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Diarrheal Diseases

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Epidemiology and Global Burden of Diarrhea

The WHO defines diarrhea as the passage of three or more loose or liquid stools per day, or more frequently than is normal for the individual. Diarrhea is the leading cause of mortality among children under 5 years of age accounting for one in ten child deaths worldwide annually. It disproportionally affects young children in low- and middle-income countries (Figure 1). In 2010, there were 1.731 billion episodes of diarrhea (36 million of which progressed to severe episodes) and in 2011, an estimated 700 000 deaths were due to diarrhea. Incidence and mortality from diarrhea and pneumonia vary by age (Figure 2) with the burden of disease mainly concentrated in the younger age groups. The epidemiology of childhood diarrhea and pneumonia overlap, likely because of shared risk factors, such as undernutrition, suboptimum breastfeeding, and zinc deficiency. Children are at the highest risk during the first 2 years of life, with 72% of deaths being secondary to diarrhea. Diarrheal mortality rates are declining by about 4% annually with disease incidence decreasing from an estimated 3.4 episodes/child-year in 1990 to 2.9 episodes/child-year in 2010. The highest burden of disease has remained consistent with respect to age in the 6–11-month-old age group having the highest incidence. The burden of mortality due to diarrhea in children less than 5 years of age in 2010 was highest in the WHO regions of Africa and Southeast Asia. It is estimated that a third of severe diarrhea episodes is preventable by vaccination (i.e., against rotavirus and cholera). Furthermore, under nutrition is a key underlying risk factor for morbidity and mortality associated with both diarrhea and pneumonia. Diarrhea disease severity in children under-five is mostly mild (~65% cases for which no care was sought/no dehydration) lasting about 4 days or moderate (~35% cases for which care was sought/any dehydration on presentation) with only 0.5% of cases being severe (cases for which care was sought, with severe dehydration on presentation) and lasting 8 days. Older children and adults have predominantly mild episodes (95%) with 4.95% being moderate and 0.05% being severe. Among individuals 16 years or older, severe episodes typically last ~3 days and cause dehydration in ~93% of cases.

Morbidity and Risk Factors for Diarrhea

Despite reduction of diarrheal mortality by use of oral rehydration therapy, persistent global burden of enteric infections results in high morbidity of up to 43% of stunted growth, affecting one-fifth of children worldwide and one-third of children in developing countries. Children suffering from diarrhea during the first 2 years of life might have on average an 8 cm growth shortfall and 10 IQ point decrement by the time they are 7–9 years old. The proposed link between enteric infections and child growth and development is a double burden of enteric infections and malnutrition, and the potential link of both of these factors to obesity later in life is an interrelated 'triple burden' (Figure 3). Important risk factors for diarrhea include lack of exclusive breastfeeding in infants younger than 6 months, undernutrition and zinc deficiency. While evidence suggests that vitamin A deficiency increases the risk of severe diarrhea, it is not an important risk factor for the incidence of diarrhea. Associations of specific water and sanitation risk factors (i.e., unwashed hands and poor water quality) with diarrhea morbidity and mortality have been shown. However, for some outcomes such as inappropriate excreta disposal, poor availability of evidence permits only rough estimates of risk. In a stratified subgroup of infants aged less than 6 months, acute lower-respiratory-tract infections are a risk factor for diarrhea. Measles is an established risk factor for diarrhea. A study from the 1980s showed that with moderate coverage of the measles vaccine (45–90%) in infants, the incidence of diarrhea could be reduced by 0.6–3.8%, and diarrhea mortality reduced by 6–26% in children younger than 5 years. Table 1 shows the effect sizes for specific confirmed biological risk factors for diarrhea.

Diarrhea Classification and Pathophysiology

Diarrhea can be classified based on duration as prolonged/acute (1–13 days) and persistent (14 days or more). Prolonged diarrhea can further be classified as prolonged/acute watery diarrhea which is loose or watery stools at least three times in a 24 h period or prolonged/acute invasive diarrhea which is gross blood (by history or inspection) in the stool of less than 14 days duration, typically accompanied by fever. Diarrhea can be secondary to one or more of the following pathophysiological processes: secretory, osmotic and inflammatory diarrhea. *Secretory diarrhea* occurs when there is a significant increase in the volume of intestinal fluid output which exceeds the reabsorptive ability of the gastrointestinal epithelium. Research initially done in patients with cholera revealed that while the secretory diarrhea in cholera does lead to significant fecal water and electrolytes loss, the gut still retains the ability to reabsorb water and electrolytes due to an intact Na-coupled solute cotransport mechanism. Chloride-mediated secretion is stimulated by second messengers in diarrheal infections secondary to *Vibrio cholerae* 01 and 139, Shigella, Salmonella, *Escherichia coli* strains and other bacterial pathogens who produce enterocyte receptor binding pathogens, causing chloride-mediated secretion stimulated by second messengers (e.g., cAMP, cGMP, and calcium). It is important to recognize that there may be a combination of osmotic and secretory diarrhea such as in the case of Rotavirus where there enterotoxin mediated secretory diarrhea along with osmotic diarrhea secondary to enterocyte

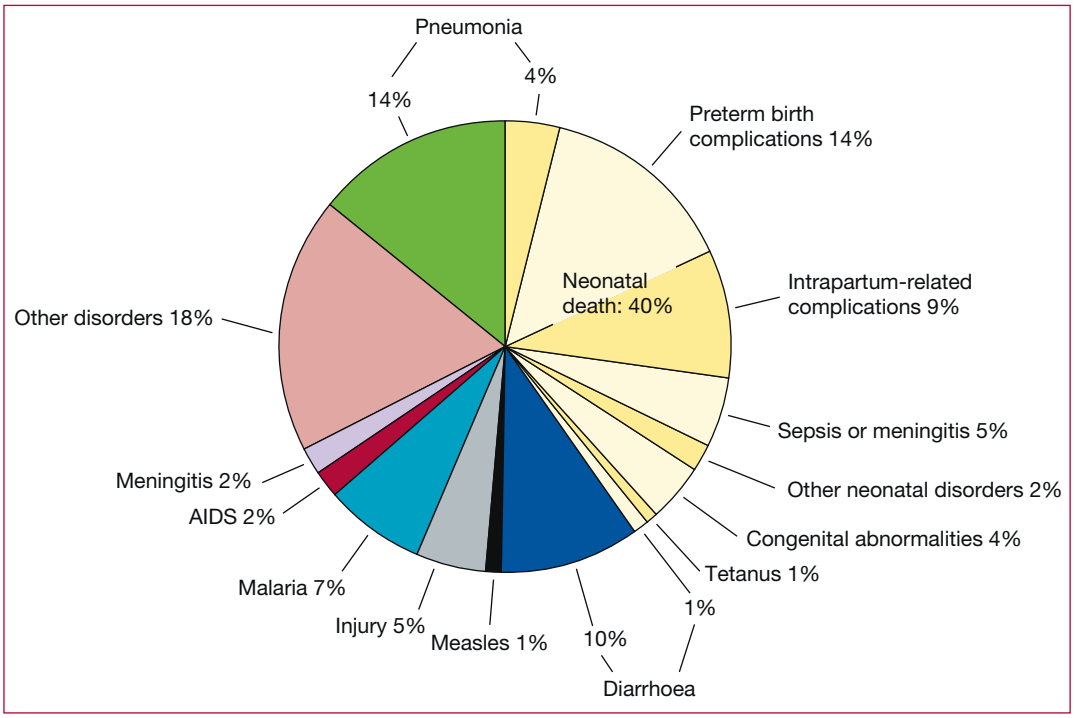

Figure 1 Global causes of childhood deaths in 2010, diarrhea kills 2195 children daily – more than malaria, measles, and AIDS combined. (Note – new figures show that neonatal component may be 44%). Reproduced from Liu, L., Johnson, H.L., Cousens, S., et al. (2012). Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet* **379**(9832), 2151–2161.

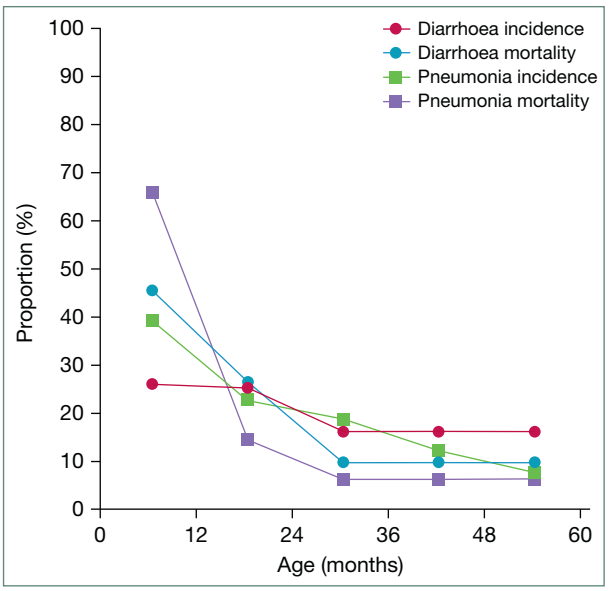

Figure 2 Distribution of cases of and deaths from diarrhea and pneumonia in children aged 0–4 years. Reproduced from Walker, C.L., Rudan, I., Liu, L., et al. (2013). Global burden of childhood pneumonia and diarrhoea. *Lancet* **381**(9875), 1405–1416.

damage. Phosphorylation-induced activation (by increase in cAMP, cGMP, or calcium) of these channels can be set off by exogenous or endogenous substances. Exogenous mediators include bacterial toxins such as cholera or shiga toxins, or parasites. Endogenous mediators can be endocrine, such as vasoactive intestinal peptide or serotonin, or released by the immune system, such as histamine, serotonin, prostaglandins, or interleukin-1. Lastly, increased intestinal permeability due to loss of cellular tight junctions can lead to increased intestinal fluid loss (Figure 4).

Poorly absorbed osmotically active substances in the gut lumen retain fluid, pull water and secondarily ions to maintain osmotic equilibrium with body fluids – this is the key underlying process behind *osmotic diarrhea*. This can occur secondary to an absorptive defect or enzyme deficiency from pancreas or intestinal wall causing maldigestion and/or malabsorption. An osmotic gradient is created that can only be neutralized by maintaining excessive amounts of water within the intestine. Examples include, malabsorption with congenital or acquired lactase deficiency, gluten-sensitive enteropathy (celiac disease) and maldigestion, as seen in pancreatic insufficiency (Figure 5).

Gastrointestinal barrier disruption by bacteria (Salmonella, *E. coli*, Campylobacter), viruses (rotaviruses, coronaviruses), and protozoa (Cryptosporium, Giardia) in addition to idiopathic inflammatory bowel diseases are common causes of *inflammatory* diarrhea. Immune cells after activation release inflammatory mediators and cytokines which stimulate secretion and activate enteric nerves. Subepithelial myofibroblasts destroy the basement membrane by metalloproteinases, damaged enterocytes are extruded, and villous atrophy develops followed by regenerative crypt hyperplasia in the small intestine and colon. These surfaces are covered with immature enterocytes that typically are deficient in the brush border enzymes and transporters necessary for absorption of nutrients and water.

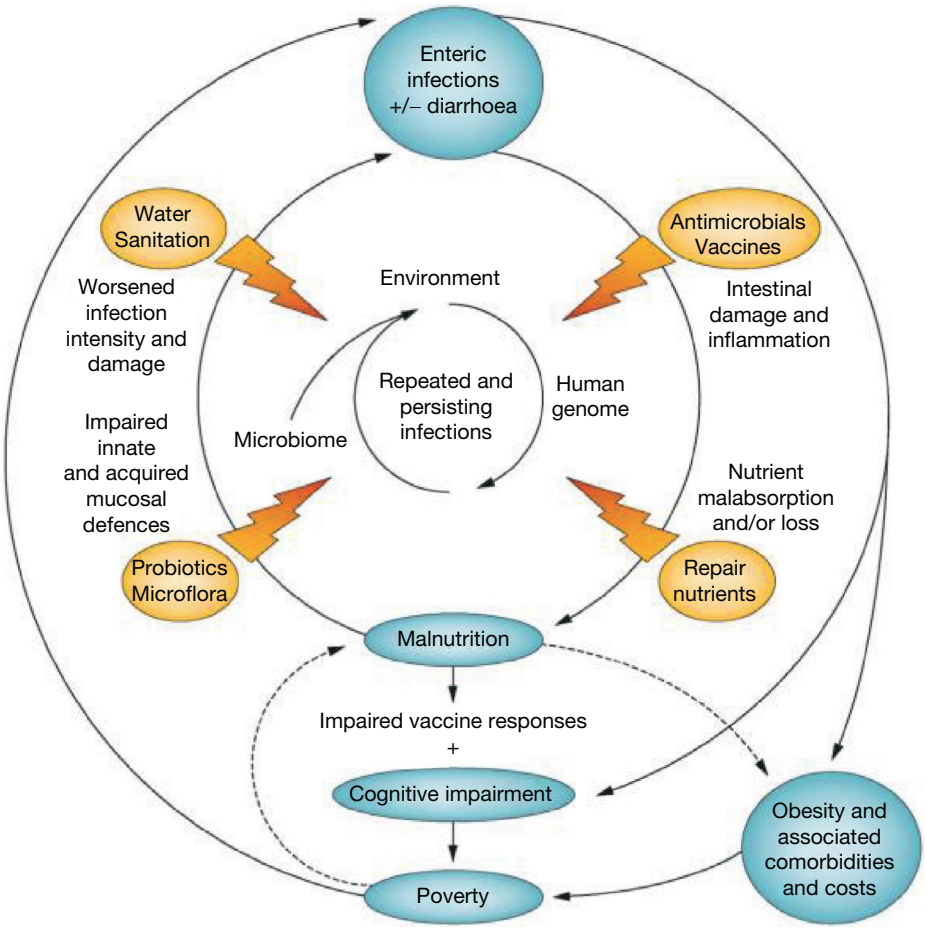

Figure 3 The vicious cycles of diseases of poverty. Enteric infections, especially in the first 2–3 years of life, with or without overt diarrhea, can predispose an individual to malnutrition and stunted growth through multiple mechanisms. Stunting by 2 years of age, in turn, is associated with impaired cognitive development that extends into later childhood and even adulthood and adult productivity. In addition, malnourished children experience both greater frequency and duration of diarrheal illnesses, and, documented in animal models, heavier infections. The latter is documented with Cryptosporidium and with enteroaggregative *E. coli*. Finally, enteric infections or stunting can predispose to obesity and its comorbidities of diabetes, hypertension, cardiovascular disease, metabolic syndrome and burgeoning healthcare expenditures, contributing to individual and societal poverty in vicious cycles. Reproduced from Guerrant, R.L., DeBoer, M.D., Moore, S.R., Scharf, R.J., and Lima, A.A. (2013). The impoverished gut – a triple burden of diarrhoea, stunting and chronic disease. *Nature Reviews Gastroenterology & Hepatology* **10**(4), 220–229.

Etiology of Diarrhea

Major etiologies for prolonged/acute and persistent diarrhea are outlined in Table 2. The most predominant cause of diarrhea in developing countries is infectious (viral, bacterial, parasitic). A systematic review of articles published between 1990 and 2011 reporting etiological agents causing diarrhea in hospitalized children less than 5 years of age showed that rotavirus, calicivirus, enteropathogenic, and enterotoxigenic *E. coli* cause more than half of all diarrheal deaths in this age group globally. A recent 3-year prospective study in four sites in Africa (the Gambia, Mali, Mozambique, Kenya) and three in Asia (India, Bangladesh, Pakistan) showed the most attributable cases of moderate to severe diarrhea in children aged 0–59 months was secondary to infection with rotavirus, Shigella, ST-ETEC, cryptosporidium, and enteropathogenic *E. coli*. Table 3 shows a comparison of viral, bacterial, and parasitic etiologic agents of diarrhea in developing countries and the United States. There is a seasonality in the transmission patterns of infectious agents in developing countries with bacterial diarrheas peaking in the hot months and viral diarrheas typically occurring throughout the year with some peaking in the cooler months. More than one pathogenic agent can exist with 11% (in community studies) and 12% (in hospital based studies) of diarrhea cases documented as having two or more enteric pathogens. Transmission of infectious agents causing diarrhea is primarily 'fecal–oral' in the setting of poor hand washing hygiene, unsanitary water and dirty food preparation. The dose of infectious agent required to cause diarrhea also matters with low infectious dose (e.g., shigella, giardia, rotavirus, cryptosporidium) can be transmitted by person-to-person contact and high infectious dose (e.g., salmonella, *E. coli*, vibrios) usually transmitted by water or food.

Table 1 Risk factors with direct biological links to diarrhea

	Morbidity	*Mortality*
Not exclusively breastfeeding (0–5 months; vs. exclusive breastfeeding)		
Partially breastfed	RR 1.7 (95% CI 1.0–2.8)[a]	RR 4.6 (95% CI 1.8–11.8)[a]
Not breastfed	RR 2.7 (95% CI 1.7–4.1)[a]	RR 10.5 (95% CI 2.8–39.6)[a]
No breastfeeding (6–23 months; vs. receives any breast milk)	RR 1.3 (95% CI 1.1–1.6)[b]	RR 2.2 (95% CI 1.1–4.2)[a]
Underweight (vs. >−2 WAZ for morbidity and >−1 WAZ for mortality)		
−2 to <−1 WAZ	–	OR 2.1 (95% CI 1.6–2.7)[c]
−3 to <−2 WAZ	RR 1.2 (95% CI 1.1–1.4)[d]	OR 3.4 (95% CI 2.7–4.4)[c]
Less than <−3 WAZ	–	OR 9.5 (95% CI 5.5–16.5)[c]
Stunting (vs. >−1 HAZ)		
−2 to <−1 HAZ	–	OR 1.2 (95% CI 0.9–1.7)[c]
−3 to <−2 HAZ	–	OR 1.6 (95% CI 1.1–2.5)[c]
<−3 HAZ	–	OR 4.6 (95% CI 2.7–8.1)[c]
Wasting[c] (vs. >−WHZ)		
−2 to <−1 WHZ	–	OR 1.2 (95% CI 0.7–1.9)[c]
−3 to <−2 WHZ	–	OR 2.9 (95% CI 1.8–4.5)[c]
<−3 WHZ	–	OR 6.3 (95% CI 2.7–14.7)[c]
Vitamin A deficiency (vs. not deficient)		RR 1.5 (95% CI 1.3–1.8)[e]
Zinc deficiency (vs. not deficient)	RR 1.2 (95% CI 1.1–1.2)[f]	RR 1.2 (95% CI 1.0–1.6)[f]

Abbreviations: RR, relative risk; WAZ, weight-for age *z*-score; OR, odds ratio; HAZ, height-for-age *z*-score; WHZ, weight-for-height *z*-score.

[a]Mix of cohort, observational, and case–control studies. Adjusted risk relations from individual studies used when available.

[b]Mix of cohort, observational, and case–control studies. Adjusted risk relations from individual studies used when available. Data only available for ages 6–11 months for this risk relation.

[c]Prospective datasets adjusted for socioeconomic and non-nutritional determinants of mortality.

[d]Mix of cohort, observational and case–control studies; analysis done with unadjusted risk estimates.

[e]Meta-analysis of observed risk reductions from supplementation trials.

[f]Meta-analysis of observed risk reductions from randomized controlled trials.

Source: Walker, C.L., Rudan, I., Liu, L., et al. (2013). Global burden of childhood pneumonia and diarrhoea. *Lancet* 381(9875), 1405–1416.

Diagnosis and Management of Acute/Prolonged and Persistent Diarrhea

Despite clinical clues, determining the causative agent of diarrhea in an individual patient on the basis of clinical grounds alone can be difficult. Both acute/prolonged and persistent diarrheas have similar initial evaluation and management. This chapter focuses on assessing the severity of illness and the need for rehydration. A brief history and directed clinical exam can help determine this and further guide the management.

History

Specific points in history include, time of onset of diarrhea, frequency, amount, consistency, and contents (blood, mucous, pus) of stool, associated signs and symptoms (fever, abdominal pain, nausea, vomiting, bloating, flatus, tenesmus), recent travel, dietary history, exposure to pets or cattle, drug history (specifically antibiotics and laxatives), pertinent past medical and surgical history, family history and day care attendance. For persistent diarrhea, the age of symptom onset and a detailed dietary history with relation between onset of symptoms and introduction to new foods is relevant.

Physical Examination

The initial physical exam focuses on signs and symptoms of dehydration (discussed below) and sepsis (fever and toxic look) which are major complications of acute and chronic diarrhea and require urgent management. Nutritional assessment is necessary and includes height, weight, vital signs, and global nutritional appearance.

Assessing Dehydration and IMCI Guidelines

Early recognition of dehydration, which is the main cause of mortality, is the most critical part of diarrhea management. Loss of water and electrolytes (sodium, chloride, potassium, and bicarbonate) via liquid stools, emesis, sweat, urine, and breathing leads to dehydration if left unreplaced. The WHO suggests assessment of dehydration on a scale of three (Figure 6).

1. Early dehydration with no signs or symptoms,
2. Moderate dehydration notable for thirst, restless, or irritable behavior, decreased skin elasticity, sunken eyes,
3. Severe dehydration when symptoms become more severe with diminished consciousness, lack of urine output, cool, moist extremities, a rapid and feeble pulse, low or undetectable blood pressure, and pale skin in the setting of clinical shock.

Lab Evaluation

For acute diarrhea, maintaining adequate intravascular volume and correcting fluid and electrolyte disturbances take priority over the identification of the causative agent. Stool cultures are usually unnecessary for immune-competent patients who present within 24 h after the onset of acute, watery diarrhea. Lab testing including

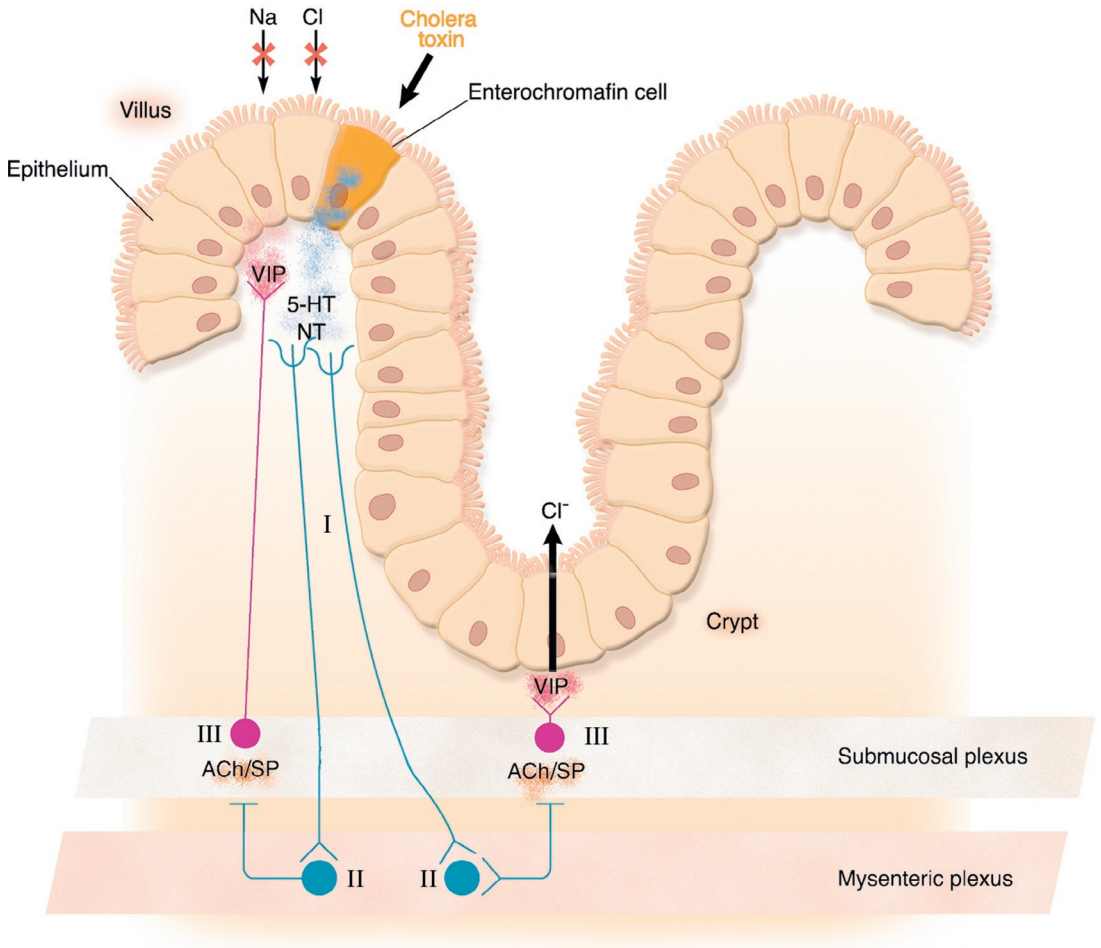

Figure 4 Pathophysiology of secretory diarrhea: diarrhea secondary to cholera toxin cholera toxin induces secretion, in part, through activation of an intramural neural reflex. Toxin attaches to enterochromaffin cells in the epithelium, causing an increase in (cAMP) there. In response to the latter, serotonin (5-HT), neurotensin (NT), and possibly additional peptides are released. These activate afferent neurons (I), whose axons course from close to the epithelium to the myenteric neural plexus, where they connect with interneurons (II) that, in turn, through release of acetylcholine (ACh) and/or substance P (SP), activate secreto-motor neurons (III) in the submucosal neural plexus. Axons from these secreto-motor neurons reach the epithelial surface, in both the villus and the crypt regions, releasing VIP and thereby stimulating secretion in crypts and inhibiting nutrient-independent salt absorption in villi. Reproduced from Field, M. (2003). Intestinal ion transport and the pathophysiology of diarrhea. *The Journal of Clinical Investigation* **111**(7), 931–943.

stool studies, blood tests, intestinal imaging, and immunologic and serologic evaluation are indicated in bloody diarrhea, high fever (>104 F), systemic illness, severe, or prolonged diarrhea, history suggestive of food poisoning, recent history of travel overseas or possibility of immune dysfunction. Supplementary laboratory studies, including serum electrolytes, to assess patients with acute diarrhea usually are unnecessary.

Treatment Approach

Fluids Resuscitation

Dehydration is the primary cause of death in patients with diarrhea and effectively addressing this is the cornerstone of diarrhea treatment. Oral rehydration solution (ORS), developed in the 1960s and 1970s by researchers in South Asia, is a simple cost-effective solution containing glucose and electrolytes that can be used to prevent and treat dehydration due to diarrhea of any cause across all ages. Development of the ORS took advantage of the glucose-coupled intestinal sodium transport mechanism discovered in the 1960s by Robert Crane. Absorption of sodium and glucose molecules across the luminal membrane is facilitated by the protein sodium glucose co-transporter 1 (SGLT1). Although nutrient-independent sodium absorption across the intestinal epithelial brush border membrane is impaired in diarrhea, cotransport of sodium and glucose is preserved. This allows absorption of sodium and thus water as provided by ORSs (Figure 7).

Once in the enterocyte, the transport of glucose into the blood is facilitated by GLUT2 (glucose transporter type 2) in the basolateral membrane with the Na+K+ATPase provides the gradient that drives the process. Key in the success of use of ORS for rehydration is the fact that these physiological processes stay intact, even in the setting of severe diarrhea.

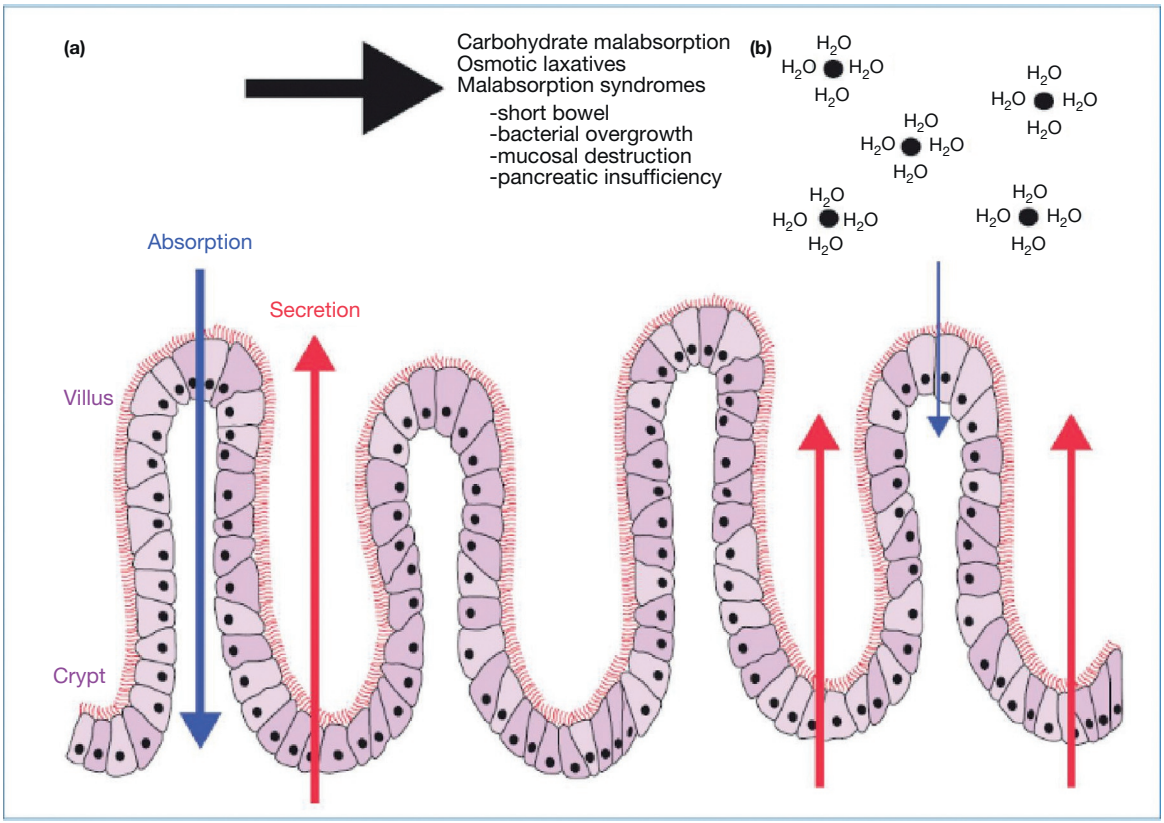

Figure 5 Pathophysiology of osmotic diarrhea. The figure demonstrates the pro-secretory effects of osmotic agents on intestinal fluid movement. (a) Represents the normal luminal environment and (b) represents the effects of osmotic agents such as non-absorbed carbohydrates. Image reproduced from the Internet http://cancerlink.ru/?page_id=1612 – free image source.

The original ORS recommended by the WHO in the 1970s had a formulation with a total osmolarity of 311 mmol l^{-1} (Table 4) but subsequent investigations lead to the current WHO recommendations from 2004 of a low osmolarity ORS (total osmolarity of 245 mmol l^{-1}, decreased concentrations of glucose and sodium). The current formulation when compared to the original formulation is associated with decrease in stool volume by about 25% when compared to the original World Health Organization/United Nations Children's Fund (WHO/UNICEF) ORS solution, reduced vomiting by almost 30%, and reduced need for unscheduled IV therapy by more than 30%. A 2010 review by Munos and colleagues assessed 205 studies and showed that universal coverage with ORS would reduce diarrhea-related deaths by 93%. There are two phases to treatment: rehydration and maintenance. In the rehydration phase, there is quick replacement of the fluid deficit over 3–4 h to achieve clinical hydration. In the maintenance phase, maintenance calories and fluids are administered with reintroductions of enteral feeding with an age-appropriate unrestricted diet, including solids. In children with mild to moderate dehydration, 50–100 ml of ORS/kg body weight during 2–4 h should be administered to replace the estimated fluid deficit, with additional ORS administered to replace ongoing losses. In the setting of severe dehydration, there is an emergent immediate need for IV rehydration. Lactated Ringer's solution, normal saline, or a similar solution should be administered (20 ml kg^{-1} body weight) until pulse, perfusion, and mental status return to normal.

Zinc Supplementation

Zinc deficiency is widespread among young children in low- and middle-income countries. It contributes to mortality and morbidity related to diarrhea, malaria, pneumonia, and restricts growth. Children with diarrhea suffer due to poor baseline dietary zinc intake with aggravated net losses of zinc during the period of illness. The WHO and UNICEF has recommended zinc for the treatment of diarrhea since 2004. Evidence suggests that zinc administration (20 mg per day until the diarrhea ceases) reduces the duration, severity and hospital admissions associated with diarrheal episodes in children in developing countries. Zinc for the treatment of diarrhea is estimated to decrease diarrhea mortality by 23% as well as significantly reducing the severity and duration of diarrheal episodes in children as well as a reduction in treatment failure or deaths in diarrheal episodes of longer duration (>14 days).

Diet

Current WHO guidelines for the management and treatment of diarrhea in children strongly recommend continued feeding alongside appropriate management. An extensive review on

Table 2 Differential diagnosis for prolonged/acute and persistent diarrhea

Prolonged/acute diarrhea (1–13d)	
Infectious	Viral (rotavirus, Norwalk, enterovirus, calcivirus); bacterial (*E. coli*, Shigella, Salmonella, Yersinia, Campylobacter, *C. difficile*, *V. cholera*, Aeromonas); Protozoa (Giardia, cryptosporidium, *E. histolytica*)
Allergy	Short exposure to allergen, challenge to known allergen
Toxic	Drug side effects, acute abdomen with diarrhea as presenting symptom, intussusception
Extra-intestinal infections	Respiratory, urinary, sepsis
Persistent diarrhea (>=14 days)	
Infantile protracted diarrhea with villous atrophy	Post infectious, food allergy, malnutrition congenital histological dysmorphism (e.g., tufting enteropathy, microvillus inclusion disease)
Infectious	Bacterial, parasitic
Inborn errors of metabolism	Familial chloride diarrhea, sodium–hydrogen exchange defect, abetalipoproteinemia and hypobetalipoproteinemia, Galactosemia, Tyrosinemia, Acrodermatitis enteropathica
Carbohydrate malabsorption	Congenital (lactase deficiency, glucose–galactose malabsorption, sucrase–isomaltase deficiency, fructose malabsorption) secondary (acquired mono and disaccharidase deficiencies)
GI organ pathology	Small intestine (celiac disease, tropical sprue, Whipple's disease, intestinal lymphangiectasia, eosinophilic gastroenteropathy, enterokinase deficiency); short bowel syndrome; ischemia; lymphoma; motility disorders (for e.g., small bowel overgrowth); pancreas (all conditions with exocrine insufficiency for e.g., cystic fibrosis); liver (all conditions leading to cholestasis, bile salt deficiency)
Immune defects	Isolated IgA deficiency, SCIDS, AIDS, autoimmune enteropathy
IBD	Crohn's disease, ulcerative colitis
Fecal impaction with overflow	Hirschsprung's disease, anorectal malfunction, functional constipation
Dietary	Overfeeding, nondigestible carbohydrates
Others	Toddler's diarrhea, Munchausen by proxy, factitious diarrhea, non-GI causes (tumors – APUDoma, ganglioneuroma, neuroblastoma)

Source: Robert Wyllie, J.S.H. (2011). *Pediatric gastrointestinal and liver disease* (4th ed). Diarrhea.

Table 3 Comparison of viral, bacterial, and parasitic etiologic agents of diarrhea in developing countries and the United States

Etiologic agent	*Developing country*	*United States*
Viral		
Rotavirus	Important	Very important
Noroviruses	Probably important	Important
Enteric adenoviruses	Minor	Probably important
Bacteria		
Enterotoxigenic *E. coli*	Very important	Minor
Campylobacter	Important	Important
Shigella	Important	Minor
Salmonella	Variable	Important
Enterohemorrhagic *E. coli*	Minor	Important
Parasites		
Cryptosporidium	Important	Minor
Giardia	Minor	Minor
Strongyloides	Minor	Minor
Entamoeba histolytica	Minor	Minor

Source: Table modified from Lanata, C.F., Fischer-Walker, C.L., Olascoaga, A.C., Torres, C.X., Aryee, M.J., Black, R.E., and Child Health Epidemiology Reference Group of the World Health Organization and UNICEF (2013). Global causes of diarrheal disease mortality in children <5 years of age: a systematic review. *PLoS One* **8**(9), e72788.

feeding strategies and food-based interventions in children younger than 5 years with diarrhea in low- and middle-income countries showed that although illness duration was shorter and risk of treatment failure 47% lower in children with acute diarrhea who consumed lactose-free diet, there was no effect of lactose avoidance on stool output or weight gain. WHO recommends the following:

- An age-appropriate diet regardless of the fluid used for ORT (oral rehydration therapy)/maintenance
- More frequent breastfeeding or bottle feeding – special formulas or dilutions are unnecessary
- Age-appropriate fluid resuscitation
- Frequent, small meals throughout the day (six meals/day)
- Energy and micronutrient-rich foods (grains, meats, fruits, and vegetables)
- Increasing energy intake as tolerated following the diarrheal episode
- Avoid: canned fruit juices and other high-sugar food and drinks – these are hyperosmolar and can aggravate diarrhea.

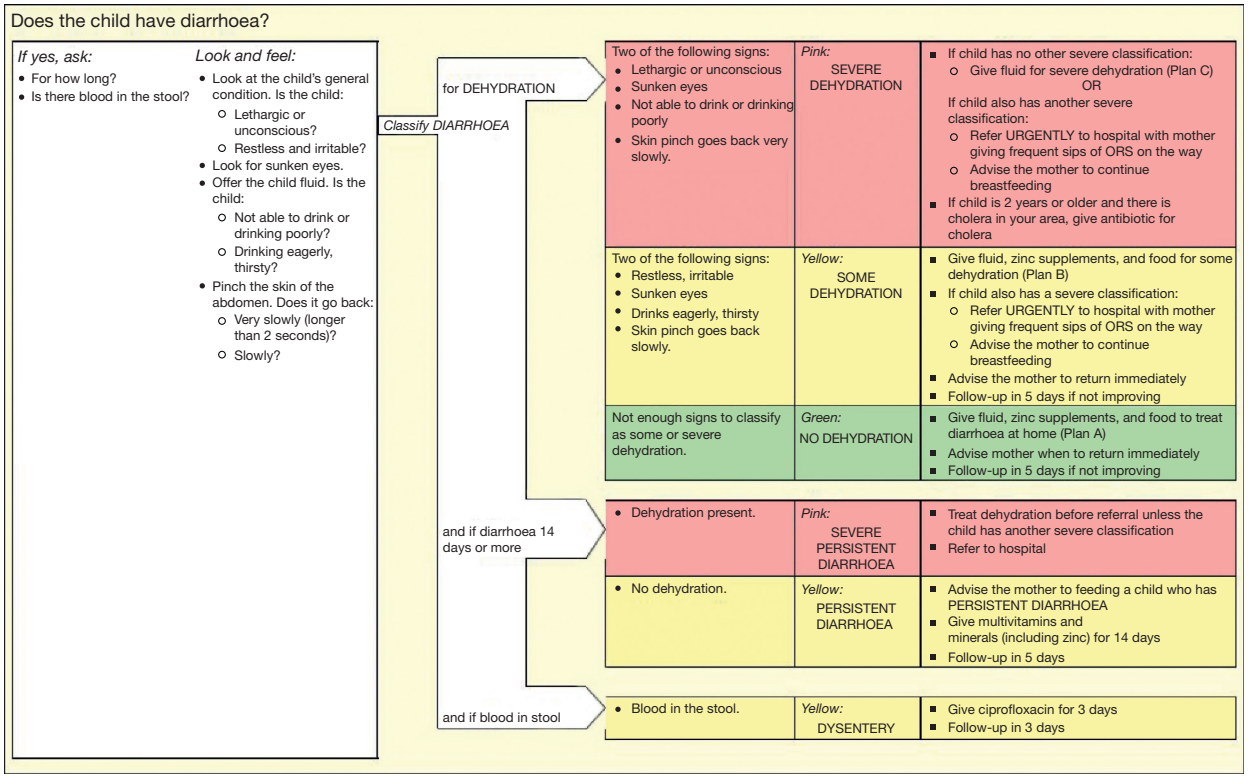

Figure 6 IMCI flow chart for diarrhea in children under 5 years of age. Reproduced from WHO (2014). *Maternal, newborn, child and adolescent health*. IMCI Chart Booklet. Page 3/76.

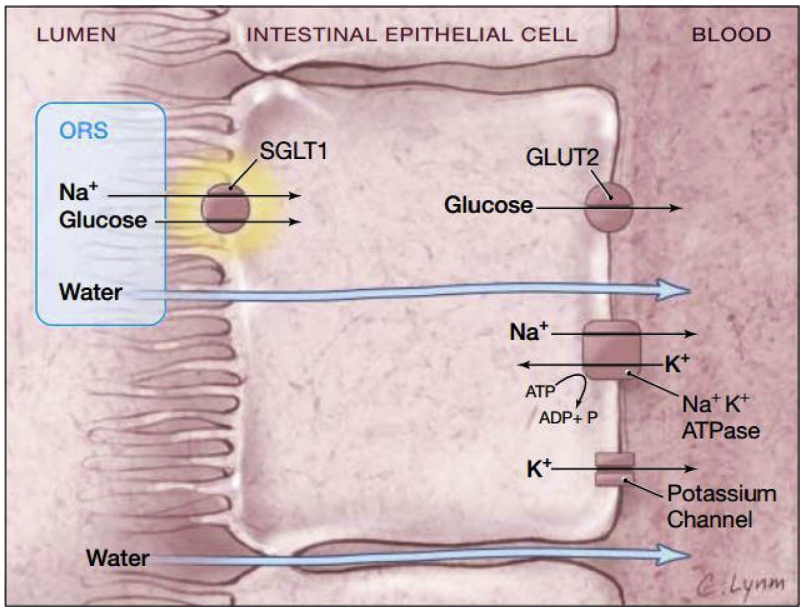

Figure 7 Coupled transport of sodium and glucose in intestinal epithelial cells. Reproduced from Duggan, C., Fontaine, O., Pierce, N.F., et al. (2004). Scientific rationale for a change in the composition of oral rehydration solution. *JAMA* **291**(21), 2628–2631.

Antibiotics for Cholera, Shigella, and Cryptosporidium

Antibiotics should not be used for relatively mild, self-limited infectious diarrhea to minimize development of drug resistance. When the diarrhea is hemorrhagic, seriously dehydrating, associated with serious systemic signs and symptoms, or of longer than 5 days' duration without improvement, antibiotic use is appropriate. A review by Traa and colleagues assessed the effectiveness of WHO-recommended antibiotics – ciprofloxacin, ceftriaxone, and pivmecillinam – for the treatment of dysentery, and concluded that antibiotics can be expected to

Table 4 Composition of standard and reduced-osmolarity WHO ORS

	Standard WHO (1975)	*Reduced-osmolarity WHO (2002)*
Glucose (mmol l^{-1})	111	75
Sodium (mequiv. l^{-1})	90	75
Potassium (mequiv. l^{-1})	20	20
Chloride (mequiv. l^{-1})	80	65
Citrate (mmol l^{-1})	10	10
Osmolarity (mOsml l^{-1})	311	245

Abbreviations: ORS, oral rehydration solution; WHO, World Health Organization.
Source: Duggan, C., Fontaine, O., Pierce, N.F. et al. (2004). Scientific rationale for a change in the composition of oral rehydration solution. *JAMA* **291**(21), 2628–2631.

decrease diarrhea mortality attributable to dysentery by more than 99%. There is evidence to recommend antibiotic use for reduction of morbidity and mortality due to cholera, Shigella spp. and cryptosporidium – Das et al. showed that in the developing country setting antibiotic management of cholera resulted in a 63% reduction in rates of clinical failure and a 75% reduction in rates of bacteriological failure. They also showed that antibiotic management of Shigella resulted in an 82% reduction in rates of clinical failure and a 96% reduction in rates of bacteriological failure. Antibiotics for treatment of cryptosporidiosis reduced mortality by 76%, rates of clinical failure by 52%, and rates of parasitological failure by 38%. The empiric antibiotic regimen should be determined by host factors, severity of illness, local resistance patterns, and history of travel to an area with increased resistance.

Probiotics

Probiotics are defined by the joint Food and Agriculture Organization/WHO Working Group as 'live microorganisms that when administered in adequate amount concern a health benefit on the host.' Recent Cochrane systematic reviews on the use of probiotics as an adjunct therapy to ORS have shown that probiotics shorten the duration of diarrhea and reduce stool frequency but the observation remains inconclusive due to few trials with small numbers of participants. Most commonly used probiotics in trials include Bifidobacterium, two genera of lactic acid bacteria (Lactobacillus and Streptococcus) and the yeast Saccharomyces. There is insufficient evidence to recommend their widespread use at this time.

Antiemetics

Vomiting associated with diarrhea causes significant additional physical discomfort and is of concern for both parents and physicians. Additionally, vomiting can limit the success of ORS and can result in increased use of intravenous (IV) rehydration, need for prolonged emergency department stays and hospitalizations. A recent systematic review evaluated seven RCTs which used ondansetron, metoclopramide, dimenhydrinate, and dexamethasone in children aged 0–12 years. They found that use of antiemetics significantly reduced the incidence of vomiting and hospitalization by 54% and reduced IV fluid requirements by 60%. A 2011 Cochrane Review on the use of antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents concluded that oral ondansetron increased the proportion of patients who had ceased vomiting and reduced the number needing IV rehydration and immediate hospital admission. IV ondansetron and metoclopramide reduced the number of episodes of vomiting and hospital admission, and dimenhydrinate as a suppository reduced the duration of vomiting. Antiemetics are effective for the management of gastroenteritis in children and have the potential to decrease morbidity and mortality burden due to diarrhea.

Breast Feeding

Breast milk provides various immunological, psychological, social, economic, and environmental benefits, and is therefore recommended as the best feeding option for newborn babies and young infants in developing countries, including HIV-infected populations. Lamberti and colleagues reviewed 18 studies from developing countries reporting the effect of breastfeeding on diarrhea morbidity and mortality. The investigators estimated that not breastfeeding was associated with a 165% increase in diarrhea incidence and mortality in 0–23-month-olds.

Vaccines for Rotavirus

Rotavirus is the most common cause of severe dehydrating diarrhea in infants worldwide. Rotavirus vaccines represent an important preventive approach to reducing the burden of diarrheal disease due to rotavirus. Since 2006 two rotavirus vaccines are currently licensed for vaccinating infants in North and South American, European, and Eastern Mediterranean countries: RotaTeq® (Merck) and Rotarix® (GlaxoSmithKline). RotaTeq®/RV5 – is a live, oral vaccine that contains five reassortant rotaviruses developed from human and bovine parent rotavirus strains and is given orally in three doses at ages 2, 4, and 6 months. Rotarix®/RV1 is a live, oral vaccine licensed in 2008 for use in the United States that contains a human rotavirus strain, this is given orally in two doses at ages 2 and 4 months. This first dose of either vaccine is most effective if it is given before a child is 15 weeks of age and children should receive all doses of rotavirus vaccine before they turn 8 months old.

In the global health setting, there is evidence suggesting that rotavirus vaccine efficacy may vary by setting due to regional differences in circulating rotavirus vaccine strains, and reduced efficacy of oral vaccines in countries with high burden of malnutrition and enteric infections. A meta-analyses by Munos et al. assessed the effectiveness of two currently marketed vaccines the pentavalent human-bovine reassortant rotavirus vaccine and monovalent attenuated human rotavirus vaccine in Phase III trials in European and Latin American sites for both vaccines, as well as the United States (including Navajo and Apache populations) and Taiwanese sites for the pentavalent vaccine. The effectiveness studies of the monovalent and pentavalent vaccines were conducted in northern Australia and Nicaragua, respectively. The authors estimated that these rotavirus vaccines could prevent

74% of rotavirus deaths and 47–57% of rotavirus hospitalizations. Data published from a randomized, placebo-controlled, multicenter trial in South Africa and Malawi evaluating the efficacy of a live, oral rotavirus vaccine in preventing severe rotavirus gastroenteritis showed that the rotavirus vaccine significantly reduced the incidence of severe rotavirus gastroenteritis among African infants during the first year of life. The ROTAVAC rotavirus vaccine study group recently published results from a Phase III clinical trial using ROTAVAC which is a new rotavirus vaccine that consists of a strain of the virus that was isolated, manufactured, and tested in India. Infants aged 6–7 weeks received three doses of oral human-bovine natural reassortant vaccine (116E) with efficacy results from the study showing the vaccine to be effective and well tolerated in Indian infants.

Vaccines for Cholera

Although case management with oral rehydration therapy has substantially improved case-fatality rates for cholera, the infection can still kill rapidly, especially in outbreak settings. Old-generation injectable cholera vaccines, abandoned since the 1970s because of their restricted effectiveness and local side effects. However, studies have shown vaccines to be effective in reducing risk of cholera infection in children younger than 5 years by 52%, increase in vibriocidal antibodies by 124% and a relative risk of one or more adverse events of 1.4. Such evidence for the effectiveness of oral cholera vaccines makes them good candidates for cholera control in endemic areas.

Improved Water Provision, Use, Sanitation, and Hygiene Promotion

Maintaining water quality (protection or treatment of water at source or point of use) is more effective than improving water supply (improved source of water or improved distribution, or both). Cairncross and colleagues estimated the effect of water, sanitation, and hygiene strategies and estimated risk reductions for diarrhea of 48% for hand washing with soap, 17% with improved water quality, and 36% with proper excreta disposal.

Community-Based Approaches

Although evidence confirms the efficacy and effectiveness of many interventions, many interventions are not accessible to people in need; hence, the focus on delivery strategies has increased. One method of community-based case management is to provide these amenities through community health workers with home visitation and community-based sessions for education and promotion of care seeking. These approaches have been assessed and concluded that that community-based interventions are associated with a 160% significant increase in the use of ORS and an 80% increase in the use of zinc in diarrhea. Furthermore, findings showed a 9% increase in care seeking for diarrhea and noted a 75% significant decline in inappropriate use of antibiotics for diarrhea.

Global Action Plan for Pneumonia and Diarrhea

The 2013 Lancet Childhood Pneumonia and Diarrhea series reviewed existing preventive and therapeutic interventions that could have a role in reducing the morbidity and mortality burden in children younger than 5 years due to diarrhea and pneumonia. The interventions with the maximum effect include breastfeeding, ORS, and community case management. The series concluded that despite a large global burden childhood diarrhea and pneumonia deaths are avoidable and 15 interventions delivered at scale can prevent most of these deaths (Figures 8 and 9). Estimates modeled with the Lives Saved Tool showed that if the interventions are scaled up by 80% in the 75 countdown countries, 95% of diarrheal, and 67% of pneumonia deaths in children younger than 5 years can be prevented by 2025. Scaling up of diarrheal and pneumonia interventions would cost US$ 6.715 billion, only $2.9 billion more than present levels of spending. Assessment is needed of the cost-effectiveness of these interventions in national health delivery frameworks. We have a clear idea of effective interventions for both diarrhea and pneumonia and with community health-worker programs increasingly being employed to reach underserved populations, real opportunities exist to scale-up community advocacy/education programs, early case detection and management strategies.

The series also included summary recommendations after a series of consultations with several hundred front line public health practitioners in target countries were held to identify key barriers to scaling up of evidence-based interventions to reduce pneumonia and diarrhea mortality. Critical barriers included: absence of national coordination within ministries and other stakeholders to deliver interventions, insufficient financial resources, inadequate training and support for health workers, poor systems for monitoring and assessment of key programmatic indicators and sporadic availability of key commodities. The final list of recommendations included: (1) Improve coordination between various groups working on preventive and treatment interventions to control pneumonia and diarrhea. (2) Substantially increase resources for child survival programs, with an emphasis on pneumonia and diarrhea control efforts. (3) Enhance efforts to attract, train, and retain a competent work force of caregivers. (4) Invest in better systems for harmonization of the collection of essential programmatic indicators, and ensure that this information is shared throughout the system. (5) Strengthen supply systems that deliver essential commodities. In summary, the cost to achieve the end of preventable deaths from pneumonia and diarrhea by 2025 is estimated to be around US$ 6.715 billion. Despite large reductions in child mortality between 2000 and 2010 (both in all-cause mortality, and specifically diarrhea and pneumonia associated), these diseases remain causes for preventable deaths. The achievement of the fourth Millennium Development Goal and the longer-term target of reduction of child mortality to 20 deaths or fewer per 1000 live births in all countries by 2035 requires significant decreases in mortality from both diarrhea and

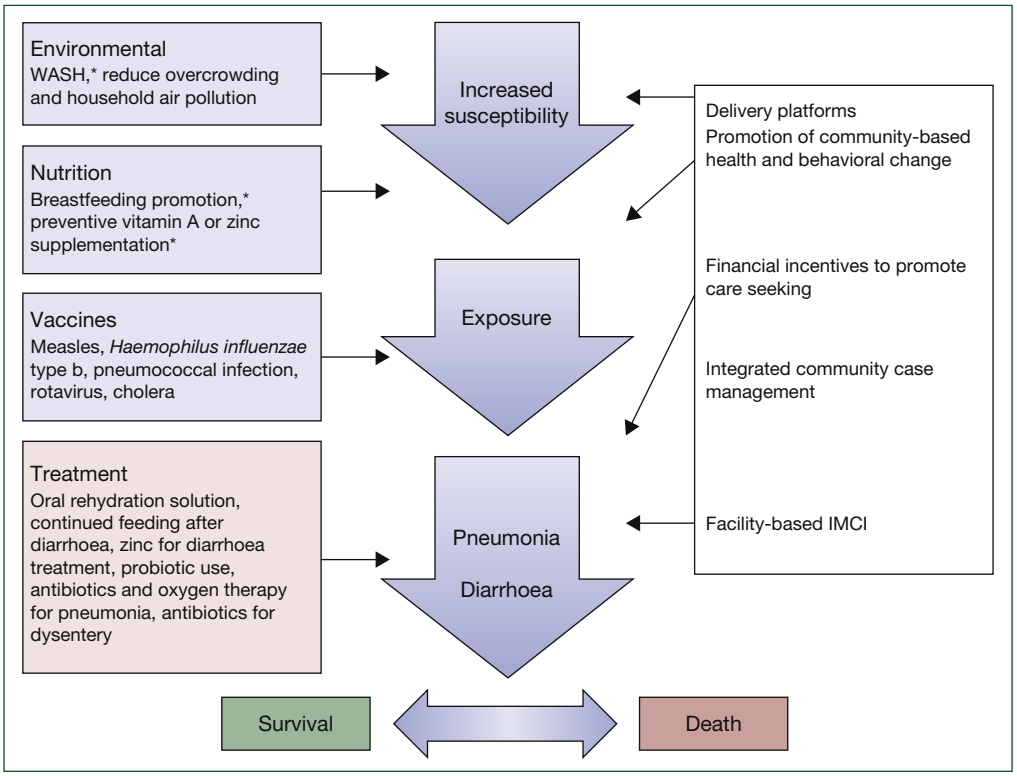

Figure 8 Conceptual framework of the effect of interventions for diarrhea and pneumonia – WASH, water, sanitation, and hygiene; IMCI, Integrated Management of Childhood Illness. Asterisk (*), interventions common to both diarrhoea and pneumonia. Reproduced from Bhutta, Z.A., Das, J.K., Walker, N., et al. (2013). Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? *Lancet* **381** (9875), 1417–1429.

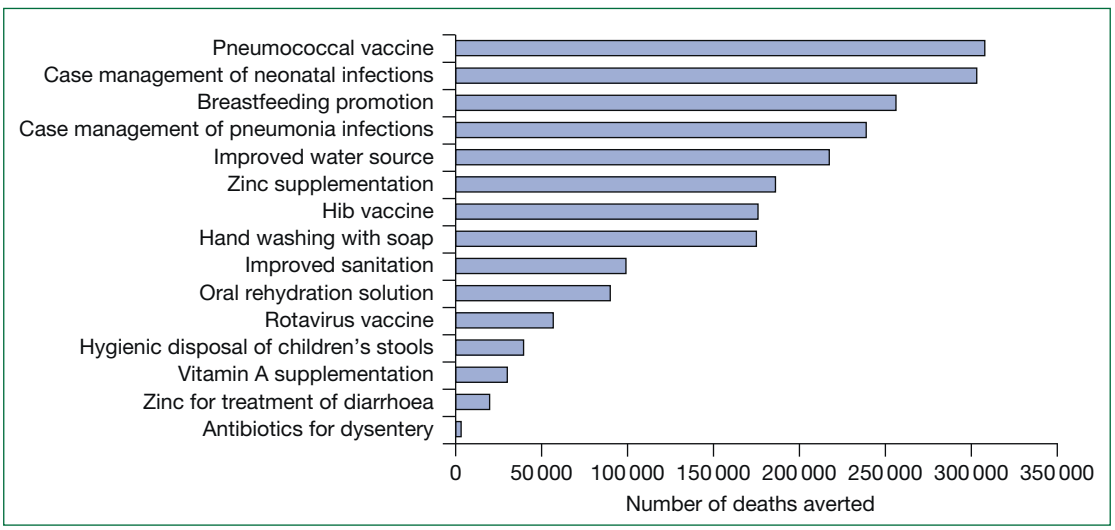

Figure 9 Sequential effect of 15 individual interventions on deaths due to diarrhea and pneumonia Haemophilus influenzae type b – Hib. Reproduced from Bhutta, Z.A., Das, J.K., Walker, N., et al. (2013). Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? *Lancet* **381**(9875), 1417–1429.

pneumonia. Our knowledge on diarrhea has drastically evolved over the past five decades and the present challenge is to implement these evidence-based strategies for reducing morbidity and mortality due to diarrhea.

See also: *Clostridium botulinum*; *Clostridium*: Food Poisoning by *Clostridium perfringens*; *Clostridium*: Occurrence and Detection of *Clostridium botulinum* and Botulinum Neurotoxin; *Clostridium*: Occurrence and Detection of *Clostridium perfringens*; Colon: Structure and Function; *Escherichia coli* and Other *Enterobacteriaceae*: Food Poisoning and Health Effects; *Escherichia coli* and Other *Enterobacteriaceae*: Occurrence and Detection; Malnutrition: Concept, Classification and Magnitude; Malnutrition: Prevention and Management; Nutrition and Infection; Probiotics; *Salmonella*: Detection; *Salmonella*: Properties and Occurrence; *Salmonella*: Salmonellosis; Sanitization; *Staphylococcus*: Food Poisoning; World Health Organization; Zinc: Physiology and Health Effects; Zinc: Properties and Determination.

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