and acidosis caused by probiotics are very rare, though caution may be prudent in immunocompromized patients.

ECONORM, STIBS: *Saccharomyces boulardii* 250 mg sachet.
BIFILAC: *Lactobacillus* 50 M (million), *Streptococcus faecalis* 30 M, *Clostridium butyricum* 2M, *Bacillus mesentericus* 1M per cap/sachet.
BIFILIN: *Lactobacillus sp*, 1 billion (B) *Bifidobacterium bifidum* 1B, *Streptococcus thermophillus* 0.25B, *Saccharomyces boulardii* 0.25B cap and sachet.
ACTIGUT: *Lactobacillus sp*., *Bifidobacterium sp*. cap.
ENTEROGERMINA: *Bacillus clausii* 2 billion spores/5 ml oral amp.

3. Drugs for inflammatory bowel disease (IBD)

IBD is a chronic relapsing inflammatory disease of the ileum, colon, or both, that may be associated with systemic manifestations. It is idiopathic, but appears to have an important immune component triggered by a variety of factors. The two major types of IBD are ulcerative colitis (UC) and Crohn's disease (CrD).

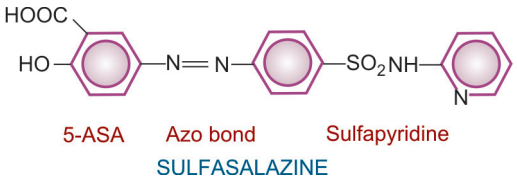
Ulcerative colitis It involves only the colon starting from the anal canal. It may remain restricted to the rectum or extend proximally in a contiguous manner to variable extent upto caecum. The lesions are mucosal and may be diffuse or confluent.

Crohn's disease In CrD lesions are patchy and transmural; may involve any part of the g.i.t. from mouth to the anus. Majority of patients have ileocaecal disease upto ascending colon, but in some it may be restricted to the small intestine, while in others to the colon. Because the lesions are transmural, complications like perforation, abscess, fistula, strictures, etc. occur. CrD is less amenable to medical therapy than is UC. Though UC and CrD are distinct clinical entities, few patients have features of both and cannot be clearly categorized into UC or CrD.

The drugs used in UC and CrD are the same, but their roles and efficacy do differ. Drugs used in IBD can be grouped into:

- 5-Amino salicylic acid (5-ASA) compounds
- Corticosteroids
- Immunosuppressants
- TNFα inhibitors

Sulfasalazine (Salicylazosulfapyridine) It is a compound of 5-aminosalicylic acid (5-ASA) with sulfapyridine linked through an azo bond, and has a specific therapeutic effect in IBD.



SULFASALAZINE

Having low solubility, it is poorly absorbed from the ileum. The azo bond is split by colonic bacteria to release 5-ASA and sulfapyridine. The former exerts a local antiinflammatory effect, the mechanism of which is not clear. Though it inhibits both COX and LOX, decreased PG and LT production appears to play a minor role in the therapeutic effect. Inhibition of cytokine, PAF, TNFα and nuclear transcription factor (NFκB) generation seems to be more important. Migration of inflammatory cells into bowel wall is interfered and mucosal secretion is reduced, affording symptomatic relief in UC and to a lesser extent in colon-restricted CrD (releases 5-ASA only in colon). Given during active phase of the disease it reduces number of stools, abdominal cramps and fever, but is less effective than corticosteroids; may be employed for mild to moderate exacerbation. A dose of 3–4 g/day induces remission over a few weeks in many patients, but relapses are common after stoppage. Maintenance therapy with 1.5–2 g/day has been found to postpone relapse in majority, but not all cases. The primary value of sulfasalazine is in maintaining remission in UC, but not in CrD, while corticosteroids are reserved to treat acute exacerbations.

The beneficial effect of sulfasalazine is clearly not due to any antibacterial action (bowel flora remains largely unaffected). The sulfapyridine moiety only serves to carry 5-ASA to the colon without being absorbed proximally. However, most of the released sulfapyridine is absorbed in the colon and is responsible for adverse effects like rashes, fever, joint pain, haemolysis and blood dyscrasias. Nausea, vomiting, headache, malaise and anaemia are other frequent dose related side effects. Upto 1/3rd patients suffer intolerable adverse effects. Oligozoospermia and male infertility is reported. Sulfasalazine interferes with

folate absorbtion. Folic acid supplementation should always be given during its use.

Sufasalazine has also been used as a disease modifying drug in rheumatoid arthritis. The absorbed sulfapyridine moiety appears to be responsible for the therapeutic effect (*see* p. 211).
SALAZOPYRIN, SAZO-EN 0.5 g tab.

Mesalazine (Mesalamine) These are the official names given to 5-ASA. Realizing that 5-ASA is the active moiety in UC, but is not effective orally because of inability to reach the large bowel (it is absorbed in the small intestine), it has been formulated as a delayed release preparation or has been coated with pH sensitive acrylic polymer. The pattern of release over the length of jejunum, ileum and colon differs among the different formulations. The coated formulation (ASACOL, MESACOL) delivers 5-ASA to the distal small bowel and colon. A daily dose of 2.4 g has been found to improve over 50% patients of UC (upto 80% mild-to-moderate cases). Less than half of the 5-ASA released from these preparations is absorbed systemically, acetylated in the liver and excreted in urine. Like sulfasalazine, the primary use of mesalazine is in preventing relapse of UC, though it may also be employed to treat mild-to-moderate exacerbations or as adjunct to corticosteroid in more severe active disease. Higher dose of coated mesalazine may induce remission in mild cases of Crohn's colitis as well, but efficacy is uncertain. It is not useful in maintaining remission in CrD.
MESACOL 400 mg, 800 mg tab, 0.5 g suppository; ASACOL, TIDOCOL 400 mg tab; ETISA 500 mg sachet.

Adverse effects Coated mesalazine is much better tolerated than sulfasalazine. Side effects noted are nausea, diarrhoea, abdominal pain and headache, but are mild and less frequent. Serious adverse effects are fever, itching and leucopenia. Rashes and hypersensitivity reactions are rare. Bone marrow depression and decreased sperm count has not occurred. Mesalazine has nephrotoxic potential, because 30–40% of 5-ASA is released in the ileum and is absorbed. It is contraindicated in renal and hepatic impairment.

Drug interactions Coated mesalazine may enhance the gastric toxicity of glucocorticoids and hypoglycaemic action of sulfonylureas. Interaction with coumarins, furosemide, spironolactone, methotrexate and rifampicin are possible.

5-ASA enema Another mode of delivery of 5-ASA to colon is to administer it by a retention enema: 4 g enema once or twice daily is effective in distal ulcerative colitis and proctitis, including some refractory cases.5-ASA enema is not useful for maintenance of remission.
MESACOL ENEMA 4 g/60 ml.

Olsalazine It consists of two molecules of 5-ASA coupled together by azo bond. It is poorly absorbed in the ileum, the azo bond is split in the colon to provide 5-ASA locally. No separate carrier moiety is needed. Olsalazine is probably the most reliable preparation for delivery of 5-ASA to the colon. However, it often aggravates diarrhoea initially by decreasing transit time through the bowels.

Balsalazide This is 5-ASA linked to 4-aminobenzoyl-β-alanine as the carrier which, unlike sulfapyridine, is inert. The 5-ASA is released in the colon, and the carrier is poorly absorbed. It can be used as a safer alternative to sulfasalazine.
Dose: 1.5 g BD to 2.25 g TDS.
COLOREX 750 mg cap and per 5 ml syr., INTAZIDE 750 mg tab.

Corticosteroids Prednisolone (40–60 mg/day) or equivalent are highly effective in controlling symptoms as well as in inducing remission in both UC and CrD. They are the drugs of choice for moderately severe exacerbations. In responsive patients symptomatic relief usually starts within 3–7 days and remission is induced in 2–3 weeks. In more severe disease with extraintestinal manifestations and for rapid relief therapy may be initiated with i.v. methyl prednisolone 40–60 mg 12 to 24 hourly for few days. Hydrocortisone enema, or foam (ENTOFOAM 10%) can be used for topical treatment of proctitis and distal ulcerative colitis, but is less effective. Corticosteroids are generally used for short term, and discontinued after remission is induced. Mesalazine started during steroid therapy is continued to prevent relapses. Corticosteroids are neither effective nor

suitable for maintaining remission either in UC or CrD.

A sizeable percentage of severe IBD patients either relapse on stoppage of the steroid (*steroid-dependent*) or do not respond to it (*steroid-resistant*). Specific immunosuppressant drugs are strongly indicated in such IBD patients, and are now frequently prescribed. They also serve to avoid long-term steroid therapy which carries hazards.

Immunosuppressants *(see Ch. 62, 63)*

Immunosuppressants have now come to play an important role in the long-term management of IBD, especially CrD. About 60% patients with CrD and substantial number of UC patients require immunosuppressive therapy. However, risks of chronic immunosuppression must be weighed in each patient before instituting therapy with these drugs. Because of long latency of response, they are not suitable for acute flareups of the disease, but have good remission maintaining and steroid-sparing property.

Azathioprine This purine antimetabolite is the most effective and most commonly used immunosuppressant in IBD. 6-Mercaptopurine (in to which azathioprine is converted in the body) can be used in its place. It is indicated in steroid-dependent, streroid-resistant and relatively severe cases of IBD, or those who experience frequent flareups. Although, azathioprine has its own adverse effect potential, the same is rated lower than that of prolonged steroid therapy. Some patients experience higher bone marrow toxicity of azathioprine and 6-MP due to genetic abnormality of one of its metabolizing enzymes TPMT. These drugs cannot be used in such patients.

Dose: Azathioprine 1.5–2.5 mg/kg/day, 6-MP 1–1.5 mg/kg/day for IBD.

Methotrexate This dihydrofolate reductase inhibitor with immunosuppressant property is a 2nd line drug in IBD, especially CrD. It acts faster than azathioprine and has remission inducing property as well. The doses effective in IBD are higher than those for rheumatoid arthritis. Weekly parenteral therapy is needed, since absorption and efficacy by oral route are poor in IBD. Toxicity therefore is higher. Thus, it has a limited role in severe CrD and in patients not responsive to or not tolerating azathioprine.

Cyclosporine This potent immunosuppressant is occasionally used in severe UC patients who do not improve with corticosteroid therapy. In this setting, i.v. cyclosporine usually controls symptoms in 7–10 days, and can be used as 'bridge' therapy for 2–3 months till azathioprine takes effect. Though, cyclosporine has remission maintaining effect in UC and CrD, it is not preferred for this purpose because of its renal toxicity and poor efficacy in IBD by the oral route.

TNFα inhibitors

Infliximab It is chimeric anti-TNFα antibody that is indicated in severe active CrD, fistulating CrD and severe UC which has not improved with i.v. corticosteroids and immunosuppressants, or when the latter are inappropriate. Infused i.v. every 2–8 weeks, it decreases acute flareups and helps in fistula closure. Therapy is continued till response is maintained. Infliximab produces substantial toxicity, including acute reactions, formation of antibodies and lowering of resistance to infections. Thus, it is only a reserve drug for selected patients with refractory disease.

Adalimumab and some other TNFα inhibitors are also being used in severe and refractory IBD.

4. Nonspecific antidiarrhoeal drugs

These drugs can be grouped into:

A. Absorbants and adsorbants
B. Antisecretory drugs
C. Antimotility drugs

A. Absorbants These are colloidal bulk forming substances like ispaghula, methyl cellulose, carboxy methyl cellulose which absorb water and swell. They modify the consistency and frequency of stools and give an impression of improvement, but do not reduce the water and electrolyte loss. They are of value in selected conditions like diarrhoea phase of IBS, and to increase the consistency of faeces in colostomy patients. Ispaghula and other bulk forming colloids are useful in both constipation and diarrhoea phases of IBS and reduce abdominal pain as well. Substances that do not ferment in colon are preferred for diarrhoea.

Adsorbants like kaolin, pectin, attapulgite are believed to adsorb bacterial toxins in the gut and coat/protect the mucosa. They were ones very popular ingredients of diarrhoea remedies, but are now banned in India, because there is no objective proof of their efficacy.

B. Antisecretory drugs

Racecadotril This recently introduced prodrug is rapidly converted to *thiorphan,* an enkephalinase

inhibitor. It prevents degradation of endogenous enkephalins (ENKs) which are mainly δ opioid receptor agonists. Racecadotril decreases intestinal hypersecretion, without affecting motility (motility appears to be regulated through μ receptors) by lowering mucosal cAMP due to enhanced ENK action. It is indicated in the short-term treatment of acute secretory diarrhoeas. In contrast to loperamide/diphenoxylate, it is not contraindicated in children. The elimination t½ as thiorphan is 3 hr. Side effects are nausea, vomiting, drowsiness, flatulence.

Dose: 100 mg (children 1.5 mg/kg) TDS for not more than 7 days.

CADOTRIL, RACIGYL 100 mg cap, 15 mg sachet; REDOTIL 100 mg cap. ZEDOTT, ZOMATRIL 100 mg tab, 10 mg and 30 mg sachet and dispersible tab.

Bismuth subsalicylate Taken as suspension (60 ml 6 hourly) it is thought to act by decreasing PG synthesis in the intestinal mucosa, thereby reducing Cl^- secretion. It has some prophylactic value in travellers' diarrhoea (probably due to weak antibacterial action as well), but it is rather inconvenient to carry and take.Though quite popular in USA, it is not used in India and UK.

Anticholinergics Atropinic drugs can reduce bowel motility and secretion, but have poor efficacy in secretory diarrhoeas. They may benefit nervous/drug (neostigmine, metoclopramide) induced diarrhoeas and provide some symptomatic relief in dysenteries, diverticulitis.

Octreotide This somatostatin analogue (*see* p. 238) has a long plasma t½ (90 min) as well as potent antisecretory/antimotility action on the gut. It has been used to control diarrhoea in carcinoid and vasoactive intestinal peptide (VIP) secreting tumours, and for refractory diarrhoea in AIDS patients, but needs to be given by s.c. injection.

Opioids In addition to their well recognized antimotility action, opioids reduce intestinal secretion. Loperamide has been clearly shown to reduce secretion, probably through specific opioid receptors, but does not affect mucosal cAMP or cGMP levels.

C. Antimotility drugs

These are opioid drugs which increase small bowel tone and segmenting activity, reduce propulsive movements and diminish intestinal secretions while enhancing absorption. They afford only symptomatic relief in diarrhoea. The major action appears to be mediated through μ opioid receptors located on enteric neuronal network, but direct action on intestinal smooth muscle and secretory/absorptive epithelium has also been demonstrated. The δ receptors are believed to promote absorption and inhibit secretion, while the μ receptors enhance absorption and decrease propulsive movements. Overall they increase resistance to luminal transit and allow more time for the absorptive processes. No tolerance develops to their constipating action.

Codeine (*see* p. 474) This opium alkaloid has prominent constipating action at a dose of 60 mg TDS. The antidiarrhoeal effect is attributed primarily to its peripheral action on small intestine and colon. It does have central effects, but dependence producing liability is low. Side effects are nausea, vomiting and dizziness. Due to its abuse potential and availability of loperamide, codeine is seldom, if ever, used for diarrhoea.

Diphenoxylate (2.5 mg) + *atropine* (0.025 mg):

LOMOTIL tab and in 5 ml liquid.

Dose: 5–10 mg, followed by 2.5–5 mg 6 hourly.

It is a synthetic opioid, chemically related to pethidine; used exclusively as constipating agent; action is similar to codeine. The antidiarrhoeal action is most prominent, but because it is absorbed systemically and crosses blood-brain barrier—CNS effects do occur. Atropine is added in subpharmacological dose to discourage abuse by taking several tablets. Abuse liability is rated low, and overdose will produce disturbing atropinic side effects. It has caused respiratory depression, paralytic ileus and toxic megacolon in children. Response is more variable in them—contraindicated below 6 years of age. Loperamide has largely superseded it.

Loperamide It is an opiate analogue with major peripheral μ opioid and additional weak anticholinergic property. As a constipating agent it is much more potent than codeine. Because of poor water solubility—little is absorbed from the intestines. Entry into brain is negligible—CNS effects are rare and occur only with high doses; no abuse liability. The duration of action is longer (12 hr) than codeine and diphenoxylate.

In addition to its opiate like action on motility, loperamide also inhibits secretion. Direct

interaction with calmodulin may be responsible for the antidiarrhoeal action. Faecal continence is improved by enhancement of anal sphincter tone.

Adverse effects Abdominal cramps and rashes are the most common side effects. Paralytic ileus, toxic megacolon with abdominal distension is a serious complication in young children—fatalities have occurred, probably due to absorption of toxins from the intestines. Loperamide is contraindicated in children < 4 yr. However, it appears to be the most effective and most suitable of the antimotility antidiarrhoeal drugs.

Dose: 4 mg followed by 2 mg after each motion (max. 10 mg in a day); 2 mg BD for chronic diarrhoea.

IMODIUM, LOPESTAL, DIARLOP: 2 mg tab, cap.

Liquid formulation has been withdrawn to prevent use in young children.

The utility of antimotility drugs in diarrhoea is limited to noninfective diarrhoea, mild traveller's diarrhoea, and when diarrhoea is exhausting or idiopathic diarrhoea in AIDS patients. Low doses may be used for chronic diarrhoea in IBS, but higher doses must be avoided. Their use is a short-term measure only.

Antimotility drugs are contraindicated in acute infective diarrhoeas because they delay clearance of the pathogen from the intestine. If invasive organisms (*Shigella*, EPEC, EH, etc.) are present, antimotility drugs can be disastrous by increasing the risk of systemic invasion. Careful use may be made in mild IBD when loose motions and urgency are interfering with daily activities, but antimotility drugs are contraindicated in severe disease, since they may raise intraluminal pressure.

Antimotility drugs can be used to induce deliberate short-term constipation, e.g. after anal surgery, and to reduce the volume, fluidity and bag cleaning frequency in ileostomy/colostomy patients.

NOTE: Drugs Controller General of India has banned the following category of antidiarrhoeal drugs:

1. Containing adsorbants like Kaolin, pectin, attapulgite, activated charcoal, etc.
2. Containing phthalylsulfathiazole, succinylsulfathiazole, sulfaguanidine, neomycin, streptomycin, dihydrostreptomycin.
3. *For pediatric use* containing diphenoxylate, loperamide, atropine, belladonna, hyosciamine, halogenated hydroxyquinolines.
4. Fixed dose combinations of antidiarrhoeals with electrolytes.
5. Fixed dose combination of loperamide with furazolidone.
6. Fixed dose combination of antidiarrhoeals with antihistaminics.

☞ PROBLEM DIRECTED STUDY

48.1 A 35-year-old man has come with complaint of acute onset diarrhoea. The stools are relatively small volume, liquid but not watery, frothy and are preceded by griping pain in abdomen. Foul smelling wind, eructation and mild fever are the other complaints. He has passed 4 loose motions in the past 8 hours and there is no appetite. He admits to have eaten spicy snacks last evening at a road side stall. Physical examination reveals body temperature 101°F, no signs of dehydration, but diffuse abdominal tenderness. A tentative diagnosis of enteroinvasive diarrhoea is made.

(a) Does this patient require rehydration therapy?

(b) Should an antibiotic be prescribed? If so, which antibiotic would be appropriate?

(c) Should an antimotility-antidiarrhoeal drug be coprescribed to reduce the number of stools?

(d) Should any other symptomatic drug be given to him?

(see Appendix-1 for solution)

SECTION 12

ANTIMICROBIAL DRUGS

Chapter 49 Antimicrobial Drugs: General Considerations

Antimicrobial drugs are the greatest contribution of the 20th century to therapeutics. Their advent changed the outlook of the physician about the power drugs can have on diseases. They are one of the few drugs which can cure, and not just palliate disease. Their importance is magnified in the developing countries, where infective diseases predominate. As a class, they are one of the most frequently used as well as misused drugs.

Drugs in this class differ from all others in that they are designed to inhibit/kill the infecting organism and to have no/minimal effect on the recipient. This type of therapy is generally called *chemotherapy* which has come to mean 'treatment of systemic infections with specific drugs that selectively suppress the infecting microorganism without significantly affecting the host.' The basis of selective microbial toxicity is the action of the drug on a component of the microbe (e.g. bacterial cell wall) or metabolic processes (e.g. folate synthesis) that is not found in the host, or high affinity for certain microbial biomolecules (e.g. trimethoprim for bacterial dihydrofolate reductase). Due to analogy between the malignant cell and the pathogenic microbes, treatment of neoplastic diseases with drugs is also called 'chemotherapy'.

Antibiotics These are substances produced by microorganisms, which selectively suppress the growth of or kill other microorganisms at very low concentrations. This definition excludes other natural substances which also inhibit microorganisms but are produced by higher forms (e.g. antibodies) or even those produced by microbes but are needed in high concentrations (ethanol, lactic acid, H_2O_2).

Chemotherapeutic agent Initially this term was restricted to synthetic compounds, but now since many antibiotics and their analogues have been synthesized, this criterion has become irrelevant; both synthetic and microbiologically produced drugs need to be included together. It would be more meaningful to use the term *Antimicrobial agent* (AMA) to designate synthetic as well as naturally obtained drugs that attenuate microorganisms.

The *history* of chemotherapy may be divided into 3 phases.

(a) The period of empirical use: of 'mouldy curd' by Chinese on boils, chaulmoogra oil by the Hindus in leprosy, chenopodium by Aztecs for intestinal worms, mercury by Paracelsus (16th century) for syphilis, cinchona bark (17th century) for fevers.

(b) Ehrlich's phase of dyes and organometallic compounds (1890–1935): With the discovery of microbes in the later half

of 19th century and that they are the cause of many diseases; Ehrlich toyed with the idea that if certain dyes could selectively stain microbes, they could also be selectively toxic to these organisms. He tried methylene blue, trypan red, etc. He developed the arsenicals—*atoxyl* for sleeping sickness, *arsphenamine* in 1906 and neoarsphenamine in 1909 for syphilis. He coined the term 'chemotherapy' because he used drugs of known chemical structure (that of most other drugs in use at that time was not known) and showed that selective attenuation of infecting parasite was a practical proposition.

(c) The modern era of chemotherapy was ushered by Domagk in 1935 by demonstrating the therapeutic effect of *Prontosil*, a sulfonamide dye, in pyogenic infection. It was soon realized that the active moiety was paraamino benzene sulfonamide, and the dye part was not essential. Sulfapyridine (M & B 693) was the first sulfonamide to be marketed in 1938.

The phenomenon of *antibiosis* was demonstrated by Pasteur in 1877: growth of anthrax bacilli in urine was inhibited by air-borne bacteria. Fleming (1929) found that a diffusible substance was elaborated by *Penicillium* mould which could destroy *Staphylococcus* on the culture plate. He named this substance *penicillin* but could not purify it. Chain and Florey followed up this observation in 1939 which culminated in the clinical use of penicillin in 1941. Because of the great potential of this discovery in treating war wounds, commercial manufacture of penicillin soon started.

In the 1940s, Waksman and his colleagues undertook a systematic search of Actinomycetes as source of antibiotics and discovered *streptomycin* in 1944. This group of soil microbes proved to be a treasure-house of antibiotics and soon tetracyclines, chloramphenicol, erythromycin and many others followed. All three groups of scientists, Domagk, Fleming-Chain-Florey and Waksman received the Nobel Prize for their discoveries.

In the past 50 years emphasis has shifted from searching new antibiotic producing organisms to developing semisynthetic derivatives of older antibiotics with more desirable properties or differing spectrum of activity. Few novel synthetic AMAs, e.g. fluoroquinolones, oxazolidinones have also been produced.

CLASSIFICATION

Antimicrobial drugs can be classified in many ways:

A. Chemical structure

1. *Sulfonamides and related drugs*: Sulfadiazine and others, Sulfones—Dapsone (DDS), Paraaminosalicylic acid (PAS).
2. *Diaminopyrimidines:* Trimethoprim, Pyrimethamine.
3. *Quinolones:* Nalidixic acid, Norfloxacin, Ciprofloxacin, Prulifloxacin, etc.
4. *β-Lactam antibiotics:* Penicillins, Cephalosporins, Monobactams, Carbapenems.
5. *Tetracyclines:* Oxytetracycline, Doxycycline, etc.
6. *Nitrobenzene derivative:* Chloramphenicol.
7. *Aminoglycosides:* Streptomycin, Gentamicin, Amikacin, Neomycin, etc.
8. *Macrolide antibiotics:* Erythromycin, Clarithromycin, Azithromycin, etc.
9. *Lincosamide antibiotics:* Lincomycin, Clindamycin.
10. *Glycopeptide antibiotics:* Vancomycin, Teicoplanin.
11. *Oxazolidinone:* Linezolid.
12. *Polypeptide antibiotics:* Polymyxin-B, Colistin, Bacitracin, Tyrothricin.
13. *Nitrofuran derivatives:* Nitrofurantoin, Furazolidone.
14. *Nitroimidazoles:* Metronidazole, Tinidazole, etc.
15. *Nicotinic acid derivatives:* Isoniazid, Pyrazinamide, Ethionamide.
16. *Polyene antibiotics:* Nystatin, Amphotericin-B, Hamycin.
17. *Azole derivatives:* Miconazole, Clotrimazole, Ketoconazole, Fluconazole.
18. *Others:* Rifampin, Spectinomycin, Sod. fusidate, Cycloserine, Viomycin, Ethambutol, Thiacetazone, Clofazimine, Griseofulvin.

B. Mechanism of action

1. *Inhibit cell wall synthesis*: Penicillins, Cephalosporins, Cycloserine, Vancomycin, Bacitracin.
2. *Cause leakage from cell membranes*: Polypeptides—Polymyxins, Colistin, Bacitracin. Polyenes—Amphotericin B, Nystatin, Hamycin.
3. *Inhibit protein synthesis:* Tetracyclines, Chloramphenicol, Erythromycin, Clindamycin, Linezolid.
4. *Cause misreading of m-RNA code and affect permeability:* Aminoglycosides—Streptomycin, Gentamicin, etc.

5. *Inhibit DNA gyrase:* Fluoroquinolones—Ciprofloxacin and others.
6. *Interfere with DNA function:* Rifampin.
7. *Interfere with DNA synthesis:* Acyclovir, Zidovudine.
8. *Interfere with intermediary metabolism:* Sulfonamides, Sulfones, PAS, Trimethoprim, Pyrimethamine, Metronidazole.

C. Type of organisms against which primarily active

1. *Antibacterial:* Penicillins, Aminoglycosides, Erythromycin, Fluoroquinolones, etc.
2. *Antifungal*: Griseofulvin, Amphotericin B, Ketoconazole, etc.
3. *Antiviral:* Acyclovir, Amantadine, Zidovudine, etc.
4. *Antiprotozoal:* Chloroquine, Pyrimethamine, Metronidazole, Diloxanide, etc.
5. *Anthelmintic:* Mebendazole, Pyrantel, Niclosamide, Diethyl carbamazine, etc.

D. Spectrum of activity

Narrow-spectrum	*Broad-spectrum*
Penicillin G	Tetracyclines
Streptomycin	Chloramphenicol
Erythromycin	

The initial distinction between narrow and broad-spectrum antibiotics is no longer clearcut. Drugs with all ranges of intermediate band width, e.g. extended spectrum penicillins, newer cephalosporins, aminoglycosides, fluoroquinolones are now available. However, the terms 'narrow-spectrum' and 'broad-spectrum' are still applied.

E. Type of action

Primarily bacteriostatic	
Sulfonamides	Erythromycin
Tetracyclines	Clindamycin
Chloramphenicol	Linezolid
	Ethambutol

Primarily bactericidal	
Penicillins	Cephalosporins
Aminoglycosides	Vancomycin
Polypeptides	Ciprofloxacin
Rifampin	Metronidazole
Isoniazid	Cotrimoxazole
Pyrazinamide	

Some primarily static drugs may become cidal at higher concentrations (as attained in the urinary tract), e.g. erythromycin, nitrofurantoin. On the other hand, some cidal drugs, e.g. cotrimoxazole, streptomycin may only be static under certain circumstances.

F. Antibiotics are obtained from:

Fungi

Penicillin	Griseofulvin
Cephalosporin	

Bacteria

Polymyxin B	Tyrothricin
Colistin	Aztreonam
Bacitracin	

Actinomycetes

Aminoglycosides	Macrolides
Tetracyclines	Polyenes
Chloramphenicol	

PROBLEMS THAT ARISE WITH THE USE OF AMAs

1. Toxicity

(a) *Local irritancy*: This is exerted at the site of administration. Gastric irritation, pain and abscess formation at the site of i.m. injection, thrombophlebitis of the injected vein are the complications. Practically all AMAs, especially erythromycin, tetracyclines, certain cephalosporins and chloramphenicol are irritants.

(b) *Systemic toxicity:* Almost all AMAs produce dose related and predictable organ toxicities. Characteristic toxicities are exhibited by different AMAs.

Some have a *high therapeutic index*—doses up to 100-fold range may be given without apparent damage to host cells. These include penicillins, some cephalosporins and erythromycin.

Others have a *lower therapeutic index*—doses have to be individualized and toxicity watched for, e.g.:

Aminoglycosides	: 8th cranial nerve and kidney toxicity.
Tetracyclines	: liver and kidney damage, antianabolic effect.
Chloramphenicol	: bone marrow depression.

Still others have a *very low therapeutic index*—use is highly restricted to conditions where no suitable alternative is available, e.g.:

Polymyxin B	: neurological and renal toxicity.
Vancomycin	: hearing loss, kidney damage.
Amphotericin B	: kidney, bone marrow and neurological toxicity.

2. Hypersensitivity reactions

Practically all AMAs are capable of causing hypersensitivity reactions. These are unpredictable and unrelated to dose. The whole range of reactions from rashes to anaphylactic shock can be produced. The more commonly involved AMAs in hypersensitivity reactions are—penicillins, cephalosporins, sulfonamides, fluoroquinolones.

3. Drug resistance

It refers to unresponsiveness of a microorganism to an AMA, and is akin to the phenomenon of tolerance seen in higher organisms.

Natural resistance Some microbes have always been resistant to certain AMAs. They lack the metabolic process or the target site which is affected by the particular drug. This is generally a group or species characteristic, e.g. gram-negative bacilli are normally unaffected by penicillin G; aerobic organisms are not affected by metronidazole; while anaerobic bacteria are not inhibited by aminoglycoside antibiotics, or *M. tuberculosis* is insensitive to tetracyclines. This type of resistance does not pose a significant clinical problem.

Acquired resistance It is the development of resistance by an organism (which was sensitive before) due to the use of an AMA over a period of time. This can happen with any microbe and is a major clinical problem. However, development of resistance is dependent on the microorganism as well as on the drug. Some bacteria are notorious for rapid acquisition of resistance, e.g. staphylococci, coliforms, tubercle bacilli. Others like *Strep. pyogenes* and spirochetes have not developed significant resistance to penicillin despite its widespread use for > 50 years. Gonococci quickly developed resistance to sulfonamides, but only slowly and low-grade resistance to penicillin. However, in the past 40 years, highly penicillin resistant gonococci producing penicillinase have appeared.

Resistance may be developed by mutation or gene transfer.

Mutation It is a stable and heritable genetic change that occurs spontaneously and randomly among microorganisms. Any sensitive population of a microbe contains a few mutant cells which require higher concentration of the AMA for inhibition. These are selectively preserved and get a chance to proliferate when the sensitive cells are eliminated by the AMA. Thus, in time it would appear that a sensitive strain has been replaced by a resistant one, e.g. when a single antitubercular drug is used. This is called *vertical transfer* of resistance; is relatively slow and usually of lower grade. Mutation and resistance may be:

(i) *Single step:* A single gene mutation may confer high degree of resistance; emerges rapidly, e.g. enterococci to streptomycin, *E. coli* and *Staphylococci* to rifampin.

(ii) *Multistep:* A number of gene modifications are involved; sensitivity decreases gradually in a stepwise manner. Resistance to erythromycin, tetracyclines and chloramphenicol is developed by many organisms in this manner.

Sometimes mutational acquisition of resistance is accompanied by decrease in virulence, e.g. certain rifampin-resistant staphylococci and low grade penicillin-resistant gonococci have decreased virulence.

Gene transfer (infectious resistance) The resistance causing gene is passed from one organism to the other; is called *horizontal transfer* of resistance. Rapid spread of resistance can occur by this mechanism and high level resistance to several antibiotics (multidrug resistance) can be acquired concurrently.

(i) *Conjugation* Sexual contact through the formation of a bridge or sex pilus is common among gram-negative bacilli of the same or another species. This may involve chromosomal or extrachromosomal (plasmid) DNA. The gene carrying the 'resistance' or 'R' factor is transferred only if another 'resistance transfer factor' (RTF) is also present. Conjugation frequently occurs in the colon where a large variety of gram-negative bacilli come in close contact. Even nonpathogenic organisms may transfer R factor to pathogenic organisms, which may become widespread by contamination of food or water. Chloramphenicol resistance of typhoid bacilli, streptomycin resistance of *E. coli*, penicillin resistance of *Haemophilus* and gonococci and many others have been traced to this mechanism.

(ii) *Transduction* It is the transfer of gene carrying resistance through the agency of a bacteriophage. The R factor is taken up by the phage and delivered to another bacterium which it infects. Many *Staph. aureus* strains have acquired resistance by transduction. Certain instances of penicillin, erythromycin and chloramphenicol resistance have been found to be phage mediated.

(iii) *Transformation* A resistant bacterium may release the resistance carrying DNA into the medium and this may be imbibed by another sensitive organism—becoming unresponsive to the drug. This mechanism is probably not clinically significant.

Resistance once acquired by any of the above mechanisms becomes prevalent due to the *selection pressure* of a widely used AMA, i.e. presence of the AMA provides opportunity for the resistant subpopulation to thrive in preference to the sensitive population.

Resistant organisms can broadly be of the following three types:

(a) *Drug tolerant* Loss of affinity of the target biomolecule of the microorganism for a particular AMA, e.g. resistant *Staph. aureus* and *E. coli* develop a RNA polymerase that does not bind rifampin, certain penicillin-resistant pneumococcal strains have altered penicillin binding proteins; trimethoprim-resistance results from plasmid-mediated synthesis of a dihydrofolate reductase that has low affinity for trimethoprim. Mutational target site modification is an important mechanism of fluoroquinolone and macrolide resistance. Another mechanism is acquisition of an alternative metabolic pathway, e.g. certain sulfonamide resistant bacteria switch over to utilizing preformed folic acid in place of synthesizing it from PABA taken up from the medium.

(b) *Drug destroying* The resistant microbe elaborates an enzyme which inactivates the drug, e.g.

(i) β-lactamases are produced by staphylococci, *Haemophilus,* gonococci, etc. which inactivate penicillin G. The β-lactamases may be present in low quantity but strategically located periplasmically (as in gram-negative bacteria) so that the drug is inactivated soon after entry, or may be elaborated in large quantities (by gram-positive bacteria) to diffuse into the medium and destroy the drug before entry.

(ii) Chloramphenicol acetyl transferase is acquired by resistant *E. coli, H. influenzae* and *S. typhi*.

(iii) Many of the aminoglycoside-resistant coliforms have been found to produce enzymes which adenylate/acetylate/phosphorylate specific aminoglycoside antibiotics.

(c) *Drug impermeable* Many hydrophilic antibiotics gain access into the bacterial cell through specific channels formed by proteins called 'porins', or need specific transport mechanisms. These may be lost by the resistant strains, e.g. concentration of some aminoglycosides and tetracyclines in the resistant gram-negative bacterial strains has been found to be much lower than that in their sensitive counterparts when both were exposed to equal concentrations of the drugs. Similarly, the low degree penicillin-resistant gonococci are less permeable to penicillin G; chloroquine-resistant *P. falciparum* accumulates less chloroquine. The bacteria may also acquire plasmid directed inducible energy dependent efflux proteins in their cell membrane which pump out

tetracyclines. Active efflux-based resistance has been detected for erythromycin and fluoroquinolones as well.

Cross resistance Acquisition of resistance to one AMA conferring resistance to another AMA, to which the organism has not been exposed, is called cross resistance. This is more commonly seen between chemically or mechanistically related drugs, e.g. resistance to one sulfonamide means resistance to all others, and resistance to one tetracycline means insensitivity to all others. Such cross resistance is often complete. However, resistance to one aminoglycoside may not extend to another, e.g. gentamicin-resistant strains may respond to amikacin. Sometimes unrelated drugs show partial cross resistance, e.g. between tetracyclines and chloramphenicol, between erythromycin and lincomycin.

Cross resistance may be two-way, e.g. between erythromycin and clindamycin and *vice versa,* or one-way, e.g. development of neomycin resistance by enterobacteriaceae makes them insensitive to streptomycin but many streptomycin-resistant organisms remain susceptible to neomycin.

Prevention of drug resistance It is of utmost clinical importance to curb development of drug resistance. Measures are:

(a) No indiscriminate and inadequate or unduly prolonged use of AMAs should be made. This would minimize the selection pressure and resistant strains will get less chance to preferentially propagate. For acute localized infections in otherwise healthy patients, symptom-determined shorter courses of AMAs are advocated.

(b) Prefer rapidly acting and selective (narrow-spectrum) AMAs whenever possible; broad-spectrum drugs should be used only when a specific one cannot be determined or is not suitable.

(c) Use combination of AMAs whenever prolonged therapy is undertaken, e.g. tuberculosis, SABE, HIV-AIDS.

(d) Infection by organisms notorious for developing resistance, e.g. *Staph. aureus, E. coli, M. tuberculosis, Proteus,* etc. must be treated intensively.

4. Superinfection (Suprainfection)

This refers to the appearance of a new infection as a result of antimicrobial therapy.

Use of most AMAs causes some alteration in the normal microbial flora of the body. The normal flora contributes to host defence by elaborating substances called *bacteriocins* which inhibit pathogenic organisms. Further, ordinarily, the pathogen has to compete with the normal flora for nutrients, etc. to establish itself. Lack of competition may allow even a normally non-pathogenic component of the flora, which is not inhibited by the drug (e.g. *Candida*), to predominate and invade. More complete the suppression of body flora, greater are the chances of developing superinfection. Thus, it is commonly associated with the use of broad/extended-spectrum antibiotics, such as tetracyclines, chloramphenicol, ampicillin, newer cephalosporins; especially when combinations of these are employed. Tetracyclines are more liable than chloramphenicol and ampicillin is more liable than amoxicillin to cause superinfection diarrhoeas because of incomplete absorption—higher amounts reach the lower bowel and cause greater suppression of colonic bacteria.

Superinfections are more common when host defence is compromised.

Conditions predisposing to superinfections

- Corticosteroid therapy
- Leukaemias and other malignancies, especially when treated with anticancer drugs (these drugs are also immunosuppressants and decrease WBC count)
- Acquired immunodeficiency syndrome (AIDS)
- Agranulocytosis
- Diabetes, disseminated lupus erythematosus

Sites involved in superinfection are those that normally harbour commensals, i.e. oropharynx; intestinal, respiratory and genitourinary tracts; occasionally skin.

Superinfections are generally more difficult to treat. The organisms frequently involved, the manifestations and drugs for treating superinfections are:

(a) *Candida albicans:* monilial diarrhoea, thrush, vulvovaginitis; treat with nystatin or clotrimazole.

(b) Resistant staphylococci: enteritis; treat with cloxacillin or vancomycin/linezolid.

(c) *Clostridium difficile*: pseudomembranous enterocolitis associated with the use of clindamycin, tetracyclines, aminoglycosides, ampicillin, etc. It is more common after colorectal surgery. The organism produces an enterotoxin which damages gut mucosa forming plaques; metronidazole and vancomycin are the drugs of choice.

(d) *Proteus*: Urinary tract infection, enteritis; treat with a cephalosporin or gentamicin.

(e) *Pseudomonas*: Urinary tract infection, enteritis; treat with carbenicillin, piperacillin, ceftazidime, cefoperazone or gentamicin.

To minimize superinfections:

(i) Use specific (narrow-spectrum) AMA whenever possible.
(ii) Do not use antimicrobials to treat trivial, self-limiting or untreatable (viral) infections.
(iii) Do not unnecessarily prolong antimicrobial therapy.

5. Nutritional deficiencies

Some of the B complex group of vitamins and vit K synthesized by the intestinal flora is utilized by man. Prolonged use of antimicrobials which alter this flora may result in vitamin deficiencies.

Neomycin causes morphological abnormalities in the intestinal mucosa—steatorrhoea and malabsorption syndrome can occur.

6. Masking of an infection

A short course of an AMA may be sufficient to treat one infection but only briefly suppress another one contacted concurrently. The other infection will be masked initially, only to manifest later in a severe form. Examples are:

(i) Syphilis masked by the use of a single dose of penicillin which is sufficient to cure gonorrhoea.
(ii) Tuberculosis masked by a short course of streptomycin given for trivial respiratory infection.

CHOICE OF AN ANTIMICROBIAL AGENT

After having established the need for using a systemic AMA in a patient by assessing that the condition is due to a treatable (mostly bacterial) infection, and that it is not likely to resolve by itself or by local measures (antiseptics, drainage of pus, etc) only, one has to choose a particular AMA from the large number available. The choice depends on the particulars of the patient, the infecting organism and the drug.

Patient factors

1. *Age* may affect kinetics of many AMAs, and certain AMAs produce age-related effects. Conjugation and excretion of chloramphenicol is inefficient in the newborn: larger doses produce *gray baby syndrome.* Sulfonamides displace bilirubin from protein binding sites—can cause kernicterus in the neonate because their blood-brain barrier is more permeable. The t½ of aminoglycosides is prolonged in the elderly and they are more prone to develop VIII nerve toxicity. Tetracyclines deposit in the developing teeth and bone—discolour and weaken them—are contraindicated below the age of 6 years.

2. *Renal and hepatic function* Cautious use and modification of the dose of an AMA (with low safety margin) becomes necessary when the organ of its disposal is defective (*see* box).

3. *Local factors* The conditions prevailing at the site of infection greatly affect the action of AMAs.

(a) Presence of pus and secretions decrease the efficacy of most AMAs, especially sulfonamides and aminoglycosides. Drainage of the abscess

Antimicrobials needing dose reduction/ avoidance in renal failure

Reduce dose even in mild failure

Aminoglycosides	Amphotericin B
Cephalosporins	Ethambutol
Vancomycin	Flucytosine

Reduce dose only in moderate-severe failure

Metronidazole	Carbenicillin
Cotrimoxazole	Fluoroquinolones
Aztreonam	Clarithromycin
Meropenem	Imipenem

Drugs to be avoided

Nalidixic acid	Talampicillin
Nitrofurantoin	Tetracyclines (except doxycycline)

Antimicrobials in liver disease

Drugs to be avoided

Erythromycin estolate	Tetracyclines
Pyrazinamide	Nalidixic acid
Talampicillin	Pefloxacin

Dose reduction needed

Chloramphenicol	Isoniazid
Metronidazole	Rifampin
Clindamycin	

reduces the population of the causative bacteria, suppresses anaerobes by exposure to oxygen, and improves diffusion of the antibiotic into the abscess.

(b) Presence of necrotic material or foreign body including catheters, implants and prosthesis makes eradication of infection practically impossible. Bacteria adhering to foreign surfaces create a biofilm around them and grow very slowly, rendering them difficult to reach and less vulnerable to the antibiotic.

(c) Haematomas foster bacterial growth; tetracyclines, penicillins and cephalosporins get bound to the degraded haemoglobin in the haematoma.

(d) Lowering of pH at the site of infection reduces activity of macrolide and aminoglycoside antibiotics.

(e) Anaerobic environment in the centre of an abscess impairs bacterial transport processes which concentrate aminoglycosides in the bacterial cell, rendering them less susceptible.

(f) Penetration barriers at certain sites may hamper the access of the AMA to the site, such as in subacute bacterial endocarditis (SABE), endophthalmitis, prostatitis. However, trimethoprim and fluoroquinolones attain high concentration in prostate due to ion trapping.

4. *Drug allergy* History of previous exposure to an AMA should be obtained. If an AMA has caused allergic reaction—it has to be avoided in that patient, e.g. drug of choice for syphilis in a patient allergic to penicillin is tetracycline. β-lactams, sulfonamides, fluoroquinolones and nitrofurantoin frequently cause allergy.

5. *Impaired host defence* Integrity of host defence plays a crucial role in overcoming an infection. Pyogenic infections occur readily in neutropenic patients, while if cell-mediated immunity is impaired (e.g. AIDS), infections by low grade pathogens and intracellular organisms abound. In an individual with normal host defence, a bacteriostatic AMA may achieve cure; while intensive therapy with cidal drugs is imperative in those with impaired host defence (conditions given on p. 693) or when the organisms are protected by a barrier—as in SABE. Even then complete eradication of the organism may not occur.

6. *Pregnancy* All AMAs should be avoided in the pregnant woman because of risk to the foetus. Penicillins, many cephalosporins and erythromycin are safe, while safety data on most others is not available. Therefore, manufacturers label 'contraindicated during pregnancy'. Tetracyclines are clearly contraindicated. They carry risk of acute yellow atrophy of liver, pancreatitis and kidney damage in the mother, as well as cause teeth and bone deformities in the offspring. Aminoglycosides can cause foetal ear damage. Animal studies indicate increased risk to the foetus, especially with fluoroquinolones, cotrimoxazole, chloramphenicol, sulfonamides and nitrofurantoin. Though metronidazole has not been found teratogenic, its mutagenic potential warrants caution in its use during pregnancy.

7. *Genetic factors* Primaquine, nitrofurantoin, sulfonamides, chloramphenicol and fluoroquinolones carry the risk of producing haemolysis in G-6-PD deficient patient.

Organism-related considerations

Each AMA has a specific effect on a limited number of microbes. Successful chemotherapy must be rational and demands a diagnosis. However, most of the time, definitive bacteriological diagnosis is not available before initiating treatment. Bacteriological testing takes time, is expensive and appropriate samples of infected material for bacteriology may not be obtainable. Empirical therapy has to be instituted. A clinical diagnosis should first be made, at least tentatively, and the likely pathogen guessed.
The following line of action may be taken:

1. *Clinical diagnosis itself directs choice of the AMA* The infecting organism and its sensitivity pattern are by-and-large known, e.g. syphilis, chancroid, diphtheria, tetanus, plague, cholera, trachoma thrush, tuberculosis, lobar pneumonia, leprosy, amoebiasis, herpes simplex, etc.

2. *A good guess can be made* from the clinical features and local experience about the type of organism and its sensitivity, e.g. tonsillitis, otitis media, boils, vaginitis, urethritis; the most appropriate specific AMA should be prescribed and the response watched for. A Gram stained smear examination of infected material may help to aid the choice.

3. *Choice to be based on bacteriological examination* No guess can be made about the infecting organism or its sensitivity, e.g. bronchopneumonia, empyema, meningitis, osteomyelitis, urinary tract infection, wound infection, etc. In these situations, an AMA should be selected on the basis of culture and sensitivity testing; but this may not be always possible.

(a) *Bacteriological services are not available:* empirical therapy to cover all likely organisms with a broad-spectrum drug like fluoroquinolone, tetracycline or a combination such as gentamicin + a cephalosporin may be used (with metronidazole or clindamycin if anaerobes are suspected). Further therapy is modified on the basis of clinical response; but hasty and arbitrary changes in the selection of AMA should be avoided.

(b) *Bacteriological services are available, but treatment cannot be delayed:* as in serious infections like meningitis, septicaemias, etc., specimens for bacteriological examination should be collected and empirical therapy started provisionally as in (a). In case of inadequate response, the AMA should be changed later in the light of bacteriological findings.

(c) *Bacteriological services are available and treatment can be delayed for a few days:* as in chronic urinary tract infection; it is better to wait for the culture and sensitivity report; start definitive therapy thereafter.

Bacteriological sensitivity testing This is generally done by disk-agar diffusion method using standardized concentrations of antibiotics based on clinically attained plasma concentrations of these. As such, they provide only qualitative results; may serve as indicators, and cannot be blindly extrapolated to the clinical situation in every patient and for every organism. Broth cultures with *break-point* concentration (concentration that demarcates between sensitive and resistant bacteria) of antibiotics probably yield more reliable results. Break-point concentrations are to be related to clinically attainable serum concentrations of the antibiotic.

Minimum inhibitory concentration (MIC), i.e the lowest concentration of an antibiotic which prevents visible growth of a bacterium after 24 hours incubation in microwell culture plates using serial dilutions of the antibiotic is more informative. Lately, the disk-diffusion method has been refined to provide a quantitative estimate of the inhibitory action of an AMA and its MIC. In this test called the *Epsilometer test* (E-test) a rectangular test strip impregnated with ascending concentrations of the AMA is placed on an inoculated agar plate and the bacterial growth is observed after a specific period, depending on the organism. The curved line separating the clear zone from the zone with bacterial growth divides the strip at the MIC value of concentration.

Minimum bactericidal concentration (MBC) of the antibiotic is determined by subculturing from tubes with no visible growth. If the organism is killed, no growth will occur; but if it was only inhibited in the parent culture—it will grow on subculturing in antibiotic-free medium. MBC is the concentration of the antibiotic which kills 99.9% of the bacteria. A small difference between MIC and MBC indicates that the antibiotic is primarily bactericidal, while a large

difference indicates bacteriostatic action. MBC is not used to guide selection of antibiotics in clinical practice.

Postantibiotic effect (PAE) After a brief exposure if the organism is placed in antibiotic-free medium, it starts multiplying again, but after a lag period which depends on the antibiotic as well as the organism. This lag period in growth resumption is known as 'postantibiotic effect' and is the time required for reattainment of logarithmic growth. It is generally calculated from the time required to attain 10 fold increase in bacterial count in the culture for antibiotic exposed and unexposed tubes. A long and dose-dependent PAE has been noted with fluoroquinolones, aminoglycosides and rifampin.

Drug factors

When any one of a number of AMAs could be used to treat an infection, choice among them is based upon specific properties of these AMAs:

1. *Spectrum of activity:* For definitive therapy, a narrow-spectrum drug which selectively affects the concerned organism is preferred, because it is generally more effective than a broad-spectrum AMA, and is less likely to disturb the normal microbial flora. However, for empirical therapy, often a broad-spectrum drug has to be used to cover all likely pathogens.
2. *Type of activity:* Many infections in patients with normal host defence respond equally well to bacteriostatic and bactericidal AMAs. But several acute infections resolve faster with a cidal than a static drug, because the cidal drug directly reduces the number of bacteria at the site of infection, while the static drug only prevents increase in their number. Many bactericidal drugs exert prolonged postantibiotic effect so that maintenance of drug level continuously above the MIC is not essential. With bacteriostatic AMAs the bacteria start multiplying quickly when drug level falls below the MIC, resulting in relapse of infection.

   A bactericidal antibiotic is clearly superior to bacteriostatic one in treating patients with impaired host defence, life-threatening infections, infections at less accessible sites (SABE) or when carrier state is possible (e.g. typhoid).
3. *Sensitivity of the organism:* Assessed on the basis of MIC values (if available) and consideration of postantibiotic effect.
4. *Relative toxicity:* Obviously, a less toxic antibiotic is preferred, e.g. a β-lactam over an aminoglycoside or erythromycin over clindamycin.
5. *Pharmacokinetic profile:* For optimum action the antibiotic has to be present at the site of infection in sufficient concentration for an adequate length of time. This depends on their pharmacokinetic characteristics. Most antibiotics are given at 2 to 4 half-life intervals—thus attaining therapeutic concentrations only intermittently. For many organisms, aminoglycosides, fluoroquinolones and metronidazole produce '*concentration-dependent inhibition*', i.e. inhibitory effect depends on the ratio of peak concentration to the MIC. The same daily dose of gentamicin produces better action when given as a single dose than if it is divided into 2–3 portions. On the other hand, β-lactams, glycopeptides and macrolides produce '*time-dependent inhibition*', i.e. antimicrobial action depends on the length of time the concentration remains above the MIC; division of daily dose improves the effect. However, the doses should be so spaced that the surviving organisms again start multiplying and a cidal action is exerted.

   Penetration to the site of infection also depends on the pharmacokinetic properties of the drug. A drug which penetrates better and attains higher concentration at the site of infection is likely to be more effective. The fluoroquinolones have excellent tissue penetration—attain high concentrations in soft tissues, lungs, prostate, joints, etc. Ciprofloxacin and rifampin have very good intracellular penetration. Cefuroxime, ceftriaxone, chloramphenicol, ciprofloxacin attain high CSF concentration. On the other hand, penicillins and aminoglycosides penetrate poorly into CSF unless meninges are inflamed. Ampicillin, cephalosporins and erythromycin attain high biliary concentration.
6. *Route of administration:* Many AMAs can be given orally as well as parenterally, but aminoglycosides, penicillin G, carbenicillin, many cephalosporins, vancomycin, etc. have to be

given by injection only. For less severe infections, an oral antibiotic is preferable; but for serious infections, e.g. meningitis, spreading cellulitis, septicaemias, a parenteral antibiotic would be more reliable.

7. *Evidence of clinical efficacy:* Relative value of different AMAs in treating an infection is decided on the basis of comparative clinical trials. Optimum dosage regimens and duration of treatment are also determined on the basis of such trials. Reliable clinical trial data, if available, is the final guide for choice of the antibiotic.

8. *Cost:* Less expensive drugs are to be preferred.

COMBINED USE OF ANTIMICROBIALS

More than one AMA are frequently used concurrently. This should be done only with a specific purpose and not blindly in the hope that if one is good, two should be better and three should cure almost any infection. The objectives of using antimicrobial combinations are:

1. To achieve synergism Every AMA has a specific effect on selected microorganisms. Depending on the drug pair as well as the organism involved, either synergism (supra-additive effect), additive action, indifference or antagonism may be observed when two AMAs belonging to different classes are used together.

Synergism may manifest in terms of decrease in the MIC of one AMA in the presence of another, or the MICs of both may be lowered. If the MIC of each AMA is reduced to 25% or less, the pair is considered synergistic, 25–50% of each is considered additive and more than 50% of each indicates antagonism. Thus, a synergistic drug sensitizes the organisms to the action of the other member of the pair. This may also manifest as a more rapid lethal action of the combination than either of the individual members resulting in faster cure of the infection. Synergistic prolongation of postantibiotic effect has also been demonstrated for combinations of β-lactams with an aminoglycoside, and by addition of rifampin to a variety of antibiotics.

Every combination is unique; the same drugs may be synergistic for one organism but antagonistic for another. However, general guidelines are:

(a) Two bacteriostatic agents are often additive, rarely synergistic, i.e. combination of tetracyclines, chloramphenicol, erythromycin, etc. A sulfonamide used with trimethoprim is a special case where supraadditive effect is obtained because of sequential block in folate metabolism of certain bacteria (Ch. 50). The combination often exerts cidal action, while the individual components are only static.

Another special example is the combination of a β-lactamase inhibitor clavulanic acid or sulbactam with amoxicillin or ampicillin for β-lactamase producing *H. influenzae, N. gonorrhoeae* and other organisms.

(b) Two bactericidal drugs are frequently additive and sometime synergistic if the organism is sensitive to both, e.g.:

- Penicillin/ampicillin + streptomycin/gentamicin or vancomycin + gentamicin for enterococcal SABE. Penicillins by acting on the cell wall may enhance the penetration of the aminoglycoside into the bacterium.
- Carbenicillin/ticarcillin + gentamicin for *Pseudomonas* infection, especially in neutropenic patients.
- Ceftazidime + ciprofloxacin for *Pseudomonas* infected orthopedic prosthesis.
- Rifampin + isoniazid in tuberculosis.

In the above cases, the combination produces faster cure and reduces the chances of relapse by more complete eradication of the pathogen.

(c) Combination of a bactericidal with a bacteriostatic drug may be synergistic or antagonistic depending on the organism. In general:

(i) If the organism is highly sensitive to the cidal drug—response to the combination is equal to the static drug given alone (apparent antagonism), because cidal drugs act primarily on rapidly multiplying bacteria, while the static drug retards multiplication. This has been seen with penicillin

+ tetracycline/chloramphenicol on pneumococci which are highly sensitive to penicillin. Pneumococcal meningitis treated with penicillin + tetracycline had higher mortality than those treated with penicillin alone. Penicillin + erythromycin for group A *Streptococci* and nalidixic acid + nitrofurantoin for *E. coli* have also shown antagonism.

(ii) If the organism has low sensitivity to the cidal drug—synergism may be seen, e.g.:

- Penicillin + sulfonamide for actinomycosis
- Streptomycin + tetracycline for brucellosis
- Streptomycin + chloramphenicol for *K. pneumoniae* infection
- Rifampin + dapsone in leprosy.

Thus, wherever possible, synergistic combinations may be used to treat infections that are normally difficult to cure. Full doses of individual drugs are given for this purpose.

2. To reduce severity or incidence of adverse effects This is possible only if the combination is synergistic so that the doses can be reduced. This is needed for AMAs with low safety margin, which when used alone in effective doses, produce unacceptable toxicity, e.g.

- Streptomycin + penicillin G for SABE due to *Strep. faecalis.*
- Amphotericin B + rifampin or minocycline: the latter drugs are not themselves antifungal, but enhance the action of amphotericin B.
- Amphotericin B + flucytosine: a shorter course is needed, specially for cryptococcal meningitis, than when amphotericin is used alone.

Otherwise, the doses of individual drugs in a synergistic pair should generally not be reduced.

3. To prevent emergence of resistance Mutation conferring resistance to one AMA is independent of that conferring resistance to another. If the incidence of resistant mutants of a bacillus infecting an individual for drug P is 10^{-5} and for drug Q is 10^{-7}, then only one out of 10^{12} bacilli will be resistant to both. The chances of its surviving host defence and causing a relapse would be meagre.

This principle of using two or more AMAs together is valid primarily for chronic infections needing prolonged therapy; has been widely employed in tuberculosis, leprosy, HIV and now adopted for *H. pylori,* malaria as well. It is of little value in most acute and short-lived infections. However, rifampin given with ciprofloxacin prevents development of resistance to the latter by *Staph. aureus*.

4. To broaden the spectrum of antimicrobial action This is needed in:

(a) *Treatment of mixed infection* Bronchiectasis, peritonitis, certain urinary tract infections, brain abscesses, diabetic foot infection, bedsores, gynaecological infections are mostly mixed infections. Often, aerobic and anaerobic organisms sensitive to different drugs are involved. Obviously two or more AMAs have to be used to cover the pathogens. Drugs should be chosen on the basis of bacteriological diagnosis and sensitivity pattern (known or presumed), and should be employed in full doses. Clindamycin or metronidazole are generally included to cover anaerobes. However, it may sometimes be possible to find a single agent effective against all the causative organisms.

(b) *Initial treatment of severe infections* For empirical therapy, since bacterial diagnosis is not known; drugs covering gram-positive and gram-negative (in certain situations anaerobes as well), e.g. penicillin + streptomycin; cephalosporin or erythromycin + an aminoglycoside ± metronidazole or clindamycin, may be given together. Rational combinations improve the certainty of curing the infection in the first attempt, but should be continued only till bacteriological data become available. When the organism and its sensitivity has been determined, severity of infection is in itself not an indication for combination therapy. Combinations should not be used as a substitute for accurate diagnosis.

(c) *Topically* Generally, AMAs which are not used systemically, are poorly absorbed from the local site and cover a broad range of gram-

positive and gram-negative bacteria are combined for topical application, e.g. bacitracin, neomycin, polymyxin B.

Disadvantages of antimicrobial combinations

1. They foster a casual rather than rational outlook in the diagnosis of infections and choice of AMA.
2. Increased incidence and variety of adverse effects. Toxicity of one agent may be enhanced by another, e.g. vancomycin + tobramycin and gentamicin + cephalothin produce exaggerated kidney failure.
3. Increased chances of superinfections.
4. If inadequate doses of nonsynergistic drugs are used—emergence of resistance may be promoted.
5. Higher cost of therapy.

PROPHYLACTIC USE OF ANTIMICROBIALS

This refers to the use of AMAs for preventing the setting in of an infection or suppressing contacted infection before it becomes clinically manifest. The latter is also called *'preemptive therapy'*, which capitalizes on the small population of pathogen in the body before the disease is manifest. AMAs are frequently given prophylactically, but in a number of circumstances this is at best wasteful if not harmful. The difference between treating an infection and preventing it is that treatment is directed against a specific organism infecting an individual patient (targeted therapy), while prophylaxis is often against all organisms that may cause infection. The valid as well as improper prophylactic uses may be categorized as:

1. Prophylaxis against specific organisms This in general is highly satisfactory and the choice of drug is clearcut, because it is targeted.

(a) Rheumatic fever: A long acting penicillin G is the drug of choice for preventing infection by group A *streptococci* which cause recurrences.

(b) Tuberculosis: Children, HIV positive and other susceptible contacts of open cases need to be protected. Isoniazid alone or with rifampin is recommended.

(c) *Mycobacterium avium* complex (MAC): HIV/AIDS patients with low CD4 count may be protected against MAC infection by azithromycin/clarithromycin.

(d) HIV infection: Health care workers exposed to blood by needle stick injury are to be protected by zidovudine + lamivudine ± indinavir. Offspring of HIV positive woman can be protected by zidovudine given to pregnant mother and then to the newborn for 6 weeks.

(e) Meningococcal meningitis: during an epidemic, especially in contacts; rifampin/ sulfadiazine/ceftriaxone may be used.

(f) Gonorrhoea/syphilis: before or immediately after contact: ampicillin/ceftriaxone.

(g) Recurrent genital herpes simplex: Acyclovir prophylaxis may be given when four or more recurrences occur in a year.

(h) Malaria: Travellers to endemic areas with high transmission rate many be covered by mefloquine or doxycycline.

(i) Influenza A_2 : during an epidemic, especially in contacts: amantadine.

(j) Cholera: tetracycline prophylaxis may be given to close contacts of a case.

(k) Whooping cough: non-immunized child contact during the incubation period: erythromycin can abort clinical disease.

(l) Plague: Doxycycline prophylaxis is recommended for contacts during an epidemic.

(m) *Pneumocystis jiroveci* pneumonia: Transplant recipients on immunosuppressants/ leukaemia or AIDS patients may be protected by cotrimoxazole.

2. Prevention of infection in high risk situations Such use of AMAs may be valid and satisfactory in certain situations, but is controversial in others.

(a) Dental extraction, tonsillectomy, endoscopies cause damage to mucosa harbouring bacteria and induce bacteremia. This is harmless in most

subjects, but in those with valvular defects, this can cause endocarditis. Appropriate prophylaxis with amoxicillin or clindamycin may be given few hours before to few hours after the procedure.

(b) Catheterization or instrumentation of urinary tract: prophylaxis with cotrimoxazole or norfloxacin decreases the risk of urinary tract infection (UTI). Patients with cardiac valvular lesions may be protected with ampicillin, gentamicin or vancomycin during catheterization.

(c) To prevent recurrences of UTI in patients with abnormalities of the tract: cotrimoxazole or nitrofurantoin may be given on a long-term basis since the organism mostly is *E. coli.*

(d) Chronic obstructive lung disease, chronic bronchitis: ampicillin/doxycycline/ciprofloxacin has been used to prevent acute exacerbations; but are of doubtful value.

(e) Immunocompromized patients (receiving corticosteroids or antineoplastic chemotherapy or immunosuppressants after organ transplantation, neutropenic patients): penicillin/cephalosporin ± an aminoglycoside or fluoroquinolone are often used to prevent respiratory tract infections and septicaemia, but incidence of superinfections is high.

Prophylaxis of surgical site infection

Surgical site infection (SSI) includes superficial incisional infections (e.g. stitch abscess), deep incisional infection (of soft tissue) and organ/space infection. The purpose of surgical prophylaxis is to reduce the incidence of SSI with minimal alteration of normal microbial flora of the host and minimal adverse effects.

For grading the need and intensity of antimicrobial prophylaxis, the operative wounds have been classified into 4 categories with increasing risk of SSI (*see* box).

Classification of operative wounds* with increasing risk of infection

- *Clean:* Elective, nontraumatic surgery, no viscera or tract (respiratory, g.i., biliary, genitourinary) entered, no infection at site, no break in technique.
- *Clean-contaminated:* Otherwise clean but emergency surgery, or elective surgery with opening of any viscera/tract but minimal spillage, no contact with infected material or minor break in technique.
- *Contaminated:* Gross spillage from g.i. tract (gut resection), opening of infected biliary or genitourinary tract, penetrating injury < 4 hr old, grafting on chronic open wound, major break in technique.
- *Dirty:* Opening of abscess or purulent site, preoperative perforation of g.i./respiratory/genitourinary tract/penetrating injury > 4 hr old.

* based on National Research Council (NRC) criteria.

Wound infection occurs due to microbial contamination of the surgical site. It is important for the surgeon to see that the wound left after surgery does not get infected. Use of sterile instruments, cross-infection control measures (antiseptic/disinfectant, etc.) and good surgical technique to minimise tissue damage, haematoma and devascularization are the primary, and often the only, measures needed. However, extensive, prolonged and often combined use of AMAs is made for prophylaxis of infection after practically all surgeries. Such misuse is particularly rampent in developing countries, probably because of unreliability of infection control measures. The SSI is directly related to the number of bacteria present in the surgical wound at the time of closure. Systemic antimicrobial prophylaxis should be employed only when there is clear risk of more than the critical number of bacteria remaining in the wound at the time of closure and occurrence of SSI. In general, it is not required for clean surgery, except in patient at special risk. Clean surgery in otherwise healthy subjects is associated with very low risk of SSI.

Incidence of postoperative infection is higher when surgery had lasted 2 hours or more. Prophylaxis should be given for surgeries in which a prosthesis is inserted into the bone or soft tissue. Even clean surgery needs to be covered by AMA in diabetics, corticosteroid recipients and other immunocompromised subjects, infants, elderly, malnourished and when there is extensive tissue handling/use of electrocautery, etc.

The selection of drug, dose, timing and duration of prophylactic medication is crucial. It is important that the antibiotic is not started

prematurely and is not continued beyond the time when bacteria have access to the surgical wound. Administration of the AMA has to be so timed that peak blood levels occur when clot is forming in the surgical wound, and it is present throughout the procedure. Thus, most of the oral drugs are given 1 hour before incision, while i.v. administration just before/after anaesthesia best ensures effective blood levels of the AMA during surgery. Most AMAs do not penetrate the clot once it is formed and is older than 3 hours. Thus, late and prolonged presence of the antibiotic in circulation serves no purpose, but can foster resistant organisms. In case of prolonged surgery, the AMA may be repeated i.v. during the procedure. Postoperative administration of the AMA, especially after 4 hours of wound closure is recommended only in case of contaminated and dirty surgery, in which case it may be given for upto 5 days.

To be maximally effective, a relatively high dose of the AMA is selected which yields peak blood level several times higher than MIC for the likely pathogens. The drug or combination of drugs is selected based on the knowledge of the organism most commonly causing SSI in a given procedure. Local patterns of wound infection (e.g. prevalence of MRSA) and sensitivities of the causative organisms should guide the selection. The commonly employed AMAs for prophylaxis in case of clean and clean-contaminated surgeries are listed in the box.

Dirty contaminated wounds (including road side accidents): The antimicrobial regimens generally administered for 5 days in case of contaminated dirty wounds are:

1. Cefazolin 1 g i.v. 8 hourly
   + vancomycin 1 g i.v. 12 hourly.
2. Cefoxitin 1 g i.v. 6 hourly/ceftizoxime 1 g i.v. 12 hourly.
3. Clindamycin 0.6 g i.v. 8 hourly
   + Gentamicin 80 mg i.v. 8 hourly.
4. Ampicillin 2 g i.v. 6 hourly/vancomycin 1 g i.v. 12 hourly
   + Gentamicin 80 mg i.v. 8 hourly
   + Metronidazole 0.5 g i.v. 8 hourly.
5. Amoxicillin 1 g + Clavulanate 0.2 g i.v. 12 hourly.

   All given for 5 days

Commonly used antimicrobials drugs for surgical prophylaxis

Oral (single dose given 1 hour before procedure)

1. Amoxicillin 2 g (50 mg/kg)
2. Cephalexin 2 g (50 mg/kg)
3. Cefadroxil 2 g (50 mg/kg)
4. Clindamycin 600 mg (20 mg/kg)
5. Azithromycin 500 mg (15 mg/kg)
6. Clarithromycin 500 mg (15 mg/kg)

For patients allergic to penicillin

Parenteral (single injection just before procedure)

1. Ampicillin 2 g (50 mg/kg) i.m./i.v.
2. Cefazolin 1 g (25 mg/kg) i.v.
3. Vancomycin 1 g (20 mg/kg) i.v. (in MRSA prevalent areas and/or penicillin allergic patients).
4. Clindamycin 600 mg (20 mg/kg) i.v. (for penicillin allergic patients).
5. Cefuroxime 1.5 g (30 mg/kg) i.v. + Metronidazole 0.5 g (10 mg/kg) i.v.
6. Gentamicin 160 mg (3 mg/kg) i.v. + Metronidazole 0.5 g (10 mg/kg) i.v.

For gut and biliary surgery

3. Prevention of infection in general This is highly unsatisfactory in most cases and must be condemned. Examples are:

(a) Neonates, especially after prolonged or instrumental delivery.

(b) To prevent postpartum infections in the mother after normal delivery.

(c) Viral upper respiratory tract infections: to prevent secondary bacterial invasion.

(d) To prevent respiratory infections in unconscious patients or in those on respirators.

Antimicrobial prophylaxis in these situations may be hazardous. Infection by resistant organisms, fungal and other superinfections can occur, because it is not possible to prevent all infections, at all times, in all individuals.

FAILURE OF ANTIMICROBIAL THERAPY

The success of antimicrobial therapy can be measured either clinically in terms of improvement in symptoms/signs or microbiologically as eradication of the infecting organism.

Antimicrobials may fail to cure an infection/fever, or there may be relapses. This is rare when antimicrobial therapy was begun, in the first place, on sound clinical and/or bacteriological basis. When a real or apparent failure of the antimicrobial regimen occurs, the diagnosis and therapy should be reviewed. One of the following causes will usually be identified.

1. Improper selection of drug, dose, route or duration of treatment.
2. Treatment begun too late.
3. Failure to take necessary adjuvant measures, e.g. drainage of abscesses, empyema, etc.; removal of renal stones, other foreign bodies or infected gall bladder, adjustment of proper urinary pH in case of UTI; cavity closure; control of diabetes, etc.
4. Poor host defence—as in leukaemias, neutropenia and other causes, especially if a bacteriostatic AMA is used.
5. Infecting organism present behind barriers, such as vegetation on heart valves (SABE), inside the eyeball, blood brain-barrier.
6. Trying to treat untreatable (viral) infections or other causes of fever (malignancy, collagen diseases).
7. Presence of dormant or altered organisms (the persisters) which later give rise to a relapse.

☞ PROBLEM DIRECTED STUDY

49.1 A lady aged 40 years and weighing 60 kg is to undergo elective cholecystectomy for multiple gallstones. She is asymptomatic.

(a) Does she require antimicrobial prophylaxis?

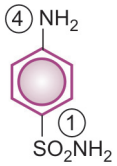
(b) If she does, which antimicrobial(s) should be selected? When, by what route and dose, and how long the antimicrobial(s) should be administered?

(see Appendix-1 for solution)

Chapter 50 Sulfonamides, Cotrimoxazole and Quinolones

SULFONAMIDES

Sulfonamides were the first antimicrobial agents (AMAs) effective against pyogenic bacterial infections. Sulfonamido-chrysoidine (Prontosil Red) was one of the dyes included by Domagk to treat experimental streptococcal infection in mice and found it to be highly effective. Subsequently an infant was cured of staphylococcal septicaemia (which was 100% fatal at that time) by prontosil. By 1937, it became clear that prontosil was broken down in the body to release sulfanilamide which was the active antibacterial agent. A large number of sulfonamides were produced and used extensively in the subsequent years, but because of rapid emergence of bacterial resistance and the availability of many safer and more effective antibiotics, their current utility is limited, except in combination with trimethoprim (as cotrimoxazole) or pyrimethamine (for malaria).



SULFANILAMIDE

Chemistry All sulfonamides may be considered to be derivatives of sulfanilamide (p-aminobenzene sulfonamide). Individual members differ in the nature of N^1 (Sulfonamido N) substitution, which governs solubility, potency and pharmacokinetic property. A free amino group in the para position (N^4) is required for antibacterial activity.

Sulfonamides that are still of clinical interest are:

1. *Short acting (4–8 hr): Sulfadiazine*
2. *Intermediate acting (8–12 hr): Sulfamethoxazole*
3. *Long acting (~7 days): Sulfadoxine, Sulfamethopyrazine*
4. *Special purpose sulfonamides*: *Sulfacetamide sod., Mafenide, Silver sulfadiazine, Sulfasalazine*

ANTIBACTERIAL SPECTRUM

Sulfonamides are primarily bacteriostatic against many gram-positive and gram-negative bacteria. However, bactericidal concentrations may be attained in urine. Sensitivity patterns among microorganisms have changed from time-to-time and place-to-place. Those still sensitive are:

many *Strepto. pyogenes, Haemophilus influenzae, H. ducreyi, Calymmatobacterium granulomatis, Vibrio cholerae. Only a* few *Staph. aureus,* gonococci, meningococci, pneumococci, *Escherichia coli,* and *Shigella* respond, but majority are resistant.
Anaerobic bacteria are not susceptible.

Chlamydiae: trachoma, lymphogranuloma venereum, inclusion conjunctivitis, are sensitive, as are *Actinomyces, Nocardia* and *Toxoplasma*.

Mechanism of action Many bacteria synthesize their own folic acid (FA) of which p-aminobenzoic acid (PABA) is a constituent, and is taken up from the medium. Woods and Fildes (1940) proposed the hypothesis that sulfonamides, being structural analogues of PABA, inhibit bacterial folate synthase → FA is not formed and a number of essential metabolic reactions suffer. Sulfonamides competitively inhibit the union of PABA with pteridine residue to form dihydropteroic acid which conjugates with glutamic acid

NOTE: Nonabsorbable sulfonamides—Phthlylsulfathiazole, Succinyl sulfathiazole, Sulfaganidine are banned in India

to produce dihydrofolic acid. Also, being chemically similar to PABA, the sulfonamide may itself get incorporated to form an altered folate which is metabolically injurious.

Human cells also require FA, but they utilize preformed FA supplied in diet and are unaffected by sulfonamides. Evidences in favour of this mechanism of action of sulfonamides are:

(a) PABA, in small quantities, antagonizes the antibacterial action of sulfonamides.
(b) Only those microbes which synthesize their own FA, and cannot take it from the medium are susceptible to sulfonamides.

Pus and tissue extracts contain purines and thymidine which decrease bacterial requirement for FA and antagonize sulfonamide action. Pus is also rich in PABA.

Resistance to sulfonamides Most bacteria are capable of developing resistance to sulfonamides. Prominent among these are gonococci, pneumococci, *Staph. aureus*, meningococci, *E. coli, Shigella* and some *Strep. pyogenes, Strep. viridans* and anaerobes. The resistant mutants either:

(a) produce increased amounts of PABA, or
(b) their folate synthase enzyme has low affinity for sulfonamides, or
(c) adopt an alternative pathway in folate metabolism.

Resistance developed *in vivo* is quite persistent. Sensitivity patterns have changed depending on the extent of use. When an organism is resistant to one sulfonamide, it is resistant to them all. No cross resistance between sulfonamides and other AMAs has been noted. Development of resistance has markedly limited the clinical usefulness of this class of compounds.

PHARMACOKINETICS

Sulfonamides are rapidly and nearly completely absorbed from g.i.t. Extent of plasma protein binding differs considerably (10–95%) among different members. The highly protein bound members are longer acting. Sulfonamides are widely distributed in the body—enter serous cavities easily. The free form of sulfadiazine attains the same concentration in CSF as in plasma. They cross placenta freely.

The primary pathway of metabolism of sulfonamides is acetylation at N^4 by nonmicrosomal acetyl transferase, primarily in liver. There are slow and fast acetylators, but the difference is mostly insufficient to be clinically significant. The extent of metabolism differs for different members. The acetylated derivative is inactive, but can contribute to the adverse effects. It is generally less soluble in acidic urine than the parent drug—may precipitate and cause crystalluria.

Sulfonamides are excreted mainly by the kidney through glomerular filtration. Both renal tubular secretion and reabsorption occur. The more lipid-soluble members are highly reabsorbed in the tubule, therefore are longer acting.

Sulfadiazine It is the prototype of the general purpose sulfonamides that is rapidly absorbed orally and rapidly excreted in urine. Plasma protein binding is 50%, and it is 20–40% acetylated. The acetylated derivative is less soluble in urine, crystalluria is likely. It has good penetrability in brain and CSF—was the preferred compound for meningitis.
Dose: 0.5 g QID to 2 g TDS; SULFADIAZINE 0.5 g tab.

Sulfamethoxazole It has slower oral absorption and urinary excretion resulting in intermediate duration of action; t½ in adults averages 10 hours. It is the preferred compound for combining with trimethoprim because the t½ of both is similar. However, a high fraction is acetylated, which is relatively insoluble—crystalluria can occur.
Dose: 1 g BD for 2 days, then 0.5 g BD. GANTANOL 0.5 g tab.

Sulfadoxine, Sulfamethopyrazine These are ultralong acting compounds, action lasting > 1 week because of high plasma protein binding and slow renal excretion (t½ 5–9 days). They attain low plasma concentration (of free form) and are not suitable for treatment of acute pyogenic infections, but are used in combination with pyrimethamine in the treatment of malaria (especially chloroquine resistant *P. falciparum*; *See* Ch. 59), *Pneumocystis jiroveci* pneumonia in AIDS patients and in toxoplasmosis. Because they have caused serious cutaneous reactions, large-scale use of the combination for prophylaxis of malaria is not recommended.

Sulfacetamide sod. It is a highly soluble compound yielding neutral solution which is only mildly irritating to the eye in concentrations up to 30%. It is used topically for ocular infections due to susceptible bacteria and chlamydia, including ophthalmia neonatorum caused by *Ch. oculogenitalis*. It attains high concentrations in anterior segment and aqueous humour after topical instillation. The incidence of sensitivity reactions with ocular use of sulfacetamide sod. has been low; but it must be promptly stopped when they occur.
LOCULA, ALBUCID 10%, 20%, 30% eye drops, 6% eye oint.

Mafenide It is not a typical sulfonamide, because a —CH_2— bridge separates the benzene ring and the amino group. It is used only topically—inhibits a variety of gram- positive and gram-negative bacteria. In contrast to typical sulfonamides, it is active in the presence of pus and against *Pseudomonas*, clostridia which are not inhibited by typical sulfonamides. It has been mainly employed for burn dressing to prevent infection, but not to treat already infected cases.

The biggest limitation is that mafenide produces burning sensation and severe pain when applied to raw surface. It is rapidly absorbed from the raw surface, metabolized and excreted in urine. Mafenide and its metabolite are carbonic anhydrase (CAse) inhibitors. Accordingly, they alkalinize urine, can cause acidosis and hyperventilation. Mafenide must not be applied over large areas. Allergic reactions, particularly rashes also occur.

SULFAMYLON 1% cream for surface application.

Silver sulfadiazine Used topically as 1% cream, it is active against a large number of bacteria and fungi, even those resistant to other sulfonamides, e.g. *Pseudomonas*. It slowly releases silver ions which appear to be largely responsible for the antimicrobial action. It is considered to be one of the most effective drugs for preventing infection of burnt surfaces and chronic ulcers and is well tolerated. However, it is not good for treating established infection.

SILVIRIN 1% cream, ARGENEX 1% cream with chlorhexidine 0.2%.

Local side effects are—burning sensation on application and itch.

Released sulfadiazine may be absorbed systemically and produce its own adverse effects.

Sulfasalazine (*see* p. 211, 683) used in ulcerative colitis and rheumatoid arthritis.

ADVERSE EFFECTS

Adverse effects to sulfonamides are relatively common. These are:

- Nausea, vomiting and epigastric pain.
- Crystalluria is dose related, but infrequent now. Precipitation in urine can be minimized by taking plenty of fluids and by alkalinizing the urine in which sulfonamides and their acetylated derivatives are more soluble.
- Hypersensitivity reactions occur in 2–5% patients. These are mostly in the form of rashes, urticaria and drug fever. Photosensitization is reported. Stevens-Johnson syndrome and exfoliative dermatitis are serious reactions reported with the long-acting agents.
- Hepatitis, unrelated to dose, occurs in 0.1% patients.
- Topical use of sulfonamides is not allowed, because of risk of contact sensitization. However, ocular use is permitted.
- Haemolysis can occur in G-6-PD deficient individuals with high doses of sulfonamides. Neutropenia and other blood dyscrasias are rare.
- Kernicterus may be precipitated in the newborn, especially premature, whose blood-brain barrier is more permeable, by displacement of bilirubin from plasma protein binding sites.

Interactions Sulfonamides inhibit the metabolism (possibly displace from protein binding also) of phenytoin, tolbutamide and warfarin—enhance their action.

They displace methotrexate from binding sites and decrease its renal excretion—toxicity can occur.

Fixed dose combinations of sulfonamides with penicillin are banned in India.

USES

Systemic use of sulfonamides alone (not combined with trimethoprim or pyrimethamine) is rare now. Though they can be employed for suppressive therapy of chronic urinary tract infection, for streptococcal pharyngitis and gum infection; such uses are outmoded.

Combined with trimethoprim (as cotrimoxazole) sulfamethoxazole is used for many bacterial infections, *P. jiroveci* and nocardiosis (*see* below). Along with pyrimethamine, certain sulfonamides are used for malaria (*see Ch.* 59) and toxoplasmosis.

Ocular sulfacetamide sod. (10–30%) is a cheap alternative in trachoma/inclusion conjunctivitis, though additional systemic azithromycin or tetracycline therapy is required for eradication of the disease. Topical silver sulfadiazine or mafenide are used for preventing infection on burn surfaces.

COTRIMOXAZOLE

The fixed dose combination of trimethoprim and sulfamethoxazole is called *cotrimoxazole.* Trimethoprim is a diaminopyrimidine related to the antimalarial drug pyrimethamine which selectively inhibits *bacterial* dihydrofolate reductase (DHFRase). Cotrimoxazole introduced in 1969 causes sequential block of folate metabolism as depicted in Fig. 50.1. Trimethoprim

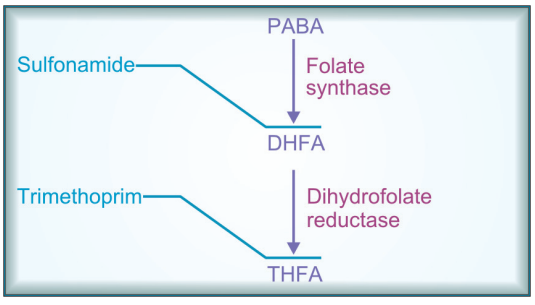


Fig. 50.1: Sequential block in bacterial folate metabolism
PABA—Para aminobenzoic acid; DHFA—Dihydrofolic acid; THFA—Tetrahydrofolic acid

is >50,000 times more active against bacterial DHFRase than against the mammalian enzyme. Thus, human folate metabolism is not interfered at antibacterial concentrations of trimethoprim. Individually, both sulfonamide and trimethoprim are bacteriostatic, but the combination becomes cidal against many organisms. Maximum synergism is seen when the organism is sensitive to both the components, but even when it is moderately resistant to one component, the action of the other may be enhanced.

Sulfamethoxazole was selected for combining with trimethoprim because both have nearly the same t½ (~ 10 hr). Optimal synergy in case of most organisms is exhibited at a concentration ratio of sulfamethoxazole 20 : trimethoprim 1, the MIC of each component may be reduced by 3–6 times. This ratio is obtained in the plasma when the two are given in a dose ratio of 5 : 1, because trimethoprim enters many tissues, has a larger volume of distribution than sulfamethoxazole and attains lower plasma concentration. However, the concentration ratio in many tissues is less than 20 : 1. Trimethoprim adequately crosses blood-brain barrier and placenta, while sulfamethoxazole has a poorer entry. Moreover, trimethoprim is more rapidly absorbed than sulfamethoxazole—concentration ratios may vary with time. Trimethoprim is 40% plasma protein bound, while sulfamethoxazole is 65% bound. Trimethoprim is partly metabolized in liver and excreted in urine.

Spectrum of action Antibacterial spectra of trimethoprim and sulfonamides overlap considerably. Additional organisms covered by the combination are—*Salmonella typhi, Serratia, Klebsiella, Enterobacter, Yersinia enterocolitica, Pneumocystis jiroveci* and many sulfonamide-resistant strains of *Staph. aureus, Strep. pyogenes, Shigella,* enteropathogenic *E. coli, H.influenzae,* gonococci and meningococci.

Resistance Bacteria are capable of acquiring resistance to trimethoprim mostly through plasmid mediated acquisition of a DHFRase having lower affinity for the inhibitor. Resistance to the combination has been slow to develop compared to either drug alone, but widespread use of the combination over a long period has resulted in reduced responsiveness of over 30% originally sensitive strains.

Adverse effects All adverse effects seen with sulfonamides can be produced by cotrimoxazole.

- Nausea, vomiting, stomatitis, headache and rashes are the usual manifestations.
- Folate deficiency (megaloblastic anaemia) is infrequent, occurs only in patients with marginal folate levels.
- Blood dyscrasias occur rarely.

Cotrimoxazole should not be given during pregnancy. Trimethoprim being an antifolate, there is theoretical teratogenic risk. Neonatal haemolysis and methaemoglobinaemia can occur if it is given near term.

- Patients with renal disease may develop uremia. Dose should be reduced in moderately severe renal impairment.
- A high incidence (upto 50%) of fever, rash and bone marrow hypoplasia has been reported among AIDS patients with *Pneumocystis jiroveci* infection when treated with high dose cotrimoxazole.
- The elderly are also at greater risk of bone marrow toxicity from cotrimoxazole.
- Diuretics given with cotrimoxazole have produced a higher incidence of thrombocytopenia.

Preparations SEPTRAN, SEPMAX, BACTRIM, CIPLIN, ORIPRIM, SUPRISTOL, FORTRIM

Trimethoprim			*Sulfamethoxazole*
80	mg	+	400 mg tab: 2 BD for 2 days then 1 BD.
160	mg	+	800 mg tab: double strength (DS); 1 BD.
20	mg	+	100 mg pediatric tab.
40	mg	+	200 mg per 5 ml susp; infant 2.5 ml (not to be used in newborns), children 1–5 yr 5 ml, 6–12 year 10 ml (all BD).
160	mg	+	800 mg per 3 ml for i.m. injection 12 hourly. (CIPLIN, ORIPRIM-IM)
80	mg	+	400 mg per 5 ml for i.v. injection (WK-TRIM, ORIPRIM-IV) 10–15 ml BD.

Cotrimazine It is a combination of trimethoprim with sulfadiazine. Its utility is similar to that of cotrimoxazole.

Trimethoprim		*Sulfadiazine*	
90 mg	+	410 mg:	AUBRIL tab, 2 tab BD for 2 days, then 1 BD.
180 mg	+	820 mg:	TRIGLOBEFORTE tab.

Uses

Though cotrimoxazole is still used, its popularity in the treatment of systemic infections has declined. Common indications are:

1. *Urinary tract infections* Most acute uncomplicated infections respond rapidly. Single dose therapy with 4 tablets of cotrimoxazole has been used successfully for acute cystitis. Courses of 3–10 days have been advised for lower and upper urinary tract infections, according to associated features. Cotrimoxazole is specially valuable for chronic or recurrent cases or in prostatitis, because trimethoprim is concentrated in prostate.

2. *Respiratory tract infections* Both upper and lower respiratory tract infections, including chronic bronchitis and facio-maxillary infections, otitis media caused by gram positive cocci and *H. influenzae* respond well.

3. *Bacterial diarrhoeas and dysentery* Cotrimoxazole may be used for severe and invasive infections by *E. coli, Shigella,* nontyphoid *Salmonella*, and *Y. enterocolitica* (*see* p. 682). Though response rate is lower than previously, and fluoroquinolones are more commonly used, it is still a valuable alternative for empirical therapy of infective diarrhoea.

4. *Pneumocystis jiroveci* causes severe pneumonia in neutropenic and AIDS patients. Cotrimoxazole has prophylactic as well as therapeutic value, but high doses are needed. One DS tablet 4–6 times/day for 2–3 weeks may be curative, but adverse effects necessitate discontinuation in upto 20% cases. One DS tab. daily has been used for prophylaxis and this is better tolerated.

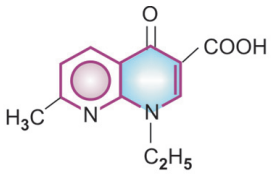
5. *Chancroid* Cotrimoxazole (800 + 160 mg) BD for 14 days is a 3rd choice, but less expensive, alternative to ceftriaxone, azithromycin or ciprofloxacin.

6. *Typhoid* *Initially cotrimoxazole was an effective alternative to chloramphenicol. However, it has become unreliable, and is seldom used now.*

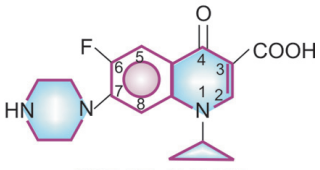
7. Cotrimoxazole is an alternative to penicillin for protecting *agranulocytosis patients* and for treating respiratory or other infections in them. Intensive parenteral cotrimoxazole therapy has been used successfully in septicaemias, but other drugs are more commonly employed now.

QUINOLONES

These are synthetic antimicrobials having a quinolone structure that are active primarily against gram-negative bacteria, though the newer fluorinated compounds also inhibit gram-positive ones. The first member *Nalidixic acid* introduced in mid-1960s had usefulness limited to urinary and g.i. tract infections because of low potency, modest blood and tissue levels, restricted spectrum and high frequency of bacterial resistance. A breakthrough was achieved in the early 1980s by fluorination of the quinolone structure at position 6 and introduction of a piperazine substitution at position 7 resulting in derivatives called *fluoroquinolones* with high potency, expanded spectrum, slow development of resistance, better tissue penetration and good tolerability.



NALIDIXIC ACID



CIPROFLOXACIN

Nalidixic acid

It is active against gram-negative bacteria, especially coliforms: *E. coli, Proteus, Klebsiella, Enterobacter, Shigella* but not *Pseudomonas*. It acts by inhibiting bacterial DNA gyrase and is bactericidal. Resistance to nalidixic acid develops rather rapidly.

Nalidixic acid is absorbed orally, highly plasma protein bound and partly metabolized in liver: one of the metabolites is active. It is excreted in urine with a plasma t½ ~8 hrs. Concentration of the free drug in plasma and most tissues attained with the usual doses is nontherapeutic for systemic infections (MIC values for most susceptible bacteria just approach the 'break-point' concentration). However, high concentration attained in urine (20–50 times that in plasma) and gut lumen is lethal to the common urinary pathogens and diarrhoea causing coliforms.

Adverse effects These are relatively infrequent, consist mostly of g.i. upset and rashes.

Most important toxicity is neurological—headache, drowsiness, vertigo, visual disturbances, occasionally seizures (especially in children).

Phototoxicity is rare. Individuals with G-6-PD deficiency may develop haemolysis.

Nalidixic acid is contraindicated in infants.

Dose: 0.5–1 g TDS or QID; GRAMONEG 0.5 g tab, 0.3 g/5 ml susp, DIARLOP 0.3 g/5 ml susp.

Use

1. Nalidixic acid is primarily used as a urinary antiseptic, generally as a second line drug in recurrent cases or on the basis of sensitivity reports.

Nitrofurantoin should not be given concurrently—antagonism occurs.

2. It has also been employed in diarrhoea caused by *Proteus, E. coli, Shigella* or *Salmonella*, but norfloxacin/ciproloxacin are more commonly used now.

FLUOROQUINOLONES

These are quinolone antimicrobials having one or more fluorine substitutions. The 'first generation' fluoroquinolones (FQs) introduced in 1980s have one fluoro substitution. In the 1990s, compounds with additional fluoro and other substitutions have been developed—further extending antimicrobial activity to gram-positive cocci and anaerobes, and/or confering metabolic stability (longer t½). These are referred to as 'second generation' FQs.

First generation fluoroquinolones	
Norfloxacin	Ofloxacin
Ciprofloxacin	Pefloxacin

Second generation fluoroquinolones	
Levofloxacin	Moxifloxacin
Lomefloxacin	Gemifloxacin
Sparfloxacin	Prulifloxacin

Mechanism of action The FQs inhibit the enzyme *bacterial DNA gyrase* (primarily active in gram negative bacteria), which nicks double-stranded DNA, introduces negative supercoils and then reseals the nicked ends. This is necessary to prevent excessive positive supercoiling of the strands when they separate to permit replication or transcription. The DNA gyrase consists of two A and two B subunits: The A subunit carries out nicking of DNA, B subunit introduces negative supercoils and then A subunit reseals the strands. FQs bind to A subunit with high affinity and interfere with its strand cutting and resealing function. In gram-positive bacteria the major target of FQ action is a similar enzyme *topoisomerase IV* which nicks and separates daughter DNA strands after DNA replication. Greater affinity for topoisomerase IV may confer higher potency against gram-positive bacteria. The bactericidal action probably results from digestion of DNA by exonucleases whose production is signalled by the damaged DNA.

In place of DNA gyrase or topoisomerase IV, the mammalian cells possess an enzyme topoisomerase II (that also removes positive supercoils) which has very low affinity for FQs—hence the low toxicity to host cells.

Mechanism of resistance Because of the unique mechanism of action, plasmid mediated transferable resistance is less likely. Resistance noted so far is due to chromosomal mutation producing a DNA gyrase or topoisomerase IV

with reduced affinity for FQs, or due to reduced permeability/increased efflux of these drugs across bacterial membranes. In contrast to nalidixic acid which selects single step resistant mutants at high frequency, FQ-resistant mutants are not easily selected. Therefore, resistance to FQs has been slow to develop. However, increasing resistance has been reported among *Salmonella, Pseudomonas,* staphylococci, gonococci and pneumococci.

Ciprofloxacin (prototype)

It is the most potent first generation FQ active against a broad range of bacteria, the most susceptible ones are the aerobic gram-negative bacilli, especially the Enterobacteriaceae and *Neisseria.* The MIC of ciprofloxacin against these bacteria is usually < 0.1 µg/ml, while gram-positive bacteria are inhibited at relatively higher concentrations. The spectrum of action is summarized below:

Highly susceptible

E. coli	*Neisseria gonorrhoeae*
K. pneumoniae	*N. meningitidis*
Enterobacter	*H. influenzae*
Salmonella typhi	*H. ducreyi*
Nontyphoid *Salmonella*	*Campylobacter jejuni*
Shigella	*Yersinia enterocolitica*
Proteus	*Vibrio cholerae*

Moderately susceptible

Pseudomonas aeruginosa	*Legionella*
Staph. aureus	*Brucella*
(including few *MRSA)*	*Listeria*
Staph. epidermidis	*Bacillus anthracis*
Branhamella catarrhalis	*Mycobact. tuberculosis*

Organisms which have shown low/variable susceptibility are: *Strep. pyogenes, Strep. faecalis, Strep. pneumoniae, Mycoplasma, Chlamydia, Mycobact. kansasii, Mycobact. avium.*

Notable resistant bacteria are: *Bacteroides fragilis, Clostridia*, anaerobic cocci.

The distinctive microbiological features of ciprofloxacin (also other FQs) are:

- Bactericidal activity and high potency: MBCs are close to MICs.
- Relatively long post-antibiotic effect on Enterobacteriaceae, *Pseudomonas* and *Staph.*
- Low frequency of mutational resistance.
- Low propensity to select plasmid type resistant mutants.
- Protective intestinal streptococci and anaerobes are spared.
- Active against many β-lactam and aminoglycoside resistant bacteria.
- Less active at acidic pH.

Pharmacokinetics Ciprofloxacin is rapidly absorbed orally, but food delays absorption, and first pass metabolism occurs. The pharmacokinetic characteristics are given in Table 50.1. Ciprofloxacin (and other FQs) have good tissue penetrability: concentration in lung, sputum, muscle, prostate and phagocytes exceeds that in plasma, but CSF and aqueous levels are lower. It is excreted primarily in urine, both by glomerular filtration and tubular secretion. Urinary and biliary concentrations are 10–50 fold higher than plasma.

Adverse effects Ciprofloxacin has good safety record: side effects occur in ~10% patients, but are generally mild; withdrawal is needed only in 1.5%.

- Gastrointestinal: nausea, vomiting, bad taste, anorexia. Because gut anaerobes are not affected—diarrhoea is infrequent.
- CNS: dizziness, headache, restlessness, anxiety, insomnia, impairment of concentration and dexterity (caution while driving). Tremor and seizures are rare, occur only at high doses or when predisposing factors are present: possibly reflect GABA antagonistic action of FQs.
- Skin/hypersensitivity: rash, pruritus, photosensitivity, urticaria, swelling of lips, etc. Serious cutaneous reactions are rare.
- Tendinitis and tendon rupture: a few cases have occurred. Risk of tendon damage is higher in patients above 60 years of age and in those receiving corticosteroids. The FQ should be stopped at the first sign of tendinitis.

TABLE 50.1 Pharmacokinetic characteristics and doses of fluoroquinolones

		CIPROFL	NORFL	PEFL	OFL	LEVOFL	GEMI	PRULI	MOXI
1.	Oral bioavailability (%)	60–80	35–45	90–100	85–95	~100	70	90	85
2.	Plasma protein binding (%)	20–35	15	20–30	25	25	55–73	45	40
3.	Vol. of distribution (L/kg)	3–4	2	2	1.5	1.3	—	—	2
4.	Percent metabolized	20	25	85	5–10	5	—	>90	70–80
5.	Elimination t½ (hr)	3–5	4–6	8–14	5–8	8	7	10–12	10–15
6.	Routes of administration	oral, i.v.	oral	oral, i.v.	oral, i.v.	oral, i.v.	oral	oral	oral, i.v.
7.	Dose (mg) : oral	250–750 (BD)	400 (BD)	400 (BD)	200–400 (BD)	500 (OD)	320 (OD)	600 (OD)	400 (OD)
	: iv	100–200	—	400	200	500	—	—	400

Ciprofloxacin and other FQs are contraindicated during pregnancy.

On the basis of the finding that administered to immature pups ciprofloxacin (and other FQs) caused cartilage damage in weight bearing joints, the FQs were contraindicated in children. However, under pressing situations like *Pseudomonas* pneumonia in cystic fibrosis and multi-resistant typhoid, ciprofloxacin has been administered to millions of children in India and elsewhere. Though a few cases of joint pain and swelling have been reported, cartilage damage has not occurred. Caution, nevertheless, is needed while using FQs in children.

Interactions

- Plasma concentration of theophylline, caffeine and warfarin is increased by ciprofloxacin (also by norfloxacin and pefloxacin) due to inhibition of metabolism: CNS toxicity can occur by concurrent use of theophylline and a FQ.
- NSAIDs may enhance the CNS toxicity of FQs; seizures are reported.
- Antacids, sucralfate and iron salts given concurrently reduce absorption of FQs.

CIFRAN, CIPLOX, CIPROBID, QUINTOR, CIPROLET 250, 500, 750 mg tab, 200 mg/100 ml i.v. infusion, 3 mg/ml eye drops.

Uses Ciprofloxacin is effective in a broad range of infections. Because of wide-spectrum bactericidal activity, oral efficacy and good tolerability, it is being extensively employed for empirical therapy of any infection, but should not be used for minor cases or where gram-positive organisms and/or anaerobes are primarily causative. In severe infections, therapy may be initiated by i.v. infusion and then switched over to oral route.

1. *Urinary tract infections:* High cure rates, even in complicated cases or those with indwelling catheters/prostatitis, have been achieved. Comparative trials have reported higher success rates than with cotrimoxazole. Chronic *Pseudomonas* infections respond less completely.

2. *Gonorrhoea:* Initially a single 500 mg dose was nearly 100% curative in non-PPNG as well as PPNG infections, but cure rate has declined due to emergence of resistance, and it is no longer a first line drug; may be used if strain is sensitive.

3. *Chancroid:* 500 mg BD for 3 days is a second line alternative drug to ceftriaxone/azithromycin.

4. *Bacterial gastroenteritis:* Currently, it is the most commonly used drug for empirical therapy of diarrhoea. However, it should be reserved for severe cases due to EPEC, *Shigella, Salmonella* and *Campy. jejuni* infection. Ciprofloxacin can reduce stool volume in cholera.

5. *Typhoid:* Ciprofloxacin is one of the first choice drugs in typhoid fever since chloramphenicol, ampicillin and cotrimoxazole have become unreliable due to development of resistance. In India and elsewhere up to 95% *S. typhi* isolates were sensitive to ciprofloxacin. However, increasing number of nonresponsive cases are being reported. Ceftriaxone (or cefotaxime/cefoperazone) are more commonly

used. Ciprofloxacin given in a dose of 750 mg BD for 10 days is recommended. Patients unable to take the drug orally may be treated with 200 mg. i.v. 12 hourly in the beginning. Being bactericidal the advantages of ciprofloxacin are:

- Quick defervescence: fever usually subsides in 4–5 days but may take longer now.
- Early abetment of symptoms; low incidence of complications and relapse.
- Prevention of carrier state due to cidal action, good penetration into infected cells, high biliary and intestinal mucosal concentration.

It can also be used to treat typhoid carriers (750 mg BD for 4–8 weeks). This has been found to achieve 92% eradication rate compared to 50% by ampicillin.

(For alternative drugs *see* box)

6. *Bone, soft tissue, gynaecological and wound infections:* caused by resistant *Staph.* and gram-negative bacteria respond to ciprofloxacin. High cure rates have been obtained in osteomyelitis and joint infections but prolonged treatment (6–8 weeks) with high doses (750 mg BD) is required. Used along with clindamycin/metronidazole (to cover anaerobes) it is a good drug for diabetic foot.

7. *Respiratory infections:* Ciprofloxacin should not be used as the primary drug because pneumococci and streptococci have low and variable susceptibility. However, it can treat *Mycoplasma*, *Legionella*, *H. influenzae, Branh. catarrhalis* and some streptococcal and pneumococcal infections besides gram-negative ones. Several 2nd generation FQs have now become available for the treatment of pneumonias and chronic bronchitis.

The US-FDA has approved use of ciprofloxacin for post exposure treatment of inhalational *anthrax* which may occur due to bioterrorism.

8. *Tuberculosis* It is a second line drug which can be used as a component of combination chemotherapy against multidrug resistant tuberculosis. Recently, even FQ-resistant TB (extensively drug resistant or XDR-TB) have arisen.

Drugs for typhoid fever

1. **Ceftriaxone** (*see* p. 728): Currently, it is the most reliable and fastest acting bactericidal drug for enteric fever. Practically all *S. typhi* isolates, including multidrug resistant ones, are susceptible. However, it has to be injected i.v. (4 g daily for 2 days followed by 2 g/day till 2 days after fever subsides; children 75 mg/kg/day) and is expensive. Generally 7–10 days treatment is required. Being bactericidal, it also prevents relapses and carrier state. Ceftriaxone is to be preferred over FQs in children, pregnant women and in areas with FQ resistance.
   Cefoperazone and *cefotaxime* are the other third generation cephalosporins used in typhoid.
2. **Fluoroquinolones:** Ciprofloxacin (750 mg BD) is mostly used. Ofloxacin (400 mg BD), levofloxacin (500 mg OD/BD) are nearly equally efficacious alternatives.
3. **Chloramphenicol** (*see* p. 741): Since majority of *S. typhi* strains are now chloramphenicol resistant, it has become clinically unreliable. It is seldom used, only in case the local strain is known to be sensitive and clinical experience supports its use. It is administered orally (0.5 g 6 hourly till fever subsides, then 0.25 g 6 hourly for another 5–7 days).
4. **Azithromycin** (500 mg OD for 7 days) is a second line alternative in multidrug resistant typhoid, and in patients to whom the 1st line drugs cannot be given.
5. **Cotrimoxazole** (*see* p. 708): It was effective in typhoid till plasmid mediated multidrug resistance spread among *S. typhi*. Now it is rarely used.
6. **Ampicillin/amoxicillin** (*see* p. 722): These antibiotics are no longer dependable therapy for typhoid because of multi-drug resistance. Response rate is low and defervescence takes longer even in patients who respond.
7. **Combination therapy:** There is no evidence that combination of any two or more AMAs is better than the single drug to which the infecting strain of *S. typhi* is responsive.

9. *Gram-negative septicaemias:* Parenteral ciprofloxacin may be combined with a third generation cephalosporin or an aminoglycoside.

10. *Meningitis:* Though penetration in CSF is not very good, ciprofloxacin has been successfully used in gram-negative bacterial meningitis, especially that occurring in immunocompromised patients or those with CSF shunts.

11. *Prophylaxis:* of infections in neutropenic/cancer and other susceptible patients.

12. *Conjunctivitis:* by gram-negative bacteria: topical therapy is effective.

Norfloxacin It is less potent than ciprofloxacin: MIC values for most gram-negative bacteria are 2–4 times higher. Many *Pseudomonas* and gram-positive organisms are not inhibited. Moreover, it attains lower concentration in tissues which are non-therapeutic. Unchanged drug as well as metabolites are excreted in urine.

Norfloxacin is primarily used for urinary and genital tract infections. Given for 8–12 weeks, it can treat chronic UTI. It is also good for bacterial diarrhoeas, because high concentrations are present in the gut, and anaerobic flora of the gut is not disturbed. Norfloxacin is not recommended for respiratory and other systemic infections.

NORBACTIN, NORFLOX 200, 400, 800 mg tab, 3 mg/ml eye drops; UROFLOX, NORILET 200, 400 mg tab. BACIGYL 400 mg tab, 100 mg/5 ml susp.

Pefloxacin It is the methyl derivative of norfloxacin which is more lipid soluble, completely absorbed orally, penetrates tissues better and attains higher plasma concentrations. Passage into CSF is greater than other FQs—preferred for meningeal infections. It is highly metabolized—partly to norfloxacin which contributes to its activity. Pefloxacin has longer t½: cumulates on repeated dosing achieving plasma concentrations twice as high as after a single dose. Because of this it is effective in many systemic infections as well. Dose of pefloxacin needs to be reduced in liver disease, but not in renal insufficiency. It is less effective in gram-positive coccal and *Listeria* infections.

PELOX, 200, 400 mg tab, to be taken with meals; 400 mg/5 ml inj (to be diluted in 100–250 ml of glucose solution but not saline, because it precipitates in presence of Cl^- ions), PERTI, 400 mg tab.

Ofloxacin This FQ is somewhat less active than ciprofloxacin against gram-negative bacteria, but equally or more potent against gram-positive ones and certain anaerobes. Good activity against *Chlamydia* and *Mycoplasma* has been noted. It is an alternative drug for nonspecific urethritis, cervicitis and atypical pneumonia caused by *Chlamydia trachomatis*. It also inhibits *M. tuberculosis*; can be used in resistant cases of TB. High activity is exhibited against *M. leprae*, and it is being used in alternative multidrug therapy regimens.

Ofloxacin is relatively lipid soluble; oral bioavailability is high, and higher plasma concentrations are attained. Food does not interfere with its absorption. It is excreted largely unchanged in urine; dose needs to be reduced in renal failure.

Ofloxacin is comparable to ciprofloxacin in the therapy of systemic and mixed infections. It is suitable for chronic bronchitis and other respiratory or ENT infections. Inhibition of theophylline metabolism is less marked.

Gonorrhoea caused by FQ sensitive strains has been treated with a single 200 to 400 mg dose. It is also useful in chlamydia urethritis as an alternative drug.

ZANOCIN, TARIVID 100, 200, 400 mg tab; 200 mg/100 ml i.v. infusion, ZENFLOX also 50 mg/5 ml susp.
ZANOCIN, OFLOX, EXOCIN 0.3% eye drops.

Levofloxacin It is the active levo(s) isomer of ofloxacin having improved activity against *Strep. pneumoniae* and some other gram-positive and gram-negative bacteria. Anaerobes are moderately susceptible. Oral bioavailability of levofloxacin is nearly 100%; oral and i.v. doses are similar. It is mainly excreted unchanged, and a single daily dose is sufficient because of slower elimination and higher potency.

Theophylline, warfarin, cyclosporine and zidovudine pharmacokinetics has been found to remain unchanged during levofloxacin treatment. The primary indication of levofloxacin is community acquired pneumonia and exacerbations of chronic bronchitis in which upto 90% cure rate has been obtained. High cure rates have been noted in sinusitis, pyelonephritis, prostatitis and other UTI, as well as skin/soft tissue infections.

TAVANIC, GLEVO 500 mg tab, 500 mg/100 ml inj.
LOXOF, GLEVO, LEVOFLOX, LEVODAY 250, 500, 750 mg tabs, 500 mg/100 ml inj; GLEVO 0.5% eye drops.

Lomefloxacin It is a second generation difluorinated quinolone, equal in activity to ciprofloxacin but more active against some gram-negative bacteria and chlamydia. Because of longer t½ and persistence in tissues, it is suitable for single daily administration. However, due to higher incidence of phototoxicity and Q-T prolongation, it has been withdrawn in USA and some other countries, but is available in India, though infrequently used.

LOMEF-400, LOMEDON, LOMADAY 400 mg tab.
LOMIBACT, LOX 0.3% eye drops.

Sparfloxacin Another second generation difluorinated quinolone which has enhanced activity against gram-positive bacteria (especially *Strep. pneumoniae, Staphylococcus, Enterococcus*), *Bacteroides fragilis,* other anaerobes and mycobacteria. Its major indications include pneumonia, exacerbations of chronic bronchitis, sinusitis and other ENT infections. However, it has frequently caused phototoxic reactions: recipients should be cautioned not to go out in the sun. Prolongation of QTc interval has been noted in 3% recipients. Fatal arrhythmias have occurred in patients taking other Q-T prolonging drugs concurrently. It has been discontinued in many countries including USA, but not yet in India.

Dose: 200–400 mg OD oral.

TOROSPAR 200, 400 mg tab; SPARTA, SPARQUIN, SPARDAC 100, 200 mg tab, ZOSPAR, SPARC, EYPAR 0.3% eye drops.

Gatifloxacin This 2nd generation FQ with higher affinity for bacterial topoisomerase IV was frequently used for gram positive coccal (mainly respiratory and ENT) infections. However, it caused Q-T prolongation, arrhythmias, phototoxicity, and unpredictable hypoglycaemia, because of which it was discontinued in most countries and has been banned in India since March 2011.

Moxifloxacin A long-acting 2nd generation FQ having high activity against *Str. pneumoniae,* other gram-positive bacteria including β-lactam/macrolide resistant ones and some anaerobes. It is the most potent FQ against *M. tuberculosis.* Bacterial topoisomerase IV is the major target of action. Moxifloxacin is primarily used for pneumonias, bronchitis, sinusitis, otitis media, in which efficacy is comparable to β-lactam antibiotics. However, it is not good for urinary tract infections. It is primarily metabolized in liver; should not be given to liver disease patients. Side effects are similar to other FQs. It should not be given to patients predisposed to seizures and to those receiving proarrhythmic drugs, because it can prolong Q-T_c interval. Phototoxicity occurs rarely.

Dose: 400 mg OD; MOXIF 400 mg tab; STAXOM 400 mg tab, 400 mg/250 ml i.v. infusion.
MOXICIP, MILFLOX, VIGAMOX 0.5% eye drops for conjunctivitis caused by gram-positive as well as negative bacteria.

Gemifloxacin Another broad spectrum FQ, active mainly against aerobic gram positive bacteria, especially *Strep. pneumoniae, H. influenzae, Moraxella, Mycoplasma pneumoniae, Chlamydia pneumophila, Klebsiella* including some multidrug resistant strains. Some anaerobes are also inhibited. It is rapidly absorbed, undergoes limited metabolism, and is excreted in urine as well as faeces, both as unchanged drug and as metabolites. Dose needs to be halved if creatinine clearance is <40 ml/min.

Side effects are diarrhoea, nausea, headache, dizziness and rise in serum amino-transferases. Skin rashes are more common. It can enhance warfarin effect, and carries the risk of additive Q-T prolongation. Gemifloxacin is indicated in community acquired pneumonia and for acute exacerbations of chronic bronchitis.

Dose: 320 mg OD for 5–7 days.

TOPGEM, GEMBAX, GEMISTAR, GEMI 320 mg tab.

Prulifloxacin This newer 2nd generation FQ is a prodrug of *Ulifloxacin*, a broad spectrum antibacterial active against both gram positive as well as gram negative bacteria, including many resistant strains. Prulifloxacin is rapidly absorbed and converted to ulifloxacin during first pass metabolism. Ulifloxacin is then excreted primarily unchanged in urine. Prulifloxacin has shown good efficacy in acute exacerbations of chronic bronchitis, as well as in uncomplicated or complicated UTI. Its side effect profile is similar to that of ciprofloxacin. Gastrointestinal and CNS disturbances, urticaria and photosensitivity are reported. It is claimed not to prolong Q-T interval. Photosensitivity, blood dyscrasias and renal toxicity are rare.

Dose: 600 mg OD, single dose in uncomplicated lower UTI; upto 10 days treatment for complicated UTI and bronchitis.

ALPRULI, PRULIFOX, PRULIFACT 600 mg tab.

☞ PROBLEM DIRECTED STUDY

50.1 A 62-year-old lady presented with acute onset frontal headache which is worse in the morning, thick, yellowish discharge from the nose, nasal blockage and fever for the past 2 days. She has been suffering from cold and cough for the last one week. The forehead is tender on pressing, particularly in the middle. A plain X-ray of the face and head showed both sided frontal sinusitis. Her husband informed that 3 months back she sufferred an episode of depression, for which she is receiving Tab amitryptyline 75 mg once daily at bed time and her mental condition is stable now. The doctor decides to start empirical therapy with moxifloxacin 400 mg once daily for 10 days. He also prescribes paracetamol 500 mg 8 hourly for fever and oxymetazoline nasal drops twice daily for blocked nose.

(a) Is the choice of antibiotic appropriate for her? If yes, what could be the considerations for selecting moxifloxacin. If no, then give reasons, and suggest the alternative antibiotic(s) that would be appropriate.

(see Appendix-1 for solution)

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.

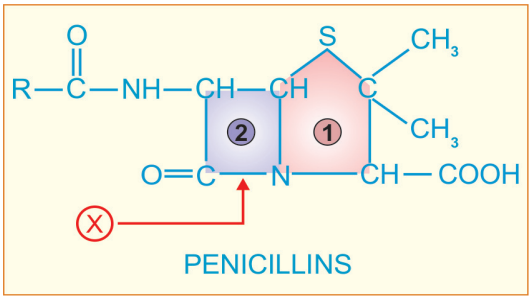


Fig. 51.1: Chemical structure of penicillins. (1) Thiazolidine ring; (2) β-lactam ring; (X) Bond which is broken by penicillinase

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

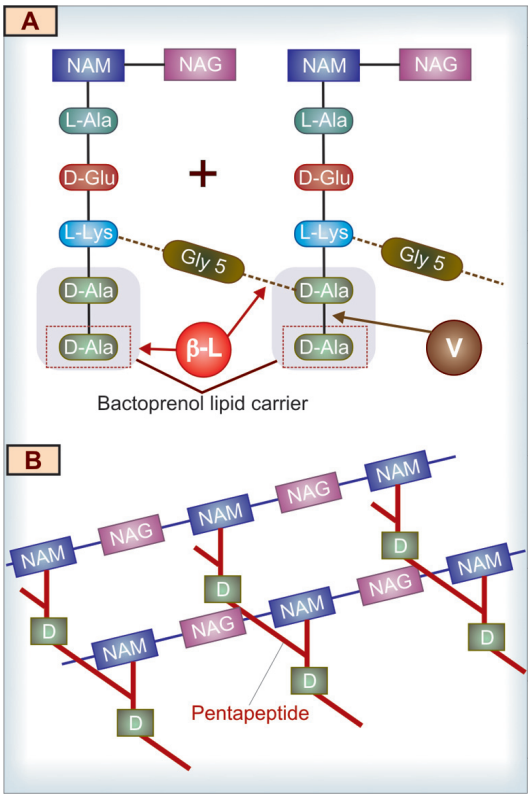


Fig. 51.2: Key features of bacterial cell wall synthesis and cell wall structure, depicting the site of action of β-lactam antibiotics and vancomycin.

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).

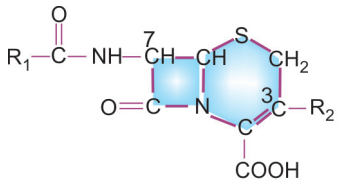
Pain at site of injection, thrombophlebitis of injected vein, rash and diarrhoea are the main adverse effects.

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?

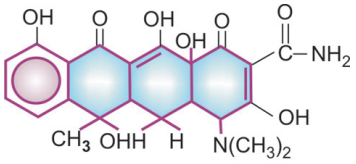
(c) Should a single antibiotic or a combination be used?

(*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

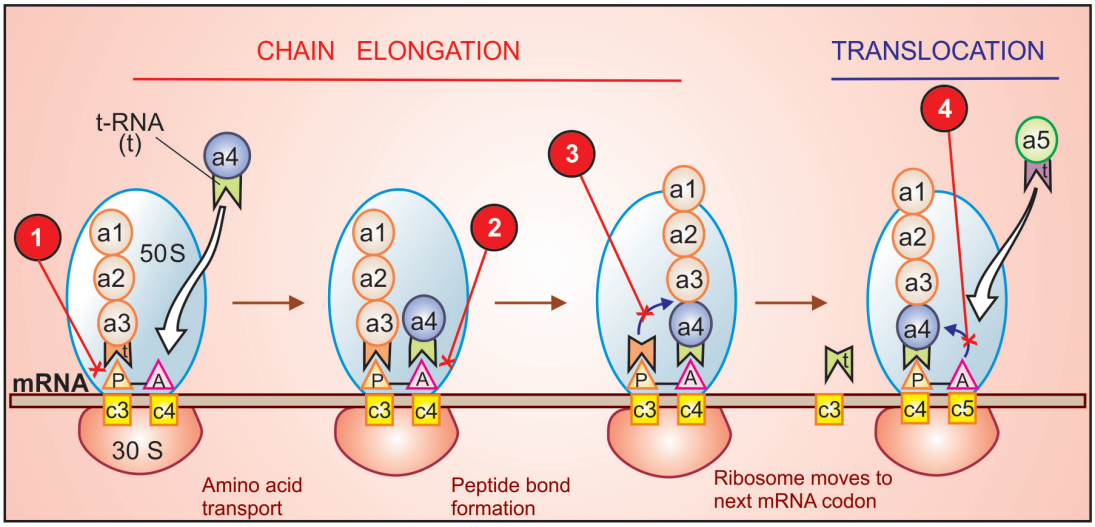


Fig. 52.1: Bacterial protein synthesis and the site of action of antibiotics

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.

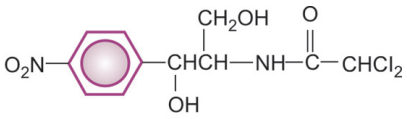
Dose: 100 mg loading dose, followed by 50 mg 12 hourly by i.v. infusion over 30–60 min, for 5–14 days.
TYGACIL, TEVRAN, TIGIMAX 50 mg lyophilized powder/vial inj.

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