STUDY OF PATHOGENESIS, DIAGNOSIS AND VARIOUS TREATMENT APPROACHES FOR DIARRHOEA IN INFANTS

Dr. Puneesh Agarwal
Assistant Professor Dept of Pediatrics, Prasad Institute of Medical Sciences, Sarai Shahzadi, Bhanthara, Kanpur Road, Lucknow (U.P)

Article Info: Received 02 December 2021; Accepted 05 January 2022
DOI: https://doi.org/10.32553/ijmbs.v6i1.2452
Corresponding author: Dr. Puneesh Agarwal
Conflict of interest: No conflict of interest.

Abstract
Diarrhea is common in infants (children less than 2 years of age), usually acute, and, if chronic, commonly caused by allergies and occasionally by infectious agents. Congenital diarrheas and enteropathies (CODEs) are rare causes of devastating chronic diarrhea in infants. Evaluation of CODEs is a lengthy process and infrequently leads to a clear diagnosis. However, genomic analyses and the development of model systems have increased our understanding of CODE pathogenesis. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition and the European Society of Paediatric Infectious Diseases guide to the use of probiotics for the management of acute gastroenteritis, particularly those with documented efficacy such as Lactobacillus rhamnosus GG, Lactobacillus reuteri, and Saccharomyces boulardii.

Studies of microbial pathogens and the toxins they produce are important for determining the mechanisms by which they cause disease and spread throughout a population. Some bacteria produce secretory enterotoxins (such as cholera toxin or the heat-labile or stable enterotoxins produced by Escherichia coli) that invade cells directly. Others invade cells or produce cytoxins (such as those produced by Shigella, enteroinvasive E. coli, or Clostridium difficile) that damage cells or trigger host responses that cause small or large bowel diseases (such as enteroinvasive or enteropathogenic E. coli or Salmonella). Viruses (such as noroviruses and rotaviruses) and protozoa (such as Cryptosporidium, Giardia, or Entamoeba histolytica) disrupt cell functions and cause short- or long-term disease.

KEYWORDS: Diagnosis & Treatment, Diarrhoea, Acute infective gastroenteritis, Oral rehydration solution, Vomiting

Introduction

A battle is ongoing between the host microbiome of normal flora and microbial invaders from the outside. When the invaders win, a range of problems can be created for the host. Symptomatic infections can alter the intestinal barrier and absorptive functions or lead to rapidly fatal dehydrating diarrhea, toxic megacolon, or shock. Asymptomatic infections can go unrecognized, but they have long-lasting consequences for children’s growth and development.[1,2] Therefore, proper diagnosis and treatment are of critical importance, not only for the individual, whose life and cognitive development are at risk, but also for the communities among whom uncontrolled pathogens can spread. Most are acquired through contaminated food or water; however, only small numbers of some pathogens (such as Shigella, Cryptosporidium, Giardia, rotaviruses, or noroviruses) can cause infection. New sensitive and specific diagnostic methods, such as direct polymerase chain reaction (PCR) analysis of fecal specimens, have been used to identify pathogens such as enteroinvasive Escherichia coli (EAEC) [3]; this technology is only used in research settings but might someday be used in diagnosis currently, careful collection of a patient’s history and simple tests, such as analysis of fecal leukocytes or inflammatory markers such as lactoferrin, neopterin, or calprotectin, are used in diagnosis and selection of therapy.

PATHOPHYSIOLOGY OF BACTERIAL DIARRHEA
The best diagnostics and therapeutics for diarrheal diseases have been developed based on an understanding of the basic pathophysiology of the pathogens involved. Upper small bowel infections are relatively noninvasive and noninflammatory, causing watery diarrhea. Typically described as secretory, this type of diarrhea results from increased chloride secretion, decreased sodium absorption, or increased mucosal permeability. Cholera, the prototype of secretory diarrhea, is caused by the enterotoxin of Vibrio cholerae (cholera toxin). Cholera toxin binds to the epithelial receptor GM1 to activate adenyl cyclase, which produces cyclic adenosine 3',5'-monophosphate (cAMP). Continuous cAMP production activates chloride channels, resulting in unabated water and electrolyte secretion that leads to voluminous watery diarrhea.[4] Similar to V. cholerae, enterotoxigenic E. coli (ETEC; the main cause of traveler’s diarrhea) produce enterotoxins that activate adenylate or guanylate, causing chloride secretion to the intestinal lumen. In addition, impaired sodium absorption
and intestinal permeability have been implicated in this process.\(^5,6\)

Other pathogens that cause secretory diarrhea have pathogenic mechanisms that include increased ion secretion, impaired absorption secondary to microvillus blunting, or disrupted intercellular junctions. Secretory diarrhea is also caused by bacterial pathogens such as EAEC or EPEC, which activate cell signaling pathways that contribute to bowel disease and symptoms. These microbes colonize the gastrointestinal (GI) tract and then trigger inflammatory or “attaching and effacing” responses in host cells. They also produce toxins that can disrupt intestinal absorptive function and cause diarrhea.\(^7,8\)

Viral and protozoan pathogens act through different mechanisms to induce secretory diarrhea. Rotaviruses, noroviruses, and protozoa such as Cryptosporidium primarily infect and damage the absorptive villus tips, leaving secretory crypts unbalanced, to cause net secretion and diarrhea. Rotaviruses cause winter- or dry-season diarrhea in young children worldwide, whereas noro viruses are the main causes of winter diarrhea in people of all ages in temperate regions as well as dry-season diarrhea in tropical areas. The protozoa Giardia intestinalis, Cryptosporidium parvum or hominis, and Strongyloides stercoralis (the predominant helminth that causes diarrhea in tropical areas) disrupt absorptive villus architecture by direct infection or by triggering host epithelial or inflammatory responses.\(^9,10\)

**Figure No. 1: Normal Physiology & Alteration by Pathogen & Their Toxins**

**DIAGNOSTIC METHODS**

For many years, enteric infections were diagnosed by analysis of bacterial cultures and microscopy to detect ova and parasites. Selective agars allow culture of specific Salmonella, Shigella, Vibrio, Yersinia, and Campylobacter species. Isolation of cultured organisms is still an invaluable tool for determining sensitivity to antimicrobial agents in clinical settings and for identifying specific strains, virulence factors, or toxins during investigations of outbreaks. Light microscopy to view ova and parasites had been the traditional technique used to diagnose intestinal parasitism. Although microscopy has the advantage of low cost, its sensitivity depends on the burden of infection, the freshness of the specimen, and the experience level of the microscopist.

Enteric viruses are difficult to grow in cell cultures, so when they were first discovered, in the 1970s, definitive diagnoses of infection could only be made based on electron microscopy results. However, the impracticality and inaccessibility of electron microscopes necessitated that rotavirus or norovirus infections be diagnosed on the basis of epidemiologic clues and the clinical presentation.
of the patients. Currently, sensitive ELISA and latex agglutination analyses can rapidly determine whether a patient is infected with rotavirus.\[11,12\] Although molecular diagnostics are still used primarily in research laboratories, they are highly sensitive and specific in detecting infections in small samples and can simultaneously identify multiple infections. Multiplex genetic assays are used to detect different toxins, pathogens, and species or genotypes of the same pathogen.\[13\]

Figure No. 2: Evaluation of Infant Diarrhoea\[14\]

TREATMENT
Rehydration therapy
Dehydration is probably the main complication of gastroenteritis in childhood. WHO classification of patients’ hydration status is based on the presence of symptoms and signs. The presence of one of these signs or symptoms immediately classifies the patient as a more severe case.\[15,16\] According to current WHO recommendations, oral rehydration therapy (ORT) is considered the treatment of choice to replace fluid and electrolyte losses caused by diarrhea in children with mild to moderate dehydration. Intravenous rehydration is the treatment of choice in cases of failure of ORT, and it has to be reserved for patients with severe dehydration or who eliminate more than 10–20 mL/kg/hour. In the 1960s, efforts by young scientists and researchers led to the development of ORT for the treatment of dehydration that often accompanies acute attacks of diarrhea.

Antisecretory drugs
Pediatric presentations of rcecadotril were first authorized in France in 1999, and today it is approved and widely used in seven European countries (France, Spain, Italy, Portugal, Greece, Bulgaria, and Romania) and outside Europe. This antisecretory drug is a peripherally acting enkephalinase
inhibitor that reduces intestinal water and electrolyte hyper-secretion acting on the enkephalins (neurotransmitters of the gastrointestinal tract) through the selective stimulation of delta receptors inhibit adenylate cyclase activity by reducing the intracellular concentration of cAMP, thus reducing the secretion of water and electrolyte in the intestinal lumen. The result is a reduction of water and electrolyte secretion without changes in intestinal motility.[17]

**Antiemetics**

Children presenting with AGE often have high levels of vomiting that can interfere with the oral rehydration process, which could limit the success of the oral therapy. Ondansetron is widely used in the pediatric emergency department for vomiting and AGE; it can help with the successful delivery of ORT, thereby reducing the need to treat with IVT. A recent study evaluated the spectrum of diagnoses for which ondansetron is used in the pediatric emergency room. Medical records of patients 3 months to 18 years of age given ondansetron for 2 years were retrospectively reviewed.[18]

**Zinc supplements**

Zinc is an important trace element, as over 300 enzymes require zinc for their activation and nearly 2000 transcription factors require zinc for gene expression. Zinc is essential for epithelial barrier integrity, tissue repair, cell-mediated immunity, and immune function. Zinc as an antioxidant and anti-inflammatory agent is effective in gastrointestinal structure and function. Diarrhea is associated with significant zinc loss, and the use of zinc supplements can reduce the duration and severity of diarrhea in children.[19]

**Probiotics**

The physiological composition of intestinal microflora is essential to maintain an appropriate balance of microbiota and the intestinal barrier. Probiotics, also defined as food supplements, improve the intestinal microbial balance of the host, have beneficial effects on health, prevent outbreaks of community-acquired diarrhea, reduce colonization of infants with pathogenic microorganisms, and reduce the duration and severity of diarrheal infections, balancing the intestinal ecosystem.[20]

**Antibiotics**

For *Campylobacter jejuni*, antibiotics are initiated in cases of febrile diarrhea, especially those believed to have moderate to severe disease. Considering the increased incidence of *C. jejuni* and the resistance of the great majority of isolated strains to quinolones, the administration of azithromycin empirically for acute diarrhea, when indicated, could be appropriate. Moreover, erythromycin treatment of acute *C. jejuni* diarrhea demonstrated antibacterial efficacy by reducing the mean number of days until first negative stool culture.[21]

**CONCLUSION**

AGE remains a major problem in children and still represents one of the leading causes of illness costs and of deaths, as an estimated 2.5 million gastroenteritis deaths occur each year in children less than 5 years of age throughout the world, especially in resource-constrained countries. In rich countries, transmission occurs much more frequently from contaminated food compared to direct person-to-person contact, except for enteric viruses, which can also be transmitted by aerosol formation after vomiting.

Patients with the common problem of infectious diarrhea require prompt rehydration; then clinical and epidemiologic assessments should be done. Gaining a better understanding of the pathophysiology of infectious diarrhea and the factors that promote the dissemination of infectious agents that cause it will lead to practical approaches for preventing and responding to outbreaks.

**REFERENCES**

1. Guerrant RL, Kosek M, Lima AA, Lorntz B, Guyatt HL. Updating the DALYs for diarrhoeal disease. Trends Parasitol 2002 May; 18:191–193.
2. Checkley W, Buckley G, Gilman RH, et al. Multi-country analysis of the effects of diarrhoea on childhood stunting. Int J Epidemiol 2008;37:816–830.
3. Nataro JP, Mai V, Johnson J, et al. Diarrheagenic *Escherichia coli* infection in Baltimore, Maryland, and New Haven, Connecticut. Clin Infect Dis 2006;43:402–407.
4. Brito GA, Alcantara C, Carneiro-Filho BA, Guerrant RL. Pathophysiology and impact of enteric bacterial and protozoal infections: new approaches to therapy. Chemotherapy 2005; 51(Suppl 1):23–35.
5. Lucas ML, Duncan NW, O’Reilly NF, Mcllvenny TJ, Nelson YB. Lack of evidence in vivo for a remote effect of *Escherichia coli* heat stable enterotoxin on jejunal fluid absorption. Neurogastroenterol Motil 2008;20:532–538.
6. Lucas ML. Enterocyte chloride and water secretion into the small intestine after enterotoxin challenge: unifying hypothesis or intellectual dead end? J Physiol Biochem 2008;64:69–88.
7. Jiang ZD, Okhuysen PC, Guo DC, et al. Genetic susceptibility to enterogaegregative *Escherichia coli* diarrhea: polymorphism in the interleukin-8 promotor region. J Infect Dis 2003;188(4): 506–511.
8. Steiner TS, Lima AA, Nataro JP, Guerrant RL. Enterohaegregative *Escherichia coli* produce intestinal inflammation and growth impairment and cause interleukin-8 release from intestinal epithelial cells. J Infect Dis 1998;177:88–96.
9. Dionisio D, Manneschi LI, di Lollo S, et al. *Strongyloides stercoralis*: ultrastructural study of newly hatched larvae within human duodenal mucosa. J Clin Pathol 2000;53:110–116.

10. Ruest N, Couture Y, Faubert GM, Girard C. Morphological changes in the jejunum of calves naturally infected with *Giardia* spp. and *Cryptosporidium* spp. Vet Parasitol 1997;69:177–186.

11. Iijima Y, Tanaka S, Miki K, Kanamori S, Toyokawa M, Asari S. Evaluation of colony-based examinations of diarrheagenic *Escherichia coli* in stool specimens: low probability of detection because of low concentrations, particularly during the early stage of gastroenteritis. Diagn Microbiol Infect Dis 2007;58:303–308.

12. Garcia LS, Shimizu RY. Evaluation of nine immunoassay kits (enzyme immunoassay and direct fluorescence) for detection of *Giardia lamblia* and *Cryptosporidium parvum* in human fecal specimens. J Clin Microbiol 1997;35:1526–1529.

13. Haque R, Roy S, Siddique A, et al. Multiplex real-time PCR assay for detection of *Entamoeba histolytica*, *Giardia intestinalis*, and *Cryptosporidium* spp. Am J Trop Med Hyg 2007;76:713–717.

14. Vogel GF, Janecke AR, Krainer IM, et al. Abnormal Rab11-Rab8-vesicles cluster in enterocytes of patients with microvillus inclusion disease. Traffic 2017;18:453–464.

15. Kligler B, Hanaway P, Cohrsen A. Probiotics in children. Pediatr Clin North Am. 2007;54:949–967.

16. Quigley MA, Kelly YJ, Sacker A. Breast-feeding and hospitalization for diarrhoeal and respiratory infection in the United Kingdom Millennium Cohort Study. *Pediatrics*. 2007;119:e837–e842.

17. Quigley MA, Cumberland P, Cowden JM, et al. How protective is breast-feeding against diarrheal disease in infants in 1990s England? A case-control study. *Arch Dis Child*. 2006;91:245–250.

18. Satyanarayana L, Kumar S. Water supplementation in exclusively breastfed infants during summer in the tropics. *Lancet*. 1991;337:929–933.

19. Williams HG. And not a drop to drink – why water is harmful for newborns. *Breastfeed Rev*. 2006;14:5–9.

20. Mansour AM, Abd Elkhalek R, et al. Burden of *Aeromonas hydrophila*-associated diarrhea among children younger than 2 years in rural Egyptian community. *J Infect Dev Ctries*. 2012;6:842–846.

21. Bhutta ZA. Acute gastroenteritis in children. In Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. *Nelson’s Textbook of Pediatrics*, 18th ed. Philadelphia: Saunders; 2007.