

Essential Drugs

Diarrhoeal diseases in adults

Acute diarrhoea in adults

Cases of acute, sporadic infective diarrhoea occur everywhere. They are particularly common in travellers to developing countries who may have little or no immunity against indigenous enteropathogens. Some 20 to 50% of such travellers are estimated to experience an acute diarrhoeal illness. Enterotoxigenic *Escherichia coli* is the most common cause of these infections. Less frequently, other bacterial enteropathogens including *Shigella* spp, and *Salmonella* spp, certain viruses and intestinal parasites such as *Giardia lamblia* and *Cryptosporidium parvum* are implicated.

It is relevant to note that a newly-identified enteropathogen, *Microsporidium* spp, is now recognized as an important diarrhoeal agent in patients with HIV infection.

These infections are most commonly acquired through ingestion of contaminated food or water. Some may also be transmitted by person-to-person contact. The illness, which seldom lasts for more than four days, typically results in several loose or watery stools per day and is often accompanied by abdominal pain and cramps. Occasionally, the diarrhoea is more severe, somewhat more persistent, and associated with fever, vomiting or bloody stools.

Prevention

Careful choice and preparation of food and drink offers the best protection. Food should be thoroughly and freshly cooked; foods that are prepared in advance need to be maintained at temperatures either below 10° C or above 60° C to ensure their safety, or else reheated until thoroughly hot before eating. Cooked food held at ambient temperatures (15-40° C) for more than 5 hours provides a substrate for bacterial colonization and is the source of much food-borne disease. Unpasteurized milk should be boiled before consumption, and water should always be boiled or chlorinated and filtered unless its purity can be assured. Use of slow-release disinfectant agents and filter attachments to domestic taps also offer some protection. At certain times of the year, various species of fish and shellfish contain poisonous biotoxins, even when

they are well cooked. Advice should be sought from local public health authorities.

Treatment

Travellers should always carry oral rehydration salts. When they travel to destinations where safe drinking water may not be available, they should also take water disinfectant tablets.

Various antimicrobial drugs and preparations of bismuth subsalicylate have been used prophylactically, but their value is limited in most cases. Moreover, routine prophylactic use of antibiotics encourages the development of drug resistance. These preparations should be reserved for adults who are not in good health and who intend to spend no more than three weeks in areas where clean food and water cannot be guaranteed, or when it is particularly important that travel plans should not be disrupted.

Dehydration resulting from diarrhoea can be dangerous at any age. It can be countered by drinking plentifully, preferably oral rehydration salts solution. Symptomatic relief may be obtained with antidiarrhoeal drugs such as codeine, bismuth subsalicylate or loperamide. However, they should be used only on occasions when it is essential to suppress diarrhoea. They should never be prescribed for infants and young children because of the risk of colonic dilatation and — in the case of loperamide — of paralytic ileus.

Bacterial dysentery, protozoal infections and intestinal helminthic infections require specific antimicrobial or antiparasitic treatment.

ORAL REHYDRATION SALTS

	g/litre of clean water
sodium chloride	3.5
trisodium citrate dihydrate	2.9
potassium chloride	1.5
glucose (anhydrous)	20.00

Oral rehydration solution is optimally constituted to correct the fluid and electrolyte loss which results

from acute diarrhoea in infants, older children and adults.

When glucose and trisodium citrate are not available, these ingredients may be replaced, respectively, by:

sucrose (common sugar)	g/litre 18.00
sodium chloride	3.0

Uses

Prevention and treatment of dehydration from acute diarrhoea.

Severely dehydrated patients must be treated initially with intravenous fluids until they are able to take fluids by mouth.

Preparation, dosage and administration

The solution may be prepared either from prepackaged mixtures, or from bulk substances, and water. Care should be taken to ensure that all ingredients are completely dissolved in the correct quantity of clean drinking-water.

A solution containing the recommended quantities of sucrose and sodium chloride only may be used to prevent dehydration when the other ingredients are not immediately available. Four level teaspoons of sugar and one half level teaspoon of table salt should be dissolved in one litre of water.

A rice-based ORS solution may be made by replacing the glucose or sucrose with 50 grams of rice powder. This should be boiled in one litre of water for 5 minutes and the solution allowed to cool before adding the other ingredients.

The solution should be given as soon as diarrhoea starts. Adults should drink one to two cupfuls (200–500 ml) after each loose stool. If they are thirsty and want more, more should be given. When there are signs of dehydration, subjects require 2.2 – 4 litres of ORS solution over 4 hours, giving 40 – 60 ml every five minutes.

Precautions

Solutions must be freshly prepared, preferably with water that has been recently boiled and cooled.

Accurate weighing and thorough mixing of the ingredients are important. Administration of more concentrated solutions can result in hypernatraemia.

Storage

Pre-packaged ORS solutions are widely available. Solutions which have become discoloured should be discarded.

Chronic Diarrhoea

A mild malabsorption syndrome, that rarely requires therapy, occurs commonly among people living in tropical countries. This mucosal enteropathy is apparently a consequence of frequent enteric infections. Elsewhere, most cases of chronic diarrhoea — which is generally defined as diarrhoea persisting for more than 4 weeks — are attributed to non-infectious inflammatory conditions.

Inflammatory bowel disease

Inflammatory bowel disease is a term that is applied to any chronic inflammatory condition of the gastrointestinal tract, whether it arises from infection, dietary, immunological or other factors. In many instances, the cause of the condition is uncertain, and such cases are often attributed on inconclusive grounds to autoimmune mechanisms. The term includes two common and well characterized clinical conditions: ulcerative colitis and Crohn's disease. Although these two diseases share similar clinical and pathologic features, they are distinct diagnostic entities. Both occur more commonly in developed than in developing countries, and there is evidence that the incidence of Crohn's disease, in particular, is continuing to rise in western Europe and the United States. There are also indications that ulcerative colitis is becoming more common in developing countries. This disease should consequently be considered whenever a patient presents with chronic diarrhoea and persistent blood in the stools.

The inflammatory process in ulcerative colitis, which is confined to the mucosa and superficial submucosa of the large bowel, can cause extensive mucosal ulceration. Typically, the lesions first appear in the rectal mucosa and subsequently extend proximally. Pathologically, the process is characterized initially by infiltration of lymphocytes, plasma cells, eosinophils and polymorphonuclear cells into the mucosa and later by multiple ulcers and abscesses involving the mucosal crypts.

Clinically, the disease is characterized by an irregular sequence of exacerbations and remissions during which patients may remain without symptoms for months or even years. Initially, it presents

insidiously with the onset of bloody diarrhoea which commonly increases in intensity over a period of several weeks. Severe exacerbations result in fluid and electrolyte disturbances and anaemia, often accompanied by secondary manifestations such as anorexia and tachycardia.

The inflammatory process in Crohn's disease, which is also a chronic recurrent illness, is more complex. The pathological lesions are typically focal and, although any part of the alimentary tract can be affected, the terminal ileum and colon are most frequently involved. All layers of the bowel become infiltrated by macrophages and lymphocytes, and this process often extends into the mesentery and regional lymph nodes. The clinical presentation varies with the severity and extent of the disease. Diarrhoea, abdominal pain, fever, weight loss and rectal bleeding are characteristic. Glossitis and mouth ulcers are common features. Malabsorption, which is particularly conspicuous in ileal disease, can result in iron-deficiency anaemia and other signs of nutritional deficiency.

Both ulcerative colitis and Crohn's disease are associated with a wide variety of complications, some — including toxic megacolon, as well as the fistula formation and perforation of the bowels that occur in Crohn's disease — are secondary to intestinal inflammation. Others, including arthritis and inflammatory conditions of the eye and skin (erythema nodosa), are indicative of extraintestinal involvement. In the longer term, both diseases are associated with an increased risk of colorectal cancer.

Treatment

Mild exacerbations, particularly in patients with ulcerative colitis, commonly remit spontaneously without therapeutic intervention. However, more than 80% of patients with Crohn's disease and about 30% of patients with ulcerative colitis ultimately require surgery, either because of chronic unremitting disease, severe exacerbation unresponsive to medical treatment, or premalignant mucosal changes in long-standing extensive disease.

Corticosteroids remain the mainstay of medical treatment for acute exacerbations of inflammatory bowel disease, but adverse effects are common and dose-related. Short courses of oral prednisolone may be necessary to promote remission of severe exacerbations. Long-term treatment with corticosteroids is rarely justified.

In many cases, remission is achieved with less risk of adverse systemic effects by topical administration of steroids in a retention enema. Prednisolone 21-phosphate, a water-soluble salt which is less adsorbed than prednisone itself, is commonly administered by this route. Retention enemas containing hydrocortisone, which is the least potent of the corticosteroids, are also used, particularly in disease confined to the rectum and sigmoid colon.

Sulfasalazine has been used in the treatment of ulcerative colitis for more than 50 years. It is effective in mild or moderately active ulcerative colitis and colonic Crohn's disease and is also commonly used as maintenance therapy during remission in ulcerative colitis. It is now recognized that the therapeutic activity of sulfasalazine derives from the aminosalicyclic acid moiety. The sulfa component, which is responsible for many adverse effects, adds little if any benefit. This has resulted in the relatively recent development of mesalazine and other comparably effective and better tolerated aminosalicyclic acid compounds.

The potential role of immunosuppressant agents in these diseases remains under investigation. Intramuscular methotrexate has been shown to be of value in refractory disease and promising results have also been obtained with azathioprine. The value of ciclosporin is currently being investigated in the treatment of severe disease.

HYDROCORTISONE

suppository 25 mg (acetate); retention enema 100 mg (as sodium succinate)

Hydrocortisone diffuses across the cell membrane and binds to specific cytoplasmic receptors. Its therapeutic effects result from vasoconstriction, reduction of membrane permeability, and suppression of mitotic activity and the immune response.

Uses

Topical treatment of proctitis and proctosigmoiditis.

Dosage and administration

Proctitis: 25 mg suppositories may be used night and morning.

Proctosigmoiditis: A retention enema containing 100 mg of hydrocortisone should be given nightly until symptoms are relieved or to a maximum of 14 days.

Precautions

Hydrocortisone is the least potent of the corticosteroids. Infection involving the rectal and/or colonic mucosa should be effectively treated before hydrocortisone is administered. Only when treatment with this preparation fails should the use of preparations containing more potent corticosteroids be considered.

Any secondary infection should be treated promptly with appropriate antimicrobial therapy.

Use in pregnancy

Use of hydrocortisone should be reduced during pregnancy to the minimum necessary to relieve exacerbation of disease.

Adverse effects

Hydrocortisone administered topically to the bowel over short periods is unlikely to induce serious local or systemic adverse effects.

Storage

Preparations should be stored in well-closed containers.

PREDNISOLONE*tablet 5 mg*

Prednisolone is a synthetic glucocorticoid with weak mineralocorticoid properties. Its therapeutic effect results from inhibition of macrophage accumulation, reduction of capillary wall permeability and oedema formation and reduction of fibroblast proliferation and collagen deposition. It is readily absorbed from the gastrointestinal tract, is extensively protein bound and has a plasma half-life of about 8 hours.

Uses

Severe exacerbations of ulcerative colitis and Crohn's disease requiring systemic corticosteroid therapy.

Dosage and administration

The lowest dosage necessary to produce an acceptable clinical response should be used. Dosage is dependent upon the disease, its severity and the response to treatment.

In general, an initial daily dose of 30 – 60 mg is gradually tapered over a period of 6 to 12 weeks depending on the patient's response.

Long-term treatment is not recommended because of the high risk of adverse effects.

Contraindications

Known hypersensitivity.

Prednisolone increases susceptibility to, and masks the symptoms of infection. Every effort should be made to treat active viral or bacterial infections before treatment is started.

Precautions

The response of the pituitary-adrenal axis to stress is reduced and may remain depressed for many months after withdrawal. Dosage may need to be doubled or restarted temporarily during this period if intercurrent infection occurs.

Patients must appreciate the importance of following dosage instructions rigorously. They should be instructed immediately to seek medical advice and to double the next dose should they become unwell while taking prednisolone.

Corticosteroids should be used only for serious exacerbations of inflammatory disease in patients with diabetes, tuberculosis, peptic ulcer, hypertension, heart failure, epilepsy, a history of mental disorder or psoriasis.

Patients previously treated for tuberculosis should receive prophylactic chemotherapy during prolonged corticosteroid therapy.

Persons exposed to chickenpox or other viral infections of childhood during corticosteroid therapy and who may not have developed specific immunity should receive a course of appropriate immunoglobulin. They should not receive live virus vaccines.

Use in pregnancy

Systemically administered corticosteroids should not be administered during pregnancy unless the health of the mother is otherwise endangered. Adrenal development may be impaired in the fetus and an association with cleft palate and other abnormalities may exist, particularly in the case of fluorinated compounds. Dosage should be kept as low as possible.

Adverse effects

Doses in excess of 20 mg daily are immunosuppressive. Infections contracted during therapy can be overwhelming in the absence of effective treatment. Quiescent tuberculosis may be reactivated.

Continuous dosage in excess of normal physiological requirements (approximately 10 mg daily) is liable to result in:

- stunting of growth in children, which may be averted by alternate day dosage schedules or by giving corticotrophin;
- features of hypercorticism, including moonface, hirsutism, acne, bruising, striae, redistribution of fat, muscle wasting, hypertension;
- spinal osteoporosis and vertebral collapse, which may be retarded by calcium supplements and small doses of vitamin D;
- aseptic osteonecrosis, particularly of the femoral head;
- subcapsular cataracts, glaucoma;
- development or aggravation of peptic ulcer;
- diabetes mellitus;
- depression and psychosis, with risk of suicide;
- raised intracranial pressure and convulsions, particularly in children;
- increased coagulability of blood;
- delayed tissue healing;
- myopathy characterized by weakness of proximal muscles of arms and legs.

Psoriasis may be seriously exacerbated on withdrawal of corticosteroid therapy.

Drug interactions

Hepatic enzyme inducers including phenobarbitone, phenytoin and rifampicin may accelerate the metabolism of prednisolone.

The response to oral anticoagulants may be altered. Inhibition is characteristic, but isolated reports of potentiation are on record.

The risk of hypokalaemia is increased when corticosteroids are taken concomitantly with potassium-losing diuretics.

Overdosage

In the event of a single large overdosage, specific treatment is unlikely to be required. Symptomatic treatment is indicated for reactions due to chronic poisoning.

Storage

Tablets should be stored in well-closed containers.

SULFASALAZINE

tablet 500 mg

Sulfasalazine is composed of sulfapyridine and 5-aminosalicylic acid joined by a diazo bond. It is poorly absorbed from the small intestine of the component parts, sulfapyridine is absorbed but the active component, 5-aminosalicylic acid, remains largely in the colon and is released as a result of bacterial activity.

Uses

Treatment of mild to moderately severe ulcerative colitis.

Treatment of Crohn's disease involving the colon.

Dosage and administration

Adults: 1–2 g four times daily may be required in severe attacks. This can be reduced to 2 g daily in ulcerative colitis for maintenance of remission.

Contraindications

Known hypersensitivity to sulfonamides or salicylates.

Precautions

The blood count should be monitored at the start of treatment and at monthly intervals thereafter.

Liver function tests should be carried out at regular intervals.

Patients with glucose-6-phosphate dehydrogenase deficiency should be closely observed for signs of haemolytic anaemia.

Adverse effects

Nausea, headache, loss of appetite and fever are common adverse effects.

Folate deficiency is common; adequate dietary intake should be assured.

Hypersensitivity reactions include generalized skin rashes and urticaria and, occasionally, life-threatening Stevens-Johnson syndrome or anaphylaxis.

Patients with glucose-6-phosphate dehydrogenase deficiency are at particular risk of haemolytic anaemia.

Bone marrow depression occurs rarely.

Toxic hepatitis has been reported.

Reversible oligospermia and male infertility have been described.

Use in pregnancy

There is no evidence that sulfasalazine has teratogenic potential.

Drug interaction

Sulfasalazine can impair the absorption of digoxin

and an interval of 2–3 hours should elapse between oral administration of these drugs.

Overdosage

Emesis and gastric lavage may be of value within a few hours of overdosage. Otherwise, treatment is supportive.

Storage

Tablets should be stored in well-closed containers.