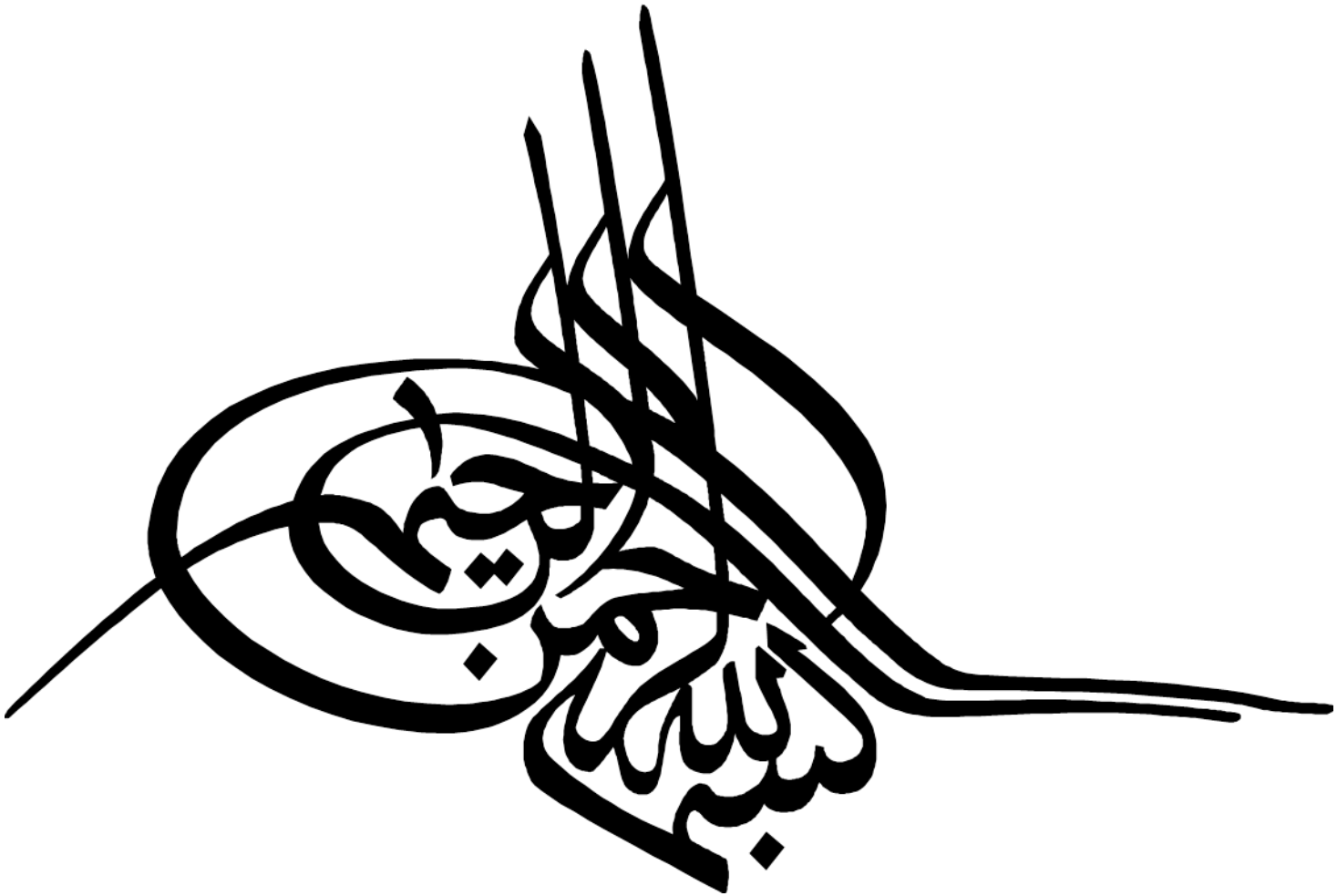
بسم الله الرحمن الرحيم

ANTITUBERCULOSIS DRUGS ADVERSE EFFECTS

Ali Hossein Samadi MD.
Assistant Professor of Internal Medicine(Pulmonologist)
Ardabil University of Medical Science

FIRST-LINE ANTITUBERCULOSIS DRUGS

✓ Isoniazid

- Isoniazid is a critical drug for treatment of both TB disease and LTBI.
- Isoniazid has excellent bactericidal activity against both intracellular and extracellular, actively dividing M. tuberculosis.
- Isoniazid does not require dosage adjustment in patients with renal disease.
- The recommended daily dose of isoniazid for the treatment of TB in the United States is 5 mg/kg for adults and 10–20 mg/kg for children, with a maximal daily dose of 300 mg for both.

- Although isoniazid is generally well tolerated, drug-induced liver injury and peripheral neuropathy are significant adverse effects associated with this agent.

- Isoniazid may cause asymptomatic transient elevation of aminotransferase levels (often termed hepatic adaptation) in up to 20% of recipients.

- Other adverse reactions include rash (2%), fever (1.2%), anemia, acne, arthritic symptoms, a systemic lupus erythematosus–like syndrome, optic atrophy, seizures, and psychiatric symptoms.

- Symptomatic hepatitis occurs in fewer than 0.1% of persons treated with isoniazid alone for LTBI, and fulminant hepatitis with hepatic failure occurs in fewer than 0.01%.

- Isoniazid- associated hepatitis is idiosyncratic, but its incidence increases with age, with daily alcohol consumption, and in women who are within 3 months postpartum.

- In patients who have liver disorders or HIV infection, who are pregnant or in the 3-month postpartum period, who have a history of liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cirrhosis), who use alcohol regularly, who have multiple medical problems, or who have other risk factors for chronic liver disease, the risks and benefits of treatment for LTBI should be weighed.

- If treatment is undertaken, these patients should have serum concentrations of ALT determined at baseline.

- Routine baseline hepatic ALT testing based solely on an age of >35 years is optional and depends on individual concerns.

- Monthly biochemical monitoring during isoniazid treatment is indicated for patients whose baseline liver function tests yield abnormal results and for persons at risk for hepatic disease, including the groups just mentioned.

- ✓ Guidelines recommend that isoniazid be discontinued in the presence of hepatitis symptoms or jaundice and an ALT level three times the upper limit of normal or in the absence of symptoms with an ALT level five times the upper limit of normal.

- Peripheral neuropathy associated with isoniazid occurs in up to 2% of patients given 5 mg/kg.
- Isoniazid appears to interfere with pyridoxine (vitamin B6) metabolism.
- The risk of isoniazid-related neurotoxicity is greatest for patients with preexisting disorders that also pose a risk of neuropathy, such as HIV infection; for those with diabetes mellitus, alcohol abuse, or malnutrition; and for those simultaneously receiving other potentially neuropathic medications, such as stavudine.
- These patients should be given prophylactic pyridoxine (25–50 mg/d).

✓ Rifampin

- The most active antimycobacterial agent available, rifampin is the keystone of first-line treatment for TB.

- The drug is also active against an array of other organisms, including some gram-positive and gram-negative bacteria, Legionella, M. kansasii, and Mycobacterium marinum.

- Rifampin is excreted primarily through the bile and enters the enterohepatic circulation; <30% of a dose is renally excreted.

- The daily dosage of rifampin is 10 mg/kg for adults and 10–20 mg/kg for children, with a maximum of 600 mg/d for both.

- No adjustments of dose or frequency are necessary in patients with renal insufficiency.

- Adverse events associated with rifampin are infrequent and generally mild.

- Hepatotoxicity due to rifampin alone is uncommon in the absence of preexisting liver disease and often consists of isolated hyperbilirubinemia rather than aminotransferase elevation.

- Other adverse reactions include rash, pruritus, gastrointestinal symptoms, and pancytopenia.

- Rarely, a hypersensitivity reaction may occur with intermittent therapy, manifesting as fever, chills, malaise, rash, and—in some instances—renal and hepatic failure.

✓ Ethambutol

- Ethambutol is a bacteriostatic antimycobacterial agent first synthesized in 1961.
- A component of the standard first-line regimen, ethambutol provides synergy with the other drugs in the regimen and is generally well tolerated.
- Among first-line drugs, ethambutol is the least potent against M. tuberculosis.

- Serum levels peak at 2–4 μg/mL after the standard adult daily dose of 15 mg/kg.
- Ethambutol is well distributed throughout the body except in the CSF.
- To prevent toxicity, the dosage must be lowered and the frequency of administration reduced for patients with renal insufficiency.
- Ethambutol is usually well tolerated and has no significant interactions with other drugs.

- Optic neuritis, the most serious adverse effect reported, typically presents as reduced visual acuity, central scotoma, and loss of the ability to see green (or, less commonly, red).

- The cause of this neuritis is unknown, but it may be due to an effect of ethambutol on the amacrine and bipolar cells of the retina.

- Symptoms typically develop several months after initiation of therapy, but ocular toxicity soon after initiation of ethambutol has been described.

- The risk of ocular toxicity is dose dependent, with occurrence in 1–5% of patients, and can be increased by renal insufficiency.

- The routine use of ethambutol in younger children is not recommended because monitoring for visual complications can be difficult. If drug-resistant TB is suspected, ethambutol can be used for treatment of children.

- All patients starting therapy with ethambutol should have a baseline test for visual acuity, visual fields, and color vision and should undergo an examination of the optic fundus.

- Visual acuity and color vision should be monitored monthly or less often as needed.

- Cessation of ethambutol in response to early symptoms of ocular toxicity usually results in reversal of the deficit within several months. Recovery of all visual function may take up to 1 year.

- In the elderly and in patients whose symptoms are not recognized early, deficits may be permanent.
- Some experts think that supplementation with hydroxycobalamin (vitamin B12) is beneficial for patients with ethambutol-related ocular toxicity.
- Other adverse effects of ethambutol are rare.
- Peripheral sensory neuropathy occurs in rare instances.

✓ Pyrazinamide

- Pyrazinamide is an important bactericidal drug used in the initial phase of TB treatment.

- Its administration for the first 2 months of therapy with rifampin and isoniazid allows treatment duration to be shortened from 9 to 6 months and decreases rates of relapse.

- This agent is active only in acidic environments (pH <6.0), as are found within phagocytes or granulomas.

- Pyrazinamide is well absorbed after oral administration, with peak serum concentrations of 20–60 μg/mL at 1–2 h after ingestion of the recommended adult daily dose of 15–30 mg/kg (maximum, 2 g/d).

- It distributes well to various body compartments, including CSF, and is an important component of treatment for tuberculous meningitis.

- Pyrazinamide is metabolized in the liver. A high proportion of pyrazinamide and its metabolites (~70%) is excreted in the urine. The dosage must be adjusted according to the level of renal function in patients with reduced creatinine clearance.

- At the higher dosages used previously, hepatotoxicity was seen in as many as 15% of patients treated with pyrazinamide.

- However, at the currently recommended dosages, hepatotoxicity now occurs less commonly when this drug is administered with isoniazid and rifampin during the treatment of TB.

- Older age, active liver disease, HIV infection, and low albumin levels may increase the risk of hepatotoxicity.

- Hyperuricemia is a common adverse effect of pyrazinamide therapy that usually can be managed conservatively.
- Clinical gout is rare.
- Although pyrazinamide is recommended by international TB organizations for routine use in pregnancy, it is not recommended in the United States because of inadequate teratogenicity data.

- OTHER FIRST-LINE DRUGS

✓ Rifabutin

- Rifabutin is recommended in place of rifampin for the treatment of TB in HIV-co- infected individuals who are taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors, particularly nevirapine.
- Rifabutin's effect on hepatic enzyme induction is less pronounced than that of rifampin.
- Unlike rifampin, rifabutin and its metabolites are partially cleared by the hepatic microsomal system. Rifabutin's slow clearance results in a mean serum half-life of 45 h— much longer than the 3- to 5-h half-life of rifampin.

- The most common adverse effects of rifabutin treatment are gastrointestinal; other reactions include rash, headache, asthenia, chest pain, myalgia, and insomnia.

- Less common adverse reactions include fever, chills, a flu-like syndrome, anterior uveitis, hepatitis, Clostridium difficile–associated diarrhea, a diffuse polymyalgia syndrome, and yellow skin discoloration ("pseudo-jaundice").

- Laboratory abnormalities include neutropenia, leukopenia, thrombocytopenia, and increased levels of liver enzymes.

✓ Rifapentine

- Currently, it is an alternative to rifampin in the continuation phase of treatment for noncavitary drug-susceptible pulmonary TB in HIV-seronegative patients who have negative sputum smears at completion of the initial phase of treatment.
- Because of higher rates of relapse, this regimen is not recommended for patients with TB disease and HIV co-infection; moreover, it has not been approved for children <12 years of age.
- The adverse-effects profile of rifapentine is similar to that of other rifamycins. Rifapentine is teratogenic in animal models and is relatively contraindicated in pregnancy.

✓ Streptomycin

- Streptomycin was the first antimycobacterial agent used for the treatment of TB.
- Streptomycin is bactericidal against dividing M. tuberculosis organisms but has only low-level early bactericidal activity. This drug is administered only by the IM and IV routes.
- This agent penetrates poorly into the CSF, reaching levels that are only 20% of serum levels.
- The usual daily dose of streptomycin (given IM either daily or 5 days per week) is 15 mg/kg for adults and 20–40 mg/kg for children, with a maximum of 1 g/d for both.

- For patients ≥60 years of age, 10 mg/kg is the recommended daily dose, with a maximum of 750 mg/d.

- Because streptomycin is eliminated almost exclusively by the kidneys, its use in patients with renal impairment should be avoided or implemented with caution, with lower doses and less frequent administration.

- Adverse reactions occur frequently with streptomycin (10–20% of patients). Ototoxicity (primarily vestibulotoxicity), neuropathy, and renal toxicity are the most common and the most serious reactions.
- Renal toxicity, usually manifested as nonoliguric renal failure, is less common with streptomycin than with other frequently used aminoglycosides, such as gentamicin.
- Manifestations of vestibular toxicity include loss of balance, vertigo, and tinnitus.
- Patients receiving streptomycin must be monitored carefully for these adverse effects, undergoing audiometry at baseline and monthly thereafter.

- SECOND-LINE ANTITUBERCULOSIS DRUGS

✓ Fluoroquinolones

- A single randomized trial showed that a regimen of daily moxifloxacin/rifampin/ pyrazinamide/ethambutol for 2 months followed by once-weekly 1200 mg rifapentine plus 400 mg of moxifloxacin for 4 continuation-phase months was associated with relapse rates similar to those documented with the standard 6-month regimen given daily in patients with drug sensitive TB.
- Gatifloxacin has fallen out of favor because of significant dysglycemia.
- Ciprofloxacin and ofloxacin are no longer recommended for the treatment of TB because of poor efficacy

- Despite documented resistance to early-generation fluoroquinolones (e.g., ofloxacin and ciprofloxacin), use of a later-generation fluoroquinolone in patients with XDR-TB has been associated with favorable outcomes.

- Levofloxacin and moxifloxacin have both been used effectively in the treatment of MDR-TB.

- The optimal dose of levofloxacin for this indication is being actively studied, but doses of at least 750 mg are commonly used.

- Adverse effects are relatively infrequent (0.5–10% of patients) and include gastrointestinal intolerance, rashes, dizziness, and headache.

- Although the potential to prolong the QTc interval, leading to cardiac arrhythmias, has been a source of concern with fluoroquinolones, cessation of treatment due to this adverse effect is rare.

- Because the benefits may outweigh the risks in treatment of drug-resistant TB, there is increasing interest in the use of fluoroquinolones in children, which has traditionally been avoided because of the risks of tendon rupture and cartilage damage.

✓ CAPREOMYCIN

- Capreomycin is administered by the IM route; an inhaled preparation is under study. A dose of 15 mg/kg per day is given five to seven times per week (maximal daily dose, 1 g) and results in peak blood levels of 20–40 µg/mL.
- For patients with renal insufficiency, the drug should be given intermittently and at lower dosage (12–15 mg/kg two or three times per week).
- A minimal duration of 3 months is recommended for MDR-TB treatment. Penetration of capreomycin into the CSF is believed to be poor.

- Adverse effects of capreomycin are relatively common. Significant hypokalemia and hypomagnesemia as well as oto- and renal toxicity have been reported.

✓ AMIKACIN AND KANAMYCIN

- Amikacin and kanamycin are aminoglycosides that exert mycobactericidal activity by binding to the 16S ribosomal subunit.

- Although amikacin is highly active against M. tuberculosis, it is used only infrequently because of its significant side effects.

- The usual daily adult dosage of both amikacin and kanamycin is 15–30 mg/kg given IM or IV (maximal daily dose, 1 g), with a reduction to 10 mg/kg for patients ≥60 years old.

- Adverse effects of amikacin include ototoxicity (in up to 10% of recipients, with auditory dysfunction occurring more commonly than vestibulotoxicity), nephrotoxicity, and neurotoxicity.

- Kanamycin has a similar side-effects profile, but adverse reactions are thought to be less frequent and less severe.

✓ ETHIONAMIDE

- Ethionamide is bacteriostatic against metabolically active M. tuberculosis and some NTM.

- It is used in the treatment of drug-resistant TB, but its use is limited by severe gastrointestinal reactions (including abdominal pain, nausea, and vomiting) as well as significant central and peripheral neurologic side effects, reversible hepatitis (in ~5% of recipients), hypersensitivity reactions, and hypothyroidism.

- Ethionamide should be taken with food to reduce gastrointestinal effects and with pyridoxine (50–100 mg/d) to limit neuropathic side effects.

✓ CYCLOSERINE

- Cycloserine is well absorbed after oral administration and is widely distributed throughout body fluids, including CSF.
- The usual adult dosage is 250 mg two or three times per day.
- Serious potential side effects include seizures and psychosis (with suicide in some cases), peripheral neuropathy, headache, somnolence, and allergic reactions.
- Drug levels are monitored to achieve optimal dosing and to reduce the risk of adverse effects, especially in patients with renal failure.

✓ PARA-AMINOSALICYLIC ACID

- Para-aminosalicylic acid (PAS, 4- aminosalicylic acid) is an oral agent used in the treatment of MDR-TB and XDR-TB.
- Its bacteriostatic activity is due to inhibition of folate synthesis and of iron uptake. PAS has relatively little activity as an anti-TB agent.
- Adverse effects may include high-level nausea, vomiting, and diarrhea. PAS may cause hemolysis in patients with glucose-6- phosphate dehydrogenase deficiency.
- The drug should be taken with acidic foods to improve absorption. Enteric-coated PAS granules (4 g orally every 8 h) appear to be better tolerated.

✓ CLOFAZIMINE

- Clofazimine is a fat-soluble riminophenazine dye used primarily in the treatment of leprosy worldwide.
- It is currently gaining popularity in the management of MDR-TB and XDR-TB because of its low cost and its intracellular and extracellular activity.
- Common side effects include gastrointestinal intolerance, and reversible orange to brownish discoloration of skin, bodily fluids, and secretions.
- Dose adjustment may be necessary in patients with severe hepatic impairment.


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