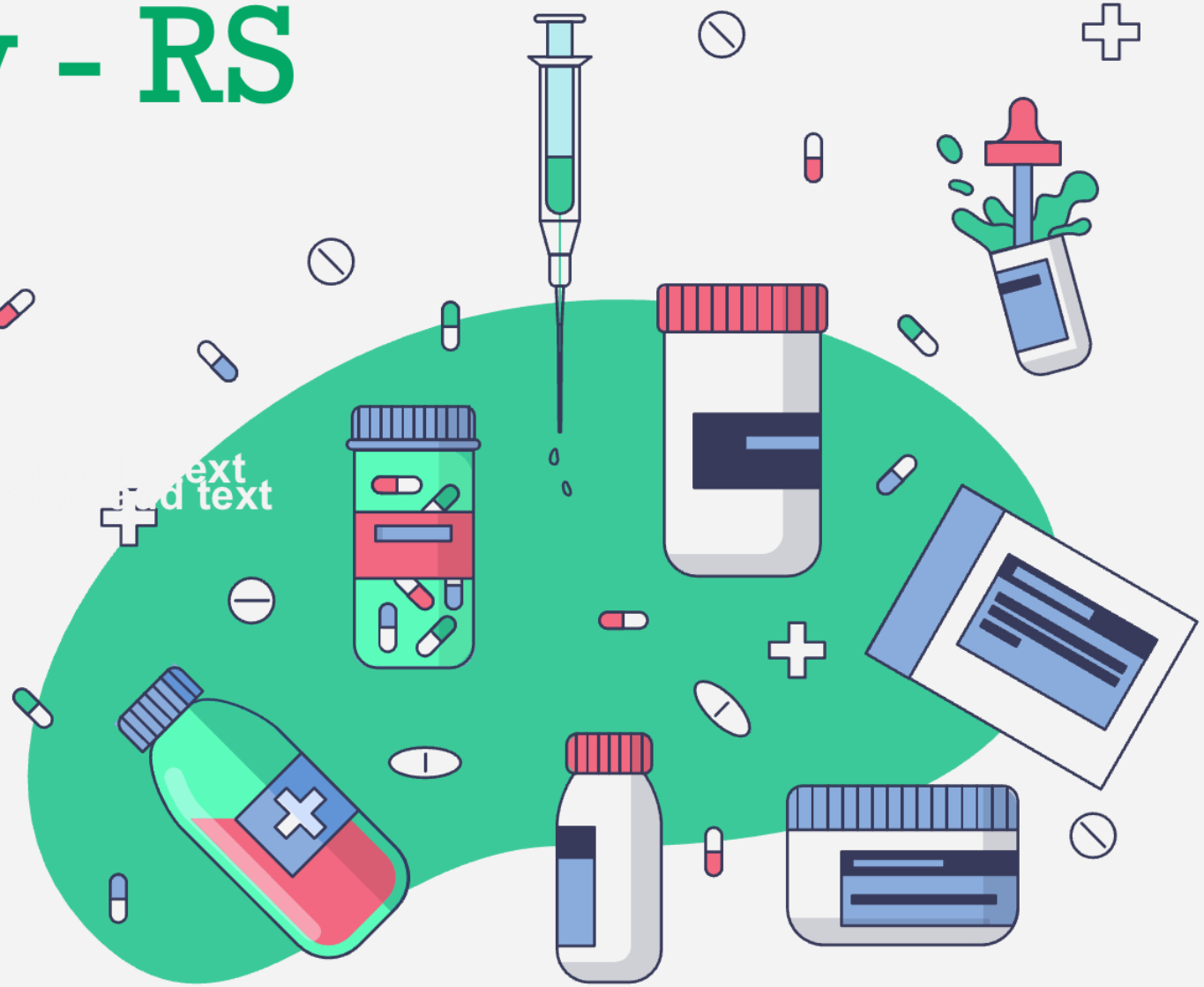

النادي الطلابي
كلية الطب

Drug Treatment of Tuberculosis

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In the past , TB was the disease of low socioeconomic status communities
Now TB also is a disease of high socioeconomic status communities

Drug Treatment of Tuberculosis

Worldwide, TB is the 13th leading cause of death and the second leading infectious killer after COVID-19 (above HIV/AIDS). In 2018, 1.7 billion people were infected by TB bacteria.

TB disappeared in the past then came back

Recommended Duration of Therapy

Regimen (in Approximate Order of Preference)	Duration in Months
Isoniazid, rifampin, pyrazinamide	6
Isoniazid, rifampin	9
Rifampin, ethambutol, pyrazinamide	6
Rifampin, ethambutol	12
Isoniazid, ethambutol	18
All others	≥24

مش للحفظ بس اعرفو انو العلاج بوخد وقت طويل

The most characteristic point in the therapy of TB is the need for prolonged and combination treatment

Antituberculous Agents

Primary or First Line Drugs:

Isoniazid (INH)

Rifampin "Rifadin" or "Rimactane"

Ethambutal

Pyrazinamide

Streptomycin: in patients that have previously been treated for TB.

Why these drugs are considered as primary or first line drugs?
Because these drugs are easier to use and less toxic

Streptomycin: The first effective drug which was used in the treatment of TB in 1943.
Then they stopped using it and classified as secondary line drug ,but they use it as first line drug only if the patient have previously been treated for TB

Isoniazid(INH)

Iso-nicotinic acid hydrazide

- **Most active.**
- **Small molecule, water soluble,** Easily absorbed
- **Structurally related to Pyridoxine.** Vitamin B6

Cause vitamin B6 deficiency

- **Prodrug, activated by KatG(the mycobacterial catalase-peroxidase).**

Prodrug in the human body , when it reaches the mycobacterium it will convert into its active form by KatG (⬇️ toxicity)

- **Blocks mycolic acid synthesis, and consequently mycobacterial cell wall synthesis, leading to a bactericidal effect in growing TB cells.** Specific

Isoniazid (INH)

- **When used alone, resistance is 1 in $10^{6.}$**
- **A TB lesion usually contains more than 10^{8} cells.**
- **When used in combination, the probability of resistance will be 1 in $10^{6} * 10^{6} = 10^{12.}$**

The resistance neglected

- **Readily absorbed**
- **Widely distributed, penetrates into macrophages.**

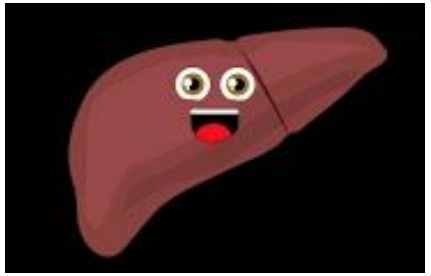
Good pharmacokinetic properties

- **Metabolized by acetylation:**
  - **Slow and Fast Acetylators**

✓ Acetylation is genetically determined
✓ People are divided into slow acetylators or rapid acetylators

✓ Acetylation takes place in the liver the drug is not metabolized by cyt P-450

If you are interested to know how the liver looks like



Isoniazid(INH)

- **Adverse Reactions:**

Hepatitis: in about 1% Especially in the fast acetylators

Anorexia, N (nausea)**,V** (vomiting) **,jaundice, pain, death.**

Depends on age, alcohol use, and pregnancy The healthiness of the liver

Neuropathy:10-20%

More in slow acetylators, malnutrition, alcoholism, DM, AIDS,uremia.

Due to pyridoxine deficiency. To prevent this side effect we give the patient supplemental pyridoxine doses.

Neurotoxicity: Memory loss, Psychosis, Seizures.

Hematologic, Tinnitus, GIT, Interactions

Drugs interactions

Neuropathy: peripheral neuropathy
Neurotoxicity: is central neurotoxicity

Usually these side effects & toxicities are tolerable and could be corrected, if we compare the benefits versus the risks of treatment with the INH, the patient should take INH as it's the most effective

Rifampin

Antibiotic derived from :

- ***Stretomyces miditerranei.***
- **Gram+ve and –ve** Wide spectrum antibiotic
- **Mycobacteria, enterococci and chlamydia.**
- **Binds to the beta subunit of bacterial DNA-dependant RNA polymerase and therefore inhibits RNA synthesis.**

The wide use of rifampin increased the resistance of the TB

Nowadays its use is limited to the treatment of TB

Rifampin

- **Bactericidal**
- **Well absorbed, highly bound to proteins.**
- **Widely distributed.**
- **Hepatic metabolism and exhibits enterohepatic recirculation.**

Very good pharmacokinetic properties

Uses of Rifampin

- **TB**
- **Leprosy**

الجذام
ما بقتل بس بشوه المريض (بعلم عليه)🔪

- **Meningococcal Carrier State**
- **Prophylaxis in *H.influenzae*.**
- **Serious Staph osteomyelitis and valve endocarditis.**
- **Was *loosely used in the treatment of Staph infections*.**

In the past

Toxicity of Rifampin

- **Imparts harmless orange color to secretions(tears, urine, sweat).**
- **Nephritis**
- **Rashes**
- **Hepatitis**
- **Flu-like syndrome**
- **Liver Enzyme Inducer, so can lower serum levels of many drugs**

Interferes with the metabolism of other drugs metabolized in the liver

Streptomycin

It's the first aminoglycoside antibiotic

Gentamycin—aminoglycoside (for urinary tract) – resistant staphylococcus

- **First aminoglycoside antibiotic, 1943.**
- **Primary---Second-line------ Primary anti-tuberculus agent.**
- **Plague, Tuleremia (حمى الأرانب), Brucellosis.**
- **Endocarditis.** (الحمى المالطية)

Toxic: Givin by injection every day for 6-9 months

Allergy: Fever, Rashes

Pain, after i.m. injection.

Vestibular toxicity---- Irreversible.

Hearing loss (very famous in cause hearing loss, irreversible even if the drug is stopped)

Nephrotoxicity

Renal failure (very common in gentamicin than hearing loss)

Antituberculous Agents

Secondary or Second Line Drugs:

- Ethionamide
- Capreomycin
- Cycloserine
- Para-Amino-Salicylic Acid (PAS)
- Amikacin
- Flouroquinolones
- Linezolid
- Rifabutin
- Rifapentine

Indications for Secondary or Second Line Drugs

- **1. Resistance to first –line drugs.**
- **2. Failure of clinical response to conventional therapy.**
- **3. Occurrence of serious treatment-limiting adverse drug reactions.**
- **4. When expert guidance is available to deal with the toxic effects to second line drugs.**

Secondary or Second Line Drugs

Ethionamide:

Related to Isoniazid

Blocks mycolic acid synthesis

Oral, Good distribution

Poorly tolerated:

- **Severe GIT irritation**
- **Neurotoxic**
- **Hepatotoxic**

Secondary or Second Line Drugs

Capreomycin: Antibiotic

Peptide protein synthesis inhibitor

Injectable

Nephrotoxic, ototoxic

Local pain and sterile abscesses may occur.

Secondary or Second Line Drugs

Cycloserine:

Inhibits cell wall synthesis.

Peripheral neuropathy and CNS toxicity including depression and psychotic reactions.

Secondary or Second Line Drugs

Para-Amino-Salicylic Acid (PAS):

Folate synthesis antagonist

Causes folic acid deficiency

Well absorbed

Dose 8-12 gm/day, *Too large !!!*

Widely distributed, except CNS

Excreted in urine.

GI toxicity

Hypersensitivity reactions

Crystalluria

Renal stones

The compliance الالتزام بالعلاج of the patient is essential

It was thought that the treatment of TB is pure oxygen & good nutrition

معلومات ما بتهمكم :
مستشفى البشير كان زمان مستشفى خاص بمرض السل بس فكان اسمه مستشفى السل
سموه البشير نسبة ل وزير الصحة البشير اللي مات مع الملكة علياء الله يرحمهم

Secondary or Second Line Drugs

- **Amikacin:**

Another aminoglycoside antibiotic.

Multidrug-resistant strains

Atypical mycobacteria

Secondary or Second Line Drugs

- **Flouroquinolones:**

Are an important addition New drugs relatively

Resistance develops rapidly if used alone.

In TB treatments , if we use one or two drugs only –resistance develops very rapidly

Secondary or Second Line Drugs

Linezolid:

Multidrug-resistant strains.

Bone marrow suppression

Irreversible peripheral and optic neuropathy.

Drug of last resort

Rifabutin

Rifapentine

Related to Rifampin.

Inhibit bacterial RNA polymerase.

Both, like Rifampin, are inducers for CYP P450 enzymes. But Rifabutin is less potent inducer.

Rifabutin is indicated in place of Rifampin in the treatment of TB in HIV-infected patients receiving protease inhibitor or nonnucleoside reverse transcriptase inhibitor (e.g. efavirenz)

Drug-Resistant TB (3)

Mono-resistant	Resistant to any one TB treatment drug
Poly-resistant	Resistant to at least any 2 TB drugs (but not both isoniazid and rifampin)
Multidrug resistant (MDR TB)	Resistant to at least isoniazid and rifampin, the 2 best first-line TB treatment drugs
Extensively drug resistant (XDR TB)	Resistant to isoniazid and rifampin, PLUS resistant to any fluoroquinolone AND at least 1 of the 3 injectable second-line drugs (e.g., amikacin, kanamycin, or capreomycin)

احفظوه سهل
الدكتور قرأه كامل

Dr read the whole table

- Annually, 9 million cases are recorded.
- 5% of these are multi drug-resistant tuberculosis.
- Forty-nine percent of those with XDR-TB died compared to 19 percent of patients with ordinary MDR-TB,

Nowadays it might take two years to be treated

ممكن يمتد العلاج لسنتين
هي أهم معلومة من هي السلايد

الدكتور قرأه بس
واضحة يعني

الدكتور بقلكم سامحونا عالتقصير
يخلف عليكم كثر الله خيركم

اخر فارما لهاي الفصل
ادعولنا + موفقين...