SECTION 11

GASTROINTESTINAL DRUGS

Chapter 46 Drugs for Peptic Ulcer and Gastroesophageal Reflux Disease

PEPTIC ULCER

Peptic ulcer occurs in that part of the gastrointestinal tract (g.i.t.) which is exposed to gastric acid and pepsin, i.e. the stomach and duodenum. The etiology of peptic ulcer is not clearly known. It results probably due to an imbalance between the *aggressive* (acid, pepsin, bile and *H. pylori*) and the *defensive* (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, high mucosal blood flow, innate resistance of the mucosal cells) factors. A variety of psychosomatic, humoral and vascular derangements have been implicated and the importance of *Helicobacter pylori* infection as a contributor to ulcer formation and recurrence has been recognized.

In *gastric ulcer*, generally acid secretion is normal or low, while deficient mucosal defence (mostly impaired mucus and bicarbonate secretion) plays a greater role. In *duodenal ulcer*, acid secretion is high in about half of the patients but normal in the rest. Notwithstanding whether production of acid is normal or high, it does contribute to ulceration as an aggressive factor, reduction of which is the main approach to ulcer treatment. An understanding of the mechanism and control of gastric acid secretion will elucidate the targets of antisecretory drug action.

Regulation of gastric acid secretion

The mechanisms operating at the gastric parietal cells are summarized in Fig. 46.1. The terminal enzyme H^+K^+ATPase (proton pump) which secretes H^+ ions in the apical canaliculi of parietal cells can be activated by histamine, ACh and gastrin acting *via* their own receptors located on the basolateral membrane of these cells. Out of the three physiological secretagogues, histamine, acting through H_2 receptors, plays the dominant role, because the other two, gastrin and ACh act partly directly and to a greater extent indirectly by releasing histamine from paracrine enterochromaffin-like (ECL) cells called "histaminocytes" located in the oxyntic glands. While H_2 receptors activate H^+K^+ATPase by generating cAMP, muscarinic and gastrin/cholecystokinin (CCK_2) receptors appear to function through the phospholipase C $\rightarrow$ IP_3–DAG pathway that mobilizes intracellular Ca^{2+}. The cAMP mediated proton pump activation also involves Ca^{2+}. The secretomotor response to gastrin and cholinergic agonists is expressed fully only in the presence of cAMP generated by H_2 activation. As such, histamine participates in the acid response to gastrin and ACh at more than one levels, and H_2 antagonists suppress not only histamine, but also ACh, pentagastrin and in fact any gastric acid secretory stimulus.

Gastrin is secreted from the antrum in response to rise in antral pH, food constituents and vagally mediated reflexes involving ganglion cells of the enteric nervous system (ENS). The postganglionic ENS neurones elicit gastrin release from gastrin secreting 'G' cells by elaborating ACh as well as gastrin releasing peptide (GRP). The dominant muscarinic receptor mediating vagal responses is of the M_1 subtype. Its location

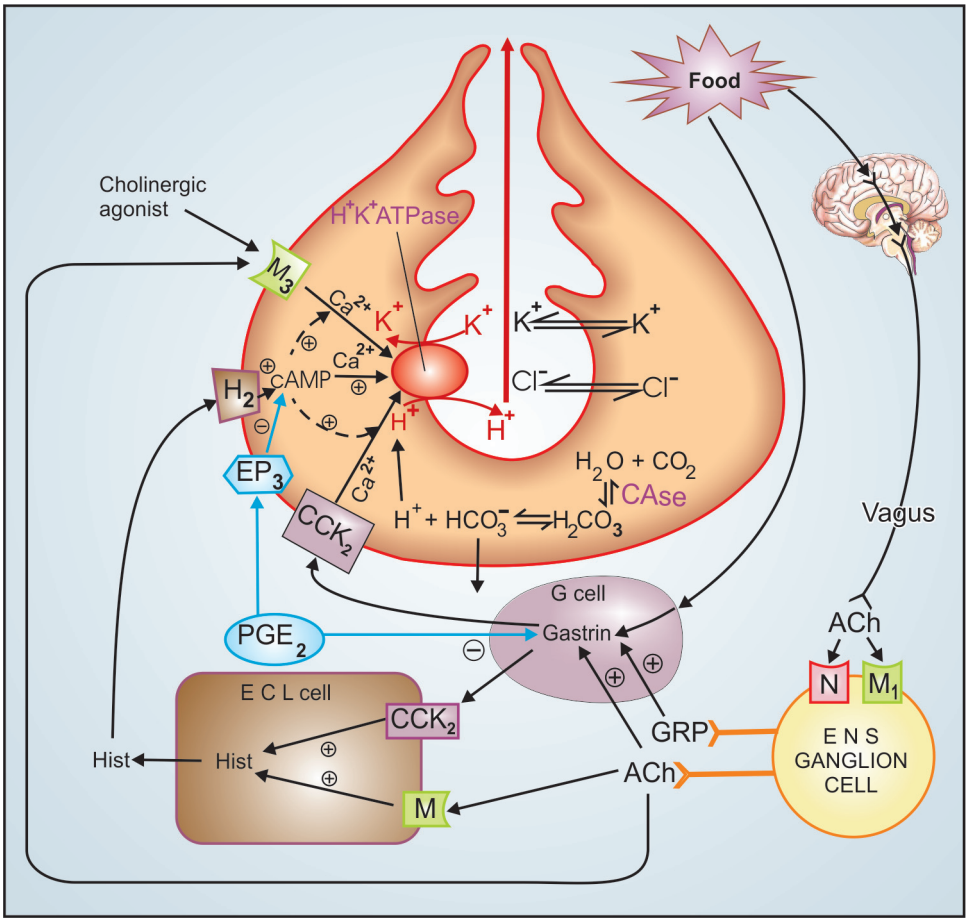


Figure 46.1: Secretion of HCl by gastric parietal cell and its regulation
C.Ase.—Carbonic anhydrase; Hist.—Histamine; ACh.—Acetylcholine; CCK_2—Gastrin cholecystokinin receptor; M.—Muscarinic receptor; N—Nicotinic receptor; H_2—Histamine H_2 receptor; EP_3—Prostaglandin receptor; ENS—Enteric nervous system; ECL cell—Enterochromaffin-like cell; GRP—Gastrin releasing peptide; + Stimulation; – Inhibition.

on the ganglion cells of the intramural plexuses has been confirmed. The parietal cell muscarinic receptor is of the M_3 subtype, but the subtype of muscarinic receptor on ECL cells has not been defined. Vagus releases ACh in close proximity to ECL cells and 'G' cells, but apparently at a distance from the parietal cells. As such, vagal effects are exerted largely indirectly through histamine and gastrin.

Prostaglandins have been ascribed a "cytoprotective" role in the gastric mucosa by augmenting mucus and bicarbonate secretion. from gastric mucosal epithelial cells, as well as other actions. Soon after secretion, the gastric mucus transforms into an adherent gell-like film over the mucosa which traps the secreted HCO_3^- ions and prevents their neutralization by creating a barrier for the H^+ ions in the juice. It also sheilds the mucosa from attack by pepsin. PGE_2 produced by gastric mucosa, inhibits acid secretion by opposing cAMP generation (in parietal cells) and gastrin release (from antral G cells).

Peptic ulcer (especially duodenal) is a chronic remitting and relapsing disease lasting several years. The goals of antiulcer therapy are:

- Relief of pain
- Ulcer healing
- Prevention of complications (bleeding, perforation)
- Prevention of relapse.

Approaches for the treatment of peptic ulcer are:

1. *Reduction of gastric acid secretion*
   (a) *H_2 antihistamines*: Cimetidine, Ranitidine, Famotidine, Roxatidine
   (b) *Proton pump inhibitors*: Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Dexrabeprazole
   (c) *Anticholinergic drugs*: Pirenzepine, Propantheline, Oxyphenonium
   (d) *Prostaglandin analogue:* Misoprostol

2. *Neutralization of gastric acid (Antacids)*
   (a) *Systemic:* Sodium bicarbonate, Sod. citrate
   (b) *Nonsystemic:* Magnesium hydroxide, Mag. trisilicate, Aluminium hydroxide gel, Magaldrate, Calcium carbonate

3. *Ulcer protectives:* Sucralfate, Colloidal bismuth subcitrate (CBS)

4. *Anti-H. pylori drugs:* Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline

H_2 ANTAGONISTS

These are the first class of highly effective drugs for acid-peptic disease, but have been surpassed by proton pump inhibitors (PPIs). Four H_2 antagonists cimetidine, ranitidine, famotidine and roxatidine are available in India; many others are marketed elsewhere. Their interaction with H_2 receptors has been found to be competitive in case of cimetidine, ranitidine and roxatidine, but competitive-noncompetitive in case of famotidine. Cimetidine was the first H_2 blocker to be introduced clinically and is described as the prototype, though other H_2 blockers are more commonly used now.

Pharmacological actions

1. *H_2 blockade* Cimetidine and all other H_2 antagonists block histamine-induced gastric secretion, cardiac stimulation (prominent in isolated preparations, especially in guinea pig), uterine relaxation (in rat) and bronchial relaxation (H_2 blockers potentiate histamine induced bronchospasm). They attenuate fall in BP due to histamine, especially the late phase response seen with high doses. They are highly selective: have no effect on H_1 mediated responses or on the action of other transmitters/autacoids.

2. *Gastric secretion* The only significant *in vivo* action of H_2 blockers is marked inhibition of gastric secretion. All phases (basal, psychic, neurogenic, gastric) of secretion are suppressed dose-dependently, but the basal nocturnal acid secretion is suppressed more completely. Secretory responses to not only histamine but all other stimuli (ACh, gastrin, insulin, alcohol, food) are attenuated. This reflects the permissive role of histamine in amplifying responses to other secretagogues. The volume, pepsin content and intrinsic factor secretion are reduced, but the most marked effect is on acid. However, normal vit B_{12} absorption is not interfered: no vit B_{12} deficiency occurs even after prolonged use.

The usual ulcer healing doses produce 60–70% inhibition of 24 hr acid output. The H_2 blockers have antiulcerogenic effect. Gastric ulceration due to stress and drugs (NSAIDs, cholinergic, histaminergic) is prevented. They do not have any direct effect on gastric or esophageal motility or on lower esophageal sphincter (LES) tone.

Pharmacokinetics

Cimetidine is adequately absorbed orally, though bioavailability is 60–80% due to first pass hepatic metabolism. Absorption is not interfered by presence of food in stomach. It crosses placenta and reaches milk, but penetration in brain is poor because of its hydrophilic nature. About 2/3 of a dose is excreted unchanged in urine and bile, the rest as oxidized metabolites. The elimination t½ is 2–3 hr. Dose reduction is needed in renal failure.

Adverse effects

Cimetidine is well tolerated by most patients: adverse effects occur in < 5%. These are generally mild.

- Headache, dizziness, bowel upset, dry mouth, rashes.
- Cimetidine (but not other H_2 blockers) has antiandrogenic action (displaces dihydrotestosterone from its cytoplasmic receptor), increases plasma prolactin and inhibits degradation of estradiol by liver. High doses given for long periods have produced gynaecomastia, loss of libido, impotence and temporary decrease in sperm count.
- Transient elevation of plasma aminotransferases; but hepatotoxicity is rare.

Interactions

Cimetidine inhibits several cytochrome P-450 isoenzymes and reduces hepatic blood flow. It inhibits the metabolism of many drugs so that they can accumulate to toxic levels, e.g. theophylline, phenytoin, carbamazepine, phenobarbitone, sulfonylureas, metronidazole, warfarin, imipramine, lidocaine, nifedipine, quinidine. Metabolism of propranolol and diazepam is also retarded, but this may not be clinically significant.

Antacids reduce absorption of all H_2 blockers. When used concurrently a gap of 2 hr should be allowed. Ketoconazole absorption is decreased by H_2 blockers due to reduced gastric acidity.

Dose: For ulcer healing—400 mg BD or 800 mg at bed time orally; maintenance—400 mg at bed time.

For stress ulcer—50 mg/hr i.v. infusion. Rapid or higher dose i.v. injection can cause confusional state, hallucinations, convulsions, bradycardia, arrhythmias, coma or cardiac arrest.

CIMETIDINE 200 mg, 400 mg, 800 mg tabs, 200 mg/2 ml inj., LOCK-2 200 mg tab.

Ranitidine A nonimidazole (has a furan ring) H_2 blocker, it has several desirable features compared to cimetidine:

- About 5 times more potent than cimetidine. Though its pharmacokinetic profile and t½ of 2–3 hr is similar to cimetidine, a longer duration of action with greater 24 hr acid suppression is obtained clinically because of higher potency.
- No antiandrogenic action, does not increase prolactin secretion or spare estradiol from hepatic metabolism—no effect on male sexual function or gynaecomastia.
- Lesser permeability into the brain: lower propensity to cause CNS effects. In fact, little effect outside g.i.t. has been observed.
- Less marked inhibition of hepatic metabolism of other drugs; drug interactions mostly have no clinical relevance.
- Overall incidence of side effects is lower: headache, diarrhoea/constipation, dizziness have an incidence similar to placebo.

Dose: for ulcer healing 300 mg at bed time or 150 mg BD; for maintenance 150 mg at bed time. Parenteral dose—50 mg i.m. or slow i.v. inj. every 6–8 hr (rapid i.v. injection can cause hypotension), 0.1–0.25 mg/kg/hr by i.v. infusion has been used for prophylaxis of stress ulcers. For gastrinoma 300 mg 3–4 times a day.

ULTAC, ZINETAC 150 mg, 300 mg tabs; HISTAC, RANITIN, ACILOC, RANTAC 150 mg, 300 mg tabs, 50 mg/2 ml inj.

Famotidine A thiazole ring containing H_2 blocker which binds tightly to H_2 receptors and exhibits longer duration of action despite an elimination t½ of 2.5–3.5 hr. Some inverse agonistic action on H_2 receptors (in the absence of histamine) has been demonstrated. It is 5–8 times more potent than ranitidine. Antiandrogenic action is absent. Because of low affinity for cytochrome P450 and the low dose, drug metabolism modifying propensity is minimal.

The oral bioavailability of famotidine is 40–50%, and it is excreted by the kidney, 70% in the unchanged form. Incidence of adverse effects is low: only headache, dizziness, bowel upset, rarely disorientation and rash have been reported. Because of the higher potency and longer duration, it has been considered more suitable for ZE syndrome and for prevention of aspiration pneumonia.

Dose: 40 mg at bed time or 20 mg BD (for healing); 20 mg at bed time for maintenance; upto 480 mg/day in ZE syndrome; parenteral dose 20 mg i.v. 12 hourly or 2 mg/hr i.v. infusion.

FAMTAC, FAMONITE, TOPCID 20 mg, 40 mg tabs; FAMOCID, FACID 20, 40 mg tabs, 20 mg/2 ml inj.

Roxatidine The pharmacodynamic, pharmacokinetic and side effect profile of roxatidine is similar to that of ranitidine, but it is twice as potent and longer acting. It has no antiandrogenic or cytochrome P450 inhibitory action.

Dose: 150 mg at bed time or 75 mg BD; maintenance 75 mg at bed time.

ROTANE, ZORPEX 75 mg, 150 mg SR tabs.

Uses

The H_2 blockers are used in conditions in which it is profitable to suppress gastric acid secretion. Used in appropriate doses, all available agents have similar efficacy. However, PPIs, because of higher efficacy and equally good tolerability, have outstripped H_2 blockers.

1. *Duodenal ulcer* H_2 blockers produce rapid and marked pain relief (within 2–3 days); 60–85% ulcers heal at 4 weeks and 70–95% ulcers at 8 weeks, but they are seldom used now to heal existing ulcers.

Suppression of nocturnal secretion by single high bed time dose is equally efficacious and physiologically more sound. About ½ of the patients relapse within 1 year of healing with H_2 blockers. Maintenance therapy with bed time dose reduces the relapse rate to 15–20% per year as long as given.

2. *Gastric ulcer* Healing rates obtained in gastric ulcer are somewhat lower (50–75% at 8 weeks). However, doses remain the same. H_2 blockers can heal NSAID associated ulcers, but are less effective than PPIs or misoprostol.

3. *Stress ulcers and gastritis* Acutely stressful situations like hepatic coma, severe burns and trauma, prolonged surgery, prolonged intensive care, renal failure, asphyxia neonatorum, etc. are associated with gastric erosions and bleeding. Mucosal ischaemia along with acid is causative. Intravenous infusion of H_2 blockers successfully prevents the gastric lesions and haemorrhage as well as promotes healing of erosions that have occurred.

4. *Zollinger-Ellison syndrome* It is a gastric hypersecretory state due to a rare tumour secreting gastrin. H_2 blockers in high doses control hyperacidity and symptoms in many patients, but PPIs are the drugs of choice. Definitive treatment is surgical.

5. *Gastroesophageal reflux disease (GERD)* H_2 blockers afford symptomatic relief and facilitate healing of esophageal erosions, but are less effective than PPIs. They are indicated only in mild or stage-1 cases of GERD (*see* p. 659).

6. *Prophylaxis of aspiration pneumonia* H_2 blockers given preoperatively (preferably evening before also) reduce the risk of aspiration of acidic gastric contents during anaesthesia and surgery.

7. *Other uses* H_2 blockers have adjuvant beneficial action in certain cases of urticaria who do not adequately respond to an H_1 antagonist alone.

PROTON PUMP INHIBITORS (PPIs)

Omeprazole It is the prototype member of substituted benzimidazoles which inhibit the final common step in gastric acid secretion. The PPIs have overtaken H_2 blockers for acid-peptic disorders. The only significant pharmacological action of omeprazole is dose dependent suppression of gastric acid secretion; without anticholinergic or H_2 blocking action. It is a powerful inhibitor of gastric acid: can totally abolish HCl secretion, both resting as well as that stimulated by food or any of the secretagogues, without much effect on pepsin, intrinsic factor, juice volume and gastric motility.

Omeprazole is inactive at neutral pH, but at pH < 5 it rearranges to two charged cationic forms (a sulphenic acid and a sulphenamide configurations) that react covalently with SH groups of the H^+K^+ATPase enzyme and inactivate it irreversibly, especially when two molecules of omeprazole react with one molecule of the enzyme. After absorption into bloodstream and subsequent diffusion into the parietal cell, it gets concentrated in the acidic pH of the canaliculi because the charged forms generated there are unable to diffuse back. Moreover, it gets tightly bound to the enzyme by covalent bonds. These features and the specific localization of H^+K^+ATPase to the apical membrane

of the parietal cells confer high degree of selectivity of action to omeprazole. Acid secretion resumes only when new H^+K^+ATPase molecules are synthesized (reactivation half time 18 hours). It also inhibits gastric mucosal carbonic anhydrase.

Pharmacokinetics All PPIs are administered orally in enteric coated (e.c.) form to protect them from molecular transformation in the acidic gastric juice. The e.c. tablet or granules filled in capsules should not be broken or crushed before swallowing. Oral bioavailability of omeprazole is ~50% due to acid lability. As the gastric pH rises, a higher fraction (up to 3/4) may be absorbed. Bioavailability of all PPIs is reduced by food; they should be taken in empty stomach, followed 1 hour later by a meal to activate the H^+K^+ ATPase and make it more susceptible to the PPI. Omeprazole is highly plasma protein bound, rapidly metabolised in liver by CYP2C19 and CYP3A4 (plasma t½ ~1 hr). The metabolites are excreted in urine. No dose modification is required in elderly or in patients with renal/hepatic impairment. Because of tight binding to its target enzyme—it can be detected in the gastric mucosa long after its disappearance from plasma. As such, inhibition of HCl secretion occurs within 1 hr, reaches maximum at 2 hr, is still half maximal at 24 hr and lasts for 2–3 days. Since only actively acid secreting proton pumps are inhibited, and only few pumps may be active during the brief interval that the PPI is present (all have 1–2 hours plasma t½), antisecretory action increases on daily dosing to reach a plateau after 4 days. At steady-state all PPIs produce 80–98% suppression of 24 hour acid output with conventional doses. Secretion resumes gradually over 3–5 days of stopping the drug.

Uses

1. *Peptic ulcer:* Omeprazole 20 mg OD is equally or more effective than H_2 blockers. Relief of pain is rapid and excellent. Faster healing has been demonstrated with 40 mg/day: some duodenal ulcers heal even at 2 weeks and the remaining (over 90%) at 4 weeks. Gastric ulcer generally requires 4–8 weeks. It has caused healing of ulcers in patients not responding to H_2 blockers. Continued treatment (20 mg daily or thrice weekly) can prevent ulcer relapse. PPIs are an integral component of anti-*H. pylori* therapy. PPIs are the drugs of choice for NSAID induced gastric/duodenal ulcers. Healing may occur despite continued use of the NSAID. However, higher doses given for longer periods are generally required. When the NSAID cannot be stopped, it is advisable to switch over to a COX-2 selective NSAID. Maintenance PPI treatment reduces recurrence of NSAID associated ulcer.

2. *Bleeding peptic ulcer:* Acid enhances clot dissolution promoting ulcer bleed. Suppression of gastric acid has been found to facilitate clot formation reducing blood loss and rebleed. High dose i.v. PPI therapy (pantoprazole 40–120 mg/day or rabeprazole 40–80 mg/day) profoundly inhibits gastric acid, and has been shown to reduce rebleeding after therapeutic endoscopy. Even in cases where the bleeding vessel could not be visualized, i.v. followed by oral PPI reduces recurrence of bleeding and need for surgery.

3. *Stress ulcers:* Intravenous pantoprazole/rabeprazole is as effective prophylactic (if not more) for stress ulcers as i.v. H_2 blockers (*see* p. 651).

4. *Gastroesophageal reflux disease (GERD):* Omeprazole produces more complete round-the-clock inhibition of gastric acid resulting in rapid symptom relief and is more effective than H_2 blockers in promoting healing of esophageal lesions. PPIs are the drugs of choice (*see* p. 659). Higher doses than for peptic ulcer or twice daily administration is generally needed.

5. *Zollinger-Ellison syndrome:* Omeprazole is more effective than H_2 blockers in controlling hyperacidity in Z-E syndrome. However, 60–120 mg/day or more (in 2 divided doses) is often

required for healing of ulcers. Inoperable cases have been treated for >6 years with sustained benefit and no adverse effects. Other gastric hypersecretory states like systemic mastocytosis, endocrine adenomas, etc. also respond well.

6. *Aspiration pneumonia:* PPIs are an alternative to H_2 blockers for prophylaxis of aspiration pneumonia due to prolonged anaesthesia.

OMIZAC, NILSEC 20 mg cap. OMEZ, OCID, OMEZOL 10, 20 mg caps, PROTOLOC 20, 40 mg caps containing enteric coated granules. Capsules must not be opened or chewed; to be taken in the morning before meals.

Adverse effects PPIs produce minimal adverse effects. Nausea, loose stools, headache, abdominal pain, muscle and joint pain, dizziness are complained by 3–5%. Rashes (1.5% incidence), leucopenia and hepatic dysfunction are infrequent. On prolonged treatment atrophic gastritis has been reported occasionally.

No harmful effects of PPIs during pregnancy are known. Though manufacturers advise to avoid, PPIs have often been used for GERD during pregnancy.

Because of marked and long-lasting acid suppression, compensatory hypergastrinemia has been observed. This induces proliferation of parietal cells and gastric carcinoid tumours in rats, but not in humans. Though patients have been treated continuously for > 11 years without any problem, it may appear prudent to be apprehensive of prolonged achlorhydria and hypergastrinaemia; and if possible, avoid long-term use of PPIs.

Lately, few reports of gynaecomastia and erectile dysfunction (possibly due to reduced testosterone level) on prolonged use of omeprazole have appeared. Accelerated osteoporosis among elderly patients (possibly due to reduced calcium absorption) has been recently associated with high-dose long-term use of PPIs for GERD.

Interactions Omeprazole inhibits oxidation of certain drugs: diazepam, phenytoin and warfarin levels may be increased. It interferes with activation of clopidogrel by inhibiting CYP2C19. Reduced gastric acidity decreases absorption of ketoconazole and iron salts. Clarithromycin inhibits omeprazole metabolism and increases its plasma concentration.

Esomeprazole It is the S-enantiomer of omeprazole; claimed to have higher oral bioavailability and to produce better control of intragastric pH than omeprazole in GERD patients because of slower elimination and longer t½. Higher healing rates of erosive esophagitis and better GERD symptom relief have been reported in comparative trials with omeprazole. Side effect and drug interaction profile is similar to the racemic drug.

Dose: 20–40 mg OD; NEXPRO, RACIPER, IZRA 20, 40 mg tabs.

Lansoprazole Somewhat more potent than omeprazole but similar in properties. Inhibition of H^+ K^+ ATPase by lansoprazole is partly reversible. It has higher oral bioavailability, faster onset of action and slightly longer t½ than omeprazole. Dose should be reduced in liver disease. Side effects are similar, but drug interactions appear to be less significant; diazepam and phenytoin metabolism may be reduced.

Ulcer healing dose: 15–30 mg OD; LANZOL, LANZAP, LEVANT, LANPRO 15, 30 mg caps.

Pantoprazole It is similar in potency and clinical efficacy to omeprazole, but is more acid stable and has higher oral bioavailability. It is also available for i.v. administration; particularly employed in bleeding peptic ulcer and for prophylaxis of acute stress ulcers. Affinity for cytochrome P450 is lower than omeprazole or lansoprazole: risk of drug interactions is minimal.

Dose: 40 mg OD; PANTOCID, PANTODAC 20, 40 mg enteric coated tab; PANTIUM , PANTIN 40 mg tab, 40 mg inj for i.v. use.

S-Pantoprazole It is the active single enantiomer, twice as potent as the racemate.

PANPURE, ZOSECTA 20 mg tab.

Rabeprazole This newer PPI is claimed to cause fastest acid suppression. Due to higher pKa, it is more rapidly converted to the active species. However, potency and efficacy are similar to omeprazole.

Dose: 20 mg OD; ZE syndrome — 60 mg/day.

RABLET, RABELOC, RABICIP, RAZO, HAPPI 10, 20 mg tab, 20 mg/vial inj.

Dexrabeprazole It is the active dextro-isomer of rabeprazole; produces similar acid suppression at half the dose, *i.e.* 10–20 mg daily.

DEXPURE 5, 10 mg tabs.

ANTICHOLINERGICS (See Ch. 8)

Atropinic drugs reduce the volume of gastric juice without raising its pH unless there is food in stomach to dilute the secreted acid. Stimulated gastric secretion is less completely inhibited. Effective doses (for ulcer healing) of nonselective antimuscarinic drugs (atropine, propantheline, oxyphenonium) invariably produce intolerable side effects. Introduction of H_2 blockers and PPIs has sent them into oblivion.

Pirenzepine (*see* p. 117) It is a selective M_1 anticholinergic that has been used in Europe for peptic ulcer. Gastric secretion is reduced by 40–50% without producing intolerable side effects, but side effects do occur with slight excess. It has not been used in India and USA.

PROSTAGLANDIN ANALOGUE

PGE_2 and PGI_2 are produced in the gastric mucosa and appear to serve a protective role by inhibiting acid secretion and promoting mucus as well as HCO_3^- secretion (*see* Ch. 13). In addition, PGs inhibit gastrin release, increase mucosal blood flow and probably have an ill-defined "cytoprotective" action. However, the most important appears to be their ability to reinforce the mucus layer covering gastric and duodenal mucosa which is buffered by HCO_3^- secreted into this layer by the underlying epithelial cells.

Natural PGs have very short t½. *Misoprostol* (methyl-PGE_1 ester) is a longer acting synthetic PGE_1 derivative which inhibits acid output dose dependently. However, reduction in 24 hour acid production is less than H_2 blockers because of shorter duration of action (~3 hr.) Ulcer healing rates comparable to cimetidine have been obtained in 4–8 weeks, but misoprostol is poorer in relieving ulcer pain. Some patients may even complain of increased pain during the first week of therapy.

Dose: 200 µg QID;

CYTOLOG 200 µg tab; MISOPROST 100 µg, 200 µg tabs.

Major problems in the use of misoprostol are—diarrhoea, abdominal cramps, uterine bleeding, abortion, and need for multiple daily doses. Patient acceptability is poor.

The primary indication of misoprostol is the prevention and treatment of NSAID associated gastrointestinal injury and blood loss. However, it is seldom employed now because PPIs are more effective, more convenient, better tolerated and cheaper.

ANTACIDS

These are basic substances which neutralize gastric acid and raise pH of gastric contents. Peptic activity is indirectly reduced if the pH rises above 4, because pepsin is secreted as a complex with an inhibitory terminal moiety that dissociates below pH 5: optimum peptic activity is exerted between pH 2 to 4.

Antacids do not decrease acid production; rather, agents that raise the antral pH to > 4 evoke reflex gastrin release → more acid is secreted, especially in patients with hyperacidity and duodenal ulcer; "acid rebound" occurs and gastric motility is increased.

The potency of an antacid is generally expressed in terms of its *acid neutralizing capacity* (ANC), which is defined as number of mEq of 1N HCl that are brought to pH 3.5 in 15 min (or 60 min in some tests) by a unit dose of the antacid preparation. This takes into consideration the rate at which the antacid dissolves and reacts with HCl. This is important because a single dose of any antacid taken in empty stomach acts for 30–60 min only, since in this time any gastric content is passed into duodenum. Taken with meals antacids may act for at the most 2–3 hr.

Systemic Antacids

Sodium bicarbonate It is water soluble, acts instantaneously, but the duration of action is short. It is a potent neutralizer (1 g → 12 mEq HCl), pH may rise above 7. However, it has several demerits:

(a) Absorbed systemically: large doses will induce alkalosis.
(b) Produces CO_2 in stomach → distention, discomfort, belching, risk of ulcer perforation.
(c) Acid rebound occurs, but is usually short lasting.
(d) Increases Na^+ load: may worsen edema and CHF.

Use of sod. bicarbonate is restricted to casual treatment of heartburn. It provides quick symptomatic relief. Other uses are to alkalinize urine and to treat acidosis.

Sodium citrate Properties similar to sod. bicarbonate; 1 g neutralizes 10 mEq HCl; CO_2 is not evolved.

Nonsystemic Antacids

These are insoluble and poorly absorbed basic compounds; react in stomach to form the corresponding chloride salt. The chloride salt again reacts with the intestinal bicarbonate so that HCO_3^- is not spared for absorption—no acid-base disturbance occurs. However, small amounts that are absorbed have the same alkalinizing effect as $NaHCO_3$.

Mag. hydroxide has low water solubility: its aqueous suspension (milk of magnesia) has low concentration of OH^- ions and thus low alkalinity. However, it reacts with HCl promptly and is an efficacious antacid (1 g → 30 mEq HCl). Rebound acidity is mild and brief.

MILK OF MAGNESIA 0.4 g/5 ml suspension: 5 ml neutralizes 12 mEq acid.

Magnesium trisilicate has low solubility and reactivity; 1 g can react with 10 mEq acid, but in clinical use only about 1 mEq is neutralized.

About 5% of administered Mg is absorbed systemically—may cause problem if renal function is inadequate. All Mg salts have a laxative action by generating osmotically active $MgCl_2$ in the stomach and through Mg^{2+} ion induced cholecystokinin release. Soluble Mg salts are used as osmotic purgatives.

Aluminium hydroxide gel It is a bland, weak and slowly reacting antacid. On keeping it slowly polymerizes to variable extents into still less reactive forms. Thus, the ANC of a preparation gradually declines on storage. Also, the product from different manufacturers may have differing ANCs; usually it varies from 1–2.5 mEq/g. Thus, 5 ml of its suspension may neutralize just 1 mEq HCl. As such, little worthwhile acid neutralization is obtained at conventional doses.

The Al^{3+} ions relax smooth muscle. Thus, it delays gastric emptying. Alum. hydrox. frequently, causes constipation due to its smooth muscle relaxant and mucosal astringent action.

Alum. hydrox. binds phosphate in the intestine and prevents its absorption—hypophosphatemia occurs on regular use. This may:

(a) cause osteomalacia

(b) be used therapeutically in hyperphosphatemia and phosphate stones.

Small amount of Al^{3+} that is absorbed is excreted by kidney. This is impaired in renal failure—aluminium toxicity (encephalopathy, osteoporosis) can occur.

ALUDROX 0.84 g tab, 0.6 g/10 ml susp.

Magaldrate It is a hydrated complex of hydroxymagnesium aluminate that initially reacts rapidly with acid and releases alum. hydrox. which then reacts more slowly. The freshly released alum. hydrox. is in the unpolymerized more reactive form. Thus, magaldrate cannot be equated to a physical mixture of mag. and alum. hydroxides. It is a good antacid with prompt and sustained neutralizing action. Its ANC is estimated to be 28 mEq HCl/g.

STACID 400 mg tab, 400 mg/5 ml susp.; ULGEL 400 mg with 20 mg simethicone per tab or 5 ml susp.

Calcium carbonate It is a potent and rapidly acting acid neutralizer (1 g → 20 mEq HCl), but ANC of commercial preparations is less and variable due to differing particle size and crystal structure. Though it liberates CO_2 in the stomach at a slower rate than $NaHCO_3$, it can cause distention and discomfort. The Ca^{2+} ions are partly absorbed.

The greatest drawback of $CaCO_3$ as an antacid is that Ca^{2+} ions diffuse into the gastric mucosa—increase HCl production directly by parietal cells as well as by releasing gastrin. Acid rebound occurs. Mild constipation or rarely loose motions may be produced. The absorbed calcium can be dangerous in renal insufficiency.

Milk alkali syndrome In the past, large quantity of milk was prescribed with $CaCO_3$ (or $NaHCO_3$) for peptic ulcer. Such regimen often produced a syndrome characterized by headache, anorexia, weakness, abdominal discomfort, abnormal Ca deposits and renal stones due to concurrent hypercalcaemia and alkalosis. It is rare now.

Antacid combinations A combination of two or more antacids is frequently used. These may be superior to any single agent on the following accounts:

(a) Fast (Mag. hydrox.) and slow (Alum. hydrox.) acting components yield prompt as well as sustained effect.

(b) Mag. salts are laxative, while alum. salts are constipating: combination may annul each other's action and bowel movement may be least affected.

(c) Gastric emptying is least affected; while alum. salts tend to delay it, mag./cal. salts tend to hasten it.

(d) Dose of individual components is reduced; systemic toxicity (dependent on fractional absorption) is minimized.

Some available antacid combinations are:

ACIDIN: Mag. carb. 165 mg, dried alum. hydrox. gel 232 mg, cal. carb. 165 mg, sod. bicarb. 82 mg, with kaolin 105 mg and belladonna herb 30 µg per tab.

ALMACARB: Dried alum. hydrox. gel 325 mg, mag. carb. 50 mg, methyl polysilox. 40 mg, deglycyrrhizinated liquorice 380 mg per tab.

ALLUJEL-DF: Dried alum. hydrox. gel 400 mg, mag. hydrox. 400 mg, methyl polysilox. 30 mg per 10 ml susp.

DIGENE: Dried alum. hydrox. gel 300 mg, mag. alum. silicate 50 mg, mag. hydrox. 25 mg, methylpolysilox. 10 mg per tab.

DIGENE GEL: Mag. hydrox. 185 mg, alum. hydrox. gel 830 mg, sod. carboxymethyl cellulose 100 mg, methylpolysilox. 25 mg per 10 ml susp.

GELUSIL: Dried alum. hydrox. gel 250 mg, mag. trisilicate 500 mg per tab.

GELUSIL LIQUID: Mag. trisilicate 625 mg, alum. hydrox. gel 312 mg per 5 ml susp.

MUCAINE: Alum. hydrox. 290 mg, mag. hydrox. 98 mg, oxethazaine 10 mg per 5 ml susp.

TRICAINE-MPS: Alum. hydrox. gel 300 mg, mag. hydrox. 150 mg, oxethazaine 10 mg, simethicone 10 mg per 5 ml gel.

MAYLOX: Dried alum. hydrox. gel 225 mg, mag. hydrox. 200 mg, dimethicone 50 mg per tab and 5 ml susp.

POLYCROL FORTE GEL: Mag. hydrox. 100 mg, dried alum. hydrox. gel 425 mg, methylpolysilox. 125 mg per 5 ml susp.

Drug interactions By raising gastric pH and by forming complexes, the non-absorbable antacids decrease the absorption of many drugs, especially tetracyclines, iron salts, fluoroquinolones, ketoconazole, H_2 blockers, diazepam, phenothiazines, indomethacin, phenytoin, isoniazid, ethambutol and nitrofurantoin. Stagger their administration by 2 hours. The efficacy of nitrofurantoin is also reduced by alkalinization of urine.

Uses Antacids are no longer used for healing peptic ulcer, because they are needed in large and frequent doses, are inconvenient, can cause acid rebound and bowel upset, afford little nocturnal protection and have poor patient acceptability. Antacids are now employed only for intercurrent pain relief and acidity, mostly self-prescribed by the patients as over the counter preparations. They continue to be used for nonulcer dyspepsia and minor episodes of heartburn.

Gastroesophageal reflux Antacids afford faster symptom relief than drugs which inhibit acid secretion, but do not provide sustained benefit. May be used off and on for acid eructation and heartburn.

ULCER PROTECTIVES

Sucralfate It is a basic aluminium salt of sulfated sucrose; a drug of its own kind. Sucralfate polymerizes at pH < 4 by cross linking of molecules, assuming a sticky gel-like consistency. It preferentially and strongly adheres to ulcer base, especially duodenal ulcer; has been seen endoscopically to remain there for ~ 6 hours. Surface proteins at ulcer base are precipitated, together with which it acts as a physical barrier preventing acid, pepsin and bile from coming in contact with the ulcer base. Dietary proteins get deposited on this coat, forming another layer.

Sucralfate has no acid neutralizing action, but delays gastric emptying—its own stay in stomach is prolonged. Augmented gastric mucosal PG synthesis may supplement physical protective action of sucralfate.

Sucralfate is minimally absorbed after oral administration. Its action is entirely local. It promotes healing of both duodenal and gastric ulcers. Healing efficacy has been found similar to cimetidine at 4 weeks, and may be superior in patients who continue to smoke. However, sucralfate is infrequently used now because of need for 4 large well-timed daily doses and the availability of simpler and more effective H_2 blockers/PPIs.

Dose: The ulcer healing dose of sucralfate is 1 g taken in empty stomach 1 hour before the 3 major meals and at bed time for 4–8 weeks. Antacids should not be taken with sucralfate because its polymerization is dependent on acidic pH.
ULCERFATE, SUCRACE, RECULFATE 1 g tab.

Side effects are few; constipation is reported by 2% patients. It has potential for inducing hypophosphatemia by binding phosphate ions in the intestine. Dry mouth and nausea are infrequent.

Other uses Bile reflux, gastritis and prophylaxis of stress ulcers.

In intensive care units, acid suppressant (with i.v./intragastric H_2 blocker/PPI) prophylaxis of stress ulcers is almost routinely used now. This practice is considered to contribute to occurrence of pneumonia due to overgrowth of bacteria in the stomach. Intragastric sucralfate provides effective prophylaxis of stress ulcers without acid suppression, and is an alternative to i.v. H_2 blocker/PPI..
As a suspension in glycerol, it has been tried in stomatitis.

A topical formulation of sucralfate PEPSIGARD LIGHT GEL is available for application on burns, bedsores, diabetic/radiation ulcers, excoriated skin, etc. as a protective.

Interactions Sucralfate adsorbs many drugs and interferes with the absorption of tetracyclines, fluoroquinolones, cimetidine, phenytoin and digoxin. Antacids given concurrently reduce the efficacy of sucralfate.

Colloidal bismuth subcitrate (CBS; Tripotassium dicitratobismuthate)

It is a colloidal bismuth compound; water soluble but precipitates at pH < 5. It is not an antacid but heals 60% ulcers at 4 weeks and 80–90% at 8 weeks. The mechanism of action of CBS is not clear; probabilities are:

- May increase gastric mucosal PGE_2, mucus and HCO_3^- production.
- May precipitate mucus glycoproteins and coat the ulcer base.
- May detach and inhibit *H.pylori* directly.

Gastritis and nonulcer dyspepsia associated with *H. pylori* are also improved by CBS. The regimen for CBS is 120 mg (as Bi_2O_3) taken ½ hr before 3 major meals and at bedtime for 4–8 weeks. Milk and antacids should not be taken concomitantly.
TRYMO, DENOL 120 mg tab.

Most of the ingested CBS passes in the faeces. Small amounts absorbed are excreted in urine. Side effects are diarrhoea, headache and dizziness. Patient acceptance of CBS is

compromised by blackening of tongue, dentures and stools; and by the inconvenience of dosing schedule. Presently, it is used occasionally as a component of triple drug anti-*H. pylori* regimen.

ANTI-*HELICOBACTER PYLORI* DRUGS

H. pylori is a gram negative bacillus uniquely adapted to survival in the hostile environment of stomach. It attaches to the surface epithelium beneath the mucus, has high urease activity—produces ammonia which maintains a neutral microenvironment around the bacteria, and promotes back diffusion of H^+ ions. It has been found as a commensal in 20–70% normal individuals, and is now accepted as an important contributor to the causation of chronic gastritis, dyspepsia, peptic ulcer, gastric lymphoma and gastric carcinoma. *H. pylori* infection starts with a neutrophilic gastritis lasting 7–10 days which is usually asymptomatic. Once established, *H. pylori* generally persists for the life of the host. Up to 90% patients of duodenal and gastric ulcer have tested positive for *H. pylori*.

Eradication of *H. pylori* concurrently with H_2 blocker/PPI therapy of peptic ulcer has been associated with faster ulcer healing and largely prevents ulcer relapse. All *H. pylori* positive ulcer patients should receive *H. pylori* eradication therapy. In the absence of *H. pylori* testing, all cases with failed conventional ulcer therapy and relapse cases must be given the benefit of *H. pylori* eradication.

Antimicrobials that are used clinically against *H. pylori* are: amoxicillin, clarithromycin, tetracycline and metronidazole/tinidazole. However, any single antibiotic is ineffective. Resistance develops rapidly, especially to metronidazole/tinidazole and clarithromycin, but amoxicillin resistance is infrequent. In tropical countries, metronidazole resistance is more common than clarithromycin resistance. Since bismuth (CBS) is active against *H. pylori* and resistance does not develop to it, combination regimens including bismuth may be used in case of metronidazole and clarithromycin double resistance. Routine use of CBS is precluded by poor patient acceptability. Acid suppression by PPIs/H_2 blockers enhances effectiveness of anti-*H. pylori* antibiotics, and optimum benefits are obtained when gastric pH is kept >5 for at least 16–18 hours per day. This is a higher degree of round-the-clock acid suppression than is needed for duodenal ulcer healing or for reflux esophagitis. Only twice daily PPI dosing can achieve this degree of acid suppression. The PPIs benefit by altering the acid environment for *H. pylori* as well as by direct inhibitory effect. One of the PPIs is an integral component of all anti-*H. pylori* regimens along with 2 (triple drug) or 3 (quadruple drug) antimicrobials.

A number of 3 drug regimens of 1 or 2 weeks are being used. One week regimens are adequate for many patients, but 2 week regimens achieve higher (upto 96%) eradication rates, though compliance is often poor due to side effects. Some commonly used 1 week and 2 weeks triple drug regimens are given in the box.

Anti-*H. pylori* Regimens*

Proton pump inhibitor	*Amoxicillin*	*Clarithromycin*	*Metronidazole/Tinidazole*
	One week-twice daily		
Omeprazole (20 mg) or	1.0 g	500 mg	—
Esomeprazole (20 mg) or	—	250 mg	400 mg/500 mg
Lansoprazole (30 mg) or	1.0 g	—	400 mg/500 mg
Pantoprazole (40 mg) or			
Rabeprazole (20 mg)			
	Two weeks-twice daily		
Omeprazole (20 mg) or	750 mg	—	400 mg/500 mg
Lansoprazole (30 mg) or	—	250 mg	400 mg/500 mg
Pantoprazole (40 mg)	750 mg	500 mg	—

* Adopted from British National Formulary (BNF) Sept. 2010

The US-FDA approved regimen is:

Lansoprazole 30 mg + Amoxicillin 1000 mg + clarithromycin 500 mg, all given twice daily for 2 weeks.

This has achieved 86–92% eradication rate. Better tolerability of regimens which exclude a nitroimidazole favour using amoxicillin + clarithromycin + PPI, particularly in India where metronidazole resistance is more prevalent. However, for the sake of simplicity and economy, the National Formulary of India (NFI, 2010) suggests a model *H. pylori* eradication regimen of 1 week consisting of:

- Omeprazole 40 mg OD + Metronidazole 400 mg TDS + Amoxicillin 500 mg TDS.

For large ulcers (> 10 mm in diameter) or those complicated by bleeding/perforation, the PPI should be continued beyond the 2 weeks-triple drug regimen till complete healing occurs. For patients who have, in the near past, received a nitroimidazole (for other infections) or a macrolide antibiotic, metronidazole or clarithromycin, as the case may be, should be excluded.

Quadruple therapy with CBS 120 mg QID + tetracycline 500 mg QID + metronidazole 400 mg TDS + omeprazole 20 mg BD is advocated for eradication failure cases.

All regimens are complex and expensive, side effects are frequent and compliance is poor. Higher failure rates (20–40%) of *H. pylori* eradication have been reported from India. Also, 5 year recurrence rate of *H. pylori* infection is higher. Three week treatment is being advocated by some. Nevertheless, long-term benefits of anti-*H. pylori* therapy include lowering of ulcer disease prevalence and prevention of gastric carcinoma/lymphoma; but benefits in nonulcer dyspepsia are equivocal.

H. pylori vaccines are under development.

Some available anti-*H. pylori* kits (one kit to be taken daily in 2 doses)

HP-KIT, HELIBACT, OMXITIN: Omeprazole 20 mg 2 cap + Amoxicillin 750 mg 2 tab + Tinidazole 500 mg 2 tab.
PYLOMOX: Lansoprazole 15 mg 2 cap + Amoxicillin 750 mg 2 tab + Tinidazole 500 mg 2 tab.
LANSI KIT: Lansoprazole 30 mg 1 cap + Amoxicillin 750 mg 1 tab + Tinidazole 500 mg 1 tab (one kit twice a day)
PYLOKIT, HELIGO: Lansoprazole 30 mg 2 cap + Clarithromycin 250 mg 2 cap + Tinidazole 500 mg 2 tab.
LANPRO AC: Lansoprazole 30 mg 2 cap + Clarithromycin 250 mg 2 tab + Amoxicillin 750 mg 2 tab.

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

Reflux is a very common problem presenting as 'heart-burn', acid eructation, sensation of stomach contents coming back in the foodpipe, especially after a large meal, aggravated by stooping or lying flat. Some cases have an anatomical defect (hiatus hernia) but majority are only functional, wherein there is relaxation of lower esophageal sphincter (LES) in the absence of swallowing. Repeated reflux of acid gastric contents into lower ⅓rd of esophagus causes esophagitis, erosions, ulcers, pain on swallowing, dysphagia, strictures, and increases the risk of esophageal carcinoma.There may also be extraesophageal complications.

The primary barrier to reflux is the tone of LES which can be altered by several influences:

Inherent tone: of sphincteric smooth muscle.
Hormonal: gastrin increases, progesterone decreases (reflux is common in pregnancy).
Neurogenic: vagus is motor to the sphincter, promotes esophageal peristalsis.
Dietary: fats, alcohol, coffee, chocolates decrease, while protein rich foods increase LES tone.
Drugs: anticholinergics, tricyclic antidepressants, Ca^{2+} channel blockers, nitrates reduce LES tone.
Smoking: relaxes LES.

Delayed gastric emptying and increased intragastric pressure may overcome the LES barrier to reflux. GERD is a wide spectrum of conditions from occasional heartburn (majority of cases) to persistent incapacitating reflux which interferes with sleep and results in esophageal, laryngotracheal and pulmonary complications. Severity of GERD may be graded as:

Stage 1: occasional heartburn (<3 episodes/week), mostly only in relation to a precipitating factor, mild symptoms, no esophageal lesions.

Stage 2: ≥ 3 episodes/week of moderately severe symptoms, nocturnal awakening due to regurgitation, esophagitis present or absent.

Stage 3: Daily/chronic symptoms, disturbed sleep, esophagitis/erosions/stricture/extraesophageal symptoms like laryngitis, hoarseness, dry cough, asthma. Symptoms recur soon after treatment stopped.

Though GERD is primarily a g.i. motility disorder, acidity of gastric contents is the most important aggressive factor in causing symptoms and esophageal lesions. The functional abnormality is persistent; though short-term remissions do occur. Dietary and other lifestyle measures (light early dinner, raising head end of bed, weight reduction and avoidance of precipitating factors) must be taken.

Treatment of GERD is individualized according to severity and stage of the disorder.

The site and mechanism of benefit afforded by different classes of drugs in GERD is depicted in Fig. 46.2.

1. *Proton pump inhibitors (PPIs)* These are the most effective drugs, both for symptomatic relief as well as for healing of esophageal lesions.

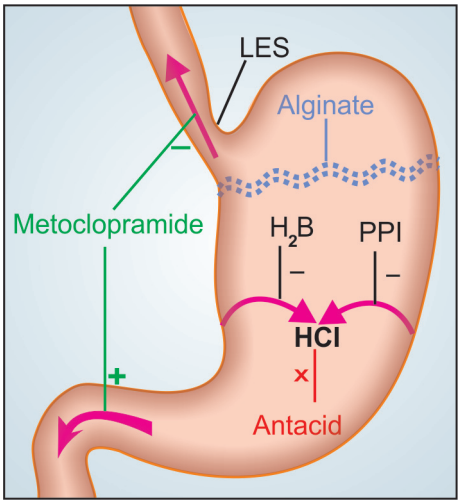


Figure 46.2: Sites and mechanisms of drug action in gastroesophageal reflux disease.
Metoclopramide increases lower esophageal sphincter (LES) tone and promotes gastric emptying. Proton pump inhibitor (PPI) and H_2 blocker (H_2B) inhibit acid secretion, while antacids neutralize it. Alginate floats on gastric contents and prevents contact of esophageal mucosa with gastric acid

Intragastric pH >4 maintained for ~18 hr/day is considered optimal for healing of esophagitis. This level of acid suppression can be consistently achieved only by PPIs. Therefore, PPIs are the drugs of choice for patients with all stages of GERD, particularly stage 2 and 3 cases. Symptom relief is rapid and 80–90% esophageal lesions heal in 4–8 weeks. Dose titration is needed according to response in individual patients. Some patients, especially stage 2 and 3 cases, need twice daily dosing. Prolonged (often indefinite) therapy is required in chronic cases because symptoms recur a few days after drug stoppage. PPIs have no effect on LES tone.

2. *H_2 blockers* They reduce acidity of gastric contents and have no effect on LES tone. H_2 blockers cause less complete acid suppression than PPIs, *viz* elevate intragastric pH to >4 for less than 8 hours in 24 hours with the conventional doses given twice daily. Adequate symptom relief is obtained only in mild cases; healing of esophagitis may occur in 50–70% patients. H_2 antagonists are indicated in stage-1 cases, or as alternative to PPIs in stage 2 or 3 cases. The daily dose should be divided into 2–3 portions for better response.

3. *Antacids* Their use in GERD is limited to occasional or intercurrent relief of heartburn because they act within few minutes. Antacids are no longer employed for healing of esophagitis, which they are incapable of.

4. *Sodium alginate* It forms a thick frothy layer which floats on the gastric contents like a raft may prevent contact of acid with esophageal mucosa. It has no effect on LES tone. Combination of alginate with antacids may be used in place of antacids alone, but real benefit is marginal.
REFLUX LIQUID: Sod. alginate 200 mg + alum. hydrox. gel 300 mg + mag. trisilicate 125 mg/10 ml susp; REFLUX FORTE Aginic acid 20 mg + sod. bicarb. 70 mg + alum. hydrox. 300 mg tab; GAVISCON Alginic acid 500 mg + mag. trisilicate 25 mg + alum. hydrox. gel 100 mg + sod. bicarb. 170 mg tab.

5. *Prokinetic drugs* Metoclopramide, cisapride and other prokinetic drugs may relieve regurgitation and heartburn by increasing LES tone, improving esophageal clearance and facilitating gastric emptying, but do not affect gastric acidity or promote healing of esophagitis.

Symptom control afforded by prokinetic drugs is much inferior to that by PPIs/H_2 blockers. Their use in GERD has declined. Prokinetic drugs are often coprescribed with PPI/H_2 blocker therapy, but whether this improves outcome is not clear.

☞ PROBLEM DIRECTED STUDY

46.1 A 45-year-old male patient presents with dyspepsia and dull epigastric pain which has been worsening gradually over the last one month. The pain is partly relieved by food, but becomes worse after 2 hours or so. Heart burn and pain which awakens him is often felt at night. Epigastric tenderness is detected on palpation. Upper gastrointestinal endoscopy reveals an ulcer measuring 12 mm X 18 mm in the 1st part of duodenum. His medical records show that he suffered similar episode of pain about 9 months ago. No endoscopy was done, but he was treated with omeprazole 20 mg OD for 6 weeks. Subsequently, nearly 3 months back, he suffered from loose motions and abdominal pain which was treated with a 5 day course of metronidazole + norfloxacin. Facility for *H. pylori* testing is not available. There is no history of NSAID use.

(a) What would be the most appropriate treatment option for him to achieve fast symptom relief, ulcer healing and prevention of further recurrences?

(see Appendix-1 for solution)

Chapter 47 Antiemetic, Prokinetic and Digestant Drugs

Emesis Vomiting occurs due to stimulation of the *emetic (vomiting) centre* situated in the medulla oblongata. Multiple pathways can elicit vomiting (Fig. 47.1). The *chemoreceptor trigger zone (CTZ)* located in the area postrema and the *nucleus tractus solitarius (NTS)* are the most important relay areas for afferent impulses arising in the g.i.t, throat and other viscera. The CTZ is also accessible to blood-borne drugs, mediators, hormones, toxins, etc. because it is unprotected by the blood-brain barrier. Cytotoxic drugs, radiation and other g.i. irritants release 5-HT from enterochromaffin cells → acts on 5-HT_3 receptors present on extrinsic primary afferent neurones (PAN) of the enteric nervous system (ENS). These neurones connect with vagal and spinal visceral afferents to send impulses to NTS and CTZ. Released in large quantity, 5-HT may also spill into circulation and reach CTZ *via* the vascular route. 5-HT may as well be released from platelets by inflammatory mediators. However, 5-HT is not the only mediator of such signals: many peptides, e.g. substance P and other messengers are also involved.

The CTZ and NTS express a variety of receptors, e.g. histamine H_1, dopamine D2, serotonin 5-HT_3, cholinergic M, neurokinin NK_1 (activated by substance P), cannabinoid CB_1 and opioid μ receptors through which the emetic signals are relayed and which could be targets of antiemetic drug action.

The vestibular apparatus generates impulses when body is rotated or equilibrium is disturbed or when ototoxic drugs act. These impulses reach the vomiting centre mainly relayed from the cerebellum and utilize muscarinic as well as H_1 receptors. Various unpleasant sensory stimuli such as bad odour, ghastly sight, severe pain as well as fear, recall of an obnoxious event, anticipation of an emetic stimulus (repeat dose of cisplatin) cause nausea and vomiting through higher centres.

Nausea is accompanied by reduced gastric tone and peristalsis. In the emetic response fundus and body of stomach, esophageal sphincter and esophagus relax, glottis closes, while duodenum and pyloric stomach contract in a retrograde manner. Rhythmic contractions of diaphragm and abdominal muscles then compress the stomach and evacuate its contents *via* the mouth. Conditions that inhibit gastric emptying predispose to vomiting.

EMETICS

These are drugs used to evoke vomiting.

1. *Act on CTZ* : Apomorphine
2. *Act reflexly and on CTZ* : Ipecacuanha

Vomiting needs to be induced only when an undesirable substance (poison) has been ingested. Powdered mustard suspension or strong salts solution may be used in emergency. They act reflexly by irritating the stomach.

Apomorphine It is a semisynthetic derivative of morphine; acts as a dopaminergic agonist on the CTZ. Injected i.m./s.c. in a dose of 6 mg, it promptly (within 5 min) induces vomiting. It should not be used if respiration is depressed, because it has inherent respiratory and CNS depressant actions. Oral use of apomorphine is not recommended because the emetic dose is larger, slow to act and rather inconsistent in action.

Apomorphine has a therapeutic effect in parkinsonism, but is not used due to side effects.

Ipecacuanha The dried root of *Cephaelis ipecacuanha* contains emetine and is used as *syrup ipecac* (15–30 ml in adults, 10–15 ml in children, 5 ml in infants) for inducing vomiting. It is less dependable than parenteral apomorphine and takes 15 min or more for the effect, but is safer; has been used as a household remedy. It acts by irritating gastric mucosa as well as through CTZ.

All emetics are contraindicated in:

(a) Corrosive (acid, alkali) poisoning: risk of perforation and further injury to esophageal mucosa.

(b) CNS stimulant drug poisoning: convulsions may be precipitated.

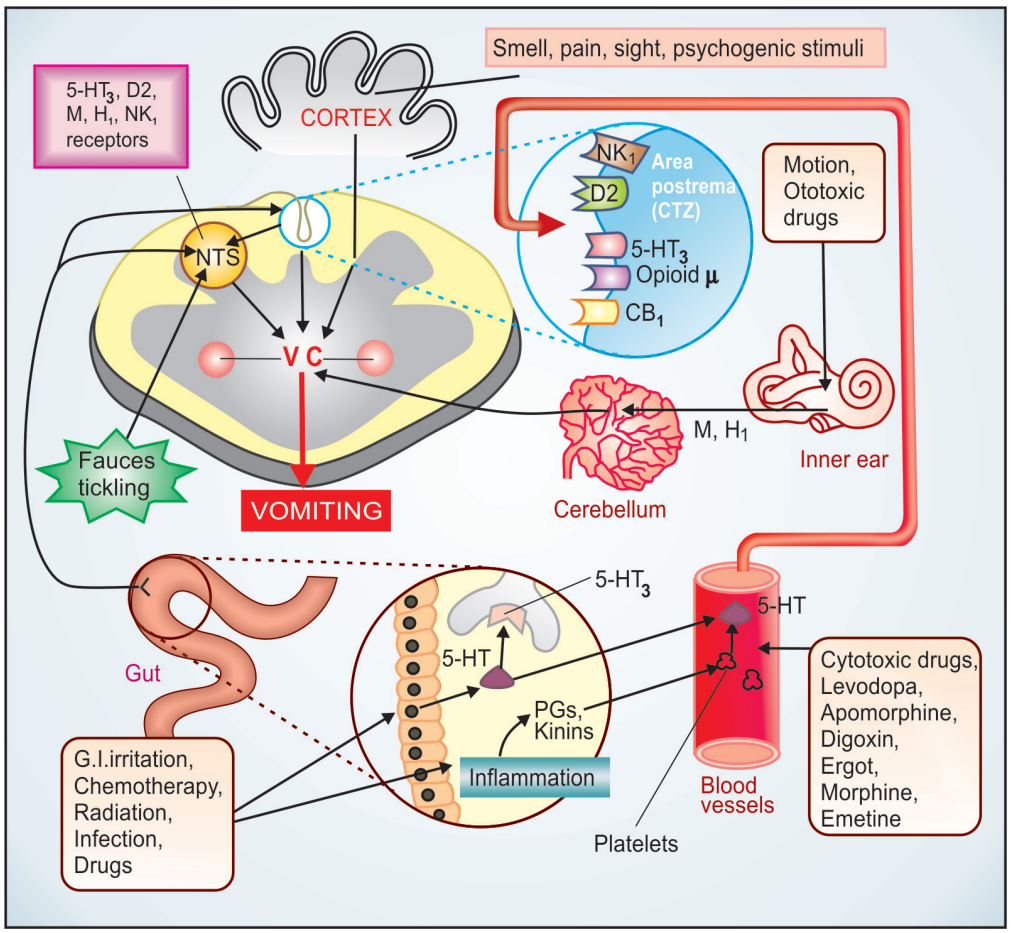


Fig. 47.1: Major central and visceral structures involved in emesis and the neurohumoral receptors mediating the emetic response.
NTS–Nucleus tractus solitarius; VC–Vomiting centre; CTZ—Chemoreceptor trigger zone; 5-HT_3–5-HT_3 receptor; H_1–Histamine H_1 receptor; D2–Dopamine 2 receptor; M–Muscarinic receptor; NK_1–Neurokinin$_1$ receptor; CB_1–Cannabinoid 1 receptor

(c) Kerosine (petroleum) poisoning: chances of aspiration of the liquid (due to low viscosity) and chemical pneumonia are high.
(d) Unconscious patient: may aspirate the vomitus, because laryngeal reflex is likely to be impaired.
(e) Morphine or phenothiazine poisoning: emetics may fail to act.

ANTIEMETICS

These are drugs used to prevent or suppress vomiting.

CLASSIFICATION

1. *Anticholinergics*	Hyoscine, Dicyclomine
2. *H_1 antihistaminics*	Promethazine, Diphenhydramine, Dimenhydrinate, Doxylamine, Meclozine (Meclizine), Cinnarizine.
3. *Neuroleptics (D2 blockers)*	Chlorpromazine, Trifluprazine, Prochlorperazine, Haloperidol, etc.

4. *Prokinetic drugs*	Metoclopramide, Domperidone, Cisapride, Mosapride, Itopride
5. *5-HT$_3$ antagonists*	Ondansetron, Granisetron, Palonosetron, Ramosetron
6. *NK$_1$ receptor antagonists*	Aprepitant, Fosaprepitant
7. *Adjuvant antiemetics*	Dexamethasone, Benzodiazepines, Dronabinol, Nabilone

ANTICHOLINERGICS (*See* Ch. 8)

Hyoscine (0.2–0.4 mg oral, i.m.) is the most effective drug for motion sickness. However, it has a brief duration of action; produces sedation, dry mouth and other anticholinergic side effects; suitable only for short brisk journies. Antiemetic action is exerted probably by blocking conduction of nerve impulses across a cholinergic link in the pathway leading from the vestibular apparatus to the vomiting centre and has poor efficacy in vomiting of other etiologies.

A transdermal patch containing 1.5 mg of hyoscine, to be delivered over 3 days has been developed. Applied behind the pinna, it suppresses motion sickness while producing only mild side effects.

Dicyclomine (10–20 mg oral) has been used for prophylaxis of motion sickness and for morning sickness. It has been cleared of teratogenic potential.

H$_1$ ANTIHISTAMINICS (*See* Ch. 11)

Some antihistaminics are antiemetic. They are useful mainly in motion sickness and to a lesser extent in morning sickness, postoperative and some other forms of vomiting. Their antiemetic effect appears to be based on anticholinergic, antihistaminic, weak antidopaminergic and sedative properties.

Promethazine, diphenhydramine, dimenhydrinate These drugs afford protection of motion sickness for 4–6 hours, but produce sedation and dryness of mouth. By their central anticholinergic action they block the extrapyramidal side effects of metoclopramide while supplementing its antiemetic action. Promethazine is a phenothiazine; has weak central antidopaminergic action as well. Their combination has been used in chemotherapy induced nausea and vomiting (CINV).

Promethazine theoclate (AVOMINE 25 mg tab.) This salt of promethazine has been specially promoted as an antiemetic, but the action does not appear to be significantly different from promethazine HCl.

Doxylamine It is a sedative H$_1$ antihistaminic with prominent anticholinergic activity. Marketed in combination with pyridoxine, it is specifically promoted in India for 'morning sickness' (vomiting of early pregnancy), although such use is not made in UK and many other countries.

After over 2 decades of worldwide use of a combination product of doxylamine for morning sickness, some reports of foetal malformation appeared and the product was withdrawn in 1981. Subsequent studies have both supported and refuted its teratogenic potential. Though the US-FDA and CSM in UK found no credible evidence of increase in birth defects, they did not rule out the possibility. The product remained suspended in these countries, probably to avoid litigation, but not due to safety or efficacy concerns. Recently, the American College of Obstetricians and Gynaecologists have recommended a combination of doxylamine + pyridoxine as first line treatment of morning sickness. However, it is still not used in U.K.

Oral absorption of doxylamine is slow, and its t½ is 10 hr. The side effects are drowsiness, dry mouth, vertigo and abdominal upset.

Dose: 10–20 mg at bed time; if needed additional doses may be given in morning and afternoon.

DOXINATE, GRAVIDOX, VOMNEX, NOSIC 10 mg with pyridoxine 10 mg tab.

Meclozine (meclizine) It is less sedative and longer-acting; protects against sea sickness for nearly 24 hours.

DILIGAN: meclozine 12.5 mg + nicotinic acid 50 mg tab; PREGNIDOXIN: meclozine 25 mg + caffeine 20 mg tab.

Cinnarizine It is an antivertigo drug having antimotion sickness property. It probably acts by inhibiting influx of Ca^{2+} from endolymph into the vestibular sensory cells which mediates labyrinthine reflexes.

Motion sickness Antiemetics with anticholinergic-antihistaminic property are the first choice drugs for *motion sickness*. Antidopaminergic and anti-HT_3 drugs are less effective. All antimotion sickness drugs act better when taken ½–1 hour before commencing journey. Once sickness has started, it is more difficult to control; higher doses/parenteral administration may be needed.

Morning sickness The antihistaminics are suspected to have teratogenic potential, but there is no conclusive proof. Nevertheless, it is better to avoid them for morning sickness. Most cases of morning sickness can be managed by reassurance and dietary adjustment. If an antiemetic has to be used, dicyclomine, promethazine, prochlorperazine or metoclopramide may be prescribed in low doses.

NEUROLEPTICS (*see* Ch. 32)

The older neuroleptics (phenothiazines, haloperidol) are potent antiemetics; act by blocking D2 receptors in the CTZ; antagonize apomorphine induced vomiting and have additional antimuscarinic as well as H_1 antihistaminic property. They have broad spectrum antiemetic action effective in:

(a) Drug induced and postoperative nausea and vomiting (PONV).
(b) Disease induced vomiting: gastroenteritis, uraemia, liver disease, migraine, etc.
(c) Malignancy associated and cancer chemotherapy (mildly emetogenic) induced vomiting.
(d) Radiation sickness vomiting (less effective).
(e) Morning sickness: should not be used except in hyperemesis gravidarum.

Neuroleptics are less effective in motion sickness: the vestibular pathway does not involve dopaminergic link.

Most of these drugs produce significant degree of sedation. Acute muscle dystonia may occur after a single dose, especially in children and girls. The antiemetic dose is generally much lower than antipsychotic doses. These agents should not be administered until the cause of vomiting has been diagnosed; otherwise specific treatment of conditions like intestinal obstruction, appendicitis, etc. may be delayed due to symptom relief.

Prochlorperazine This D2 blocking phenothiazine is a labyrinthine suppressant, has selective antivertigo and antiemetic actions. It is highly effective when given by injection in vertigo associated vomiting, and to some extent in CINV. Prochlorperazine is used as an antiemetic, but not as antipsychotic. Muscle dystonia and other extrapyramidal side effects are the most important limiting features.

Dose: 5–10 mg BD/TDS oral, 12.5–25 mg by deep i.m. injection.

STEMETIL 5 mg tabs., 12.5 mg/ml inj, 1 ml amp, VOMTIL 5 mg tab.

PROKINETIC DRUGS

These are drugs which promote gastrointestinal transit and speed gastric emptying by enhancing coordinated propulsive motility. This excludes traditional cholinomimetics and anti-ChEs which produce tonic and largely uncoordinated contraction.

Metoclopramide

Metoclopramide, a substituted benzamide, is chemically related to procainamide, but has no pharmacological similarity with it. Introduced in early 1970s as a 'gastric hurrying' agent, it is a commonly used antiemetic.

Actions

GIT: Metoclopramide has more prominent effect on upper g.i.t.; increases gastric peristalsis while relaxing the pylorus and the first part of duodenum → speeds gastric emptying, especially if it was slow. This action is independent of vagal innervation, but is stronger when vagus is intact. Lower esophageal sphincter (LES) tone is increased and gastroesophageal reflux is opposed. It also increases intestinal peristalsis to some extent, but has no significant action on colonic motility and gastric secretion.

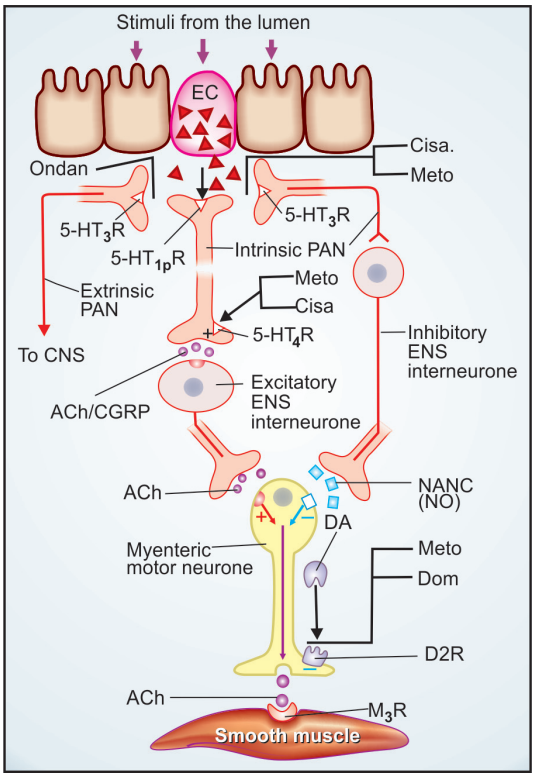


Fig. 47.2: Schematic depiction of seronergic (5-HT) regulation of peristaltic reflex, and sites of action of prokinetic drugs.

Distention and other luminal stimuli trigger 5-HT release from the enterochromaffin cells (EC) located in the enteric mucosa. This stimulates intrinsic and extrinsic primary afferent neurones (PAN) of the enteric nervous system (ENS) through peripheral variant of 5-HT_1 receptor (5-HT_{1P}R) and 5-HT_3 receptor (5-HT_3R). The extrinsic PAN convey impulses to the CNS *via* vagus and dorsal root ganglia and participate in the causation of vomiting when stimulation is strong. Ondansetron (Ondan) acts partly by blocking activation of extrinsic PAN through 5-HT_3R.

The intrinsic PAN interact with excitatory and inhibitory interneurones of the ENS to mediate both contraction (of proximal gut muscles) and relaxation (of distal gut muscles) to coordinate the peristaltic reflex, respectively through release of acetylcholine (ACh)/calcitonin gene related peptide (CGRP) and nonadrenergic–noncholinergic (NANC) transmitter, which mainly is nitric oxide (NO). Cisapride (Cisa.) and metoclopramide (Meto.) activate the pre-junctional 5-HT_4 receptors (5-HT_4R) located on the terminals of the intrinsic PAN and promote ACh/CGRP release, and thereby the contractile activity. The weak 5-HT_3 blocking action of Cisa. and Meto., in addition, reduces activity in the inhibitory interneurone (minor action).

Domperidone (Dom) and Meto also block the action of dopamine (DA) on prejunctional D2 receptor (D2R) which normally inhibits ACh release from the myenteric motor neurone, and thus augment smooth muscle contraction elicited through muscarinic M_3 receptor (M_3R)

CNS Metoclopramide is an effective antiemetic; acting on the CTZ, blocks apomorphine induced vomiting. The gastrokinetic action may contribute to the antiemetic effect. However, it has no chlorpromazine (CPZ) like antipsychotic property, though it does share the extrapyramidal and prolactin secretion augmenting action of CPZ.

Mechanism of action: Metoclopramide acts through both dopaminergic and serotonergic receptors (*see* Fig. 47.2)

(a) *D2 antagonism* Dopamine (acting through D2 receptors) is an inhibitory transmitter in the g.i.t.— normally acts to delay gastric emptying when food is present in stomach. It also appears to cause gastric dilatation and LES relaxation attending nausea and vomiting. Metoclopramide blocks D2 receptors and has an opposite effect—hastening gastric emptying and enhancing LES tone by augmenting ACh release. However, clinically this action is secondary to that exerted through $5HT_4$ receptors.

The central antidopaminergic (D2) action of metoclopramide on CTZ is clearly responsible for its antiemetic property. Other manifestations of D2 blockade are antagonism of apomorphine induced vomiting, CPZ like extrapyramidal effects and hyperprolactinaemia.

(b) *5-HT_4 agonism* Metoclopramide acts in the g.i.t. to enhance ACh release from myenteric motor neurones. This results from 5-HT_4 receptor activation on primary afferent neurones (PAN) of the ENS *via* excitatory interneurones (Fig. 47.2). The *gastric hurrying* and *LES tonic* effects are mainly due to this action which is synergised by bethanechol and attenuated by atropine.

(c) *5-HT$_3$ antagonism* At high concentrations metoclopramide can block 5-HT$_3$ receptors present on inhibitory myenteric interneurones and in NTS/CTZ. The peripheral action can augment ACh release in the gut, but appears to be minor. The central anti 5-HT$_3$ action appears to be significant only when large doses are used to control CINV.

Pharmacokinetics Metoclopramide is rapidly absorbed orally, enters brain, crosses placenta and is secreted in milk. It is partly conjugated in liver and excreted in urine within 24 hours; t½ is 3–6 hours. Orally it acts in ½–1 hr, but within 10 min after i.m. and 2 min after i.v. injection. Action lasts for 4–6 hours.

Interactions It hastens the absorption of many drugs, e.g. aspirin, diazepam, etc. by facilitating gastric emptying. The extent of absorption of digoxin is reduced by allowing less time for it. Bioavailability of cimetidine is also reduced.

By blocking DA receptors in basal ganglia, it abolishes the therapeutic effect of levodopa.

Adverse effects Metoclopramide is generally well tolerated.

Sedation, dizziness, loose stools, muscle dystonias (especially in children) are the main side effects. Long-term use can cause parkinsonism, galactorrhoea and gynaecomastia, but it should not be used to augment lactation. No harmful effects are known when used during pregnancy. Though the amount secreted in milk is small, but suckling infant may develop loose motions, dystonia, myoclonus.

Dose: 10 mg (children 0.2–0.5 mg/kg) TDS oral or i.m. For CINV 0.3–2 mg/kg slow i.v./i.m.

PERINORM, MAXERON, REGLAN, SIGMET, 10 mg tab; 5 mg/5 ml syr; 10 mg/2 ml inj.; 50 mg/10 ml inj.

Uses

1. *Antiemetic:* Metoclopramide is an effective and popular drug for many types of vomiting—postoperative, drug induced, disease associated (especially migraine), radiation sickness, etc, but is less effective in motion sickness. Though ondansetron is preferred, metoclopramide continues to be used for prophylaxis and treatment of vomiting induced by emetogenic anticancer drugs (cisplatin, etc.). A higher dose (1–2 mg/kg i.v.) is often needed, but is effective when phenothiazines and antihistamines do not work. Promethazine, diphenhydramine, diazepam or lorazepam injected i.v. along with metoclopramide supplement its antiemetic action and reduce the attending dystonic reactions. Dexamethasone i.v. also augments the efficacy of metoclopramide.

   Though no teratogenic effects have been reported, metoclopramide should be used for morning sickness only when not controlled by other measures.

2. *Gastrokinetic:* To accelerate gastric emptying:
   (a) When emergency general anaesthesia has to be given and the patient has taken food less than 4 hours before.
   (b) To relieve postvagotomy or diabetic gastroparesis associated gastric stasis.
   (c) To facilitate duodenal intubation.

   Clinical efficacy is moderate.

3. *Dyspepsia* and other functional g.i. disorders. Metoclopramide may succeed in stopping persistent hiccups.

4. *Gastroesophageal reflux disease (GERD)* Metoclopramide may benefit milder cases of GERD, but is much less effective than PPIs/H$_2$ blockers. It does not aid healing of esophagitis, but may be used as adjuvant to acid suppressive therapy. Any additional benefit is uncertain.

Domperidone It is a D2 receptor antagonist, chemically related to haloperidol, but pharmacologically related to metoclopramide. The antiemetic and prokinetic actions have a lower ceiling. Unlike metoclopramide, its prokinetic action is not attenuated by atropine and is based only on D2 receptor blockade in upper g.i.t. Domperidone crosses blood-brain barrier poorly. Accordingly, extrapyramidal side effects are rare, but hyperprolactinaemia can occur. The antiemetic action is exerted mainly through CTZ which is not protected by blood-brain barrier. Because of poor entry into CNS, it does not block the therapeutic effect of

levodopa and bromocriptine in parkinsonism, but counteracts their dose-limiting emetic action.

Domperidone is absorbed orally, but bioavailability is only ~15% due to first pass metabolism. It is completely biotransformed and metabolites are excreted in urine. Plasma t½ is 7.5 hr.

Side effects Are much less than with metoclopramide. Dry mouth, loose stools, headache, rashes, galactorrhoea are generally mild. Cardiac arrhythmias have developed on rapid i.v. injection.

Its indications are similar to that of metoclopramide, but it is a less efficacious gastrokinetic and not useful against highly emetogenic chemotherapy.

Dose: 10–40 mg (Children 0.3–0.6 mg/kg) TDS.

DOMSTAL, DOMPERON, NORMETIC 10 mg tab, 1 mg/ml susp, MOTINORM 10 mg tab, 10 mg/ml drops.

Cisapride This benzamide derivative is a prokinetic with little antiemetic property, because it lacks D2 receptor antagonism. Effects of cisapride on gastric motility resemble metoclopramide, i.e. gastric emptying is accelerated, LES tone is improved and esophageal peristalsis is augmented. It restores and facilitates motility throughout the g.i.t., including colon (metoclopramide/domperidone do not accelerate colonic transit). The prokinetic action is exerted mainly through 5-HT_4 agonism which promotes ACh release from myenteric neurones, aided by weak 5-HT_3 antagonism which suppresses inhibitory transmission in myenteric plexus. Enteric neuronal activation *via* 5-HT_4 receptor also promotes cAMP-dependent Cl^- secretion in the colon, increasing water content of stools. Thus, cisapride often produces loose stools by enhancing colonic motility and secretion. It is devoid of action on CTZ, and does not produce extrapyramidal symptoms or hyperprolactinaemia.

Cisapride is primarily inactivated by CYP3A4 with a t½ of ~ 10 hours.

Safety of cisapride was challenged by reports of serious ventricular arrhythmias and death, mainly among patients who took CYP3A4 inhibitors like azole antifungals, macrolide antibiotics, antidepressants, HIV protease inhibitors, etc. concurrently. At high concentrations, cisapride blocks delayed rectifying K^+ channels in heart—prolongs Q-Tc interval and predisposes to *torsades de pointes*/ventricular fibrillation. Following such reports, cisapride was suspended from marketing in most countries several years back, but was available in India till it was banned in March 2011. In USA it is made available only for limited investigational use.

Mosapride A subsequently introduced congener of cisapride with similar gastrokinetic and LES tonic action due to 5-HT_4 agonistic (major) and 5-HT_3 antagonistic (minor) action in the myenteric plexus. Like cisapride, it has no clinically useful antiemetic action and does not produce extrapyramidal or hyperprolactinaemic side effects because of absence of D2 blocking property. Side effects are diarrhoea, abdominal pain, headache, dizziness and insomnia.

Preclinical studies showed that it may not have the potential to prolong Q-T interval and carry risk of arrhythmias. Therefore, it was introduced as a safe prokinetic. However, after general use some reports of Q-T prolongation and arrhythmias, including *torsades de pointes*, among recipients have appeared. Like cisapride, its plasma concentration is elevated by erythromycin and other CYP3A4 inhibitors increasing the risk of Q-T prolongation. Though, it has not been banned, it may not be as safe as considered earlier. Indications of mosapride are—nonulcer dyspepsia, diabetic gastroparesis, GERD (as adjuvant to H_2 blockers/PPIs), and some cases of chronic constipation. However, efficacy is not impressive.

Dose: 5 mg (elderly 2.5 mg) TDS.

KINETIX 5 mg tab, MOZA, MOZASEF, MOPRIDE 2.5 mg, 5 mg tabs; MOZA MPS: 5 mg + methylpolysiloxane 125 mg tab.

Itopride Another substituted benzamide produced in Japan and marketed in few countries, but not in UK or USA, as a prokinetic drug. It has D2 antidopaminergic and anti-ChE (ACh potentiating) activity, but very low affinity for 5-HT_4 receptor. Thus, the basis of prokinetic action may be different from that of cisapride and mosapride. Animal studies showed that it lacked Q-T prolonging potential. In healthy volunteers it was found unlikely to cause cardiac arrhythmias. This may be due to its low affinity for cardiac 5-HT_4 receptors which have been implicated in the adverse cardiac effects of cisapride.

Itopride is metabolized mainly by flavin monooxygenases and not by CYP450 isoenzymes. Thus, unlike cisapride and mosapride, it is devoid of drug interactions with CYP3A4 inhibitors (macrolides, azoles, etc.) resulting in cardiac arrhythmias. As such, itopride may be a safer prokinetic drug. Side effects of itopride are

diarrhoea, abdominal pain, headache; galactorrhoea and gynaecomastia occur infrequently. No extrapyramidal effects are reported.

Dose: 50 mg TDS before meals.

GANATON, ITOFLUX, ITOKINE, ITOPRID 50 mg tab.

5-HT_3 ANTAGONISTS

Ondansetron It is the prototype of a distinct class of antiemetic drugs developed to control cancer chemotherapy/radiotherapy induced vomiting, and later found to be highly effective in PONV and disease/drug associated vomiting as well. It blocks the depolarizing action of 5-HT exerted through 5-HT_3 receptors on vagal afferents in the g.i.t. as well as in NTS and CTZ. Cytotoxic drugs/radiation produce nausea and vomiting by causing cellular damage → release of mediators including 5-HT from intestinal mucosa → activation of vagal afferents in the gut → emetogenic impulses to the NTS and CTZ. Ondansetron blocks emetogenic impulses both at their peripheral origin and their central relay. It does not block dopamine receptors. Apomorphine or motion sickness induced vomiting is not suppressed. A weak gastrokinetic action due to 5-HT_3 blockade has been detected, but this is clinically insignificant. A minor 5-HT_4 antagonistic action has also been shown, but seems to have no clinical relevance.

Pharmacokinetics: Oral bioavailability of ondansetron is 60–70% due to first pass metabolism. It is hydroxylated by CYP1A2, 2D6 and 3A, followed by glucuronide and sulfate conjugation. No clinically significant drug interactions have been noted. It is eliminated in urine and faeces, mostly as metabolites; t½ is 3–5 hrs, and duration of action is 8–12 hrs (longer at higher doses).

Dose and efficacy: For cisplatin and other highly emetogenic drugs—8 mg i.v. by slow injection over 15 min ½ hr before chemotherapeutic infusion, followed by 2 similar doses 4 hour apart. Single 24 mg i.v. dose on first day has also been used. To prevent delayed emesis 8 mg oral is given twice a day for 3–5 days. For PONV 4–8 mg i.v. given before induction is repeated 8 hourly. For less emetogenic drugs and for radiotherapy, an oral dose of 8 mg is given 1–2 hr prior to the procedure and repeated twice 8 hrly. It is effective in 60–80% cases; similar to or better than high doses of metoclopramide, but does not cause dystonias or sedation like the latter. However, many patients obtain only partial relief, and adjuvant drugs are now mostly used along with it to improve chances of complete response.

EMESET, VOMIZ, OSETRON, EMSETRON 4,8 mg tabs, 2 mg/ml inj in 2 ml and 4 ml amps. ONDY, EMESET 2 mg/5 ml syrup.

In patients who do not obtain optimum protection by ondansetron alone, addition of dexamethasone, promethazine/diazepam or both dexamethasone + NK_1 antagonist aprepitant enhances antiemetic efficacy. Adjuvant drugs are more often required for delayed phase vomiting that occurs on the second to fifth day of cisplatin therapy, in some, but not all patients.

Ondansetron alone is less effective in delayed vomiting than in acute vomiting which occurs within 24 hours of cisplatin dose in all patients.

Other types of vomiting: Efficacy of 5-HT_3 antagonists in prevention and treatment of PONV is now well established. Since this vomiting is multifactorial in origin, many other classes of antiemetic drugs are also protective. In comparative trials, superiority of ondansetron in terms of efficacy as well as lack of side effects and drug interactions has been demonstrated over metoclopramide and phenothiazines. Administered before surgery ondansetron (4–8 mg i.v.) repeated after 4 hours has become the first choice antiemetic at many centres.

Vomiting occurring as side effect of drugs or due to drug overdosage, g.i. disorders, uraemia and neurological injuries is also suppressed. However, efficacy in motion sickness is poor. Due to lack of safety data, ondansetron (also other 5-HT_3 antagonists) should be used during pregnancy only when unavoidable, such as in hyperemesis gravidarum.

Side effects: Ondansetron is generally well tolerated: the only common side effect is headache and dizziness. Mild constipation and abdominal discomfort occur in few patients. Hypotension, bradycardia, chest pain and allergic reactions are reported, especially after i.v. injection.

Granisetron It is 10 times more potent than ondansetron and probably more effective during the repeat cycle of chemotherapy. The weak 5-HT_4 blockade seen in ondansetron has not been detected in granisetron. Its plasma t½ is longer (8–12 hrs) and it needs to be given only twice on the day of chemotherapy. Side effect profile is similar to ondansetron.

Dose: 1–3 mg diluted in 20–50 ml saline and infused i.v. over 5 min before chemotherapy, repeated after 12 hr. For less emetogenic regimen 2 mg oral 1 hr before chemotherapy or 1 mg before and 1 mg 12 hr after it. For PONV 1 mg diluted in 5 ml and injected i.v. over 30 sec before starting anaesthesia or 1 mg orally every 12 hours.

GRANICIP, GRANISET 1 mg, 2 mg tabs; 1 mg/ml inj. (1, 3 ml amps).

Palonosetron It is longest acting 5-HT_3 blocker having the highest affinity for the 5-HT_3 receptor. Efficacy against acute phase CINV is comparable to ondansetron, but it is more effective in suppressing delayed vomiting occurring between 2nd to 5th days, probably because of its longer duration of action (elimination t½ is 40 hours). It is the only drug of its class approved by US-FDA for delayed CINV. Antiemetic efficacy is maintained during repeat cycles of chemotherapy.

Palonosetron is metabolized in liver as well as in kidney, mainly by CYP2D6, but also by CYP3A4 and CYP1A2. Side effects are headache, fatigue, dizziness, abdominal pain. Additive Q-T prolongation can occur when given with moxifloxacin, erythromycin, anti-psychotics, antidepressants, etc. Rapid i.v. injection has caused blurring of vision.

Dose: 250 µg by slow i.v. injection 30 min before chemotherapy. Do not repeat before 7 days.

For PONV 75 µg i.v. as a single injection just before induction.

PALONOX 0.25 mg/ml inj, PALZEN 0.25 mg/50 ml inj.

Ramosetron It is a potent 5-HT_3 antagonist developed in Japan and marketed only in few Southeast Asian countries. The general properties are similar to ondansetron. It is used for CINV in a dose of 0.3 mg injected i.v. before chemotherapy, and repeated once daily. For low emetogenic chemotherapy, it can be given orally in a dose of 0.1 mg once daily. Ramosetron 0.3 mg i.v. is as effective as ondansetron 8 mg i.v. in preventing PONV. Since it has shown potential to normalize disturbed colonic function, ramosetron is also indicated for diarrhoea-predominant irritable bowel syndrome.

NOZIA 0.1 mg tab, 0.3 mg in 2 ml amp.

NK_1 RECEPTOR ANTAGONISTS

Realizing that activation of neurokinin (NK_1) receptor in CTZ and NTS by substance P released due to emetogenic chemotherapy and other stimuli plays a role in the causation of vomiting, selective antagonists of this receptor have been produced, and are being used as antiemetic.

Aprepitant It is a recently introduced selective, high affinity NK_1 receptor antagonist that blocks the emetic action of substance P, with little effect on 5 HT_3 and D2 or other receptors. Gastrointestinal motility is not affected. Oral aprepitant (125 mg + 80 mg + 80 mg over 3 days) combined with standard i.v. ondansetron + dexamethasone regimen significantly enhanced the antiemetic efficacy against high emetogenic cisplatin based chemotherapy. Greater additional protection was afforded against delayed vomiting than against acute vomiting. It was particularly useful in patients undergoing multiple cycles of chemotherapy. Adjuvant benefit of aprepitant has also been demonstrated in cyclophosphamide based moderately emetogenic chemotherapy. A single (40 mg) oral dose of aprepitant has been found equally effective as ondansetron in PONV as well.

Aprepitant is well absorbed orally. It penetrates blood-brain barrier and is metabolized in liver, mainly by CYP3A4. Metabolites are eliminated *via* bile in faeces and in urine; t½ is 9–13 hours, but clearance is reduced with increase in dose. Inducers and inhibitors of CYP3A4 are likely to interact with aprepitant. Dose of dexamethasone and warfarin needs to be reduced. Aprepitant should not be given with Q-T interval prolonging drugs like cisapride.

Tolerability of aprepitant is good. Adverse effects of combined regimen were similar to those produced by ondansetron + dexamethasone without aprepitant. Symptoms attributed to aprepitant are weakness, fatigue, flatulence and rearely rise in liver enzymes.

Dose: For CINV—125 mg before chemotherapy + 80 mg each on 2nd and 3rd day (all oral) along with i.v. ondansetron + dexamethasone.
For PONV—40 mg (single dose) oral before abdominal or other surgery.
APRECAP, APRESET, APRELIFE, EMPOV 125 mg (one cap) + 80 mg (2 caps) kit.

Fosaprepitant It is a parenterally administered prodrug of aprepitant.

ADJUVANT ANTIEMETICS

Corticosteroids (e.g. dexamethasone 8–20 mg i.v.) can partly alleviate nausea and vomiting due to moderately emetogenic chemotherapy, but are more often employed to augment the efficacy of other primary antiemetic drugs like metoclopramide and ondansetron against highly emetogenic regimens. Corticosteroids benefit both acute and delayed emesis. The basis of the effect appears to be their anti-inflammatory action. They also serve to reduce certain side effects of the primary antiemetic.

Benzodiazepines The weak antiemetic property of BZDs is primarily based on the sedative action. Used as adjuvant to metoclopramide/ondansetron, diazepam/lorazepam (oral/i.v.) help by relieving the psychogenic component, anticipatory vomiting and produce amnesia for the unpleasant procedure. They also suppress dystonic side effects of metoclopramide.

Cannabinoids Δ^9 Tetrahydrocannabinol (Δ^9 THC) is the active principle of the hallucinogen *Cannabis indica* that possesses antiemetic activity against moderately emetogenic chemotherapy. It probably acts through the CB_1 subtype of cannabinoid receptors located on neurones in the CTZ and/or the vomiting centre itself.

Dronabinol is pure Δ^9THC produced synthetically or extracted from *Cannabis*. In a dose of 5–10 mg/m^2 BSA orally (repeated as required) it can be used as an alternative antiemetic for moderately emetogenic chemotherapy in patients who cannot tolerate other antiemetics or are unresponsive to them. The hallucinogenic, disorienting and other central sympathomimetic effects (described on p. 452) are produced, and some subjects may experience a 'high', that may lead to addiction. The CNS actions limit the use of dronabinol to few nonresponsive patients. Its antiemetic action can be supplemented by dexamethasone.

Dronabinol is an appetite stimulant as well; has been used in lower doses to improve feeding in cachectic/AIDS patients.

Nabilone is another cannabinoid with antiemetic property.

DIGESTANTS

These are substances intended to promote digestion of food. A number of proteolytic, amylolytic and lipolytic enzymes are marketed in combination formulations and are vigorously promoted for dyspeptic symptoms, and as appetite stimulants or health tonics. They are occasionally beneficial, only when elaboration of enzymes in g.i.t. is deficient. Their routine use in tonics and appetite improving mixtures is irrational.

1. *Pepsin* May be used along with HCl in gastric achylia due to atrophic gastritis, gastric carcinoma, pernicious anaemia, etc.

2. *Papain* It is a proteolytic enzyme obtained from raw papaya. Its efficacy after oral ingestion is doubtful.

3. *Pancreatin* It is a mixture of pancreatic enzymes obtained from hog and pig pancreas. It contains amylase, trypsin and lipase, and is indicated in chronic pancreatitis or other exocrine pancreatic deficiency states. Fat and nitrogen content of stools may be reduced and diarrhoea/steatorrhoea may be prevented. It has to be used as enteric coated tablets or capsules to protect the enzymes from being themselves digested in stomach by pepsin. Nausea, diarrhoea and hyperuricaemia are the occasional side effects.

4. *Diastase and Takadiastase* These are amylolytic enzymes obtained from the fungus *Aspergillus oryzae*. They have been used in pancreatic insufficiency, but efficacy is equivocal.

Preparations

ARISTOZYME: Fungal diastase 50 mg, pepsin 10 mg, simethicone 50 mg cap and per 5 ml liquid.

DIGEPLEX: Diastase 62.5 mg, pepsin 20 mg per 10 ml after dissolving the tablet in sorbitol base provided.

ENTOZYME: Fungal diastase 50 mg, pepsin 10 mg per 5 ml syr.

LUPIZYME: Pepsin 125 mg, fungal diastase 18.75 mg, thiamine 2 mg, riboflavine 1 mg, pyridoxine 1.5 mg, vit B_{12} 1 µg, nicotinamide 15 mg per cap and per 5 ml syr.

PANZYNORM: Pancreatine 100 mg, bile ext. 40 mg, dry stomach ext. 110 mg tab.

UNIENZYME: Fungal diastase 20 mg, papain 30 mg, simethicone 50 mg, nicotinamide 25 mg, activated charcoal 75 mg tab.

VITAZYME: Fungal diastase 40 mg, cinnamon oil 0.25 mg, caraway oil 0.5 mg, cardamom oil 0.5 mg per 10 ml liq.

Enzyme preparations containing an antispasmodic or a laxative and fixed dose combinations of pancreatine or pancrelipase containing amylase, protease and lipase with any other enzyme are banned in India.

Methyl polysiloxane (Dimethyl polysiloxane, Simethicone, Dimethicone) It is a silicone polymer, a viscous amphiphilic liquid—reduces surface tension and collapses froth, 'antifoaming agent'. It is not absorbed from g.i.t. and is pharmacologically inert. Added to antacid, digestant and antireflux preparations (*see* above), it is briskly promoted as a remedy for 'gas', a very

common gastric complaint. It is also claimed to coat and protect ulcer surface, to aid dispersion of antacids in gastric contents, and to prevent gastroesophageal reflux. However clinical efficacy is equivocal.

Dose: 40–120 mg 3 to 4 times a day.
DIMOL 40 mg tab. (single ingredient).

GALLSTONE DISSOLVING DRUGS

Cholesterol (CH) remains dissolved in bile with the help of bile salts (salts of cholic acid and chenodeoxycholic acid conjugated with glycine and taurine) because bile salts are highly amphiphilic. A high CH : bile salt ratio favours crystallization of CH in bile; these crystals act as nidi for stone formation. *Chenodeoxycholic acid* (Chenodiol) and *Ursodeoxycholic acid* (Ursodiol) decrease CH content of bile, enabling solubilization of CH from stone surface. These two bile acids act differently.

	CHENODIOL	URSODIOL
1.	Acts primarily by inhibiting CH synthesis in liver.	Little inhibition of hepatic CH synthesis.
	Does not reduce intestinal CH absorption.	Acts primarily by inhibiting intestinal CH absorption.
2.	Raises plasma LDL-CH by reducing LDL receptors in liver.	Does not raise plasma LDL-CH level.
3.	Reduces CH secretion in bile after prolonged administration.	Promptly reduces CH secretion in bile.
4.	Generates a more litholytic bile acid pool.	Itself lowers CH saturation index of bile.
5.	Promotes micellar solubilization of CH.	Promotes solubilization by liquid crystal formation.

Chenodiol Administered daily it has been found to partially or completely dissolve CH gallstones in about 40% patients over 1/2 to 2 years. However, only 1/3 of these had complete dissolution.

Diarrhoea is common.
Aminotransferase level may rise, but overt liver damage occurs in only 3% patients.
Gastric and esophageal mucosal resistance to acid is impaired favouring ulceration.

Ursodiol It is a hydroxy epimer of chenodiol, is more effective and needs to be used at lower doses. Complete dissolution of CH stones has been achieved in upto 50% cases. It is also much better tolerated. Diarrhoea and hypertransaminaemia are infrequent, but effect on mucosal resistance is similar to chenodiol. Calcification of some gall stones may be induced.

Dose: 450–600 mg daily in 2–3 divided doses after meals;
UDCA, UDIHEP 150 mg tab.

Dissolution of gallstones is a very slow process: patient compliance is often poor. However, medical treatment is now possible in selected patients:

Once treatment is discontinued after stone dissolution, recurrences are common, because bile returns to its CH supersaturated state. Repeat courses may have to be given. Because of these problems the pros and cons of medical therapy must be weighed against cholecystectomy.

☞ PROBLEM DIRECTED STUDY

47.1 A 4-year-old girl is brought to the hospital emergency. The parents are very alarmed by her condition that has developed over the past one hour, when she started making bizarre faces. The neck has become rigid and head has tilted to one side. The teeth are clinched and she is not speaking. The eyes are staring in one direction and there are intermittent purposeless movements of the upper limbs. The parents inform that she had vomited twice in the morning and was taken to a local doctor, who had given her an injection. The vomiting had stopped, but after about 2 hours of the injection she developed the above symptoms.

(a) What is the most likely cause of her symptoms? Could it be due to the injection given to her? If so, which drug could have caused it?

(b) How should this patient be treated?

(see Appendix-1 for solution)

Chapter 48 Drugs for Constipation and Diarrhoea

LAXATIVES
(Aperients, Purgatives, Cathartics)

These are drugs that promote evacuation of bowels. A distinction is sometimes made according to the intensity of action.

(a) *Laxative or aperient*: milder action, elimination of soft but formed stools.

(b) *Purgative or cathartic*: stronger action resulting in more fluid evacuation.

Many drugs in low doses act as laxative and in larger doses as purgative.

CLASSIFICATION

1. *Bulk forming*
   Dietary fibre: Bran, Psyllium (Plantago) Ispaghula, Methylcellulose
2. *Stool softener*
   Docusates (DOSS), Liquid paraffin
3. *Stimulant purgatives*
   (a) *Diphenylmethanes*
   Phenolphthalein, Bisacodyl, Sodium picosulfate
   (b) *Anthraquinones (Emodins)*
   Senna, Cascara sagrada
   (c) *5-HT_4 agonist*
   Prucalopride
   (d) *Fixed oil*
   Castor oil
4. *Osmotic purgatives*
   Magnesium salts: sulfate, hydroxide
   Sodium salts: sulfate, phosphate
   Sod. pot. tartrate
   Lactulose

MECHANISM OF ACTION

All purgatives increase the water content of the faeces by:

(a) A hydrophilic or osmotic action, retaining water and electrolytes in the intestinal lumen—increase volume of colonic content and make it easily propelled.

(b) Acting on intestinal mucosa, decrease net absorption of water and electrolyte; intestinal transit is enhanced indirectly by the fluid bulk.

(c) Increasing propulsive activity as primary action—allowing less time for absorption of salt and water as a secondary effect.

For some of the drugs, controversy continues as to whether they increase water content of stools as the primary action or it is a consequence of increased motility, because the amount of water absorbed largely depends on transit time. However, certain purgatives do increase motility through an action on the myenteric plexuses. Laxatives modify the fluid dynamics of the mucosal cell and may cause fluid accumulation in gut lumen by one or more of following mechanisms:

(a) Inhibiting Na^+K^+ATPase of *villous cells*—impairing electrolyte and water absorption.

(b) Stimulating adenylyl cyclase in *crypt cells*—increasing water and electrolyte secretion.

(c) Enhancing PG synthesis in mucosa which increases secretion.

(d) Increasing NO synthesis which enhances secretion and inhibits non-propulsive contrations in colon.

(e) Structural injury to the absorbing intestinal mucosal cells.

BULK PURGATIVES

Dietary fibre: bran Dietary fibre consists of unabsorbable cell wall and other constituents of vegetable food—cellulose, lignins, gums, pectins,

glycoproteins and other polysaccharides. Bran is the residual product of flour industry which consists of ~40% dietary fibre. It absorbs water in the intestines, swells, increases water content of faeces—softens it and facilitates colonic transit. Osmotically active products may be formed in the colon by bacterial degradation of pectins, gums, etc. which act to retain water. Dietary fibre supports bacterial growth in colon which contribute to the faecal mass. Certain dietary fibres (gums, lignins, pectins) bind bile acids and promote their excretion in faeces → degradation of cholesterol in liver is enhanced → plasma LDL-cholesterol may be somewhat lowered.

Increased intake of dietary fibres is the most appropriate method for prevention of functional constipation. It is the first line approach for most patients of simple constipation. Prolonged intake of bran and other bulk forming agents reduces rectosigmoid intraluminal pressure and helps to relieve symptoms of irritable bowel syndrome (IBS) including pain, constipation as well as diarrhoea. Symptoms of chronic diverticulosis may also be relieved. It is also useful when straining at stools has to be avoided.

Drawbacks: Bran is generally safe, but it is unpalatable, large quantity (20–40 g/day) needs to be ingested. It has been included in some breakfast cereals, biscuits, etc. Full effect requires daily intake for at least 3–4 days. It does not soften faeces already present in colon or rectum. As such, bran is useful for prevention of constipation, but not for treating already constipated subjects. Flatulence may occur.

It should not be used in patients with gut ulcerations, adhesions, stenosis and when faecal impaction is a possibility.

Psyllium (Plantago) **and Ispaghula** They contain natural colloidal mucilage which forms a gelatinous mass by absorbing water. It is largey fermented in colon: increases bacterial mass and softens the faeces. Refined ispaghula husk 3–8 g is freshly mixed with cold milk, fruit juice or water and taken once or twice daily. It acts in 1–3 days. It should not be swallowed dry (may cause esophageal impaction).

Ispaghula husk (refined): ISOGEL (27 g/ 30 g), NATURE CURE (49 g/100 g), FYBOGEL (3.5 g/5.4 g) powder FIBRIL (3.4 g/11 g) powder;
Psyllium hydrophilic mucilloid: ISOVAC (65 g/100 g) granules.

Methylcellulose A semi-synthetic, colloidal, hydrophilic derivative of cellulose that remains largely unfermented in colon. A dose of 4–6 g/day is satisfactory in most individuals.

Generous amounts of water must be taken with all bulk forming agents. The choice among different bulking agents is a matter of personal preferences.

STOOL SOFTENER

Docusates (Dioctyl sodium sulfosuccinate: DOSS) It is an anionic detergent, softens the stools by net water accumulation in the lumen by an action on the intestinal mucosa. It emulsifies the colonic contents and increases penetration of water into the faeces. By a detergent action, it can disrupt the mucosal barrier and enhance absorption of many nonabsorbable drugs, e.g. liquid paraffin—should not be combined with it. It is a mild laxative; especially indicated when straining at stools must be avoided.

Dose: 100–400 mg/day; acts in 1–3 days.
CELLUBRIL 100 mg cap; LAXICON 100 mg tab, DOSLAX 150 mg cap.
As enema 50–150 mg in 50–100 ml;
LAXICON 125 mg in 50 ml enema.

Cramps and abdominal pain can occur. It is bitter; liquid preparations may cause nausea. Hepatotoxicity is feared on prolonged use.

Liquid paraffin It is a viscous liquid; a mixture of petroleum hydrocarbons, that was introduced as a laxative at the turn of 19th century. Millions of gallons have passed through the intestinal pipeline since then. It is pharmacologically inert. Taken for 2–3 days, it softens stools and is said to lubricate hard scybali by coating them.
Dose: 15–30 ml/day—oil as such or in emulsified form.

Disadvantages

(a) It is bland but very unpleasant to swallow because of oily consistency.

(b) Small amount passes into the intestinal mucosa—is carried into the lymph → may produce foreign body granulomas in the intestinal submucosa, mesenteric lymph nodes, liver and spleen.
(c) While swallowing it may trickle into lungs—cause lipid pneumonia.
(d) Carries away fat soluble vitamins with it into the stools: deficiency may occur on chronic use.
(e) Leakage of the oil past anal sphincter may embarrass.
(f) May interfere with healing in the anorectal region. Thus, it should be used only occasionally.

STIMULANT PURGATIVES

They are powerful purgatives: often produce griping. They irritate intestinal mucosa and thus were thought to primarily stimulate motor activity. Though some of them do directly increase motility by acting on myenteric plexuses, the more important mechanism of action is accumulation of water and electrolytes in the lumen by altering absorptive and secretory activity of the mucosal cell. They inhibit Na^+K^+ATPase at the basolateral membrane of villous cells—transport of Na^+ and accompanying water into the interstitium is reduced. Secretion is enhanced by activation of cAMP in crypt cells as well as by increased PG synthesis. The laxative action of bisacodyl and cascara is shown to be partly dependent upon increased NO synthesis/action in the colon.

Larger doses of stimulant purgatives can cause excess purgation resulting in fluid and electrolyte imbalance. Hypokalaemia can occur on regular intake. Routine and long-term use must be discouraged, because it can produce colonic atony. They can reflexly stimulate gravid uterus, therefore are contraindicated during pregnancy. Subacute or chronic intestinal obstruction is another contraindication.

Diphenylmethanes

Phenolphthalein is a litmus-like indicator which is in use as purgative from the beginning of the 20th century. It turns urine pink if alkaline.

Bisacodyl is a later addition and is more popular.

They are partly absorbed and reexcreted in bile. The enterohepatic circulation is greater in case of phenolphthalein which can produce protracted action. Bisacodyl is activated in the intestine by deacetylation. The primary site of action of diphenyl methanes is in the colon where they irritate the mucosa, produce mild inflammation and increase secretion. One or two semi-formed motions occur after 6–8 hours. Optimum doses vary considerably among individuals. Average doses are:

Phenolphthalein 60–130 mg: LAXIL 130 mg tab. To be taken at bedtime (tab. not to be chewed).

Bisacodyl 5–15 mg: DULCOLAX 5 mg tab; 10 mg (adult), 5 mg (child) suppository: CONLAX 5 mg, 10 mg suppository, BIDLAX-5 5 mg tab.

These doses may be ineffective in some individuals, but produce fluid evacuations and cramps in others. Morphological alterations in the colonic mucosa have been observed; the mucosa becomes more leaky.

Allergic reactions—skin rashes, fixed drug eruption and Stevens-Johnson syndrome have been reported.

Phenolphthalein has been found to produce tumours in mice and genetic damage. The US-FDA has ordered its withdrawal from the market.

Bisacodyl is also available as 5 mg (infant) and 10 mg (adult) suppository, which acts by irritating the anal and rectal mucosa → reflex increase in motility → evacuation occurs in 20–40 min. But it can cause inflammation and mucosal damage.

Sodium picosulfate: Another diphenylmethane related to bisacodyl. It is hydrolysed by colonic bacteria to the active form, which then acts locally to irritate the mucosa and activate myenteric neurones. Bowel movement generally occurs after 6–12 hours of oral dose. Along with mag. citrate solution, it has been used to evacuate the colon for colonoscopy and colonic surgery.

Dose: 5–10 mg at bed time. Indications and side effects are similar to bisacodyl.

CREMALAX, LAXICARE 10 mg tab; PICOFIT 5 mg/5 ml syr.

Anthraquinones

These are plant products used in household/traditional medicine for centuries.

Senna is obtained from leaves and pods of certain *Cassia sp*., while *Cascara sagrada* is the powdered bark of the buck-thorn tree. These and a number of other plant purgatives contain anthraquinone glycosides, also called *emodins*. Senna is most popularly used. The glycosides are not active as such. Unabsorbed in the small intestine, they are passed to the colon where bacteria liberate the active *anthrol* form, which either acts locally or is absorbed into circulation—excreted in bile to act on small intestine. Thus, they take 6–8 hours to produce action. Taken by lactating mothers, the amount secreted in milk is sufficient to cause purgation in the suckling infant.

The purgative action and uses of anthraquinones are quite similar to those of diphenylmethanes. Taken at bed time—a single, soft but formed evacuation generally occurs in the morning. Cramps and excessive purging occur in some individuals. The active principle of these drugs acts on the myenteric plexus to increase peristalsis and decrease segmentation. They also promote secretion and inhibit salt and water absorption in the colon. Senna anthraquinone has been found to stimulate PGE_2 production in rat intestine. This is prevented by indomethacin and the purgative action is reduced.

Skin rashes, fixed drug eruption are the occasional adverse effects.

Regular use for 4–12 months causes colonic atony and mucosal pigmentation (melanosis).

Sennosides (Cal. salt): GLAXENNA 11.5 mg tab; PURSENNID 18 mg tab; SOFSENA 12 mg tab.

Prucalopride It is a selective 5-HT_4 receptor agonist marketed recently in Europe, UK and Canada for the treatment of chronic constipation in women, when other laxatives fail to provide adequate relief. It activates prejunctional 5-HT_4 receptors on intrinsic enteric neurones to enhance release of the excitatory transmitter ACh, thereby promoting propulsive contractions in ileum and more prominently in colon. Colonic transit and stool frequency is improved in constipation-predominant irritable bowel syndrome (IBS).

A 5-HT_4 receptor partial agonist tegaserod with similar action on colon was introduced few years back, but was withdrawn soon after when postmarketing studies showed that it increased the risk of edema, heart attack and stroke. These adverse consequences were ascribed to its interaction with 5-$HT_{1B/1D}$ receptors in addition to 5-HT_4 receptors. Prucalopride is shown to have low affinity for 5-$HT_{1B/1D}$ receptor, as well as for cardiac K^+ channels. It is therefore, believed to be free of cardiovascular risk. No Q-T prolongation has been noted during clinical trial. Side effects are headache, dizziness, fatigue, abdominal pain and diarrhoea; but generally subside during use. *Dose*: 2 mg OD, elderly start with 1 mg OD.

Lubiprostone This PG analogue (EP_4 receptor agonist), developed recently, represents a new strategy in the treatment of constipation-predominant IBS and chronic constipation by stimulating mucosal Cl^- channels and increasing intestinal secretion. Its comparative value is being investigated.

Castor oil

It is one of the oldest purgatives. Castor oil is a bland vegetable oil obtained from the seeds of *Ricinus communis*. It mainly contains triglyceride of ricinoleic acid which is a polar long-chain fatty acid. Castor oil is hydrolysed in the ileum by lipase to ricinoleic acid and glycerol. Ricinoleic acid, being polar, is poorly absorbed. It was believed to irritate the mucosa and stimulate intestinal contractions. The primary action is now shown to be decreased intestinal absorption of water and electrolytes, and enhanced secretion by a detergent like action on the mucosa. Structural damage to the villous tips has also been observed. Peristalsis is increased secondarily. *Dose:* 15–25 ml (adults) 5–15 ml (children) is generally taken in the morning. Because the site of action is small intestine, purgation occurs in 2–3 hours—motion is semifluid and often accompanied by griping.

Due to its unpalatability, frequent cramping, a rather violent action, possibility of dehydration and after-constipation (due to complete evacuation of colon), it is no longer a favoured purgative. Regular use is particularly to be avoided—may damage intestinal mucosa.

OSMOTIC PURGATIVES

Solutes that are not absorbed in the intestine retain water osmotically and distend the bowel—increasing peristalsis indirectly.

Magnesium ions release cholecystokinin which augments motility and secretion, contributing to purgative action of Mag. salts. All inorganic salts used as osmotic (saline) purgatives have similar action—differ only in dose, palatability and risk of systemic toxicity.

- Mag. sulfate (Epsom salt): 5–15 g; bitter in taste, may nauseate.
- Mag. hydroxide (as 8% W/W suspension—milk of magnesia) 30 ml; bland in taste, also used as antacid.
- Sod. sulfate (Glauber's salt): 10–15 g; bad in taste.
- Sod. phosphate: 6–12 g, taste not unpleasant.
- Sod. pot. tartrate (Rochelle salt): 8–15 g, relatively pleasant tasting.

The salts taken in above mentioned doses, dissolved in 150–200 ml of water, produce 1–2 fluid evacuations within

1–3 hours with mild cramping; cause nearly complete emptying of bowels. Smaller doses may have a milder laxative action.

Mag. salts are contraindicated in renal insufficiency, while Sod. salts should not be given to patients of CHF and other Sod. retaining states. Repeated use of saline purgatives can cause fluid and electrolyte imbalance.

Saline purgatives are not used now for the treatment of constipation because they are inconvenient/unpleasant, produce watery stools and after constipation. However, they may be preferred for preparation of bowel before surgery and colonoscopy; in food/drug poisoning and as after-purge in the treatment of tapeworm infestation.

Lactulose It is a semisynthetic disaccharide of fructose and lactose which is neither digested nor absorbed in the small intestine—retains water. Further, it is broken down in the colon by bacteria to osmotically more active products. In a dose of 10 g BD taken with plenty of water, it produces soft formed stools in 1–3 days. Flatulence and flatus is common, cramps occur in few. Some patients feel nauseated by its peculiar sweet taste.

In patients with hepatic encephalopathy, lactulose causes reduction of blood NH_3 concentration by 25–50%. The breakdown products of lactulose are acidic—lower the pH of stools. Ammonia produced by bacteria in colon is converted to ionized NH_4^+ salts that are not absorbed. For this purpose 20 g TDS or more may be needed. Loose motions are produced at this dose.

LACSAN, MTLAC 10 g/15 ml liq. DUPHALAC, LIVO-LUK 6.67 g/10 ml liq.

Other drugs used to reduce blood NH_3 in hepatic coma are *sod. benzoate* and *sod. phenyl acetate.* They combine with NH_3 in blood to form hippuric acid or phenyl acetic glutamine respectively: these are rapidly excreted in urine.

CHOICE AND USE OF PURGATIVES

Laxatives are as important for their harmfulness as they are for their value in medicine.

All laxatives are *contraindicated* in:

(i) A patient of undiagnosed abdominal pain, colic or vomiting.

(ii) Organic (secondary) constipation due to stricture or obstruction in bowel, hypothyroidism, hypercalcaemia, malignancies and certain drugs, e.g.—opiates, sedatives, anticholinergics including antiparkinsonian, antidepressants and antihistaminics, oral iron, clonidine, verapamil and laxative abuse itself.

The primary cause should be treated in these cases.

Valid indications of laxatives are:

1. *Functional constipation* Constipation is infrequent production of hard stools requiring straining to pass, or a sense of incomplete evacuation. A stool frequency of once in 2 days to 2–3 times per day is considered normal by different individuals. Constipation is a symptom rather than a disease. Various aspects of the patient's lifestyle may contribute:
   (a) Misconception about the normal/necessary frequency, amount or consistency of stools.
   (b) Inadequate fibre in diet, less fluid intake.
   (c) Lack of exercise, sedentary nature of work.
   (d) Irregular bowel habits, rushing out for job.

Proper assessment of the causative factor in the patient and its correction leaves only a minority of cases to be treated by drugs.

Constipation may be spastic or atonic.

(i) *Spastic constipation* (irritable bowel): The stools are hard, rounded, stone like and difficult to pass. The first choice laxative is dietary fibre or any of the bulk forming agents taken over weeks/months. Stimulant purgatives are contraindicated.

(ii) *Atonic constipation* (sluggish bowel): mostly due to advanced age, debility or laxative abuse. Non-drug measures like plenty of fluids, exercise, regular habits and reassurance should be tried. In resistant cases a bulk forming agent should be prescribed. In case of poor compliance or if the patient is not satisfied—bisacodyl or senna may be given once or twice a week for as short a period as possible.

2. *Bedridden patients* (myocardial infarction, stroke, fractures, postoperative): bowel movement may be sluggish and constipation can be anticipated.

To prevent constipation: Give bulk forming agents on a regular schedule; docusates, lactulose and liquid paraffin are alternatives.

To treat constipation: Enema (soap-water/ glycerine) is preferred; bisacodyl or senna may be used.

Alvimopan It is a recently approved peripherally acting μ opioid receptor antagonist for the treatment of postoperative ileus and constipation following abdominal surgery. Alvimopan absorption from gut and its penetration into brain is poor due to its polar nature. Administered orally before and after surgery, it hastened recovery of bowel function.

3. *To avoid straining at stools* (hernia, cardiovascular disease, eye surgery) and in perianal afflictions (piles, fissure, anal surgery) it is essential to keep the faeces soft. One should not hesitate to use adequate dose of a bulk forming agent, lactulose or docusates.

4. *Preparation of bowel for surgery, colonoscopy, abdominal X-ray* The bowel needs to be emptied of the contents including gas. Saline purgative, bisacodyl or senna may be used; castor oil only in exceptional circumstances.

5. *After certain anthelmintics* (especially for tapeworm) Saline purgative or senna may be used to flush out the worm and the anthelmintic drug.

Fixed dose combinations of an anthelmintic (other than piperazine) with a purgative is banned in India, as are laxatives with enzyme preparations.

6. *Food/drug poisoning* The idea is to drive out the unabsorbed irritant/poisonous material from the intestines. Only saline purgatives are satisfactory.

The choice of a purgative depends on the latency of action and type of stools desired. This is given in Table 48.1.

TABLE 48.1 **Type of stools and latency of action of purgatives employed in usually recommended doses**

Soft, formed faeces (take 1–3 days)	*Semifluid stools (take 6–8 hrs)*	*Watery evacuation (within 1–3 hrs)*
Bulk forming Docusates Liquid paraffin Lactulose	Phenolphthalein Bisacodyl Sod. picosulfate Senna	Saline purgatives Castor oil

Some combined preparations

AGAROL: Liquid paraffin 9.5 ml, phenolphthalein 400 mg, agar 60 mg per 30 ml emulsion.

CREMAFFIN: Milk of magnesia 11.25 ml, liq. paraffin 3.75 ml per 15 ml emulsion; CREMAFFIN PINK with phenolphthalein 50 mg per 15 ml.

JULAX: Bisacodyl 10 mg, casanthranol 10 mg dragees.

PURSENNID-IN (with DOS): Purified senna ext. (cal salt) 18 mg, docusates 50 mg tab.

Purgative abuse Some individuals are obsessed with using purgatives regularly. This may be the reflection of a psychological problem. Others use a purgative casually, obtain thorough bowel evacuation, and by the time the colon fills up for a proper motion (2–3 days) they get convinced that they are constipated and start taking the drug regularly. Chronic use of purgatives must be discouraged. Once the purgative habit forms, it is difficult to break. Dangers of purgative abuse are:

1. Flairing of intestinal pathology, rupture of inflamed appendix.
2. Fluid and electrolyte imbalance, especially hypokalaemia.
3. Steatorrhoea, malabsorption syndrome.
4. Protein losing enteropathy.
5. Spastic colitis.

TREATMENT OF DIARRHOEAS

Diarrhoea is too frequent, often too precipitate passage of poorly formed stools. It is defined by WHO as 3 or more loose or watery stools in a 24 hour period. In pathological terms, it occurs due to passage of excess water in faeces.This may be due to:

- Decreased electrolyte and water absorption.
- Increased secretion by intestinal mucosa.
- Increased luminal osmotic load.
- Inflammation of mucosa and exudation into lumen.

Diarrhoeal diseases constitute a major cause of morbidity and mortality worldwide; especially in developing countries. It is more prevalent among children. The global burden of pediatric diarrhoea is estimated to be 1.5 billion episodes with 1.5–2.5 million deaths under 5 years of age per year. In India around 1000 children die every day due to diarrhoea. Recurrent or protracted diarrhoea is also a major cause of protein-calorie malnutrition in developing countries. Even mild diarrhoea, and that in adults, is a disabling symptom and an inconvenience.

Relevant pathophysiology

Water and electrolytes are absorbed as well as secreted in the intestine. Jejunum is freely permeable to salt and water which are passively absorbed secondary to nutrient (glucose, amino acids, etc.) absorption. In the ileum and colon active Na^+K^+ATPase mediated salt absorption occurs, primarily in the mature cells lining the villous tips, water follows isoosmotically. In addition *glucose facilitated Na^+ absorption* takes place in the ileum by Na^+-glucose cotransporter; one Na^+ ion is transported along with each molecule of glucose absorbed. This mechanism remains intact even in severe diarrhoeas.

Absorption of Cl^- and HCO_3^- is passive (paracellular) as well as by exchange of HCO_3^- for Cl^- (transcellular). Bicarbonate is absorbed also by the secretion of H^+ (similar to that in proximal tubule of kidney) and Na^+ accompanies it. K^+ is excreted in faecal water by exchange with Na^+, as well as by secretion into mucus and in desquamated cells. The osmotic load of luminal contents plays an important role in determining final stool water volume. When nonabsorbable solutes are present and in disaccharidase deficiency (which occurs during starvation), the stool water is increased. Inhibition of Na^+K^+ATPase and structural damage to mucosal cell (by Rota virus) causes diarrhoea by reducing absorption.

Intracellular cyclic nucleotides are important regulators of absorptive and secretory processes (Fig. 48.1). Stimuli enhancing cAMP or cGMP cause net loss of salt and water, both by inhibiting NaCl absorption in villous cells and by promoting anion secretion (Na^+ accompanies) in the crypt cells which are primarily secretory. Many bacterial toxins, e.g. cholera toxin, exotoxin elaborated by *Enterotoxigenic E. coli* (ETEC), *Staph. aureus, Salmonella,* etc. activate adenylyl cyclase which enhances secretion that reaches its peak after 3–4 hours and persists until the stimulated cells are shed in the normal turnover, i.e. 36 hours after a single exposure. Concurrent inhibition of absorption adds to the rate of salt and water loss. Prostaglandins (PGs) and intracellular Ca^{2+} also stimulate the secretory process. All acute enteric

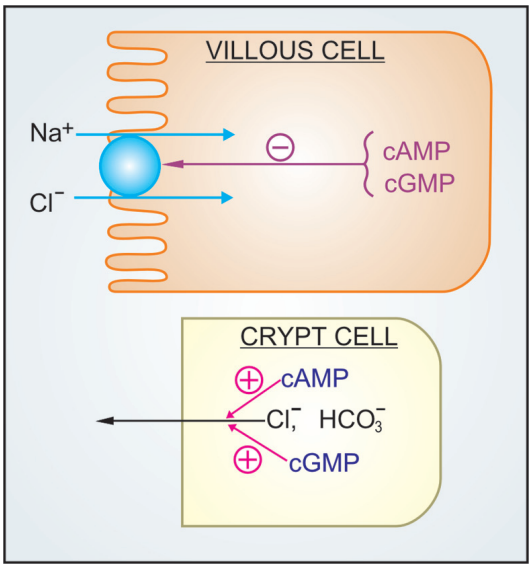


Fig. 48.1: Action of cyclic nucleotides on electrolyte transport of intestinal mucosal cells. In crypt cells cAMP plays the dominant role

infections produce secretory diarrhoea. The heat stable toxin (ST) of ETEC, *Clostridium difficile* and *E. histolytica* cause accumulation of cGMP which also stimulates anion secretion (less potent than cAMP) and inhibits Na^+ absorption.

Diarrhoea associated with carcinoid (secreting 5-HT) and medullary carcinoma of thyroid (secreting calcitonin) is mediated by cAMP. Excess of bile acids also cause diarrhoea by activating adenylyl cyclase.

Traditionally, hypermotility of bowel has been ascribed a crucial role in diarrhoea. However, changes in intestinal motility are now thought to be of secondary importance and may be due to fluid accumulation in the lumen. Decreased segmenting activity in the intestine may promote diarrhoea by allowing less time for the absorptive processes.

Principles of management

Rational management of diarrhoea depends on establishing the underlying cause and instituting specific therapy (only if necessary), since most diarrhoeas are self-limiting. Majority of enteropathogens are taken care of by motility and other

defence mechanisms of the gut. Therapeutic measures may be grouped into:

(a) Treatment of fluid depletion, shock and acidosis.
(b) Maintenance of nutrition.
(c) Drug therapy.

The relative importance of each measure is governed by the severity and nature of diarrhoea.

REHYDRATION

In majority of cases, this is the only measure needed. Rehydration can be done orally or i.v.

Intravenous rehydration It is needed only when fluid loss is severe, i.e. > 10% body weight, (if not promptly corrected, it will lead to shock and death) or if patient is losing > 10 ml/kg/hr, or is unable to take enough oral fluids due to weakness, stupor or vomiting. The recommended composition of i.v. fluid (Dhaka fluid) is:

NaCl	85 mM = 5 g	in 1 L of water or 5% glucose solution.
KCl	13 mM = 1 g	
$NaHCO_3$	48 mM = 4 g	

This provides 133 mM Na^+, 13 mM K^+, 98 mM Cl^- and 48 mM HCO_3^-. Ringer lactate (Na^+ 130, Cl^- 109, K^+ 4, lactate 28 mM) recommended by WHO (1991) could be used alternatively.

Volume equivalent to 10% BW should be infused over 2–4 hours; the subsequent rate of infusion is matched with the rate of fluid loss. In most cases, oral rehydration can be instituted after the initial volume replacement.

Oral rehydration Advent of oral rehydration therapy (ORT) is considered a major advance of recent times. If the fluid loss is mild (5–7% BW) or moderate (7.5–10% BW) ORT can be instituted from the very beginning.

Rationale of ORS composition

Oral rehydration is possible if glucose is added with salt. It capitalizes on the intactness of glucose coupled Na^+ absorption, even when other mechanisms have failed or when intestinal secretion is excessive, because the secreted fluid lacks glucose and cannot be reabsorbed. The composition of oral rehydration salt/solution (ORS) has been debated. The general principles are:

(a) It should be isotonic or somewhat hypotonic, i.e. total osmolarity 200–310 mOsm/L (diarrhoea fluids are approximately isotonic with plasma).

(b) The molar ratio of glucose should be equal to or somewhat higher than Na^+ (excess glucose will be utilized in absorbing Na^+ present in the intestinal secretions in addition to that present in ORS itself), but not exceed 110 mM.

(c) Enough K^+ (15–25 mM) and bicarbonate/citrate (8–12 mM) should be provided to make up the losses in stool.

The WHO recommended a standard formula which provided Na^+ 90 mM, K^+ 20 mM, Cl^- 80 mM, citrate (base) 10 mM, glucose 110 mM and had a total osmolarity of 310 mOsm/L. Trisod. citrate was included in place of sod. bicarbonate because bicarbonate containing powder caked and developed a brown colour due to formation of furfural compounds with glucose: had a short shelf life.

The above formula propounded by WHO in 1984 was based on the composition of cholera stools in children. When given to children with noncholera diarrhoea, it often produced periorbital edema due to excess Na^+ absorption. Based on the Na^+ content of ETEC stools, many paediatricians favoured 60 mM Na^+ and 90 mM glucose ORS.

New formula WHO-ORS In 2002 a new formula low Na^+ low glucose ORS was released by the WHO. Over the past 20 years WHO sponsored studies were carried out in several developing countries among children and adults suffering from diarrhoeas. It was found that maximum water absorption occurs from a slightly hypotonic solution and when glucose concentration is between 60–110 mM. At higher concentrations, glucose appears in the stools and takes its osmotic penalty—stool volume is increased. A combined analysis of studies using low osmolarity ORS has revealed that stool volume is reduced by 20% and incidence of vomiting by 30%. It also permits faster water absorption, precludes risk of hypernatremia and is cheaper. The new formula ORS has proven as effective and as safe in cholera as well, but there is some risk of hyponatremia in adults with cholera.

The WHO and UNICEF have recommended replacement of standard (310 mOsm/L) ORS formula by the new (245 mOsm/L).

New formula WHO-ORS

Content		*Concentrations*	
NaCl	: 2.6 g	Na^+	— 75 mM
KCl	: 1.5 g	K^+	— 20 mM
Trisod. citrate	: 2.9 g	Cl^-	— 65 mM
Glucose	: 13.5 g	Citrate	— 10 mM
Water	: 1 L	Glucose	— 75 mM
Total osmolarity 245 mOsm/L			

(available as ORETRAL-A, ELECTROBION, ELECTRAL 21 g sachet for 1000 ml; WALYTE, RELYTE 4.2 g sachet for 200 ml).

Potassium is an important constituent of ORS, since in most acute diarrhoeas K^+ loss is substantial. The base (bicarbonate, citrate, lactate) is added to correct acidosis due to alkali loss in stools. It may independently promote Na^+ and water absorption. However, relying on the ability of the kidney to restore acid-base balance, acidotic states have been managed without an exogenous base. Base free ORS has been found to be equally effective in rehydrating, but correction of acidosis is slower. Thus, there is a trend to consider base as a nonessential constituent of ORS, but if present it may be beneficial, especially in severe cases with overt acidosis.

Administration of ORT Patients are encouraged to drink ORS at ½–1 hourly intervals. Initially 5–7.5% BW volume equivalent is given in 2–4 hours (5 ml/kg/hr in children). Thirst due to volume depletion provides an adequate driving force. Subsequently it may be left to demand, but should at least cover the rate of loss in stools. In a weak child who refuses to drink ORS at the desired rate, it can be given by intragastric drip; restoring hydration within 6 hours should be aimed.

ORT is not designed to stop diarrhoea, but to restore and maintain hydration, electrolyte and pH balance until diarrhoea ceases, mostly spontaneously. It is the best and not a second choice approach to i.v. hydration.

Non-diarrhoeal uses of ORT

(a) Postsurgical, postburn and post-trauma maintenance of hydration and nutrition (in place of i.v. infusion).
(b) Heat stroke.
(c) During changeover from intravenous to enteral alimentation.

Zinc in pediatric diarrhoea Recent studies have shown that administration of Zinc along with low osmolarity ORS reduces the duration and severity of acute diarrhoea episodes in children below 5 years of age. Continued Zinc supplementation (20 mg/day for 6–60 months age; 10 mg/day for 0–6 month age) for 10–14 days following the episode also reduces recurrences of diarrhoea for the next 2–3 months. Accordingly, the WHO jointly with UNICEF and USAID have recommended that all children with acute diarrhoea should be given Zinc supplementation along with ORS and continued for the next 10–14 days. The Indian Academy of Pediatrics has endorsed the WHO recommendation and the Govt. of India has initiated providing Zinc in addition to ORS through its National Rural Health Mission.

The mechanism of benefit of Zinc in diarrhoea is not known. *In vitro* studies have suggested that Zinc could reduce fluid secretion in the intestine by indirectly inhibiting cAMP dependent Cl^- transport across the mucosa through an action on the basolateral membrane K^+ channels. It could also strengthen the immune response and help regeneration of intestinal epithelium.

Zinc can be administered to children by dissolving Zinc sulfate dispersible tablets.

ULSEEL (50 mg Zn) Cap (for adults)
ZIORAL 10 mg and 20 mg (Zn) dispersible tabs for infants and children respectively.

MAINTENANCE OF NUTRITION

Contrary to traditional view, patients of diarrhoea should not be starved. Fasting decreases brush border disaccharidase enzymes and reduces absorption of salt, water and nutrients; may lead to malnutrition if diarrhoea is prolonged or recurrent. Feeding during diarrhoea has been shown to increase intestinal digestive enzymes and cell proliferation in mucosa. Simple foods like breast milk or ½ strength buffalo milk, boiled potato, rice, chicken soup, banana, sago, etc. should be given as soon as the patient can eat.

DRUG THERAPY

Drugs used in diarrhoeas may be categorised into:
1. Specific antimicrobial drugs
2. Probiotics
3. Drugs for inflammaory bowel disease (IBD)
4. Nonspecific antidiarrhoeal drugs.

1. Antimicrobials in diarrhoea

One or more antimicrobial agent is almost routinely prescribed to most patients of diarrhoea. However, such drugs have a limited role in the overall treatment of diarrhoeal diseases; the reasons are:

- Bacterial pathogen is responsible for only a fraction of cases.
- Even in bacterial diarrhoea, antimicrobials alter the course of illness only in selected cases.
- Antimicrobials may prolong the carrier state.

Diarrhoea patients can be broadly placed in one of the two categories:

(a) Abundant watery diarrhoea lacking mucus or blood, usually dehydrating with frequent vomiting, but little or no fever. These are generally caused by adhesive but noninvasive enterotoxigenic bacteria such as cholera, ETEC, *Salmonella enteritidis* or by rota virus and other viruses which stimulate massive secretion by activating cAMP in intestinal mucosal cell. ORS and not antimicrobials are the main therapy.

(b) Slightly loose, smaller volume stools, frequently with mucus and/or blood, mild dehydration, usually attended with fever and abdominal pain, but not vomiting. These symptoms are indications of mucosal invasion, generally caused by enteroinvasive organisms like *Shigella*, enteropathogenic *E. coli* (EPEC), *Campy. jejuni, Salmonella typhimurium, Yersinia enterocolitica, E. histolytica, Clostri. difficile*. Antimicrobials are needed in many of these.

A. *Antimicrobials are of no value* In diarrhoea due to *noninfective causes*, such as:

(i) Irritable bowel syndrome (IBS)
(ii) Coeliac disease
(iii) Pancreatic enzyme deficiency
(iv) Tropical sprue (except when there is secondary infection)
(v) Thyrotoxicosis.

Rotavirus is an important pathogen of acute diarrhoea, especially in children in developed countries. Along with other diarrhoea causing viruses, it is not amenable to chemotherapy.

Salmonella food poisoning is generally a self-limiting disease. Antibiotics have been widely used, but may be harmful rather than beneficial. Treated patients have been found to pass organisms in stool for longer periods than untreated patients. However, very severe illness or that in infants/elderly or immunocompromized patients may be treated with ciprofloxacin or azithromycin or i.v. ceftriaxone.

B. *Antimicrobials are useful only in severe disease* (but not in mild cases):

(i) Travellers' diarrhoea: mostly due to ETEC, *Campylobacter* or virus: cotrimoxazole, norfloxacin, doxycycline reduce the duration of diarrhoea and total fluid needed only in severe cases.

Rifaximin It is a minimally absorbed oral rifamycin (related to rifampin) active against *E. coli* and many other gut pathogens. It is recently approved by US-FDA for the empiric treatment of travellers' diarrhoea caused by non-invasive strains of *E.coli*. Approval has also been granted in 33 countries for various conditions. A review of data from controlled trials using rifaximin 200 mg TDS for 3 days has rated it to be superior to placebo, and as effective as ciprofloxacin in reducing duration of travellers' diarrhoea, irrespective of whether the causative pathogen was identified or not. It has also been used in diarrhoeal phase of IBS as well as for prophylaxis before and after gut surgery. A higher strength (550 mg) tablet is marketed for reducing risk of hepatic encephalopathy recurrence by suppressing NH_3 forming gut bacteria.

The tolerability profile of rifaximin is similar to placebo. Side effects are flatulence, abdominal pain, defecation urgency and headache. Because

of poor absorption, systemic toxicity is not expected. Clinical experience with rifaximin is limited, and efficacy for empirical treatment of diarrhoea is still to be convincingly established against local strains of the bacteria.

RIFAGUT, TORFIX, 200 mg tab; RACFAX 200, 400 mg tabs.

(ii) *EPEC:* is less common, but causes *Shigella*-like invasive illness. Cotrimoxazole, or a fluoroquinolone or colistin may be used in acute cases and in infants.

(iii) *Shigella* enteritis: only when associated with blood and mucus in stools may be treated with ciprofloxacin or norfloxacin. Cotrimoxazole and ampicillin are alternatives, but many strains are resistant to these.

(iv) *Nontyphoid Salmonella* enteritis is often invasive; severe cases may be treated with a fluoroquinolone, cotrimoxazole or ampicillin.

(v) *Yersinia enterocolitica:* common in colder places, not in tropics. Cotrimoxazole is the most suitable drug in severe cases; ciprofloxacin is an alternative.

C. Antimicrobials are regularly useful in:

(i) Cholera: Though only fluid replacement is life saving, tetracyclines reduce stool volume to nearly half. Cotrimoxazole is an alternative, especially in children. Lately, multidrug resistant cholera strains have arisen. These can be treated with norfloxacin/ciprofloxacin. Ampicillin and erythromycin are also effective.

(ii) *Campylobacter jejuni:* Norfloxacin and other fluoroquinolones eradicate the organism from the stools and control diarrhoea. Erythromycin is fairly effective and is the preferred drug in children.

(iii) *Clostridium difficile:* produces antibiotic associated pseudomembranous enterocolitis. The drug of choice for this superinfection is metronidazole, while vancomycin given orally is an alternative. The offending antibiotic must be stopped.

(iv) Diarrhoea associated with bacterial growth in blind loops/diverticulitis may be treated with tetracycline or metronidazole.

(v) Amoebiasis, (vi) Giardiasis } metronidazole, diloxanide furoate, are effective drugs (*see* Ch. 60).

2. Probiotics in diarrhoea

These are microbial cell preparations, either live cultures or lyophillised powders, that are intended to restore and maintain healthy gut flora or have other health benefits. Diarrhoeal illnesses and antibiotic use are associated with alteration in the population, composition and balance of gut microflora. Recolonization of the gut by non-pathogenic, mostly lactic acid forming bacteria and yeast is believed to help restore this balance. Organisms most commonly used are—*Lactobacillus sp*., *Bifidobacterium*, *Streptococcus faecalis*, *Enterococcus sp.* and the yeast *Saccharomyces boulardii*, etc.

Several reviews and metaanalysis of clinical trials have suggested that probiotics significantly reduce antibiotic-associated diarrhoea, acute infective diarrhoea and risk of traveller's diarrhoea. They also note that most of the randomised placebo controlled trials have been carried out in health-care setting in developed countries, while data from community based studies carried out in resource-poor countries is minimal. Several probiotic strains, either alone or in combination, have been used in different studies, but the protective effect has been more or less similar, though collation of data is difficult.

While probiotics appear to be useful adjuncts to conventional therapy of acute infectious diarrhoea, and are loudly promoted as well as frequently prescribed, convincing evidence of their efficacy is lacking. This prevents them from being accepted as a standard component of diarrhoea therapy. Stronger evidence of efficacy has emerged against antibiotic-associated diarrhoea, but there is no justification yet for routine use of probiotics along with antibiotics. Natural curd/yogurt is an abundant source of lactic acid producing organisms, which can serve as probiotic. For all practical purposes, probiotics are safe. Infections

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).

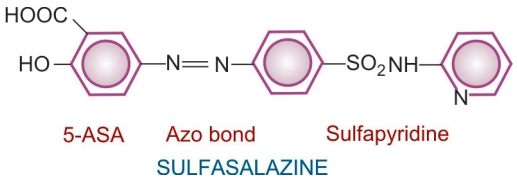
Ulcerative colitis It involves only the colon starting from the anal canal. It may remain restricted to the rectum or extend proximally in a contiguous manner to variable extent upto caecum. The lesions are mucosal and may be diffuse or confluent.

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?

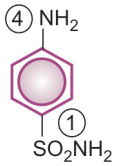
(b) If she does, which antimicrobial(s) should be selected? When, by what route and dose, and how long the antimicrobial(s) should be administered?

(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

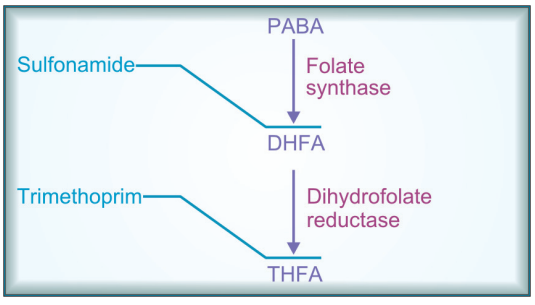


Fig. 50.1: Sequential block in bacterial folate metabolism
PABA—Para aminobenzoic acid; DHFA—Dihydrofolic acid; THFA—Tetrahydrofolic acid

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.

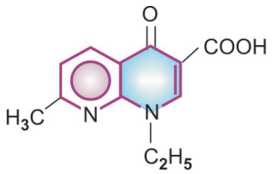
5. *Chancroid* Cotrimoxazole (800 + 160 mg) BD for 14 days is a 3rd choice, but less expensive, alternative to ceftriaxone, azithromycin or ciprofloxacin.

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

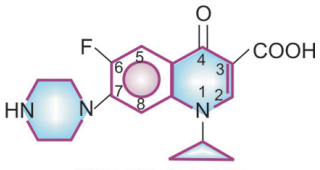
7. Cotrimoxazole is an alternative to penicillin for protecting *agranulocytosis patients* and for treating respiratory or other infections in them. Intensive parenteral cotrimoxazole therapy has been used successfully in septicaemias, but other drugs are more commonly employed now.

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)