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AN OVERVIEW ON PATHOGENESIS OF DIARRHEA IN INFANTS AND CHILDREN

By

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Abstract

Diarrhea is frequent, loose, or watery bowel movements (BMs) that differ from a child's normal pattern, as is a very common problem, leading cause of child mortality and morbidity worldwide. In children acute watery diarrhea (several hours or days), acute bloody diarrhea (dysentery), and persistent diarrhea, which lasts 14 days or longer. Gastroenteritis most common symptoms regardless of cause, are vomiting, diarrhea, and sometimes abdominal cramps, fever, and poor appetite.

The risky complication of gastroenteritis is dehydration. The dehydrated children become listless, irritable, or sluggish (lethargic), but dehydrated infants develop serious side effects with hospitalized medical care. The causative agents of diarrhea in children are viruses, particularly rotavirus (preventable with a vaccine) and norovirus, as well as adenovirus and arbovirus, bacteria like *E. coli*, salmonella and cholera. Protozoal parasites causing diarrhea as *Cryptosporidium, Entamoeba, Giardia*, *Balantidium coli* and *Cystoisospora belli* as well as helminths as *Strongyloides, Schistosoma* and *Trichuris* may cause chronic diarrhea especially in immunocompromised individuals. Apart from microorganism agents, diet, antibiotics and others can cause children diarrhea.

Key words: Children, Diarrhea, Pathogenesis, Bacteria, Parasites, Viruses, Others.

Introduction

Diarrheal diseases have been a major human health problem worldwide long ago. Prior to the advent of modern medicine, severe diarrhea was often fatal and disease outbreaks spread quickly, affecting large populations (Meckel, 1990). Today, despite the success of interventions such as oral and intravenous rehydration therapy, diarrheal diseases remain a substantial cause of mortality and morbidity worldwide, particularly in children and elderly (Thompson and Keeling 2012). In fact, death among volume depleted children with diarrheal disease is the second leading cause of death among the under-five children word wide (Liu *et al,* 2012). It was estimated that globally 577,000 children aged <5 years and 502,000 adults aged >70 years died from diarrhea (WHO, 2016). Although the basic principles on fluid and electrolytes therapy have been known for decades, but consensus on clinical management protocol is difficult to reach more adverse events are reported from the fluid administration than for any other drug (Regina, 2017). In spite of etiology, the evaluation and management of a diarrheic infant or child, one must know the physiology of fluids and electrolyte transport in gastrointestinal tract (Barrett and Keely, 2000).

This overview focused on the pathophysiology of fluid absorption and secretion in diarrhea and a classification of diarrhea relevant to diagnostic evaluations.

Review and General Discussion

Diarrhea: The presence of diarrhea can be defined in a number of ways, either related to volume and/or consistency of stool, or frequency of bowel movements. In hospital settings where the stools volume can be measured, diarrhea is defined as stool more volume than 20gm/kg/day in infants and toddlers (<10kg), or more than 200gm/day in older children, or teenagers (Vanderhoof, 1998). Generally, the common definition is the passage of three more loose or liquid stools per day, or more frequent passage than in the normal individu-

al (WHO, 2019). In infants and children, it can be difficult to establish the presence of diarrhea based on stool frequency or consistency, as the normal range for these parameters can vary greatly by age and diet. As some healthy breastfed infants pass eight or more loose stools daily. Diarrhea is generally considered acute if it lasts less than two weeks and chronic if it lasts more than two weeks. However, there remains a lack of clear consensus on the use of symptom-based and/or duration-based definitions of diarrhea (Johnston *et al,* 2010). There are 3 clinical types of diarrhea: 1- Acute watery diarrhea lasts several hours or days and includes cholera, 2- Acute bloody diarrhea, also called dysentery, and 3- Persistent diarrhea that lasts 14 days or longer. Diarrhea is a symptom of an intestinal tract infection, which can be caused by a variety of bacterial, viral and parasitic organisms, and spread by contaminated food or drinking-water, or from person-to-person as a result of poor hygiene (WHO, 2024a).

Normal fluid movement in gastrointestinal tract absorption and secretion: Large quantities of fluid are transported bidirectional across epithelial barriers in the gastrointestinal tract for secretion of saliva, gastric juice, bile, and pancreatic fluid, and for fluid absorption in the intestine. The quantity of fluid transported in the intestine is second only to kidney, where about 180L of fluid per day are filtered by the glomerulus and processed by various nephron segments (Masyuk *et al,* 2002).

In the healthy adults (fig. 1) several liters of fluid are absorbed and secreted by the different segments of the intestine each day. Salivary glands produce about 1.5L of fluid/day, stomach secretes 2.5L of gastric juice; liver produces 0.5L of bile; and pancreas produces 1.5L of enzyme and bicarbonate-rich fluid, small intestine absorbs 6.5L of fluid, and colon absorbs 1.3L of fluid against the significant osmotic gradients (Thiagarajah and Verkman, 2012).

The small intestine performs fluid absorption (83%) in gastrointestinal tract. So, diseases affect the small intestine often result in clinically significant diarrhea. Although the colon absorbs a much smaller volume of fluid than small intestine, yet it is critical for generation of formed feces. The intestinal contents enter colon with a water content 90% that leave colon as feces, with a water content of 65 to 75% that significant alteration of colonic function alone leading to clinical diarrhea as well (Camilleri *et al,* 2016).

Molecular mechanical movement of fluid (fig. 2) between intestinal lumen and blood is driven by the active transport of ions (mainly Na^+, Cl^-, HCO_3^-, & K^+) and nutrients (mainly glucose). Fluid absorption or secretion involves the coordinated activity of membrane transporters located on apical (lumen-facing), and basolateral (circulation-facing) epithelial membranes. The intestinal epithelium is structurally configured into long, finger-like (3 dimensional pathological sections), or leaf-like projections (2 villi dimensions), and glandular tube-like structures (crypts). The stem cells at the crypt base provide various differential epithelial cell types, including the more numerous enterocytes that ascend and populate the villus structure. In small bowl, each villus is supported by at least ten distinct crypts, but in colon, the crypts are considerably longer than in the small bowel and produce epithelium that covers the flat luminal surface devoid of villi. Functionally, both ion and fluid absorption and secretion occur in enterocytes located in both villi and crypts, although, in small intestine, secretory processes predominate in crypts and absorptive processes in villi. The intestinal fluids absorption is driven by the active transport of Na^+ across epithelium with a parallel Cl^- or HCO_3^- absorption (Krishnan *et al*, 1999). The electrochemical driving force process is provided by the basolateral Na^+/K^+-ATPase that exports intracellular Na^+. In small intestine, fluid absorption is facilitated by Na^+/H^+ exchanger 3 (NHE3, known as SLC9A3), Na^+/glucose co-transporter 1 (SGLT1= SLC5A1), & Cl^-/ HCO_3^- exchangers (DRA= SLC-26A3) & PAT1=SLC-26A6). Electroneutral fluid absorption is carried out by NHE3 coordinated activity with

Cl^-/HCO_3^- exchangers (PAT1 for HCO_3^- absorption in jejunum, and DRA for Cl^- absorption in ileum and colon). Substrate-specific transporters such as SLC5A1 facilitate co-transport of Na^+ across apical membrane together with D-glucose (or D-galactose), with electro-neutral glucose transporter SLC2A2 facilitating glucose exit across the basolateral membrane (Yeo *et al,* 1994). In colon, in addition to electroneutral Na^+ transport by Na^+/H^+ exchange (proximal colon), absorption is facilitated by epithelial Na^+ channel (eNaC) and short-chain fatty acid transporters (sodium-coupled monocarboxylate transporter, or SMCT (Zaharia *et al,* 2001).

Intestinal fluid secretion is driven by transepithelial Cl^- secretion through basolateral, and apical Cl^- channels and transporters transported into cell at basolateral membrane by a $Na^+/K^+/Cl^-$ symporter (NKCC1, known as SLC12A2), driven by Na^+ concentration gradient produced by Na^+/K^+-ATPase K^+ channels (KCNQ1/KNE3 and KCNN4) provide electrochemical driving force for the apical Cl^- exit across Cl^- channels that are primarily cyclic-nucleotide-activated cystic fibrosis transmembrane conductance regulator (CFTR) & Ca^{2+}-activated Cl^- channels (CaCCs). Enteric nerves and cell surface receptors such as calcium-sensing receptor (CaSR) are thought to modulate intracellular signaling pathways and hence the electrolyte absorption and secretion (Chattopadhyay *et al,* 1998).

Pathophysiology of fluid transport in diarrhea (fig. 3): Water movement in intestine occurs by osmosis across the semipermeable barrier formed by the lining epithelial cells, similar to other fluid-transporting surfaces in the body. Diarrhea occurs when excessive fluid amounts remain within the intestinal lumen (Surawicz, 2010). This occurs because of increased secretion into the intestinal lumen, or reduced absorption of water from the lumen to the body. In either case there is an increased concentration of osmotically active particles (nutrients, and/or electrolytes) within the lumen of the intestine, resulting in a net increase in the water content of the intestinal contents. Increased concentrations of osmoticcally active particles in the lumen occur via three primary mechanisms: 1- Loss of nutrient absorption or the presence of non-absorbable solutes in the intestinal lumen include the loss of nutrient absorption seen in celiac disease or in inflammation, and diarrhea caused by laxatives such as the polyethylene glycol 3350. This mechanism underlies diet-induced (previously classified as osmotic) diarrhea, which improves with fasting. 2- Increased secretion or reduced absorption of electrolytes (Na^+, Cl^-, K^+, & HCO_3^-) across epithelium include diarrhea secondary to *Vibrio cholerae* infection that causes excessive secretion of chloride and loss of electroneutral sodium absorption that underlies electrolyte transport-related (previously classified as secretory) diarrhea, which fails to improve with fasting (Priyamvada *et al,* 2015). 3- Rapid intestinal transit causing time reduction for fluid absorption include a variety of conditions causing hypermotility of the intestine, including the functional diarrhea in infants and toddlers, or toddlers diarrhea (Guirl *et al,* 2003). Many underlying etiologies in children cause diarrhea via a combination of these primary mechanisms as inflammatory bowel disease, inflammation causes a loss of absorptive surface area and capacity causing loss of nutrient transport as well as increasing active Cl^- secretion and intestinal motility (Wenz, 2012).

Mechanisms of altered fluid transport in diarrheal diseases characterized by loss of nutrient-driven electrolyte transport (Hodges and Gill, 2010). Patients with lactase deficiency cannot hydrolyze lactose into glucose and galactose leads to loss of fluid absorption driven by Na^+/glucose co-transporter (SGLT1), and increased osmolality in intestinal lumen (Drozdowski and Thomson, 2006). Lactase deficiency can be either acquired congenital, or genetically driven age-dependent acquired deficiency or even hypolactasia (Wanes *et al,* 2019).

Certain enterotoxigenic pathogens can cause diarrhea by stimulating the fluid secretion (fig. 4). As examples, *Vibrio cholera* and ent-

erotoxigenic *Escherichia coli* release bacterial enterotoxins (cholera toxin, heat-stable enterotoxin) alter intracellular levels of second messenger molecules such as cAMP, cGMP and Ca^{2+} Ca^{2+} (Berkes *et al,* 2003). These are signal to the key channels that drive fluid absorption and secretion. Cholera toxin induces elevations in cAMP leading to active the chloride channel CFTR and inhibition of Na^{+} exchanger NHE3, resulting in a massive secretory diarrhea. Bacteria can also increase various humoral agonists, neurotransmitters or neuropeptide receptors such as 5-hydroxytryptamine, vasoactive intestinal peptides (VIP) and the galanin receptor type 1, also activates Cl^{-} secretion and inhibiting Na^{+} absorption. Meanwhile, diarrhea caused by viruses is partly due to active viral enterotoxins such as rotavirus NSP4, which results in intracellular Ca^{2+} elevation, inhibition of Na^{+} absorption, and increased Cl^{-} secretion (Morris *et al,* 1999). Rotaviruses, double-stranded, non-enveloped RNA viruses, are a global health concern, associated with acute gastroenteritis, and secretory-driven watery diarrhea, mainly in the infants and young children, and in acute gastroenteritis, it is linked to various neurological disorders, hepatitis and cholestasis, type 1 diabetes, respiratory illness, myocarditis, renal failure, and thrombocytopenia (Dian *et al,* 2021). The most common viruses causing watery diarrhea, with rarely contain mucus or blood in infants and children are the rotavirus (last 5 to 7 days), norovirus (lasts 1 to 3 day), adenovirus (mild vomiting 1or 2 days and diarrhea last 1 to 2 weeks), and astrovirus (as a mild rotavirus infection). Other less common ones are sapovirus, coronaviruses, and picobirnaviruses, but all are highly infectious and spread by droplets infection among children, through contaminated surfaces, and fecal-oral routes, with rotavirus is the severe diarrhea leading cause in children less than five years (Xiao *et al,* 2023).

Other bacteria cause diarrhea through an inflammatory mechanism are the invasive bacteria such as *Salmonella*, *Shigella* and *Campylobacter* cause a tissue inflammatory response involving recruitment of immune cells and release of cytokines, resulting in intracellular Ca^{2+} signaling (CDC, 2014). Enteropathogenic and invasive bacteria also result in alterations in channel protein expression, with the consequent impaired Na^{+} and Cl^{-} absorption (Kaur and Dudeja, 2023). Common bacterial pathogens are *Salmonella, Shigella, Campylobacter jejuni, Yersinia enterocolitica, Clostridioides difficile,* and *Escherichia coli*. Although, most bacterial infections are self-limited, but can lead to severe complications like sepsis, seizures, hemolytic uremic syndrome, Guillain-Barré syndrome, and death (Akhondi *et al,* 2025).

Apart from bacteria and viruses, intestinal protozoa cause malabsorption primarily inhabit and damage the small intestine, but not typically the colon, a most nutrient absorption already occurred, main culprits are *Cryptosporidium parvum, Giardia lamblia, Entameba histolytica, Cystoisospora belli,* and *Cyclospora cayetanensis* and helminthes are mainly *Strongyloides stercoralis* and *Capillaria philippinensis* (Ramakrishna *et al,* 2006). Besides, Bourée and Bisaro (2007) in France reported that helminthic diseases, either cosmopolitan (*Ascaris, Enterobius*, and *Taenia*) or tropical (hookworms, *Strongyloides*, and *Schistosoma mansoni*), cause diarrhea with blood hyper-eosinophilia.

Moreover, Cleveland Clinic (2023) reported that some foods can upset the digestive system in lactose intolerant causing diarrhea as body struggles to digest lactose, the sugar in dairy, and some people have trouble digesting fructose, a sugar in honey and fruits that's added as a sweetener to some foods. Also, adiarrhea is due to body has trouble breaking down gluten, a protein in wheat.

Role of colon: Because the bulk of daily fluid absorption is carried out in the small intestine, any disease that significantly affects the small intestine (e.g., celiac disease, short bowel syndrome, enteric infections) can result in clinically significant diarrhea (Peery *et al,* 2024). But, fluid absorption in the colon can often compensate for moderate loss of the

small intestinal absorptive function (Spiller, 1994). Although the colon absorbs a much smaller volume of fluid than the small intestine, it is critical for generation of formed (dehydrated) feces (Naftalin, 1994). Consequently, any condition that alters colonic fluid transport or osmotic forces or exudation from a disrupted intestinal mucosa, or increases colonic motility tends to in abnormal watery stool and therefore diarrhea (Warren, 1983). The colonic microbes drive fluid absorption in the colon by fermenting dietary carbohydrates produce short-chain fatty acids (SCFAs) like the acetate, propionate, and butyrate (den Besten *et al*, 2013). Disruption of short-chain fatty acid production may therefore play a role in the antibiotic-associated diarrhea, and stabilization of colonic microbiome via administration of probiotics can reduce diarrhea associated with the used antibiotic (Biazzo and Deidda, 2022). Alterations to commensal bacteria in the colon after antibiotic administration allows opportunistic pathogens such as *C. difficile* to displace normal flora, and can result in the toxin-mediated inflammation, and diarrhea (Vincent and Manges, 2015).

The presence of excessive bile acids in colon as occurs in an ileal resection or disease (e.g., Crohn's disease) that activates colonic Cl^- secretion resulting in the bile-acid diarrhea (Bunnett, 2014). The bile acid-enriched state is thought to occur in a subset of patients with diarrhea-predominant irritable bowel syndrome, inducing fluid secretion and reducing transit time through the colon causing the incomplete fecal dehydration and diarrhea (Wong *et al*, 2012). Apart from the Crohn's disease, Cleveland Clinic (2023) added that ulcerative colitis and irritable bowel syndrome (IBS), which can cause diarrhea especially with stress and anxiety IBS with the worsen symptoms.

Again apart from bacteria, viruses and parasites cause children diarrhea, Hammer *et al.* (1989) in USA reported that diet-induced osmotic diarrhea is due to poorly absorbable aqueous solutes are ingested, their osmotic force quickly pulls water and, secondarily, ions into intestinal lumen developing osmotic diarrhea, such as lactulose, sorbitol (chew sugar-free gum), Mg^{2+} as antacids or bowel purgatives, or carbohydrate with gluten-sensitive enteropathy (celiac disease) or in pancreatic insufficiency, unabsorbed carbohydrates and lipids on the colon, are hydrolyzed by bacteria into short-chain organic acids, the qua nti ty of which may overwhelm colon's capacity for their absorption. Avitzur *et al.* (2024) in Canada reported that congenital diarrheas & enteropathies (CODE= nutrient elimination, nutrient supplementation, and generalized nutrient restriction) is a group of heterogenous, monogenic, and rare disorders in the neonatal period and infancy presented with chronic mild/severe diarrhea and are occasionally associated with the extra-intestinal manifestations. Mayo-Clinic (2025) reported that antibiotic-associated diarrhea about 1/5 people is passing loose, watery stools 3 or more times a day after taking antibiotics to treat bacterial infections. Mild cases tend to begin shortly after taking antibiotics and usually ends after a few days on antibiotics or shortly post treatment. The diarrhea that doesn't end on its own or is more serious usually requires stopping the antibiotic, and shift to different antibiotic. Moreover, the antibiotic-associated diarrhea occurs commonly with many antibiotics prescribed for children, include amoxicillin, amoxicillin with clavulanic acid, cephalosporins, and/or clindamycin (Turck *et al*, 2003). The direct toxic effects of antibiotics on the intestines include altered digestive function secondary to reduce concentrations of gut bacteria or overgrowth of pathogenic microorganisms causing the diarrhea (Kuehn *et al*, 2015). Tanir Basaranoğlu *et al.* (2023) in Turkey reported that the potential duration of antibiotics' gastrointestinal effects in a pediatric outpatient population, which might avoid from prescribing antibiotics in unnecessary clinical states, especially in children Electrolyte transport-related (secretory) a diarrhea occurs as a result of alterations in ion trans-port mechanisms in the epithelial cells, with clinical types

of diarrheal diseases: 1- Enterotoxigenic bacteria, although rarely encountered in resource-rich nations caused by the *V. cholerae* that cholera toxin causes massive fluid secretion of Cl^- and water, and also other bacterial enterotoxins produced by *Clostridium perfringens* and *C. difficile*, and heat-stable enterotoxin of *Escherichia coli* (Baron, 1996). 2- Enterotoxigenic viruses enterotoxins, also can cause secretory diarrhea, a nonstructural glycoprotein (NSP4) causes Ca^{2+}-dependent trans-epithelial Cl^- secretion from the crypt cells as in viral hemorrhagic Ebola (Melnik *et al,* 2022).

Other noninfectious secretory diarrheas are caused by gastrointestinal peptides; such as the vaso-active intestinal peptide, and gastrin as in hypokalemia and hypochloremia (Kanik *et al,* 2014).

Congenital defects or congenital chloride diarrhea as mutations in the SLC26A3 gene cause a severe disease called congenital chloride diarrhea (Kumar *et al,* 2025). The changes in gastro-intestinal motility can significantly influence fluid absorption, particularly in the colon cause imbalances in the composition and function of these intestinal microbes associated with diseases ranging from localized gastroenterological disorders including constipation to psychoneurotic, respiratory, metabolic, hepatic, and cardiovascular illnesses (Lynchand and Pedersen, 2016).

Treatment: It includes oral rehydration solutions and several classes of drugs (table 1). Oral rehydration solution (ORS) is an orally ingested solution stimulates the intestineal Na^+ absorption by Na^+/glucose co-transporter1 ecadotril, an enkephalinase inhibitor, is used in Europe and South America as an antidiarrheal agent, with various efficacies, however not USA/FDA approved. It inhibits the breakdown of endogenous enkephalins that exert anti-secretory effects by activation the enkephalin-stimulated of the epithelial opioid receptors (Salazar-Lindo *et al,* 2000). A natural anti-secretory product, Crofelemer (كروفيليمير) a compound extracted from the stem bark latex of the Croton lechleri tree in the western Amazonian region of South America (Cottreau *et al,* 2012). Crofelemer acts (SGLT1 or SLC5A1) & Na^+ coupled amino acid transporters. The ORS was hypo-osmolar hyponatremia (245mOsm/L), with optimized glucose to Na^+ ratios to increase the water absorption. ORS is a highly effective treatment that depends on the fact that SGLT1 transport is preserved in electrolyte transportrelated (secretory) diarrheas such as those ca used by the bacterial enterotoxins (Hahn and Holzgreve, 2002). The beverages commercially marketed for hydration during the exercises as sports, which have the highest concentcentrations of glucose and higher osmolality that reduces the fluid absorption, which are less effective for oral rehydration (Buono *et al,* 2007). The alternative ORS solutions may include rice starch or amino acids have proved to be effective in maintaining the hydration during diarrhea (Binder *et al,* 2014). In addition, hypo-hydration may impair aerobic performance and deterriorate cognitive function during the exercise (Pérez-Castillo *et al,* 2023).

Anti-motility agents: Drugs inhibit intestinal motility extensively to treat diarrhea by increasing Na^+ and fluid absorption due to slow intestinal transit (Singh *et al,* 2013). Diphenoxylate and Atropine, a combined medication for treating diarrhea is USA/FDA approved therapeutic option for the healthcare professionals. But, its action, adverse all care team members with vital insights necessary to optimize patient care in the gastrointestinal conditions (Jain and Wylie, 2024).

Anti-secretory agents: Inhibiting intestinal fluid secretion, another mechanism to reduce diarrhea, is bismuth subsalicylate with an antidiarrheal efficacy, but now rarely used. Racby inhibiting Cl^- channels in apical membrane and clinical improved chronic diarrhea in HIV patients (Macarthur *et al,* 2013). Drugs directly targeting ion channels, such as the absorbable inhibitors of the chloride channel CFTR (BPO-27), are still under clinical development (Thiagarajah *et al,* 2015).

Treatment for the childhood diarrhea caused by parasites, such as giardiasis and amebi-

asis, typically involves anti-parasitic medications like metronidazole, tinidazole, or nitazoxanide, depending on the specific parasite.

Good guidelines on the clinical management of diarrhea among the world's most vulnerable children therefore remain critical. There are two simple and effective treatments for the clinical management of acute diarrhea: 1- use of low concentration oral rehydration salts (ORS), & 2-routine use of zinc supplementation, at a dosage of 20milligrams per day for children older than six months or 10-mg per day in those younger than six months, for 1014 days (WHO, 2004)

WHO (2005) for physicians and other senior nurses to treated diarrhea recommended: 1- Give vitamin A to all children > 6 months of age every 6 months (100 000 IU for 6–12 months and 200 000 IU for ≥12 months) up to 5 years of age, 2- Treat dehydration with ORS solution (or an intravenous electrolyte solution in cases of severe dehydration), 3- With increased fluids and continued feeding, all children with diarrhea should be given zinc supplementation at 20mg for 10-14 days; infants < 6 months should receive 10 mg. Use antibiotics only when appropriate (i.e. bloody diarrhea), and abstain from administering anti-diarrheal drugs, 4- Ciprofloxacin is the most appropriate drug for treatment of bloody diarrhoea, rather than nalidixic acid, which leads to rapid development of resistance must be used at an oral dose of 15 mg/kg twice daily for 3 days, 5- Advise mothers to increase fluids and continue feeding during future episodes, 6- Give multivitamins and micronutrients daily for 2 weeks to all children with persistent diarrhea (folate 50 µg, zinc 10 mg, vitamin A 400 µg, iron 10 mg, copper 1 mg, magnesium 80 mg), 7- Give lactose-free (or low-lactose) diet to children > 6 months with persistent diarrhea and who are unable to breastfeed, 8-Assess every child with persistent diarrhea for non-intestinal infections (pneumonia, sepsis, urinary tract infection, oral thrush, otitis media), and treat appropriately, and 9- Test children of unknown HIV status, who are living in areas of where HIV prevalence is 1% or more and who present to a health facility.

For prevention WHO (2024b) gave key measures to prevent diarrhea include: 1-Access to safe drinking-water, 2- Use of improved sanitation water, 3- Good hand washing with soap, 4- Exclusive breastfeeding for the first six months of life, 5- Good personal and food hygiene health education about how infections spread, and 6- Rotavirus vaccination.

Conclusion

Clinically, diarrhea is defined as the passage of three or more loose or liquid stools/day, or more frequent passage than is normal for a person. Normal movement of fluid between intestinal lumen and blood is driven by active transport of ions (mainly Na^+, Cl^-, HCO_3^-, and K^+) and nutrients (mainly glucose). Fluid absorption is driven by the active transport of Na^+ across the epithelium with parallel Cl^- or HCO_3^- absorption. Fluid secretion is driven by transepithelial Cl^- secretion via basolateral and apical Cl^- channels and transporters.

Diarrhea occurs by excessive fluid maintained within the intestinal lumen due to either loss of the nutrient absorption or presence of non-absorbable solutes in the intestinal lumen, increased secretion or reduced absorption of electrolytes, event profile, and contraindications equips he-rapid intestinal transit, or combination of these factors. Diarrhea are categorized as diet-induced (osmotic), electrolyte transport-related (secretory), motility-related, or inflammation-related, but multiple mechanisms are involved.

Diet-induced (=osmotic) diarrhea can occur with loss of absorption of a normally absorbed dietary solute, such as lactose, or non-absorbable solute such as polyethylene glycol 3350, resulting in water retention within the intestinal lumen. Electrolyte transport-related (=secretory) diarrheas occur as a result of alterations in ion transport mechanisms in epithelial cells caused by an infectious agent (Cholera, Rotavirus, and some forms of *Escherichia coli*), gastrointestinal peptides secretion (vasoactive intestinal peptide & gastrin), or by the stimulatory effect of bile acids, and

laxatives.

Disorders associated with reduced intestinal motility cause diarrhea indirectly by intestinal stasis and bacterial overgrowth causing bile acid malabsorption, and increased intestinal motility causes diarrhea by reducing intestinal transit time and absorption. Some rare inherited disorders of intestinal transport, such as the congenital chloride diarrhea, also may cause children secretory diarrhea.

Inflammatory processes can destruct epithelial cells and/or loss or dysfunction of electrolyte transporters, leading to diarrhea by the osmotic and secretory mechanisms, as well as exudation of mucus, proteins, and blood into intestinal lumen. This is caused by infectious agent (as *Shigella* or *Salmonella*), inflammatory bowel disease, or by an immune-mediated process (as Celiac disease).

Many oral rehydration solutions and a variety of drugs or other interventions are available to treat diarrhea by altering the underlying pathophysiologic processes.

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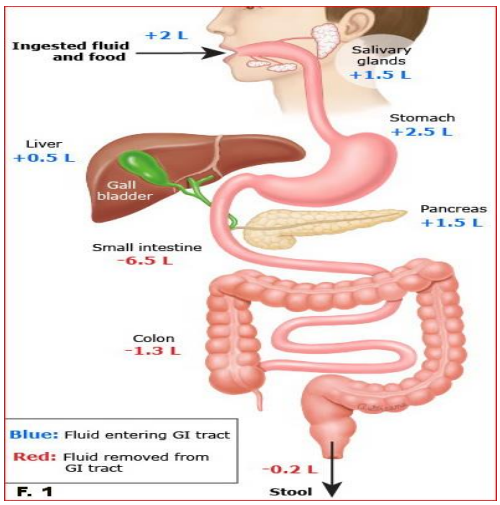
Explanation of figures

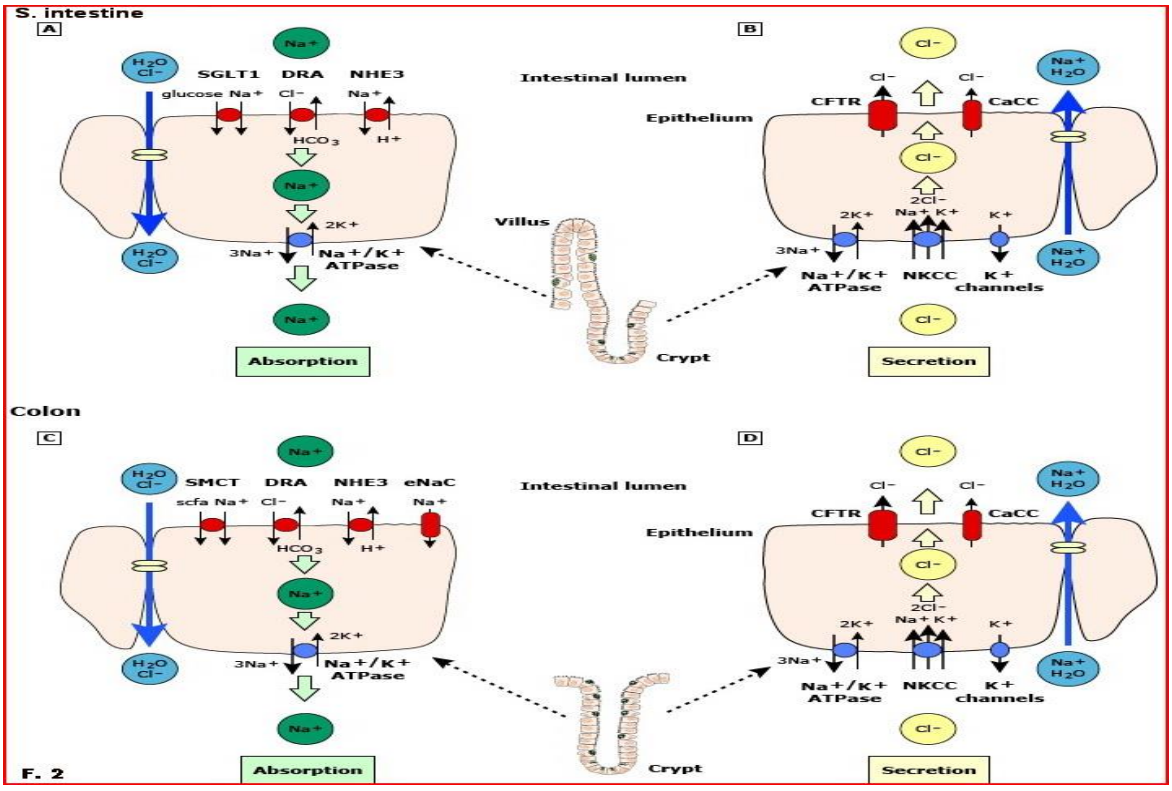
Fig. 1: Fluid movement in human gastrointestinal tract (After Thiagarajah and Verkman, 2012).

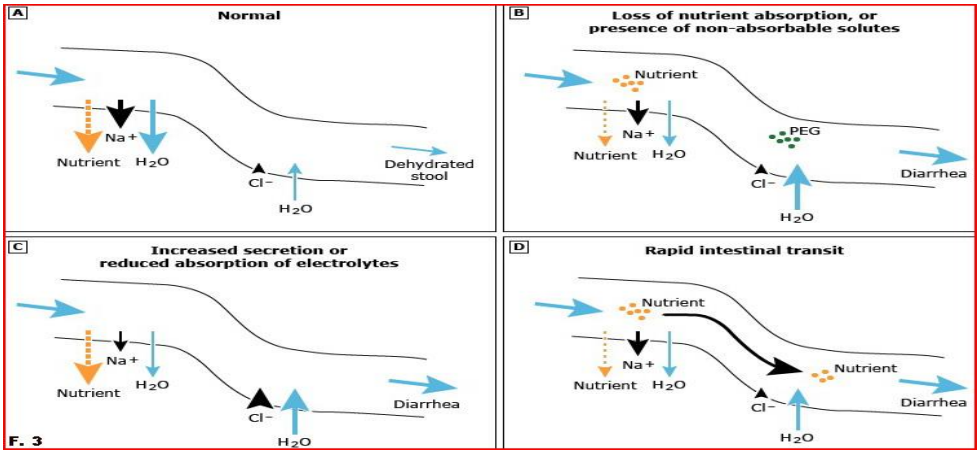
Fig. 2: Intestinal transport mechanisms: A: Fluid absorption in primarily villus epithelial cells showed active trans-epithelial transport of sodium via apical membrane transporters (sodium-glucose cotransporter, sodium-hydrogen exchanger, chloride/bicarbonate exchanger, and basolateral Na^+/K^+ ATPase with corresponding passive chloride and water flux. B: Fluid secretion in primarily crypt epithelial cells showed active transport of chloride from basolateral side via the sodium-chloride transporter (NKCC) and apical chloride channels (cystic fibrosis transmembrane regulator, calcium-activated chloride channels with corresponding passive sodium and water flux. C: Fluid absorption in both surface and crypt epithelial cells showed active trans-epithelial transport of sodium, via apical membrane transporters and channels (epithelial sodium channel, sodium-hydrogen exchanger, and sodium-driven short-chain fatty acid transporter. D: Fluid secretion in primarily crypt epithelial cells showed active transport of chloride from the basolateral side, via sodium-chloride transporter and apical chloride channels (cystic fibrosis transmembrane regulator, calcium-activated chloride channels) with corresponding passive sodium & water flux (After Thiagarajah and Verkman, 2012).

Fig. 3: Mechanisms causing diarrhea. A: Normal: During normal function, sodium and nutrient absorption drives fluid absorption, with a small basal amount of electrolyte-driven fluid secretion, allowing efficient reabsorption of fluid leading to minimal fluid loss via feces. B: Loss of nutrient absorption, or presence of non-absorbable solutes (osmotic) - Loss of nutrient absorption because of damage or loss of required transporter, or presence of polyethylene glycol prevents fluid absorption and promotes fluid secretion into intestinal lumen causing diarrhea. C: Increased secretion or reduced absorption of electrolytes (secretory) - Excessive anion-driven fluid secretion and reduced electrolyte-driven fluid absorption, as cholera, leads to accumulation of fluid in intestinal lumen and diarrhea. D: Rapid intestinal transit (motility-related) - Increased intestinal motility reduces time to absorb electrolytes and nutrients, leading to excessive unabsorbed substrates in intestine and reduced fluid absorption causing diarrhea

Fig. 4: Pathophysiology of abnormal electrolyte transport in bacterial and viral diarrheas (After Thiagarajah *et al*, 2015) A: Some bacteria secrete enterotoxins increase intracellular cyclic nucleotides, resulting in (Cl^-) secretion and inhibition of (NHE3) and (Na^+) absorption. Invasive bacteria cause a tissue inflammatory response involving recruitment of immune cells and release of cytokines, giving intracellular calcium ion (Ca^{2+}) signaling. B: Rotaviral protein NSP4 elevates cytoplasmic Ca^{2+} binds to integrin-alpha 1 & beta 2, galanin, and/or activating enteric nerves, and also inhibits NHE3 & SGLT1. *Escherichia coli*, CFTR: cystic fibrosis transmembrane conductance regulator; DRA: downregulated in adenoma Cl^-/HCO_3 exchanger (SLC26A3); NHE3: sodium-hydrogen exchanger 3; CaCC: calcium-activated chloride channel; ENaC: epithelial Na^+ channel; CT: cholera toxin; STa: heat-stable toxin; EC cells: enterochromaffin cells; cGMP: cyclic guanine monophosphate; cAMP: cyclic adenosine monophosphate; 5-HT: 5-hydroxytryptamine; VIP: vasoactive intestinal peptide; ENS: enteric nervous system; NKCC: $Na^+/K^+/Cl^-$ symporter; IL-6: interleukin-6; IL-8: interleukin-8; TNF: tumor necrosis factor; SGLT1: sodium/glucose co-transporter (SLC5A1); NSP4: nonstructural protein 4; Gal: galanin; GALR1: galanin receptor 1.







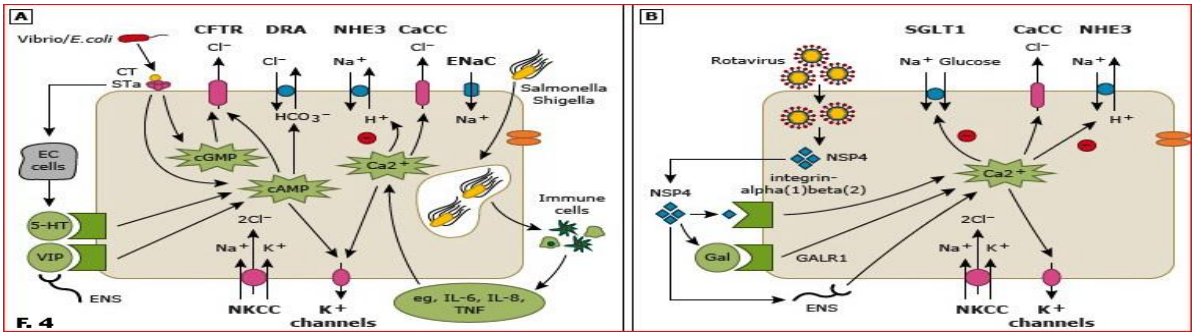


Table 1: Mechanism and uses of antidiarrheal therapies (adopted from Thiagarajah *et al*, 2015).

Therapy Adult dose,	Mechanism of action	Indications	Notes and adverse effects
Alosetron (Lotronex) Adults: 1 to 2mg daily, in divided doses, oral	5-hydroxytryptamine$_3$ receptor antagonist; anti-motility, & anti-isecretory.	Refractory diarrhea-predominant irritable bowel syndrome in women.	Not with constipated patients; intestinal ileus, obstruction, perforation, impaction, toxic mega-colon, or ischemic colitis.
Cholestyramine resin (Questran) 4 to 24g daily, in 2 doses, oral Colesevelam (Welchol; Lodalis) 3.75g daily, oral	Binds with bile acids in intestine to form an insoluble complex that is fecal excreted; antisecretory, promotes absorption.	Bile acid malabsorption diarrhea; ileal resection	Unlabeled indication. Side-effects: impaired absorption of other drugs; malabsorption of fat-soluble vitamins; nausea, bloating, cramping, constipation, impaction, & elevated aminotransferases.
Crofelemer (Fulyzaq) 250mg daily, in divided doses, oral	Blocks chloride secretion & water loss in diarrhea; CFTR & CaCC channel inhibitor; anti-secretory.	For diarrhea with antiretroviral for HIV/AIDS.	Not approved for infectious or other diarrheas, with limited practice.
Diphenoxylate and atropine (Lomotil) Adults: 5 to 20mg daily, in divided doses, oral	Synthetic muopioid receptor agonist within intestinal wall, antimotility. Atropine ingredient at subtherapeutic doses, & intended to discourage abuse.	Acute nonspecific diarrhea, chronic diarrhea, reduce stool fluidity & volume in patients with colostomies or ileostomies.	Not for diarrhea associated with enterotoxigenic bacteria, pseudomembranous colitis, & ulcerative colitis. Side-effects: CNS depression, dizziness, paralytic ileus, anorexia, nausea, vomiting, & discomfort.
Loperamide (Imodium; Diamode) 4 to 16mg daily, in divided doses, oral	Synthetic mu-opioid receptor agonist in intestinal wall, with minimal systemic exposure when given at recommended doses; anti-motility.	Acute nonspecific or chronic diarrhea; chemotherapy-with diarrhea; reduce stool fluidity & patients with colostomies or ileostomies.	Contraindicated in bacterial enterocolitis, pseudomembranous colitis, and ulcerative colitis. Side-effects: constipation, nausea, urinary retention, & paralytic ileus. Overdose may cause CNS depression & QT prolongation.
Racecadotril (Tiorfan)100 to 300mg daily, 2/3doses, oral	Enkephalinase inhibits ndogenous opioids breakdown, antisecretory.	Acute nonspecific diarrhea.	Not approved in USA. Side-effects: headache
Bismuth subsalicylate (Bismatrol & many others) Adults: about 0.5 to 4 g daily, oral	Anti-secretory & anti-microbial can provide some anti-inflammatory action.	Acute mild nonspecific diarrhea.	Fecal & tongue discolored, tinnitus, CNS depression, dizziness, Reye syndrome in children (due salicylate). Toxic long use (bone/joint, encephalopathy).