Chapter 51 Beta-Lactam Antibiotics

These are antibiotics having a β-lactam ring. The two major groups are penicillins and cephalosporins. Monobactams and carbapenems are relatively later additions.

PENICILLINS

Penicillin was the first antibiotic to be used clinically in 1941. It is a miracle that the least toxic drug of its kind was the first to be discovered. It was originally obtained from the fungus *Penicillium notatum*, but the present source is a high yielding mutant of *P. chrysogenum*.

Chemistry and properties The penicillin nucleus consists of fused thiazolidine and β-lactam rings to which side chains are attached through an amide linkage (Fig. 51.1). Penicillin G (PnG), having a benzyl side chain at R (benzyl penicillin), is the original penicillin used clinically.

The side chain of natural penicillin can be split off by an amidase to produce 6-aminopenicillanic acid. Other side chains can then be attached to it resulting in different semisynthetic penicillins with unique antibacterial activities and different pharmacokinetic profiles.

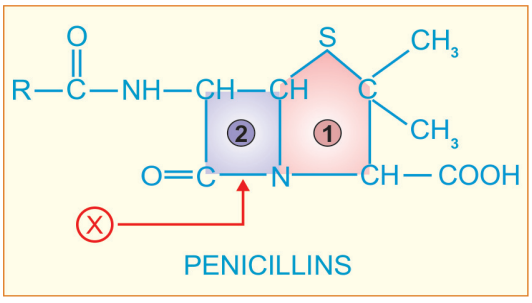


Fig. 51.1: Chemical structure of penicillins. (1) Thiazolidine ring; (2) β-lactam ring; (X) Bond which is broken by penicillinase

At the carboxyl group attached to the thiazolidine ring, salt formation occurs with Na^+ and K^+. These salts are more stable than the parent acid. Sod. PnG is highly water soluble. It is stable in the dry state, but solution deteriorates rapidly at room temperature, though it remains stable at 4°C for 3 days. Therefore, PnG solutions are always prepared freshly. PnG is also thermolabile and acid labile.

Unitage 1 U of crystalline sod. benzyl penicillin = 0.6 µg of the standard preparation. Accordingly, 1 g = 1.6 million units or 1 MU = 0.6 g.

Mechanism of action

All β-lactam antibiotics interfere with the synthesis of bacterial cell wall. The bacteria synthesize UDP-N-acetylmuramic acid pentapeptide, called 'Park nucleotide' (because Park in 1957 found it to accumulate when susceptible *Staphylococcus* was grown in the presence of penicillin) and UDP-N-acetyl glucosamine. The peptidoglycan residues are linked together forming long strands and UDP is split off. The final step is cleavage of the terminal D-alanine of the peptide chains by transpeptidases; the energy so released is utilized for establishment of cross linkages between peptide chains of the neighbouring strands (Fig. 51.2). This cross linking provides stability and rigidity to the cell wall.

The β-lactam antibiotics inhibit the transpeptidases so that cross linking (which maintains the close knit structure of the cell wall) does not take place. These enzymes and related proteins constitute the *penicillin binding proteins (PBPs)* which have been located in the bacterial cell membrane. Each organism has several PBPs, and PBPs obtained from different

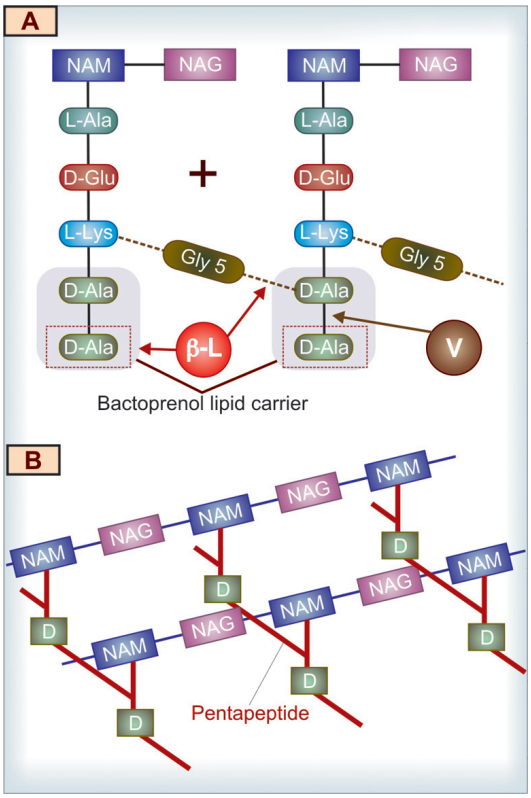


Fig. 51.2: Key features of bacterial cell wall synthesis and cell wall structure, depicting the site of action of β-lactam antibiotics and vancomycin.

A. Cross linking of peptidoglycan residues of neighbouring strands by cleavage of terminal D-alanine (D-Ala/D) and transpeptidation with the chain of 5 glycine (Gly5) residues. The β-lactam antibiotics (β-L) block cleavage of terminal D-Ala and transpeptidation. The peptidoglycan units are synthesized within the bacterial cell and are transported across the cell membrane by attachment to a bactoprenol lipid carrier for assembly into strands. Vancomycin (V) binds tightly to the terminal D-Ala-D-Ala sequence and prevents its release from the carrier, so that further transpeptidation cannot take place.

B. The highly cross linked peptidoglycan strands in bacterial cell wall

NAM—N-acetyl muramic acid
NAG—N-acetylglucosamine
L-Ala—L-alanine
D-Glu—D-glutamic acid
L-Lys—L-Lysine

species differ in their affinity towards different β-lactam antibiotics. This fact probably explains their differing sensitivity to the various β-lactam antibiotics.

When susceptible bacteria divide in the presence of a β-lactam antibiotic—cell wall deficient (CWD) forms are produced. Because the interior of the bacterium is hyperosmotic, the CWD forms swell and burst → bacterial lysis occurs. This is how β-lactam antibiotics exert bactericidal action. Under certain conditions and in case of certain organisms, bizarre shaped or filamentous forms, which are incapable of multiplying, result. Grown in hyperosmotic medium, globular 'giant' forms or *protoplasts* are produced. Lytic effect of these antibiotics may also be due to derepression of some bacterial autolysins which normally function during cell division.

Rapid cell wall synthesis occurs when the organisms are actively multiplying; β-lactam antibiotics are more lethal in this phase.

The peptidoglycan cell wall is unique to bacteria. No such substance is synthesized (particularly, D-alanine is not utilized) by higher animals. This is why penicillin is practically nontoxic to man.

In gram-positive bacteria, the cell wall is almost entirely made of peptidoglycan, which is >50 layers thick and extensively cross linked, so that it may be regarded as a single giant muco-peptide molecule. In gram-negative bacteria, it consists of alternating layers of lipoprotein and peptidoglycan (each layer 1–2 molecule thick with little cross linking). This may be the reason for higher susceptibility of the gram-positive bacteria to PnG.

Blood, pus, and tissue fluids do not interfere with the antibacterial action of β-lactam antibiotics.

PENICILLIN-G (BENZYL PENICILLIN)

Antibacterial spectrum PnG is a narrow spectrum antibiotic; activity is limited primarily to gram-positive bacteria, few gram negative ones and anaerobes.

Cocci: *Streptococci* (except *viridans,* group D or enterococci) are highly sensitive, so are many pneumococci. *Staph. aureus*, though originally very sensitive, has acquired resistance to such an extent that it must be counted out of PnG spectrum. Gram negative cocci—*Neisseria gonorrhoeae* and *N. meningitidis* are susceptible to PnG, though increasing number of gonococci have developed partial and others high degree resistance.

Bacilli: Gram-positive bacilli—majority of *B. anthracis, Corynebacterium diphtheriae,* and practically all *Clostridia (tetani* and others), *Listeria* are highly sensitive, so are spirochetes (*Treponema pallidum, Leptospira,* and others), but *Bacteroides fragilis* is largely resistant.

Actinomyces israelii is only moderately sensitive.
Majority of aerobic gram-negative bacilli, *Mycobacterium tuberculosis*, rickettsiae, chlamydiae, protozoa, fungi and viruses are totally insensitive to PnG.

Bacterial resistance Many bacteria are inherently insensitive to PnG because in them the target enzymes and PBPs are located deeper under lipoprotein barrier where PnG is unable to penetrate or have low affinity for PnG. The primary mechanism of acquired resistance is production of penicillinase.

Penicillinase It is a narrow spectrum β-lactamase which opens the β-lactam ring and inactivates PnG and some closely related congeners. Majority of *Staphylococci* and some strains of gonococci, *B. subtilis, E. coli, H. influenzae* and few other bacteria produce penicillinase. The gram-positive penicillinase producers elaborate large quantities of the enzyme which diffuses into the surroundings and can protect other inherently sensitive bacteria. In gram-negative bacteria, penicillinase is found in small quantity, but is strategically located inbetween the lipoprotein and peptidoglycan layers of the cell wall. Staphylococcal penicillinase is inducible, and methicillin is an important inducer; while in gram-negative organisms, it is mostly a constitutive enzyme.

Penicillinase has been successfully used to destroy PnG in patient's blood sample so that it does not interfere with bacterial growth when such blood is cultured.

Some resistant bacteria become *penicillin tolerant* and not penicillin destroying. Their target enzymes are altered to have low affinity for penicillin, e.g. highly resistant pneumococci isolated in some areas have altered PBPs. The methicillin-resistant *Staph. aureus* (MRSA) have acquired a PBP which has very low affinity for β-lactam antibiotics. Some penicillin resistant pneumococci and enterococci have altered PBPs. The low level penicillin-resistant gonococci are less permeable to the drug, while high degree resistant ones produce penicillinase, as do highly resistant *H. influenzae*. Both these appear to have acquired the penicillinase plasmid by conjugation or transduction and then propagated it by selection.

The gram-negative bacteria have 'porin' channels formed by specific proteins located in their outer membrane. Permeability of various β-lactam antibiotics through these channels differs: ampicillin and other members which are active against gram-negative bacteria cross the porin channels much better than PnG. Some gram-negative bacteria become resistant by loss or alteration of porin channels.

Pharmacokinetics

Penicillin G is acid labile, therefore destroyed by gastric acid. As such, less than 1/3rd of an oral dose is absorbed in the active form. Absorption of sod. PnG from i.m. site is rapid and complete; peak plasma level is attained in 30 min. It is distributed mainly extracellularly; reaches most body fluids, but penetration in serous cavities and CSF is poor. However, in the presence of inflammation (sinovitis, meningitis, etc.) adequate amounts may reach these sites. About 60% is plasma protein bound. It is little metabolized because of rapid excretion.

The pharmacokinetics of PnG is dominated by very rapid renal excretion; about 10% by glomerular filtration and the rest by tubular secretion. The plasma t½ of PnG in healthy adult is 30 min. Neonates have slower tubular secretion—t½ of PnG is longer; but approaches adult value at 3 months and then is even shorter during childhood. Aged and those with renal failure excrete penicillin slowly. Tubular secretion of PnG can be blocked by probenecid—higher and longer lasting plasma concentrations are achieved. Probenecid also decreases the volume of distribution of penicillins.

Preparations and dose

1. *Sod. penicillin G (crystalline penicillin) injection* 0.5–5 MU i.m./i.v. 6–12 hourly. It is available as dry powder in vials to be dissolved in sterile water at the time of injection. BENZYL PENICILLIN 0.5, 1 MU inj.

Repository penicillin G injections These are insoluble salts of PnG which must be given by deep i.m. (never i.v.) injection. They release PnG slowly at the site of injection, which then meets the same fate as soluble PnG.

1. *Procaine penicillin G inj.* 0.5–1 MU i.m. 12–24 hourly as aqueous suspension. Plasma concentrations attained are lower, but are sustained for 12–24 hours; PROCAINE PENICILLIN-G 0.5, 1 MU dry powder in vial.

Fortified procaine penicillin G inj: contains 3 lac U procaine penicillin and 1 lac U sod. penicillin G to provide rapid as well as sustained blood levels. FORTIFIED P.P. INJ 3+1 lac U vial; BISTREPEN 6+4 lac U/vial.

2. *Benzathine penicillin G* 0.6–2.4 MU i.m. every 2–4 weeks as aqueous suspension. It releases penicillin extremely slowly—plasma concentrations are very low but remain effective for prophylactic purposes for up to 4 weeks: PENIDURE-LA (long acting), LONGACILLIN, PENCOM, 0.6, 1.2, 2.4 MU as dry powder in vial.

Adverse effects

Penicillin G is one of the most nontoxic antibiotics; up to 20 MU has been injected in a day without any organ toxicity.

Local irritancy and direct toxicity Pain at i.m. injection site, nausea on oral ingestion and thrombophlebitis of injected vein are dose-related expressions of irritancy.

Toxicity to the brain may be manifested as mental confusion, muscular twitchings, convulsions and coma, when very large doses (> 20 MU) are injected i.v.; especially in patients with renal insufficiency. Bleeding has also occurred with such high doses due to interference with platelet function. Intrathecal injection of PnG is no longer recommended because it has caused arachnoiditis and degenerative changes in spinal cord.

Accidental i.v. injection of procaine penicillin produces CNS stimulation, hallucinations and convulsions due to procaine. Being insoluble, it may also cause microembolism.

Hypersensitivity These reactions are the major problem in the use of penicillins. An incidence of 1–10% is reported. Individuals with an allergic diathesis are more prone to develop penicillin reactions. PnG is the most common drug implicated in drug allergy, because of which it has practically vanished from use in general practice.

Frequent manifestations of penicillin allergy are—rash, itching, urticaria and fever. Wheezing, angioneurotic edema, serum sickness and exfoliative dermatitis are less common. Anaphylaxis is rare (1 to 4 per 10,000 patients), but may be fatal.

All forms of natural and semisynthetic penicillins can cause allergy, but it is more commonly seen after parenteral than oral administration. Incidence is highest with procaine penicillin: procaine is itself allergenic. The course of penicillin hypersensitivity is unpredictable, i.e. an individual who tolerated penicillin earlier may show allergy on subsequent administration and *vice versa*.

There is partial cross sensitivity between different types of penicillins; an individual who has exhibited immediate type of hypersensitivity—urticaria, angioedema, bronchospasm, anaphylaxis or serum sickness with one penicillin should not be given any other type of penicillin. However, if the earlier reaction had been only a rash, penicillin may be given cautiously—often no untoward effect is seen. History of penicillin allergy must be elicited before injecting it. A scratch test or intradermal test (with 2–10 U) may be performed first. On occasions, this itself has caused fatal anaphylaxis. Testing with benzylpenicilloyl-polylysine is safer. However, a negative intradermal test does not rule out delayed hypersensitivity. It should also be realised that presence of antibodies to penicillin does not mean allergy to it, because practically everyone who receives penicillin develops antibodies to it.

For the development of antibodies, penicillin or a product of it (mostly penicilloyl moiety—major determinant) acts as a hapten. There are many minor determinants as well.

Topical application of penicillin is highly sensitizing (contact dermatitis and other reactions). Therefore, all topical preparations of penicillin (including eye ointment) have been

banned, except for use in eye as freshly prepared solution in case of gonococcal ophthalmia.

If a patient is allergic to penicillin, it is best to use an alternative antibiotic. Hyposensitization by the injection of increasing amounts of penicillin intradermally at hourly intervals may be tried only if there is no other choice.

Superinfections These are rare with PnG because of its narrow spectrum; though bowel, respiratory and cutaneous microflora does undergo changes.

Jarisch-Herxheimer reaction Penicillin injected in a syphilitic patient (particularly secondary syphilis) may produce shivering, fever, myalgia, exacerbation of lesions, even vascular collapse. This is due to sudden release of spirochetal lytic products and lasts for 12–72 hours. It does not recur and does not need interruption of therapy. Aspirin and sedation afford relief of symptoms.

Uses

Penicillin G is the drug of choice for infections caused by organisms susceptible to it, unless the patient is allergic to this antibiotic. However, use has declined very much due to fear of causing anaphylaxis.

1. *Streptococcal infections* Like pharyngitis, otitis media, scarlet fever, rheumatic fever respond to ordinary doses of PnG because *Strep. pyogenes* has not developed significant resistance. However, the risk of injecting PnG for this infection is seldom taken now. For subacute bacterial endocarditis (SABE) caused by *Strep. viridans* or *faecalis* high doses (10–20 MU i.v. daily) along with gentamicin given for 2–6 weeks is needed.

2. *Pneumococcal infections* PnG is not used now for empirical therapy of pneumococcal (lobar) pneumonia and meningitis because many strains have become highly penicillin resistant. However, PnG 3–6 MU i.v. every 6 hours is the drug of choice if organism is sensitive.

3. *Meningococcal infections* are still mostly responsive; meningitis and other infections may be treated with intravenous injection of high doses.

4. *Gonorrhoea* PnG has become unreliable for treatment of gonorrhoea due to spread of resistant strains. For alternative regimens *see* Table 54-1.

The treatment of ophthalmia neonatorum due to sensitive *N. gonorrhoeae* consists of saline irrigation + sod. PnG 10,000–20,000 U/ml 1 drop in each eye every 1–3 hours. In severe cases, give 50,000 U i.m. BD for 1 week in addition.

5. *Syphilis* *T. pallidum* has not shown any resistance and PnG is the drug of choice. Early and latent syphilis is treated either with daily i.m. injection of 1.2 MU of procaine penicillin for 10 days or with 1–3 weekly doses of 2.4 MU benzathine penicillin. For late syphilis, benzathine penicillin 2.4 MU weekly for 4 weeks is recommended. Cardiovascular and neurosyphilis requires sod. PnG 5 MU i.m. 6 hourly for 10–14 days followed by the above regimen. *Leptospirosis:* PnG 1.5 MU injected i.v. 6 hourly for 7 days is curative.

6. *Diphtheria* Antitoxin therapy is of prime importance. Procaine penicillin 1–2 MU daily for 10 days is used to prevent carrier state.

7. *Tetanus and gas gangrene* Antitoxin and other measures are more important; PnG 6–12 MU/day is used to kill the causative organism and has adjuvant value.

8. Penicillin G is the drug of choice for rare infections like anthrax, actinomycosis, rat bite fever and those caused by *Listeria monocytogenes, Pasteurella multocida.*

For trench mouth or acute necrotizing ulcerative gingivitis (ANUG) which is a mixed infection caused by spirochetes and fusobacteria, PnG (i.m.)/penicillin V (oral) or amoxicillin are generally combined with metronidazole.

9. *Prophylactic uses*

(a) Rheumatic fever: Low concentrations of penicillin prevent colonization by streptococci that are indirectly responsible for rheumatic fever. Benzathine penicillin 1.2 MU every 4 weeks till 18 years of age or 5 years after an attack, whichever is more.

(b) Bacterial endocarditis: Dental extractions, endoscopies, catheterization, etc. cause bacteremia which in patients with valvular defects can cause endocarditis. PnG can afford protection, but amoxicillin is preferred now.

(c) Agranulocytosis patients: Penicillin has been used alone or in combination with streptomycin to prevent respiratory and other acute infections, but cephalosporins + an aminoglycoside or fluoroquinolone are preferred now.

SEMISYNTHETIC PENICILLINS

Semisynthetic penicillins are produced by chemically combining specific side chains (in place of benzyl side chain of PnG) or by incorporating specific precursors in the mould cultures. Thus, procaine penicillin and benzathine penicillin are salts of PnG and *not* semisynthetic penicillins. The aim of producing semisynthetic penicillins has been to overcome the shortcomings of PnG, which are:

1. Poor oral efficacy.

2. Susceptibility to penicillinase.
3. Narrow spectrum of activity.
4. Hypersensitivity reactions (this has not been overcome in any preparation).

In addition, some β-lactamase inhibitors have been developed which themselves are not antibacterial, but augment the activity of penicillins against β-lactamase producing organisms.

CLASSIFICATION

1. *Acid-resistant alternative to penicillin G* Phenoxymethyl penicillin (Penicillin V).
2. *Penicillinase-resistant penicillins* Methicillin, Cloxacillin, Dicloxacillin.
3. *Extended spectrum penicillins*
   (a) *Aminopenicillins:* Ampicillin, Bacampicillin, Amoxicillin.
   (b) *Carboxypenicillins*: Carbenicillin.
   (c) *Ureidopenicillins*: Piperacillin, Mezlocillin.

β-lactamase inhibitors Clavulanic acid Sulbactam, Tazobactam

ACID-RESISTANT ALTERNATIVE TO PENICILLIN-G

Phenoxymethyl penicillin (Penicillin V)

It differs from PnG only in that it is acid stable. Oral absorption is better; peak blood level is reached in 1 hour and plasma t½ is 30–60 min.

The antibacterial spectrum of penicillin V is identical to PnG, but it is about 1/5 as active against *Neisseria*, other gram negative bacteria and anaerobes. It cannot be depended upon for more serious infections and is used only for streptococcal pharyngitis, sinusitis, otitis media, prophylaxis of rheumatic fever (when an oral drug has to be selected), less serious pneumococcal infections and trench mouth.

Dose: 250–500 mg, infants 60 mg, children 125–250 mg; given 6 hourly, (250 mg = 4 lac U). CRYSTAPEN-V, KAYPEN 125, 250 mg tab, 125 mg/5 ml dry syr—for reconstitution, PENIVORAL 65, 130 mg tab.

PENICILLINASE-RESISTANT PENICILLINS

These congeners have side chains that protect the β-lactam ring from attack by staphylococcal penicillinase. However, this also partially protects the bacteria from the β-lactam ring: nonpenicillinase producing organisms are much less sensitive to these drugs than to PnG. Their only indication is infections caused by penicillinase producing *Staphylococci,* for which they are the drugs of choice, except in areas where methicillin resistant *Staph. aureus* (MRSA) has become prevalent. These drugs are not resistant to β-lactamases produced by gram negative bacteria.

Methicillin It is highly penicillinase resistant but not acid resistant—must be injected. It is also an inducer of penicillinase production.

MRSA have emerged in many areas. These are insensitive to all penicillinase-resistant penicillins and to other β-lactams as well as to erythromycin, aminoglycosides, tetracyclines, etc. The MRSA have altered PBPs which do not bind penicillins. The drug of choice for these organisms is vancomycin/linezolid, but ciprofloxacin can also be used.

Haematuria, albuminuria and reversible interstitial nephritis are the specific adverse effects of methicillin. It has been replaced by cloxacillin.

Cloxacillin/Dicloxacillin It has an isoxazolyl side chain and is highly penicillinase as well as acid resistant. Activity against PnG sensitive organisms is weaker, and it should not be used as a substitute for PnG. It is more active than methicillin against penicillinase producing *Staph*, but not against MRSA.

Cloxacillin/dicloxacillin are incompletely but dependably absorbed from oral route, especially if taken in empty stomach. It is > 90% plasma protein bound. Elimination occurs primarily by kidney, also partly by liver. Plasma t½ is about 1 hour.

Dose: 0.25–0.5 g orally every 6 hours; for severe infections 0.25–1 g may be injected i.m. or i.v.—higher blood levels are produced.

KLOX, BIOCLOX, 0.25, 0.5 g cap; 0.25, 0.5 g/vial inj., CLOPEN 0.25, 0.5 g cap.

Oxacillin, Flucloxacillin (Floxacillin) are other isoxazolyl penicillins, similar to cloxacillin, but not marketed in India. Nafcillin is another parenteral penicillinase resistant penicillin.

EXTENDED SPECTRUM PENICILLINS

These semisynthetic penicillins are active against a variety of gram-negative bacilli as well. They can be grouped according to their spectrum of activity.

1. Aminopenicillins

This group, led by ampicillin, has an amino substitution in the side chain. Some are prodrugs and all have quite similar antibacterial spectra. None is resistant to penicillinase or to other β-lactamases.

Ampicillin It is active against all organisms sensitive to PnG. In addition, many gram-negative bacilli, e.g. *H. influenzae, E. coli, Proteus, Salmonella Shigella* and *Helicobacter pylori* are inhibited. However, due to wide-spread use, many of these have developed resistance; usefulness of this antibiotic has decreased considerably.

Ampicillin is more active than PnG for *Strep. viridans,* enterococci and *Listeria;* equally active for pneumococci, gonococci and meningococci (penicillin-resistant strains are resistant to ampicillin as well); but less active against other gram-positive cocci. Penicillinase producing *Staph*. are not affected, as are other gram-negative bacilli, such as *Pseudomonas, Klebsiella*, indole positive *Proteus* and anaerobes like *Bacteroides fragilis.*

Pharmacokinetics Ampicillin is not degraded by gastric acid; oral absorption is incomplete but adequate. Food interferes with absorption. It is partly excreted in bile and reabsorbed—enterohepatic circulation occurs. However, primary channel of excretion is kidney, but tubular secretion is slower than for PnG; plasma t½ is 1 hr.

Dose: 0.5–2 g oral/i.m./i.v. depending on severity of infection, every 6 hours; children 50–100 mg/kg/day.

AMPILIN, ROSCILLIN, BIOCILIN 250, 500 mg cap; 125, 250 mg/5 ml dry syr; 100 mg/ml pediatric drops; 250, 500 mg and 1.0 g per vial inj.

Uses

1. Urinary tract infections: Ampicillin has been the drug of choice for most acute infections, but resistance has increased and fluoroquinolones/cotrimoxazole are now more commonly used for empirical therapy.
2. Respiratory tract infections: including bronchitis, sinusitis, otitis media, etc. are usually treated with ampicillin, but higher doses (50–80 mg/kg/day) are generally required now.
3. Meningitis: Ampicillin has been a first line drug, but a significant number of meningococci, pneumococci and *H. influenzae* are now resistant. For empirical therapy, it is now used only in combination with a third generation cephalosporin with or without another antibiotic.
4. Gonorrhoea: It is one of the first line drugs for oral treatment of nonpenicillinase producing gonococcal infections. A single dose of 3.5 g ampicillin + 1 g probenecid (ROSCIND, DYNACIL-PRB cap) is adequate and convenient for urethritis.
5. Typhoid fever: Due to emergence of resistance, it is now rarely used, only when the organism is shown to be sensitive.

   Salmonella diarrhoeas should usually not be treated with antimicrobials, including ampicillin.
6. Bacillary dysentery: due to *Shigella* often responds to ampicillin, but many strains are now resistant; quinolones are preferred.
7. Cholecystitis: Ampicillin is a good drug because high concentrations are attained in bile.
8. Subacute bacterial endocarditis: Ampicillin 2 g i.v. 6 hourly is used in place of PnG. Concurrent gentamicin is advocated.
9. *H. pylori:* Though amoxicillin is mostly used for eradication of *H. pylori* from stomach and duodenum, ampicillin is also active.
10. Septicaemias and mixed infections: Injected ampicillin may be combined with gentamicin or one of the third generation cephalosporins.
11. *ANUG*: Ampicillin/amoxicillin are generally preferred over penicillin V for combining with metronidazole in treating this condition.

Adverse effects Diarrhoea is frequent after oral administration. Ampicillin is incompletely

absorbed—the unabsorbed drug irritates the lower intestines as well as causes marked alteration of bacterial flora.

It produces a high incidence (up to 10%) of rashes, especially in patients with AIDS, EB virus infections or lymphatic leukaemia. Concurrent administration of allopurinol also increases the incidence of rashes. Sometimes the rashes may not be allergic, but toxic in nature.

Patients with a history of immediate type of hypersensitivity to PnG should not be given ampicillin as well.

Interactions Hydrocortisone inactivates ampicillin if mixed in the i.v. solution.
By inhibiting colonic flora, it may interfere with deconjugation and enterohepatic cycling of oral contraceptives → failure of oral contraception. Probenecid retards renal excretion of ampicillin.

Bacampicillin It is an ester prodrug of ampicillin which is nearly completely absorbed from the g.i.t.; and is largely hydrolysed during absorption. Thus, higher plasma levels are attained. Incidence of diarrhoea is claimed to be lower, because of lesser alteration in intestinal ecology.

Dose: 400–800 mg BD; PENGLOBE 200, 400 mg tab.

Talampicillin, Pivampicillin, Hetacillin are other prodrugs of ampicillin.

Note: A fixed dose combination of ampicillin + cloxacillin (AMPILOX and others) containing 250 mg of each per cap or per vial for injection is vigorously promoted for postoperative, skin and soft tissue, respiratory, urinary and other infections. This combination is not synergistic since cloxacillin is not active against gram-negative bacteria, while ampicillin is not active against staphylococci. Since mixed staphylococcal and gram-negative bacillary infections are uncommon, for any given infection, one of the components is useless but adds to the cost and adverse effects. Since the amount of the drug which is actually going to act in any individual patient is halved (when the combination is used), efficacy is reduced and chances of selecting resistant strains are increased. Both drugs are ineffective against MRSA. Blind therapy with this combination is irrational and harmful.

Amoxicillin It is a close congener of ampicillin (but not a prodrug); similar to it in all respects except:

- Oral absorption is better; food does not interfere with absorption; higher and more sustained blood levels are produced.
- Incidence of diarrhoea is lower.
- It is less active against *Shigella* and *H. influenzae*.
- It is more active against penicillin resistant *Strep. pneumoniae*.

Many physicians now prefer it over ampicillin for bronchitis, urinary infections, SABE and gonorrhoea. It is a component of most triple drug *H. pylori* eradication regimens (*see* p. 657).

Dose: 0.25–1 g TDS oral/i.m.; or slow i.v. injection, child 25–75 mg/kg/day. AMOXYLIN, NOVAMOX, SYNAMOX 250, 500 mg cap, 125 mg/5 ml dry syr. AMOXIL, MOX 250, 500 mg caps; 125 mg/5 ml dry syr; 250, 500 mg/vial inj. MOXYLONG: Amoxicillin 250 mg + probenecid 500 mg tab (also 500 mg + 500 mg DS tab).

2. Carboxypenicillins

Carbenicillin The special feature of this penicillin congener is its activity against *Pseudomonas aeruginosa* and indole positive *Proteus* which are not inhibited by PnG or aminopenicillins. It is less active against *Salmonella, E. coli* and *Enterobacter*, while *Klebsiella* and gram-positive cocci are unaffected by it. *Pseudomonas* strains less sensitive to carbenicillin have developed in some areas, especially when inadequate doses have been used.

Carbenicillin is neither penicillinase-resistant nor acid resistant. It is inactive orally and is excreted rapidly in urine ($t_{½}$ 1 hr). It is used as sodium salt in a dose of 1–2 g i.m. or 1–5 g i.v. every 4–6 hours. At the higher doses, enough Na may be administered to cause fluid retention and CHF in patients with borderline renal or cardiac function.

High doses have also caused bleeding by interferring with platelet function. This appears to result from perturbation of agonist receptors on platelet surface.

CARBELIN 1 g, 5 g, per vial inj.

The indications for carbenicillin are—serious infections caused by *Pseudomonas* or *Proteus*, e.g. burns, urinary tract infection, septicaemia, but piperacillin is now mostly used. Carbenicillin

may be combined with gentamicin, but the two should not be mixed in the same syringe.

Carbenicillin indanyl is an orally active ester of carbenicillin, used for treatment of UTI caused by *Pseudomonas* and *Proteus*.

3. Ureidopenicillins

Piperacillin This antipseudomonal penicillin is about 8 times more active than carbenicillin. It has good activity against *Klebsiella*, many Enterobacteriaceae and some *Bacteroides*. It is frequently employed for treating serious gram-negative infections in neutropenic/immunocompromised or burn patients. Elimination t½ is 1 hr. Concurrent use of gentamicin or tobramycin is advised.

Dose: 100–150 mg/kg/day in 3 divided doses (max 16 g/day) i.m. or i.v. The i.v. route is preferred when > 2 g is to be injected.
PIPRAPEN 1 g, 2 g vials; PIPRACIL 2 g, 4 g vials for inj; contains 2 mEq Na^+ per g.

Mezlocillin Another antipseudomonas penicillin, not available in India.

BETA-LACTAMASE INHIBITORS

β-lactamases are a family of enzymes produced by many gram-positive and gram-negative bacteria that inactivate β-lactam antibiotics by opening the β-lactam ring. Different β-lactamases differ in their substrate affinities. Three inhibitors of this enzyme *clavulanic acid*, *sulbactam* and *tazobactam* are available for clinical use.

Clavulanic acid Obtained from *Streptomyces clavuligerus*, it has a β-lactam ring but no antibacterial activity of its own. It inhibits a wide variety (class II to class V) of β-lactamases (but not class I cephalosporinase) produced by both gram-positive and gram-negative bacteria.

Clavulanic acid is a 'progressive' inhibitor: binding with β-lactamase is reversible initially, but becomes covalent later—inhibition increasing with time. Called a 'suicide' inhibitor, it gets inactivated after binding to the enzyme. It permeates the outer layers of the cell wall of gram-negative bacteria and inhibits the periplasmically located β-lactamase.

Pharmacokinetics Clavulanic acid has rapid oral absorption and a bioavailability of 60%; can also be injected. Its elimination t½ of 1 hr and tissue distribution matches amoxicillin, with which it is combined (called coamoxiclav). However, it is eliminated mainly by glomerular filtration and its excretion is not affected by probenecid. Moreover, it is largely hydrolysed and decarboxylated before excretion, while amoxicillin is primarily excreted unchanged by tubular secretion.

Uses Addition of clavulanic acid re-establishes the activity of amoxicillin against β-lactamase producing resistant *Staph. aureus* (but not MRSA that have altered PBPs), *H. influenzae*, *N. gonorrhoeae, E. coli, Proteus, Klebsiella, Salmonella* and *Shigella*. Though *Bact. fragilis* and *Branhamella catarrhalis* are not responsive to amoxicillin alone, they are inhibited by the combination. Clavulanic acid does not potentiate the action of amoxicillin against strains that are already sensitive to it. Coamoxiclav is indicated for:

- Skin and soft tissue infections, intra-abdominal and gynaecological sepsis, urinary, biliary and respiratory tract infections: especially when empiric antibiotic therapy is to be given for hospital acquired infections.
- Gonorrhoea (including PPNG) single dose amoxicillin 3 g + clavulanic acid 0.5 g + probenecid 1 g is highly curative.

AUGMENTIN, ENHANCIN, AMONATE: Amoxicillin 250 mg + clavulanic acid 125 mg tab; also 500 mg + 125 mg tab; 125 mg + 31.5 mg per 5 ml dry syr; CLAVAM 250 + 125 mg tab, 500 + 125 mg tab, 875 + 125 mg tab, 125 mg + 32 mg per 5 ml dry syr, 1–2 tab TDS.
Also AUGMENTIN, CLAVAM: Amoxicillin 1 g + clavulanic acid 0.2 g vial and 0.5 g + 0.1 g vial; inject 1 vial deep i.m. or i.v. 6–8 hourly for severe infections.
It is more expensive than amoxicillin alone.

Adverse effects are the same as for amoxicillin alone; but g.i. tolerance is poorer—especially in children. Other adverse effects are *Candida* stomatitis/vaginitis and rashes. Some cases of hepatic injury have been reported with the combination.

Sulbactam It is a semisynthetic β-lactamase inhibitor, related chemically as well as in activity to clavulanic acid. It is also a progressive inhibitor, highly active against class II to V but poorly active against class I β-lactamase. On weight basis, it is 2–3 times less potent than clavulanic acid for most types of the enzyme, but the same level of inhibition can be obtained at the higher concentrations achieved clinically. Sulbactam does not induce chromosomal β-lactamases, while clavulanic acid can induce some of them.

Oral absorption of sulbactam is inconsistent. Therefore, it is preferably given parenterally. It has been combined with ampicillin for use against β-lactamase producing resistant strains. Absorption of its complex salt with ampicillin—*sultamicillin tosylate* is better, which is given orally. Indications are:

- PPNG gonorrhoea; sulbactam *per se* also inhibits *N. gonorrhoeae.*
- Mixed aerobic-anaerobic infections, intra-abdominal, gynaecological, surgical and skin/soft tissue infections, especially those acquired in the hospital.

SULBACIN, AMPITUM: Ampicillin 1 g + sulbactam 0.5 g per vial inj; 1–2 vial deep i.m. or i.v. injection 6–8 hourly.
Sultamicillin tosylate: BETAMPORAL, SULBACIN 375 mg tab.
Sulbactam has been combined with cefoperazone and ceftriaxone also (*see* p.728).

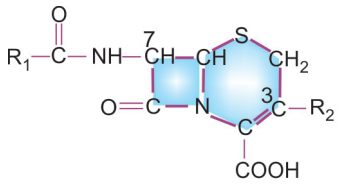
Pain at site of injection, thrombophlebitis of injected vein, rash and diarrhoea are the main adverse effects.

Tazobactam It is another β-lactamase inhibitor similar to sulbactam. Its pharmacokinetics matches with piperacillin with which it has been combined for use in severe infections like peritonitis, pelvic/urinary/respiratory infections caused by β-lactamase producing bacilli. However, the combination is not active against piperacillin-resistant *Pseudomonas,* because tazobactam (like clavulanic acid and sulbactam) does not inhibit inducible chromosomal β-lactamase produced by Enterobacteriaceae. It is also of no help against *Pseudomonas* that develop resistance by losing permeability to piperacillin.

Dose: 0.5 g combined with piperacillin 4 g injected i.v. over 30 min 8 hourly.
PYBACTUM, TAZACT, TAZOBID, ZOSYN 4 g + 0.5 g vial for inj.
Tazobactam has been combined with ceftriaxone as well (*see* p. 728).

CEPHALOSPORINS

These are a group of semisynthetic antibiotics derived from 'cephalosporin-C' obtained from a fungus *Cephalosporium*. They are chemically related to penicillins; the nucleus consists of a β-lactam ring fused to a dihydrothiazine ring, (7-aminocephalosporanic acid). By addition of different side chains at position 7 of β-lactam ring (altering spectrum of activity) and at position 3 of dihydrothiazine ring (affecting pharmacokinetics), a large number of semisynthetic compounds have been produced. These have been conventionally divided into 4 generations. This division has a chronological sequence of development, but more importantly, takes into consideration the overall antibacterial spectrum as well as potency.



CEPHALOSPORIN

All cephalosporins are bactericidal and have the same mechanism of action as penicillin, i.e. inhibition of bacterial cell wall synthesis. However, they bind to different proteins than those which bind penicillins. This may explain differences in spectrum, potency and lack of cross resistance.

Acquired resistance to cephalosporins could have the same basis as for penicillins, i.e.:

(a) alteration in target proteins (PBPs) reducing affinity for the antibiotic.
(b) impermeability to the antibiotic or its efflux so that it does not reach its site of action.

First generation cephalosporins	
Parenteral	*Oral*
Cefazolin	Cephalexin
	Cefadroxil
Second generation cephalosporins	
Parenteral	*Oral*
Cefuroxime	Cefaclor
Cefoxitin*	Cefuroxime axetil
	Cefprozil
Third generation cephalosporins	
Parenteral	*Oral*
Cefotaxime	Cefixime
Ceftizoxime	Cefpodoxime proxetil
Ceftriaxone	Cefdinir
Ceftazidime	Ceftibuten
Cefoperazone	Ceftamet pivoxil
Fourth generation cephalosporins	
Parenteral	
Cefepime	
Cefpirome	

*Not available in India

(c) elaboration of β-lactamases which destroy specific cephalosporins (cephalosporinases); the most common mechanism.

Though the incidence is low, resistance has been developed by some organisms, even against the third generation compounds. Individual cephalosporins differ in their:

(a) Antibacterial spectrum and relative potency against specific organisms.
(b) Susceptibility to β-lactamases elaborated by different organisms.
(c) Pharmacokinetic properties—many have to be injected, some are oral; majority are not metabolized, and are excreted rapidly by the kidney; have short t½s, probenecid inhibits their tubular secretion.

FIRST GENERATION CEPHALOSPORINS

These were developed in the 1960s, have high activity against gram-positive but weaker against gram-negative bacteria.

Cefazolin It is the prototype first generation cephalosporin that is active against most PnG sensitive organisms, i.e. *Streptococci (pyogenes* as well as *viridans)*, gonococci, meningococci, *C. diphtheriae, H. influenzae,* clostridia and *Actinomyces*. Activity against *Klebsiella, Moraxella catarrhalis* and *E. coli* is relatively high, but it is quite susceptible to staphylococcal β-lactamase. It can be given i.m. (less painful) as well as i.v. and has a longer t½ (2 hours) due to slower tubular secretion; attains higher concentration in plasma and in bile. It is the preferred parenteral first generation cephalosporin, especially for surgical prophylaxis.

Dose: 0.5 g 8 hourly (mild cases), 1 g 6 hourly (severe cases), children 25–50 mg/kg/day i.m. or i.v.; surgical prophylaxis 1.0 g 1/2 hour before surgery.

REFLIN, ALCIZON, ORIZOLIN 0.25 g, 0.5 g, 1 g per vial inj.

Cephalexin It is the most commonly used orally effective first generation cephalosporin, similar in spectrum to cefazolin, but less active against penicillinase producing staphylococci and *H. influenzae*. Plasma protein binding is low; it attains high concentration in bile and is excreted unchanged in urine; t½ ~60 min.

Dose: 0.25–1 g 6–8 hourly (children 25–100 mg/kg/day).

CEPHACILLIN 250, 500 mg cap; SPORIDEX, ALCEPHIN, CEPHAXIN 250, 500 mg cap, 125 mg/5 ml dry syr., 100 mg/ml pediatric drops.

ALCEPHIN-LA: Cephalexin + probenecid (250 + 250 mg and 500 + 500 mg) tabs.

Cefadroxil A close congener of cephalexin; has good tissue penetration—exerts more sustained action at the site of infection, because of which it can be given 12 hourly despite a t½ of 1 hr. It is excreted unchanged in urine; the dose needs to be reduced only if creatinine clearance is < 50 ml/min. The antibacterial activity of cefadroxil and indications are similar to those of cephalexin.

Dose: 0.5–1 g BD. DROXYL 0.5, 1 g tab, 250 mg/5 ml syr; CEFADROX 0.5 g cap, 125 mg/5 ml syr and 250 mg kid tab; KEFLOXIN 0.5 g cap, 0.25 g Distab, 125 mg/5 ml susp.

SECOND GENERATION CEPHALOSPORINS

These were developed subsequent to the first generation compounds and are more active against gram-negative organisms, with some members active against anaerobes as well, but none inhibits *P. aeruginosa.* They are weaker

than the first generation compounds against gram positive bacteria. Their utility has declined in favour of the 3rd generation agents.

Cefuroxime It is resistant to gram-negative β-lactamases: has high activity against organisms producing these enzymes including PPNG and ampicillin-resistant *H. influenzae,* while retaining significant activity on gram-positive cocci and certain anaerobes, but not *B. fragilis*. It is well tolerated by i.m. route and attains relatively higher CSF levels, but has been superseded by 3rd generation cephalosporins in the treatment of meningitis. It can be employed for single dose i.m. therapy of gonorrhoea due to PPNG.

CEFOGEN, SUPACEF, FUROXIL 250 mg and 750 mg/vial inj; 0.75–1.5 g i.m. or i.v. 8 hourly, children 30–100 mg/kg/day. For gonorrhoea 1.5 g divided at 2 sites i.m. inj + probenecid 1.0 g oral single dose.

Cefuroxime axetil This ester of cefuroxime is effective orally, though absorption is incomplete. The activity depends on *in vivo* hydrolysis and release of cefuroxime.

Dose: 250–500 mg BD, children half dose; CEFTUM, SPIZEF 125, 250, 500 mg captab and 125 mg/5 ml susp.

Cefaclor It retains significant activity by the oral route and is more active than the first generation compounds against *H. influenzae, E. coli, Pr. mirabilis* and some anaerobes.

Dose: 0.25–1.0 g 8 hourly

KEFLOR, VERCEF, DISTACLOR 250 mg cap, 125 and 250 mg distab, 125 mg/5 ml dry syr, 50 mg/ml ped. drops.

Cefprozil This 2nd generation cephalosporin has good oral absorption (>90%) with augmented activity against *Strep. pyogenes*, *Strep. pneumoniae*, *Staph. aureus*, *H. influenzae*, *Moraxella* and *Klebsiella*. It is excreted by the kidney, with a t½ of 1.3 hours. The primary indications are bronchitis, ENT and skin infections.

Dose: 250–500 mg BD, (child 20 mg/kg/day).

ORPROZIL, ZEMETRIL 250, 500 mg tab; REFZIL 250, 500 mg tab., 125 mg/5 ml and 250 mg/5 ml syr.

THIRD GENERATION CEPHALOSPORINS

These compounds introduced in the 1980s have highly augmented activity against gram-negative Enterobacteriaceae; and few members inhibit *Pseudomonas* as well. All are highly resistant to β-lactamases from gram-negative bacteria. However, they are less active on gram-positive cocci and anaerobes.

Cefotaxime It is the prototype of the third generation cephalosporins; exerts potent action on aerobic gram-negative as well as some gram-positive bacteria, but is not active on anaerobes (particularly *Bact. fragilis*), *Staph. aureus* and *Ps. aeruginosa*. Prominent indications are meningitis caused by gram-negative bacilli (attains relatively high CSF levels), life-threatening resistant/hospital-acquired infections, septicaemias and infections in immunocompromised patients. It is an alternative to ceftriaxone for typhoid fever, and can be utilized for single dose therapy (1 g i.m. + 1 g probenecid oral) of PPNG urethritis, but is not dependable for *Pseudomonas* infections.

Cefotaxime is deacetylated in the body; the metabolite exerts weaker but synergistic action with the parent drug. The plasma t½ of cefotaxime is 1 hr, but is longer for the deacetylated metabolite—permitting 12 hourly doses in many situations. Penetration into CSF is good.

Dose: 1–2 g i.m./i.v. 6–12 hourly, children 50–100 mg/kg/day.

OMNATAX, ORITAXIM, CLAFORAN 0.25, 0.5, 1.0 g per vial inj.

Ceftizoxime It is similar in antibacterial activity and indications to cefotaxime, but inhibits *B. fragilis* also. It is not metabolized—excreted by the kidney at a slower rate; t½ 1.5–2 hr.

Dose: 0.5–2.0 g i.m./i.v. 8 or 12 hourly.

CEFIZOX, EPOCELIN 0.5 and 1 g per vial inj.

Ceftriaxone The distinguishing feature of this cephalosporin is its longer duration of action (t½ 8 hr), permitting once, or at the most twice daily dosing. Penetration into CSF is good and elimination occurs equally in urine and bile.

Ceftriaxone has shown high efficacy in a wide range of serious infections including bacterial meningitis (especially in children), multiresistant typhoid fever, complicated urinary tract infections, abdominal sepsis and septicaemias.

A single dose of 250 mg i.m. has proven curative in gonorrhoea including PPNG, and in chancroid.

Hypoprothrombinaemia and bleeding are the specific adverse effects. Haemolysis is reported.

OFRAMAX, MONOCEF, MONOTAX 0.25, 0.5, 1.0 g per vial inj.

For skin/soft tissue/urinary infections: 1–2 g i.v. or i.m./day.

Meningitis: 4 g followed by 2 g i.v. (children 75–100 mg/kg) once daily for 7–10 days.

Typhoid: 4 g i.v. daily × 2 days followed by 2 g/day (children 75 mg/kg) till 2 days after fever subsides.

To overcome resistance, it has been combined with sulbactam or tazobactam.

CEFTICHEK, SUPRAXONE ceftriaxone + sulbactam 250 mg + 125 mg and 1.0 g + 0.5 g vial.

MONTAZ, EXTACEF-TAZO, FINECEF-T ceftriaxone 1 g + tazobactam 125 mg vial.

Ceftazidime The most prominent feature of this third generation cephalosporin is its high activity against *Pseudomonas aeruginosa*, and the specific indications are—febrile neutropenic patients with haematological malignancies, burn, etc. Its activity against Enterobacteriaceae is similar to that of cefotaxime, but it is less active on *Staph. aureus*, other gram positive cocci and anaerobes like *Bact. fragilis*. Its plasma t½ is 1.5–1.8 hr.

Neutropenia, thrombocytopenia, rise in plasma transaminases and blood urea have been reported.

Dose: 0.5–2 g i.m. or i.v. every 8 hr, children 30 mg/kg/day. Resistant typhoid 30 mg/kg/day.

FORTUM, CEFAZID, ORZID 0.25, 0.5 and 1 g per vial inj.

Cefoperazone Like ceftazidime, it differs from other third generation compounds in having stronger activity on *Pseudomonas* and weaker activity on other organisms. It is good for *S. typhi* and *B. fragilis* also, but more susceptible to β-lactamases. The indications are—severe urinary, biliary, respiratory, skin-soft tissue infections, typhoid, meningitis and septicaemias. It is primarily excreted in bile; t½ is 2 hr. It has hypoprothrombinaemic action but does not affect platelet function. A disulfiram-like reaction with alcohol has been reported.

Dose: 1–3 g i.m./i.v. 8–12 hourly.

MAGNAMYCIN 0.25 g, 1, 2 g inj; CEFOMYCIN, NEGAPLUS 1 g inj.

It has been combined with sulbactam.

CEFOBETA, KEFBACTUM Cefoperazone 500 mg + sulbactam 500 mg vial, CEFACTUM 1 g + 1 g vial.

Cefixime It is an orally active third generation cephalosporin highly active against Enterobacteriaceae, *H. influenzae, Strep. pyogenes,* and is resistant to many β-lactamases. However, it is not active on *Staph. aureus*, most pneumococci and *Pseudomonas*. It is longer acting (t½ 3 hr) and has been used in a dose of 200–400 mg BD for respiratory, urinary and biliary infections. Stool changes and diarrhoea are the most prominent side effects.

TOPCEF, ORFIX 100, 200 mg tab/cap, CEFSPAN 100 mg cap, 100 mg/5 ml syr, TAXIM-O 100, 200 mg tab, 50 mg/5 ml inj.

Cefpodoxime proxetil It is the orally active ester prodrug of 3rd generation cephalosporin cefpodoxime. In addition to being highly active against Enterobacteriaceae and streptococci, it inhibits *Staph. aureus*. It is used mainly for respiratory, urinary, skin and soft tissue infections.

Dose: 200 mg BD (max 800 mg/day)

CEFOPROX, CEPODEM, DOXCEF 100, 200 mg tab, 50 mg/5 ml and 100 mg/5 ml dry syr.

Cefdinir This orally active 3rd generation cephalosporin has good activity against many β lactamase producing organisms. Most respiratory pathogens including gram-positive cocci are susceptible. Its indications are pneumonia, acute exacerbations of chronic bronchitis, ENT and skin infections.

Dose: 300 mg BD

SEFDIN, ADCEF 300 mg cap, 125 mg/5 ml susp.

Ceftibuten Another oral 3rd generation cephalosporin, active against gram-positive and few gram-negative bacteria, but not *Staph. aureus*. It is stable to β-lactamases, and is indicated in respiratory and ENT infections; t½ 2–3 hours.

Dose: 200 mg BD or 400 mg OD.

PROCADAX 400 mg cap, 90 mg/5 ml powder for oral suspension.

Ceftamet pivoxil This ester prodrug of ceftamet, a 3rd generation cephalosporin has high activity against gram-negative bacteria, especially Enterobacteriaceae and *N. gonorrhoea;* used in respiratory, skin-soft tissue infections, etc.

Dose: 500 mg BD–TDS.

ALTAMET 250 mg tab; CEPIME-O 500 mg tab.

FOURTH GENERATION CEPHALOSPORINS

The distinctive feature of this last developed subgroup of cephalosporins is non-susceptibility to inducible chromosomal β lactamases in addition to high potency against Enterobacteriaceae and spectrum of activity resembling the 3rd generation compounds.

Cefepime Developed in 1990s, this 4th generation cephalosporin has antibacterial spectrum similar to that of 3rd generation compounds, but is highly resistant to β-lactamases, hence active against many bacteria resistant to the earlier drugs. *Ps. aeruginosa* and *Staph. aureus* are also inhibited but not MRSA. Due to high potency and extended spectrum, it is effective in many serious infections like hospital-acquired pneumonia, febrile neutropenia, bacteraemia, septicaemia. Higher concentrations are attained in the CSF, and it is excreted by the kidney with a t½ of 2 hours.

Dose: 1–2 g i.v. 8–12 hourly. Child with febrile neutropenia 50 mg/kg i.v. 8 hourly.

KEFAGE, CEFICAD, CEPIME 0.5, 1.0 g inj.

Cefpirome This 4th generation cephalosporin is indicated for the treatment of serious and resistant hospital-acquired infections including septicaemias, lower respiratory tract infections, etc. Its zwitterion character permits better penetration through porin channels of gram-negative bacteria. It is resistant to many β-lactamases; inhibits type 1 β-lactamase producing Enterobacteriaceae and it is more potent against gram-positive and some gram-negative bacteria than the 3rd generation compounds.

Dose: 1–2 g i.m./i.v. 12 hourly;

CEFROM, CEFORTH 1 g inj; BACIROM, CEFOR 0.25, 0.5, 1.0 g inj.

Adverse effects

Cephalosporins are generally well tolerated, but are more toxic than penicillin.

1. *Pain* after i.m. injection occurs with many cephalosporins, but some can be injected i.m., while others are injected only i.v. (*see* individual compounds). Thrombophlebitis of injected vein can occur.

2. *Diarrhoea* due to alteration of gut ecology or irritative effect is more common with orally administered compounds like cephalexin, cefixime and parenteral cefoperazone, which is largely excreted in bile.

3. *Hypersensitivity reactions* are the most important adverse effects of cephalosporins. Manifestations are similar to penicillin, but incidence is lower. Rashes are the most frequent manifestation, but anaphylaxis, angioedema, asthma and urticaria have also occurred. About 10% patients allergic to penicillin show cross reactivity with cephalosporins. Those with a history of immediate type of reactions to penicillin should better not be given a cephalosporin. Skin tests for sensitivity to cephalosporins are unreliable.

   A positive Coombs' test occurs in many patients, but haemolysis is rare.

4. *Nephrotoxicity* Some cephalosporins have low-grade nephrotoxicity which may be accentuated by preexisting renal disease, concurrent administration of an aminoglycoside or loop diuretic.

5. *Bleeding* occurs with cephalosporins having a methylthiotetrazole or similar substitution at position 3 (cefoperazone, ceftriaxone). This is due to hypoprothrombinaemia caused by the same mechanism as warfarin and is more common in patients with cancer, intra-abdominal infection or renal failure.

6. Neutropenia and thrombocytopenia are rare adverse effects reported with ceftazidime and some others.

7. A disulfiram-like interaction with alcohol has been reported with cefoperazone.

Uses

Currently cephalosporins are one of the most commonly used antibiotics. Among them they cover a wide range of gram-positive and gram-

negative bacteria including some anaerobes but not *B. fragilis*, or MRSA, enterococci, mycobacteria and chlamydia. Their indications are:

1. As alternatives to penicillins for ENT, upper respiratory and cutaneous infections, one of the first generation compounds may be used.

2. Respiratory, urinary and soft tissue infections caused by gram-negative organisms, especially *Klebsiella, Proteus, Enterobacter, Serratia*. Cephalosporins preferred for these infections are cefuroxime, cefotaxime, ceftriaxone.

3. Penicillinase producing staphylococcal infections.

4. Septicaemias caused by gram-negative organisms: an aminoglycoside may be combined with a cephalosporin.

5. Surgical prophylaxis: the first generation cephalosporins are popular drugs. Cefazolin (i.m. or i.v.) is employed for most types of surgeries including those with surgical prosthesis such as artificial heart valves, artificial joints, etc.

6. Meningitis: Optimal therapy of pyogenic meningitis requires bactericidal activity in the CSF, preferably with antibiotic concentrations several times higher than the MBC for the infecting organism. For empirical therapy before bacterial diagnosis, i.v. cefotaxime/ceftriaxone is generally combined with ampicillin or vancomycin or both. Ceftazidime + gentamicin is the most effective therapy for *Pseudomonas* meningitis.

7. Gonorrhoea caused by penicillinase producing organisms: ceftriaxone is a first choice drug for single dose therapy of gonorrhoea if the penicillinase producing status of the organism is not known. Cefuroxime and cefotaxime have also been used for this purpose. For chancroid also, a single dose is as effective as erythromycin given for 7 days.

8. Typhoid: Currently, ceftriaxone and cefoperazone injected i.v. are the fastest acting and most reliable drugs for enteric fever. They are preferred over fluoroquinolones (especially in children) for empirical therapy, since many *S. typhi* strains are resistant to chloramphenicol, ampicillin, cotrimoxazole, and FQs.

9. Mixed aerobic-anaerobic infections in cancer patients, those undergoing colorectal surgery, obstetric complications: cefuroxime, cefaclor or one of the third generation compounds is used.

10. Hospital acquired infections, especially respiratory and other infections in intensive care units, resistant to commonly used antibiotics: cefotaxime, ceftizoxime or a fourth generation drug may work.

11. Prophylaxis and treatment of infections in neutropenic patients: ceftazidime or another third generation compound, alone or in combination with an aminoglycoside.

MONOBACTAMS

Aztreonam It is a novel β-lactam antibiotic in which the other ring is missing (hence monobactam), but acts by binding to specific PBPs. It inhibits gram-negative enteric bacilli and *H. influenzae* at very low concentrations and *Pseudomonas* at moderate concentrations, but does not inhibit gram-positive cocci or faecal anaerobes. Thus, it is a β-lactam antibiotic with a spectrum resembling aminoglycosides, and is resistant to gram-negative β-lactamases. The main indications of aztreonam are hospital-acquired infections originating from urinary, biliary, gastrointestinal and female genital tracts.

Lack of cross sensitivity with other β-lactam antibiotics except ceftazidime (which has chemical similarity to aztreonam) is the most prominent feature of aztreonam: permiting its use in patients allergic to penicillins or cephalosporins. Rashes and rise in serum aminotransferases are the notable adverse effects. It is eliminated unchanged in urine with a t½ of 1.8 hr.

Dose: 0.5–2 g i.m. or i.v. 6–12 hourly.

AZENAM, TREZAM 0.5, 1.0, 2.0 g/vial inj.

CARBAPENEMS

Imipenem A derivative of thienamycin, imipenem is an extremely potent and broad-spectrum β-lactam antibiotic whose range of activity includes gram-positive cocci, Enterobacteriaceae, *Ps. aeruginosa, Listeria* as well as anaerobes like *Bact. fragilis* and *Cl. difficile*. It is resistant to most β-lactamases; inhibits penicillinase producing staphylococci. Though some MRSA are inhibited, it is not reliable for treating such infections.

A limiting feature of imipenem is its rapid hydrolysis by the enzyme dehydropeptidase I located on the brush border of renal tubular cells. An innovative solution to this problem is its combination with cilastatin, a reversible inhibitor of dehydropeptidase I, which has matched pharmacokinetics with imipenem (t½ of both is 1 hr) and protects it.

Imipenem-cilastatin 0.5 g i.v. 6 hourly (max 4 g/day) has proved effective in a wide range of serious hospital-acquired respiratory, urinary, abdominal, pelvic, skin and soft tissue infections including those in neutropenic, cancer and AIDS patients. For *Ps. aeruginosa* infections, it should be combined with gentamicin.

Imipenem has propensity to induce seizures at higher doses and in predisposed patients. Diarrhoea, vomiting, skin rashes and other hypersensitivity reactions are the side effects.
IMINEM: Imipenem + cilastatin 250 mg + 250 mg and 500 mg + 500 mg/vial inj.
LASTINEM: Imipenem + cilastatin 125 + 125 mg, 250 + 250 mg, 500 + 500 mg and 1000 mg + 1000 mg/vial inj.

Meropenem This newer carbapenem is not hydrolysed by renal peptidase; does not need to be protected by cilastatin. Like imipenem, it is active against both gram-positive and gram-negative bacteria, aerobes as well as anaerobes; somewhat more potent on gram-negative aerobes, especially *Ps. aeruginosa* but less potent on gram-positive cocci.

Meropenem is a reserve drug for the treatment of serious nosocomial infections like septicaemia, febrile neutropenia, intraabdominal and pelvic infections, etc. caused by cephalosporin-resistant bacteria and diabetic foot. For *Ps. aeruginosa* infections, it should be combined with an aminoglycoside. The adverse effects of meropenem are similar to imipenem, but it is less likely to cause seizures.
Dose: 0.5–2.0 g (10–40 mg/kg) by slow i.v. injection 8 hourly.
MERONEM, MENEM, UBPENEM 0.5, 1.0 g/vial inj.

Faropenem Another carbapenem β-lactam antibiotic that is orally active against many gram-positive as well as gram-negative bacteria, including some anaerobes. *Strep. pneumoniae, H. influenzae, Moraxella catarrhalis* are highly susceptible. It has been mainly used in respiratory, ENT and genitourinary infections. Usual side effects are diarrhoea, abdominal pain, nausea and rashes.
Dose: 150–300 mg oral TDS; FARONEM, FAROZET 150 mg, 200 mg tab.

Doripenem Introduced recently, this carbapenem has antimicrobial activity similar to meropenem, but is more active against some resistant *Pseudomonas*. Other properties, including nonsusceptibility to renal peptidase, as well as clinical indications are also similar to meropenem. Adverse effects are nausea, diarrhoea, superinfections and phlebitis of the injected vein. Seizures are less likely.
Dose: 500 mg by slow i.v. infusion over 1 hr, every 8 hours.
DORIGLEN 500 mg/vial inj., SUDOPEN 250, 500 mg/vial inj.

☞ PROBLEM DIRECTED STUDY

51.1 A 10-year-old boy weighing 25 kg is brought with continuous fever for the past 7 days. Initially the fever was mild, but has gradually increased and the body temp. now is 103°F. The boy also complains of abdominal pain, bloating, loose motions, loss of appetite, occasional vomiting, weakness, malaise and cough. A local doctor had given some tablets for the past 3 days, but the condition has worsened. He looks ill, mildly dehydrated with coated tongue; pulse is 70/min, abdomen is distended and tender on pressing. Liver and spleen are palpable. The total leucocyte count is 5000/cumm. Blood for culture is sent. A provisional diagnosis of *typhoid (enteric)* fever is made.

(a) Should antibiotic therapy be started right away, or the report of blood culture awaited?

(b) If treatment is to be started, which antibiotic would be the most appropriate, and why? What should be the dose and duration of antibiotic therapy?

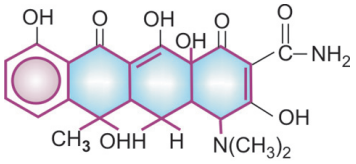
(c) Should a single antibiotic or a combination be used?

(*see* Appendix-1 for solution)

Chapter 52 Tetracyclines and Chloramphenicol
(Broad-Spectrum Antibiotics)

TETRACYCLINES

These are a class of antibiotics having a nucleus of four cyclic rings.



TETRACYCLINE

All are obtained from soil actinomycetes. The first to be introduced was chlortetracycline in 1948 under the name *aureomycin* (because of the golden yellow colour of *S. aureofaciens* colonies producing it). It contrasted markedly from penicillin and streptomycin (the other two antibiotics available at that time) in being active orally and in affecting a wide range of microorganisms—hence called 'broad-spectrum antibiotic'. Oxytetracycline soon followed; others were produced later, either from mutant strains or semisynthetically. A new synthetic subclass 'glycylcyclines' represented by *Tigecycline* has been added recently.

All tetracyclines are slightly bitter solids which are slightly water soluble, but their hydrochlorides are more soluble. Aqueous solutions are unstable. All have practically the same antimicrobial activity (with minor differences). The subsequently developed members have high lipid solubility, greater potency and some other differences. The tetracyclines still available in India for clinical use are:

Tetracycline	Doxycycline
Oxytetracycline	Minocycline
Demeclocycline	

Glycylcycline: Tigecycline

Many others like Chlortetracycline, Methacycline, Rolitetracycline, Lymecycline are no longer commercially available.

Mechanism of action The tetracyclines are primarily bacteriostatic; inhibit protein synthesis by binding to 30S ribosomes in susceptible organism. Subsequent to such binding, attachment of aminoacyl-t-RNA to the acceptor (A) site of mRNA-ribosome complex is interferred with (Fig. 52.1). As a result, the peptide chain fails to grow.

The sensitive organisms have an energy dependent active transport process which concentrates tetracyclines intracellularly. In gram-negative bacteria tetracyclines diffuse through porin channels as well. The more lipid-soluble members (doxycycline, minocycline) enter by passive diffusion also (this is partly responsible for their higher potency). The carrier involved in active transport of tetracyclines is absent in the host cells. Moreover, protein synthesizing apparatus of host cells is less susceptible to tetracyclines. These two factors are responsible for the selective toxicity of tetracyclines for the microbes.

Antimicrobial spectrum When originally introduced, tetracyclines inhibited practically all types of pathogenic microorganisms except fungi and viruses; hence the name 'broad-spectrum antibiotic'. However, promiscous and often indiscriminate use has gradually narrowed the field of their usefulness.

1. Cocci: All gram-positive and gram-negative cocci were originally sensitive, but now only few *Strep. pyogenes*, *Staph. aureus* (including MRSA) and enterococci respond. Responsiveness of *Strep. pneumoniae* has decreased somewhat. Tetracyclines (especially minocycline) are now active against relatively few *N. gonorrhoeae* and *N. meningitidis*.
2. Most gram-positive bacilli, e.g. *Clostridia* and other anaerobes, *Listeria, Corynebacteria, Propionibacterium acnes, B. anthracis* are

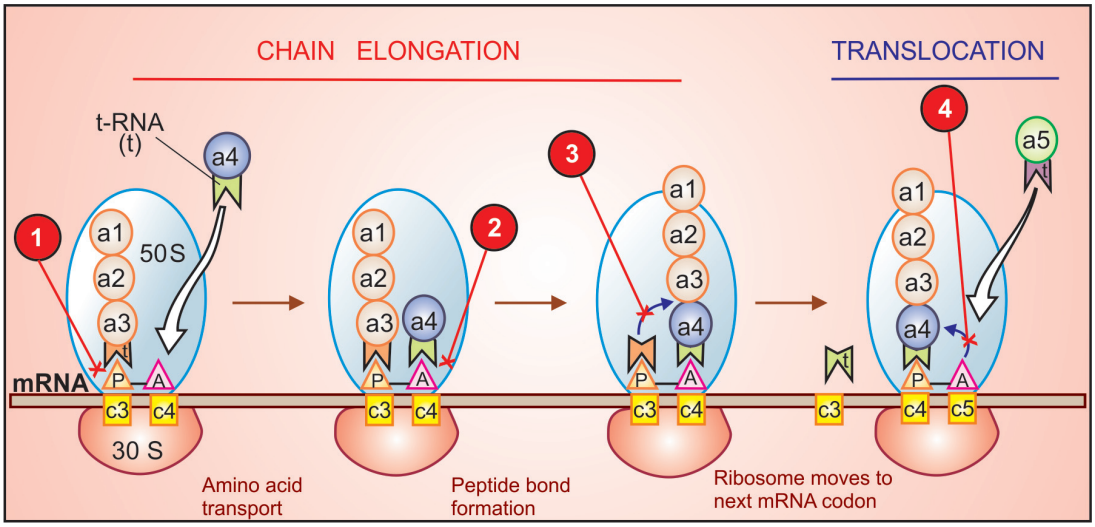


Fig. 52.1: Bacterial protein synthesis and the site of action of antibiotics

The messenger RNA (mRNA) attaches to the 30S ribosome. The initiation complex of mRNA starts protein synthesis and polysome formation. The nacent peptide chain is attached to the peptidyl (P) site of the 50S ribosome. The next amino acid (a) is transported to the acceptor (A) site of the ribosome by its specific tRNA which is complementary to the base sequence of the next mRNA codon (C). The nascent peptide chain is transferred to the newly attached amino acid by peptide bond formation. The elongated peptide chain is shifted back from the 'A' to the 'P' site and the ribosome moves along the mRNA to expose the next codon for amino acid attachment. Finally the process is terminated by the termination complex and the protein is released.
(1) Aminoglycosides bind to several sites at 30S and 50S subunits as well as to their interface—freeze initiation, interfere with polysome formation and cause misreading of mRNA code.
(2) Tetracyclines bind to 30S ribosome and inhibit aminoacyl tRNA attachment to the 'A' site.
(3) Chloramphenicol binds to 50S subunit—interferes with peptide bond formation and transfer of peptide chain from 'P' site.
(4) Erythromycin and clindamycin also bind to 50S ribosome and hinder translocation of the elongated peptide chain back from 'A' site to 'P' site and the ribosome does not move along the mRNA to expose the next codon. Peptide synthesis may be prematurely terminated.

inhibited but not *Mycobacteria*, except *M. leprae* (to minocycline) and some atypical ones.

3. Sensitive gram-negative bacilli are—*H. ducreyi, Calymmatobacterium granulomatis, V. cholerae, Yersinia pestis, Y. enterocolitica, Campylobacter, Helicobacter pylori, Brucella, Pasteurella multocida, F. tularensis* and many anaerobes. Some *H. influenzae* have become insensitive.

Enterobacteriaceae are now largely resistant. Notable bacilli that are not inhibited are *Pseudomonas aeruginosa, Proteus, Klebsiella, Salmonella typhi* and many *Bact. fragilis*. MIC against anaerobes is relatively higher.

4. Spirochetes, including *T. pallidum* and *Borrelia* are quite sensitive.

5. All rickettsiae (typhus, etc.) and chlamydiae are highly sensitive.

6. *Mycoplasma* and *Actinomyces* are moderately sensitive.

7. Protozoa like *Entamoeba histolytica* and *Plasmodia* are inhibited at high concentrations.

Resistance Resistance to tetracyclines develops slowly in a graded manner. In such bacteria, usually the tetracycline concentrating mechanism becomes less efficient or the bacteria acquire capacity to pump it out. Another mechanism is plasmid mediated synthesis of a 'protection' protein which protects the ribosomal binding site from tetracycline. Elaboration of tetracycline inactivating enzymes is an unimportant mechanism of the tetracycline

resistance. Due to widespread use, tetracycline resistance has become common among gram-positive cocci, *E. coli, Enterobacter* and many others.

Incomplete cross resistance is seen among different members of the tetracycline group. Some organisms not responding to other tetracyclines may be inhibited by therapeutically attained concentrations of doxycycline and minocycline (the most potent agent).

Partial cross resistance between tetracyclines and chloramphenicol has been noted.

Pharmacokinetics

The pharmacokinetic differences between individual tetracyclines are included in Table 52.1. The older tetracyclines are incompletely absorbed from g.i.t.; absorption is better if taken in empty stomach. Doxycycline and minocycline are completely absorbed irrespective of food. Tetracyclines have chelating property—form insoluble and unabsorbable complexes with calcium and other metals. Milk, iron preparations, nonsystemic antacids and sucralfate reduce their absorption. Administration of these substances and tetracyclines should be staggered, if they cannot be avoided altogether.

Tetracyclines are widely distributed in the body (volume of distribution > 1 L/kg). Variable degree of protein binding is exhibited by different members. They are concentrated in liver, spleen and bind to the connective tissue in bone and teeth. Intracellularly, they bind to mitochondria. Minocycline being highly lipid soluble accumulates in body fat. The CSF concentration of most tetracyclines is about 1/4 of plasma concentration, whether meninges are inflamed or not.

Most tetracyclines are primarily excreted in urine by glomerular filtration; dose has to be reduced in renal failure; doxycycline is an exception to this. They are partly metabolized and significant amounts enter bile—some degree of enterohepatic circulation occurs. They are secreted in milk in amounts sufficient to affect the suckling infant.

Enzyme inducers like phenobarbitone and phenytoin enhance metabolism and shorten the t½ of doxycycline.

Administration Oral capsule is the dosage form in which tetracyclines are most commonly administered. The capsule should be taken ½ hr before or 2 hr after food. Liquid oral preparations for pediatric use are banned in India.

Tetracyclines are not recommended by i.m. route because it is painful and absorption from the injection site is poor. Slow i.v. injection may be given in severe cases, but is rarely required now.

A variety of topical preparations (ointment, cream, etc.) are available, but should not be used, because there is high risk of sensitization. However, ocular application is not contraindicated.

Preparations

1. Oxytetracycline: TERRAMYCIN 250, 500 mg cap, 50 mg/ml in 10 ml vials inj; 3% skin oint, 1% eye/ear oint.
2. Tetracycline: ACHROMYCIN, HOSTACYCLINE, RESTECLIN 250, 500 mg cap. 3% skin oint, 1% eye/ear drops and oint.
3. Demeclocycline (Demethylchlortetracycline): LEDERMYCIN 150, 300 mg cap/tab.
4. Doxycycline: TETRADOX, DOXICIP, DOXT, NOVADOX 100 mg cap.
5. Minocycline: CYANOMYCIN, CNN 50, 100 mg caps.

Adverse effects

Irritative effects Tetracyclines have irritant property; can cause epigastric pain, nausea, vomiting and diarrhoea on oral ingestion. The irritative diarrhoea is to be distinguished from that due to superinfection. Odynophagia and esophageal ulceration has occurred by release of the material from capsules in the esophagus during swallowing, especially with doxycycline. Intramuscular injection of tetracyclines is very painful; thrombophlebitis of the injected vein can occur, especially on repeated i.v. injection.

Organ toxicity This is dose related.

1. *Liver damage* Fatty infiltration of liver and jaundice occurs occasionally. Oxytetracycline and

TABLE 52.1 Comparative features of tetracyclines

	Tetracycline (T) *Oxytetracycline (OxyT)*	*Demeclocycline*	*Doxycycline (Doxy)* *Minocycline (Mino)*
1. Source	Oxy T: *S. rimosus* T: semisynthetic	*S. aureofaciens* (mutant)	Doxy: semisynthetic Mino: semisynthetic
2. Potency	Low	Intermediate	High (Doxy < Mino)
3. Intestinal absorption	60–80%	60–80%	95–100% no interference by food
4. Plasma protein binding	Oxy T: Low T: Moderate	High	High
5. Elimination	T: } Rapid renal Oxy T: } excretion	Partial metabolism, slower renal excretion	Doxy: Primarily excreted in faeces as conjugate Mino: Primarily metabolized, excreted in urine and bile
6. Plasma t½	6–10 hr.	16–18 hr.	18–24 hr.
7. Dosage	250–500 mg QID or TDS	300 mg BD	200 mg initially, then 100–200 mg OD
8. Alteration of intestinal flora	Marked	Moderate	Least
9. Incidence of diarrhoea	High	Intermediate	Low
10. Phototoxicity	Low	Highest	Doxy: High
11. Specific toxicity	Oxy T: less tooth discolouration	More phototoxic, diabetes insipidus	Doxy: Low renal toxicity. Mino: Vestibular toxicity, less superinfections

tetracycline are safer in this regard. Tetracyclines are risky in pregnant women; can precipitate acute hepatic necrosis which may be fatal.

2. *Kidney damage* It is a risk only in the presence of existing kidney disease. All tetracyclines, except doxycycline, accumulate and enhance renal failure. A reversible *Fanconi syndrome* like condition is produced by outdated tetracyclines. This is caused by degraded products—epitetracycline, anhydrotetracycline and epianhydrotetracycline which damage proximal tubules. Exposure to acidic pH, moisture and heat favours such degradation.

3. *Phototoxicity* A sunburn-like or other severe skin reaction on exposed parts is seen in some individuals. A higher incidence has been noted with demeclocycline and doxycycline. Distortion of nails occurs occasionally.

4. *Teeth and bones* Tetracyclines have chelating property. Calcium-tetracycline chelate gets deposited in developing teeth and bone. Given from midpregnancy to 5 months of extrauterine life, the deciduous teeth are affected: brown discolouration, ill-formed teeth which are more susceptible to caries. Tetracyclines given between 3 months and 6 years of age affect the crown of permanent anterior dentition. Repeated courses are more damaging.

Given during late pregnancy or childhood, tetracyclines can cause temporary suppression of bone growth. The ultimate effect on stature is mostly insignificant, but deformities and reduction in height are a possibility with prolonged use.

5. *Antianabolic effect* Tetracyclines reduce protein synthesis and have an overall catabolic effect. They induce negative nitrogen balance and can increase blood urea.

6. *Increased intracranial pressure* is noted in some infants.

7. *Diabetes insipidus* Demeclocycline antagonizes ADH action and reduces urine concentrating ability of the kidney. It has been tried in patients with inappropriate ADH secretion.

8. *Vestibular toxicity* Minocycline can cause ataxia, vertigo and nystagmus, which subside when the drug is discontinued.

Hypersensitivity This is infrequent with tetracyclines. Skin rashes, urticaria, glossitis, pruritus ani and vulvae, even exfoliative dermatitis have been reported. Angioedema and anaphylaxis are extremely rare. Complete cross sensitization is exhibited by different tetracyclines.

Superinfection Tetracyclines are frequently responsible for superinfections, because they cause more marked suppression of the resident flora.

Though mouth, skin or vagina may be involved, intestinal superinfection by *Candida albicans* is most prominent (for details *see* p. 693); pseudomembranous enterocolitis is rare but serious. Higher doses suppress the flora more completely—greater chance of superinfection: doses on the lower side of the range should be used whenever possible. The tetracycline should be discontinued at the first sign of superinfection and appropriate therapy instituted.

Doxycycline and minocycline are less liable to cause diarrhoea, because only small amounts reach the lower bowel in the active form.

Precautions

1. Tetracyclines should not be used during pregnancy, lactation and in children.
2. They should be avoided in patients on diuretics: blood urea may rise in such patients.
3. They should be used cautiously in renal or hepatic insufficiency.
4. Preparations should never be used beyond their expiry date.
5. Do not mix injectable tetracyclines with penicillin—inactivation occurs.
6. Do not inject tetracyclines intrathecally.

Uses

Although tetracyclines are broad-spectrum antibiotics, they should be employed only for those infections for which a more selective and less toxic AMA is not available. Clinical use of tetracyclines has very much declined due to availability of fluoroquinolones and other efficacious AMAs.

1. *Empirical therapy* Tetracyclines are often employed when the nature and sensitivity of the infecting organism cannot be reasonably guessed. However, they are not dependable for empirical treatment of serious/life-threatening infections. They may also be used for initial treatment of *mixed infections,* although a combination of β-lactam and an aminoglycoside antibiotic or a third generation cephalosporin or a fluoroquinolone are now preferred.

2. *Tetracyclines are the first choice drugs:* Despite development of resistance by many organisms, tetracyclines are still the preferred drugs for:

(a) *Venereal diseases:*

- *Chlamydial nonspecific urethritis/endocervicitis:* 7 day doxycycline treatment is as effective as azithromycin single dose.
- *Lymphogranuloma venereum:* resolves in 2–3 weeks (*see* Table 54.1).
- *Granuloma inguinale*: due to *Calymm. granulomatis*: a tetracycline administered for 3 weeks is the most effective treatment.

(b) *Atypical pneumonia:* due to *Mycoplasma pneumoniae:* duration of illness is reduced by tetracycline therapy. Psittacosis is treated in 2 weeks by tetracyclines.

(c) *Cholera:* Tetracyclines have adjuvant value by reducing stool volume and limiting the duration of diarrhoea.

(d) *Brucellosis:* Tetracyclines are highly efficacious; cause rapid symptomatic relief; therapy

of choice is doxycycline 200 mg/day + rifampin 600 mg/day for 6 weeks. Gentamicin may be combined with doxycycline in acute cases.

(e) *Plague:* Tetracyclines are highly effective in both bubonic and pneumonic plague. They are preferred for blind/mass treatment of suspected cases during an epidemic, though streptomycin often acts faster.

(f) *Relapsing fever:* due to *Borrelia recurrentis* responds adequately.

(g) *Rickettsial infections:* typhus, rocky mountain spotted fever, Q fever, etc. respond dramatically. Chloramphenicol is an alternative.

3. *Tetracyclines are second choice drugs:*

(a) To penicillin/ampicillin for tetanus, anthrax, actinomycosis and *Listeria* infections.

(b) To ceftriaxone, amoxicillin or azithromycin for gonorrhoea, especially for penicillin resistant non-PPNG; also in patients allergic to penicillin, but response rate has decreased.

(c) To ceftriaxone for syphilis in patients allergic to penicillin; early syphilis can be treated in 2 weeks but late syphilis requires 1 month.

(d) To penicillin for leptospirosis; doxycycline 100 mg BD for 7 days is curative. Weekly doxycycline (200 mg) has been used as prophylactic in subjects at risk during an epidemic.

(e) To azithromycin for pneumonia due to *Chlamydia pneumoniae.* Oral as well as topical tetracycline has been used in trachoma.

(f) To ceftriaxone/azithromycin for chancroid.

(g) To streptomycin for tularemia.

4. *Other situations in which tetracyclines may be used are:*

(a) Urinary tract infections: Odd cases in which the organism has been found sensitive.

(b) Community-acquired pneumonia, when a more selective antibiotic cannot be used.

(c) Amoebiasis: along with other amoebicides for chronic intestinal amoebiasis.

(d) As adjuvant to quinine or artesunate for chloroquine-resistant *P. falciparum* malaria (*see* p. 829).

(e) Acne vulgaris: prolonged therapy with low doses may be used in severe cases (since *Propionibacterium acnes* is sensitive to tetracyclines), but simpler treatments are preferred in most cases (*see* Ch. 64).

(f) Chronic obstructive lung disease: prophylactic use may reduce the frequency of exacerbations, but the risk : benefit ratio is controversial.

Tigecycline

It is the first member of a new class of synthetic tetracycline analogues (glycyl-cyclines) which are active against most bacteria that have developed resistance to the classical tetracyclines. Thus, they have the braodest spectrum of activity. Tigecycline is a derivative of minocycline, and was introduced in 2005.

Tigecycline is active against most gram-positive and gram-negative cocci and anaerobes, including tetracycline resistant strains of *Strep. pyogenes*, *Strep. pneumoniae, Staph. aureus,* MRSA, VRSA, *Enterococcus faecalis* and VRE, most Enterobacteriaceae, *Acinetobacter*, as well as tetracycline sensitive organisms like *Rickettsia, Chlamydia, Mycoplasma, Legionella*, etc. However, *Pseudomonas* and *Proteus* are inherently nonresponsive to tigecycline.

Tigecycline acts in the same manner as tetracyclines. The lack of cross resistance between the two groups is mainly because the tetracycline efflux pumps acquired by many resistant bacteria have low affinity for tigecycline and are unable to pump it out. In other resistant bacteria, the ribosomal protection protein against tetracycline is less active in protecting the ribosomal binding site from tigecycline. Thus, the two most important mechanisms of tetracycline resistance do not operate against tigecycline.

Tigecycline is poorly absorbed from g.i.t; the only route of administration is by slow i.v. infusion. It is widely distributed in tissues, volume of distribution is large (>7 L/kg). Consequently, plasma concentrations are low. It is eliminated mainly in the bile; dose adjustment is not needed in renal insufficiency. The duration of action is long; elimination t½ is 37–67 hours.

Though, tigecycline can be used in many infections, it is approved only for treatment of serious and hospitalized patients of community acquired pneumonia, complicated skin and skin structure infections (but not diabetic foot), complicated intraabdominal infections caused by enterococci, anaerobes and Enterobacteriaceae. It is not recommended for hospital acquired/ventilator-associated chest infections, because in a comparative trial, all cause mortality was higher in tigecycline group than in the comparator group receiving other antibiotics. It is also not suitable for urinary tract infection, because only low concentrations are attained in urine. The clinical efficacy of tigecycline in other infective conditions is still to be established.

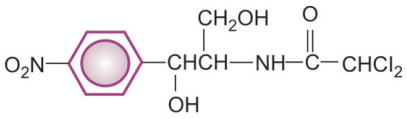
Dose: 100 mg loading dose, followed by 50 mg 12 hourly by i.v. infusion over 30–60 min, for 5–14 days.
TYGACIL, TEVRAN, TIGIMAX 50 mg lyophilized powder/vial inj.

The most common side effect is nausea and occasionally vomiting. Others are epigastric distress, diarrhoea, skin reactions, photosensitiviy and injection site complications. Superinfections and other adverse effects of tetracyclines can occur with tigecycline as well. It is not recommended for children and during pregnancy. Few cases of pancreatitis are reported.

CHLORAMPHENICOL

Chloramphenicol was initially obtained from *Streptomyces venezuelae* in 1947. It was soon synthesized chemically and the commercial product now is all synthetic.

It is a yellowish white crystalline solid, aqueous solution is quite stable, stands boiling, but needs protection from light. The nitrobenzene moiety of chloramphenicol is probably responsible for the antibacterial activity as well as its intensely bitter taste.



CHLORAMPHENICOL

Mechanism of action Chloramphenicol inhibits bacterial protein synthesis by interfering with 'transfer' of the elongating peptide chain to the newly attached aminoacyl-tRNA at the ribosome-mRNA complex. It specifically attaches to the 50S ribosome near the acceptor (A) site and prevents peptide bond formation between the newly attached aminoacid and the nascent peptide chain (*see* Fig. 52.1) without interfering with the aminoacyl-tRNA attachment to the 30S ribosome (the step blocked by tetracycline).

At high doses, it can inhibit mammalian mitochondrial protein synthesis as well. Bone marrow cells are especially susceptible.

Antimicrobial spectrum Chloramphenicol is primarily bacteriostatic, though high concentrations have been shown to exert cidal effect on some bacteria, e.g. *H. influenzae* and *N. meningitidis*. It is a broad-spectrum antibiotic, active against nearly the same range of organisms (gram-positive and negative cocci and bacilli, rickettsiae, mycoplasma) as tetracyclines. Notable differences between these two are:

(a) Chloramphenicol was highly active against *Salmonella* including *S. typhi*, but resistant strains are now rampant.

(b) It is more active than tetracyclines against *H. influenzae* (though some have now developed resistance), *B. pertussis, Klebsiella, N. meningitidis* and anaerobes including *Bact. fragilis.*

(c) It is less active against gram-positive cocci, spirochetes, certain Enterobacteriaceae and *Chlamydia. Entamoeba* and *Plasmodia* are not inhibited.

Like tetracyclines, it is ineffective against *Mycobacteria, Pseudomonas*, many *Proteus*, viruses and fungi.

Resistance Most bacteria are capable of developing resistance to chloramphenicol, which generally emerges in a graded manner, as with tetracyclines. Being orally active, broad-spectrum and relatively cheap, chloramphenicol

was extensively and often indiscriminately used, especially in developing countries, resulting in high incidence of resistance among many gram-positive and gram-negative bacteria.

In many areas, highly chloramphenicol resistant *S. typhi* have emerged due to transfer of R factor by conjugation. Resistance among gram-negative bacteria is generally due to acquisition of R plasmid encoded for an acetyl transferase—an enzyme which inactivates chloramphenicol. Acetyl-chloramphenicol does not bind to the bacterial ribosome. In many cases, this plasmid has also carried resistance to ampicillin and tetracycline. Multidrug-resistant *S. typhi* have arisen.

Decreased permeability into the resistant bacterial cells (chloramphenicol appears to enter bacterial cell both by passive diffusion as well as by facilitated transport) and lowered affinity of bacterial ribosome for chloramphenicol are the other mechanisms of resistance. Partial cross resistance between chloramphenicol and erythromycin/clindamycin has been noted, because all these antibiotics bind to 50S ribosome at adjacent sites and one may hinder access of the other to its site of action. Some cross resistance with tetracyclines also occurs, though the latter binds to 30S ribosome.

Pharmacokinetics

Chloramphenicol is rapidly and completely absorbed after oral ingestion. It is 50–60% bound to plasma proteins and very widely distributed: volume of distribution 1 L/kg. It freely penetrates serous cavities and blood-brain barrier: CSF concentration is nearly equal to that of unbound drug in plasma. It crosses placenta and is secreted in bile and milk.

Chloramphenicol is primarily conjugated with glucuronic acid in the liver and little is excreted unchanged in urine. Cirrhotics and neonates, who have low conjugating ability, require lower doses. The metabolite is excreted mainly in urine. Plasma t½ of chloramphenicol is 3–5 hours in adults. It is increased only marginally in renal failure: dose need not be modified.

Preparations and administration

The commonest route of administration of chloramphenicol is oral—as capsules; 250–500 mg 6 hourly (max. 100 mg/kg/day), children 25–50 mg/kg/day. Significant bioavailability differences among different market preparations have been shown. It is also available for application to eye/ear, but topical use at other sites is not recommended.

CHLOROMYCETIN, ENTEROMYCETIN, PARAXIN, 250 mg, 500 mg cap, 1% eye oint, 0.5% eye drops, 5% ear drops, 1% applicaps.

Chloramphenicol palmitate (CHLOROMYCETIN PALMITATE, ENTEROMYCETIN, PARAXIN 125 mg/5 ml oral susp) is an insoluble tasteless ester of chloramphenicol, which is inactive as such. It is nearly completely hydrolysed in the intestine by pancreatic lipase and absorbed as free chloramphenicol, but produces lower plasma concentration.

Chloramphenicol succinate (ENTEROMYCETIN, CHLOROMYCETIN SUCCINATE, KEMICETINE 1 g/vial inj, PHENIMYCIN 0.25, 0.5, 1.0 g inj. is the soluble but inactive ester which is used in the parenteral preparations. Intramuscular injection is painful and produces lower blood levels. It is hydrolysed in tissues to the free active form. However, bioavailability even on i.v. injection is only 70% due to renal excretion of the ester before hydrolysis.

also VANMYCETIN 0.4% eye drops, 250 mg opticaps, LYKACETIN 1% skin cream, 10% otic solution, OCUCHLOR 0.5% eye drops.

Adverse effects

1. *Bone marrow depression* Of all drugs, chloramphenicol is the most important cause of aplastic anaemia, agranulocytosis, thrombocytopenia or pancytopenia. Two forms are recognized:

(a) *Non-dose related idiosyncratic reaction*: This is rare (1 in 40,000), unpredictable, but serious, often fatal, probably has a genetic basis and is more common after repeated courses. Aplastic anaemia is the most common manifestation. Apparently, a longer latent period of onset of marrow aplasia is associated with higher mortality. Many victims, even if they survive, develop leukaemias later.

(b) *Dose and duration of therapy related myelosuppression:* a direct toxic effect, predictable and probably due to inhibition of mitochondrial enzyme synthesis in the erythropoietic cells. This is often reversible without long-term sequelae. Liver and kidney disease predisposes to such toxicity.

2. *Hypersensitivity reactions* Rashes, fever, atrophic glossitis, angioedema are infrequent.

3. *Irritative effects* Nausea, vomiting, diarrhoea, pain on injection.

4. *Superinfections* These are similar to tetracyclines, but less common.

5. *Gray baby syndrome* It occurred when high doses (~100 mg/kg) were given prophylactically to neonates, especially premature. The baby stopped feeding, vomited, became hypotonic and hypothermic, abdomen distended, respiration became irregular; an ashen gray cyanosis developed in many, followed by cardiovascular collapse and death. Blood lactic acid was raised.

It occurs because of inability of the newborn to adequately metabolize and excrete chloramphenicol. At higher concentration, chloramphenicol blocks electron transport in the liver, myocardium and skeletal muscle, resulting in the above symptoms. Chloramphenicol should be avoided in neonates, and even if given, dose should be ~ 25 mg/kg/day.

Interactions Chloramphenicol inhibits metabolism of tolbutamide, chlorpropamide, warfarin, cyclophosphamide and phenytoin. Toxicity can occur if dose adjustments are not done. Phenobarbitone, phenytoin, rifampin enhance chloramphenicol metabolism → reduce its concentration → failure of therapy may occur.

Being bacteriostatic, chloramphenicol can antagonize the cidal action of β-lactams/aminoglycosides on certain bacteria.

Uses

Clinical use of chloramphenicol for systemic infections is now highly restricted due to fear of fatal toxicity. Because of risk of serious (though rare) bone marrow aplasia:

(a) Never use chloramphenicol for minor infections or those of undefined etiology.

(b) Do not use chloramphenicol for infections treatable by other safer antimicrobials.

(c) Avoid repeated courses.

(d) Daily dose not to exceed 2–3 g; duration of therapy to be < 2 weeks, total dose in a course < 28 g.

(e) Regular blood counts (especially reticulocyte count) may detect dose-related bone marrow toxicity but not the idiosyncratic type.

(f) Combined formulation of chloramphenicol with any drug meant for internal use is banned in India.

Indications of chloramphenicol are:

1. *Pyogenic meningitis:* Third generation cephalosporins (± vancomycin) are presently the first line drugs for empirical therapy of bacterial meningitis (*see* Ch. 51). Chloramphenicol in a dose of 50–75 mg/kg/day may be used as a second line drug for *H. influenzae* and meningococcal meningitis, especially in young children and cephalosporin allergic patients, because it has excellent penetration into CSF and clinical efficacy has been demonstrated.

2. *Anaerobic infections* caused by *Bact. fragilis* and others (wound infections, intraabdominal infections, pelvic abscess, and brain abscess, etc.) respond well to chloramphenicol. However, clindamycin or metronidazole are mostly used for these. Chloramphenicol may be given in addition, or as an alternative in patients not tolerating these drugs. A penicillin/cephalosporin is generally combined since most of these are mixed infections.

3. *Intraocular infections* Chloramphenicol given systemically attains high concentration in ocular fluid. It is the preferred drug for endophthalmitis caused by sensitive bacteria.

4. *Enteric fever:* Chloramphenicol was the first antibiotic and the drug of choice for typhoid fever till the 1980s when resistant *S. typhi* emerged and spread globally, including most parts of India. As a result, it became clinically unreliable; 50–80% isolates showed *in vitro* resistance. Many of these are multidrug resistant—not responsive to ampicillin and cotrimoxazole as well. However, few recent reports from certain parts of India indicate return of sensitivity to chloramphenicol. Being orally active and inexpensive, it may be used only if the local strain is known to be sensitive and responsive clinically. The dose is 0.5 g 6 hourly (children 50 mg/kg/day) till fever subsides, then 0.25 g 6 hourly for another 5–7 days, because bacteriological cure takes longer.

Being bacteriostatic, relapses occur in ~ 10% chloramphenicol treated patients. Also, it does not prevent or cure the carrier state. Bactericidal action is required to eradicate carrier state, because in this state, host defence mechanisms do not operate against these pathogenic bacteria; as if they were commensals.

5. *As second choice drug*

(a) to tetracyclines for brucellosis and rickettsial infections, especially in young children and pregnant women in whom tetracyclines are contraindicated.

(b) to erythromycin for whooping cough.

6. *Urinary tract infections* Use of chloramphenicol is improper when safer drugs are available. It should be used only when kidney substance is involved and the organism is found to be sensitive only to this drug.

7. *Topically* In conjunctivitis, external ear infections—chloramphenicol 0.5–5.0% is highly effective. Topical use on skin or other areas is not recommended because of risk of sensitization.

☞ PROBLEM DIRECTED STUDY

52.1 A 30-year-old mother of 2 children attends the gynaecology OPD of the District Hospital with the complaint of whitish watery foul smelling vaginal discharge for the past 2 months. She also suffers lower backache and feels deep pelvic pain during intercourse, which she has irregularly, because her husband works in the city and visits her off and on. She feels weak, but there is no fever. Her periods are regular, but somewhat painful. Last menstruation was 10 days back. Vaginal examination reveals mucopurulent discharge from the cervical canal and pelvic tenderness, but there is no pelvic mass or abscess. She expresses inability to get any investigations done, as she is poor and has to return to her village. A provisional diagnosis of chlamydial nonspecific endocervicitis is made, with possibility of gonococcal infection, concurrently or alone.

(a) What is the most appropriate drug treatment for her?

(b) Should her husband be also examined and treated?

(see Appendix-1 for solution)

Chapter 53 Aminoglycoside Antibiotics

These are a group of natural and semisynthetic antibiotics having polybasic amino groups linked glycosidically to two or more aminosugar (streptidine, 2-deoxy streptamine, garosamine) residues.

Unlike penicillin, which was a chance discovery, aminoglycosides are products of deliberate search for drugs effective against gram-negative bacteria. *Streptomycin* was the first member discovered in 1944 by Waksman and his colleagues. It assumed great importance because it was active against tubercle bacilli. Others were produced later, and now aminoglycosides are a sizable family. All aminoglycosides are produced by soil actinomycetes and have many common properties (*see* box).

Systemic aminoglycosides

Streptomycin	Amikacin
Gentamicin	Sisomicin
Kanamycin	Netilmicin
Tobramycin	Paromomycin

Topical aminoglycosides

Neomycin	Framycetin

Common properties of aminoglycoside antibiotics

1. All are used as sulfate salts, which are highly water soluble; solutions are stable for months.
2. They ionize in solution; are not absorbed orally; distribute only extracellularly; do not penetrate brain or CSF.
3. All are excreted unchanged in urine by glomerular filtration.
4. All are bactericidal and more active at alkaline pH.
5. They act by interfering with bacterial protein synthesis.
6. All are active primarily against aerobic gram-negative bacilli and do not inhibit anaerobes.
7. There is only partial cross resistance among them.
8. They have relatively narrow margin of safety.
9. All exhibit ototoxicity and nephrotoxicity.

MECHANISM OF ACTION

The aminoglycosides are bactericidal antibiotics, all having the same general pattern of action which may be described in two main steps:
(a) Transport of the aminoglycoside through the bacterial cell wall and cytoplasmic membrane.
(b) Binding to ribosomes resulting in inhibition of protein synthesis.

Transport of aminoglycoside into the bacterial cell is a multistep process. They diffuse across the outer coat of gram-negative bacteria through porin channels. Entry from the periplasmic space across the cytoplasmic membrane is carrier mediated which is linked to the electron transport chain. Thus, penetration is dependent upon maintenance of a polarized membrane and on oxygen dependent active processes (energy dependent phase I or EDP_1 entry). These processes are inactivated under anaerobic conditions; anaerobes are not sensitive and facultative anaerobes are more resistant when O_2 supply is deficient, e.g. inside big abscesses. Penetration is also favoured by high pH; aminoglycosides are ~20 times more active in alkaline than in acidic medium. Inhibitors of bacterial cell wall (β-lactams, vancomycin) enhance entry of aminoglycosides and exhibit synergism.

Once inside the bacterial cell, streptomycin binds to 30S ribosomes, but other aminoglycosides bind to additional sites on 50S subunit, as well as to 30S-50S interface. They freeze initiation of protein synthesis (*see* Fig. 52.1), prevent polysome formation and promote their disaggregation to monosomes so that only one ribosome is attached to each strand of mRNA. Binding of aminoglycoside to 30S-50S juncture causes distortion of mRNA codon recognition resulting in misreading of the code: one or more

wrong amino acids are entered in the peptide chain and/or peptides of abnormal lengths are produced. Different aminoglycosides cause misreading at different levels depending upon their selective affinity for specific ribosomal proteins.

The cidal action of these drugs appears to be based on secondary changes in the integrity of bacterial cell membrane, because other antibiotics which inhibit protein synthesis (tetracyclines, chloramphenicol, erythromycin) are only static. After exposure to aminoglycosides, sensitive bacteria become more permeable; ions, amino acids and even proteins leak out followed by cell death. This probably results from incorporation of the defective proteins into the cell membrane. One of the consequences of aminoglycoside induced alteration of cell membrane is augmentation of the carrier-mediated energy-dependent phase II (EDP_2) entry of the antibiotic. This reinforces their lethal action.

The cidal action of aminoglycosides is concentration dependent, i.e. rate of bacterial cell killing is directly related to the ratio of the peak antibiotic concentration to the MIC value. They also exert a long and concentration dependent 'postantibiotic effect' (*see* p. 697). It has, therefore, been argued that despite their short t½ (2–4 hr), single injection of the total daily dose of aminoglycoside may be more effective and possibly less toxic than its conventional division into 2–3 doses.

MECHANISM OF RESISTANCE

Resistance to aminoglycosides is acquired by one of the following mechanisms:

(a) Acquisition of cell membrane bound inactivating enzymes which phosphorylate/ adenylate or acetylate the antibiotic. The conjugated aminoglycosides do not bind to the target ribosomes and are incapable of enhancing active transport like the unaltered drug. These enzymes are acquired mainly by conjugation and transfer of plasmids. Nosocomial microbes have become rich in such plasmids, some of which encode for multidrug resistance. This is the most important mechanism of development of resistance to aminoglycosides. Susceptibility of different aminoglycosides to these enzymes differs. Thus, cross resistance was found between gentamicin and tobramycin or netilmicin, but not between these and streptomycin. Many nosocomial gram-negative bacilli resistant to gentamicin/tobramycin respond to amikacin.

(b) Mutation decreasing the affinity of ribosomal proteins that normally bind the aminoglycoside: this mechanism can confer high degree resistance, but operates to a limited extent, e.g. *E. coli* that develop streptomycin resistance by single step mutation do not bind the antibiotic on the polyribosome. Only a few other instances are known. This type of resistance is specific for a particular aminoglycoside.

(c) Decreased efficiency of the aminoglycoside transporting mechanism: either the pores in the outer coat become less permeable or the active transport is interfered. This again is not frequently encountered in the clinical setting. In some *Pseudomonas* which develop resistance, the antibiotic induced 2nd phase active transport has been found to be deficient.

SHARED TOXICITIES

The aminoglycosides produce toxic effects which are common to all members, but the relative propensity differs (*see* Table 53.1).

TABLE 53.1 Comparative toxicity of aminoglycoside antibiotics (tentative)

Systemically used aminoglycoside	*Ototoxicity*		*Nephrotoxicity*
	vestibular	*cochlear*	
1. Streptomycin	++	±	+
2. Gentamicin	++	+	++
3. Kanamycin	+	++	++
4. Tobramycin	+±	+	+
5. Amikacin	+	++	++
6. Sisomicin	++	+	++
7. Netilmicin	+±	+	++

1. Ototoxicity This is the most important dose and duration of treatment related adverse effect. The vestibular or the cochlear part may be primarily affected by a particular aminoglycoside. These drugs are concentrated in the labyrinthine fluid and are slowly removed from it when the plasma concentration falls. Ototoxicity is greater when plasma concentration of the drug is persistently high and above a threshold value. For gentamicin this is estimated to be ~ 2 µg/ml; if the trough level is above this value, vestibular damage becomes concentration dependent. It is recommended that dosing of gentamicin should be such that the measured trough plasma concentration is < 1 µg/ml to avoid toxicity. The vestibular/cochlear sensory cells and hairs undergo concentration dependent destructive changes. Aminoglycoside ear drops can cause ototoxicity when instilled in patients with perforated eardrum; are contraindicated in them.

Cochlear damage It starts from the base and spreads to the apex; hearing loss affects the high frequency sound first, then progressively encompasses the lower frequencies. No regeneration of the sensory cells occurs; auditory nerve fibres degenerate in a retrograde manner—deafness is permanent. Older patients and those with preexisting hearing defect are more susceptible. Initially, the cochlear toxicity is asymptomatic and can be detected only by audiometry. Tinnitus then appears, followed by progressive hearing loss. On stopping the drug, tinnitus disappears in 4–10 days, but frequency loss persists.

Vestibular damage Headache is usually first to appear, followed by nausea, vomiting, dizziness, nystagmus, vertigo and ataxia. When the drug is stopped at this stage, it passes into a chronic phase lasting 6 to 10 weeks in which the patient is asymptomatic while in bed and has difficulty only during walking. Compensation by visual and proprioceptive positioning and recovery (often incomplete) occurs over 1–2 years. Permanency of changes depends on the extent of initial damage and the age of the patient (elderly have poor recovery).

2. Nephrotoxicity It manifests as tubular damage resulting in loss of urinary concentrating power, low g.f.r., nitrogen retention, albuminuria and casts. Aminoglycosides attain high concentration in the renal cortex (proximal tubules) and toxicity is related to the total amount of the drug received by the patient. However, in patients with normal renal function, single daily dosing regimen appears to cause lesser nephrotoxicity than the conventional thrice daily dosing. It is more in the elderly and in those with preexisting kidney disease. Provided the drug is promptly discontinued renal damage caused by aminoglycosides is totally reversible. It has been postulated that aminoglycosides interfere with the production of PGs in the kidney and that this is causally related to the reduced g.f.r. An important implication of aminoglycoside-induced nephrotoxicity is reduced clearance of the antibiotic resulting in higher and more persistent blood levels causing enhanced ototoxicity. Streptomycin and possibly tobramycin are less nephrotoxic than the other aminoglycosides.

3. Neuromuscular blockade All aminoglycosides reduce ACh release from the motor nerve endings. They interfere with mobilization of centrally located synaptic vesicles to fuse with the terminal membrane (probably by antagonizing Ca^{2+}) as well as decrease the sensitivity of the muscle endplates to ACh. The effect of this action is not manifested ordinarily in the clinical use of these drugs. However, apnoea and fatalities have occurred when streptomycin/neomycin was put into peritoneal or pleural cavity after an operation, especially if a curare-like muscle relaxant was administered during surgery. Rapid absorption form the peritoneum/pleura produces high blood levels and adds to the residual action of the neuromuscular blocker.

Neomycin and streptomycin have higher propensity than kanamycin, gentamicin or amikacin, while tobramycin is least likely to produce this effect. The neuromuscular block produced by aminoglycosides can be partially antagonized by i.v. injection of a calcium salt. Neostigmine has inconsistent reversing action.

Myasthenic weakness is accentuated by these drugs. Neuromuscular blockers should be used cautiously in patients receiving aminoglycosides.

PRECAUTIONS AND INTERACTIONS

1. Avoid aminoglycosides during pregnancy: risk of foetal ototoxicity.

2. Avoid concurrent use of other nephrotoxic drugs, e.g. NSAIDs, amphotericin B, vancomycin, cyclosporine and cisplatin.
3. Cautious use of other potentially ototoxic drugs like vancomycin, minocycline and furosemide, though clinical evidence of potentiated ototoxicity is meagre.
4. Cautious use in patients >60 years age and in those with kidney damage.
5. Cautious use of muscle relaxants in patients receiving an aminoglycoside.
6. Do not mix aminoglycoside with any drug in the same syringe/infusion bottle.

PHARMACOKINETICS

All systemically administered aminoglycosides have similar pharmacokinetic features. They are highly ionized, and are neither absorbed nor destroyed in the g.i.t. However, absorption from injection site in muscles is rapid: peak plasma levels are attained in 30–60 minutes. They are distributed only extracellularly, so that volume of distribution (~0.3 L/kg) is nearly equal to the extracellular fluid volume. Low concentrations are attained in serous fluids like synovial, pleural and peritoneal, but these levels may be significant after repeated dosing. Relatively higher concentrations are present in endolymph and renal cortex, which are responsible for ototoxicity and nephrotoxicity. Penetration in respiratory secretions is poor. Concentrations in CSF and aqueous humour are nontherapeutic even in the presence of inflammation. Aminoglycosides cross placenta and can be found in foetal blood/amniotic fluid. Their use during pregnancy can cause hearing loss in the offspring, and must be avoided unless absolutely essential. The plasma protein binding of aminoglycosides is clinically insignificant, though streptomycin is bound to some extent.

Aminoglycosides are not metabolized in the body, and are excreted unchanged in urine. Glomerular filtration is the main channel, because tubular secretion as well as reabsorption are negligible. The plasma t½ ranges between 2–4 hours, but small amount of drug persists longer in tissues. After chronic dosing, the drug may be detectable in urine for 2–3 weeks. Renal clearance of aminoglycosides parallels creatinine clearance (CLcr), and is approximately 2/3 of it. The t½ is prolonged and accumulation occurs in patients with renal insufficiency, in the elderly and in neonates who have low g.f.r. Reduction in dose or increase in dose-interval is essential in these situations. This should be done according to the measured CLcr. Nomograms are available to help calculation of CLcr, but actual measurement in the individual patient is preferable. Generally, there is no need to reduce the daily dose till CLcr is above 70 ml/min. A simple guide to dose calculation below this level is given in the box.

Guideline for dose adjustment of gentamicin in renal insufficiency

CLcr (ml/min)	*% of daily dose*
70	70% daily
50	50% daily
30	30% daily
20–30	80% alternate day
10–20	60% alternate day
<10	40% alternate day

DOSING REGIMENS

Because of low safety margin, the daily dose of systemically administered aminoglycosides must be precisely calculated accordingly to body weight and level of renal function. For an average adult with normal renal function (CLcr >70 ml/min), the usual doses are:

Gentamicin/tobramycin/sisomicin/netilmicin } 3–5 mg/kg/day

Streptomycin/kanamycin/amikacin } 7.5–15 mg/kg/day

Considering the short t½ (2–4 hr) of aminoglycosides the daily doses are conventionally divided into 3 equal parts and injected i.m. (or i.v. slowly over 60 min) every 8 hours. However, most authorities now recommend a single total daily dose regimen for patients with normal renal function. This is based on the considerations that:

- Aminoglycosides exert concentration dependent bactericidal action and a long post-antibiotic effect, therefore higher plasma concentrations attained after the single daily dose will be equally or more effective than the divided doses.
- With the single daily dose, the plasma concentration will remain subthreshold for ototoxicity and nephrotoxicity for a longer period each day allowing washout of the drug from the endolymph and the renal cortex.

Several comparative studies with gentamicin and few other aminoglycosides and meta-analyses of these studies have validated this concept. The single daily dose regimen has been found to be less nephrotoxic, but no dosing regimen appears to be less ototoxic than another. Both regimens are equally effective. Single daily doses are also more convenient and cheaper (require less man power). However, the safety of the high dose extended interval regimen in patients with renal insufficiency and in children is not established, and is therefore avoided. It is also not recommended when gentamicin is combined with a β-lactam antibiotic for obtaining cidal effect in bacterial endocarditis, etc.

Gentamicin

It was the 3rd systemically administered aminoglycoside antibiotic to be introduced for clinical use, and was obtained from *Micromonospora purpurea* in 1964. It quickly surpassed streptomycin because of higher potency and broader spectrum of activity. Currently, it is the most commonly used aminoglycoside for acute infections and may be considered prototype of the class. It is active mainly against aerobic gram-negative bacilli, including *E. coli*, *Klebsiella pneumoniae*, *Enterobacter*, *H. influenzae*, *Proteus*, *Serratia* and *Pseudomonas aeruginosa*. Many strains of *Brucella*, *Campylobacter*, *Citrobacter*, *Fransisella* and *Yersinia* are also sensitive. Limited number of gram-positive bacteria are susceptible, especially *Staph. aureus*, *Strep. faecalis* and some *Listeria*, but *Strep. pyogenes*, *Strep. pneumoniae* and enterococci are usually insensitive.

Gentamicin is ineffective against *Mycobacterium tuberculosis* and other mycobacteria. It is more potent (its MIC are lower) than streptomycin, kanamycin and amikacin, but equally potent as tobramycin, sisomicin and netilmicin. Bacteria that acquire resistance against gentamicin generally exhibit cross resistance to tobramycin and sisomicin also. It synergises with β-lactam antibiotics, especially against *Enterococcus* (endocarditis) and *Pseudomonas* (meningitis).

Dose: 3–5 mg/kg/day (single dose or divided in 3 doses) i.m. or in an i.v. line over 30–60 min.

GARAMYCIN, GENTASPORIN, GENTICYN 20, 60, 80, 240 mg per vial inj; also 0.3% eye/ear drops, 0.1% skin cream.

Uses Gentamicin is the cheapest (other than streptomycin) and the first line aminoglycoside antibiotic. It is often added when a combination antibiotic regimen is used empirically to treat serious infections by extending the spectrum of coverage. Because of low therapeutic index, its use should be restricted to serious gram-negative bacillary infections.

1. Gentamicin is very valuable for preventing and treating respiratory infections in critically ill patients; in those with impaired host defence (receiving anticancer drugs or high-dose corticosteroids; AIDS; neutropenic), patients in resuscitation wards, with tracheostomy or on respirators; postoperative pneumonias; patients with implants and in intensive care units. It is often combined with a penicillin/cephalosporin or another antibiotic in these situations. However, resistant strains have emerged in many hospitals and nosocomial infections are less amenable to gentamicin now. Another aminoglycoside (tobramycin, amikacin, netilmicin) is then selected on the basis of the local sensitivity pattern, but strains resistant to gentamicin are generally cross resistant to tobramycin and sisomicin. Aminoglycosides should not be used to treat community acquired pneumonias which are mostly caused by gram-positive cocci and anaerobes.

Gentamicin is often added to the peritoneal dialysate to prevent or treat peritonitis.

2. *Pseudomonas, Proteus* or *Klebsiella* infections: burns, urinary tract infection, pneumonia, lung abscesses, osteomyelitis, middle ear infection, septicaemia, etc., caused mostly by the above bacteria are an important area of use of gentamicin. It may be combined with piperacillin or a third generation cephalosporin for serious infections. Topical use on infected burns and in conjunctivitis is permissible.

3. Meningitis caused by gram negative bacilli: Because this is a serious condition, drug combinations including an aminoglycoside are often used. The third generation cephalosporins alone or with an aminoglycoside are favoured for this purpose.

4. Subacute bacterial endocarditis (SABE): Gentamicin (1 mg/kg 8 hourly i.m.) is generally combined with penicillin/ampicillin/vancomycin.

Streptomycin

It is the oldest aminoglycoside antibiotic obtained from *Streptomyces griseus*; which was used extensively in the past, but is now practically restricted to treatment of tuberculosis. It is less potent (MICs are higher) than many other aminoglycosides. The antimicrobial spectrum of streptomycin is relatively narrow: primarily covers aerobic gram-negative bacilli. Sensitive organisms are—*H. ducreyi, Brucella, Yersinia pestis, Francisella tularensis, Nocardia, Calym. granulomatis, M. tuberculosis*. Only few strains of *E. coli, H. influenzae, V. cholerae, Shigella, Klebsiella*, enterococci and some gram-positive cocci are now inhibited, that too at higher concentrations. All other organisms including *Pseudomonas* are unaffected.

Resistance Many organisms rapidly develop resistance to streptomycin, either by one-step mutation or by acquisition of plasmid which codes for inactivating enzymes. In the intestinal and urinary tracts, resistant organisms may emerge within 2 days of therapy. *E. coli, H. influenzae, Str. pneumoniae, Str. pyogenes, Staph. aureus* have become largely resistant. If it is used alone, *M. tuberculosis* also become resistant.

Streptomycin dependence Certain mutants grown in the presence of streptomycin become dependent on it. Their growth is promoted rather than inhibited by the antibiotic. This occurs when the antibiotic induced misreading of the genetic code becomes a normal feature for the organism. This phenomenon is probably significant only in the use of streptomycin for tuberculosis.

Cross resistance Only partial and often unidirectional cross resistance occurs between streptomycin and other aminoglycosides.

Adverse effects About 1/5 patients given streptomycin 1 g BD i.m. experience vestibular disturbances. Auditory disturbances are less common.

Streptomycin has the lowest nephrotoxicity among aminoglycosides; probably because it is not concentrated in the renal cortex. Hypersensitivity reactions are rare; rashes, eosinophilia, fever and exfoliative dermatitis have been reported. Anaphylaxis is very rare. Topical use is contraindicated for fear of contact sensitization.

Superinfections are not significant. Pain at injection site is common. Paraesthesias and scotoma are occasional. It is contraindicated during pregnancy due to risk of foetal ototoxicity.

AMBISTRYN-S 0.75, 1 g dry powder per vial for inj.

Acute infections: 1 g (0.75 g in those above 50 yr age) i.m. OD or BD for 7–10 days.

Tuberculosis: 1 g or 0.75 g i.m. OD or thrice weekly for 30–60 days.

Uses

1. Tuberculosis: *see* Ch. 55.
2. Subacute bacterial endocarditis (SABE): Streptomycin (now mostly gentamicin) is given in conjunction with penicillin/ampicillin/vancomycin for 4–6 weeks.
3. Plague: It effects rapid cure (in 7–12 days); may be employed in confirmed cases, but tetracyclines have been more commonly used for mass treatment of suspected cases during an epidemic.
4. Tularemia: Streptomycin is the drug of choice for this rare disease; effects cure in 7–10 days. Tetracyclines are the alternative drugs, especially in milder cases.

In most other situations, e.g. urinary tract infection, peritonitis, septicaemias, etc. where

streptomycin was used earlier, gentamicin or one of the newer aminoglycosides is now preferred due to widespread resistance to streptomycin and its low potency.

Oral use of streptomycin for diarrhoea is banned in India.

Kanamycin

Obtained from *S. kanamyceticus* (in 1957), it was the second systemically used aminoglycoside to be developed after streptomycin. It is similar to streptomycin in all respects including efficacy against *M. tuberculosis* and lack of activity on *Pseudomonas*. However, it is more toxic, both to the cochlea and to kidney. Hearing loss, which is irreversible, is more common than vestibular disturbance.

Because of toxicity and narrow spectrum of activity, it has been largely replaced by other aminoglycosides for treatment of gram-negative bacillary infections; may be used only if mandated by sensitivity report of the infecting strain. It is occasionally used as a second line drug in resistant tuberculosis.

Dose: 0.5 g i.m. BD (15 mg/kg/day); KANAMYCIN, KANCIN, KANAMAC 0.5 g, 0.75 g, 1.0 g inj.

Tobramycin

It was obtained from *S. tenebrarius* in the 1970s. The antibacterial and pharmacokinetic properties, as well as dosage are almost identical to gentamicin, but it is 2–4 times more active against *Pseudomonas* and *Proteus*, including some resistant to gentamicin, but majority are cross resistant. However, it is not useful for combining with penicillin in the treatment of enterococcal endocarditis. It should be used only as an alternative to gentamicin. Serious infections caused by *Pseudomonas* and *Proteus* are its major indications. Ototoxicity and nephrotoxicity is probably less than gentamicin.

Dose: 3–5 mg/kg day in 1–3 doses.

TOBACIN 20, 60, 80 mg in 2 ml inj. 0.3% eye drops.

TOBRANEG 20, 40, 80 mg per 2 ml inj, TOBRABACT 0.3% eye drops.

Amikacin

It is a semisynthetic derivative of kanamycin to which it resembles in pharmacokinetics, dose and toxicity. The outstanding feature of amikacin is its resistance to bacterial aminoglycoside inactivating enzymes. Thus, it has the widest spectrum of activity, including many organisms resistant to other aminoglycosides. However, relatively higher doses are needed for *Pseudomonas*, *Proteus* and *Staph.* infections.

The range of conditions in which amikacin can be used is the same as for gentamicin. It is recommended as a reserve drug for empirical treatment of hospital acquired gram-negative bacillary infections where gentamicin/tobramycin resistance is high. It is effective in tuberculosis, but used only for multidrug resistant infection. More hearing loss than vestibular disturbance occurs in toxicity.

Dose: 15 mg/kg/day in 1–3 doses; urinary tract infection 7.5 mg/kg/day.

AMICIN, MIKACIN, MIKAJECT 100 mg, 250 mg, 500 mg in 2 ml inj.

Sisomicin

Introduced in 1980s, it is a natural aminoglycoside from *Micromonospora inyoensis* that is chemically and pharmacokinetically similar to gentamicin, but somewhat more potent on *Pseudomonas*, a few other gram-negative bacilli and β haemolytic *Streptococci*. It is moderately active on faecal *Streptococci*—can be combined with penicillin for SABE. However, it is susceptible to aminoglycoside inactivating enzymes and offers no advantage in terms of ototoxicity and nephrotoxicity. It can be used interchangeably with gentamicin for the same purposes in the same doses.

ENSAMYCIN, SISOPTIN 50 mg, 10 mg (pediatric) per ml in 1 ml amps, 0.3% eyedrops, 0.1% cream.

Netilmicin

This semisynthetic derivative of gentamicin has a broader spectrum of activity than gentamicin. It is relatively resistant to many aminoglycoside inactivating enzymes and thus effective against some gentamicin-resistant strains. It is more active against *Klebsiella, Enterobacter* and *Staphylococci*, but less active against *Ps. aeruginosa*.

Pharmacokinetic characteristics and dosage of netilmicin are similar to gentamicin. Experimental studies have shown it to be less ototoxic than gentamicin and tobramycin, but clinical evidence is inconclusive: hearing loss occurs, though fewer cases of vestibular damage have been reported.

A marginal improvement in antibacterial spectrum, clinical efficacy and possibly reduced toxicity indicates that netilmicin could be a useful alternative to gentamicin.

Dose: 4–6 mg/kg/day in 1–3 doses; NETROMYCIN 10, 25, 50 mg in 1 ml, 200 mg in 2 ml and 300 mg in 3 ml inj., NETICIN 200 mg (2 ml), 300 mg (3 ml) inj.

Neomycin

Obtained from *S. fradiae*, it is a wide-spectrum aminoglycoside, active against most gram-negative bacilli and some gram-positive cocci. However, *Pseudomonas* and *Strep. pyogenes* are not sensitive. Neomycin is highly toxic to the internal ear (mainly auditory) and to kidney. It is, therefore, not used systemically. Absorption from the g.i.t. is minimal. Oral and topical administration does not ordinarily cause systemic toxicity.

Dose: 0.25–1 g QID oral, 0.3–0.5% topical.

NEOMYCIN SULPHATE 350, 500 mg tab, 0.3% skin oint, 0.5% skin cream, eye oint.

NEBASULF: Neomycin sulph. 5 mg, bacitracin 250 U, sulfacetamide 60 mg/g oint. and powder for surface application.

POLYBIOTIC CREAM: Neomycin sulph. 5 mg, polymyxin 5,000 IU, gramicidin 0.25 mg/g cream.

NEOSPORIN: Neomycin 3400 iu, polymyxin B 5000 iu, bacitracin 400 iu/g oint and powder for surface application. NEOSPORIN-H: Neomycin 3400 iu, polymyxin B 5000 iu, hydrocortisone 10 mg per g oint and per ml ear drops.

Uses

1. Topically (often in combination with polymyxin, bacitracin, etc.) for infected wound, ulcers, burn, external ear infections, conjunctivitis, but like other topical antiinfective preparations, benefits are limited.
2. Orally for:

(a) Preparation of bowel before surgery: (3 doses of 1.0 g along with metronidazole 0.5 g on day before surgery) may reduce postoperative infections.

(b) Hepatic coma: Normally NH_3 is produced by colonic bacteria. This is absorbed and converted to urea by liver. In severe hepatic failure, detoxication of NH_3 does not occur, blood NH_3 levels rise and produce encephalopathy. Neomycin, by suppressing intestinal flora, diminishes NH_3 production and lowers its blood level; clinical improvement is seen within 2–3 days. However, because of toxic potential it is infrequently used for this purpose; Lactulose (*see* p. 676) is preferred.

Adverse effects

Applied topically neomycin has low sensitizing potential. However, rashes do occur.

Oral neomycin has a damaging effect on intestinal villi. Prolonged treatment can induce malabsorption syndrome with diarrhoea and steatorrhoea. It can decrease the absorption of digoxin and many other drugs, as well as bile acids.

Due to marked suppression of gut flora, superinfection by *Candida* can occur.

Small amounts that are absorbed from the gut or topical sites are excreted unchanged by kidney. This may accumulate in patients with renal insufficiency—cause further kidney damage and ototoxicity. Neomycin is contraindicated if renal function is impaired.

Applied to serous cavities (peritoneum), it can cause apnoea due to muscle paralysing action.

Neomycin containing antidiarrhoeal formulations are banned in India.

Framycetin

Obtained from *S. lavendulae*, it is very similar to neomycin. It is too toxic for systemic administration and is used topically on skin, eye, ear in the same manner as neomycin.

SOFRAMYCIN, FRAMYGEN 1% skin cream, 0.5% eye drops or oint.

Paromomycin

Chemically related to neomycin, this aminoglycoside antibiotic has pronounced activity against many protozoan parasites, including *E. histolytica*, *Giardia lamblia, Trichomonas vaginalis, Cryptosporidium* and *Leishmania*, in addition to many bacteria sensitive to neomycin. Like other aminoglycosides, it is not absorbed from the gut. An oral formulation was marketed in many countries, including India, in the 1960s for treatment of intestinal amoebiasis and giardiasis, but was soon discontinued when metronidazole gained popularity. Recently, it has been reintroduced and is described in Ch. 60. For its antibacterial activity in the gut, it can be used as an alternative to neomycin for hepatic encephalopathy. Parenterally, it is being used for visceral leishmaniasis (*see* Ch. 60).

Dose: Oral 500 mg TDS (25–30 mg/kg/day)

PAROMYCIN, HUMATIN 250 mg cap.

☞ PROBLEM DIRECTED STUDY

53.1 A 75-year-old unconscious male patient of cerebral stroke is maintained on ventilator in the intensive care unit of the hospital. On the 4th day he developed fever, and the total leucocyte count rose to 14000/µL, along with signs of chest infection. A sample of bronchial aspirate is sent for bacteriological tests, and it is decided to institute empirical treatment with cefotaxime and gentamicin. His body weight is 60 kg and creatinine clearance is estimated to be 50 ml/min.

(a) What should be the appropriate dose and dosing regimen for gentamicin and cefotaxime for this patient?

(see Appendix-1 for solution)

Chapter 54 Macrolide, Lincosamide, Glycopeptide and Other Antibacterial Antibiotics; Urinary Antiseptics

MACROLIDE ANTIBIOTICS

These are antibiotics having a macrocyclic lactone ring with attached sugars. *Erythromycin* is the first member discovered in the 1950s, *Roxithromycin, Clarithromycin* and *Azithromycin* are the later additions.

ERYTHROMYCIN

It was isolated from *Streptomyces erythreus* in 1952. Since then it has been widely employed, mainly as alternative to penicillin. Water solubility of erythromycin is limited, and the solution remains stable only when kept in cold.

Mechanism of action Erythromycin is bacteriostatic at low but cidal (for certain bacteria only) at high concentrations. Cidal action depends on the organism concerned and its rate of multiplication. Sensitive gram-positive bacteria accumulate erythromycin intracellularly by active transport which is responsible for their high susceptibility to this antibiotic. Activity is enhanced several fold in alkaline medium, because the nonionized (penetrable) form of the drug is favoured at higher pH.

Erythromycin acts by inhibiting bacterial protein synthesis. It combines with 50S ribosome subunits and interferes with 'translocation' (*see* Fig. 52.1). After peptide bond formation between the newly attached amino acid and the nacent peptide chain at the acceptor (A) site, the elongated peptide is translocated back to the peptidyl (P) site, making the A site available for next aminoacyl tRNA attachment. This is prevented by erythromycin and the ribosome fails to move along the mRNA to expose the next codon. As an indirect consequence, peptide chain may be prematurely terminated: synthesis of larger proteins is especifically suppressed.

Antimicrobial spectrum It is narrow, includes mostly gram-positive and a few gram-negative bacteria, and overlaps considerably with that of penicillin G. Erythromycin is highly active against *Str. pyogenes* and *Str. pneumoniae, N. gonorrhoeae, Clostridia, C. diphtheriae* and *Listeria,* but penicillin-resistant *Staphylococci* and *Streptococci* are now resistant to erythromycin also.

In addition, *Campylobacter, Legionella, Branhamella catarrhalis, Gardnerella vaginalis* and *Mycoplasma,* that are not affected by penicillin, are highly sensitive to erythromycin. Few others, including *H. ducreyi, H. influenzae, B. pertussis, Chlamydia trachomatis, Str. viridans, N. meningitidis* and *Rickettsiae* are moderately sensitive. Enterobacteriaceae, other gram-negative bacilli and *B. fragilis* are not inhibited.

Resistance All cocci readily develop resistance to erythromycin, mostly by acquiring the capacity to pump it out. Resistant Enterobacteriaceae have been found to produce an erythromycin esterase. Alteration in the ribosomal binding site for erythromycin by a plasmid encoded methylase enzyme is an important mechanism of resistance in gram-positive bacteria. All the above types of resistance are plasmid mediated. Change in the 50S ribosome by chromosomal mutation reducing macrolide binding affinity occurs in some gram-positive bacteria.

Bacteria that develop resistance to erythromycin are cross resistant to other macrolides as well. Cross resistance with clindamycin and

chloramphenicol also occurs, because the ribosomal binding sites for all these antibiotics are proximal to each other.

Pharmacokinetics Erythromycin base is acid labile. To protect it from gastric acid, it is given as enteric coated tablets, from which absorption is incomplete and food delays absorption by retarding gastric emptying. Its acid stable esters are better absorbed.

Erythromycin is widely distributed in the body, enters cells and into abscesses, crosses serous membranes and placenta, but not blood-brain barrier. Therapeutic concentration is attained in the prostate. It is 70–80% plasma protein bound, partly metabolized and excreted primarily in bile in the active form. Renal excretion is minor; dose need not be altered in renal failure. The plasma t½ is 1.5 hr, but erythromycin persists longer in tissues.

Preparations and dose

Dose: 250–500 mg 6 hourly (max. 4 g/day), children 30–60 mg/kg/day.

1. Erythromycin (base): ERYSAFE 250, mg tabs, EROMED 333 mg tab, 125 mg/5 ml susp.
2. Erythromycin stearate: blood levels produced are similar to those after erythromycin base. ERYTHROCIN 250, 500 mg tab, 100 mg/5 ml susp., 100 mg/ml ped. drops. ETROCIN, ERYSTER 250 mg tab, 100 mg/5 ml dry syr.
3. Erythromycin estolate (lauryl sulfate): it is relatively acid stable and better absorbed after oral administration. However, concentration of free and active drug in plasma may be the same as after administration of erythromycin base. Certain organisms hydrolyse it to liberate the free form intracellularly and are more susceptible to it.

ALTHROCIN 250, 500 mg tab, 125 mg kid tab, 125 mg/5 ml and 250 mg/5 ml dry syr, 100 mg/ml ped. drops, E-MYCIN 100, 250 mg tab, 100 mg/5 ml dry syr, EMTHROCIN 250 mg tab, 125 mg/5 ml dry syr.

4. Erythromycin ethylsuccinate: well absorbed orally; ERYNATE 100 mg/5 ml dry syr, ERYTHROCIN 100 mg/ml drops, 125 mg/5 ml syr.

A 30% ointment (GERY OINTMENT) is marketed for topical treatment of boils, carbuncles and skin infections, but efficacy is doubtful.

Adverse effects Erythromycin base is a remarkably safe drug, but side effects do occur.

1. *Gastrointestinal* Mild-to-severe epigastric pain is experienced by many patients, especially children, on oral ingestion. Diarrhoea is occasional.

Erythromycin stimulates motilin (an upper gastrointestinal peptide hormone) receptors in the g.i.t.—thereby induces gastric contractions, hastens gastric emptying and promotes intestinal motility without significant effect on colonic motility. On the basis of this action erythromycin has been occasionally used to afford short-term symptomatic relief in diabetic gastroparesis.However, tolerance quickly develops to this action (probably due to receptor down-regulation) and undesirable alteration of bacterial flora limit use of erythromycin as a prokinetic agent. Contribution of this action to the g.i. side effects of erythromycin is not known.

2. Very high doses of erythromycin have caused reversible hearing impairment.

3. *Hypersensitivity* Rashes and fever are infrequent. Other allergic manifestations are rare with erythromycin base or esters other than estolate.

Hepatitis with cholestatic jaundice resembling viral hepatitis or extrahepatic biliary obstruction occurs with the estolate ester (rarely with ethyl succinate or stearate ester) after 1–3 weeks. Incidence is higher in pregnant women. It clears on discontinuation of the drug, and is probably due to hypersensitivity to the estolate ester; erythromycin base or other esters can be given to these patients without recurrence. Though the estolate is acid stable, tasteless and better absorbed, it has been banned in some countries (but not in India).

Interaction Erythromycin inhibits hepatic oxidation of many drugs. The clinically significant interactions are—rise in plasma levels of theophylline, carbamazepine, valproate, ergotamine and warfarin.

Several cases of Q-T prolongation, serious ventricular arrhythmias and death have been reported due to inhibition of CYP3A4 by erythromycin/clarithromycin resulting in high blood levels of concurrently administered terfenadine/astemizole/cisapride (*see* p. 166 and 667).

Uses

A. As an alternative to penicillin

1. Streptococcal pharyngitis, tonsillitis, mastoiditis and community acquired respiratory infections caused by pneumococci and *H. influenzae* respond equally well to erythromycin. It is an alternative drug for prophylaxis

of rheumatic fever and SABE. However, many bacteria resistant to penicillin are also resistant to erythromycin.
2. Diphtheria: For acute stage as well as for carriers—7 day treatment is recommended. Some prefer it over penicillin. Antitoxin is the primary treatment.
3. Tetanus: as an adjuvant to antitoxin, toxoid therapy.
4. Syphilis and gonorrhoea: only if other alternative drugs, including tetracyclines also cannot be used: relapse rates are higher.
5. Leptospirosis: 250 mg 6 hourly for 7 days in patients allergic to penicillins.

B. As a first choice drug for

1. Atypical pneumonia caused by *Mycoplasma pneumoniae*: rate of recovery is hastened.
2. Whooping cough: a 1–2 week course of erythromycin is the most effective treatment for eradicating *B. pertussis* from upper respiratory tract. However, effect on the symptoms depends on the stage of disease when treatment is started.
   (a) Prophylactic: during the 10 day incubation period—disease is prevented.
   (b) Catarrhal stage: which lasts for about a week—erythromycin may abort the next stage or reduce its duration and severity.
   (c) Paroxysmal stage: lasting 2–4 weeks—no effect on the duration and severity of 'croup' despite eradication of the causative organism.
   (d) Convalescent stage: during which 'croup' gradually resolves (4–12 weeks)—is not modified.

Azithromycin, clarithromycin, and chloramphenicol are the alternative antimicrobials. Cough sedatives are not very effective. Corticosteroids may reduce the duration of paroxysmal stage but increase the risk of superinfections and carrier stage; they should be reserved for severe cases only. Adrenergic β_2 stimulants may reduce the severity of paroxysms, and are more useful in infants.

3. Chancroid : erythromycin 2 g/day for 7 days is one of the first line drugs, as effective as single dose azithromycin or ceftriaxone (*see* p. 763).

C. As a second choice drug in

1. *Campylobacter* enteritis: duration of diarrhoea and presence of organisms in stools is reduced. However, fluoroquinolones are superior.
2. Legionnaires' pneumonia: 3 week erythromycin treatment is effective, but azithromycin/ciprofloxacin are preferred.
3. *Chlamydia trachomatis* infection of urogenital tract: erythromycin 500 mg 6 hourly for 7 days is an effective alternative to single dose azithromycin (*see* p. 763).
4. Penicillin-resistant *Staphylococcal* infections: its value has reduced due to emergence of erythromycin resistance as well. It is not effective against MRSA.

NEWER MACROLIDES

In an attempt to overcome the limitations of erythromycin like narrow spectrum, gastric intolerance, gastric acid lability, low oral bioavailability, poor tissue penetration and short half-life, a number of semisynthetic macrolides have been produced, of which roxithromycin, clarithromycin and azithromycin have been marketed.

Roxithromycin It is a semisynthetic longer-acting acid-stable macrolide whose antimicrobial spectrum resembles closely with that of erythromycin. It is more potent against *Branh. catarrhalis, Gard. vaginalis* and *Legionella* but less potent against *B. pertussis*. Good enteral absorption and an average plasma t½ of 12 hr making it suitable for twice daily dosing, as well as better gastric tolerability are its desirable features.

Though its affinity for cytochrome P450 is lower, drug interactions with terfenadine, cisapride and others are not ruled out. Thus, it is an alternative to erythromycin for respiratory, ENT, skin and soft tissue and genital tract infections with similar efficacy.

Dose: 150–300 mg BD 30 min before meals, children 2.5–5 mg/kg BD.

ROXID, ROXIBID, RULIDE 150, 300 mg tab, 50 mg kid tab, 50 mg /5 ml liquid; ROXEM 50 mg kid tab, 150 mg tab.

Clarithromycin The antimicrobial spectrum of clarithromycin is similar to erythromycin; in addition, it includes *Mycobact. avium* complex (MAC), other atypical mycobacteria, *Mycobact. leprae* and some anaerobes but not *Bact. fragilis.*

It is more active against *Helicobacter pylori*, *Moraxella, Legionella, Mycoplasma pneumoniae* and sensitve strains of gram-positive bacteria. However, bacteria that have developed resistance to erythromycin are resistant to clarithromycin also.

Clarithromycin is more acid-stable than erythromycin, and is rapidly absorbed; oral bioavailability is ~50% due to first pass metabolism; food delays but does not decrease absorption. It has slightly larger tissue distribution than erythromycin and is metabolized by saturation kinetics—t½ is prolonged from 3–6 hours at lower doses to 6–9 hours at higher doses. An active metabolite is produced. About 1/3 of an oral dose is excreted unchanged in urine, but no dose modification is needed in liver disease or in mild-to-moderate kidney failure.

Clarithromycin is indicated in upper and lower respiratory tract infections, sinusitis, otitis media, whooping cough, atypical pneumonia, skin and skin structure infections due to *Strep. pyogenes* and some *Staph. aureus*. Used as a component of triple drug regimen (*see* p. 657) it eradicates *H. pylori* in 1–2 weeks. It is a first line drug in combination regimens for MAC infection in AIDS patients and a second line drug for other atypical mycobacterial diseases as well as leprosy.

Dose: 250 mg BD for 7 days; severe cases 500 mg BD up to 14 days.

CLARIBID 250, 500 mg tabs, 250 mg/5 ml dry syr; CLARIMAC 250, 500 mg tabs; SYNCLAR 250 mg tab, 125 mg/5 ml dry syr.

Side effects of clarithromycin are similar to those of erythromycin, but gastric tolerance is better. High doses can cause reversible hearing loss. Few cases of pseudomembranous enterocolitis, hepatic dysfunction or rhabdomyolysis are reported. Its safety in pregnancy and lactation is not known. It inhibits CYP3A4, and the drug interaction potential is similar to erythromycin.

Azithromycin This azalide congener of erythromycin has an expanded spectrum, improved pharmacokinetics, better tolerability and drug interaction profiles. It is more active than other macrolides against *H. influenzae*, but less active against gram-positive cocci. High activity is exerted on respiratory pathogens—*Mycoplasma, Chlamydia pneumoniae, Legionella, Moraxella* and on others like *Campylobacter. Ch. trachomatis*, *H. ducreyi, Calymm. granulomatis, N. gonorrhoeae*. However, it is not active against erythromycin-resistant bacteria. Penicillinase producing *Staph. aureus* are inhibited but not MRSA. Good activity is noted against MAC.

The remarkable pharmacokinetic properties are acid-stability, rapid oral absorption (from empty stomach), larger tissue distribution and intracellular penetration. Concentration in most tissues exceeds that in plasma. Particularly high concentrations are attained inside macrophages and fibroblasts; volume of distribution is ~30 L/kg. Slow release from the intracellular sites contributes to its long terminal t½ of >50 hr. It is largely excreted unchanged in bile, renal excretion is ~ 10%.

Because of higher efficacy, better gastric tolerance and convenient once a day dosing, azithromycin is now preferred over erythromycin as **first choice** drug for infections such as:

(a) *Legionnaires'* pneumonia: 500 mg OD oral/i.v. for 2 weeks. Erythromycin or a FQ are the alternatives.

(b) *Chlamydia trachomatis*: nonspecific urethritis and genital infections in both men and women —1 g single dose is curative, while 3 weekly doses are required for lymphogranuloma venereum (*see* p. 763). It is also the drug of choice for chlamydial pneumonia and is being preferred over tetracycline for trachoma in the eye.

(c). Donovanosis caused by *Calymmatobacterium granulomatis:* 500 mg OD for 7 days or 1.0 g weekly for 4 weeks is as effective as doxycycline.

(d) Chancroid and PPNG urethritis: single 1.0 g dose is highly curative (*see* p. 763).

The other indications of azithromycin are pharyngitis, tonsillitis, sinusitis, otitis media, pneumonias, acute exacerbations of chronic

bronchitis, streptococcal and some staphylococcal skin and soft tissue infections. In combination with at least one other drug it is effective in the prophylaxis and treatment of MAC in AIDS patients. Other potential uses are in multidrug resistant typhoid fever in patients allergic to cephalosporins; and in toxoplasmosis.

Dose: 500 mg once daily 1 hour before or 2 hours after food (food decreases bioavailability); (children above 6 month—10 mg/kg/day) for 3 days is sufficient for most infections.

AZITHRAL 250, 500 mg cap and 250 mg per 5 ml dry syr; AZIWOK 250 mg cap, 100 mg kid tab, 100 mg/5 ml and 200 mg/5 ml susp. AZIWIN 100, 250, 500 mg tab, 200 mg/5 ml liq. Also AZITHRAL 500 mg inj.

Side effects are mild gastric upset, abdominal pain (less than erythromycin), headache and dizziness. Azithromycin has been found not to affect hepatic CYP3A4 enzyme. Interaction with theophylline, carbamazepine, warfarin, terfenadine and cisapride is not likely, but caution may be exercised.

Spiramycin This macrolide antibiotic, though available for more than a decade, has been employed only sporadically. It resembles erythromycin in spectrum of activity and properties. Distinctively, it has been found to limit risk of transplacental transmission of *Toxoplasma gondii* infection. Its specific utility is for toxoplasmosis and recurrent abortion in pregnant women; 3 week courses of 3 MU 2–3 times a day are repeated after 2 week gaps till delivery. Other indications are similar to erythromycin, for which 6 MU/day is given for 5 days. Side effects are gastric irritation, nausea, diarrhoea and rashes.

ROVAMYCIN 1.5 MU, 3 MU tabs, 0.375 MU/ 5 ml susp.

LINCOSAMIDE ANTIBIOTICS

Clindamycin

This potent lincosamide antibiotic is similar in mechanism of action (inhibits protein synthesis by binding to 50S ribosome) and spectrum of activity to erythromycin with which it exhibits partial cross resistance. Modification of the ribosomal binding site by the constitutive methylase enzyme confirs resistance to both, but not the inducible enzyme. Antibiotic efflux is not an important mechanism of clindamycin resistance. Clindamycin inhibits most gram-positive cocci (including most species of streptococci, penicillinase producing *Staph*., but not MRSA), *C. diphtheriae, Nocardia, Actinomyces, Toxoplasma* and has slow action on *Plasmodia.* However, the distinctive feature is its high activity against a variety of anaerobes, especially *Bact. fragilis.* Aerobic gram-negative bacilli, spirochetes, *Chlamydia, Mycoplasma* and *Rickettsia* are not affected.

Oral absorption of clindamycin is good. It penetrates into most skeletal and soft tissues, but not in brain and CSF; accumulates in neutrophils and macrophages. It is largely metabolized and metabolites are excreted in urine and bile. The t½ is 3 hr.

Side effects are rashes, urticaria, abdominal pain, but the major problem is diarrhoea and pseudomembranous enterocolitis due to *Clostridium difficile* superinfection which is potentially fatal. The drug should be promptly stopped and oral metronidazole (alternatively vancomycin) given to treat it. Thrombophlebitis of the injected vein can occur on i.v. administration.

Because of the potential toxicity, use of clindamycin is restricted to anaerobic and mixed infections, especially those involving *Bact. fragilis* causing abdominal, pelvic and lung abscesses. It is a first line drug for these conditions, and is generally combined with an aminoglycoside or a cephalosporin. Metronidazole and chloramphenicol are the alternatives to clindamycin for covering the anaerobes. Skin and soft tissue infections in patients allergic to penicillins can be treated with clindamycin. Anaerobic streptococcal and *Cl. perfringens* infections, especially those involving bone and joints respond well. It has also been employed for prophylaxis of endocarditis in penicillin allergic patients with valvular defects who undergo dental surgery, as well as to prevent surgical site infection in colorectal/pelvic surgery.

In AIDS patients, it has been combined with pyrimethamine for toxoplasmosis and with primaquine for *Pneumocystis jiroveci* pneumonia. It is an alternative to doxycycline for supplementing quinine/artesunate in treating multidrug resistant falciparum malaria. Topically it is used for infected acne vulgaris.

Clindamycin, erythromycin and chloramphenicol can exhibit mutual antagonism, probably because their ribosomal binding sites are proximal; binding of one hinders access of the other to its target site. Clindamycin slightly potentiates neuromuscular blockers.

Dose: 150–300 mg (children 3–6 mg/kg) QID oral; 200–600 mg i.v. 8 hourly; DALCAP 150 mg cap; CLINCIN 150, 300 mg cap; DALCIN, DALCINEX 150, 300 mg cap, 300 mg/2 ml and 600 mg/4 ml inj. ACNESOL, CLINDAC-A 1% topical solution and gel.

Lincomycin

It is the forerunner of clindamycin; has similar antibacterial and toxic properties, but is less potent and produces a higher incidence of diarrhoea and colitis—deaths have occurred. Thus, it has been largely replaced by clindamycin. It is absorbed orally and excreted mainly in bile; plasma t½ 5 hrs.

Dose: 500 mg TDS-QID oral; 600 mg i.m. or by i.v. infusion 6–12 hrly.

LINCOCIN 500 mg cap, 600 mg/2 ml inj; LYNX 250, 500 mg cap, 125 mg/5 ml syr, 300 mg/ml inj in 1, 2 ml amp.

GLYCOPEPTIDE ANTIBIOTICS

Vancomycin

It is a glycopeptide antibiotic discovered in 1956 as a penicillin substitute which assumed special significance due to efficacy against MRSA, *Strep. viridans, Enterococcus* and *Cl. difficile*. Bactericidal action is exerted on gram-positive cocci, *Neisseria, Clostridia* and diphtheroids. However, in hospitals where it has been extensively used for surgical prophylaxis, etc., vancomycin-resistant *Staph. aureus* (VRSA) and vancomycin-resistant *Enterococcus* (VRE) have emerged. These nosocomial bacteria are resistant to methicillin and most other antibiotics as well. Gram-negative bacilli are inherently non-responsive to vancomycin.

Vancomycin acts by inhibiting bacterial cell wall synthesis. It binds to the terminal dipeptide 'D-ala-D-ala' sequence of peptidoglycan units—prevents its release from the bactoprenol lipid carrier so that assembly of the units at the cell membrane and their cross linking to form the cell wall cannot take place (*see* Fig. 51.2). Enterococcal resistance to vancomycin is due to a plasmid mediated alteration of the dipeptide target site, reducing its affinity for vancomycin.

Vancomycin is not absorbed orally. After i.v. administration, it is widely distributed, penetrates serous cavities, inflamed meninges and is excreted mainly unchanged by glomerular filtration with a t½ of 6 hours. Dose reduction is needed in renal insufficiency.

Toxicity: Systemic toxicity of vancomycin is high. It can cause plasma concentration-dependent nerve deafness which may be permanent. Kidney damage is also dose-related. Other oto- and nephrotoxic drugs like aminoglycosides must be very carefully administered when vancomycin is being used. Skin allergy and fall in BP during i.v. injection can occur. Vancomycin has the potential to release histamine by direct action on mast cells. Rapid i.v. injection has caused chills, fever, urticaria and intense flushing—called 'Red man syndrome'.

Uses: Given orally (125–500 mg 6 hourly), it is the second choice drug to metronidazole for antibiotic associated pseudomembranous enterocolitis caused by *C. difficile*. Staphylococcal enterocolitis is another indication of oral vancomycin.

Systemic use (500 mg 6 hourly or 1 g 12 hourly infused i.v. over 1 hr) is restricted to serious MRSA infections for which it is the most effective drug, and as a penicillin substitute (in allergic patients) for enterococcal endocarditis along with gentamicin. It is an alternative drug for serious skin, soft tissue and skeletal infections in which gram-positive bacteria are mostly causative. For empirical therapy of bacterial meningitis, i.v. vancomycin is usually combined with i.v. ceftriaxone/cefotaxime. It is also used in dialysis patients and those undergoing cancer chemotherapy. Penicillin-resistant pneumococcal infections and infection caused by diphtheroids respond very well to vancomycin.

Vancomycin is the preferred surgical prophylactic in MRSA prevalent areas and in penicillin allergic patients.

VANCOCIN-CP, VANCOGEN, VANCORID-CP 500 mg/vial inj; VANCOLED 0.5, 1.0 g inj. VANCOMYCIN 500 mg tab, VANLID 250 mg cap, 500 mg/vial inj.

Teicoplanin

This newer glycopeptide antibiotic is a mixture of 6 similar compounds, active against gram-positive bacteria only. The mechanism of action and spectrum of activity is similar to vancomycin. Notable features are:

- It is more active than vancomycin against enterococci, and equally active against MRSA.
- Some VRE but not VRSA are susceptible to teicoplanin.
- It can be injected i.m. as well; is largely excreted unchanged by kidney; dose needs to be reduced in renal insufficiency; has a very long t½ (3–4 days).
- Toxicity is less than vancomycin; adverse effects are rashes, fever, granulocytopenia and occasionally hearing loss. Reactions due to histamine release are rare (1 in 2500).

Teicoplanin is indicated in enterococcal endocarditis (along with gentamicin); MRSA and penicillin resistant streptococcal infections, osteomyelitis and as alternative to vancomycin for surgical prophylaxis, etc.

Dose: 400 mg first day—then 200 mg daily i.v. or i.m.; severe infection 400 mg × 3 doses 12 hourly—then 400 mg daily. TARGOCID, TECOPLAN, TECOCIN 200, 400 mg per vial inj. for reconstitution.

OXAZOLIDINONE

Linezolid

This is the first member of a new class of synthetic AMAs 'Oxazolidinones' useful in the treatment of resistant gram-positive coccal (aerobic and anaerobic) and bacillary infections. It is active against MRSA and some VRSA, VRE, penicillin-resistant *Strep. pyogenes, Strep. viridans* and *Strep. pneumoniae, M. tuberculosis, Corynebacterium, Listeria, Clostridia* and *Bact. fragilis*. It is primarily bacteriostatic, but can exert cidal action against some streptococci, pneumococci and *B. fragilis*. Gram-negative bacteria are not affected.

Linezolid inhibits bacterial protein synthesis by acting at an early step and a site different from that of other AMAs. It binds to the 23S fraction (P site) of the 50S ribosome and interferes with formation of the ternary N-formylmethionine-tRNA ($tRNA^{fMet}$) -70S initiation complex. Binding of linezolid distorts the tRNA binding site overlapping both 50S and 30S ribosomal subunits and stops protein synthesis before it starts. As such, there is no cross resistance with any other class of AMAs. Linezolid resistance due to mutation of 23S ribosomal RNA has been detected among enterococci.

Linezolid is rapidly and completely absorbed orally, partly metabolized nonenzymatically and excreted in urine. Plasma t½ is 5 hrs. Dose modification has not been necessary in renal insufficiency.

Linezolid given orally or i.v. is used for uncomplicated and complicated skin and soft tissue infections, community and hospital-acquired pneumonias, bacteraemias and other drug-resistant gram-positive infections with 83–94% cure rates. However, in order to prevent emergence of resistance to this valuable drug, use should be restricted to serious hospital-acquired pneumonias, febrile neutropenia, wound infections and others caused by multidrug-resistant gram-positive bacteria such as VRE, vancomycin resistant-MRSA, multi-resistant *S. pneumoniae,* etc. Being bacteriostatic, it is not suitable for treatment of enterococcal endocarditis.

Dose: 600 mg BD, oral/ i.v.; LIZOLID 600 mg tab; LINOX, LINOSPAN 600 mg tab, 600 mg/300 ml i.v. infusion.

Side effects to linezolid have been few; mostly mild abdominal pain, nausea, taste disturbance and diarrhoea. Occasionally, rash, pruritus, headache, oral/vaginal candidiasis have been reported. Neutropenia, anaemia and thrombocytopenia are infrequent and mostly associated with prolonged use. Optic neuropathy has occurred after linezolid is given for >4 weeks. Because linezolid is a MAO inhibitor, interactions with adrenergic/serotonergic drugs (SSRIs, etc.) and excess dietary tyramine are expected. No cytochrome P450 enzyme related interactions seem likely.

MISCELLANEOUS ANTIBIOTICS

Spectinomycin It is a chemically distinct (aminocyclitol), narrow spectrum, bacteriostatic antibiotic which inhibits a limited number of gram-negative bacteria, notably *Neisseria gonorrhoeae*. It acts by binding to 30S ribosome and inhibiting bacterial protein synthesis, but the action is distinct from that of aminoglycosides. The single approved indication of spectinomycin is treatment of drug resistant gonorrhoea, or when the first line drugs (β-lactams/macrolides, etc.) can not be used due to allergy or other contraindication.

Dose: 2.0 g i.m. single dose; for less responsive cases 4.0 g (2.0 g at 2 sites).

MYSPEC, TROBICIN 2.0 g/vial inj.

The single dose is well tolerated; chills, fever and urticaria are occasional side effects. Repeated doses may cause anaemia, renal and hepatic impairment.

Quinupristin/Dalfopristin It is a combination of two semisynthetic pristinamycin antibiotics which together exert synergistic inhibition of bacterial protein synthesis. It is active against most gram-positive cocci including MRSA, some VRSA and some VRE; as well as certain *Neisseria, Legionella* and *Chlamydia pneumoniae*. The combination is bactericidal against strepto and staphylococci but bacteriostatic against *E. faecium*.

It is being used for serious nosocomial MRSA, VRE and other resistant gram-positive infections.

Mupirocin This topically used antibiotic obtained from a species of *Pseudomonas* is active mainly against gram-positive bacteria, including *Strep. pyogenes* (penicillin sensitive/resistant), *Staph aureus.* MRSA, etc. It inhibits bacterial protein synthesis by blocking the production of t-RNA for isoleucin. As such, no cross resistance with any other antibiotic is seen. Though primarily bacteriostatic, high concentrations applied topically may be bactericidal. It is indicated in furunculosis, folliculitis, impetigo, infected insect bites and small wounds. Local itching, irritation and redness may occur.

BACTROBAN, MUPIN, T-BACT 2% oint. for topical application thrice daily.

Fusidic acid It is a narrow spectrum steroidal antibiotic, blocks bacterial protein synthesis. It is active against penicillinase producing *Staphylococci* and few other gram-positive bacteria. It is used only topically for boils, folliculitis, sycosis barbae and other cutaneous infections.

FUCIDIN-L, FUCIBACT, FUSIDERM; 2% oint. and cream.

POLYPEPTIDE ANTIBIOTICS

These are low molecular weight cationic polypeptide antibiotics. All are powerful bactericidal agents, but not used systemically due to toxicity. All are produced by bacteria. Clinically used ones are:

Polymyxin B
Colistin
Bacitracin

Polymyxin B and Colistin Polymyxin and colistin were obtained in the late 1940s from *Bacillus polymyxa* and *B. colistinus* respectively. They are active against gram-negative bacteria only; all except *Proteus, Serratia* and *Neisseria* are inhibited. Both have very similar range of activity, but colistin is more potent on *Pseudomonas, Salmonella* and *Shigella*.

Mechanism of action They are rapidly acting bactericidal agents; have a detergent-like action on the cell membrane. They have high affinity for phospholipids: the peptide molecules (or their aggregates) orient between the phospholipid and protein films in gram-negative bacterial cell membrane causing membrane distortion or pseudopore formation. As a result ions, amino acids, etc. leak out. Sensitive bacteria take up more of the antibiotic. They may also inactivate the bacterial endotoxin.

They exhibit synergism with many other AMAs by improving their penetration into the bacterial cell.

Resistance Resistance to these antibiotics has never been a problem. There is no cross resistance with any other AMA.

Adverse effects Little or no absorption occurs from oral route or even from denuded skin (burn, ulcers). Applied topically, they are safe—no systemic effect or sensitization occurs. A rash is rare.

- Given orally, side effects are limited to the g.i.t.—occasional nausea, vomiting, diarrhoea.
- Systemic toxicity of these drugs (when injected) is high: flushing and paresthesias (due to liberation of histamine from mast cells), marked kidney damage, neurological disturbances, neuromuscular blockade.

Preparation and dose

Polymyxin B: (1 mg = 10,000 U)

NEOSPORIN POWDER: 5000 U with neomycin sulf. 3400 U and bacitracin 400 U per g.

NEOSPORIN EYE DROPS: 5000 U with neomycin sulf. 1700 U and gramicidin 0.25 mg per ml.

NEOSPORIN-H EAR DROPS: 10,000 U with neomycin sulf. 3400 U and hydrocortisone 10 mg per ml.

Colistin sulfate: 25–100 mg TDS oral

WALAMYCIN 12.5 mg (25000 i.u.) per 5 ml dry syr, COLISTOP 12.5 mg/5 ml and 25 mg/5 ml dry syr.

Uses

(a) *Topically* Usually in combination with other antimicrobials for skin infections, burns, otitis externa, conjunctivitis, corneal ulcer—caused by gram-negative bacteria including *Pseudomonas*.

(b) *Orally* Gram-negative bacillary (*E. coli*, *Salmonella, Shigella*) diarrhoeas, especially in infants and children; *Pseudomonas* superinfection enteritis.

Bacitracin It is one of the earliest discovered antibiotics from a strain of *Bacillus subtilis*. In contrast to polymyxin,

it is active mainly against gram-positive organisms (both cocci and bacilli). *Neisseria, H. influenzae* and few other bacteria are also affected.

It acts by inhibiting cell wall synthesis at a step earlier than that inhibited by penicillin. Subsequently, it increases the efflux of ions by binding to cell membrane. It is bactericidal.

Bacitracin is not absorbed orally. It is not given parenterally because of high toxicity, especially to the kidney. Use is restricted to topical application for infected wounds, ulcers, eye infections—generally in combination with neomycin, polymyxin, etc.

NEBASULF Bacitracin 250 U + neomycin 5 mg + sulfacetamide 60 mg/g powder, skin oint, eye oint; in NEOSPORIN 400 U/g powder (1 U = 26 µg).

It does not penetrate intact skin, therefore, is of little value in furunculosis, boils, carbuncles, etc.

URINARY ANTISEPTICS

Some orally administered AMAs attain antibacterial concentration only in urine, with little or no systemic antibacterial effect. Like many other drugs, they are concentrated in the kidney tubules, and are useful mainly in lower urinary tract infection. They have been called *urinary antiseptics* because this may be considered as a form of local therapy. Nitrofurantoin and methenamine are two such agents; infrequently used now. Nalidixic acid (*see* p. 709) can also be considered to be a urinary antiseptic.

Nitrofurantoin

It is primarily bacteriostatic, but may be cidal at higher concentrations and in acidic urine. Its activity is enhanced at lower pH. Many gram-negative bacteria were susceptible, but due to development of resistance, activity is now restricted largely to *E. coli.* Resistance to nitrofurantoin does not develop during continued therapy. No cross resistance with any other AMA is known, though it antagonizes the bactericidal action of nalidixic acid. Susceptible bacteria enzymatically reduce nitrofurantoin to generate reactive intermediates which damage DNA.

Pharmacokinetics Nitrofurantoin is well absorbed orally; rapidly metabolized in liver and other tissues; less than half is excreted unchanged in urine; plasma t½ is 30–60 min. Antibacterial concentrations are not attained in blood or tissues. Probenecid inhibits its tubular secretion and reduces the concentration attained in urine—may interfere with its urinary antiseptic action. Renal excretion is reduced in azotaemic patients; effective concentrations may not be reached in the urine, while toxicity increases. As such, it is contraindicated in renal failure; also during pregnancy and in neonates.

Adverse effects Commonest is gastrointestinal intolerance—nausea, epigastric pain and diarrhoea.

An acute reaction with chills, fever and leucopenia occurs occasionally.

Peripheral neuritis and other neurological effects are reported with long-term use. Haemolytic anaemia is rare, except in G-6-PD deficiency. Liver damage and a pulmonary reaction with fibrosis on chronic use are infrequent events.

Urine of patients taking nitrofurantoin turns dark brown on exposure to air.

Use The only indication for nitrofurantoin is uncomplicated lower urinary tract infection not associated with prostatitis, but it is infrequently used now. Acute infections due to *E. coli* can be treated with 50–100 mg TDS (5–7 mg/kg/day) given for 5–10 days. These doses should not be used for > 2 weeks at a time. Suppressive long-term treatment has been successful with 50 mg BD or 100 mg at bed time. This dose can also be employed for prophylaxis of urinary tract infection following catheterization or instrumentation of the lower urinary tract and in women with recurrent cystitis.

FURADANTIN 50, 100 mg tab, URINIF 100 mg tab..

NEPHROGESIC: Nitrofurantoin 50 mg + phenazopyridine 100 mg tab.

Methenamine (Hexamine)

It is hexamethylene-tetramine, which is inactive as such; decomposes slowly in acidic urine to release formaldehyde which inhibits all bacteria. This drug exerts no antimicrobial activity in blood and tissues, including kidney parenchyma. Acidic urine is essential for its action; urinary pH must be kept below 5.5 by administering an organic acid which is excreted as such, e.g. mandelic acid or hippuric acid or ascorbic acid.

Methenamine is administered in enteric coated tablets to protect it from decomposing in gastric juice. Mandelic acid, given as methenamine mandelate, is excreted in urine →lowers urinary pH and promotes decomposition of methenamine. Lower urinary pH itself disfavours growth of urinary pathogens.

MANDELAMINE : Methenamine mandelate 0.5 g, 1 g tab: 1 g TDS or QID with fluid restriction (daily urine volume between 1–1.5 L) to ensure adequate concentration of formaldehyde in urine.

It is not an effective drug for acute urinary tract infections or for catheterization prophylaxis. Its use is restricted to chronic, resistant type of urinary tract infections, not involving kidney substance. Resistance to formaldehyde does not occur, but methenamine is rarely used now.

Adverse effects Gastritis can occur due to release of formaldehyde in stomach—patient compliance is poor due to this. Chemical cystitis and haematuria may develop with high doses given for long periods. CNS symptoms are produced occasionally.

URINARY ANALGESIC

Phenazopyridine It is an orange dye which exerts analgesic action in the urinary tract and affords symptomatic relief of burning sensation, dysuria and urgency due to cystitis. It does not have antibacterial property. Side effects are nausea and epigastric pain.
Dose: 200–400 mg TDS: PYRIDIUM 200 mg tab.

TREATMENT OF URINARY TRACT INFECTIONS

The general principles of use of AMAs for urinary tract infections (UTIs) remain the same as for any other infection. Some specific considerations are highlighted below.

Most UTIs are caused by gram-negative bacteria, especially coliforms. Majority of acute infections involve a single organism (commonest is *E. coli*); chronic and recurrent infections may be mixed infections. Acute infections are largely self limiting; high urine flow rates with frequent bladder voiding may suffice. Many single dose antimicrobial treatments have been successfully tried, but a three day regimen is considered optimal for lower UTIs. Upper UTIs require more aggressive and longer treatment. In any case, treatment for more than 2 weeks is seldom warranted.

Bacteriological investigations are very important to direct the choice of drug. Though, treatment may not wait till report comes, urine sample must be collected for bacteriology before commencing therapy. Most AMAs attain high concentration in urine, smaller than usual doses may be effective in lower UTIs, because antibacterial action in urine is sufficient, mucosa takes care of itself. In upper UTI (pyelonephritis) antimicrobial activity in kidney tissue is needed. Therefore, doses are similar to those for any systemic infection.

The least toxic and cheaper AMA should be used, just long enough to eradicate the pathogen. It is advisable to select a drug which does not disrupt normal gut and perineal flora. If recurrences are frequent, chronic suppressive treatment with cotrimoxazole, nitrofurantoin, methenamine, cephalexin or norfloxacin may be given.

The commonly used antimicrobial regimens for empirical therapy of uncomplicated acute UTI are given in the box.

Antimicrobial regimens for acute UTI (all given orally for 3–5 days)*

1. Norfloxacin 400 mg 12 hourly
2. Ciprofloxacin 250–500 mg 12 hourly
3. Ofloxacin 200–400 mg 12 hourly
4. Cotrimoxazole 960 mg 12 hourly
5. Cephalexin 250–500 mg 6 hourly
6. Cefpodoxime proxetil 200 mg 12 hourly
7. Amoxicillin + clavulanic acid (500 + 125 mg) 8 hourly
8. Nitrofurantoin 50 mg 8 hourly or 100 mg 12 hourly × 5–7 days

* For upper UTI (pyelonephritis), the same drugs may be given for 2–3 weeks. Nitrofurantoin is not suitable for pyelonephritis.

The status of AMAs (other than urinary antiseptics) in urinary tract infections is summarized below:

1. *Sulfonamides* Dependability in acute UTIs has decreased; they are not used now as single drug. May occasionally be employed for suppressive and prophylactic therapy.

2. *Cotrimoxazole* (*see* p. 708) Though response rate and use have declined, it may be employed empirically in acute UTI without bacteriological data, because majority of urinary pathogens, including *Chlamydia trachomatis*, are covered by cotrimoxazole. Given once daily at bed time cotrimoxazole 480 mg is often used for prophylaxis of recurrent cystitis in women, as well as in catheterized patients. It should not be used to treat UTI during pregnancy.

3. *Quinolones* (*see* p. 711) The first generation FQs, especially norfloxacin and ciprofloxacin are highly effective and currently the most popular drugs, because of potent action against gram-negative bacilli and low cost. Nalidixic acid is seldom employed. However, to preserve their efficacy, use should be restricted. FQs are particularly valuable in complicated cases, those

with prostatitis or indwelling catheters and for bacteria resistant to cotrimoxazole/ampicillin. Norfloxacin given for upto 12 weeks may achieve cure in chronic UTI. The FQs should not be given to pregnant women.

4. *Ampicillin/Amoxicillin* (*see* p. 722) Frequently used in the past as first choice drug for initial treatment of acute infections without bacteriological data, but higher failure and relapse rates have made them unreliable for empirical therapy. Many *E. coli* strains are now ampicillin-resistant. Amoxicillin + clavulanic acid is more frequently employed. Parenteral coamoxiclav is often combined with gentamicin for initial treatment of acute pyelonephritis.

5. *Cloxacillin* Use is restricted to penicillinase producing staphylococcal infection, which is uncommon in urinary tract.

6. *Piperacillin/Carbenicillin* Only in serious *Pseudomonas* infection in patients with indwelling catheters or chronic urinary obstructin (prostatic hypertrophy, calculi), and in hospitalized patients on the basis of *in vitro* sensitivity.

7. *Cephalosporins* Use is increasing, especially in women with nosocomial *Klebsiella* and *Proteus* infections. They should normally be employed only on the basis of sensitivity report, but empirical use for community acquired infection is also common. Some guidelines recommend them as one of the option for empirical treatment of acute lower UTI. Cephalexin given once daily is an alternative drug for prophylaxis of recurrent cystitis, especially in women likely to get pregnant.

8. *Gentamicin* (*see* p. 747) Very effective against most urinary pathogens including *Pseudomonas*. However, because of narrow margin of safety and need for parenteral administration, it is generally used only on the basis of *in vitro* bacteriological sensitivity testing. In acute pyelonephritis gentamicin + parenteral amoxicillin-clavulanate, may be initiated empirically before bacteriological report becomes available. The newer aminoglycosides may be needed for hospital-acquired infections.

9. *Chloramphenicol* Though effective in many cases, use should be restricted (for fear of toxicity) to pyelonephritis in cases where the causative bacteria is sensitive only to this antibiotic.

10. *Tetracyclines* They are seldom effective now, because most urinary pathogens have become resistant. Though broad spectrum, they are used only on the basis of sensitivity report and in *Ch. trachomatis* cystitis.

Urinary pH in relation to use of AMAs

Certain AMAs act better in acidic urine, while others in alkaline urine (*see* Box). However, specific intervention to produce urine of desired reaction (by administering acidifying or alkalinizing agents) is seldom required (except for methenamine), because most drugs used in UTI attain high concentration in urine and minor changes in urinary pH do not affect clinical outcome. In case of inadequate response or in complicated cases, measurement of urinary pH and appropriate corrective measure may help.

Favourable urinary pH for antimicrobial action

Acidic	*Alkaline*	*pH immaterial*
Nitrofurantoin Methenamine Tetracyclines Cloxacillin	Cotrimoxazole Aminoglycosides (Gentamicin, etc.) Cephalosporins Fluoroquinolones	Chloramphenicol Ampicillin

In certain urease positive *Proteus* (they split urea present in urine into NH_3) infections it is impossible to acidify urine. In such cases, acidification should not be attempted and drugs which act better at higher pH should be used.

Urinary infection in patients with renal impairment

This is relatively difficult to treat because most AMAs attain lower urinary concentration. Methenamine mandelate, tetracyclines (except doxycycline) and certain cephalosporins are contraindicated.

Nitrofurantoin, nalidixic acid and aminoglycosides are better avoided. Every effort must be made to cure the infection, because if it persists, kidneys may be further damaged. Bacteriological testing and followup cultures are

TABLE 54.1 **Regimens for the treatment of sexually transmitted diseases**

DISEASE/CAUSATIVE ORGANISM	*TREATMENT* *1st Choice*	*Alternatives*
1. Gonorrhoea		
Nonpenicillinase producing (Non PPNG)	Amoxicillin 3 g oral, or Ampicillin 3.5 g oral + Probenecid 1 g oral single dose	Cefixime 400 mg once oral, or Doxycycline 100 mg BD × 7 days oral, or Erythromycin 500 mg QID × 5 days oral, or
Penicillinase producing (PPNG)	Ceftriaxone 250 mg i.m. or Cefuroxime 1.5 g i.m or Azithromycin 1.0 g oral single dose + Probenecid 1 g oral single dose	Ciprofloxacin 250–500 mg oral once or Ofloxacin 200–400 mg oral once
2. Syphilis		
Early (Primary, Secondary and Latent <1 yr)	Benzathine Pen. 2.4 MU i.m., 1–3 weekly inj., or Proc. Pen.G 1.2 MU i.m. × 10 days	Doxycycline 100 mg BD oral × 15 days, or Ceftriaxone 1 g i.m. × 7 days, or Erythromycin 500 mg QID oral × 15 days
Late (>1 yr)	Benzathine Pen. 2.4 MU i.m. weekly × 4 weeks, or Proc. Pen.G 1.2 MU i.m. × 20 days	Doxycycline or Erythromycin for 30 days, or Ceftriaxone 1 g i.m./i.v. × 15 days.
3. *Chlamydia trachomatis*		
Nonspecific urethritis/endocervicitis	Azithromycin 1 g oral single dose or Doxycycline 100 mg BD oral × 7 days	Erythromycin 500 mg QID oral × 7 days Ofloxacin 400 mg BD oral X 7 days
Lymphogranuloma venereum	Azithromycin 1.0 g oral weekly × 3 weeks or Doxycycline 100 mg BD oral × 3 weeks (aspirate fluctuant lymph node)	Erythromycin 500 mg QID oral × 3 weeks
4. Granuloma inguinale/ Donovanosis (*Calymm. granulomatis*)	Tetracycline 500 mg QID oral × 3 weeks or Doxycycline 100 mg BD oral × 3 weeks or Azithromycin 500 mg OD oral × 7 days or 1.0 weekly oral × 4 weeks	Erythromycin 500 mg QID oral × 3 weeks
5. Chancroid (*H. ducreyi*)	Ceftriaxone 0.25 g i.m. single dose or Azithromycin 1.0 g oral single dose or Erythromycin 0.5 g QID oral × 7 days	Ciprofloxacin 500 mg BD oral × 3 days or Doxycycline 100 mg BD oral × 7 days or Cotrimoxazole 960 mg BD oral × 14 days
6. Genital Herpes simplex		
First episode	Acyclovir 200 mg 5 times a day/400 mg TDS oral × 10 days or Valacyclovir 0.5–1.0 g BD oral × 10 days or Famciclovir 250 mg TDS oral × 5 days (Acyclovir 5% oint locally 6 times a day × 10 days may afford relief in mild cases)	Does not prevent recurrences
Recurrent episode	The above drugs are given for 3–5 days (Topical acyclovir is ineffective)	
Suppressive treatment	Acyclovir 400 mg BD oral × 6–12 months or Valacyclovir 500 mg OD oral × 6–12 months or Famciclovir 250 mg BD oral × 6–12 months	
7. Trichomonas vaginitis	Metronidazole 2 g single dose or 400 mg TDS × 7 days, or Tinidazole 2 g single dose or 600 mg OD × 7 days (treat the male partner also if recurrent)	Clotrimazole 100 mg intravaginal every night × 6 to 12 days

a must to select the appropriate drug and to ensure eradication of the pathogen. Potassium salts and acidifying agents are contraindicated.

Prophylaxis for urinary tract infection

This may be given when:

(a) Women of child bearing age have recurrent cystitis.

(b) Catheterization or instrumentation inflicting trauma to the lining of the urinary tract is performed; bacteremia frequently occurs and injured lining is especially susceptible.

(c) Indwelling catheters are placed.

(d) Uncorrectable abnormalities of the urinary tract are present.

(e) Inoperable prostate enlargement or other chronic obstruction causes urinary stasis.

The most frequently used drugs for prophylaxis of lower UTI are:

- Cotrimoxazole 480 mg*
- Nitrofurantoin 100 mg*
- Norfloxacin 400 mg*
- Cephalexin 250 mg*

* All drugs are given once daily at bed time.

TREATMENT OF SEXUALLY TRANSMITTED DISEASES (STDs)

The effectiveness of various AMAs in treating different STDs is described with the individual drugs. The preferred drugs and regimens for important STDs are summarized in Table 54.1.

☞ PROBLEM DIRECTED STUDY

54.1 A 35-year-old woman came to the OPD with complaints of urinary urgency, pain and burning during urination, suprapubic discomfort and low-grade fluctuating fever for the past 2 days. She had 3–4 similar episodes over the last year, for which she took treatment from a local doctor. She is married, has 3 children and her last menstrual period was 10 days back. She is neither using nor is willing to use a contraceptive. Physical examination reveals tenderness in the suprapubic region and body temperature 100.4°F. A diagnosis of acute cystitis is made and she is advised to get urine culture and blood tests done.

(a) Should empirical antimicrobial treatment be started after urine sample has been taken for testing? If so, which drug(s) would be appropriate?

(b) Can any drug be given to rapidly relieve urinary symptoms?

(c) Should long-term prophylactic drug be prescribed in her case? If so, which drug would be suitable for her?

(see Appendix-1 for solution)

Chapter 55 Antitubercular Drugs

Tuberculosis is a chronic granulomatous disease and a major health problem in developing countries. About 1/3rd of the world's population is infected with *Mycobact. tuberculosis*. As per WHO statistics for 2010, there were 9.4 million active TB cases globally, to which India was the highest contributor with 2.3 million cases. India has the dubious distinction of being the highest TB burden country for the past many years; and where about 1000 people die from TB every day. In 2012, the Government of India has declared TB to be a notifiable disease, so that any doctor who treats a TB patient, has to notify it to the Govt. In India, control and treatment of TB is covered under a National programme which provides free treatment to all TB cases. The Revised National Tuberculosis Control Programme (RNTCP) was launched in 1997, and its treatment guidelines have been further revised in 2010.

A new dimension got added in the 1980s due to spread of HIV with high prevalence of tuberculosis and *Mycobact. avium* complex (MAC) infection among these patients. India has a large load of HIV infected subjects, and these patients are especially vulnerable to severe forms of tubercular/MAC infection. While lately, the increase in TB case rate associated with HIV infection has been halted in the USA, no such trend is apparent in India; out of all fresh TB cases, 1.2% are coinfected with HIV. Emergence of 'multidrug resistant' (MDR) TB which now accounts for 15% of previously treated, and 3% of new TB cases worldwide, is threatening the whole future of current antitubercular chemotherapy.

Remarkable progress has been made in the last 65 years since the introduction of *Streptomycin* in 1947 for the treatment of tuberculosis. Its full therapeutic potential could be utilized only after 1952 when *isoniazid* was produced to accompany it. The discovery of *ethambutol* in 1961, *rifampin* in 1962, and redefinition of the role of *pyrazinamide* has changed the strategies in the chemotherapy of tuberculosis. Since 1970 efficacy of short course (6–9 months) and domiciliary regimens has been demonstrated and clear-cut treatment guidelines have been formulated.

Fluoroquinolones, newer macrolides and some rifampin congeners are the recent additions to the antimycobacterial drugs, while some novel compounds are under advanced stage of development.

According to their clinical utility the anti-TB drugs can be divided into:

First line: These drugs have high antitubercular efficacy as well as low toxicity; are used routinely.

Second line: These drugs have either low antitubercular efficacy or higher toxicity or both; and are used as reserve drugs.

First line drugs

1. Isoniazid (H)
2. Rifampin (R)
3. Pyrazinamide (Z)
4. Ethambutol (E)
5. Streptomycin (S)

Second line drugs

- Ethionamide (Eto)
- Prothionamide (Pto)
- Cycloserine (Cs)
- Terizidone (Trd)
- Para-aminosalicylic acid (PAS)
- Rifabutin
- Thiacetazone (Thz)

Fluoroquinolones
- Ofloxacin (Ofx)
- Levofloxacin (Lvx/Lfx)
- Moxifloxacin (Mfx)
- Ciprofloxacin (Cfx)

Injectable drugs
- Kanamycin (Km)
- Amikacin (Am)
- Capreomycin (Cm)

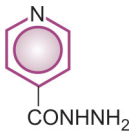
Alternative grouping of antitubercular drugs*		
Group I	First line oral anti-TB drugs	Isoniazid (INH), Rifampin, Pyrazinamide, Ethambutol
Group II	Injectable anti-TB drugs	Streptomycin, Kanamycin, Amikacin, Capreomycin
Group III	Fluoroquinolones	Ofloxacin, Levofloxacin, Moxifloxacin, Ciprofloxacin
Group IV	Second line oral anti-TB drugs	Ethionamide, Prothionamide, Cycloserine, Terizidone, Para-aminosalicylic acid
Group V	Drugs with unclear efficacy£	Thiacetazone, Clarithromycin, Clofazimine, Linezolid, Amoxicillin/clavulanate, Imipenem/cilastatin

* Adopted from: Treatment of Tuberculosis Guidelines; WHO, Fourth edition (2010) and Revised National Tuberculosis Control Programme (RNTCP), DOTS-Plus Guidelines 2010.
£ Not recommended by WHO for routine use in MDR-TB patients.

Group I: are the most potent and best tolerated oral drugs used routinely.
Group II: are potent and bactericidal, but injectable drugs.
Group III: includes fluoroquinolones (FQs) which are well tolerated bactericidal oral drugs; all patients with drug resistant TB should receive one FQ.
Group IV: are less effective, bacteriostatic/more toxic oral drugs for resistant TB.
Group V: are drugs with uncertain efficacy; not recommended for MDR-TB; may be used in extensively resistant TB (XDR-TB).

An alternative grouping of antitubercular drugs reflecting hierarchy in efficacy/priority in use has also been done (see box).

Isoniazid (Isonicotinic acid hydrazide, H)



ISONIAZID

Isoniazid is an excellent antitubercular drug, and an essential component of all antitubercular regimens, unless the patient is not able to tolerate it or bacilli are resistant. It is primarily tuberculocidal. Fast multiplying organisms are rapidly killed, but quiescent ones are only inhibited. It acts on extracellular as well as on intracellular TB (bacilli present within macrophages), and is equally active in acidic or alkaline medium. It is one of the cheapest antitubercular drugs. However, most nontubercular mycobacteria are not inhibited by INH.

The primary mechanism of action of INH is inhibition of synthesis of *mycolic acids* which are unique fatty acid components of mycobacterial cell wall. This may explain the high selectivity of INH for mycobacteria (it is not active against any other microorganism). The lipid content of mycobacteria exposed to INH is reduced. Two gene products labelled 'InhA' and 'KasA', which function in mycolic acid synthesis are the targets of INH action. INH enters sensitive mycobacteria which convert it by a catalase-peroxidase enzyme into a reactive metabolite. This then forms adduct with NAD that inhibits InhA and KasA. The reactive INH metabolite forms adduct with NADP as well which inhibits mycobacterial DHFRase resulting in interruption of DNA synthesis.

About 1 in 10^6 tubercle bacilli is inherently resistant to clinically attained INH concentrations. If INH is given alone, such bacilli proliferate selectively and after 2–3 months (sometimes even earlier) an apparently resistant infection emerges. The most common mechanism which confers high level INH resistance is by mutation of the catalase-peroxidase *(KatG)* gene so that the bacilli do not generate the reactive metabolite of INH. However, bacilli that lose catalase activity also appear to become less virulent; many physicians like to continue INH even when bacilli are apparently resistant to it *in vitro*. INH resistance may also involve mutation in the *inhA* or *kasA* genes. Resistance based on efflux of INH from the bacterial cell is also possible. Other resistant TB bacilli lose the active INH concentrating process.

The incidence of primary INH resistance varies widely among different populations, depending on the extent of use and misuse of INH in that area. According to WHO, the global weighted mean of any INH resistance (excluding MDR) among new TB patients is 7.4%. In India resistance to INH alone or in combination with other anti-TB drugs is estimated to be 18%. Combined with other drugs, INH has good resistance preventing action. No cross resistance with other antitubercular drugs occurs.

Pharmacokinetics INH is completely absorbed orally and penetrates all body tissues, tubercular cavities, placenta and meninges. It is extensively metabolized in liver; most important pathway being N-acetylation by NAT2. The acetylated metabolite is excreted in urine. The rate of INH acetylation shows genetic variation. There are either:

Fast acetylators
(30–40% of Indians) t½ of INH 1 hr.
Slow acetylators
(60–70% of Indians) t½ of INH 3 hr.

The proportion of fast and slow acetylators differs in different parts of the world. However, acetylator status does not matter if INH is taken daily, but biweekly regimens are less effective in fast acetylators. Isoniazid induced peripheral neuritis is more common in slow acetylators. A hepatotoxic minor metabolite is produced by CYP2E1 from acetylhydrazine.

Interactions Aluminium hydroxide inhibits INH absorption.

INH retards phenytoin, carbamazepine, diazepam, theophylline and warfarin metabolism by inhibiting CYP2C19 and CYP3A4, and may raise their blood levels. Since rifampin is an enzyme inducer, its concurrent use counteracts the inhibitory effect of INH. However, the net effect on metabolism of many drugs is unpredictable. PAS inhibits INH metabolism and prolongs its t½.

Dose of all first line drugs is given in Table 55.1.

Adverse effects INH is well tolerated by most patients. Peripheral neuritis and a variety of neurological manifestations (paresthesias, numbness, mental disturbances, rarely convulsions) are the most important dose-dependent toxic effects. These are due to interference with production of the active coenzyme pyridoxal phosphate from pyridoxine, and its increased excretion in urine (*see* Ch. 67). Pyridoxine given prophylactically (10 mg/day) prevents the neurotoxicity even with higher doses. Prophylactic pyridoxine must be given to diabetics, chronic alcoholics, malnourished, pregnant, lactating and HIV infected patients, but routine use is not mandatory. INH neurotoxicity is treated by pyridoxine 100 mg/day.

Hepatitis, a major adverse effect of INH, is rare in children, but more common in older people and in alcoholics (chronic alcoholism induces CYP2E1 which generates the hepatotoxic metabolite). INH hepatotoxicity is due to dose-related damage to liver cells, but is reversible on stopping the drug.

Other side effects are lethargy, rashes, fever, acne and arthralgia.

ISONEX 100, 300 mg tabs, ISOKIN 100 mg tab, 100 mg per 5 ml liq.

Rifampin (Rifampicin, R)

It is a semisynthetic derivative of rifamycin B obtained from *Streptomyces mediterranei*. Rifampin is bactericidal to *M. tuberculosis* and many other gram-positive and gram-negative bacteria like *Staph. aureus*, *N. meningitidis*, *H. influenzae*, *E. coli*, *Klebsiella*, *Pseudomonas, Proteus* and *Legionella*. Against TB bacilli, it is as efficacious as INH and better than all other drugs. The bactericidal action covers all subpopulations of TB bacilli, but acts best on slowly or intermittently dividing ones (spurters). *M. leprae* is highly sensitive, while MAC and some other mycobacteria, but not *M. fortuitum*, are moderately susceptible. Both extra- and intracellular organisms are affected. It has good sterilizing and resistance preventing actions.

Rifampin interrupts RNA synthesis by binding to β subunit of mycobacterial DNA-dependent RNA polymerase (encoded by *rpoB* gene and blocking its polymerizing function. The basis of selective toxicity is that mammalian RNA polymerase does not avidly bind rifampin.

Mycobacteria and other organisms develop resistance to rifampin rather rapidly. However, the incidence of resistant bacilli is less than 10^{-7} and it is quite unusual for a patient to have primary rifampin resistant tubercular infection. In India it is estimated to be 2%. Rifampin resistance is nearly always due to mutation in the *rpoB* gene reducing its affinity for the drug. No cross resistance with any other antitubercular drug, except rifampin congeners, has been noted.

Pharmacokinetics It is well absorbed orally, (bioavailability is ~ 70%), but food decreases absorption; rifampin is to be taken in empty stomach. It is widely distributed in the body: penetrates intracellularly, enters tubercular cavities, caseous masses and placenta. Though it crosses meninges, it is largely pumped out from CNS by P-glycoprotein. It is metabolized in liver to an active deacetylated metabolite which is excreted mainly in bile, some in urine also. Rifampin and its desacetyl derivative undergo enterohepatic circulation. The t½ of rifampin is variable (2–5 hours).

Interactions Rifampin is a microsomal enzyme inducer—increases several CYP450 isoenzymes, including CYP3A4, CYP2D6, CYP1A2 and CYP2C subfamily. It thus enhances its own metabolism (area under the plasma concentration-time curve is reduced by ~35%) as well as that of many drugs including warfarin, oral contraceptives, corticosteroids, sulfonylureas, steroids, HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), theophylline, metoprolol, fluconazole, ketoconazole, clarithromycin, phenytoin, etc. Contraceptive failures have occurred. It is advisable to switch over to an oral contraceptive containing higher dose (50 µg) of estrogen or use alternative method of contraception.

Adverse effects The incidence of adverse effects is similar to INH.

Hepatitis, a major adverse effect, generally occurs in patients with preexisting liver disease and is dose-related; infrequent with ≤ 600 mg/day dose. Development of jaundice requires discontinuation of the drug—then it is reversible. Minor reactions, usually not requiring drug withdrawal and more common with intermittent regimens, are:

- *Cutaneous syndrome*: flushing, pruritus + rash (especially on face and scalp), redness and watering of eyes.
- *Flu syndrome*: with chills, fever, headache, malaise and bone pain.
- *Abdominal syndrome*: nausea, vomiting, abdominal cramps with or without diarrhoea.

Urine and secretions may become orange-red—but this is harmless.

Other serious but rare reactions are:

- *Respiratory syndrome*: breathlessness which may be associated with shock and collapse.
- Purpura, haemolysis, shock and renal failure.

Other uses of rifampin

1. Leprosy (*see* Ch. 56)
2. Prophylaxis of *Meningococcal* and *H. influenzae* meningitis and carrier state.
3. Second/third choice drug for MRSA, diphtheroids and *Legionella* infections.
4. Combination of doxycycline and rifampin is the first line therapy of brucellosis.

RCIN 150, 300, 450, 600 mg caps, 100 mg/5 ml susp. RIMACTANE, RIMPIN 150, 300, 450 mg caps, 100 mg/5 ml syr.; RIFAMYCIN 450 mg cap, ZUCOX 300, 450, 600 mg tabs; to be taken 1 hour before or 2 hour after meals.

Pyrazinamide (Z)

Chemically similar to INH, pyrazinamide (Z) was developed parallel to it in 1952. It is weakly tuberculocidal and more active in acidic medium. It is more lethal to intracellularly located bacilli and to those at sites showing an inflammatory response (pH is acidic at both these locations). It is highly effective during the first 2 months of therapy when inflammatory changes are

present. By killing the residual intracellular bacilli it has good 'sterilizing' activity. Its inclusion has enabled duration of treatment to be shortened and risk of relapse to be reduced. The mechanism of action of Z is not well established, but like INH it is also converted inside the mycobacterial cell into an active metabolite pyrazinoic acid by an enzyme (pyrazinamidase) encoded by the *pncA* gene. This metabolite gets accumulated in acidic medium and probably inhibits mycolic acid synthesis, but by interacting with a different fatty acid synthase. Pyrazinoic acid also appears to disrupt mycobacterial cell membrane and its transport function. Resistance to Z develops rapidly if it is used alone, and is mostly due to mutation in the *pncA* gene.

Pyrazinamide is absorbed orally, widely distributed, has good penetration in CSF, because of which it is highly useful in meningeal TB; extensively metabolized in liver and excreted in urine; plasma t½ is 6–10 hours.

Hepatotoxicity is the most important dose-related adverse effect, but it appears to be less common in the Indian population than in western countries. Daily dose is now limited to 25–30 mg/kg which produces only a low incidence of hepatotoxicity. It is contraindicated in patients with liver disease. Safety during pregnancy is uncertain (*see* p. 776).

Hyperuricaemia is common and is due to inhibition of uric acid secretion in kidney: gout can occur.

Other adverse effects are abdominal distress, arthralgia, flushing, rashes, fever and loss of diabetes control: repeated blood glucose monitoring is warranted in diabetics.

PYZINA 0.5, 0.75, 1.0 g tabs, 0.3 g kid tab; PZA-CIBA 0.5, 0.75 g tabs, 250 mg/5 ml syr; RIZAP 0.75, 1.0 g tabs.

Ethambutol (E)

Ethambutol is selectively tuberculostatic and is active against MAC as well as some other mycobacteria, but not other types of bacteria. Fast multiplying bacilli are more susceptible. Added to the triple drug regimen of RHZ it has been found to hasten the rate of sputum conversion and to prevent development of resistance, the latter being the primary purpose of using it.

The mechanism of action of E is not fully understood, but it has been found to inhibit arabinosyl transferases (encoded by *embAB* genes) involved in arabinogalactan synthesis thereby interfering with mycolic acid incorporation in mycobacterial cell wall. Resistance to E develops slowly and is most commonly associated with mutation in *embB* gene, reducing the affinity of the target enzyme for E. No cross resistance with any other antitubercular drug has been noted.

About 3/4 of an oral dose of E is absorbed. It is distributed widely, but penetrates meninges incompletely and is temporarily stored in RBCs. Less than ½ of E is metabolized. It is excreted in urine by glomerular filtration and tubular secretion; plasma t½ is ~4 hrs. Caution is required in its use in patients with renal disease.

Patient acceptability of E is very good and side effects are few. Loss of visual acuity/colour vision, field defects due to optic neuritis is the most important dose and duration of therapy dependent toxicity. Patients should be instructed to stop the drug at the first indication of visual impairment. Because young children may be unable to report early visual impairment, it was contraindicated, but is now allowed with due precaution. With early recognition and stoppage of the drug, visual toxicity is largely reversible. It is contraindicated in patients with optic neuritis. Ethambutol produces few other symptoms: nausea, rashes, fever, rarely peripheral neuritis. Hyperuricemia is due to interference with urate excretion. It is safe during pregnancy. Ethambutol is used in MAC infection as well.

MYCOBUTOL, MYAMBUTOL, COMBUTOL 0.2, 0.4, 0.6, 0.8, 1.0 g tabs.

Streptomycin (S)

The pharmacology of streptomycin is described in Ch. 53. It was the first clinically useful antitubercular drug. It is tuberculocidal, but less effective than INH or rifampin; acts only on extracellular bacilli (because of poor penetration

into cells). Thus, other drugs and host defence mechanisms are needed to eradicate the disease. It penetrates tubercular cavities, but does not cross to the CSF, and has poor action in acidic medium.

Resistance developed rapidly when streptomycin was used alone in tuberculosis—most patients had a relapse. Recent studies indicate worldwide increase in resistance to S. In case of S-resistant infection, it must be stopped at the earliest because of risk of S-dependence, in which case the infection flourishes when the drug is continued. Most nontubercular mycobacteria are unaffected by S.

Because of need for i.m. injections and lower margin of safety (ototoxicity and nephrotoxicity, especially in the elderly and in those with impaired renal function) S is used only as an alternative to or in addition to other 1st line anti-TB drugs. Use is restricted to a maximum of 2 months. It is thus also labelled as a 'supplemental' 1st line drug.

SECOND LINE ANTI-TB DRUGS

These are less effective and/or less well tolerated anti-TB drugs that are used only in case the bacilli are resistant to one or more 1st line drugs or when these are not tolerated/are contraindicated.

1. Kanamycin (Km), Amikacin (Am)

These are tuberculocidal aminoglycoside antibiotics (described in Ch. 53), very similar in antitubercular activity, pharmacokinetic properties and types of adverse effects to S. Many S resistant and MDR strains of *M.tuberculosis* remain sensitive to them. One of these is mostly included in the regimen for MDR-TB during the intensive phase. The RNTCP standardized regimen for MDR-TB includes Km (probably because it is less expensive than Am), but in many countries Am is preferred, because it is considered less toxic. Cross resistance between Km and Am is very common. Both Km and Am produce less vestibular toxicity than hearing loss, but are equally nephrotoxic. Patients should be instructed to report vertigo and tinnitus. Audiometry and monitoring of renal function is recommended.

Dose: 0.75–1.0 g/day (10–15 mg/kg/day) i.m.

2. Capreomycin (Cm)

It is a cyclic peptide antibiotic, chemically very different from aminoglycosides, but with similar mycobactericidal activity, ototoxicity and nephrotoxicity. In addition, Cm often causes eosinophilia, rashes, fever and injection site pain. It has to be injected i.m. and is used only as alternative to aminoglycoside antibiotics. Many *M.tuberculos*is isolates resistant to S and Am, as well as MDR-TB remain susceptible to Cm.

Dose: 0.75–1.0 g/day i.m.

KAPOCIN 0.5 g, 0.75 g, 1.0 g inj, CAPREOTEC 1.0 inj.

3. Fluoroquinolones (FQs)

Fluoroquinolones (FQs) like ofloxacin (Ofx), levofloxacin (Lfx), ciprofloxacin (Cfx) and moxifloxacin (Mfx) are relatively new potent oral bactericidal drugs for TB, that have gained prominence as well tolerated alternatives to 1st line anti-TB drugs. They are active against MAC, *M. fortuitum* and some other atypical mycobacteria as well. Mfx is the most active FQ against *M.tuberculosis*, while Lvx is more active than Ofx and Cfx. On the other hand, Cfx is more active than Lfx against atypical mycobacteria. The FQs penetrate cells and kill mycobacteria lodged inside macrophages as well. Though Cfx was initially used in TB, it is not favoured now because of its extensive use in other bacterial infections and chances of resistance.

The primary indication of FQs is for treatment of drug resistant TB. They have also been tried in 1st line regimens for new cases. Substitution of E with Mfx to accompany RHZ in the four drug regimen has been found to enhance the rate of bacillary killing and cause faster sputum conversion. In contrast Cfx, Ofx and Lfx did not enhance the sterilizing ability of R and H, and were no better than E. Thus, addition of Mfx to RHZ regimen holds the possibility of reducing the duration of treatments of TB from 6 months with RHZE used currently. However, experience with Mfx in the treatment of TB is still limited, and it is not routinely used.

FQs are a key component of all regimens for MDR-TB, except when bacilli are found to be resistance to them. The RNTCP have included Ofx/Lfx in the standardized regimen for MDR-TB. If used alone, mycobacterial resistance to Ofx, Lfx and Cfx develops rapidly by mutation of DNA gyrase gene. Interestingly, experimental data indicates that resistance against Mfx is slow to

develop.

Dose: Ofloxacin 800 mg OD
Levofloxacin 750 mg OD
Moxifloxacin 400 mg OD
} For > 45 kg body weight

4. Ethionamide (Eto)

It is an antitubercular drug of moderate efficacy, introduced in 1956, which acts on both extra- and intracellular bacilli. Few atypical mycobacteria including MAC are also susceptible. Chemically it resembles INH, but contains sulfur. The mechanism of action is also similar to INH: it is converted by mycobacteria into an active intermediate which interferes with mycolic acid synthesis. Resistance to Eto mosly results from mutation of the gene that encodes for the Eto activating enzyme. Eto is nearly completely absorbed orally, distributed all over and crosses into CSF. It is completely metabolized in liver and has a short t½ of 2–3 hours.

Tolerability of Eto is poor; frequent adverse effects are—anorexia, nausea, vomiting, salivation, metallic taste, epigastric discomfort, sulfurous belching and hepatitis. It also causes aches and pains, peripheral neuritis, behavioural changes, rashes, impotence, menstrual disturbances and goiter on prolonged use. To improve tolerance, dosing may initiated at 250 mg/day, and increased every 5–6 days to reach 750 mg/day (10–15 mg/kg/day). Pyridoxine (100 mg/day) can mitigate the neurological adverse effects.

Ethionamide is used only for drug-resistant TB. It is a component of the RNTCP standardized regimen for MDR-TB and an optional drug for inclusion into the treatment regimen of MAC infection in AIDS patients. It is also a reserve drug for leprosy.

ETHIDE, MYOBID, ETHIOKOX 250 mg tab.

5. Prothionamide (Pto)

A close congener of Eto, to which it resembles in antimycobacterial property, mechanism of action, pharmacokinetics and adverse effects. Clinically it is cosidered interchangeable with Eto for use in MDR-TB, MAC infection, etc.

PROTHICID, PETHIDE 250 mg tab.

6. Cycloserine (Cs)

This antibiotic obtained from *S.orchidaceus* is an analogue of D-alanine. Accordingly, it inhibits bacterial cell well synthesis by inactivating the enzymes which racemize L-alanine and link two D-alanine residues. Cs is tuberculostatic; in addition inhibits MAC as well as some other gram-positive bacteria, *E.coli* and *Chlamydia*. Resistance to Cs develops slowly; no cross resistance with any other anti-TB drugs occurs.

Oral absorption of Cs is good; it diffuses all over the body; CSF concentration is equal to that in plasma. About 1/3 of a dose is metabolized; the rest is excreted unchanged in urine; plasma t½ is 9 hours. Adverse effects of Cs are primarily neurological; about half of the recipients experience neuropsychiatric symptoms, *viz.* sleepiness, headache, tremor, slurring of speech, altered behaviour, depression or frank psychosis. Seizures are infrequent. Pyridoxine 100 mg/day can reduce neurotoxicity and prevent convulsions. Fall in BP has been noted. Cs is contraindicated in patients with a history of mental illness or seizures. Cycloserine is used only for resistant TB, especially MDR cases. It is included in the standardized regimen used by RNTCP for MDR-TB.

Dose: Start with 250 mg BD, increase if tolerated to 750 mg/day for patients with body weight >45 kg.

CYCLORINE, COXERIN, MYSER 250 mg cap.

7. Terizidone

It contains 2 molecules of cycloserine and has antibacterial properties as well as mechanism of action similar to it; but is believed to be less neurotoxic; reported incidence of adverse effects is lower. It is used as a substitute of Cs, especially in genitourinary TB, because it attains higher and longer lasting concentration in urine. Dosage are similar to Cs; 500–750 mg/day.

TERICOX 250 mg cap.

8. Para-amino salicylic acid (PAS)

Introduced in 1946, PAS is related to sulfonamides and acts probably by the same mechanism, i.e. inhibition of folate synthase. It is not active against other bacteria, and this selectivity may be due to difference in the affinity for folate synthase of *M.tuberculosis* compared to that of other bacteria. However, other mechanisms of action are also possible.

PAS is tuberculostatic and one of the least active drugs: does not add to the efficacy of more active drugs that are given with it; only delays development of resistance—probably by directly inhibiting episomal resistance transfer. Resistance to PAS is slow to develop. It is used as the sodium salt (large doses that are needed may cause Na^+ overload) or calcium salt (better gastric tolerance is claimed).

PAS is absorbed completely by the oral route and distributed all over except in CSF. About 50% PAS is acetylated; competes with acetylation of INH and prolongs its t½. It is excreted rapidly by glomerular filtration and tubular secretion; t½ is short, ~1 hour.

Patient acceptability of PAS is poor because of frequent anorexia, nausea and epigastric pain. Other adverse effects are rashes, fever, malaise, hypokalaemia, goiter, liver dysfunction and rarely blood dyscrasias.

PAS is used only in resistant TB. The RNTCP includes it in the standardized regimen for MDR-TB only when one of the tuberculocidal drugs (Km, Ofx, Z, Eto) or both the static drugs (E, Cs) cannot be used.

Dose: 10–12 g (200 mg/kg) per day in divided doses;

SODIUM-PAS 0.5 g tab, 80 g/100 g granules.

9. Thiacetazone (Thz)

Its efficacy in TB is now considered uncertain, and it is not indicated, even as a reserve drug, in MDR-TB.

10. Rifabutin

It is related to rifampin in structure and mechanism of action, but is less active against *M.tuberculosis*, and more active against MAC. Majority of *M.tuberculosis* isolates resistant to R are cross resistant to rifabutin. Thus, it is not an option for treatment of MDR-TB. The only place of rifabutin

in the treatment of TB is as a substitute for R to minimise drug interactions due to strong enzyme inducing property of R. Rifabutin is a much weaker inducer of CYP enzymes than R. This is especially needed in HIV coinfected patients of TB who receive a protease inhibitor (PI) and/or a non-nucleoside reverse transcriptase inhibitor (NNRTI) whose metabolism is markedly induced by R rendering them ineffective.

The primary indication of rifabutin is for prophylaxis and treatment of MAC infection in HIV-AIDS patients. For prophylaxis of MAC, rifabutin alone 300 mg/day is an alternative to azithromycin/clarithromycin, while for treatment of MAC infection, it is combined with 2–3 other anti-MAC drugs. Gastrointestinal intolerance, rashes, granulocytopenia, myalgia and uveitis have been reported with rifabutin. Reactions similar to those caused by R can also occur. Oral bioavailability of rifabutin is low (~20%), but t½ is much longer (>30 hours).

Dose: 300 mg (5 mg/kg) OD oral; RIBUTIN 150 mg tab.

Some antitubercular combinations

RIFATER: Rifampin 120 mg, isoniazid 80 mg, pyrazinamide 250 mg tab.
R-CINEX: Rifampin 600 mg, isoniazid 300 mg tab; R-CINEX-Z: Rifampin 225 mg, isoniazid 150 mg, pyrazinamide 750 mg tab.
RIMACTAZID, RIFADIN-INH, Rifampin 450 mg, isoniazid 300 mg tab.
MYCONEX 600 and 800; Isoniazid 300 mg, ethambutol 600 mg or 800 mg tab, COMBUNEX Isoniazid 300 mg, ethambutol 800 mg tab.
ARZIDE, ISORIFAM: Rifampin 450 mg, isoniazid 300 mg cap.
BI-TEBEN, ISOZONE, UNITHIBEN: Isoniazid 75 mg, thiacetazone 37.5 mg tab, ISOZONE FORTE—double strength.
INAPAS: sod PAS 834 mg, isoniazid 25 mg tab; sod PAS 3.34 g + isoniazid 100 mg per measure granules.
INABUTOL: Isoniazid 150 mg, ethambutol 400 mg tab; INABUTOL FORTE—double strength.
ISOKIN–300: Isoniazid 300 mg, vit B_6 10 mg tab.
IPCAZIDE: Isoniazid 100 mg, vit B_6 5 mg per 5 ml liq.

Antitubercular combipacks (packs of 1 day's dose)

AKT-4:	R 450 mg 1 cap + Z 750 mg 2 tab + E 800 mg H 300 mg 1 tab.
AKT-3:	R 450 mg 1 cap + E 800 mg H 300 mg 1 tab.
CX-5:	R 450 mg 1 cap + Z 750 mg 2 tab + E 800 mg H 300 mg pyridoxine 10 mg 1 tab.
RIFACOM-Z and: RIMACTAZIDE-Z	R 450 mg H 300 mg 1 tab. + Z 750 mg 2 tab.
RIFACOM-EZ:	R 450 mg H 300 mg 1 tab. + Z 750 mg 2 tab + E 800 mg 1 tab.

Fixed dose combination of antitubercular drugs with vitamins (except INH + Vit B_6) are banned in India.

TREATMENT OF TUBERCULOSIS

The therapy of tuberculosis has undergone remarkable changes.

The 'conventional' 12–18 month treatment has been replaced by more effective and less toxic 6 month (short course) treatment which also yields higher completion rates. This has been possible due to better understanding of the biology of tubercular infection and the differential properties of the antitubercular drugs.

Biology of tubercular infection *M. tuberculosis* is an aerobic organism. In unfavourable conditions it grows only intermittently or remains dormant for prolonged periods. Several subpopulations of bacilli, each with a distinctive metabolic state, could exist in an infected patient, e.g.:

(a) *Rapidly growing with high bacillary load* as in the wall of a cavitary lesion where oxygen tension is high and pH is neutral. These bacilli are highly susceptible to H and to a lesser extent to R, E and S.

(b) *Slow growing* located intracellularly (inside macrophages) and at inflamed sites where pH is low. They are particularly vulnerable to Z, while H, R and E are less active, and S is inactive.

(c) *Spurters* found mostly within caseous material where oxygen tension is low but pH is neutral: the bacilli grow intermittently with occasional spurts of active metabolism. R is most active on this subpopulation.

(d) *Dormant* some bacilli remain totally inactive for prolonged periods. No antitubercular drug is significantly active against them.

However, there is continuous shifting of bacilli between these subpopulations.

The goals of antitubercular chemotherapy are:

(a) *Kill dividing bacilli* Drugs with early bactericidal action rapidly reduce bacillary load in the patient and achieve quick sputum negativity so that the patient is non-contagious to the community: transmission of TB is interrupted. This also affords quick symptom relief.

(b) *Kill persisting bacilli* To effect cure and prevent relapse. This depends on sterilizing capacity of the drug.

(c) *Prevent emergence of resistance* So that the bacilli remain susceptible to the drugs.

The relative activity of the first line drugs in achieving these goals differs, e.g. H and R are the most potent bactericidal drugs active against all populations of TB bacilli, while Z acts best on intracellular bacilli and those at inflamed

sites. It thus has very good sterilizing activity. On the other hand S is active only against rapidly multiplying extracellular bacilli. E is bacteriostatic—mainly serves to prevent resistance and may hasten sputum conversion.

Drug combinations are selected to maximise the above actions together with considerations of cost, convenience and feasibility. The general principles of antitubercular chemotherapy are:

- Use of any single drug in tuberculosis results in the emergence of resistant organisms and relapse in almost 3/4th patients. A combination of two or more drugs must be used. The rationale is: the incidence of resistant bacilli to most drugs ranges from 10^{-8} to 10^{-6}. Because an average patient of pulmonary tuberculosis harbours 10^{8} to 10^{10} bacilli, the number of organisms that will not respond to a single drug is high and cannot be dealt by the host defence. During protracted treatment, these bacilli multiply and become dominant in 3–4 months. Because insensitivity to one drug is independent of that to another, i.e. incidence of H resistance among bacilli resistant to R will be 10^{-6} and *vice versa*; only few bacilli will be resistant to both; these can be handled by host defence. By the same rationality, massive infection ($>10^{10}$ organisms) has to be treated by at least 3 drugs; and a single drug is sufficient for prophylaxis, because the number of bacilli is small.
- Isoniazid and R are the most efficacious drugs; their combination is definitely synergistic—duration of therapy is shortened from > 12 months to 9 months. Addition of Z for the initial 2 months further reduces duration of treatment to 6 months.
- A single daily dose of all first line antitubercular drugs is preferred. The 'directly observed treatment short course' (DOTS) was recommended by the WHO in 1995.
- Response is fast in the first few weeks as the fast dividing bacilli are eliminated rapidly. Symptomatic relief is evident within 2–4 weeks. The rate of bacteriological, radiological and clinical improvement declines subsequently as the slow multiplying organisms respond gradually. Bacteriological cure takes much longer. The adequacy of any regimen is decided by observing sputum conversion rates and 2–5 year relapse rates after completion of treatment.

Conventional regimens These consist of H + Tzn or E with or without S (for initial 2 months) and require 12–18 months therapy. Failure rates are high, compliance is poor—therefore not used now.

SHORT COURSE CHEMOTHERAPY

After several years of trial, the WHO introduced 6–8 month multidrug 'short course' regimens in 1995 under the DOTS programme. An expert group framed clearcut treatment guidelines in 1997 for different categories of TB patients, who were grouped according to site and severity of disease, sputum smear positivity/negativity and history of previous treatment (new case/previously treated case) into 4 categories:

Category I: New case of sputum smear positive or severe pulmonary TB, or severe forms of extrapulmonary TB (meningitis, etc.).

Category II: Defaulted, irregularly treated and relapse cases.

Category III: New sputum smear negative pulmonary TB and less severe forms of extrapulmonary TB (glandular/skin TB, etc.).

Category IV: Chronic cases who remained or again became sputum smear positive after receiving fully supervised category II treatment.

The dose of all first line drugs was standardized on body weight basis, applicable to both adults and children. These guidelines were implemented by India and other WHO member countries, making major progress in global TB control. The 'stop TB strategy' of WHO was launched in 2006 and the spread of MDR-TB was taken into account. On the basis of experience gained, new guideline with revised categorization of patients has been brought out in 2010. According to these, the category III has been merged with category I, and patients of TB are now classified only as "New cases' or 'Previously treated' patients, and drug resistant including MDR-TB. The recommended doses of first line drugs are given in Table 55.1 and the treatment regimens are summarized in Table 55.2.

TABLE 55.1 Recommended doses of antitubercular drugs@

DRUG	Daily dose		3 times per week dose	
	mg/kg	maximum	mg/kg	daily maximum
Isoniazid (H)	5 (4–6)	300 mg	10 (8–12)	900 mg
Rifampin (R)	10 (8–12)	600 mg	10 (8–12)	600 mg
Pyrazinamide (Z)	25 (20–30)	-	35 (30–40)	-
Ethambutol (E)	15 (15–20)	-	30 (25–35)	-
Streptomycin (S)*	15 (12–18)	-	15 (12–18)	1000 mg

* Patients over 60 years age—10 mg/kg or 500–750 mg/day (i.m.).
@ Adopted from Treatment of Tuberculosis: Guidelines, 4th edition (2010), WHO, Geneva.

TABLE 55.2 Categorywise treatment regimens for tuberculosis (adopted from WHO guidelines 2010)*

Category	Intensive phase	Continuation phase	Duration (months)	Comment
I New patient	2$ HRZE daily	4$ HR daily	6$	Optimal
	2 HRZE daily	4 HR thrice weekly	6	Acceptable if DOT ensured
	2 HRZE thrice weekly	4 HR thrice weekly	6	Acceptable if DOT ensured, and no HIV coinfection or its risk
II Previously treated patients pending DST result	2 HRZES daily + 1 HRZE daily	5 HRE daily	8	For patient with low/medium risk of MDR-TB (failure, default, etc.)
	Empirical£ (standardized) MDR-regimen	Empirical (standardized) MDR-regimen	18–24 or till DST result	For patient with high risk of MDR-TB (failure, 2nd default, contact of MDR-TB, etc.)

DST—Drug sensitivity testing; DOT—Directly observed therapy
H, R, Z, E, S—Standard codes for isoniazid, rifampin, pyrazinamide, ethambutol and streptomycin, respectively.
$—The neumerals indicate duration of a phase/total duration in months.
£—Empirical (Standardized) MDR regimen is country specific depending upon local data and situation (Indian regimen on p.776)

*Treatment of tuberculosis: Guidelines, 4th edition (2010), WHO, Geneva.

All regimens have an initial *intensive phase* with 4–5 drugs lasting 2–3 months aimed to rapidly kill the bacilli, bringing about sputum conversion and afford fast symptomatic relief. This is followed by a *continuation phase* with 2–3 drugs lasting 4–5 months during which the remaining bacilli are eliminated so that relapse does not occur.

New patient (Category I)

Initial treatment with 4 drugs (HRZE) including 3 bactericidal drugs reduces the risk of selecting resistant bacilli, especially in the face of increasing primary H resistance which is now 7–18% among new cases. After the intensive phase when few bacilli are left, only 2 highly effective cidal drugs in the continuation phase are enough to effect cure. Extension of intensive phase beyond

2 months (suggested earlier for patients who remain sputum positive at 2 months) is not recommended now. However, in such cases, some authorities recommend 9 month treatment instead of 6 months.

The frequency of dosing during the intensive phase or the continuation phase or both can be daily or thrice weekly (Table 55.2). Daily treatment during both phases is considered optimal, because it may help to prevent acquisition of resistance even in patients who start with primary H resistance. However, keeping in view the constraints in organizing daily supervision of drug administration, and to reduce drug costs, thrice weekly therapy is acceptable in the continuation phase, provided each dose is supervised. If constraints are still pressing, even the intensive phase could be thrice weekly, but then HIV coinfection or possibility of contacting it during therapy is to be ruled out. In areas with high level of primary H resistance, WHO suggests inclusion of E (along with H and R) in the continuation phase.

Previously treated patients (Category II)

Smear positive TB patients who in the past have been exposed to anti-TB drugs, but did not complete the course or took inadequate/irregular medication, or relapsed after responding, or failed to respond run a higher risk of harbouring drug resistant (DR) bacilli.

As per WHO data 13% of globally notified TB patients in 2007 were retreatment cases. In 2010 India notified a total of about 1.52 million TB patients out of which about 0.29 million (~ 19%) were retreatment cases (RNTCP data).

The bacilli may be resistant to one or more 1st line drugs. It is crucial to identify MDR cases, because in them continuing treatment with Ist line drugs alone is not only ineffective, but also amplifies drug resistance. It is important to culture the bacilli in each of the retreatment cases and determine drug sensitivity, which will help in identifying MDR cases and in devising the most appropriate drug therapy for that patient. Drug sensitivity testing (DST) is still mostly done by conventional methods which take atleast 4–6 weeks. However, rapid DSTs are now available at few places which take <10 days, but are expensive and not routinely done. Most of the time the DST results are not available before starting treatment. The recommended strategy in such situation is outlined in Table 55.2.

The option of thrice weekly drug therapy is not available for retreatment cases, because all types of DR-TB must receive daily treatment. The risk of MDR-TB should be assessed in each case taking help of the local surveillance data. In general defaulting, interrupted treatment and relapse patients have lower risk of MDR-TB compared to failure cases, especially those who fail after receiving R for 6 months, or those who interrupt treatment more than once or have contacted infection from a MDR-TB case.

If the risk of MDR-TB in a particular patient is assessed as low or medium, a regimen containing 1st line drugs is prescribed. In the intensive phase HRZES (5 drugs) are given daily for 2 months and HRZE (4 drugs) for another month. This is followed by the continuation phase of 3 drugs (HRE) for the next 5 months. This 8 month empirical regimen should not be augmented by an injectable 2nd line drug or a FQ, because this may compromise efficacy of these drugs which are crucial for treatment of MDR-TB. The treatment regimen should be modified as and when result of DST becomes available. Outcome of all regimens should be monitored by clinical assessment as well as by sputum smear and culture examination.

Retreatment patients whose MDR-TB risk is assessed as high should be started on an empirical/standardized MDR-TB regimen which is formulated by each country according to its local surveillance data and other factors. These patients are treated as presumed MDR cases till DST results become available. The definitive regimen is decided thereafter.

Multidrug-resistant (MDR) TB

MDR-TB is defined as resistance to both H and R, and may be any number of other (1st line) drug(s). MDR-TB has a more rapid course with worse outcomes. Its treatment requires complex

multiple 2nd line drug regimens which are longer, more expensive and more toxic. In India MDR-TB accounts for 2.8% of all new TB cases and 12–17% of retreatment cases in different states. These figures are close to the global average incidence. As per WHO, India has the highest number of MDR-TB cases in South-East Asia. The general principles of treatment of MDR-TB are:

- The regimen should have at least 4 drugs certain to be effective. Often 5–6 drugs are included, since efficacy of some may be uncertain.
- Reliance about efficacy may be placed on survey of similar patients who have been treated, DST results (applicable to H, R, Km, Am, Cm, FQs), and the anti-TB drugs used previously in that individual.
- Avoid combining cross resistance drugs, e.g. two FQs, Km with Am or Eto with Pto, or Cs with terizidone.
- Include drugs from group I to group IV (alternative classification) in a hierarchial order. Group I drugs (except H and R) can be included, add one injectable drug (group II), One FQ (group III) and one or two group IV drugs.

The RNTCP initiated the DOTS-plus programme in the year 2000 to cover the diagnosis and treatment of MDR-TB. It has updated its strategy and brought up the revised DOTS-Plus guidelines in 2010, so that they are in consonance with the current WHO guidelines. According to the DOTS-Plus guidelines a case of R resistance is also treated as MDR-TB. The RNTCP has devised a 'standardized' treatment regimen (also called category IV regimen), of 6 drugs intensive phase lasting 6–9 months and 4 drugs continuation phase of 18 months (*see* box), which is used in all confirmed or suspect MDR-TB cases, unless DST results or other specifics (intolerance, etc.) of an individual case necessitate use of an 'individualized regimen', which is constructed taking into account these individual specific features.

The minimal 6 month intensive phase is extended by 1 month each time till a maximum of 9 months, if the sputum culture put up at the end of 4th, 5th and 6th month respectively are positive. PAS is substituted in place of any one of the cidal drugs (Km, Ofx, Z or Eto) or two of the static drugs (E, Cs) when these are not tolerated. Pyridoxine 100 mg/day is given to all patients during the whole course of therapy to prevent neurotoxicity of the anti-TB drugs. This standardized regimen used under DOTS-Plus has been found to be highly successful, with failure rate of 6% among category-2MDR cases (patients who had failed 1st line treatment) and 2% among category-1MDR cases (contacts of MDR-TB).

Standardized RNTCP regimen for MDR-TB*

Intensive phase (6–9 months)	*Continuation phase (18 months)*
1. Kanamycin (Km) 2. Ofloxacin (Ofx) or Levofloxacin (Lfx) 3. Ethionamide (Eto) 4. Cycloserine (Cs) 5. Pyrazinamide (Z) 6. Ethambutol (E)	1. Ofloxacin or Levofloxacin 2. Ethionamide 3. Cycloserine 4. Ethambutol
+ Pyridoxine 100 mg/day	

* Revised National Tuberculosis Control Programme: DOTS-Plus Guidelines (2010); Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare, New Delhi.

Extensively drug-resistant TB These are MDR-TB cases that are also resistant to FQs as well as one of the injectable 2nd line drugs and may be any number of other drugs. The bacilli thus are resistant to at least 4 most effective cidal drugs, *viz*. H,R,FQ and one of Km/Am/Cm.

In USA 3% of MDR-TB cases have been found to be XDR. The exact incidence of XDR-TB in India is not known, but with expanding laboratory facilities to conduct sensitivity tests for 2nd line drugs more XDR-TB cases are likely to be confirmed. The MDR-TB treatment failure cases (between 2–6%) may be presumed to be XDR.

The XDR-TB is very difficult to treat, has a rapid course and high mortality. However, to prevent further amplification of resistance, the standardized MDR regimen (category IV treatment) must be immediately stopped when XDR-

TB is detected or suspected. An expert panel may decide on instituting category V treatment, including the group V drugs (alternative classification, *see* p. 766), which have uncertain efficacy and are expensive. Some new drugs like PA-824 and TMC-207 are also being evaluated.

Tuberculosis in pregnant women The WHO and British Thoracic Society consider H, R, E and Z to be safe to the foetus and recommend the standard 6 month (2HRZE + 4HR) regimen for pregnant women with TB. S is contraindicated because it is ototoxic to the foetus. However, Z is not recommended in the USA (due to lack of adequate teratogenicity data). In India, it is advised to avoid Z, and to treat pregnant TB patients with 2 HRE + 7HR (total 9 months). Treatment of TB should not be withheld or delayed because of pregnancy. All pregnant women being treated with INH should receive pyridoxine 10–25 mg/day.

Treatment of breastfeeding women All anti-TB drugs are compatible with breastfeeding; full course should be given to the mother, but the baby should be watched (*See* Appendix-4). The infant should receive BCG vaccination and 6 month isoniazid preventive treatment after ruling out active TB.

Management of patients with adverse drug reactions to antitubercular drugs Minor side effects are to be managed symptomatically without altering medication; e.g. nausea, anorexia—give the drugs with small meals; drowsiness—give drugs before bed time; flu syndrome due to intermittent dosing of R—change to daily dosing of R; Z induced arthralgia can be treated by analgesic-NSAIDs; peripheral neuritis due to H can be mitigated by pyridoxine. If more severe reactions like skin rashes, itching develop, all drugs should be stopped promptly. After resolution of the reaction, the drugs are to be reintroduced one at a time by challenging with small doses and increasing every 3 days. When the offendng drug is identified, it should be stopped and the regimen reconstituted. However, R should never be reintroduced in case of severe reaction such as haemolysis, thrombocytopenia or renal failure. Ethambutol should be discontinued at the first sign of optic neuritis.

Hepatotoxicity is the most common problem with antitubercular drugs. Any one or more of H, R and Z could be causative and the reaction occurs more frequently when, as per standard protocol, combination of these drugs is used. In case hepatitis develops, all drugs should be stopped and the reaction allowed to subside. If TB is severe nonhepatotoxic drugs S + E + One FQ should be started while the reaction clears. Subsequently, drugs are restarted one at a time. Generally, R is resumed first followed 7 days later by H. If hepatitis recurs, the last added drug is stopped permanently and the regimen is reconstructed. In case both R and H are tolerated—do not restart Z but prolong therapy with R and H to 9 months. If R is the culprit, HES may be given for 2 months followed by HE for 10 months. If H is implicated, REZ may be given for 9 months. If both R and H cannot be given, the S, E, FQ regimen should be administered for 18–24 months.

Chemoprophylaxis The purpose is to prevent progression of latent tubercular infection to active disease. This is indicated only in :

(a) Contacts of open cases who show recent Mantoux conversion.

(b) Children with positive Mantoux and a TB patient in the family.

(c) Neonate of tubercular mother.

(d) Patients of leukaemia, diabetes, silicosis, or those who are HIV positive but are not anergic, or are on corticosteroid therapy who show a positive Mantoux.

(e) Patients with old inactive disease who are assessed to have received inadequate therapy.

The standard drug for chemoprophylaxis of TB is H 300 mg (10 mg/kg in children) daily for 6 months. This is as effective in HIV patients as in those with normal immune function. Because of spread of INH resistance, a combination of H (5 mg/kg) and R (10 mg/kg, maximum 600 mg) daily given for 3 months is preferred in some areas. The

CDC (USA) recommends 4 months R prophylaxis in case H cannot be used.

Several regimens, including one with E + Z ± one FQ, have been suggested for subjects exposed to MDR-TB. However, there is no consensus about the most appropriate drug(s) or duration of prophylaxis that should be used. The RNTCP therefore recommend that MDR-TB contacts should be watched without giving any prophylactic medication, and treated promptly if they develop active disease.

Role of corticosteroids Corticosteroids should not be ordinarily used in tubercular patients. However, they may be used under adequate chemotherapeutic cover:

(a) In seriously ill patients (miliary or severe pulmonary TB) to buy time for drugs to act.
(b) When hypersensitivity reactions occur to antitubercular drugs.
(c) In meningeal/renal/pericardial TB or pleural effusion—to reduce exudation, prevent its organisation and strictures, etc.
(d) In AIDS patients with severe manifestations of tuberculosis.

Corticosteroids are contraindicated in intestinal tuberculosis because silent perforation can occur.

Corticosteroids, if given, should be gradually withdrawn when the general condition of the patient improves.

Tuberculosis in AIDS patients The association of HIV and TB infection is a serious problem. HIV positive cases have a higher incidence of extrapulmonary, more severe, more lethal and more infectious TB. HIV infection is the strongest risk factor for unmasking latent TB. Moreover, adverse reactions to anti-TB drugs are more common in HIV patients. It is estimated that 2.4 million Indians are currently living with HIV. Recent countrywide data shows that 5% of TB patients in India are HIV positive.

On the other hand, institution of 'highly active antiretroviral therapy' (HAART) and improvement in CD4 cell count of the subject markedly reduces the incidence of TB among HIV-AIDS patients. When CD4 count is <150 cells/µL, extrapulmonary and dual TB is more commonly encountered.

In case of *M. tuberculosis* infection, drugs used are the same as in non-HIV cases, and at least 4 drugs are used. Initial intensive phase therapy with daily HRZE for 2 months is started immediately on the diagnosis of TB, and is followed by a continuation phase of HR for 4–7 months (total 6–9 months). Thrice weekly regimen should not be used, because it is associated with 2–3 times higher rate of relapse and failure among HIV positive patients, and risk of acquiring resistance to R is increased compared to daily treatment. Some experts recommend prolonging the continuation phase with HR from 4 months to 7 months or to give 3 drugs (HRE) for 4 months in the continuation phase. Pyridoxine 25–50 mg/day is routinely given along with H to counteract its neurological side effects, which are more likely in AIDS patients. All HIV positive TB patients should also receive cotrimoxazole preventive therapy at least throughout the anti-TB regimen. This has been found to reduce mortality, probably by preventing *Pneumocystis jirovecii* and other infections.

Consideration also has to be given to possible drug interactions between anti-TB and anti-retroviral (ARV) drugs. Rifampin, a potent inducer of CYP isoenzymes, markedly enhances the metabolism of protease inhibitors (PIs, *viz.* indinavir, nelfinavir, ritonavir) and of NNRTIs, *viz.* nevirapine, efavirenz (to a lesser extent) making them ineffective. In patients receiving these drugs, rifabutin (a less potent enzyme inducer) given for 9–12 months may be substituted for rifampin. The metabolism of nucleoside reverse transcriptase inhibitors (NRTIs, zidovudine, etc.) is not induced by rifampin, and no dose adjustment is needed. An alternative regimen of 3 NRTIs (zidovudine + lamivudine + abacavir) has been advocated for patients who are to be treated by rifampin. If 2 NRTI + NNRTI is to be used, efavirenz should be selected as the NNRTI because its metabolism is induced to a lesser extent.

MDR-TB in HIV-AIDS patients should be treated in the same way as that in non-HIV infected patient for a total of 18–24 months.

Mycobacterium avium complex (MAC) infection

MAC is an opportunistic pathogen which causes disseminated and multifocal disease in immunocompromized (HIV-AIDS) patients. The disease develops when cell mediated immunity is markedly depressed, i.e. when CD4 count drops to <50 cells/µL, HIV-RNA load is high and other opportunistic infections (*P. jirovecii*, etc.) are also present. The newer macrolide antibiotics are particularly active drugs against MAC.

Clarithromycin and azithromycin have weak activity against *M.tuberculosis* but are the most active drugs against MAC, *M. fortuitum, M. kansasii* and *M. marinum*. Clarithromycin has lower MICs against these mycobacteria than azithromycin, but the latter may be equally efficacious due to its higher tissue and intracellular levels as well as longer stay in the body.

Therapy of MAC infection Eradication of MAC has not been achieved by any drug or regimen. Therapy is directed to suppress the disease and afford symptomatic relief untill immune status of the patient improves by HAART. A favoured regimen consists of 3 or 4 drug intensive phase followed by 2 drug maintenance phase as outlined in the box. The benefit of adding a FQ as the 4th drug is not clear.

The duration of intensive phase is dependent on the response, *viz.* till CD4 count rises > 100 cells/µL and symptomatic relief is obtained, which may take 2–6 months. The maintenance therapy is continued till a minimum of 12 months, or the patient becomes asymptomatic for MAC infection and CD4 count stays > 100 cell/µL for at least 6 months. All patients must simultaneously receive HAART for the HIV infection. Despite therapy, mortality remains high.

Regimen for treatment of MAC infection

Intensive phase

1. Clarithromycin 500 mg twice daily *or*
   Azithromycin 500 mg once daily
2. Ethambutol 1000 mg (15 mg/kg) per day
3. Rifabutin 300 mg per day

±

Ciprofloxacin 500 mg twice daily *or*
Levofloxacin 500 mg once daily *or*
Moxifloxacin 400 mg once daily

Maintenance phase*

1. Clarithromycin/Azithromycin
2. Ethambutol/Rifabutin/One fluoroquinolone

* Doses in the maitenance phase are the same as in intensive phase

Prophylaxis of MAC infection

This is aimed at protecting the AIDS patient from developing active MAC disease during the period CD4 count remains below 50 cell/µL. A single drug is used—azithromycin 1200 mg/week or clarithromycin 500 mg twice a day are the preferred drugs. Rifabutin 300 mg/day is used if either of these drugs cannot be given. This is continued till the simultaneously instituted HAART achieves complete suppression of HIV replication, CD4 count rises above 100 cell/µL and stays there for at least 3 months.

☞ PROBLEM DIRECTED STUDY

55.1 A 45-year-old male factory worker weighing 60 kg reports to the hospital with cough and expectoration, mild chest pain, weakness and fatigue for the last one month. In addition he has developed low grade fever for the last one week. He gives history of having suffered from TB of the lung one year back for which he took treatment from the hospital and became all right in 2 months. He stopped taking the medicines after another 1 month, though he was told by the doctor to continue treatment. The sputum was found to be positive for AFB and X-ray chest showed a 5 cm cavitary lesion in the right middle lobe and fibrotic changes in the upper lobe. He was diagnosed to be a defaulted patient of pulmonary TB.

(a) Should any specific laboratory test be ordered in this case; if so, should the treatment start immediately or after the report is available?

(b) What should be the regimen of antitubercular drugs for this patient? Can he be treated with a thrice weekly dosing regimen?

(*see* Appendix-1 for solution)