

Causes and management of diarrhoea in children in a clinical setting

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Abstract

Diarrhoeal disease and its complications remain a major cause of morbidity and mortality in children, especially in developing countries. Diarrhoea is characterised by an increased frequency and volume, and decreased consistency of stool from the norm. Pathogens vary between developed and developing world settings. Rotavirus diarrhoea is the most important aetiological agent implicated in severe dehydrating diarrhoea. Although it is important to recognise the specific microbiological causation of diarrhoea in order to target appropriate treatment, the broader preventive aspects put forward by the World Health Organization (WHO) indicate the fundamental contributors to the massive burden of disease in developing countries. The management of a child presenting with acute diarrhoea must include a thorough history and examination with evaluation of hydration status, nutritional status and comprehensive clinical evaluation for any complications or associated illnesses. The most recent advances in the area of acute diarrhoeal disease include zinc supplementation, reduced osmolarity oral rehydration solution (ORS) and rotavirus vaccination.

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Diarrhoeal disease and its complications remain a major cause of morbidity and mortality in children, especially in developing countries. It is the second most common cause of death in children under five years of age worldwide and is responsible for 2.4 million deaths each year.¹ The Medical Research Council Burden of Disease report indicates that in South Africa, it is the third biggest killer of children under five, responsible for over 10 000 deaths annually (10.2% of total deaths).² There are approximately 1.5 billion episodes of diarrhoea per year so knowledge of aetiology and appropriate management is essential for all health care practitioners. The most recent advances in the area of acute diarrhoeal disease include zinc supplementation, reduced osmolarity oral rehydration solution (ORS) and rotavirus vaccination.

Definitions

Diarrhoea is characterised by an increased frequency and volume, and decreased consistency of stool from the norm. It must be remembered that frequency of passing stool varies with age and is higher in infants.⁴ Dysentery is defined as the passage of blood and mucous in diarrhoeal stools. Persistent diarrhoea occurs when the duration of symptoms exceeds seven days and chronic diarrhoea when it lasts more than 14 days.^{4,5}

Causes of diarrhoea

The commonest causes of infectious diarrhoea are shown in Table I.

The incidence of these pathogens varies between developed and developing world settings. In developed countries about 70% of

Table I: Common pathogens causing childhood diarrhoea

Viruses

- Rotavirus
- Norovirus
- Enteric adenovirus
- Other: caliciviruses, astroviruses, enteroviruses

Bacteria

- *Campylobacter jejuni*
- Non-typhoid *Salmonella* sp
- Enteropathogenic *E. Coli*
- *Shigella* spp
- *Salmonella typhi*
- Shiga-toxin producing *E. Coli* (ETEC)
- *Vibrio cholera*

Protozoa

- *Cryptosporidium parvum*
- *Giardia lamblia*
- *Entamoeba histolytica*

Unidentified

Mixed infections

diarrhoea cases are of viral (40% rotavirus), 10–20% of bacterial and < 10% of protozoal origin.^{3,5,6,7} In developing countries 50–60% of cases are of bacterial (Enteropathogenic *E. Coli* 25%, *Campylobacter jejuni* 10–18%, *Shigella* spp and *Salmonella* spp 5% each), 35% of viral (15–25% rotavirus) origin, and in many the cause is unidentified or mixed.^{3,5,6,7,8} In developing countries the prevalence of diarrhoea also varies widely by country. For instance, there are many more

cases of cholera in India and South east Asia, whilst in Africa rotavirus has been shown to be the causative agent in 28–49% of cases in Ethiopia but only 14 % of cases in Tanzania.^{7,8} The incidence of rotavirus diarrhoea varies widely even within each country with studies from South Africa indicating a range of 14–34% of cases in Johannesburg, 20–55% in Durban⁷ and 18% in Cape Town.⁹

There is also a marked seasonality that is associated with the incidence of infectious childhood diarrhoea. This is best reflected in rotavirus infection, classically described in dry winter months in temperate climates.^{5,7,8} This is documented in studies from Durban and Johannesburg, but not in the summer peak of diarrhoea in Cape Town and other developing countries.^{7,9} This pattern is most likely due to the Mediterranean climate in Cape Town with wet winters and hot dry summers.

Bacterial pathogens like *Campylobacter jejuni* and *Salmonella* spp invade the lining of the small and large intestine and trigger inflammation so children tend to have higher fevers and a dysentery-like picture. These organisms can spread systemically especially in young children. *Shigella dysenteriae* and ETEC infections can also be complicated by the haemolytic uraemic syndrome.⁵

Certain organisms are more closely associated with chronic diarrhoea, and these include *Giardia lamblia* and *Cryptosporidium parvum*.³

Rotavirus diarrhoea is the most important aetiological agent worldwide implicated in severe dehydrating diarrhoea requiring hospitalisation. The annual burden of disease is estimated as more than 110 million diarrhoeal episodes, 25 million clinic visits, 2 million hospitalisations and 600 000 childhood deaths per year.^{7,8,10,11} More than 90% of rotavirus deaths occur in developing countries. Improvements in water supply and sanitation have been shown to reduce the transmission of enteric bacteria and parasites, but do not appear to have a major impact on rotavirus diarrhoea, so the introduction of a vaccine shows the greatest promise in reducing the burden of disease. The peak age of infection is quoted as six months to two years. In developing countries, however, children often present younger, with the median age of hospitalisation of all-cause diarrhoea being nine months when compared with that of six months in rotavirus diarrhoea, with 97% of cases occurring in children younger than 18 months. Some studies indicate that up to 38% of patients with rotavirus diarrhoea were < 6 months of age. A small infectious dose is required (< 100 virus particles) for the virus to enter the small intestinal epithelium where it elaborates a potent enterotoxin which damages epithelial cells causing blunted villi and massive viral shedding. This results in a profuse watery non-inflammatory diarrhoea, rapid dehydration and electrolyte disturbances. It is often associated with initial fever and vomiting for two to three days, and the course of the infection lasts two to seven days.^{8,10,11}

The recent outbreak of cholera in Zimbabwe with rice-water stools and rapid dehydration, has highlighted the risks of the spread and severity of illness. A travel history is important when considering the

aetiology of diarrhoea as management may differ, including the need for isolation and notification.³ When a child presents with diarrhoea, especially in chronic non-dehydrating diarrhoea, *noninfectious causes* must also always be considered in the differential diagnosis⁵ (Table II).

Table II: Differential diagnosis in children presenting with diarrhoea

- Infections outside the GIT, like meningitis and urinary tract infection
- Surgical conditions like intussusception and malrotation, especially if prominent/bile-stained vomiting is present
- Immunodeficiency e.g. HIV disease
- Spurious diarrhoea – faecal impaction with overflow
- Side-effects of medications e.g. antibiotics
- Primary gastrointestinal tract pathology e.g. cystic fibrosis, inflammatory bowel disease, coeliac disease
- Toddler's diarrhoea

GIT = Gastrointestinal tract

The aetiological approach in *nosocomial diarrhoea* will also differ as one needs to consider *Clostridium difficile* infection. This is a spore forming anaerobe, and patients colonised with a toxin producing strain can develop disease especially when treated with antibiotics. Rotavirus and astrovirus are other important causes of nosocomial diarrhoea outbreaks through the faecal-oral transmission and contamination of environmental surfaces.³

Although it is important to recognise the specific microbiological causation of diarrhoea in order to target appropriate treatment, the broader preventive aspects put forward by the WHO indicate the fundamental contributors to the massive burden of disease in developing countries. In a global setting where up to a quarter of children are malnourished, over a billion people do not have access to safe water and over two billion have inadequate sanitation, together with a low breastfeeding prevalence, social disruption from war and natural disasters as well as poor maternal education, the vicious cycle of infection, diarrhoea and malnutrition is perpetuated.³

Management

Management of a child presenting with acute diarrhoea must include a thorough history and examination with evaluation of hydration status, nutritional status and comprehensive clinical evaluation for any complications or associated illnesses.^{4,5} A decision then needs to be made on method of rehydration, feeding, and if there are indications for any specialised investigations. Pharmacologic therapy is usually limited to micronutrient support.^{4,5}

Clinical evaluation

After obtaining a history of diarrhoea with or without vomiting, the first priority in initial evaluation is to identify and treat shock. The clinical features and initial management of shock are shown in Table III. These children require rapid venous access, and after the initial fluid bolus, a 10 ml/kg bolus should be repeated if signs of shock persist. Such children may also need additional general supportive care including oxygen and must be continuously and very intensively monitored.^{5,12}

Table III: Features and management of shock and dehydration (modified from WHO and IMCI)^{4,5}

No visible dehydration	Some dehydration	Severe dehydration	Shock
Features: <ul style="list-style-type: none"> • alert with normal eyes • not thirsty • normal skin pinch 	2 or more signs: <ul style="list-style-type: none"> • restless and irritable • thirsty and drinks eagerly • skin pinch returns slowly • fontanelle is sunken 	2 or more signs: <ul style="list-style-type: none"> • lethargic or sleepy • deeply sunken eyes and fontanelle • very slow skin pinch 	Signs of: <ul style="list-style-type: none"> • depressed level of consciousness or weakness • weak or absent peripheral pulses • a prolonged capillary refill time of > 3 seconds • tachycardia of > 120 bpm Usually but not always with evidence of severe extravascular dehydration
Initial fluid management <ul style="list-style-type: none"> • treated at home with additional fluids • Other supportive measures 	<ul style="list-style-type: none"> • ORS orally or nasogastrically • Continue breastfeeding or formula milk within 4 hours • Replace ongoing losses with ORS 	<ul style="list-style-type: none"> • Intravenous rehydration with ½ Darrows Dextrose • Continue breastfeeding or formula within 4 hours • Replace ongoing losses with ORS 	<ul style="list-style-type: none"> • Rapid venous access, either an intravenous or intraosseous line • Bolus of 20 ml/kg of Ringers lactate or Normal Saline.

ORS = Oral Rehydration Solution

Further history should include information on the duration and frequency of diarrhoea, presence of blood or mucous in the stool, vomiting and whether it is bile stained, use and mixing of home rehydration fluids, as well as other usual aspects of the paediatric history including past illnesses, immunisation status, feeding, medications and related side effects. The Integrated Management of Childhood Illness (IMCI) has simplified the classification dehydration into i) no signs of dehydration, ii) some dehydration (correlating with the old classification of 5% dehydration), and iii) severe dehydration (correlating with the old classification of 10% dehydration)¹² (Table III), The indications for hospitalising a child with diarrhoea are shown in table IV.

Table IV: Indications for hospitalisation^{4,5}

- Severe dehydration with/without shock
- Altered neurological status
- Intractable vomiting or ORS failure
- Caregivers that cannot provide adequate care at home
- Young age, < 6 months with dehydration
- Children with associated chronic illness
- Enteric fever: high fever with inflammatory diarrhoea
- Dysentery especially < 1 year (IMCI)*
- Tender abdomen and any suspected surgical condition
- High output diarrhoea
- Persistent diarrhoea

* IMCI = Integrated Management of Childhood Illness

A relatively objective way of assessing dehydration is comparing current weight with a recently recorded weight, usually in the Road to Health Card (RTHC) to calculate the percentage dehydration. Capillary refill time, skin turgor and an abnormal respiratory pattern indicative of acidosis have been found by systematic review to be the best indicators of degree of dehydration.^{3,5}

Rehydration and fluid management

The observation that glucose-sodium co-transport was unaffected in cholera and recognition that secretory and absorptive processes in the intestine are separate, led to the formulation of Oral Rehydration Solution (ORS), with similar concentrations of sodium and glucose that optimise absorption together with potassium, chloride and

bicarbonate.³ It is considered one of the most important medical innovations of modern times and its active promotion as part of the WHO Control Diarrheal Disease (CDD) programme in the 1980s halved the deaths from diarrhoea over 20 years following its implementation.^{1,7}

A Cochrane review has documented that oral rehydration should be used as the first line for management of children with acute gastroenteritis and some dehydration.¹³ When this is not feasible, enteral rehydration by nasogastric route is as effective, if not better, than IV rehydration (Table V), with fewer major adverse events and shorter hospital stay. In addition, it is cheaper in terms of both consumables and human resources and less traumatic for the child.^{4,5,13}

Table V: Indications for intravenous fluids

- Shock
- Severe dehydration, especially if depressed level of consciousness
- Paralytic ileus
- Moderate dehydration with vomiting all fluid
- Children with profuse watery stools unable to keep up with fluid losses

Note: Intravenous fluids should be avoided in children who are malnourished or with underlying cardiac or respiratory disease including associated pneumonia.

The WHO, European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and American Academy of Paediatrics(AAP) all recommend rapid rehydration over four hours in mild to moderate(IMCI “some”) dehydration. Rehydration should be slower over 8–24 hours in children under three months of age, those with respiratory or cardiac disease, those with suspected or proven hypernatraemia and in malnourished children.¹³

There has been ongoing controversy regarding the ideal composition of ORS. Initial WHO preparations had higher sodium concentration due to its development in areas with high incidence of cholera (which is complicated by hyponatraemia). After multiple modifications the current WHO Guidelines recommend a *reduced osmolarity ORS* with lower concentrations of sodium (75 mmol/l vs 90 mmol/l) and glucose (75 mmol/l vs 111 mmol/l). A meta-analysis has shown its safety and efficacy in both cholera and non-cholera diarrhoea, with lower use

of intravenous fluid rescue, reduced vomiting and similar rates of hyponatraemia when reduced osmolality is compared with standard ORS.^{3,4,5} ESPGHAN in fact recommends an even lower concentration of sodium of 60 mmol/l for use in children with diarrhoea in Europe due to the different aetiology of diarrhoea in European settings.⁴

Multiple other modified formulations of ORS have also been extensively studied. Rice-based ORS can be used as an alternative therapy to standard ORS in cholera, as it adds additional substrate to the gut lumen without increasing osmolality, thereby providing additional glucose molecules for glucose-mediated absorption. However, there is no additional benefit in children with non-cholera diarrhoea. Other modifications include ORS-containing amylase-resistant starch, as it is postulated that the non-absorbed carbohydrates increase short-chain fatty acids availability which enhance colonic absorption of sodium and water, but further trials are needed to demonstrate superiority. ORS has also been combined with guar gum, a mixture of non-digestible carbohydrates, as well as with probiotics, zinc and glutamine but there is currently insufficient evidence for any of their use bearing in mind the additional considerations of increased cost, instability and availability of additional compounds.⁴

Prevention of further dehydration by supplementing maintenance fluid with ORS with each loose stool to replace ongoing losses is an essential part of further management (50–100ml per loose stool). The child's hydration status must be re-assessed regularly at least every four to six hours including a weight check, and fluids modified according to whether there is improvement or not.⁵

Maintain nutrition

Consensus from WHO, ESPGHAN and the AAP based on level 1 evidence is to continue breastfeeding at all times, and to continue normal feeds in uncomplicated gastroenteritis within four hours. There is no role for dilution or gradual re-introduction of formula or for special formulae like soya-based or lactose free. Beverages with high sugar content should not be used. An extra meal a day for at least a week following an episode of gastroenteritis should also be encouraged to allow catch-up growth^{4,5,13}.

Investigations

Testing for electrolytes should be performed on hospitalised children with severe dehydration or shock, those receiving intravenous fluids, those with associated malnutrition and in any child that looks ill out of proportion to their degree of dehydration.^{4,5} Children appearing floppy or with abdominal distension must have hypokalaemia excluded, and hypernatraemia should be suspected in well-nourished children, with a rubbery feel to the skin, those with a high pitched cry, and in any children with a history of incorrect mixing of ORS. Indications for sending a stool microscopy, culture and sensitivity (MCS) include inflammatory diarrhoea with blood and pus in the stool, high fever and systemic illness, persistent diarrhoea and in hospitalised children that develop diarrhoea, including for *C. difficile*. Routine testing for rotavirus is of epidemiologic interest but does

not change the management of diarrhoea which is supportive. Most laboratories do not test for *E. Coli* types so the yield from stool MCS is low, and routine stool testing is not recommended.^{3,4,5}

There is no role for routine full blood count and inflammatory markers like C-reactive protein in uncomplicated gastroenteritis but young children under three months and children with a high fever should have a formal septic workup.^{3,4,5}

Pharmacologic therapy

Zinc deficiency is common in young children in the developing world and is associated with impaired electrolyte and water absorption, decreased brush border enzyme activity and impaired cellular and humoral immunity. Meta-analyses have confirmed that zinc supplementation reduces the duration and severity of acute and persistent diarrhoea and reduces the risk of a recurrent episode in the next 2–3 months. WHO and UNICEF recommend zinc supplementation (10 mg in children under six months and 20 mg in children over six months) for 10–14 days as a universal treatment.^{14,15,16} ESPGHAN however does not recommend it as a routine treatment modality in European children, unless they are malnourished.⁴

Probiotics may be an effective adjunct to the management of diarrhoea, but it is important to prescribe those that have been documented to be effective. *Lactobacillus GG* and *Saccharomyces boulardii* have the most consistently documented efficacy data. Best results have been demonstrated in young infants with viral gastroenteritis when the probiotic is administered early in the course of the diarrhoea, at a dose of 10¹⁰ CFU/day. The advantages include reduced duration of diarrhoea by one day thereby reducing costs of hospitalisation, reduced persistent diarrhoea and reduced spread through viral shedding. There are concerns however in the developing world regarding the use of probiotics in the management of diarrhoea because of the high prevalence of bacterial diarrhoea in such clinical settings, in which probiotics may be less efficacious and safety issues related to immunosuppression may arise.^{4,16}

Management of diarrhoea is otherwise usually supportive and non-pharmacologic. Antimotility agents like loperamide have been associated with prolonged disease in Shigellosis, toxic megacolon in *C. difficile* infection, and haemolytic-uraemic syndrome in children with Shiga-toxin producing *E. Coli* and are not recommended.^{3,4,5} The older anti-emetics are also not recommended due to risk of extra-pyramidal side-effects but some newer agents like ondansetron are effective without side-effects.^{4,5} There is no evidence to support the use of prebiotics, glutamine, folic acid, kaolin-pectin, attapulgit, activated charcoal or bismuth. There may however be potential benefit in the use of smectite, an aluminomagnesium silicate that binds digestive mucous.⁴ Vitamin A does not influence the course of acute diarrhoea but should be given according to national guidelines for its effect on reducing overall mortality.⁴ Antibiotics are not routinely recommended in viral or uncomplicated bacterial gastroenteritis (Table VI).

Table VI: Indications for systemic antibiotics.

Indications	Antibiotic regimen
<ul style="list-style-type: none"> Bacterial gastroenteritis complicated by sepsis Neonates Ill immunocompromised children Associated infection e.g. urinary tract infection or pneumonia 	<ul style="list-style-type: none"> Usually ampicillin and gentamicin OR ceftriaxone
<p>Dysentery</p> <ul style="list-style-type: none"> <i>Shigella</i> <i>Salmonella</i> spp (non-typhoid) <i>Campylobacter</i> <p>First try to exclude ETEC due to the associated with HUS</p>	<ul style="list-style-type: none"> Nalidixic acid, fluoroquinolone or ceftriaxone Erythromycin or one of above
<p>Specific infections:</p> <ul style="list-style-type: none"> Amoebiasis Giardiasis <i>Vibrio cholera</i> if complicated by severe dehydration <i>C. difficile</i> 	<ul style="list-style-type: none"> Metronidazole Metronidazole Doxycycline(> 6 years) or fluoroquinolone Metronidazole or oral vancomycin

ETEC = Enterotoxigenic *E. Coli*, HUS = Haemolytic Uraemic Syndrome

Management of children with chronic diarrhoea

As for the child presenting with acute diarrhoea, there should be a thorough history, including family history, and comprehensive clinical evaluation including effect on nutritional status for those with chronic diarrhoea.¹⁷ It is important to differentiate whether this is a persistent diarrhoea following an acute dehydrating diarrhoeal episode, as causes may include small bowel bacterial overgrowth, acquired disaccharidase deficiency, deconjugation and dehydroxylation of bile salts which induces diarrhoea, protein sensitisation i.e clinical settings that may require additional specialised treatment.¹⁸ The clinical picture of the child is also of importance since it may be indicative of the cause of diarrhoea such as the classic Toddler's Diarrhoea with a thriving child and stools containing undigested food and worsening as the day progresses. The need for any specialised investigation and treatment will depend on the clinical picture of the patient and would usually include stool MC&S to exclude parasites, stool reducing substances and elastase, and possibly sweat test or coeliac serology.¹⁷

Prevention

On discharge of a child with an episode of diarrhoea, advice must be given on measures to try to prevent another episode and appropriate home management to prevent dehydration.

The WHO Enhanced Diarrhoeal Disease Control (EDDC) focuses on a combination of public health issues like handwashing, preparation and storage of food as well as drinking water and sanitation; promotion of breastfeeding (which affords a six-fold protection); zinc supplementation and rotavirus vaccines.¹ The enormous burden of rotavirus disease has been mentioned and vaccine introduction in developing countries is thought to have the potential to save 600 000 children's lives per year and help towards the achievement of the Millennium Development Goal of reducing childhood mortality by 2/3 by 2015.^{1,8} Rotarix has been licensed in South Africa since 2006

and was introduced in the Extended Programme of Immunisation in 2009. It is a live attenuated human rotavirus strain, with two doses given orally four weeks apart, not after six months. In studies in middle-income countries the vaccine has a very good safety profile and efficacy of 85% protection. There are some concerns though about its use in the developing world. Such concerns include interference by high titres of maternal antibodies, interference by gut microorganisms as well as safety and immunogenicity in HIV-infected children. Nevertheless, the vaccine holds promise as an extremely important and much needed public health intervention to reduce the significant morbidity and mortality from diarrhoeal disease.^{8,10,11}

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