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Original Research Article

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

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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 guidelines make a stronger recommendation for 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 cytotoxins (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 enteroaggregative 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 longterm 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 enteroaggregative *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 cholera* (cholera toxin). Cholera toxin binds to the epithelial receptor GM1 to activate adenylyl 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]

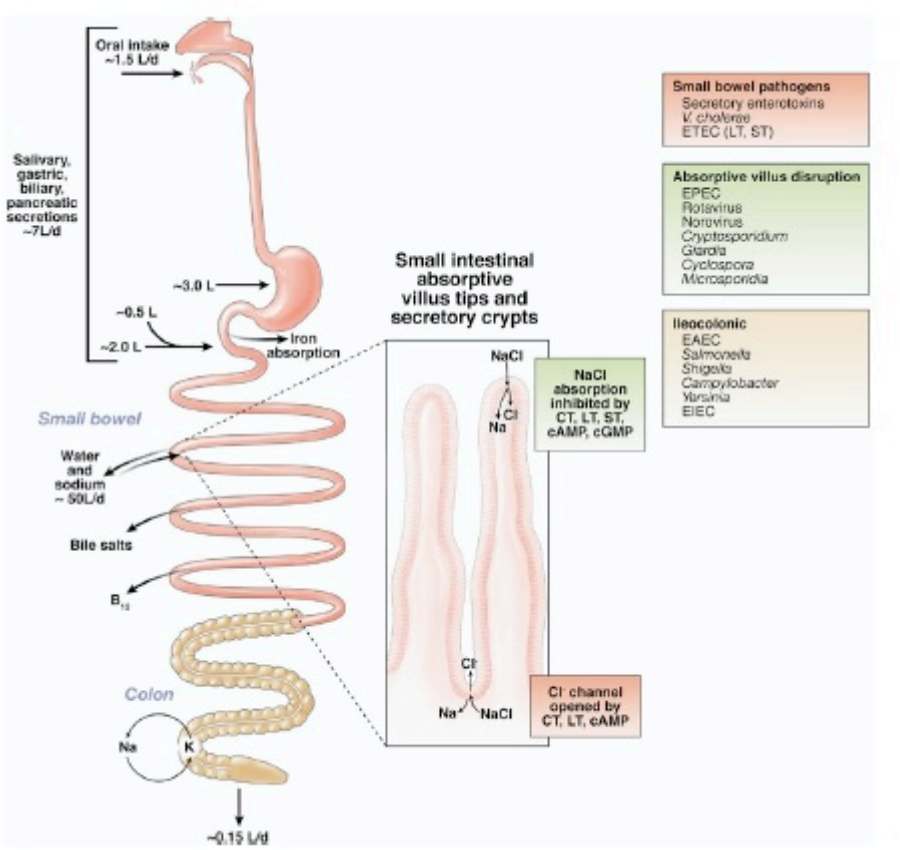

Figure No. 1: Normal Physiology & Alteration by Pathogen & Their Toxins

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]

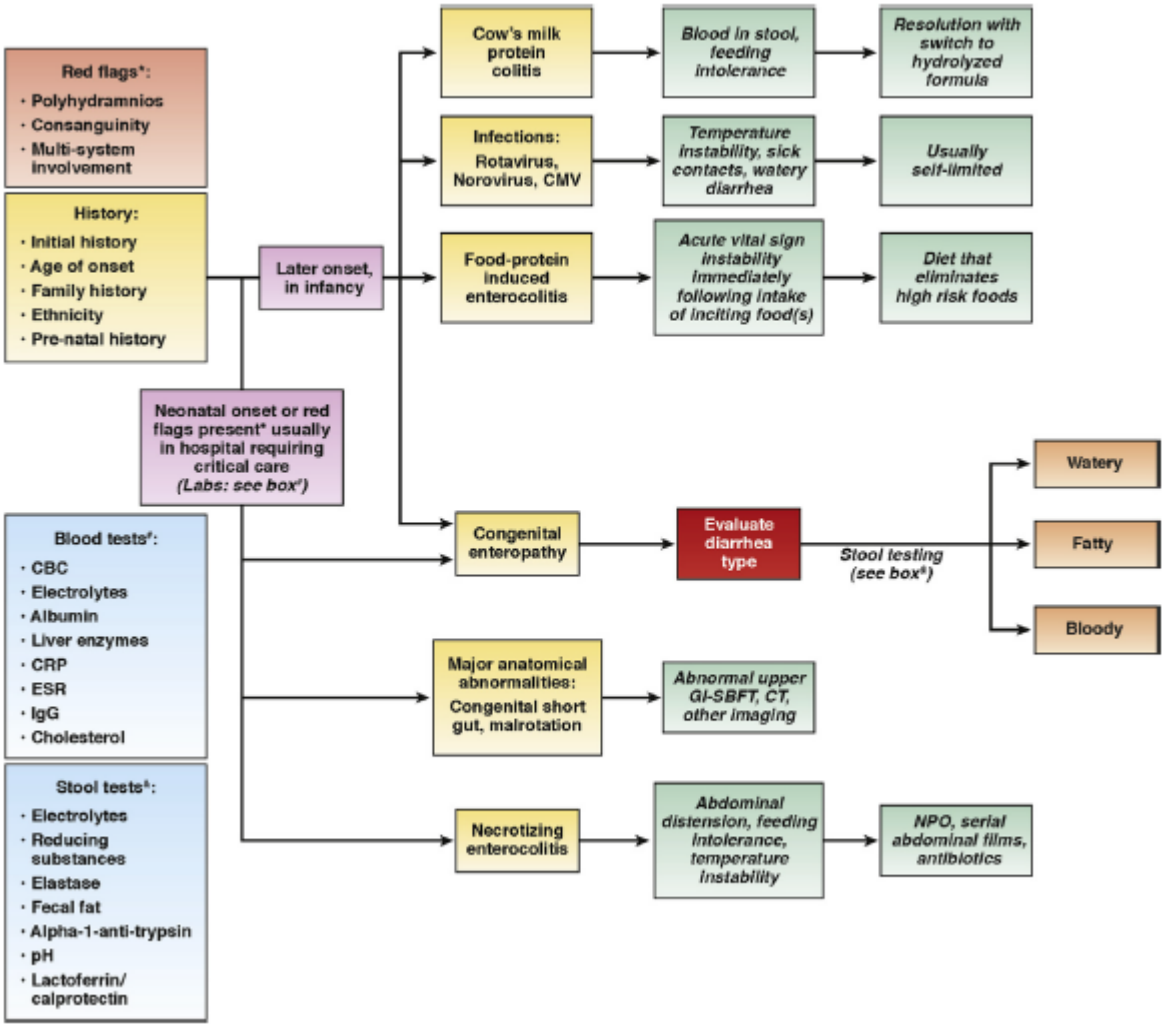

Figure No. 2: Evaluation of Infant Diarrhoea [14]

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 racecadotril 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 diarrheas, 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.

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