Infectious diarrhea, mechanisms of infections and clinical management: a review

Aseal Abdulhamid Kalantan¹*, Turki Nizar Abdulaziz Hammad¹, Abdulmajeed Adil Sagra³, Sari Abdulhamid Kalantan¹, Marwan Abdulmoomin Zakaria Sabbagh¹, Ahmed Talal Mohammed Barasayn¹

ABSTRACT

Infectious diarrhea (ID), caused by an infectious pathogen, is often accompanied by vomiting, nausea, and abdominal cramps. Diarrhea is associated with malnutrition, impaired cognitive, and physical development. There are several pathogens involved in ID, including Salmonella, Shigella, and Escherichia coli. The current study aimed to highlight the mechanism and management of ID. The articles involved in this review were obtained from scientific websites using several keywords. A total of 15 studies are included in the current review. The exact mechanism of ID varies based on causative agents; however, some pathogenic mechanisms are unknown. The management of ID includes replacing the loss of solution and electrolytes with rehydrating solutions and effective nutrients for the patient and the usage of antimicrobial agents against the pathogens.

Keywords: Infectious diarrhea, mechanism, management.

Introduction

Diarrhea, a term that refers to the alteration in the normal bowel movement, is characterized by an increase in the volume and content of water or frequency of stool excretion. The reduction of consistency means it tends to be soft or liquid, and the increase in the frequency of the bowel movement refers to three or more excretion of stool daily. When a diarrhea episode occurs for ≤14 days in duration, it is called acute diarrhea, whereas when it persists for more than 14 days, it is called persistent diarrhea, while chronic diarrhea lasts for more than 30 days. Infectious diarrhea (ID) is a type of diarrhea that is caused by an infectious agent and is often accompanied by vomiting, nausea, and abdominal cramps [1].

Diarrhea causes the mortality of more than 2 million individuals annually [2]. ID is the second most common cause of morbidity and mortality globally [3,4], and it is associated with impaired cognitive and physical development in developing countries [5]. Some serious long-term conditions result from ID, including malnutrition with or without diarrhea and hemolytic uremic syndrome with renal failure following enteraggregative Escherichia coli infections [1]. The Centers for Disease Control and Prevention [6] revealed that the most common pathogenic agents responsible for diarrhea were Salmonella, Campylobacter, Shigella, E. coli, and Cryptosporidium. Other enteropathogens for which diagnostic testing is available include Clostridium difficile, Giardia, Rotavirus, and Entamoeba histolytica. The infectious agents responsible for ID that have no routinely available tests include enteropathogenic, enterotoxigenic, enteroinvasive, and enteraggregative strains of E. coli, Staphylococcus aureus, Bacillus aureus, norovirus, and toxin-producing Clostridium perfringens [7]. Public health practitioners and clinical healthcare providers have overlapping interests in recognizing and managing ID [1]. The current review highlights the mechanism and treatment of ID.

Materials and Methods

Obtaining scientific articles to write the current review required an online search process to search for articles related to the current subject. Scientific websites, such as Pubmed and Google scholar, were used to obtain relevant studies. Several keywords were used to obtain all possible articles related to the current subject, such as “Infectious diarrhea, Management, Mechanism, Pathogenesis.” A

Correspondence to: Aseal Abdulhamid Kalantan
*Umm Al-Qura University, Makkah, Saudi Arabia.
Email: a9eelktn@gmail.com
Full list of author information is available at the end of this article.
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total of 15 articles were included to write the current review.

Discussion

Epidemiology and clinical syndromes of ID

Enteric infections that cause diarrhea are a major cause of morbidity in the world. ID contributes to malnutrition in developing countries, leading to high morbidity and mortality, especially in children. In developing countries, it was estimated that about 2-4 billion episodes of ID occur every year, with the highest rates occurring among children less than 5 years old [2].

Almost 30%-40% of acute episodes of diarrhea occur due to viral infections in the United States (US), with norovirus and rotavirus being the most common causing viruses for diarrhea [8]. In the US, rotavirus is responsible for 35% of hospitalized children cases and 10%-30% of community-based cases of diarrhea [2]. In contrast, norovirus can affect individuals of all ages and is responsible for 40% of non-bacterial outbreaks of diarrhea [9]. In developing countries, enteric bacterial pathogens, intestinal parasites, and protozoa are the major causes of ID [10]. Vibrio cholera (V. cholera) is one of the most common causative agents for diarrhea globally. Cholera-associated diarrhea is more common in the Indian subcontinent, Africa, South East Asia, and South America [11]. The pathogenic E. coli is another causative pathogen of diarrhea and is classified according to the pathogenic mechanisms. Enterotoxigenic E. coli (ETEC) is the most common cause of diarrhea among travelers and children in developing countries, such as Southeast Asia, Africa, Mexico, India, Central, and South America [12].

Shigella is an invasive pathogen accounting for 10%-20% of enteric infections throughout the globe [13]. Shigellosis is predominantly seen among children under 5 years old; however, adults of all ages are susceptible. Non-typhoidal salmonellosis is also common globally, and it is one of the most common causes of diarrhea and food poisoning [10]. Infection with C. difficile is also an important cause of diarrhea. The incidence of such infections is increasing dramatically, and it is recognized as the most common cause of nosocomial ID in developing countries [14,15].

Intestinal protozoa are important agents causing diarrhea in developing countries. Entamoeba histolytica is a significant cause of diarrhea and dysentery globally, with 34-50 million symptomatic infections occurring annually throughout the world [16]. Giardia lamblia is an intestinal parasite commonly found in children and the general population, causing diarrhea [17]. Among human immunodeficiency virus-infected individuals, Cryptosporidium infection can be observed; however, the infection can be self-limited in immunocompetent patients [18].

ID can be classified into non-inflammatory and inflammatory diarrhea according to the clinical presentation. Non-inflammatory ID shows negative fecal leukocytes, with large-volume watery non-bloody diarrhea. This class of diarrhea is caused by norovirus, Rotavirus, V. cholera, G. lamblia, ETEC, enterotoxin-producing bacteria, C. perfringens, S. aureus, and Cryptosporidium parvum. Inflammatory, ID shows positive fecal leukocytes, with bloody mucoid small volume diarrhea and abdominal cramps as clinical symptoms. Inflammatory, ID is caused by Shigella, Salmonella, C. difficile, and Amebic colitis [19].

Mechanisms of ID

Inflammatory diarrhea

The pathogenesis of diarrhea caused by invasive organisms involves ingestion followed by the colonization of the organisms. The intestinal colonization of the organisms can cause mucosal invasion. Traumatic multiplication leads to acute inflammation and diarrhea. In contrast, intestinal colonization leads to cytotoxin elaboration that directly causes acute inflammation and diarrhea, or by the action of arachidonic acid metabolites and cytokines leads directly to diarrhea [19].

Clostridium difficile: Clostridium difficile causes toxin-mediated inflammatory diarrhea. The genes encode two toxins (A & B), which contain two additional regulatory genes; tcdC and tcdD. The 2,3,7,8-Tetrachlorodibenzop-Dioxin (tsdD) gene upregulates toxin transcription, while tcdC encodes a toxin gene repressor [20]. Toxin A and B are attached to non-proteinaceous disaccharide galactose-beta1-4N-acetylgalcosamine residues on the colonic epithelial cells [21]. The toxins then enter the cell through receptor-mediated endocytosis and catalyze the transfer of a glucose residue from UDP-glucose to guanosine-triphosphate-binding rho proteins [22]. Glucosylation of rho proteins leads to the disruption of protein synthesis and cell death [20]. Activation of mean arterial pressure kinases and nuclear factor kappa-light-chain-enhancer of activated B cells occur, leading to the release of tumor necrosis factor, IL-8, and IL-1 beta, contributing to the inflammatory response of the intestine [19].

Salmonella spp: The ileum and, to a lesser extent, the colon is the target for Salmonella spp. [10]. The virulence factors of Salmonella are essential in the pathogenesis of Salmonella. The plasmid of Salmonella spp. contain genes that encode proteins vital for bacterial spread and invasion, survival within macrophages after phagocytosis, and transepithelial signaling to neutrophils, which together trigger cell destruction [23]. Also, enterotoxins and the outer membrane contribute to the pathogenesis of Salmonella. The inflammatory reaction and response to enterotoxins cause an increase in intestinal secretions [10,23].

Shigella spp: The death of intestinal epithelial cells can be caused by virulence factors of several Shigella spp.
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Shigella spp. contain a large plasmid that encodes the principal type III secretion system and other virulence factors that facilitate the invasion of the host. The contact with host intestinal cells leads to up-regulation of the plasmid copy number, which in turn leads to the alteration in the function of the actin filaments. The infection spreads through a cell-to-cell transfer of bacilli [13]. Infected enterocytes undergo apoptosis leading to the release of infective bacteria combined with inflammatory mediators such as IL-8, which cause cell destruction [24].

Entamoeba histolytica: The infection with E. histolytica is more common in developing countries than developed countries [10]. The inflammation caused by the infection with E. histolytica is related to the host’s response and the infectious agent’s virulence factors [10]. The trophozoite adheres to the colonic mucin and epithelial cells after penetrating the protective mucus barrier. After the attachment of the pathogen to the cell, amebophores, which are channel-forming peptides, are formed, causing cytolysis, resulting in swelling and lysis of the target cell, with no harm occurring to the parasite [25]. The trophozoite secretes cysteine proteinases that enhance the invasion of the tissue by burrowing through human matrix protein and colonic mucus [26]. The colonic epithelium is also disturbed by the host’s immune response to the pathogen in the form of immune-mediated tissue damage and recruitment of neutrophils [25].

Non-inflammatory diarrhea

The diarrhea-causing agents produce and secrete proteins called enterotoxin. The elaboration of such toxin or ingestion of toxin directly leads to the binding of the toxin to the receptors of the enterocytes. Then the concentration of intracellular mediators, including cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate, and Ca2+, increases, leading to activation of targets of intracellular mediators such as protein kinases. This, in turn, leads to alteration of the transporter proteins and ion channels, resulting in diarrhea [19].

Vibrio cholera: Vibrio cholerae produces cholera toxins leading to the disease; all the Vibrio strains produce the same enterotoxin [19]. The cholera toxin can affect the whole intestine; however, it becomes active in the proximal small intestine, which is typical of non-inflammatory diarrhea [27]. The bacterium adherence to the intestinal epithelium is essential for the survival of both invasive and enterotoxin-producing bacteria [10]. Cholera secretes the toxin after adherence [27]. The toxin of cholera includes two subunits; a single toxic active A (computed tomography angiography) and V subunit (computed tomography of the brain). The toxin enters the intestinal epithelial cell, after which the A subunits separate into two peptides A1 and A2 [19]. The A1 peptide has enzymatic adenosine diphosphate-riboseylating activity and stimulates the ribosylation of Gs, the stimulatory subunit of heterotrimeric G protein, leading to irreversible activation of adenylate cyclase [28]. As a result, the concentration of the intracytoplasmic cAMP increases, leading to alteration in electrolytes’ transportation by enterocytes in the form of elevation of the chloride secretion by crypt cells and reduction of the sodium and chloride ions absorption by villous cells resulting in diarrhea [28].

Giardia lamblia: Giardia lamblia adheres to the epithelium of the upper small intestine without invasion and damages the mucosal brush border [29]. The mechanism of diarrhea caused by G. lamblia is not clear [19].

Enterotoxigenic E. coli (ETEC): The infection with this organism causes non-inflammatory toxin-mediated diarrhea that is similar to cholera though somewhat less severe. ETEC adheres to the enterocytes surfaces of the small intestine via ligand-receptor interaction [30]. ETEC then colonizes and secretes two types of enterotoxin that cause diarrhea [19].

Rotavirus: Rotavirus causes diarrhea by producing enterotoxin and activating the enteric nervous system. It was hypothesized in studies that nonstructural glycoprotein 4 (NSP4), a non-structural protein, might be involved in the alteration of the function of the epithelial cells. NSP4 can increase chloride secretion through a calcium-dependent chloride secretory mechanism and activate the enteric nervous system leading to diarrhea [31]. Sodium-solute sympot activities in the gut can be impaired by NSP4, which contributes to diarrhea [22].

Norovirus: The exact mechanism of diarrhea caused by norovirus is not well known. The virus can cause malabsorption by damaging the small intestine. The malabsorption can be caused by blunting and broadening of villi and diminishing the activity of intestinal disaccharidases, similar to the mechanisms used by rotavirus to cause diarrhea [10].

Other enterotoxin-producing organisms: Organisms producing several endotoxins can cause poisoning of the food with no intestinal colonization, such as Bacillus cereus, S. aureus, and C. perfringens infections. The previous organisms cause diarrhea by changing the intestinal flux of water and salt in a similar method to enterotoxin-producing bacteria [10].

Management of ID

Rehydration and nutrition

The initial therapy is based on rehydration, regardless of the causative agent. Oral rehydration with a glucose-based electrolyte solution is preferred unless the patient is severely dehydrated or comatose [7]. The principle of the supplementation of a glucose-electrolyte solution is based on active carrier-mediated sodium-glucose transport [32]. The standard formulation recommended by the World Health Organization (WHO) or a newer reduced-osmolarity formula for children can be lifesaving in...
resource-poor regions and is valuable in the industrialized world for infants, the elderly, immunocompromised patients, and anyone with profuse watery diarrhea. Oral rehydration solution (ORS), containing 90 mmol/l of sodium, was recommended by the WHO. There was a concern regarding such concentration due to the significant risk of hypernatremia, so a lower sodium concentration of 50-60 mmol/l appeared to be as effective as the previous concentration [33]. Finally, in 2002, the WHO endorsed the use of low osmolality ORS with a sodium concentration of 75 mmol/l [32].

Adults with acute diarrhea should be encouraged to drink fluids and take soup with salt and salted crackers. The outcome can be improved in children by nutritional support with continuous feeding. The bananas, rice, applesauce, and toast (BRAT) diet, which includes a combination of bananas, rice, applesauce, and toast, should be used and is recommended with avoidance of the milk products, as transient lactase deficiency can occur [34]. The goal of using the BRAT diet is to replace glucose with glucose polymers, such as starches in rice and toast, to produce a low osmolality solution, with delivering an increased amount of substrate in the form of starch polymer, combined with some protein, which enhances the sodium absorption [32].

Antimicrobial therapy

The use of antibiotics for the patients who are improving and with mild symptoms isn’t necessary. The treatment is recommended for certain ID, including cholera, dysenteric shigellosis, and pseudomembranous enterocolitis caused by parasites. For some infections, the indications for antibiotics are not clear, but the treatment is recommended, such as the outbreaks of enteropathogenic E. coli and non-cholera vibrios. The patients should be managed if they are immunocompromised, have malignancy, abnormal cardiovascular system, hemolytic anemia, extremely old or young. Patients with prolonged symptoms or relapse are advised for the treatment [32].

Antibiotics can reduce the duration and severity of some intestinal infections, especially in patients with bacterial infections and infections that cause acute watery diarrhea. Some empirical and targeted antibiotics have been investigated for the treatment of ID. The efficacy of antibiotics varies from being definitely effective to possible and doubtfully effective. Antibiotic administration can be delayed after the symptom onset [32].

Non-specific symptomatic therapy

More than 400 products are sold over the counter for their traditional properties, but few of them have been demonstrated to be effective in trials [7]. Loperamide is an antimitoty agent for adults; it also has antisecretory properties and inhibits intestinal peristalsis. It does not penetrate the nervous system and has no substantial potential for addiction [35]. When Loperamide is used with antimicrobial agents for bacillary dysentery or traveler’s diarrhea, it may decrease the duration of diarrhea. Antimotility agents should be avoided in patients with suspected inflammatory diarrhea or bloody diarrhea [7].

Bismuth subsalicylate is not as effective as Loperamide, but it can relieve stool output in pediatrics and reduce diarrhea symptoms such as nausea and abdominal pain in traveler’s diarrhea. Bismuth subsalicylate can significantly reduce the median period of experimental norovirus illness from 27 to 20 hours [7].

Conclusion

ID is caused by several pathogens that vary across different regions. The mechanism of action includes the disturbance in the normal physiology of the intestine, including increased intestinal secretion of the electrolytes and fluid in the small intestine, and reduction in the absorption of the electrolytes and fluid, and in some cases, reduction in the absorbance of the nutrients. However, the exact mechanism of ID varies based on causative agents. Unfortunately, the pathogenic mechanisms of some agents are unknown. The management of ID is based on replacing the loss of solution and electrolytes with rehydrating the patient and using effective nutrients. The usage of antimicrobial agents against pathogens is recommended in certain cases.

List of Abbreviations

BRAT Bananas, rice, applesauce, and toast
Camp Cyclic AMP, or 3’,5’-cyclic adenosine monophosphate, or cyclic adenosine monophosphate
NSP4 Nonstructural glycoprotein 4
TCDD 2,3,7,8-Tetrachlorodibenzo-p-Dioxin

Conflict of interest

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Author details

Aseel Abdulhamid Kalantani1, Turki Nizar Abdulaziz Hammad1, Abdulmajeed Adil Sagri1, Sari Abdulhamid Kalantani1, Marwan Abdulmooin Zakaria Sabbagh1, Ahmed Talal Mohammed Barasayn1

1. Department of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia

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