

# Essential Drugs

## Dysentery

Where diarrhoea remains an important cause of illness and death among young children, about 10% of cases — and a somewhat higher proportion of fatalities — result from dysentery. In developing countries, the disease is often a common cause of death among malnourished infants who are highly vulnerable to infectious diseases. In industrialized countries, dysentery is rarely complicated or clinically severe and case-fatality rates are generally low.

The most common cause of dysentery is invasion of the intestinal mucosa by pathogenic bacteria. Most cases are caused by strains of *Shigella*, which are estimated to be responsible for as many as 140 million episodes annually throughout the world. Shigellosis is almost exclusively an infection of human beings and the organisms are transmitted by faecal contamination of food, hands or water. The strains *Shigella flexneri* and, to a lesser extent, *S. dysenteriae* and *S. boydii* are the most common causes of dysentery. Other causes are *Campylobacter jejuni* especially in infants and, less frequently, enteroinvasive *Escherichia coli* or *Salmonella*. *Entamoeba histolytica*, which in some regions is an important cause of dysentery in young adults, is a very uncommon cause in children under 5 years of age.

After ingestion, the bacteria pass innocuously through the stomach and small intestine to invade the colonic mucosa where they multiply rapidly in epithelial cells. The resultant inflammatory response, which is probably exacerbated by production of toxins, causes mucosal ulceration, bleeding and fluid loss which may be considerable.

The classical symptoms of shigellosis are fever, diarrhoea with blood and mucus, abdominal cramps and tenesmus. In many cases the illness resolves spontaneously within 7 days. However, severe infections due to *S. flexneri* and *S. boydii*, and epidemics due to *S. dysenteriae*, which are common in developing countries, are more likely to give rise to complications. Megacolon, rectal prolapse, and occasionally perforation of the colon may occur. Among the systemic complications, seizures are common in children during the early

stage of the illness. Severe and rapid haemolysis together with anuria (haemolytic uraemic syndrome) and septicaemia are often associated with a fatal outcome. A reactive arthritis has been associated with *S. flexneri*. Rapid weight loss and deterioration of the nutritional status due to anorexia, inversed catabolism and loss of protein from the damaged intestine progress rapidly if diarrhoea persists unchecked. Shigellosis with extensive ileal and colonic involvement has a high fatality rate, particularly when it is complicated by sepsis, measles or other secondary infection and severe malnutrition.

Infection with *Campylobacter jejuni* is common in birds and poultry, which are the largest reservoir of infection. Transmission to humans is caused by consumption of infected poultry or contact with their excreta. Dysentery caused by this agent is seldom severe. The accompanying fluid loss can be treated with oral rehydration salts. Antimicrobial therapy is effective only if begun early in the illness, which is seldom possible.

*Entamoeba histolytica* is a protozoan parasite which is usually transmitted from person to person through faecal contamination of food or hands, but may also be transmitted by sexual contact in homosexual men. Amoebic dysentery occurs when the parasites invade the intestinal wall. Abscesses may also develop in the liver or, less frequently, in the lung or brain as a result of haematogenous spread.

The availability of metronidazole — and several other 5-nitroimidazoles, including ornidazole, tinidazole and secnidazole — has made the management of most cases of amoebic dysentery simpler and safer. Parenteral formulations of metronidazole, ornidazole and tinidazole are available for patients too ill to take drugs by mouth. In severe cases of amoebic dysentery, tetracycline lessens the risk of superinfection, intestinal perforation and peritonitis when it is given in addition to a systemic amoebicide.

## Prevention

Primary health care workers in developing countries should be soundly trained to recognize the disease and to prevent its transmission. All children should

be immunized against measles at the recommended age, and vitamin A supplements should be provided when deficiency cannot be corrected from dietary sources.

Specific preventive measures include:

- feeding infants exclusively at the breast for the first 4–6 months of life, and continuing to breast feed for at least two years;
- effective sterilization of infant feeding bottles when these have to be used;
- providing clean drinking water;
- eating cooked food as soon as possible after it has been prepared;
- thoroughly reheating any food that has been kept at room temperature for more than 2 hours;
- washing hands after defecating and before preparing food or eating; and
- disposing of faeces safely.

#### Treatment

Every child with dysentery is in urgent need of treatment. Fluid and electrolyte balance should be restored and maintained, whenever possible by administration of oral rehydration solution. Feeding should be encouraged to prevent or correct any acute nutritional deficiency. Patients with severe fluid or nutritional deficiency require hospital treatment.

Initial treatment should be for shigellosis, which is the most common cause of dysentery. In contradistinction to non-specific diarrhoea, effective antibiotic therapy shortens the duration of the illness and considerably reduces the risk of serious complications. Whereas ampicillin remains the standard treatment of susceptible shigella strains, resistance is common. Sulfamethoxazole/trimethoprim is now consequently used in many countries. If improvement is evident within 2 days, no follow-up is necessary other than to ensure that the patient completes the 5-day course of antibiotic treatment. Patients who show no sign of improvement after 2 days should be transferred to another antibiotic, preferably nalidixic acid or ciprofloxacin. In areas where Shigellae are resistant to both amoxicillin and sulfamethoxazole/trimethoprim, nalidixic acid is usually the drug of choice. Amoxycillin, which is more extensively absorbed than ampicillin from the

gastrointestinal tract, is not recommended for the treatment of dysentery.

Routine stool culture is not required; however regular monitoring of the antibacterial sensitivity of shigella is important in order to guide the selection of an appropriate antimicrobial agent. Treatment for *E. histolytica* should be given only when trophozoites of *E. histolytica* containing ingested red blood cells are seen in the faeces or when there has been no improvement after giving an antimicrobial agent to which Shigellae in the area are known to be sensitive.

## ORAL REHYDRATION SALTS

(glucose-salt solution)

	g/litre of clean water
sodium chloride	3.5
trisodium citrate	2.9
potassium chloride	1.5
glucose (anhydrous)	20.0

Oral rehydration solution is optimally constituted to correct the fluid and electrolyte losses which result from acute diarrhoea in infants, older children and adults.

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

	g/litre of clean water
sucrose (common sugar)	40.00
sodium bicarbonate	2.5

#### Uses

Prevention and treatment of dehydration from shigellosis and other forms of 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 sugar/salt 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 prepared when the other ingredients are not immediately available.

An equally effective 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. It is important to administer the solution in small amounts at regular intervals as detailed in the table. For infants and young children the requirement is approximately one 5 ml teaspoonful every 1 to 2 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 is 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.

## SULFAMETHOXAZOLE + TRIMETHOPRIM

*tablet, 100 mg + 20 mg, 400 mg + 80 mg  
oral suspension, 200 mg + 40 mg/5 ml*

The two components of this combination product have a similar antibacterial spectrum. They operate synergistically because they act independently on different steps in the enzymic synthesis of tetrahydrofolic acid, an essential metabolic process in susceptible bacteria. The combination enhances the bactericidal potency of the individual constituents and impedes the emergence of resistance. Trimethoprim is absorbed more rapidly and is more widely distributed in tissues than sulfamethoxazole and readily enters the cerebrospinal fluid. Both compounds are extensively bound to plasma proteins. The plasma half-life of both compounds is about 24 hours and each is excreted largely unchanged in the urine.

#### Uses

Treatment of shigellosis when strains are known to be susceptible.

#### Dosage

*Adults:* 800 mg sulfamethoxazole + 160 mg trimethoprim in two divided doses for 5 days.

*Children:* 25 mg/kg sulfamethoxazole + 5 mg/kg trimethoprim for 5 days in two divided doses.

### Approximate amount of ORS solution to give in first 4 hours for patients with clinical evidence of dehydration

Age*	Less than 4 months	4 – 11 months	12 – 23 months	2 – 4 years	5 – 14 years	15 years or older
Weight	Less than 5 kg	5 – 7.9 kg	8 – 10.9 kg	11 – 15.9 kg	16 – 29.9 kg	30 kg or more
ORS (ml)	200 – 400	400 – 600	600 – 800	800 – 1200	1200 – 2200	2200 – 4000

\* Use the patient's age only when you do not know the weight. The approximate amount of ORS required (in ml) can also be calculated by multiplying the patient's weight (in kg) times 75.

- If the patient wants more ORS than shown, give more.
- Encourage the mother to continue breast-feeding.
- For infants under 6 months who are not breast-fed, also give 100 – 200 ml clean water during this period.

**Contraindications**

Known hypersensitivity to sulfonamides.  
Severe hepatic or renal dysfunction.

**Precautions**

Treatment should be suspended immediately should a rash, or any other manifestation of sulfonamide hypersensitivity occur.

**Use in pregnancy**

Safe use in pregnancy has not been established. However, during epidemics of dysentery treatment should not be deferred.

**Adverse effects**

Sulfonamide-induced hypersensitivity reactions, although uncommon, can be severe. They include life-threatening cutaneous reactions such as erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Other infrequent reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Occasionally, haemolysis occurs in G6PD deficient individuals.

**Storage**

Sulfamethoxazole/trimethoprim tablets should be stored in well-closed containers.

**AMPICILLIN**

*capsules or tablets 250mg, 500 mg*

Ampicillin, an aminopenicillin, is a semisynthetic penicillin which is active against many strains of enterobacteriaceae including shigellae. It is moderately absorbed from the gastrointestinal tract. Peak plasma levels are attained after approximately 2 hours. It appears in the bile, undergoes enterohepatic circulation and is excreted in the faeces. Resistance of Shigellae to ampicillin is widespread in many areas.

**Uses**

Treatment of dysentery due to susceptible organisms.

**Dosage and administration**

*Adults:* 500 mg four times daily for 5 days.

*Children:* 50 mg/kg four times daily for 5 days.

**Contraindications**

Known hypersensitivity to penicillins.

**Precautions**

Facilities should be available for treating anaphylaxis whenever penicillins are used.

Patients should be questioned carefully about previous allergic reactions.

If no improvement occurs after 2 days, patients should be transferred to another antibiotic.

**Use in pregnancy**

Amoxicillin can be used during pregnancy.

**Adverse reactions**

Hypersensitivity reactions range in severity from skin rashes to immediate anaphylaxis.

Generalized erythematous maculopapular rashes are frequent. They usually occur within 3 to 14 days after the drug has been started, initially appearing on the trunk and thereafter spreading peripherally to involve most of the body. In most instances the rash is mild and subsides after 6 to 14 days despite continuation of therapy.

Continued diarrhoea may be an adverse effect of treatment with ampicillin.

Interstitial nephritis has been reported and neutropenia and thrombocytopenia have occurred.

**Overdosage**

Overdosage can cause convulsions, paralysis and even death.

Prompt emesis and gastric lavage within a few hours of ingestion may be of value. Excessive blood concentrations can be lowered by haemodialysis.

**Storage**

Capsules or tablets should be stored in tightly closed containers, protected from light.

**NALIDIXIC ACID**

*tablet 250 mg*

Nalidixic acid is a synthetic quinolone antimicrobial agent which acts as a specific inhibitor of bacterial DNA gyrase. It is bactericidal against enterobacteriaceae including many strains of shigellae. It is rapidly and completely absorbed from the gastrointestinal tract. The plasma half-life is 1–2.5 hours and the drug is excreted as metabolites and unchanged drug in the urine.

**Uses**

Treatment of dysentery due to organisms resistant to ampicillin and sulfamethoxazole/trimethoprim.

**Dosage and administration**

*Adults:* 1 g four times daily for 5 days.

*Children:* 15 mg/kg four times daily for 5 days.

**Contraindications**

Hypersensitivity to any quinolone.

Infants under 3 months.

Pregnancy.

**Precautions**

Reduced dosage should be considered in patients with hepatic or renal impairment.

Nalidixic acid should be administered cautiously to patients with epilepsy since seizures may be precipitated.

Adequate fluid intake must be assured since crystalluria may occur.

Similar to other quinolones, nalidixic acid has caused arthropathy in the weight-bearing joints of young animals. It is recommended for use in children only if other agents are ineffective.

**Adverse effects**

The most frequently reported adverse effects are nausea and vomiting. Visual disturbances, headache, skin rash and pruritus also occur occasionally.

Allergic reactions to nalidixic acid include rash and urticaria. Eosinophilia, pruritus and photosensitivity occur occasionally.

Hepatic and renal disturbances have also been reported.

**Drug interactions**

Prolonged bleeding time has been reported in patients receiving anticoagulants concurrently.

**Overdosage**

Gastric lavage is of value if performed promptly. Electrolyte balance must be maintained.

Anticonvulsants may be needed for the treatment of seizures.

**Storage**

Tablets should be stored in well-closed containers.

**CIPROFLOXACIN****tablet 250 mg (as hydrochloride)**

Ciprofloxacin is a synthetic quinolone which acts as a specific inhibitor of bacterial DNA gyrase. It has a broad spectrum of antibacterial efficacy against both Gram-negative and Gram-positive aerobic organisms.

It is rapidly absorbed from the gastrointestinal tract; it has a plasma half-life of 3–5 hours and is excreted in the urine mainly as unchanged drug.

**Uses**

Treatment of dysentery due to organisms resistant to amoxicillin and sulfamethoxazole/trimethoprim and nalidixic acid.

**Dosage and administration**

*Adults:* 250 mg twice daily for 5 days. Shorter courses of treatment are being evaluated.

**Contraindications**

Hypersensitivity to any quinolone.

Pregnancy, adolescents and children since arthropathy has been induced in weight-bearing joints of young animals.

**Precautions**

Reduced dosage should be considered in patients with hepatic or renal impairment.

Ciprofloxacin should be administered cautiously to patients with epilepsy since seizures may be precipitated.

Adequate fluid intake must be assured since crystalluria may occur.

**Adverse effects**

Ciprofloxacin is generally well tolerated. The most frequently reported adverse effects are nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, headache, restlessness, tremor, confusion, hallucinations, dizziness, rash and pruritus. Myalgia and tendinitis have also been reported. Hepatic and renal disturbances have also been reported.

**Drug interactions**

Plasma concentrations of theophylline may be raised.

Prolonged bleeding time has been reported in patients receiving anticoagulants concurrently.

**Overdosage**

Gastric lavage is of value if performed promptly. Electrolyte balance must be maintained. Serum

concentrations of ciprofloxacin may be lowered by dialysis.

**Storage**

Tablets should be stored in well-closed containers.

**METRONIDAZOLE**

*group: antimicrobial agent*

*tablet: 200 mg, 250 mg, 400 mg, 500 mg*

*suspension: 200 mg/5 ml*

A 5-nitroimidazole derivative with antimicrobial activity against anaerobic bacteria and some protozoa, including *E. histolytica* and *G.intestinalis*. Metronidazole is almost completely absorbed following oral administration. Its plasma half-life is about 8-hours and it is excreted in the urine, both unchanged and as metabolites.

**Uses**

Treatment of giardiasis and confirmed invasive amoebiasis.

**Dosage and administration**

Metronidazole should be administered preferably with or immediately after food.

Various dosage regimens are used. The following regimen is widely accepted but definitive recommendations should be based on local experience.

*Adults and children:* 30 mg/kg daily orally in three divided doses after meals for 5 days or i.v. in three divided injections daily until the patient is able to take oral formulations.

Treatment should be given for 10 days in severe cases.

**Contraindications**

- Known hypersensitivity.
- Early pregnancy.
- Chronic alcohol dependence.

**Precautions**

Patients should be warned not to take alcohol during treatment since disulfiram-like reactions can occur.

**Use in pregnancy and lactation**

Amoebic dysentery may run a fulminating course during late pregnancy and the puerperium. Treatment with metronidazole may then be life-saving to the mother, but in some cases of severe dysentery surgical resection of the intestine may also be necessary. In less severe infections, metronidazole is best avoided in the first trimester since it has been shown to have mutagenic and carcinogenic potential in animals.

It is advisable during treatment to discontinue breast-feeding, particularly of premature infants.

**Adverse effects**

In general, metronidazole is well tolerated, but mild symptoms of headache, gastrointestinal irritation and a persistent metallic taste are common. Less frequently, drowsiness, rashes and darkening of urine occur.

More serious reactions are rare and usually occur only during extended courses of treatment. They include stomatitis and candidiasis, reversible leukopenia, and sensory peripheral neuropathy, which is usually mild and rapidly reversible.

Ataxia and epileptiform seizures have been reported among patients receiving dosages considerably higher than those currently recommended.

**Drug interactions**

The action of oral anticoagulants is potentiated. Alcohol may induce abdominal pain, vomiting, flushing and headache.

Phenobarbital and corticosteroids lower plasma levels of metronidazole whereas cimetidine raises them.

**Overdosage**

No specific treatment exists. Emesis or gastric lavage may be of value within a few hours of ingestion.

**Storage**

Tablets and suspension should be kept in well-closed containers, protected from light.

**The information in this section is subject to consultation prior to definitive publication in the WHO Model Prescribing Information series. Comments, which are invited at this stage, should be referred to: Division of Drug Management and Policies, World Health Organization, 1211 Geneva 27, Switzerland**