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15 DIARRHEAL DISEASES

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INTRODUCTION

A cautious estimate in the beginning of the 1980s concluded that approximately 4.6 million children under 5 years of age in developing countries die from diarrheal diseases each year and the annual number of diarrheal episodes in this age group is above one billion.[1] Although the majority of diarrheal episodes are not severe and may not require specific intervention, a large number are potentially fatal. Identification and proper management of the severe episodes is the most urgent target of control efforts, while prevention of all mild episodes is of lower priority.

Approximately two-thirds of diarrheal deaths are attributable to dehydration and, therefore, preventable by adequate fluid therapy. Introduction and worldwide implementation of oral rehydration therapy (ORT) has had a significant impact in reducing diarrheal mortality, although exact figures are difficult to obtain. Moreover, after initial success, progress seems to have slowed down in recent years.

The remaining one-third of diarrheal deaths are due to a number of causes, and no single intervention is available to prevent them. These deaths include those from *shigellosis* with septicemia and various gastro-intestinal complications and deaths from *measles-associated diarrhea. Persistent and prolonged diarrhea* may follow an episode initiated by any of a variety of enteropathogens. Loss of nutrients associated with persistent or repeated diarrhea results in malnutrition, failure to thrive, increased susceptibility to secondary infections, and ultimately death.

CAUSAL ORGANISMS AND DISEASE ENTITIES

The enteric pathogens causing acute diarrhea in developing countries are largely the same that are encountered in developed countries, but their proportions are different. In general, bacterial pathogens are more important in countries with poor hygienic conditions. Rotavirus is an important pathogen in developing as well as developed countries, but in developing countries it is outnumbered by the excess of bacterial pathogens.

Regional differences in the etiology of acute diarrhea of children are relatively minor. Rather, several longitudinal etiology studies of acute diarrhea have revealed a surprisingly similar distribution of causative organisms in different parts of the world.[2] Many enteropathogens are frequently found in the stools of healthy children, and detection of a potential pathogen from a patient does not necessarily imply a causal relationship with diarrhea.

Even though an etiological agent can be determined in 70–80 per cent of cases of acute diarrhea in developing countries, microbiological diagnosis is seldom required for case management. The same general principles of management are applicable in most cases of acute diarrhea, regardless of etiology.

Table 15.1. Main causative organisms of acute diarrhea in developing countries.

Pathogen	Significance
Rotavirus	Over 800 000 deaths/year 30% of diarrheal mortality in age group 6-24 months
Shigellae	Over 500 000 deaths/year Dysentery, watery diarrhea
Enterotoxigenic *E. coli* (ETEC)	Over 500 000 deaths/year Most cases in children under 2 years of age
Vibrio cholerae	Over 100 000 deaths/year Pandemic spread from Asia to Africa to Latin America
Campylobacter jejuni	Significant pathogen in infants under 6 months of age
Enteropathogenic *E. coli* (EPEC)	Significant pathogen in infants under 6 months of age
Salmonella sp.	In 'transitional' urban areas

Knowledge of etiology is needed, however, to plan preventive measures and, especially, for development of vaccines.[2] The most common etiological agents are listed in Table 15.1 and discussed briefly below.

Rotavirus

Rotavirus is the single most important causal agent of acute watery diarrhea leading to severe dehydration. Rotavirus disease is characterised by vomiting, fever, and profuse watery diarrhea; this combination rapidly results in dehydration and necessitates a visit to treatment centre, if accessible. Because of the severity of the clinical picture, rotavirus is over-represented in hospital-based etiological studies, in which it may account for up to 40 per cent of all cases. In contrast, in community-based studies the etiological role of rotavirus is less than 10 per cent of all episodes of diarrhea.

The typical age for rotavirus diarrhea is between 6 and 11 months of age, but in developing countries cases begin from 2 months and extend beyond 2 years of age. In the age group 6–23 months rotavirus has been estimated to be responsible for 30 per cent of all diarrheal deaths.[3]

Rotavirus disease typically occurs only once, but in developing countries symptomatic reinfections are more common than in developed countries. In temperate climates rotavirus occurs seasonally with a peak in the cold season; in tropical countries seasonal variation is less clear or absent. Lack of seasonality may also be a sign of poor hygienic conditions and faecal-oral spread, in contrast to aerosol transmission thought to occur in developed countries. In some countries there are two patterns of rotavirus disease: for example, in South Africa rotavirus occurs seasonally in the white population and year round in the black population.

Group B rotavirus is a distinct agent that has caused large outbreaks of acute diarrhea in China, but not elsewhere. Most of the cases have been in adults, hence the name adult rotavirus. Other viral agents appear to play only a minor role in acute diarrhea in developing countries.

Escherichia coli

Enterotoxigenic *E. coli* (ETEC) are found in 10 to 50 per cent (average about 20 per cent) of cases in hospital- or clinic-based etiological studies of acute diarrhea in developing countries.[2] ETEC may be after rotavirus the second most common cause of dehydrating diarrhea in young children, particularly in children under 2 years of age; by age 5, children in developing countries have generally acquired immunity to these bacteria. In contrast, ETEC cause traveller's diarrhea among visitors to developing countries even in adult age, due to lack of immunity.

Two types of ETEC toxins, LT (heat-labile) and ST (heat-stable) can cause diarrhea. Phenotypically, the bacteria may be ST only, LT only or both ST/LT. To cause diarrhea, ETEC must first adhere to the gut mucosa with colonisation factor antigens. These antigens appear to be targets of acquired immunity to ETEC and hence potentially useful in experimental vaccines.

Enteropathogenic *E. coli* (EPEC) also cause diarrhea in developing countries, but only in

the first months of life. Later, EPEC are found as commonly in healthy controls as is in patients with diarrhea.

Shigellae

Shigellosis commonly refers to dysentery, the clinical picture of which includes fever, abdominal cramps and bloody diarrhea with frequent, small and mucoid stools. Dysentery may be complicated by convulsions, paralytic ileus, septicemia and hemolytic-uremic syndrome, and may lead to persistent diarrhea and protein losing enteropathy. More than 500 000 children, mostly under the age of five, die annually from the various complications of shigellosis. In addition, *Shigellae* cause watery diarrhea, accounting for 10–20 per cent of cases of acute childhood diarrhea in treatment centres.

Both *S. flexneri* and *S. dysenteriae* 1 are important causes of dysentery in developing countries. In 1969, *S. dysenteriae* 1 reappeared after several decades in Central America, starting a new pandemic. Shigellosis is one of the few diarrheal infections in which antibiotics are indicated. The bacteria are often resistant to several common antibiotics, and the choice of antimicrobial therapy may pose a difficult problem. In developing countries bloody diarrhea (dysentery) should be regarded as suggestive of shigellosis and treated with antimicrobials without waiting for laboratory confirmation. Local knowledge of antimicrobial sensitivity is helpful for the choice of drug (Table 15.5). If available and affordable, new fluorokinolones are the most effective agents against multiply resistant shigellae.

Salmonellae

In contrast to the great public health significance of *Salmonella* sp. in developed countries, *Salmonellae* are generally not regarded as significant causative agents of diarrhea in developing countries. However, this may be true only for rural conditions, whereas in urban areas where processed foods are used the etiological role of *Salmonellae* in childhood diarrhea may be significant.

Apart from diarrhea, *Salmonellae* cause a disease entity called *enteric fever*. When caused by *S. typhi* the disease is *typhoid fever*, but a similar clinical picture may be associated with infection by *S. paratyphi* and occasionally other *Salmonellae*. Clinical symptoms include fever, abdominal pains, headache, and cough, and clinical signs include coated tongue, splenomegaly, rales in lungs and relative bradycardia. Usually there is no diarrhea.

Typhoid fever, although not a diarrheal disease, is transmitted by contaminated food and water like other enteric infections. In developing countries the source of infection is more often food than water, and open kitchens on street sides, which are common in many developing countries, often transmit the disease. Typically, school-age children are infected, but typhoid fever occurs from age one onwards. Typhoid fever is endemic in large parts of the world and carries an estimated death toll of 500–600 000 per year.

Campylobacter

Campylobacter infections are very common in developing countries. The source is often chickens that run freely around human dwellings. Immunity apparently develops at an early age and *Campylobacter jejuni* is usually established as a causal agent of acute diarrhea only in infants less than 6 months of age.

Vibrio cholerae

Cholera is endemic in the Indian subcontinent, where the classical biotype of *Vibrio cholerae* is encountered. The epidemic type of cholera that occurs in large parts of the world Asia, Africa and South America is caused by biotype El Tor. The El Tor pandemic (the seventh) began in Indonesia in 1961 and continues to spread. An estimated 120 000 deaths are caused annually by cholera, one-third of them in children under five, a quarter in children aged 5–14, and the remainder in adults.[3]

The number of cholera cases and associated deaths are difficult to estimate since many countries intentionally underreport cholera. When cholera broke out in the coastal region of Peru in 1991, exact figures were obtained. In 1991 there were 366 225 cases and 3893 deaths (case–fatality rate about 1 per cent) reported to the WHO by ten Latin American countries.[4]

Today most cases of cholera are manageable with ORT, although intravenous fluid therapy is commonly applied in specialised treatment centres. In addition, antimicrobials are routinely given.

Table 15.2. General principles of case management of acute diarrhea.

1. ORT = oral rehydration therapy
   - Correction of fluid deficit: ORS 70–100 ml/kg body weight in 4–6 hours.
   - Replacement of continuous fluid losses: ORS to substitute for stool volume and vomiting.
2. Dietary management
   - Breast-feeding must not be interrupted.
   - Start feeding according to age as soon as clinical signs of dehydration disappear, and continue feeding even if severe diarrhea persists.
3. Antimicrobials
   - Should be used only in special circumstances: dysentery, enteric fever, cholera.
4. Anti-diarrheal drugs
   - Should be generally avoided.

CASE MANAGEMENT OF ACUTE DIARRHEA

The general principles of case management (Table 15.2) are applicable to most cases of acute diarrhea regardless of etiology and pathogenetic mechanisms.[5]

Dehydration

Recognition of dehydration and its correction is the first priority in the treatment of acute diarrhea. Not all diarrheal episodes in developing countries are associated with dehydration and, consequently, do not require rehydration therapy. However, promotion of the basic concept that diarrhea and vomiting are likely to result in life-threatening dehydration continues to be of great importance. This educational promotion should be aimed at all levels from families to doctors.

Clinical signs of dehydration (Figure 15.1) include: sunken eyes, thirst and dry mouth, a sunken fontanelle in infants, reduced skin turgor, low urinary output, lethargy and apathy. In severe cases the patient can go into hypovolemic shock with cold sweat, a fast and weak pulse and reduced consciousness. This happens when the dehydration is equivalent to a loss of 15 per cent of body weight. Young infants may lose more fluid before critical signs appear. However, an exact estimation of the degree of dehydration is difficult without information about the child's weight before the diarrheal episode; this is usually unavailable. On the other hand, oral rehydration can be carried out safely and effectively without knowledge of the exact degree of dehydration. The WHO now recognises two intensities of dehydration, based on clinical signs: 1) some degree of dehydration; and 2) severe dehydration. Clinical signs to assess the severity of dehydration are listed in Table 15.3.[5]

Most episodes of dehydration are *isotonic*, that is the child has lost water and electrolytes in the same proportion. However, hypertonic and hypotonic dehydration can also occur and are more common in developing than developed countries.

Hypertonic dehydration occurs in young infants who are not breast-fed but receive commercial milk substitutes and carbohydrate-rich foods. It is characterised by central nervous system symptoms, such as irritability and restlessness. Such a child is severely ill even though he has not lost much weight. These cases are manageable by ORT but the rehydration should be done at a slower rate.[6]

Hypotonic dehydration is common especially in severely malnourished children, or when rehydration has been attempted with plain water, teas, or herb infusions. Treatment is not much different from isotonic dehydration.[6]

ORS

The physiological principles of oral rehydration, established in the 1960s, include: 1) water is absorbed from the intestine together with

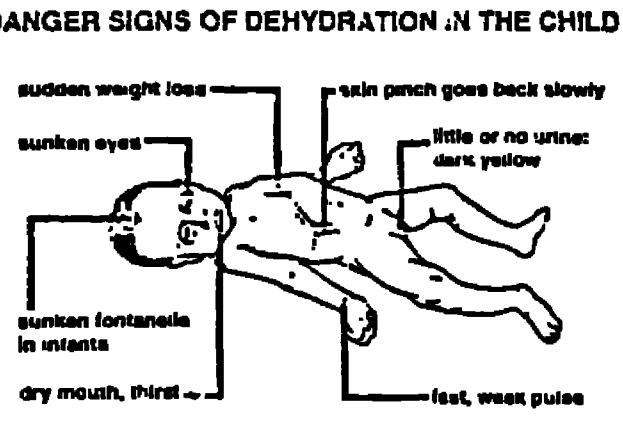


Figure 15.1. Signs of dehydration in a child (courtesy of Dr M. Merson, WHO Diarrhoeal Diseases Control Programme).

Table 15.3. Clinical signs to assess the severity of dehydration.

Sign	No dehydration	Mild/moderate	Severe
Patient's appearance	well, alert	* restless, irritable	* unconscious or limp, or too weak to move or drink (shock)
Radial pulse	normal	rapid	* very weak or absent
Thirst	not thirsty	some thirst or * thirsty, drinks eagerly	* very thirsty drinks poorly, or not able to drink
Eyes, fontanelle	normal, tears present	slightly sunken, tears present or absent	sunken, dry eyes, tears absent
Urine flow	normal	decreased	none for several hours
Skin elasticity	normal	less than normal, * skin pinch goes back somewhat slowly	poor, skin pinch goes back very slowly
Mouth and tongue	moist	dry	very dry
Hands and feet	warm or slightly cold	slightly cold	cold, usually moist and pale

* Especially important signs. Two or more signs in the column, including at least one especially important sign (*), indicates mild/moderate or severe dehydration.

sodium (Na^+), hence salt is required in the solution; 2) absorption of sodium is coupled with absorption of organic substances like glucose, amino acids or dipeptides. For this reason the solution should contain an organic molecule, usually glucose; 3) for maximal absorption of water, sodium and glucose should be present in approximately equimolar proportions.[7]

Based on these principles, a consensus was reached in the 1970s about a formula, which since then has been the ORS (oral rehydration salts) recommended by the WHO and UNICEF (Table 15.4). The composition of this ORS is a compromise between high sodium solutions required for the treatment of cholera and those of lower sodium concentration which would be sufficient for treatment of non-cholera diarrhea.

Thus the ORS-WHO may be regarded as a universal, all-purpose, solution; but does not mean that it is the optimal solution. However, it is important to have a single acceptable formula that can be recommended and promoted worldwide. ORS-WHO is an extremely safe therapeutic tool: over two billion units of ORS have been administered without serious complications.

ORS-WHO with its relatively high concentration of sodium (90 mmol/l) is particularly suitable for treatment of cholera, in which the loss of sodium (and chloride) is greater than in other types of diarrhea. The relatively high sodium content also makes ORS-WHO suitable for the correction of the sodium deficit that usually develops in the initial days of acute non-cholera diarrhea.

ORS contains a small amount of potassium which will correct only partially the potassium deficit of diarrhea that has developed if diarrhea lasted for several days or the potassium deficit that is characteristic of severe malnutrition. However, since oral rehydration should be accomplished within 4–12 hours, the remaining potassium deficit can be replenished with the introduction of foods, particularly fruits and vegetables.

Citrate acts as a base precursor and helps to correct acidosis sooner than rehydration alone would do. The ORS formula originally recommended by WHO contained bicarbonate instead of citrate; however, even when packed in sachets, bicarbonate absorbs moisture when kept in a warm and humid environment, common in developing countries. Citrate keeps much better and has substituted bicarbonate in ORS for logistic reasons. Even so, also the bicarbonate-containing formula continues to be endorsed. This is the only change that has been made in the composition of ORS over the past 20 years.

Several modifications of ORS have been attempted in the last decade. A so-called super-ORS, which contained various amino acids in

Table 15.4. Composition of oral rehydration salts solution (ORS).

Standard ORS recommended by the WHO and UNICEF			
Composition in mmol/l		**Recipe for preparation**	
Na+	90	NaCl	3.5 g
K+	20	KCl	1.5 g
Cl-	80	Na-citrate*	2.9 g
citrate	10		
glucose	111	Glucose†	20.0 g
Total osmolality	311	Water	1000.0 ml

Hypotonic ORS (not officially endorsed by the WHO)			
Composition in mmol/l		**Recipe for preparation**	
Na+	60	NaCl	1.8 g
K+	20	KCl	1.5 g
Cl-	50	Na-citrate*	2.9 g
citrate	10		
glucose	84	Glucose†	15.1 g
Total osmolality	224	Water	1000.0 ml

*Trisodium citrate dihydrate
†Anhydrous glucose

addition to glucose, has been abandoned. Rice-based or cereal-based ORS are actually somewhat more effective than the standard ORS.[8] These can be made locally, and rice-ORS is also available as dry powder. Disadvantages of rice-ORS include large size of the package, jelly-like consistency when reconstituted, and relatively short shelf-life.

A recent improvement has been the discovery that a hypotonic ORS has better absorption properties than an isotonic solution.[9] Although it has not been officially endorsed by the WHO, the use of hypotonic ORS has given good results in the treatment of dehydration due to non-cholera diarrhea. One formula for hypotonic ORS is presented in Table 15.4.

Home-made salt–sugar solutions are widely used as substitutes for ORS. These are acceptable alternatives for home use to prevent dehydration when ORS is not available, but are inadequate for treatment of dehydration at treatment centres, except in emergency. The use of home-made solutions has been often associated with hypernatremic complications.

ORS is usually packaged in aluminium sachets (Figure 15.2). On reconstitution the contents of a sachet is mixed with 1 litre of water.

Oral rehydration therapy (ORT)

In developing country conditions it usually is not possible to calculate the degree of dehydration at the onset of therapy. Fortunately this is not essential with the use of ORT, as ORS is extremely safe within a large dose range.

In all cases of moderate and moderately severe dehydration it is customary to give within the first four hours between 70 and 100 ml of the reconstituted ORS per kilogram of body weight, depending on the degree of dehydration. In milder cases, 50 ml per kilogram may be sufficient. These amounts of ORS should be given in small quantities at few minute intervals. If too much ORS is given, some periorbital puffiness may appear, but this is by no means dangerous and will soon disappear. Plain water may be given to substitute up to one third the volume of ORS. Breast feeding must not be interrupted during ORT.[5]

The success rate of ORT can be as high as 99 per cent, but to reach this figure it is necessary to be patient and continue giving ORS to the child. ORS may be given from a cup or with a spoon, in small volumes each time. In case of vomiting a pause of 15–30 minutes is

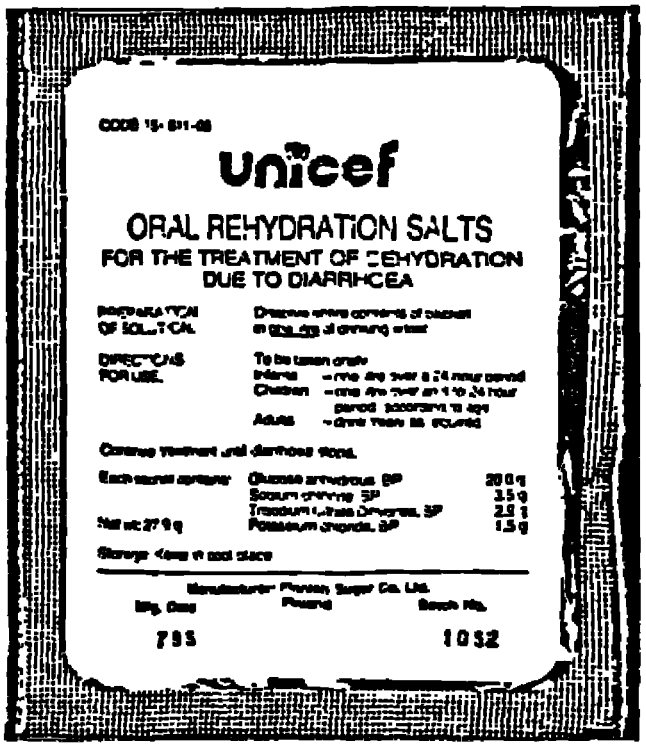


Figure 15.2. A sachet of ORS prepared for distribution by UNICEF.

acceptable, but after that another try must follow. In practice, the person who gives ORS is usually the mother, often supervised by health care personnel. Children who vomit constantly or cannot drink may require rehydration through a nasogastric tube, using an intermittent drip.

After initial rehydration, ORS should be given to compensate for the volume of fluid lost in diarrheal stools and vomit. The amount of ORS required may be about 100 ml per kilogram of body weight per day for most children, but it can be two to four times higher in cases of severe diarrhea.

ORT, using the WHO formula, is suitable for the management of all types of dehydration. In cases of hypertonic dehydration (especially if serum sodium is known to be 160 mmol/l or above), rehydration must be slower, and the required volume of fluid should be given in 12 hours rather than four hours.[6] The same is true in the case of severely malnourished children.[5]

Drug treatment

Symptomatic antidiarrheal drugs are usually not recommended for the treatment of acute diarrhea in children. Some antimotility drugs such as opiates and loperamide may cause paralytic ileus and death in children. Drugs that improve the consistency of stools, such as smectite, are advocated by some as it is believed that normalisation of stools may encourage mothers for better feeding during a diarrheal episode. However, there is no consensus on this issue.

In addition to established pharmaceuticals, many traditional antidiarrheal substances usually derived from herbs are widely used. Most are of questionable purity, and the pharmacologically active component is often not known. Some of these agents have been ineffective when investigated in controlled trials. In some areas, belief in local antidiarrheals may be so strong that they should be tolerated as long as the treatment guidelines shown in Table 15.2 are otherwise followed.

Perhaps the greatest problem associated with the widespread use of antidiarrheals is the cost, as drugs divert resources and attention from ORT and nutritional therapy. One approach to this problem is education of drug dispensers and, possibly, an increase of the price of ORS in the free market, to allow sales at a profit. It is believed that such measures might encourage drug retailers to promote ORS, rather than antidiarrheals.

Antimicrobials are not effective in uncomplicated acute diarrhea and their use should be discouraged. In contrast, antimicrobials are indicated in dysentery, cholera and typhoid fever. The drugs of choice and their alternatives are given in Table 15.5.

NUTRITIONAL THERAPY

Adequate dietary management during and after diarrheal disease is very important in order to:[10,11]

1) Reduce or prevent the damage of intestinal functions induced by withholding food.

2) Prevent or decrease the nutritional damage caused by the disease. Even though appetite is reduced, most children will eat amounts of food that are nutritionally important, and significant proportions of nutrients are absorbed during acute and persistent diarrhea.[10]

3) Shorten the duration of the disease. Many foods that are commonly eaten in developing countries produce this effect, especially in acute diarrhea.[10,11] This reduces the risk of dehydration, makes the children more comfortable, and reduces the caretaking chores of their mothers.

Table 15.5. Antimicrobial therapy for acute bacterial gastroenteritis.

Disease	Alternative antimicrobials	Comment
Dysentery	co-trimoxazole ampicillin ciprofloxacin*	bloody diarrhea is usually due to shigellosis
Typhoid fever	chloramphenicol co-trimoxazole ciprofloxacin*	antibiotics are not required for salmonellosis without enteric fever
Cholera	tetracycline furazolidone	furazolidone is recommended instead of tetracycline for children under two years of age
Traveller's diarrhea	co-trimoxazole doxycycline ciprofloxacin*	

*Other fluorokinolones may also be used

4) Allow catch-up growth and a return to good nutritional condition during convalescence.[10,12] This is especially important for children who live in unsanitary environments, and go through recurrent cycles of disease – poor dietary practices – disease.

Worsening or persistence of the disease due to food intolerance is not a frequent occurrence. Misconceptions among the general public and many health workers may lead to the reduction or rejection of the milk intake, including interruption of breast feeding, and of the intake of many common foods, based on the belief that their lactose, fibre or fat contents make the diarrhea worse. This is very unfortunate, as it is often necessary to offer familiar and palatable foods to overcome a sick child's low appetite.

Economic constraints are an important cause of poor dietary practices during diarrhea. Some of the foods often recommended by doctors are too expensive for many families. Emphasis should be placed on foods commonly available in low-income households.[10,12]

Breast milk is the food of choice for infants. In addition to its nutritional qualities, it is associated with improvement in fecal water output, number and consistency of stools, and duration of diarrhea.

Cows' milk is well tolerated by most children with diarrhea, including infants under 6 months of age who are fed milk-based formulas at the usual concentrations. Even children with some degree of intolerance do not have problems with small volumes of milk, either alone or as part of a mixed diet. In identified cases of lactose intolerance when it is desired to reduce milk intake, the recommendation should be to mix the milk or substitute part of it with another nutritious food, rather than to dilute it with water. In these cases it must be clearly explained to the mothers that full-strength milk can be given when diarrhea disappears, and that it is usually well tolerated during convalescence. When they are culturally acceptable, fermented milks and yoghurt are good options for lactose intolerance patients, or for children whose mothers are reluctant to use regular milk. It should be noted, however, that many yoghurts have as much lactose as unprocessed milk.

Many cereal-based gruels and paps are readily accepted by mothers of children with diarrhea. Rice is probably the cereal used by a wider variety of cultures. Other good cereal products that have been fed as gruels, paps or solid foods, are from maize (flour, dough, tortillas), wheat (flour, toasted grain, bread, noodles) and sorghum (flour, dough).

Good results have been obtained with mixed diets, largely of vegetable origin, previously thought to be inadequate for children with diarrhea because of their high fibre and fat content, or because they included products such as lentils and black beans.[10–12] Table 15.6 lists some examples. Good protein quality has been achieved by combining cereals with pulses, using mixtures of vegetable flours, or adding food of animal origin. Energy density has been increased with vegetable oil and sugar.

Practical recommendations

1) Food should be offered frequently, six to seven times daily to infants under 1 year and five to six times to older children, or more often if the child's appetite is markedly depressed. The mother and other care-givers must be patient and understanding to overcome the lack of appetite.

Table 15.6. Examples of diets prepared with local foods, well tolerated by most children with diarrhea. Vegetable oil and sugar are added to increase energy density.

Milk and vegetable combinations
Milk, and wheat noodles
Milk, potatoes and carrots
Milk and chickpeas
Milk and corn
Milk, rice and lentils
Other animal foods, with or without vegetables
Minced chicken
Chicken, rice and pulses
Fish, rice and banana
Egg and rice
All vegetable diets
Rice, pulses and banana
Corn-cottonseed flour, rice, corn, beans
Wheat, peas, carrots
Corn and cowpea.
Mixed diets
Chicken, lentils, rice, egg, milk, bread, bananas
Corn, beans, egg, bread, vegetables, with or without corn-cottonseed flour
Corn, beans, rice, egg, bread, chicken, fruit, vegetables and corn-soy flour or corn-cottonseed flour

2) Most children with diarrhea tolerate well cows' and other animals' milk. Practical advises for their use include: a) feed the type of milk used by the child before the disease; b) when skim milk is used, increase its energy density with 2 ml vegetable oil or 4–5 grams sucrose per 100 ml; c) feed full-strength (undiluted) milk and milk-based formulas – if signs such as increased volume of stools, weight loss, vomiting or dehydration appear, mix full-strength milk with equal amounts of other foods for one or two days, followed by full-strength milk; d) soy- and chicken-based formulas, other non-dairy foods, yoghurt or low-lactose milk can be used for children with intolerance to milk or lactose – availability, cost and cultural acceptance must be considered before recommending them; and e) tolerance to milk must be assessed again during convalescence in those children who were intolerant during diarrhea. Milk should be reintroduced in their diet according to the results.

3) Many local animal- and vegetable-based diets, which include cereals, some pulses, hard-boiled eggs, ground chicken meat, fish, sugar and vegetable oil, are well tolerated and assimilated during diarrhea. Some of these diets reduce the duration of the disease. Diets that will make stools appear more normal may influence mothers to accept the recommended feeding practices.

4) Good feeding practices are particularly important during convalescence to allow catch-up growth and nutritional recovery.

PERSISTENT OR PROLONGED DIARRHEA

This term refers to diarrheal episodes of presumed infectious etiology that have an unusually long duration. It does not include chronic or recurrent diarrheal disorders of hereditary, dietary or other acquired origins, such as gluten-sensitive enteropathy, monosaccharide intolerance, tropical sprue, blind loop syndrome or the chronic diarrhea of AIDS.

The definition of unusually long is arbitrary. Most episodes of childhood diarrhea resolve within one week or less, and the duration of the disease follows a continuous distribution that is skewed to the right. As Figure 15.3 shows, there is no clear breakpoint between episodes of shorter and longer duration. Based on the association of duration with impairment in nutritional status and an increased risk of death, most people define persistent diarrhea as that which lasts at least 14 days.[5]

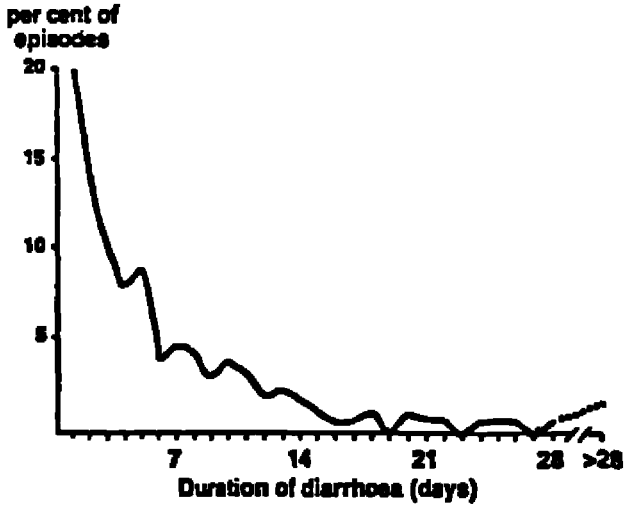


Figure 15.3. Frequency distribution of duration of diarrhea (composite data from Guatemala, Peru and Bangladesh).

Incidence and consequences

Using this definition, about 10 per cent (range 3–23 per cent) of diarrheas in children from developing countries become persistent, especially among those less than 3 years old, and more so among infants under 1 year.[4,5] Due to their long duration, as many as half of all recorded diarrhea days in a population may be from persistent episodes.

Persistent diarrhea causes substantial weight loss in most patients through a combination of reduced appetite, prolongation of malabsorption and fecal loss of nutrients, and poor – or suboptimal – dietary practices. It may be responsible for about one-third to half of all diarrhea-related deaths. Case fatality ranges widely, from less than 1 per cent in community studies to 14 per cent in hospital-based reports. From these epidemiological and clinical observations it can be concluded that while most episodes are not too severe, do not require hospitalisation and have a low mortality rate, severe cases have a high mortality. Furthermore, since persistent diarrhea is a major cause of malnutrition in developing countries, even the milder, non-fatal episodes contribute to the overall high mortality rates that are frequently associated with malnutrition in these countries.

Causes and risk factors

The pathogenesis of persistent diarrhea is not known. Several causes, probably in combination, have been proposed, including: infection with specific enteropathogens, such as enteroadherent *E. coli*, enteropathogenic *E. coli* and *Cryptosporidium*; intolerance to foods, mainly milk or its lactose content; delayed recovery of intestinal mucosal damage due to protein–energy malnutrition or vitamin A deficiency; immunodeficiency, either primary or secondary to malnutrition or to a recent systemic infections; and, inappropriate use of antibiotics.

It is not possible to foresee which children with acute diarrhea will have a prolonged episode. Although there are controversies about some of them, the risk factors more generally accepted include: young age, severe protein–energy malnutrition, previous episodes of persistent diarrhea, acute diarrhea within the preceding two months, and presence of blood and mucus in feces during acute diarrhea. Of the infectious agents, enteroadherent *E. coli* (EAEC) with autoaggregative adherence have the strongest correlation with persistent diarrhea. Moreover, infection with two or more enteric pathogens, especially with EAEC or *Cryptosporidium* is suggestive of high risk.

The role of diet and feeding practices before the illness or during an acute episode has not been clearly established. There are some suggestions that diarrhea is prolonged when it occurs shortly after the introduction of non-human milk into the diet, or when soy-based, low-fibre diets are used in the dietary management of acute diarrhea. However, there is not enough evidence to consider those foods as risk factors of persistent diarrhea.

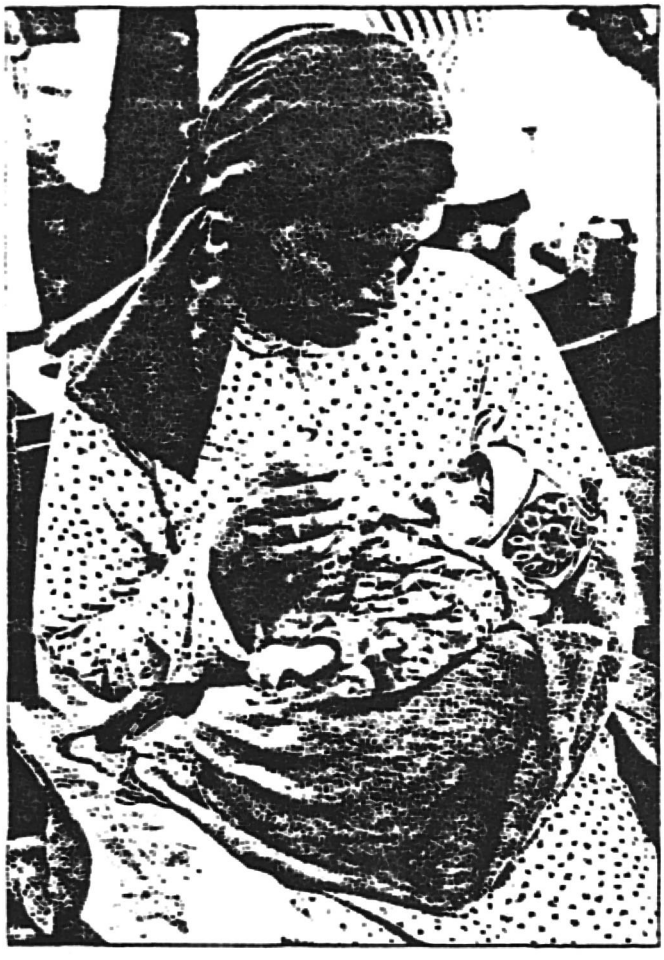
Management

The inability to provide a rational explanation for most cases of persistent diarrhea has led to empirical treatment of the disease. The most important factors to consider are maintenance of hydration and avoiding malnutrition. Successful dietary management is usually a compromise between the nutritional demands of the patients, their altered intestinal functions and the foods that are accessible and culturally acceptable. In general, management of persistent diarrhea includes:

1) Prevention or correction of dehydration, as in the management of acute diarrhea.

2) Continued feeding to correct or prevent nutritional damage. Breast-feeding should be encouraged. Diets rich in fibre and vegetable fats do not seem to have deleterious effects. Cows' milk and milk of other animals may be fed as part of mixed diets. Non-dairy diets that have been successfully used in developing countries include minced chicken, and mixtures of rice with egg (whole or egg white), or of either rice or corn with pulses (soy, beans, lentils). Energy density should be raised in all those diets to about 250 kJ (60 kcal)/100 grams with vegetable oil and sugar.

Zinc and vitamin A supplements seem to reduce the duration of diarrhea, but their effectiveness has not been fully established. Blind use of antibiotics is not effective, and they should be given only in dysenteric persistent diarrhea. Other pharmacological agents, such as cholestyramine and antisecretory/antimotility drugs, have given inconsistent results and their routine use is not recommended.



Mother feeding her baby with ORS-solution in Egypt. Photo: UNICEF/Sean Sprague

PREVENTION OF DIARRHEAL DISEASES AND THEIR CONSEQUENCES

The incidence of and mortality from diarrheal diseases in developing countries today is comparable to the situation in industrialised countries about one hundred years ago. Clean, running, chlorinated water, sewage disposal, sanitation, high standards of hygiene in food processing, refrigeration and generally improved nutrition of children have all contributed to the reduced incidence of diarrheal diseases in developed countries, and access to good medical management has controlled mortality.

The WHO Diarrhoeal Diseases Control Programme and other organisations have given first priority to the prevention of diarrheal deaths, rather than prevention of cases, and focused on promotion of ORT. The current production of ORS-sachets is equivalent to about 350 million litres per year. Most of that quantity is produced in developing countries. It is estimated that ORS is accessible to more than 60 per cent of children, and used in about 20 per cent of all diarrheal episodes. Other forms of ORT are given in a further 10 per cent of the cases.[4]

Further training on the use of ORT is required since currently less than 20 per cent of health personnel in developing countries have received formal training on the subject. In addition to ORT, the training includes nutritional management of diarrhea. Other target groups for training are medical and nursing students, pharmacists and drug sellers, and, naturally, mothers. Promotion of adequate feeding practices, including breast-feeding and weaning foods, should be emphasised.[13] Other interventions that are likely to have an effect on both the incidence and mortality include hygienic preparation and storage of foods, vitamin A supplementation, and improvement of sanitary practices such as use of latrines and hand washing.

Vaccines against diarrheal diseases may also play a role in the prevention of diarrheal diseases mortality, and morbidity, in the future. Of the existing vaccines, measles vaccine certainly has a potential in reducing mortality attributed to diarrheal diseases, since measles is associated with diarrhea in some 20 per cent of the cases. This potential has been estimated between 6 and 26 per cent.[14]

Live oral rotavirus vaccine, based on rhesus rotavirus, is being tested in field trials in both developed and developing counties.[15] Preliminary results suggest that this vaccine is efficacious in the prevention of rotavirus diarrhea in the USA, but not in Peru.

A *killed oral cholera vaccine* has recently been licensed in Sweden and is available to travellers. The vaccine has been tested in Bangladesh where it showed over 60 per cent efficacy in the native population.[16]

Typhoid vaccines could potentially have a much greater use in developing countries than currently is the case. Live attenuated oral typhoid vaccine Ty 21a is licensed in a number of countries and used primarily for the immunisation of travellers. A full immunisation schedule consists of three or four oral doses.[17]

Even if effective vaccines against diarrheal diseases become available, a final decision on their use will be with the countries. The vaccines may be cost-effective in calculations, but still not affordable to many developing countries without substantial support from outside.

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Additional reading

1. Persistent diarrhea in children in developing countries. Acta Paediatr Scand 1992;81(Suppl 381):1–154.
2. Readings on diarrhoea: Student manual. Geneva: WHO, 1990. (Document WHO/CDD/SER/90.13.)
3. Strengthening the teaching of diarrhoeal diseases to medical students. Geneva: WHO, 1991. (Document CDD/SER/91.1.)

Further information can be obtained from

WHO, Division of Diarrhoeal and Acute Respiratory Disease Control, CH-1211 Geneva 27, Switzerland. – Training materials, manuals, and technical papers on diarrheal diseases.

About the authors

Timo Vesikari is a specialist in pediatrics and virology. He is currently Professor of Virology and consulting pediatric infectious disease specialist at Tampere University Central Hospital. During 1981–87 he was acting Professor of Pediatrics in the same setting. From 1987 to 1990 he served as a scientist in the Diarrhoeal Diseases Control Programme at the WHO. He was then based in Geneva but was involved in research on diarrheal disease and enteric vaccines in several developing countries. His current research interests are rotavirus vaccine and case management of diarrheal diseases. Benjamin Torun is a specialist in physiology and human nutrition. For more than 20 years he has worked at the Institute of Nutrition of Central America and Panama in Guatemala City. His research has included clinical, metabolic and field studies on malnutrition and on diarrheal diseases. In 1986–89 he was a member of the WHO Diarrhoeal Diseases Control Programme's Scientific Working Group on Case Management, and has served as a consultant for several other international organisations. He has published extensively on nutrition and physical activity of children and adults, energy and nutrition requirements and functional consequences of malnutrition.

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16 MALARIA

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INTRODUCTION

Malaria is one of mankind's most feared and serious afflictions that causes more morbidity and mortality than any other human disease. About 55 per cent of the world's population is exposed to the infection which exerts its toll mainly on the young and the pregnant. Attempts in the 1960s to eradicate the disease by spraying the anopheline mosquito vector soon failed as insecticide resistance developed. Now the mosquitoes have shifted to new ecological niches as man becomes increasingly urbanised or as large scale irrigation has been extended. A further complication has been the rapid and widespread development of drug resistance in many areas of the world resulting in an added threat not only to local inhabitants but also to invading armies, tourists and travelling salesmen. The situation is deteriorating rapidly in many parts of the world. *P. falciparum*, the deadliest of the malaria parasites, kills alone in Africa 1–2 per cent of its children and is responsible for at least one million deaths each year.

PARASITES AND ANTIGENS

Malaria in man is due to infection with either *Plasmodium falciparum, P. malariae, P. vivax* or *P. ovale. P. falciparum* is the most common and most virulent species as it multiplies most rapidly and is able to sequester in small blood vessels causing damage to the brain and other organs. The others seldom cause death but can be difficult to cure because of relapses due to cryptic forms in liver or red cells. The infection is caused by the bite of an infected female *Anopheles* mosquito. Each parasite has a distinctive morphology and characteristic antigens at each stage of its life cycle which takes place in both the mosquito and in the liver and blood of man (Figure 16.1).

The developmental characteristics of the four species differ (Table 16.1). *P. falciparum* does not have a secondary liver cycle, and relapses are thus unknown after treatment has eradicated the parasite from the blood.

The parasite releases a toxin which is responsible for the fever. This is a phospholipid which

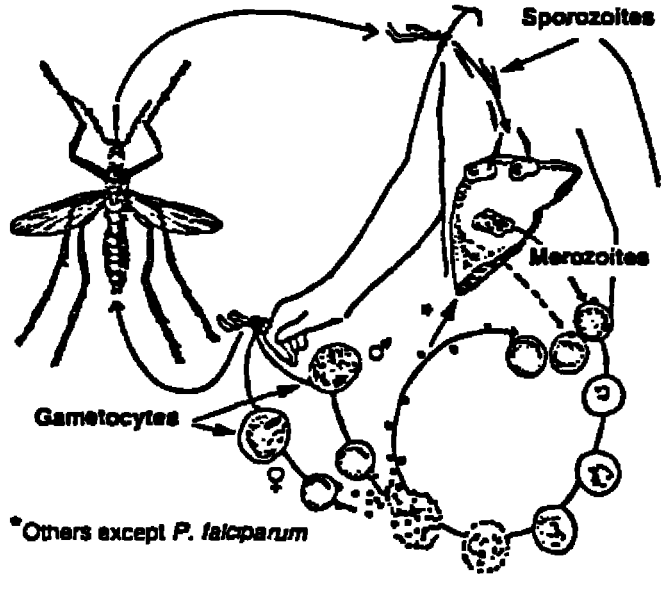

Figure 16.1. Life cycle of human malarial parasites.