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# MDR & XDR Tuberculosis

RAJENDRA PRASAD



*Foreword*
**KC Mohanty**

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Chapter 2

# Antitubercular Drugs Used in Previously Treated Patients of Tuberculosis and Their Adverse Effects

## Kanamycin

**Drug Class:** Aminoglycoside

**Activity against TB, Mechanism of Action and Metabolism**: Bactericidal, aminoglycosides: It is used as reserve drugs in MDR tuberculosis not responding to primary antitubercular drugs.[1] It was second systemically used aminoglycoside, after streptomycin, in tuberculosis.[2,3] Inhibit protein synthesis by irreversibly binding to 30S ribosomal subunit; aminoglycosides are not metabolized in the liver, they are excreted unchanged in the urine. Most strains of tuberculosis is inhibited in vitro at the concentrations of 10 µg/mL.[4]

**Distribution:** 0.2–0.4 L/kg; distributed in extracellular fluid, abscesses, ascitic fluid, pericardial fluid, pleural fluid, synovial fluid, lymphatic fluid and peritoneal fluid. Not well distributed into bile, aqueous humour, bronchial secretions, sputum and CSF.

**Preparation and dose:** Kanamycin sulfate, sterile powder for intramuscular injection in sealed vials. The powder needs to be dissolved in 2 mL of 0.9% sodium chloride or water for injections before use. The optimal dose is 15 (12–18) mg/kg body weight, usually 750 mg to 1 g given daily or 5–6 days per week, by deep intramuscular injection. Rotation of injection sites avoids local discomfort. When necessary, it is possible to give the drug at the same total dose 2 or 3 times weekly during the continuation phase, under close monitoring for adverse effects.

**Storage:** Powder stable at room temperature (15–25°C), diluted solution should be used the same day.

**Oral absorption:** There is no significant oral absorption.

**CSF penetration:** Penetrates inflamed meninges only.

### Special Circumstances

- **Pregnancy/breastfeeding:** Safety class D. Eighth cranial nerve damage has been reported following in utero exposure to kanamycin. Excreted in breast milk. The American Academy of Paediatrics considers kanamycin to be compatible with breastfeeding.

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- **Renal disease:** Use with caution. Levels should be monitored for patients with impaired renal function. Interval adjustment (12–15 mg/kg—2 or 3 times per week) is recommended for creatinine clearance < 30 mL/min. or hemodialysis.
- **Hepatic disease:** Drug levels not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, use with caution—some patients with severe liver disease may progress rapidly to hepatorenal syndrome.

## Adverse Effects (Table 2.1)

### Frequent

- Pain at injection site
- Renal failure (usually reversible).

**TABLE 2.1: Adverse effects of antitubercular drugs used in retreatment cases**

| *Drug* | *Frequent* | *Occassional* | *Rare* |
|---|---|---|---|
| Amikacin | Pain injection site<br>Proteinuria<br>Electrolyte disturbances (hypokalemia and hypomagnesemia) | Cochlear ototoxicity<br>Vestibular toxicity<br>Nephrotoxicity<br>Peripheral neuropathy<br>Rash<br>Eosinophilia | Fever |
| Capreomycin | Nephotoxicity<br>Tubular dysfunction<br>Urticaria<br>Maculopapular rash | Cochlear ototoxicity<br>Vestibular toxicity<br>Electrolyte disturbances (hypokalemia, hypomagnesemia and hypocalcemia)<br>Pain at injection site, induration and sterile abscesses at site of injection<br>Neurotoxicity | Rash |
| Clofazimine | Ichthyosis<br>Dry skin<br>Pink to brown black discolouration of skin, cornea, retina and urine<br>Anorexia<br>Abdominal pain | Hepatitis<br>Hypersensitivity<br>Nephrotoxicity<br>Acneform eruption | Phototoxicity |
| Cycloserine | Neurological disturbances (headache and tremors)<br>Psychiatric disturbances (sleep disturbances, anxiety, depression, irritability, confusion, drowsiness)<br>Inflammation of gums<br>Pale skin | Visual changes and eye pain<br>Skin rash<br>Jaundice (hepatitis)<br>Burning, tingling and numbness in hands and feet | Seizures<br>Suicidal thoughts<br>Imaired hearing in fetus<br>Hypersensitivity |

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| *Drug* | *Frequent* | *Occassional* | *Rare* |
|---|---|---|---|
| Ethinonamide and prothionamide | Severe gastrointestinal Intolerance (including nausea, vomiting, diarrhea, abdominal pain, excessive salivation metallic taste)-dose related<br>Headache<br>Anorexia and weight loss<br>Stomatitis | Neurological disturbances<br>Psychiatric disturbances (depression, restlessness, drowsiness)<br>Allergic reactions<br>Postural hypotension<br>Reversible hepatitis (transient increase in serum bilirubin)<br>Hypothyroidism (especially when combined with PAS)<br>Menstrual irregularity<br>Gynecomastia<br>Arthralgias<br>Leukopenia | Peripheral neuritis<br>Optic neuritis<br>Pellagra-like syndrome<br>Rash<br>Photosensitivity<br>Thrombocytopenia<br>Alopecia<br>Impotence<br>Purpura |
| Kanamycin | Pain at injection site<br>Renal damage (usually reversible) | Cochlear and vestibular otoxicity (usually irreversible)<br>Peripheral neuropathy<br>Rash<br>Nephrotoxicity (dose related to cumulative and peak concenteration, often irreversible) | Fever |
| Levofloxacin | Generally well tolerated | Gastrointestinal intolerance (diarrhea)<br>Neurological disturbances (insomnia, restlessness, dizziness)<br>Allergic reactions<br>Photosensitivity | QT interval prolongation<br>Peripheral neuropathy<br>Tendon rupture<br>Rash |
| Moxifloxacin | Generally well-tolerated | Gastrointestinal intolerance (diarrhea)<br>Neurological disturbances (insomnia, restlessness, dizziness)<br>Allergic reactions<br>Photosensitivity | QT internal prolongation (in isolated cases)<br>Rash |
| Ofloxacin | Generally well-tolerated | Gastrointestinal intolerance (diarrhea)<br>Neurological disturbances (headache, insomnia, restlessness) | Allergic reactions<br>Photosensitivity<br>Peripheral neuropathy<br>Tendon rupture<br>Increased liver function tests |
| P-aminosalicylic Acid (PAS) | Gastrointestinal intolerance (including metallic taste, anorexia, diarrhea)<br>Hypothyroidism, especially when combined with ethionamide | Hepatitis<br>Thyroid enlargement<br>Allergic reactions<br>Fever<br>Increased prothrombin time<br>Malabsorption syndrome (eg. Steatorrhea and low serum folate level) | |

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| *Drug* | *Frequent* | *Occassional* | *Rare* |
|---|---|---|---|
| Linezolid | Gastrointestinal intolerance<br>Rash<br>Headache | Myelosuppression<br>Peripheral neuropathy<br>Optic neuropathy | |
| Clarithromycin | Gastrointestinal<br>Intolerance (abdominal pain, nausea, vomiting, diarrhea)<br>Hepatitis<br>Ventricular arrhythmias | | Hypersensitivity reaction<br>Pseudomembranous colitis<br>Fever<br>Rash |
| Imipenem/ cilastatin | Gastrointestinal intolerance<br>Hypersensitivity reaction<br>Palpitation<br>Tachycardia | Seizure<br>Hypotension<br>Anemia<br>Thrombophlebitis | Renal failure<br>Hemorrhagic colitis<br>Pseudomembranous colitis |
| Thiacetazone | Gastrointestinal intolerance<br>Rash<br>Anemia | Hepatitis<br>Exfoliative dermatitis<br>Stevens-Johnson syndrome | Bone marrow depression<br>Ototoxicity |
| Amoxicillin/ clavulanate | Diarrhea<br>Rash<br>Hypersensitivity reaction | *Candida stomatitis*<br>Vaginitis | Hepatic injury |

### Occasional

- Vestibular and auditory damage (usually irreversible)
- Nephrotoxicity (dose related to cumulative and peak concentrations)
- Increased risk with renal insufficiency (often irreversible)
- Peripheral neuropathy
- Rash.

Ototoxicity potentiated by certain diuretics (especially loop diuretics), advanced age and prolonged use. The effect of nondepolarizing muscle relaxants may be increased.

## Drug Interactions

- **Loop diuretics** (bumetanide, furosemide, ethacrynic acid, torsemide).
  Co-administration of aminoglycosides with loop diuretics may have an additive or synergistic auditory ototoxicity. Ototoxicity appears to be dose-dependent and may be increased with renal dysfunction. Irreversible ototoxicity has been reported.
  Avoid concomitant administration; if used together, careful dose adjustments in patients with renal failure and close monitoring for ototoxicity are required.
- **Nondepolarizing muscle relaxants** (atracurium, pancuronium, tubocurarine, gallamine triethiodide): Possible enhanced action of nondepolarizing muscle relaxant resulting in possible respiratory depression. Avoid co-administration; if concurrent administration is needed, titrate the non-depolarizing muscle relaxant slowly and monitor neuromuscular function closely.
- **Nephrotoxic agents** (amphotericin B, foscarnet, cidofovir): Additive nephrotoxicity. Avoid coadministration; if used together, monitor renal function closely and discontinue if warranted.

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- **Penicillins:** In vitro inactivation (possible). Do not mix together before administration.

## Contraindications

- Pregnancy (congenital deafness seen with streptomycin and kanamycin use in pregnancy)
- Hypersensitivity to aminoglycosides
- Use with caution in renal, hepatic, vestibular or auditory impairment.

## Monitoring

Monthly creatinine and serum potassium in low-risk patients (young with no co-morbidities), more frequently in high-risk patients (elderly, diabetic, or HIV-positive patients, or patients with renal insufficiency). If potassium is low, check magnesium and calcium. Baseline audiometry and monthly monitoring in high-risk patients. For problems with balance, consider increasing dosing interval.

## Alerting Symptoms

- Problems with hearing; dizziness
- Rash
- Trouble breathing
- Decreased urination
- Swelling, pain or redness at injection site
- Muscle twitching or weakness.

## Management of Adverse Effects (Table 2.2)

Hearing loss can be prevented by:

1. Changing injectable to capreomycin if patient has documented susceptibility to capreomycin

**TABLE 2.2: Common adverse effects, suspected agent(s) and management strategies of antituberculous drugs used in retreatment patients of TB**

| *Adverse effect* | *Suspected agent* | *Suggested management strategies* |
|---|---|---|
| Seizures | **Cs**<br>H<br>Fq | • Suspend suspected agent pending resolution of seizures<br>• Initiate anticonvulsant therapy (e.g. phenytoin, valproic acid)<br>• Increase pyridoxine to maximum daily dose (200 mg per day)<br>• Restart suspected agent or reinitiate suspected agent at lower dose, if essential to the regimen<br>• Discontinue suspected agent if this can be done without compromising regimen<br>• Anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent discontinued<br>• History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/or the patient is receiving anticonvulsant<br>• Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB. |

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| *Adverse effect* | *Suspected agent* | *Suggested management strategies* |
|---|---|---|
| Peripheral neuropathy | **Cs**<br>**Lzd**<br>**H**<br>S<br>Km<br>Am<br>Cm<br>Eto/Pto<br>Fq | • Increase pyridoxine to maximum daily dose (200 mg per day)<br>• Change injectable to capreomycin if patient has documented susceptibility to capreomycin<br>• Initiate therapy with tricyclic antidepressants such as amitriptyline. Nonsteroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms<br>• Lower dose of suspected agent, if this can be done without compromising regimen<br>• Discontinue suspected agent if this can be done without compromising regimen<br>• Patients with comorbid disease (e.g. diabetes, HIV, alcohol (dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here<br>• Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended |
| Hearing loss | **S**<br>**Km**<br>**Am**<br>**Cm**<br>Clr | • Document hearing loss and compare with baseline audiometry if available<br>• Change parenteral treatment to capreomycin if patient has documented susceptibility to capreomycin<br>• Decrease frequency and/or lower dose of suspected agent if this can be done without compromising the regimen (consider administration three times per week)<br>• Discontinue suspected agent if this can be done without compromising the regimen<br>• Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR-TB therapy<br>• Hearing loss is generally not reversible<br>• The risk of further hearing loss must be weighed against the risks of stopping the injectable in the treatment regimen<br>• While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial use to determine if a patient with hearing loss can benefit from their use |
| Psychotic symptoms | **Cs**<br>**H**<br>Fq<br>Eto/Pto | • Stop suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control<br>• Initiate antipsychotic therapy<br>• Lower dose of suspected agent, if this can be done without compromising regimen<br>• Discontinue suspected agent, if this can be done without compromising regimen<br>• Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy<br>• Previous history of psychiatric disease is not a contraindication to the use of agents listed here but may increase the likelihood of psychotic symptoms developing during treatment<br>• Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent |

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| *Adverse effect* | *Suspected agent* | *Suggested management strategies* |
|---|---|---|
| Depression | **Cs**<br>Fq<br>Eto/Pto<br>H | • Offer group or individual counseling<br>• Initiate antidepressant therapy<br>• Lower dose of suspected agent, if this can be done without compromising regimen<br>• Discontinue suspected agent, if this can be done without compromising regimen<br>• Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression<br>• Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated<br>• History of previous depression is not a contraindication to the use of the agents listed but may increase the likelihood of depression developing during treatment |
| Hypothyroidism | **PAS**<br>**Eto/Pto** | • Initiate thyroxine therapy<br>• Completely reversible upon discontinuation of PAS or ethionamide/protionamide<br>• The combination of ethionamide/protionamide with PAS is more frequently associated with hypothyroidism than the individual use of each drug |
| Nausea and vomiting | **Eto/Pto**<br>**PAS**<br>H<br>E<br>Z | • Assess for dehydration; initiate rehydration if indicated<br>• Initiate antiemetic therapy<br>• Lower dose of suspected agent, if this can be done without compromising regimen<br>• Discontinue suspected agent, if this can be done without compromising regimen rarely necessary<br>• Nausea and vomiting universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy<br>• Electrolytes should be monitored, if vomiting is severe<br>• Reversible upon discontinuation of suspected agent<br>• Severe abdominal distress and acute abdomen have been reported with the use of clofazimine. Although these reports are rare, if this effect occurs, clofazimine should be suspended |
| Gastritis | **PAS**<br>**Eto/Pto** | • H2-blockers, proton-pump inhibitors, or antacids<br>• Stop suspected agent(s) for short periods of time (e.g, 1–7 days)<br>• Lower dose of suspected agent, if this can be done without compromising regimen<br>• Discontinue suspected agent, if this can be done without compromising regimen<br>• Severe gastritis, as manifested by hematemesis, melena or hematechezia, is rare<br>• Dosing of antacids should be carefully timed so as not to interfere with the absorption of antituberculosis drugs (take 2 hours before or 3 hours after antituberculosis medications)<br>• Reversible upon discontinuation of suspected agent(s) |

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| *Adverse effect* | *Suspected agent* | *Suggested management strategies* |
|---|---|---|
| Hepatitis | **Z**<br>**H**<br>**R**<br>Eto/Pto<br>PAS<br>E<br>Fq | • Stop all therapy pending resolution of hepatitis<br>• Eliminate other potential causes of hepatitis<br>• Consider suspending most likely agent permanently<br>• Reintroduce remaining drugs, one at a time while monitoring liver function<br>• History of previous hepatitis should be carefully analyzed to determine most likely causative agent(s); these should be avoided in future regimens<br>• Generally reversible upon discontinuation of suspected agent |
| Renal toxicity | **S**<br>**Km**<br>**Am**<br>**Cm** | • Discontinue suspected agent<br>• Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen<br>• Consider dosing 2 to 3 times a week if drug is essential to the regimen and patient can tolerate (close monitoring of creatinine)<br>• Adjust all antituberculosis medications according to the creatinine clearance<br>• History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these comorbidities may be at increased risk for developing renal failure<br>• Renal impairment may be permanent |
| Electrolyte disturbances (hypokalaemia and hypomagnesaemia) | **Cm**<br>**Km**<br>**Am**<br>S | • Check potassium<br>• If potassium is low, also check magnesium (and calcium, if hypocalcemia is suspected)<br>• Replace electrolytes as needed<br>• If severe hypokalemia is present, consider hospitalization<br>• Amiloride 5 to 10 mg QD or spironolactone 25 mg QD may decrease potassium and magnesium wasting and is useful in refractory cases<br>• Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhea |
| Optic neuritis | **E**<br>Eto/Pto | • Stop E<br>• Refer patient to an ophthalmologist<br>• Usually reverses with cessation of E<br>• Rare case reports of optic neuritis have been attributed to streptomycin |
| Arthralgias | **Z**<br>Fq | • Initiate therapy with nonsteroidal anti-inflammatory drugs<br>• Lower dose of suspected agent, if this can be done without compromising regimen<br>• Discontinue suspected agent, if this can be done without compromising regimen<br>• Symptoms of arthralgia generally diminish over time, even without intervention<br>• Uric acid levels may be elevated in patients on pyrazinamide. Allopurinol appears not to correct the uric acid levels in such cases |

Isoniazid (H), Rifampicin (R), Ethambutol (E), Pyrazinamide (Z), Streptomycin (S), Kanamycin (Km), Amikacin (Am), Capreomycin (Cm), Fluoroquinolones (Fq), Ethionamide (Eto), Prothionamide (Pto), Para-aminosalicylic acid (PAS), Cycloserine (Cs), Clofazimine (Cfz), Linezolid (Lzd), Clarithromycin (Clr).
*Drugs that the strongly associated with adverse effects shown in bold.*

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2. Discontinue suspected agents without compromising the regimen
3. Lower the dose of suspected agents without compromising the regimen.

In renal failure, dose reduction is needed and follow-up with serum creatinine and blood urea is required every one to two months regularly. If renal profile is uncontrolled despite of decreased dosage, then discontinue suspected agent and consider using capreomycin.

## Amikacin

**Drug class:** Aminoglycoside
**Activity against TB, mechanism of action and metabolism:** Bactericidal, inhibit protein synthesis through disruption of ribosomal function; less effective in acidic pH, aminoglycosides are not metabolized in the liver, they are excreted unchanged in the urine.
**Preparation and dose:** Amikacin sulfate, colorless solution. 250 mg/mL (2 or 4 mL vials) and 50 mg/mL (2 mL vial). The optimal dose is 15–20 mg/kg body weight, usually 750 mg to 1 g given daily or 5–6 days per week by deep intramuscular injection. Rotation of injection sites avoids local discomfort. When necessary, it is possible to give the drug at the same total dose 2 or 3 times weekly during the continuation phase under close monitoring for adverse effects.
**Storage:** Solution is stable at room temperature (15°–25°C); diluted solution is stable at room temperature for at least 3 days or in the refrigerator for at least 60 days.
**Oral absorption:** There is no significant oral absorption. Intramuscular absorption may be delayed if the same site is used consistently.
**CSF penetration:** Penetrates inflamed meninges only.

### Special Circumstances

- **Pregnancy/breastfeeding:** Safety class D. No reports linking the use of amikacin to congenital defects have been reported.
  Ototoxicity has not been reported as an effect of *in utero* exposure to amikacin; however, eighth cranial nerve toxicity in the fetus is well known following exposure to other aminoglycosides (kanamycin and streptomycin) and could potentially occur with amikacin. Only a trace amount of amikacin was found in some nursing infants. Given the poor absorption of aminoglycosides, systemic toxicity should not occur, but alteration in normal bowel flora may occur in nursing infants.
- **Renal disease:** Use with caution. Levels should be monitored for patients with impaired renal function. Interval adjustment (12–15 mg/kg—2 or 3 times per week) is recommended for creatinine clearance < 30 mL/min or hemodialysis.
- **Hepatic disease:** Drug levels not affected by hepatic disease (except a larger volume of distribution for alcoholic cirrhotic patients with ascites). Presumed to be safe in severe liver disease; however, some patients with severe liver disease may progress rapidly to hepatorenal syndrome.

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## Adverse Effects

### Frequent

- Pain at injection site
- Proteinuria
- Serum electrolyte disturbances including hypokalemia and hypomagnesemia.

### Occasional

- Cochlear ototoxicity (may be irreversible)
- Nephrotoxicity (often irreversible)
- Peripheral neuropathy
- Rash
- Vestibular toxicity (nausea, vomiting, vertigo, ataxia, nystagmus)
- Eosinophilia.

Ototoxicity potentiated by certain diuretics (especially loop diuretics), advanced age, and prolonged use. The effect of nondepolarizing muscle relaxants may be increased.

## Drug Interactions

- **Loop diuretics** (bumetanide, furosemide, ethacrynic acid, torsemide). Coadministration of aminoglycosides with loop diuretics may have an additive or synergistic auditory ototoxicity.
  Ototoxicity appears to be dose-dependent and may be increased with renal dysfunction. Irreversible ototoxicity has been reported.
  Avoid concomitant administration; if used together, careful dose adjustments in patients with renal failure and close monitoring for ototoxicity are required.
- **Nondepolarizing muscle relaxants** (atracurium, pancuronium, tubocurarine, gallamine triethiodide): possible enhanced action of non-depolarizing muscle relaxants resulting in possible respiratory depression. Nephrotoxic agents (amphotericin B, foscarnet, cidofovir): additive nephrotoxicity.
- **Penicillins:** In vitro inactivation (possible). Do not mix together before administration.

**Contraindications:** Pregnancy (congenital deafness seen with streptomycin and kanamycin use in pregnancy). Hypersensitivity to aminoglycosides.
Use with caution in renal, hepatic, vestibular, or auditory impairment.
**Monitoring:** Monthly creatinine and serum potassium in low-risk patients (young with no comorbidities), more frequently in high-risk patients (elderly, diabetic, or HIV-positive patients, or patients with renal insufficiency). If potassium is low, check magnesium and calcium. Baseline audiometry and monthly monitoring in high-risk patients. For problems with balance, consider increasing dosing interval.

## Alerting Symptoms

- Problems with hearing, dizziness or balance
- Rash or swelling of the face

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- Trouble breathing
- Decreased urination
- Swelling, pain or redness at IM site
- Muscle twitching or weakness.

### Management of Adverse Effects

Hearing loss can be prevented by:

1. Changing injectable to Capreomycin if patient has documented susceptibility to capreomycin
2. Discontinue suspected agents without compromising the regimen
3. Lower dose of suspected agents without compromising the regimen.

In renal failure, dose reduction is needed and follow-up with serum creatinine and blood urea nitrogen is required every one to two months regularly. If renal profile is uncontrolled despite a decreased dosage, then discontinue suspected agent and consider using capreomycin.

## Capreomycin

**Drug class:** Cyclic polypeptide
**Activity against TB, mechanism of action and metabolism:** Bactericidal, polypeptides appear to inhibit translocation of the peptidyl-tRNA and the initiation of protein synthesis. No cross-resistance with the aminoglycosides. 50–60% excreted via glomerulofiltration. Small amount by biliary excretion. It is obtained from *Streptomyces capreolus*.[5]
**Preparation and dose:** Capreomycin sulfate is supplied as a sterile white powder for intramuscular injection in sealed vials each containing 1000 units, approximately equivalent to 1 g capreomycin base. This should be dissolved in 2 mL of 0.9% sodium chloride in water; 2–3 minutes should be allowed for complete solution.
**Dose:** 15–20 mg/kg daily. The usual dose is 1 g in a single dose daily. When necessary, it is possible to give the drug at the same dose 2 or 3 times weekly during the continuation phase, under close monitoring for adverse effects.
**Storage:** Reconstituted capreomycin can be stored in the refrigerator for upto 24 hours before use.
**Oral absorption:** There is no significant oral absorption. Intramuscular absorption may be delayed if the same site is used consistently.
**CSF penetration:** Penetrates inflamed meninges only.

### Special Circumstances

- **Pregnancy/breastfeeding:** Less ototoxicity reported in adults with capreomycin than with aminoglycosides. Category C animal studies show teratogenic effect ('wavy ribs' when given 3.5 times the human dose). Avoid in pregnancy. Concentrations in breast milk unknown.
- **Renal disease:** Use with caution. Levels should be monitored for patients with impaired renal function. Interval adjustment (12–15 mg/kg—2 or 3

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times per week) is recommended for creatinine clearance < 30 mL/min or hemodialysis.

## Adverse Effects

### Frequent

- Nephrotoxicity (20–25%)
- Tubular dysfunction
- Azotemia
- Proteinuria
- Urticaria
- Maculopapular rash.

### Occasional

- Ototoxicity (vestibular > auditory)
- Electrolyte abnormalities (decreased blood levels of calcium, magnesium and potassium)
- Pain
- Induration
- Sterile abscesses at injection sites.

## Drug Interactions

Avoid coadministration of nondepolarizing muscle relaxants. If concurrent administration is needed, titrate the nondepolarizing muscle relaxant slowly and monitor neuromuscular function closely. Though not reported with capreomycin, neuromuscular blockade has been reported with other polypeptide antibiotics when administered with nondepolarizing muscle relaxants. Avoid use with other nephro- or ototoxic agents because of the additive effect.

**Contraindications:** Patients with hypersensitivity to capreomycin and patients having myasthenia gravis. Great caution must be exercised in patients with renal insufficiency or pre-existing auditory impairment.

**Monitoring:** Monthly creatinine and serum potassium in low-risk patients (young with no comorbidities), more frequently in high-risk patients (elderly, diabetic, or HIV-positive patients, or patients with renal insufficiency). If potassium is low, check magnesium and calcium. Electrolyte disturbances are more common with capreomycin than other injectable agents. Baseline audiometry and monthly monitoring in high-risk patients. For problems with balance, consider increasing dosing interval.

### Alerting Symptoms

- Rash
- Decreased urination
- Fever or chills
- Trouble breathing
- Bleeding or bruising
- Muscle weakness
- Problems with hearing, dizziness or balance
- Bleeding or lump at IM injection site.

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# MDR & XDR Tuberculosis

This book *MDR and XDR Tuberculosis* is written with the aim of defining a practical approach to every aspect of drug-resistant tuberculosis especially multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). Chapters practically covers all the aspects of drug-resistance tuberculosis including MDR and XDR-TB ranging from epidemiology, diagnosis and practical approach to the treatment of MDR and XDR-TB including HIV and DR-TB. Special chapters on case-based approach to treatment of MDR-TB have also been included. Chapter on DR-TB in children, DR-TB in extrapulmonary tuberculosis, flouroquinolone resistance, infection control in DR-TB and newer antituberculosis drug are also included. Chapters have been written in the background of current literature and practical experience gained from day-to-day dealing with different patients suffering from drug-resistant tuberculosis. Advances up to 2013 have been included making all the chapters well referenced with the latest references. Undergraduate, postgraduate medical students, practitioners and program managers in TB control will find this book as practical guide.



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Professor Rajendra Prasad is a nationally acclaimed chest physician and tuberculosis expert, possessing nearly 4 decades' illustrious teaching and research experience with proven excellence in quality patient care. Apart from being a clinician par excellence, he is also a very popular medical teacher in pulmonary medicine. His contribution in the field of tuberculosis and multidrug-resistant tuberculosis (MDR-TB) are widely acclaimed. His dynamic leadership in academic and administrative areas has earned him a large number of awards from various international and national scientific societies. He has been mentor of many students who are now assuming important positions in pulmonary medicine.

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