Anti-tuberculosis drug Information

1 E-learning objectives

This module is intended to:

- Increase student's knowledge on the most important anti-tuberculosis drugs used in Pavia Countries (both first and second line drugs)
- provide a detailed description of each of the drugs listed, informing the reader about their mechanisms of action, their side effects and their use in pregnancy and breastfeeding.

2. Introduction

This platform offers you 22 online flashcards on anti-tuberculosis drugs (first and second line). It is an easy and effective way to learn essential information about these drugs.

Each card includes

- Mechanism of action of the drug
- Main Side effects
- Contraindications
- Main contraindicated or major Drug interactions with Antiretroviral therapy
- Use in Pregnancy
- Use in Breastfeeding

3 FIRST-LINE ANTI-TB MEDICATIONS

First line are more effective than second line medications. The drug resistance is the main problem.

Antimycobacterials

This drug class includes: isoniazid, pyrazinamide, rifampin and ethambutol

4 ISONIAZID

Mechanism of action

Systemic: Isoniazid is a synthetic, bactericidal antitubercular agent that is active against many mycobacteria, primarily those that are actively dividing. Its exact mechanism of action is not known, but it may relate to inhibition of mycolic acid synthesis and disruption of the cell wall of the susceptible organisms.

Main Side effects

Common

- ✓ **Hepatic:** Increased liver enzymes (10% to 20%) (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Neurologic:** Neuropathy (20%), Neurotoxicity (see Main anti-tuberculosis drugs ADR symptoms and their management)

Serious

- ✓ **Dermatologic:** Rash
- ✓ **Hematologic:** Agranulocytosis, Anemia, Thrombocytopenia
- ✓ **Hepatic:** Hepatitis (Severe), Hepatotoxicity (which is age-dependent (0.3% in 21 to 35 year olds and over 2% in those over age 50), Injury of liver)
- ✓ **Immunologic:** Systemic lupus erythematosus
- ✓ **Musculoskeletal:** Rhabdomyolysis
- ✓ **Neurologic:** Seizure (see Main anti-tuberculosis drugs ADR symptoms and their management)

Contraindications

The drug is controindicate in patients with:

- ✓ Acute liver disease
- ✓ History of severe adverse reactions to isoniazid such as drug fever, chills, or arthritis
- ✓ History of isoniazid associated hepatic injury or drug induced liver injury
- ✓ Severe hypersensitivity to isoniazid

Main contraindicated or Major Drug interactions with Antiretroviral therapy in HIV-infected patients

No contraindicated or major interactions

Pregnancy

U.S. Food and Drug Administration's Pregnancy Category: Category C (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

Maternal medication usually compatible with breastfeeding.

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5 PYRAZINAMIDE

Mechanism of action

Pyrazinamide, a nicotinamide analogue, is an antituberculous agent. It may be bacteriostatic or bactericidal, depending on the concentration and the susceptibility of the organism, although the exact mechanism is unknown. It is active in vitro at an acidic pH of 5.6 or less, similar to that found in early, active tubercular inflammatory lesions

Main Side effects

Common

- ✓ **Endocrine metabolic**: Hyperuricemia
- ✓ **Gastrointestinal**: Nausea, Vomiting (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Musculoskeletal**: Arthralgia (40%) (see Main anti-tuberculosis drugs ADR symptoms and their management)

Serious

- ✓ **Hematologic**: Anemia (rare)
- ✓ **Hepatic**: Hepatotoxicity: pyrazinamide is one of the most common cause of drug-induced hepatitis (see Main anti-tuberculosis drugs ADR symptoms and their management)

Contraindications

The drug is controindicate in patients with:

- ✓ acute gout
- ✓ severe hepatic damage
- ✓ hypersensitivity to pyrazinamide

Main contraindicated or Major Drug interactions with Antiretroviral therapy in HIV-infected patients

Major

Concurrent use of PYRAZINAMIDE and ZIDOVUDINE may result in decreased efficacy of pyrazinamide.

Pregnancy

Pyrazinamide is rated as US FDA Category C (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

Infant risk cannot be ruled out. Weigh the potential benefits of treatment against potential risks before prescribing pyrazinamide during breast-feeding

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6 RIFAMPIN

Mechanism of action

Systemic: Rifampin, a semisynthetic broad-spectrum bactericidal antibiotic, inhibits bacterial RNA synthesis by binding strongly to the beta subunit of DNA-dependent RNA polymerase, preventing attachment of the enzyme to DNA, and thus blocking initiation of RNA transcription.

Main Side effects

Serious

- ✓ **Hematologic**: Agranulocytosis, Disseminated intravascular coagulation
- ✓ **Hepatic**: Hepatotoxicity (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Immunologic**: Anaphylaxis, Drug reaction with eosinophilia and systemic symptoms, Hypersensitivity reaction
- ✓ **Renal**: Nephrotoxicity, Renal failure (see Main anti-tuberculosis drugs ADR symptoms and their management)

Strange effect

- ✓ **Renal**: orange-red in discoloration of urine, sweat, and tears (benign side effect)

Contraindications

- ✓ concomitant use with atazanavir, darunavir, fosamprenavir, saquinavir (unboosted or ritonavir-boosted), or tipranavir
- ✓ concomitant use with rilpivirine or elvitegravir/cobicistat
- ✓ hypersensitivity to rifampin, any component of the product, or any of the rifamycins
- ✓ Concomitant use with praziquantel or within 4 weeks prior to praziquantel use; may restart rifampin 1 day after end of praziquantel treatment

Main contraindicated or Major Drug- drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

It is one of the most powerful known inducer of the hepatic cytochrome P450 system (including isoenzymes CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, CYP3A5 and CYP3A7)

Rifampin increases metabolism of many drugs, making them less effective, or even ineffective.

Contraindicated DDI

Concurrent use of LOPINAVIR/RITONAVIR, RILPIVIRINE, SAQUINAVIR, ATAZANAVIR, FOSAMPRENAVIR, AMPRENAVIR, NELFINAVIR, DARUNAVIR, ELVITEGRAVIR RITONAVIR, TIPRANAVIR AND RIFAMPIN may result in their decreased plasma concentrations and possibile loss or their efficacy.

Major:

- ✓ Concurrent use of NEVIRAPINE, DOLUTEGRAVIR, INDINAVIR, DELAVIRDINE, EFAVIRENZ and RIFAMPIN may result in their decreased serum concentrations and possible loss of their efficacy.

Pregnancy

No US FDA rating is available for rifampin

Breastfeeding

Rifampin is compatible with breast-feeding.

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7 ETHAMBUTOL

Mechanism of action

Ethambutol hydrochloride is an antibacterial agent which specifically targets Mycobacteria tuberculosis. It impairs cell metabolism and cell multiplication eventually leading to cell death.

Main Side effects

Serious

- ✓ **Hepatic**: Hepatotoxicity (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Immunologic**: Anaphylaxis, Hypersensitivity reaction
- ✓ **Ophthalmic**: Optic neuritis

Contraindications

The drug is controindicate in patients with:

- ✓ Hypersensitivity to ethambutol hydrochloride
- ✓ Inability to appreciate and report visual side effects or changes in vision (eg, young children or unconscious patients)
- ✓ Optic neuritis, unless clinical judgment determines that it may be used

Main contraindicated or Major Drug interactions with Antiretroviral ther py in HIV-infected p a t i e n t s

No contraindicated or major interactions

Pregnancy

Ethambutol is rated as US FDA Category C (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

It is compatible with breast-feeding.

8 KEY-POINTS

First line drugs are: isoniazid, pyrazinamide, rifampin and ethambutol

- ✓ **First line drugs are more effective than second line medications.**
- ✓ **The drug resistance is the main problem.**
- ✓ **Pyrazinamide is one of the most common cause of drug-induced hepatitis**
- ✓ **A common first –line drug-effect is hepatotoxicity**

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9 SECOND-LINE ANTI-TB MEDICATIONS

Second line medications are more toxic than the first line medications.

10 ANTIINFECTIVES FOR SYSTEMIC USE (INJECTABLES)

The aminoglycosides bacteriocidal antibiotic (Km, Amk, Cm, Sm) are active in vitro against M. tuberculosis and represent a critical component in treatment regimens during the initial phase of therapy. All of the injectable agents have potential for renal toxicity. Ototoxicity and vestibular toxicity are more common with Am than Km. This drug class includes: amikacin, capreomycin, kanamycin, streptomycin

11 AMIKACIN

Mechanism of action

Amikacin sulfate is an aminoglycoside active against susceptible gram-negative pathogens as well as gram-positive bacteria like penicillinase and nonpenicillinase-producing Staphylococcus species including methicillin-resistant strains. It exhibits synergism against gram-negative bacteria when it is combined with a beta-lactam antibiotic. High cross-resistance with kanamycin.

Main Side effects

Serious

- ✓ **Neurologic:** Neuromuscular blockade finding
- ✓ **Otic:** Ototoxicity (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Renal:** Nephrotoxicity (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Respiratory:** Respiratory tract paralysis

Contraindications

The drug is controindicate in patients with:

Hypersensitivity to amikacin or other aminoglycosides

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

No contraindicated or major interactions

Pregnancy

Amikacin is rated as US FDA Category D. (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

Infant risk cannot be ruled out. Weigh the potential benefits of treatment against potential risks before prescribing amikacin during breast-feeding.

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12 CAPREOMYCIN

Mechanism of action

Capreomycin is a cyclic polypeptide antimicrobial. The mechanism of action of capreomycin is not well understood. Mycobacterial species that have become resistant to other agents are usually still sensitive to the action of capreomycin. However, significant cross-resistance with viomycin, kanamycin, and neomycin occurs.

Main Side effects

Common

- ✓ **Hematologic**: Drug-induced eosinophilia
- ✓ **Otic**: Ototoxicity (3% apparent; 11% subclinical) (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Renal**: Serum blood urea nitrogen raised (36%

Serious

- ✓ **Endocrine metabolic**: Electrolytes abnormal
- ✓ **Neurologic**: Injury of acoustic nerve
- ✓ **Renal**: Injury of kidney, Tubular necrosis, acute (see Main anti-tuberculosis drugs ADR symptoms and their management) (if you want to receive more information, _MORE)

Contraindications

The drug is controindicate in patients with:

hypersensitivity to capreomycin

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

No contraindicated or major interactions

Pregnancy

Capreomycin is rated as US FDA Category C (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

Infant risk cannot be ruled out. Weigh the potential benefits of treatment against potential risks before prescribing capreomycin during breast-feeding.

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13 KANAMYCIN

Mechanism of action

Kanamycin is an aminoglycoside similar in structure to streptomycin and neomycin, which is isolated from Streptomyces kanamyceticus. Kanamycin "irreversibly" bind to specific 30S-subunit proteins and 16S rRNA.

Main Side effects

- ✓ **Gastrointestinal effects**: nausea, vomito, diarrhea, malabsorption syndrome (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Immunologic effects**: Cross sensitivity reaction
- ✓ **Muscoloskeletal effect:** myastenia gravis
- ✓ **Neurologic effects:** headache, nervousness, restlessness, paresthesias and blurring of vision
- ✓ **Otic:** Ototoxicity (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Renal effects:** Nephrotoxicity (see Main anti-tuberculosis drugs ADR symptoms and their management) (if you want to receive more information, more)
- ✓ **Respiratory effects:** respiratory insufficiency

Contraindications

The drug is controindicate in patients with:

- ✓ Hypersensitivity to kanamycin or other aminoglycosides
- ✓ Patients with intestinal obstructions

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

No contraindicated or major interactions

Pregnancy

Kanamycin is rated as US FDA Category D. (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

Kanamycin is compatible with breast-feeding.

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14 STREPTOMYCIN

Mechanism of action

Streptomycin sulfate is an aminoglycoside antibiotic that exhibits its bactericidal action by inhibiting normal bacterial protein synthesis. It is derived from Streptomyces griseus and is effective against most strains of bacteria including Brucella, Calymmatobacterium, E. coli, Haemophilus and Mycobacterium.

Main Side effects

Common

- ✓ **Dermatologic**: Rash, Urticaria
- ✓ **Hematologic**: Eosinophil count raised
- ✓ **Neurologic**: Facial paresthesia
- ✓ **Other**: Fever

Serious

- ✓ **Dermatologic**: Erythroderma
- ✓ **Immunologic**: Anaphylaxis
- ✓ **Otic**: ototoxicity
- ✓ **Renal**: Nephrotoxicity

- ✓ **Respiratory**: Respiratory tract paralysis, Concomitant anesthesia, muscle relaxants

Contraindications

The drug is controindicate in patients with:

hypersensitivity to streptomycin or other aminoglycosides

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

No contraindicated or major interactions

Pregnancy

Streptomycin is rated as US FDA Category D (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

It is compatible with breast-feeding.

15 KEY-POINTS

- ✓ **All of the injectable agents have potential for renal toxicity**
- ✓ **Ototoxicity and vestibular toxicity are more common with Am than Km**
- ✓ **A common drug-effect is ototoxicity and renal toxicity**

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16 ANTIBACTERIALS FOR SYSTEMIC USE

This class includes amoxicillin/clavulanic acid and Imipenem/cilastatin

17 AMOXICILLIN/CLAVULANIC ACID

Mechanism of action

Amoxicillin binds to penicillin-binding proteins within the bacterial cell wall and inhibits bacterial cell wall synthesis. Clavulanic acid is a β-lactam, structurally related to penicillin, that may inactivate certain β-lactamase enzymes.

Main Side effects

Common

- ✓ **Dermatologic**: Diaper rash (3.5% to 6%), Rash (1.1% to 3%)

- ✓ **Gastrointestinal**: Diarrhea (2.9% to 14.5%), Loose stool (1.6% to 9%), Nausea (up to 3%), Vomiting (up to 2.2%) (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Reproductive**: Mycosis (3.3%), Vaginitis (1%), Candidiasis (1.4%)

Serious

- ✓ **Dermatologic**: Erythema multiforme, Stevens-Johnson syndrome, Toxic epidermal necrolysis
- ✓ **Immunologic**: Anaphylaxis, Hypersensitivity reaction
- ✓ **Hepatic**: Cholestasis, Hepatitis, Hepatotoxicity

Contraindications

The drug is controindicate in patients with:

Serious hypersensitivity reactions, such as anaphylaxis and Stevens-Johnson syndrome, to amoxicillin or other beta-lactam antibiotics (eg, penicillins, cephalosporins)

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

No contraindicated or major interactions

Pregnancy

Amoxicillin is rated as US FDA Category B. (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

It is compatible with breast-feeding.

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18 IMIPENEM-CILASTATIN

Mechanism of action

Imipenem is a carbapenem, which inhibits bacterial cell-wall synthesis by binding to penicillin-binding proteins

Main Side effects

Common

- ✓ **Dermatologic**: Phlebitis (Pediatric, 2.2%), Rash (Up to 2.2%)

- ✓ **Gastrointestinal**: Diarrhea (Up to 3.9%), Nausea (Adult, 2%), Vomiting (Up to 1.5%) (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Hematologic**: Thrombophlebitis

Serious

- ✓ **Dermatologic**: Stevens-Johnson syndrome, Toxic epidermal necrolysis
- ✓ **Gastrointestinal**: Clostridium difficile diarrhea
- ✓ **Immunologic**: Hypersensitivity reaction
- ✓ **Neurologic**: Seizure (Adult, 0.4%; pediatric, 5.9%) (see Main anti-tuberculosis drugs ADR symptoms and their management)

Contraindications

The drug is controindicate in patients with:

Hypersensitivity to imipenem or cilastatin, or any component of the product.

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

No contraindicated or major interactions

Pregnancy

Fetal risk cannot be ruled out

Breastfeeding

Infant risk cannot be ruled out. Weigh the potential benefits of treatment against potential risks before prescribing imipenem/cilastin during breast-feeding.

19 KEY-POINTS

- ✓ **The most frequent amoxicillin/clavulanic acid's adverse drug reactions are gastrointestinal disorders.**
- ✓ **Health care professional should pay attention to serious hypersensitivity reactions, such as Stevens-Johnson syndrome to amoxicillin, imipenem or cilastatin**

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20 ANTIMYCOBACTERIALS FOR SYSTEMIC USE

This drug class includes: bedaquiline, clofazime, ethionamide, prothionamide, cycloserine, terizidone, delamanid

21 BEDAQUILINE: IT'S A NEW DRUG!

PAY MORE ATTENTION AND REPORT ALL ITS ADVERSE DRUG REACTIONS

Bedaquiline (Bdq) was approved by the U.S. FDA in 2012, by the EMA in 2013 and by the Medicines Control Council (MCC) in 2014. The WHO recommended Bdq for the treatment of MDR-TB in 2013, providing that it is used under optimal conditions, including careful selection of patients. However, with further evidence on the safety and efficacy of BDQ, the WHO in 2019 consolidated DR TB guideline, including BDQ as a core drug for the management of DR TB. The drug has a new mechanism of action. In terms of safety, the drug is relatively well-tolerated, although when compared with placebo, higher rates of liver function test abnormalities were seen. Bdq has also been associated with moderate QTc prolongation, although no clinical cardiac events were associated with its use. The h a l f -life of bedaquiline is 5.5 months. Safety and efficacy not established in pediatric patients.

Mechanism of action

Bedaquiline, a diarylquinoline, inhibits mycobacterial ATP synthase which is an enzyme required for the generation of energy in Mycobacterium tuberculosis

Main Side effects

Common

- ✓ **Cardiovascular:** Chest pain (11%)
- ✓ **Gastrointestinal:** Nausea (38%)
- ✓ **Musculoskeletal:** Arthralgia (33%) (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Neurologic:** Headache (28%)
- ✓ **Respiratory:** Hemoptysis (18%)

Serious

- ✓ **Cardiovascular:** Prolonged QT interval. Obtain ECGs before initiation, and at least 2, 12, and 24 weeks after initiation of treatment. Monitor ECGs more closely in patients at risk for QT prolongation (serum electrolytes below lower limits of normal; concomitant use of other QT prolonging drugs; or history of Torsade de Pointe, congenital long QT syndrome, hypothyroidism, bradyarrhythmias, or uncompensated heart failure)

  BLACK BOX WARNING ON CARDIOTOXICITY: An increased risk of death was seen in the bedaquiline treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. If used with drugs that prolong the QT interval it may cause additive QT prolongation. Monitor ECGs. Discontinue bedaquiline if significant ventricular arrhythmia or if QTc interval prolongation of greater than 500 milliseconds develops. (see Main anti-tuberculosis drugs ADR symptoms and their management)

- ✓ **Hepatic:** Increased liver enzymes (9% to 10.8%). Monitor liver function tests (ALT, AST, alkaline phosphatase, bilirubin) at baseline, monthly during treatment, and as needed. Monitor symptoms of liver dysfunction (eg, fatigue, jaundice, liver tenderness, hepatomegaly) at baseline, monthly during treatment, and as needed. (see Main anti-tuberculosis drugs ADR symptoms and their management)

Contraindications

Specific contraindications have not been determined.

Main contraindicated or major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

Comtraindicated:

- ✓ Concurrent use of BEDAQUILINE and SAQUINAVIR may result in increased risk of QT-interval prolongation; increased exposure of bedaquiline.
- ✓ Concurrent use of NELFINAVIR and SELECTED CYP3A4 SUBSTRATES THAT ALSO PROLONG QT INTERVAL may result in increased exposure of CYP3A4 substrate; increased risk of QT-interval prolongation.

Major:

- ✓ Concurrent use of BEDAQUILINE and EFAVIRENZ may result in decreased bedaquiline exposure and increased risk of QT interval prolongation.

Pregnancy

Bedaquiline is rated as US FDA Category B. (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

Infant risk cannot be ruled out. Weigh the potential benefits of treatment against potential risks before prescribing bedaquiline during breast-feeding.

More:

if you want to receive more information, MORE

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22 CLOFAZIMINE

Mechanism of action

Clofazimine, a substituted iminophenazine bright-red dye, is an antimycobacterial that exerts a slow bactericidal effect on Mycobacterium leprae (Hansen's bacillus). It inhibits mycobacterial growth and binds preferentially to mycobacterial DNA and also exerts anti-inflammatory properties in treating erythema nodosum leprosum reactions.

Main Side effects

Common

- ✓ **Dermatologic**: Discoloration of skin (75% to 100%). Cfz causes skin pigmentation changes that range from an orange color to a dark black/purple color. These skin changes are reversible with stopping the drug.
- ✓ **Gastrointestinal**: Abdominal pain, Diarrhea, Epigastric pain, Nausea, Vomiting (see Main anti-tuberculosis drugs ADR symptoms and their management)

Serious

- ✓ **Cardiovascular**: Prolonged QT interval, Torsades de pointes. (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Gastrointestinal**: Bowel obstruction (Less than 1%), Gastrointestinal hemorrhage (Less than 1%)
- ✓ **Psychiatric**: At risk for suicide due to skin discoloration, Reactive depression (situational)due to skin discoloration. (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Other**: Splenic infarction (Less than 1%)

Contraindications

The drug is controindicate in patients with:

Hypersensitivity to clofazimine or any product excipients

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

Contraindicated

- ✓ Concurrent use of SAQUINAVIR and QT INTERVAL PROLONGING DRUGS may result in increased risk of QT-interval prolongation.

Pregnancy

No US FDA rating is available for clofazimine.

Breastfeeding

Infant risk cannot be ruled out. Weigh the potential benefits of treatment against potential risks before prescribing clofazimine during breast-feeding.

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23 ETHIONAMIDE

Mechanism of action

The mechanism of action of ethionamide is not known, but it appears to inhibit peptide synthesis and may be bacteriostatic or bacteriocidal depending on organism susceptibility and drug concentrations at the site of infection.

Main Side effects

Common

Gastrointestinal: Abdominal pain, Diarrhea, Excessive salivation, Loss of appetite, Metallic taste, Nausea, Stomatitis, Vomiting, Weight loss (see Main anti-tuberculosis drugs ADR symptoms and their management)

Serious

- ✓ **Hepatic**: Hepatitis, Hepatotoxicity, Jaundice (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Neurologic**: Encephalopathy
- ✓ **Ophthalmic**: Optic neuritis (rare)
- ✓ **Psychiatric**: Psychotic disorder

Contraindications

The drug is controindicate in patients with:

- ✓ Hypersensitivity to ethionamide
- ✓ Severe hepatic impairment

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected patients

No contraindicated or major interactions

Pregnancy

Ethionamide is rated as US FDA Category C (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

Infant risk cannot be ruled out. Weigh the potential benefits of treatment against potential risks before prescribing ethionamide during breast-feeding.

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24 PROTIONAMIDE

Mechanism of action

Protionamide is a thioamide derivative considered to be interchangeable with ethionamide. Complete cross-resistance occurs between the two drugs. Like ethionamide, it has generally been replaced by less toxic antimycobacterials. Similar mechanism of action for prothionamide as that of ethionamide has been proposed.

Main Side effects

Overall side effect profile similar to ethionamide (see Main anti-tuberculosis drugs ADR symptoms and their management)

Contraindications

The drug is controindicate in patients with:

- ✓ Hypersensitivity to prothionamide
- ✓ Severe hepatic impairment

Main contraindicated or Major Drug interactions with Antiretroviral therapy in HIV-infected patients

Unknown

Pregnancy

Not reported

Breastfeeding

Not reported

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25 CYCLOSERINE

Mechanism of action

An isoxazole which disrupts cell-wall biosynthesis in bacteria, by inhibition of peptidoglycan synthesis

Main Side effects

It has been reported that up to 30% of patients have adverse effects, but these usually subside when cycloserine is stopped or the dosage is reduced.

Common

Neurologic: anxiety, confusion, disorientation, depression, irritability, headache, drowsiness, speech difficulties, hyperreflexia.

Serious

Neurologic: psychoses possibly with suicidal tendencies, aggression and paranoia. Vertigo, tremor, paresis, paraesthesia, coma, and convulsions.

Immunonologic: Hypersensitivity reactions

Cardiovascular: Heart failure

Contraindications

Cycloserine is contra-indicated in patients with epilepsy, depression, psychosis, severe anxiety, severe renal impairment, or in those who misuse alcohol. Cycloserine should be stopped, or the dose reduced, if skin reactions or symptoms of CNS toxicity develop.

Cycloserine has a low therapeutic index, and dosage should be adjusted according to plasma concentrations, which should be monitored at least weekly in patients with renal impairment, in those taking doses greater than 500 mg daily, and in patients showing signs of neurotoxicity. Plasma concentrations should be maintained below 30 micrograms/mL. Haematological, renal, and hepatic function should be monitored. Patients with mild to moderate renal impairment require lower doses.

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

No contraindicated or major interactions

Pregnancy

Cycloserine is rated as US FDA Category C (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

Cycloserine is compatible with breast-feeding.

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26 TERIZIDONE

Mechanism of action

An isoxazole derivative of cycloserine. The mode of action is similar to cycloserine.

Main Side effects

Possibly less side effects than cycloserine.

Contraindications

Unknown

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

Unknown

Pregnancy

Not reported

Breastfeeding

Not reported

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27 DELAMANID: IT'S A NEW DRUG!

PAY MORE ATTENTION AND REPORT ALL ITS ADVERSE DRUG REACTIONS

Delamanid (Dlm) is a new drug that was approved for the treatment of DR -TB by the EMA in 2013. The drug was recommended for the treatment of DR -TB by the WHO in 2014 providing that it is used under optimal conditions, including careful selection of patients, close patient monitoring, use in a multi - drug regimen that follows WHO principles.
In terms of safety, the drug is well tolerated, and the **main side effect reported was moderate QT c prolongation without clinical cardiac events**. Of note, the drug is metabolized by albumin, and increased rates of adverse events were seen in patients with low levels of albumin.
The half-life of the drug is 38 hours. Dlm has been recommended for children above 6 years and is considered safe in this population.

Mechanism of action

Delamanid is a antimycobacterial antibiotic that exerts its cytotoxic activity by inhibiting methoxy-mycolic and keto-mycolic acid synthesis. These are necessary components of the mycobacterial cell wall. It is a pro-drug.

Main Side effects

Drug relatively well tolerated

Common

- ✓ **Cardiovascular**: Palpitations (8.1%)
- ✓ **Endocrine metabolic**: Hyperuricemia (10% or greater), Hypokalemia (10% or greater)
- ✓ **Gastrointestinal**: Decrease in appetite (10% or greater), Diarrhea (10% or greater), Nausea (38.3%), Upper abdominal pain (10% or greater), Vomiting (33%) (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Hematologic**: Reticulocytosis (10% or greater)
- ✓ **Musculoskeletal**: Arthralgia (10% or greater), Myalgia (10% or greater) (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Neurologic**: Asthenia (10% or greater), Dizziness (30.2%), Headache (10% or greater), Insomnia (10% or greater), Paresthesia (10% or greater), Tremor (10% or greater)
- ✓ **Otic**: Tinnitus (10% or greater)
- ✓ **Respiratory**: Hemoptysis (10% or greater)

Serious

- ✓ **Cardiovascular**: Prolonged QT interval (QTcF interval greater than 500 msec(0.3%); an increase in QTcF greater than 60 msec (3.7%); overall (9.9% or greater)- Monitoring: ECG; prior to treatment and monthly while receiving treatment. Risk of QTc prolongation may be higher in persons with low albumin, as the drug is reported to be metabolized by albumin. (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Other**: Drug resistance

Contraindications

The drug is controindicate in patients with:

- ✓ Concomitant use of strong CYP3A4 inducers (eg, carbamazepine)
- ✓ Hypersensitivity to delamanid or any component of the product
- ✓ Serum albumin less than 2.8 g/dL

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

Contraindicated

- ✓ Concurrent use of SAQUINAVIR and QT INTERVAL PROLONGING DRUGS may result in increased risk of QT-interval prolongation.

Major

Concurrent use of EFAVIRENZ and QT-PROLONGING DRUGS may result in increased risk of QT interval prolongation.

All DDI with delamanid

See all CONTRAINDICATED DDI with delamanid and drug-food interaction (Table_DOC_F)

Pregnancy

No US FDA rating is available for Delamanid

Counsel women of childbearing potential to avoid pregnancy and breastfeeding during therapy is recommended. Use of adequate contraception is recommended.

Breastfeeding

Infant risk cannot be ruled out. Weigh the potential benefits of treatment against potential risks before prescribing delamanid during breast-feeding.

For more information_MORE

28 KEY-POINTS

- Bedaquiline and delamanid are new drugs

- In terms of safety bedaquiline and delamanid are relatively well-tolerated

- The main side effect reported for bedaquiline and delamanid was moderate QTc prolongation

- Gastrointestinal disorders are clofazimine and ethionamide and protionamide's common side effects

29 FLUOROQUINOLONES

The fluoroquinolones have potent in vitro and in vivo activity against M. tuberculosis and the loss of a fluoroquinolone from a DR-TB treatment regimen is associated with poor treatment outcomes. They are generally well –tolerated even if potential side effect profiles may influence choice of fluoroquinolones:

- ✓ Lfx has less effect on the QT interval compared with Mfx, therefore, Lfx may be

warranted in some cases where this is a concern such as in cases receiving Cfz and Bdq
- ✓ Mfx is frequently associated with hepatotoxicity and thus should be used with caution in cases of liver impairment

This drug class includes: levofloxacin and moxifloxacin.

30 LEVOFLOXACIN

Mechanism of action

The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Main Side effects

Common

- ✓ **Gastrointestinal**: Diarrhea , 1% to 2% ; oral or intravenous, 5%), Nausea (, 1% to 2% ; oral or intravenous, 7%) (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Neurologic**: Dizziness (3%), Headache (6% to 10%), Insomnia (4%)

Serious

- ✓ **Cardiovascular**: Aortic aneurysm, Or dissection, Cardiac arrest (0.1% to 1%), Prolonged QT interval, Torsades de pointes, Ventricular tachycardia (0.1% to 1%) (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Dermatologic**: Erythema multiforme, Stevens-Johnson syndrome
- ✓ **Endocrine metabolic**: Hypoglycemia (0.1% to 1%)
- ✓ **Hematologic**: Aplastic anemia, Pancytopenia, Thrombocytopenic purpura
- ✓ **Hepatic**: Hepatitis, Liver failure (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Immunologic**: Anaphylactoid reaction, Hypersensitivity reaction (0.1% to 1%)
- ✓ **Musculoskeletal**: Myasthenia gravis, Exacerbation, Rupture of tendon, Tendinitis (0.1% to 1%)
- ✓ **Neurologic**: Disorientated, Disturbance of attention, Guillain-Barre syndrome, Memory impairment, Peripheral neuropathy, Pseudotumor cerebri, Raised intracranial pressure, Seizure (0.1% to 1%) (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Ophthalmic**: Retinal detachment
- ✓ **Psychiatric**: Delirium, Depression (0.1% to 1%), Hallucinations (0.1% to 1%), Paranoid disorder, Psychotic disorder, Suicidal
- ✓ **Renal**: Acute renal failure (0.1% to 1%)

Contraindications

Hypersensitivity to levofloxacin, or any other quinolone antibiotics, including ofloxacin or any product components

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

Contraindicated

Concurrent use of SAQUINAVIR and QT INTERVAL PROLONGING DRUGS may result in increased risk of QT-interval prolongation.

Major

Concurrent use of EFAVIRENZ and QT-PROLONGING DRUGS may result in increased risk of QT interval prolongation.

Pregnancy

Levofloxacin is rated as US FDA Category C. (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

Infant risk cannot be ruled out. Weigh the potential benefits of treatment against potential risks before prescribing levofloxacin during breast-feeding.

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31 MOXIFLOXACIN

Mechanism of action

Moxifloxacin hydrochloride is a fluoroquinolone antibiotic that inhibits topoisomerases II and IV, which control DNA topology and assist in DNA replication, repair and transcription. It has activity against a wide range of aerobic gram-positive and gram-negative microorganisms.

Main Side effects

Common

- ✓ **Endocrine metabolic**: Hypokalemia (1%)

- ✓ **Gastrointestinal**: Abdominal pain (2%), Constipation (2%), Diarrhea (6%), Nausea (7%), Vomiting (2%) (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Hepatic**: ALT/SGPT level abnormal (1%)
- ✓ **Neurologic**: Dizziness (3%), Headache (4%)
- ✓ **Ophthalmic**: Dry eyes , 1% to 6%), Keratitis (, 1% to 6%), Pain in eye (, 1% to 6%), Reduced visual acuity (, 1% to 6%)

Serious

- ✓ **Cardiovascular**: Aortic aneurysm, Or dissection, Prolonged QT interval (Oral/IV, 0.1% to less than 1%), Torsades de pointes. (see Main anti-tuberculosis drugs ADR symptoms and their management).
- ✓ **Dermatologic**: Rash (Oral/IV, 0.1% to less than 1%), Stevens-Johnson syndrome, Toxic epidermal necrolysis
- ✓ **Endocrine metabolic**: Hyperglycemia (Oral/IV, 0.1% to less than 1%), Hypoglycemia
- ✓ **Gastrointestinal**: Clostridium difficile diarrhea
- ✓ **Hematologic**: Agranulocytosis, Aplastic anemia, Hemolytic anemia, Pancytopenia, Thrombocytopenia (Oral/IV, 0.1% to less than 1%)
- ✓ **Hepatic**: Hepatic necrosis, Hepatitis, Liver failure (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Immunologic**: Anaphylactoid reaction, Hypersensitivity reaction
- ✓ **Musculoskeletal**: Myasthenia gravis, Exacerbation, Rupture of tendon, Tendinitis
- ✓ **Neurologic**: Disorientated, Disturbance of attention, Guillain-Barre syndrome, Memory impairment, Peripheral neuropathy, Pseudotumor cerebri, Raised intracranial pressure, Seizure (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Ophthalmic**: Retinal detachment
- ✓ **Psychiatric**: Agitation, Feeling nervous (0.1% to less than 1%), Paranoid disorder, Suicidal
- ✓ **Renal**: Renal failure (0.1% to less than 1%)
- ✓ **Respiratory**: Extrinsic allergic alveolitis
- ✓ **Other**: Serum sickness due to drug

Contraindications

The drug is controindicate in patients with:

Hypersensitivity to moxifloxacin or any quinolone antibiotic

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

Contraindicated

Concurrent use of SAQUINAVIR and QT INTERVAL PROLONGING DRUGS may result in increased risk of QT-interval prolongation.

Major

Concurrent use of EFAVIRENZ and QT-PROLONGING DRUGS may result in increased risk of QT interval prolongation.

Pregnancy

Moxifloxacin is rated as US FDA Category C. (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

Infant risk cannot be ruled out. Weigh the potential benefits of treatment against potential risks before prescribing moxifloxacin during breast-feeding.

32 KEY-POINTS

- ✓ **They are generally well –tolerated even if potential side effect profiles may influence choice of fluoroquinolones**
- ✓ **Lfx has less effect on the QT interval compared with Mfx, therefore, Lfx may be warranted in some cases where this is a concern such as in cases receiving Cfz and Bdq**
- ✓ **Mfx is frequently associated with hepatotoxicity and thus should be used with caution in cases of liver impairment**
- ✓ **The most frequent side-effects are gastrointestinal reactions and CNS reactions such as dizziness and headache**.

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33 Other antibacterials for systemic use

This drug class includes: linezolid

LINEZOLID

The drug has multiple adverse events, especially when given at doses exceeding 600mg per day.

Mechanism of action

Linezolid is an oxazolidinones that inhibits bacterial reproduction of aerobic Gram-positive bacteria and certain Gram-negative and anaerobic bacteria, by selectively binding to a site on the 23S ribosomal RNA of the 50S subunit, thereby preventing initiation complex formation with the 70S ribosomal subunit. Linezolid is bacteriostatic against enterococci and staphylococci, and bactericidal for a majority of streptococci isolates.

Main Side effects

Common

Gastrointestinal: Diarrhea (Adult, 8.2% to 8.3%; pediatric, 1.6% to 10.8%), Nausea (Adult, 5.1% to 6.6%; pediatric, 1.9% to 3.7%), Vomiting (Adult, 2% to 4.3%; pediatric, 9.4%) (see Main anti-tuberculosis drugs ADR symptoms and their management)

Neurologic: Headache (Adult, 5.7% to 8.8%; pediatric, 0.9% to 6.5%)

Serious

Endocrine metabolic: Lactic acidosis

Gastrointestinal: Clostridium difficile diarrhea

Hematologic: Myelosuppression (generally reversible with discontinuation of the drug). Monitoring: CBC (complete blood count) weekly

Hepatic: Injury of liver (see Main anti-tuberculosis drugs ADR symptoms and their management)

Neurologic: Peripheral neuropathy, Seizure (seeMain anti-tuberculosis drugs ADR symptoms and their management)

Ophthalmic: Disorder of optic nerve (usually resolved over time with drug discontinuation). Monitoring: Visual function tests in patients taking linezolid for 3 months or longer and in all patients reporting new visual symptoms.

Other: Serotonin syndrome

Strange effect:

Gastrointestinal: tooth and tongue discoloration

Contraindications

- ✓ Lzd is a weak, non-selective, reversible monoamine oxidase inhibitor (MAOI), such as phenelzine or isocarboxazid. Concomitant use of MAO or use within 2 weeks of taking an MAOI.
- ✓ Hypersensitivity to linezolid or any other component of the product

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

No contraindicated or major interactions

Particular Food Interactions

Linezolid interacts with large amounts of tyramine-rich foods (such as pork, aged cheeses, alcoholic beverages, or smoked and pickled foods). Concurrent use of LINEZOLID and TYRAMINE FOODS may result in a significant pressor response.

Pregnancy

Linezolid is rated as US FDA Category C (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

Infant risk cannot be ruled out. Weigh the potential benefits of treatment against potential risks before prescribing linezolid during breast-feeding.

34 KEY-POINTS

- Main common side effects: gastrointestinal and neurologic

- Serious side effects: endocrine metabolic, gastrointestinal, hematologic, hepatic, neurologic, ophthalmic.

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35 Aminosalicylic acid and derivatives

This drug class include PAS

PARA-AMINOSALICYLIC ACID (PAS)

Mechanism of action

Aminosalicylic acid is a bacteriostatic, anti-tuberculosis agent against Mycobacterium tuberculosis. It inhibits folic acid and cell wall synthesis that leads to reduced iron uptake of M. tuberculosis. It is commonly used in multi-drug resistant tuberculosis therapy which aids in inhibiting the onset of bacterial resistance to streptomycin and isoniazid.

Main Side effects

Common

- ✓ **Gastrointestinal**: Abdominal pain, Diarrhea, Nausea, Vomiting (see Main anti-tuberculosis drugs ADR symptoms and their management)
- ✓ **Immunologic**: Hypersensitivity reaction, Rash with fever (5%)

Serious

- ✓ **Hematologic**: Thrombocytopenia
- ✓ **Hepatic**: Hepatotoxicity (up to 21%) (see Main anti-tuberculosis drugs ADR symptoms and their management)

Contraindications

The drug is controindicate in patients with:

- ✓ hypersensitivity to aminosalicylic acid products
- ✓ renal disease, end-stage

Main contraindicated or Major Drug interactions with Antiretroviral t h e r a p y in HIV-infected p a t i e n t s

No contraindicated or major interactions

Pregnancy

Aminosalicylic Acid is rated as US FDA Category C (see U.S. Food and Drug Administration's Pregnancy Category)

Breastfeeding

Aminosalicylic Acid should be given with caution during breast-feeding.

36 KEY-POINTS

- Main common side effects: gastrointestinal and immunologic

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37 Vitamins

This drug class include pyridoxime

PYRIDOXINE (Vitamin B6)

Mechanism of action

Pyridoxine is converted in erythrocytes to pyridoxal phosphate and to a lesser extent pyridoxamine phosphate, which act as coenzymes for various metabolic functions affecting protein, carbohydrate, and lipid utilization. Pyridoxine is involved in conversion of tryptophan to niacin or serotonin, breakdown of glycogen to glucose-1-phosphate, conversion of oxalate to glycine, synthesis of gamma aminobutyric acid (GABA) within the CNS, and synthesis of heme.

Main Side effects

Common

Hematologic: Decreased folic acid

Neurologic: Paresthesia, Somnolence

Contraindications

The drug is controindicate in patients with:

hypersensitivity to pyridoxine products

Contraindicated or Major Drug interactions with Antiretroviral therapy in HIV-infected patients

No contraindicated or major interactions

Pregnancy

No US FDA rating is available for pyridoxine

Breastfeeding

Infant risk is minimal: the weight of an adequate body of evidence and/or expert consensus suggests Pyridoxine poses minimal risk to the infant when used during breast-feeding.

38 KEY-POINTS

- ✓ **Main common side effects: hematologic and neurologic**

39 U.S. Food and Drug Administration's Pregnancy Category

FDA Pregnancy Category:

This table shows the US Pregnancy Category Definitions

Table. US FDA Pregnancy Category Definitions	
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
B	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

40 References

IBM_Micromedex_ Web_ Application Access

Bibliography National Programmatic management of Drug resistant TB in Ethiopia Participant's manual_May 2019

Active TB drug-safety monitoring and management (aDSM):

https://www.who.int/tb/areas-of-work/drug-resistant-tb/treatment/pharmacovigilance/en/

41 Intermediate Questionnaire

What is the mechanism of action of rifampin?

a. it inhibits mycolic acid synthesis and disrupts the cell wall of susceptible organisms

b. it inhibits bacterial RNA synthesis

c. it impairs cell metabolism and cell multiplication eventually leading to cell death

d. it inhibits normal bacterial protein synthesis

Teaching:

"Rifampin, a semisynthetic broad-spectrum bactericidal antibiotic, inhibits bacterial RNA synthesis by binding strongly to the beta subunit of DNA-dependent RNA polymerase, preventing attachment of the enzyme to DNA, and thus blocking initiation of RNA transcription.".

Kanamycin side effects include:

a. immunologic and hematologic effects

b. immunologic and ophthalmic effects

c. gastrointestinal and immunologic effects

d. gastrointestinal and ophthalmic effects

Teaching:

"Main side effects (of kanamycin): gastrointestinal effects (nausea, vomito, diarrhea, malabsorption syndrome), immunologic effects (cross sensitivity reactions), muscoloskeletal effects (myastenia gravis), neurologic effects (headache, nervousness, restlessness, paresthesias and blurring of vision), otic effects (ototoxicity), renal effects, nephrotoxicity and respiratory effects: respiratory insufficiency.".

A) Amoxicillin/clavulanic acid is compatible with breast-feeding

B) Imipenem is a carbapenem

a. A false, B false

b. A false, B true

c. B false, A true

d. B true, A true

Teaching:

"It (Amoxicillin/clavulanic acid) is compatible with breast-feeding. Imipenem is a carbapenem, which inhibits bacterial cell-wall synthesis by binding to penicillin-binding proteins.".

Bedaquiline is known to be associated with:

a. severe dermatologic toxicity, including the Stevens-Johnson syndrome

b. severe renal toxicity, including nephrotoxicity

c. increased risk of cardiotoxicity, including prolonged QT interval

d. decreased risk of cardiotoxicity

Teaching:

“Bdq has also been associated with moderate QTc prolongation, although no clinical cardiac events were associated with its use.”.

Cross-resistance typically occurs between:

a. protoniamide and ethionamide

b. levofloxacin and moxifloxacin

c. delamanid and bedaquiline

d. capreomycin and streptomycin

Teaching:

“Protionamide is a thioamide derivative considered to be interchangeable with ethionamide. Complete cross-resistance occurs between the two drugs.”.

Which one of these anti-TB drugs belongs to the vitamins class?

a. Para-aminosalicylic acid

b. levofloxacin

c. linezolid

d. pyridoxine

“This drug class (vitamins) includes pyridoxine.”.