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PATHOGENS DIARRHEA IN CHILDREN, RISKS AND TREATMENT

By
SHERIF AHMAD MEGAHED AHMAD[1] AND AYMAN TOSSON A. MORSY[2]
Department of Internal Medicine, Faculty of Medicine, Ain Shams University, Cairo 11566 (sherifmegahed@med.asu.ed.eg) and Consultant of Endemic Diseases, Misr University for Science and Technology[2], Egypt (ayman.morsy@must.edu.eg)

Abstract

Diarrhea is the condition of having at least three (or more than in normal individual), loose, liquid, or watery bowel movements each day, or for few days resulting in dehydration due to fluid loss. Signs of dehydration often begin with loss of the normal stretchiness of the skin and irritable behavior by decreased urination, loss of skin color, a fast heart rate, and a decrease in responsiveness as it becomes more severe. Loose but non-watery stools in babies who are exclusively breastfed, however, are normal. Frequent passing of formed stools is neither diarrhea, nor is the passing of loose, "pasty" stools by breastfed babies.

Diarrhea is usually a symptom of an infection in intestinal tract caused by many bacterial, viral and parasitic organisms. Infection is spread through contaminated food or water, or from person-to-person as a result of poor hygiene.

Keywords: Diarrhea, Children, Youth, Adults, Bacteria, Virus, Overview

Introduction

Diarrhea is defined as passage of three or more loose or liquid stools per day (or more frequent passage than is normal individual). Frequent passing of formed stools is not diarrhea, nor is the passing of loose, "pasty" stools by breastfed babies, defined as the passage of three or more loose or watery stools per day (WHO, 2017). Nevertheless, absolute limits of normalcy are difficult to define; any deviation from the child's usual pattern should arouse some concern (especially with ill appearance, passage of blood or mucus, or dehydration) regardless of the actual number of stools or their water content.

Diarrhea could be: 1- Acute diarrhea (including cholera), 2- Persistent diarrhea for 2 weeks or more, 3- Severe persistent diarrhea or persistent diarrhea with some or severe dehydration), and 4- Bloody diarrhea or dysentery blood in the stool (King *et al,* 2003).

Review and General Discussion

Acute infectious gastroenteritis by viruses totals for most bouts of diarrhea in resource-rich countries, resulted in more than 1.5 million outpatient visits and 200,000 hospitalized in the USA annually (Cohen, 1991)

Life-threatening conditions: Many disorders may cause life threatening diarrhea may be in children (Algorithm 1A), mainly urgent are intussusception, hemolytic uremic syndrome (HUS), pseudomembranous colitis, appendicitis, toxic megacolon, and in very young infants, congenital secretory diarrheas (Pereira and Hsu, 2016).

Intussusception: Intussusception refers to invagination (telescoping) of a part of the intestine into itself, with most common abdominal emergency in early childhood, particularly in children younger than two years of age (Lloyd and Kenny, 2004). Intussusception is most common from 6 to 12 months of age, and the vast majority of cases occur in the first two years of life. Most children with intussusception develop the sudden onset of intermittent, severe, cramp abdominal pain, accompanied by inconsolable crying and drawing up of legs toward the abdomen, but some present with bloody diarrhea. The episodes of pain usually occur at 15 to 20 minute intervals. They become more frequent and may be followed initially by emesis of gastric contents. Bilious emesis may develop as obstruction progresses. Between the painful episodes, the child may behave normally. As a result, initial symptoms can be confused with gastroenteritis. As symptoms progress, increasing lethargy develops that can be mistaken for meningitis (Fleisher, 2010).

Attacks also can be separated by periods of apathy followed by vomiting and the passage of currant jelly stool as a mixture of bl-

ood and mucus, and a sausage-shaped abdominal mass felt in right abdominal side (Yamamoto *et al,* 1997). Prevalence of blood in stool was up to 70%, if occult blood was included and increased with symptoms duration. But, classically described triad of pain, a palpable sausage-shaped abdominal mass, and currant-jelly stool is seen in <15% of patients at the presentation time. Up to 20% of young infants have no obvious pain. Patients don't pass blood or mucus or develop an abdominal mass in about 30% of cases. Some infants and many older children have pain without other signs or symptoms (Cera, 2008).

Intussusception is a common cause of bowel obstruction in young children with significant morbidity and mortality if not promptly treated (Ntoulia *et al,* 2016). Intussusception is unusual in adults, and the diagnosis is commonly overlooked. In the majority of adults, a pathologic cause was identified (Erkan *et al,* 2005). Intussusception was typically seen in 6 to 36 months of age, as the commonest cause of intestinal obstruction in this age group. About 60% of children with intussusception was < a year old, & 80 to 90% were < two years (Mandeville *et al,* 2012). Buettcher *et al.* (2007) in Switzerland on population-wide survey reported that yearly mean incidence of intussusception was 38, 31, & 26 cases/100,000 live births in first, second, and third year of life, respectively, but after the third year, rates dropped to < 0.5. Yap Shiyi and Ganapathy (2017) in Singapore reported that intussusception is usually diagnosed in younger population <1 year predominantly males. They found that older Asian children can also have intussusception. The classical triad was not a very sensitive diagnostic tool, but combination of abdominal pain, in drawing of legs, and vomiting may be a more common presenting triad in them. Park and Cho (2021) in South Korea concluded that clinical findings of ileocolic intussusception varied due to age and symptoms' duration. Younger children with paroxysmal pain, vomiting, bloody stool, poor oral intake, or lethargy must be suspected having intussusception, but older ones, non-specific abdominal pain without bloody stool was a symptom of intussusception, and contrast enema helped to diagnose intussusception in them without typical symptoms. Kaiser *et al.* (2007) reported that success of intussusception reduction was improved by air-contrasted techniques, not affected by previously failed attempts, and that delay diagnosis decreased radiologic reduction and increased risk of operative intervention of bowel resection. Zhang *et al.* (2015) found that intussusception was not usually immediately life-threatening. But, successful treated with barium, water-soluble, or an air-contrast enema, which confirmed diagnosis and successfully reduced it. Success rate was > 80%, but up to 10% may reoccur within a day.

Hemolytic uremic syndrome: Hemolytic uremic syndrome (HUS), although uncommon, merits consideration in any child with bloody diarrhea, particularly in the first five years of life, as a potential fatal illness (Gasser *et al*, 1955). It complicates 6 to 9% of entero-hemorrhagic *E. coli* O157:H7 strain infections and started 5 to 10 days after diarrhea onset, HUS with a sudden onset characterized by triad of: 1- Micro-angiopathic hemolytic anemia, 2- Thrombocytopenia, & 3- Acute renal failure (Noris and Remuzzi, 2005). The *E. coli* O157:H7 infectious dose for man was 10 to 100 organisms which was low compared to other enteric pathogenic ones (Lim *et al,* 2010): *Shigella:* 10 to 100, *Campylobacter jejuni:* $10^{(4)}$ to $10^{(6)}$, *Salmonella:* $10^{(5)}$ to $10^{(8)}$, enterotoxigenic *E. coli*: $10^{(8)}$, Vibrio cholera: $10^{(5)}$ to $10^{(8)}$, & *Yersinia enterocolitica*: $10^{(9)}$. Cattles are the *E. coli* O157:H7 natural reservoir, from 1% to 50% of healthy ones carry & shed *E. coli* in their feces at any time and contaminated ground beef is the commonest vehicle for *E. coli* O157:H7out-breaks (Dunn *et al,* 2004).

Children typically have a prodromal illness with abdominal pain, vomiting, and diarrhea that precedes the development of HUS by a few days, as a result of which a patient

may not have signs of hemolysis or renal failure when seen earlier stage. Diarrhea associated with gastrointestinal complaints may mimic those of ulcerative colitis, other enteric infections, and appendicitis. Clinical features after 3-8 days incubation, with first symptom was watery diarrhea, followed by bloody diarrhea and abdominal cramps, nausea and vomiting, but fever less commonly seen (Ahn *et al,* 2008). The most important factors associated with HUS evolution are the use of anti-motility agents, antibiotics, bloody diarrhea, leukocytosis, young age & females. Risk of developing HUS after bloody diarrhea due to *E. coli* in about 15%, but with spontaneous recovery, and 26% of the patients developed renal failure, with 3% - 5% of deaths (Verweyen *et al,* 2000).

Hematological and renal symptoms, including hemolytic anemia, low platelet counts, fragmentocytes, increased lactate dehydrogenase (LDH) and very low hemoglobin levels and various renal failure degrees may also be present. Other symptoms involved with other organs were brain, pancreas, myocardium, and malignant hypertension when associated with kidney failure and CNS involvement (Richardson *et al*, 1988). Salvadori and Bertoni (2013) in Italy highlighted the therapeutic aspects of HUS by the traditional therapy (including plasma therapy, kidney & kidney-liver transplantation) and new therapies (anti-Shiga-toxin antibodies & anti-C5 monoclonal antibody or Eculizumab®). They added that anti-C5 antibodies were more purified, less immunogenic, absorbed orally, and anti-C3 antibodies were more powerful, but less safe.

Pseudomembranous colitis: This rare, but serious disorder results from an overgrowth of toxin-producing clostridial organisms in the bowel. The typical presentation is acute watery diarrhea with lower abdominal pain, low-grade fever, and leukocytosis, starting during or shortly after antibiotic administration. The course can be fulminant, progressed from diarrhea to toxic megacolon and shock. Community-associated infection with a highly toxigenic strain of *Clostridium difficile* was reported in otherwise healthy children who had minimal or no exposure to antibiotics (Prince and Neu, 1979). *C. difficile* is an anaerobic, gram-positive, spore-forming, toxin-producing bacillus. In the environment, they survive in spores form, which are resistant to heat (even ordinary cooking heat), acid, antibiotics, and most antiseptics (Kim *et al,* 1981). Once the spores reach colon, they convert to the fully functional vegetative, toxin-producing form and become susceptible to killing by antimicrobial agents. Toxigenic strains were identified in healthy humans, food sources, farm animals, & pets, and hospital pet therapy dogs, and cultured from the environment in nursing homes, child care areas, and hospitals, particularly from the rooms of colonized or infected persons (Lefebvre and Weese, 2009). Many pediatric conditions have unique associations with *C. difficile* that may predispose to *C. difficile* infection, or exacerbated by *C. difficile* infection, or increase risk of severity or fatal *C. difficile* infection (AAP, 2009).

Conversely, however, as *C. difficile* colonIzation is common in children, the associations between fecal *C. difficile* toxin and intestinal symptoms may be completely incidental. Czepiel *et al.* (2019) found that the antibiotics of choice were vancomycin, fidaxomicin, and metronidazole, which was the least effective one. Mada and Alam (2022) updated the *C. difficile* infection management included a multi-step approach of discontinuing usage of inciting antibiotics, isolating the patient, and administering antibiotic based on infection severity. They added that antibiotics usually used were vancomycin or fidaxomicin. Asymptomatic patients with a positive stool toxin test didn't require treatment. Metronidazole IV can be used for a patient suffered from ileus where orally administration of antibiotics was delayed

Appendicitis: Appendicitis typically begins with diffuse abdominal pain followed by vomiting, always associated with constipation. Three most predictive clinical features are:

1- Pain in the right lower quadrant, 2- Abdominal wall rigidity, & 3- Periumbilical pain migration to right lower quadrant (Humes, 2006). Appendicitis was very common between ages of 10 & 20 years, but without age exempt. A male preponderance exists, with a male to female ratio of 1.4:1; overall lifetime risk was 8.6% for males and 6.7% for females in the USA (Addiss *et al,* 1990). Its' diagnosis was missed in 3.8% to 15.0% of children and in 5.9% to 23.5% of adults during emergency department visits (Galai *et al,* 2017). Appendicitis is the second common disease condition among pediatric patients & the third common one in adult malpractice insurance claims (Brown *et al,* 2010). Mahajan *et al.* (2020) in USA found that factors associated with potentially missed appendicitis included female sex, the coexistence of abdominal pain and constipation, and presence of comorbidities. Becker et *al.* (2007) in USA reported that appendicitis in pediatric patients was difficult to diagnose as children presented with many different atypical clinical features, bowel problems, as bowel movement relieve discomfort. Appendicitis diagnosis as diarrheal cause may be delayed because the classic constellation of findings was absent, which was particularly true in young children or among any aged patients with a perforated appendix with long duration illness. Most people with appendicitis need the appendectomy. If appendix didn't yet rupture, surgery would prevent its rupture and keep infection from spreading. Before surgery, the patient must receive IV antibiotics to treat infection (AAFP, 2020).

Toxic megacolon: A complication of *Shigella*, pseudomembranous colitis, Hirschsprung disease, or inflammatory bowel disease (Jalan *et al,* 1969). Tsai *et al.* (2000) in Taiwan reported that toxic megacolon in infective colitis is a fulminating illness that has a high mortality rate, and can be divided into: acute toxic stage, gut failure stage, and convalescence or deterioration stage. Autenrieth and Baumgart (2012) in Germany found that the commonest causes included: a- Inflammatory (Ulcerative colitis, & Crohn's disease), b- Infectious (*Clostridium difficile, Salmonella, Shigella, Campylobacter* colitis, Enterohemorrhagic or enteroaggregative *Escherichia coli* O157 that lead to hemolytic-uremic syndrome, *Cytomegalovirus,* & *Entamoeba).* Leifeld and Kruis (2012) in Germany reported that diagnosis easily done clinically, routine laboratory parameters and abdomen plain X-ray. They added that much difficulty was to decide between non-surgical treatment including intensive care treatment or surgery (mostly subtotal colectomy with terminal ileostomy). The non-surgical one included balancing of electrolytes and fluid volumes, broad-spectrum antibiotic as metronidazole®, positioning of patients and probably careful intermittent decompression.

Congenital secretory diarrheas: Congenital diarrheal disorders (CDDs) are group of inherited enteropathies characterized by profuse watery diarrhea began at or shortly after birth (Guarino *et al,* 1995), caused by a variety of inherited disorders that disrupt nutrient digestion, absorption, or transport, enterocyte development and function, or enteroendocrine function (Tab. 2). With the increasing use of whole-exome sequencing techniques, many more rare forms of congenital diarrhea are expected to be linked to genes contributing to appropriate intestinal fluid and electrolyte balance. An example for such discoveries was a mutation in diacylglycerol acyltransferase 1 (DGAT1), which catalyzes the final step in triglyceride synthesis; the mutation was detected associated with a familial form of congenital diarrhea in an Ashkenazi Jewish descent family (Haas *et al,* 2012). Mucosal biopsies must be done in patients with congenital diarrhea, which are a group of inherited enteropathies with a typical onset in early life, and such infants have frequently chronic diarrhea of sufficient severity for parenteral nutrition (Terrin *et al,* 2012). Undoubtedly, the results vary with etiology: 1- In the congenital chloride diarrhea (CCD) and congenital sodium diarrhea (CSD), with normal histology. Treatment was a high chl-

oride intake to prevent volume depletion. Determining optimal replacement dose was challenging because inadequate salt substitution paradoxically decreased diarrhea volume and excessive salt also increased diarrhea volume by osmotic mechanisms (Wedenoja *et al,* 2010). 2- In enteric endocrinosis, mucosal architecture was normal, but special stains demonstrate absence of enteroendocrine cells. 3- In tufting enteropathy, histopathology was characterized by villous atrophy, with disorganization of surface enterocytes and focal crowding; resembling tufts (Goulet *et al,* 2007). 4- In microvillus inclusion disease, light microscopy showed a variable degree of hypoplastic villus atrophy without crypt hyperplasia, & PAS-positive granules at the apical pole of enterocytes. Electron microscopy showed characteristic microvillus inclusions and partial to total atrophy of microvilli on mature enterocytes (Pecache *et al,* 2004), but in chylomicron retention disease, light microscopy may show lipid droplets in duodenal enterocytes. Whole-exome sequencing may be in select familial cases in which clinical, laboratory, and histologic examinations are non-revealing.

Osmotic diarrheas: They cease during fasting or upon exclusion of certain dietary components mal-digested by patient. 1- Glucose-galactose malabsorption presented by severe life-threatening diarrhea and dehydration during neonatal period, caused by deficiency in intestinal sodium/glucose transporter (Martin and Wright, 2004). Patients are symptomatic as long as the diet includes lactose or its hydrolysis products, glucose, and galactose. Diagnosis is suspected if diarrhea resolves promptly when these sugars are eliminated, confirmed by a positive glucose breath hydrogen test and normal intestinal biopsy. Treatment is with a fructose-based formula, and lifelong dietary restriction of causative sugars. 2- Congenital sucrase-isomaltase deficiency was rare in most populations, except in those of Eskimo or Canadian Native descent (Treem, 1995). Infants are asymptomatic if their diet contained only lactose (e.g., exclusively breastfed infants), but typically develop chronic diarrhea after sucrose-containing formulas or foods are introduced. Many mutations in gene encoding sucrase-isomaltase were described in affected patients, and well treated with sacrosidase (Lücke *et al,* 2009).

Evaluation: If a congenital diarrhea is suspected, stool electrolytes, pH, fat, & reducing substances must be measured, and a fasting trial must determine if it is secretory or osmotic. A marked decrease in stool output during fasting and high stool osmolarity suggested an osmotic diarrhea. In suspected cases of bile acid malabsorption, measurement of total and specific bile acids from stool or utilizing the gamma emitter selenium-75-homocholic acid taurine (SeHCAT) may be considered, although these tests are usually not available on a clinical basis. Steatorrhea may also have osmotic mechanisms, but it tends to be lower volume and has a greasy rather than watery quality

Conclusion

Two features of acute diarrheal illness, either alone or in combination, especially helpful in sorting via differential diagnosis are the fever and bloody or mucous diarrhea.

Patient with acute diarrhea who requires volume resuscitation must be quickly identified. Clinical evidence of dehydration such as decreased urine output, tachycardia, and dry mucus membranes are already apparent at a deficit of 5% of body weight. Useful predicting signs for a volume deficit of 5%, or more include delayed capillary refill time > two seconds, reduced skin turgor, and deep respirations with or without an increase in respiratory rate, particularly if a combination of such findings was present. Moreover, identifying volume depletion, a thorough examination must be performed because the systemic, non-enteric infections, particularly otitis media, may cause acute diarrhea. A palpable mass or peritonitis suggests appendicitis, intussusception or, less commonly, toxic megacolon. Generalized toxicity and/or shock can occur with the hemolytic uremic syndrome or with sepsis, such as from the *Salm-*

onella and/or staphylococcal toxic shock syndrome.

Ancillary studies in children with acute diarrhea are based upon a good history and physical examination, an initial evaluation of a chronic diarrhea child in emergency setting.

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Table 1: Etiology of diarrhea by patient's ages

manifestations	Infants and young children	Older children and adults
Gastrointestinal	Viruses, Bacteria & Parasites	
Non-gastrointestional or parenteral diarrhea	Otitis media, urinary tract infection & other systemic infection	Systemic infections
Dietary disturbances	Overfeeding, food allergy & starvation stools	Starvation stools
Anatomic abnormalities	Intussusception, Hirschsprung disease ±toxic megacolon, Partial bowel obstruction, Blind loop syndrome, Intestinal lymphangiectasis, Short gut syndrome	Appendicitis, Partial obstruction, Blind loop syndrome
Inflammatory bowel		Ulcerative colitis or Crohn's disease ± toxic megacolon
Malabsorption or increased secretion	Cystic fibrosis, Celiac disease, Disaccharidase deficiency & Acrodermatitis enteropathica	Celiac disease, Disaccharidase deficiency, Acrodermatitis enteropathica & Secretory neoplasms
Immunodeficiency	Severe combined immunodeficiencies and other genetic disorders (HIV)	Human immunodeficiency virus infection (HIV)
Endocrinopathy	Congenital adrenal hyperplasia	Hyperthyroidism, Hypoparathyroidism
Miscellaneous	Antibiotic-associated diarrhea, Pseudomembranous colitis, Toxins, Hemolytic uremic syndrome & Neonatal drug withdrawal	Antibiotic-associated diarrhea, Pseudomembranous colitis, Toxins, Irritable bowel syndrome & Psychogenic disturbance

Table 2: Molecular basis of the main forms of congenital diarrheal diseases*

Disease	Gene	Location	Function
Defects of digestion, absorption, and transport of nutrients and electrolytes			
Disaccharidase deficiency			
Congenital lactase	LCT	2q21	Lactase-phlorizin hydrolase activity
Sucrase-isomaltase	EC 3.2.1.48	3q25-q26	Isomaltase-sucrase
Maltase-glucoamylase	MGAM	7q34	Maltase-glucoamylase activity
Ion and nutrient transport defects			
Glucose-galactose malabsorption	SLC5A1 (SGLT1)	22q13.1	Na^+/glucose cotransporter
Fructose malabsorption	GLUT5	1p36	Fructose transporter
Fanconi-Bickel syndrome	GLUT2	3q26	Basolateral glucose transporter
Cystic fibrosis	CFTR	7q31.2	cAMP-dependent Cl^- channel
Acrodermatitis enteropathica	SLC39A4	8q24.3	Zn^{2+} transporter
Congenital chloride diarrhea	SLC26A3 (DRA)	7q22-q31.1	Cl^-/base exchanger
Congenital sodium diarrhea	SPINT2*	19q13.1	Serine-protease inhibitor
Familial diarrhea syndrome	GUCY2C	12p12.3	Intestinal guanylate cyclase C (ligand for bacterial heat-stable enterotoxins)
Lysinuric protein intolerance	SLC7A7	14q11	Hydrolyzes endo-/exopeptidases, amino acid basolateral transport
Congenital bile acid diarrhea	SLC10A2 (ABAT)	13q33	Ileal Na^+/bile salt transporter
Pancreatic insufficiency			
Enterokinase deficiency	PRSS7	21q21	Proenterokinase
Trypsinogen deficiency	PRSS1	7q35	Trypsinogen synthesis
Pancreatic lipase deficiency	PNLIP	10q26.1	Hydrolyzes triglycerides to fatty acids
Lipid trafficking			
Abetalipoproteinemia	MTP	4q22	Transfer lipids to apolipoprotein B
Hypobetalipoproteinemia	APOB	2p24	Apolipoprotein that forms chylomicrons
Chylomicron retention disease	SAR1B	5q31.1	Intracellular chylomicron trafficking
Defects of enterocyte differentiation and polarization			
Microvillous inclusion disease	MY05B	18q21	Intracellular protein trafficking
Congenital tufting enteropathy	EpCAM	2p21	Cell-cell interaction
Syndromic diarrhea	Unknown	Unknown	Unknown
Defects of enteroendocrine cell differentiation			
Enteric anendocrinosis	NEUROG3	10q21.3	Enteroendocrine cell fate determination
Enteric dysendocrinosis	Unknown	Unknown	Enteroendocrine cell function
Proprotein convertase	PCSK1	5q15-q21	Prohormone processing
Defects of modulation of intestinal immune response			
IPEX	FOXP3	Xp11.23-q13.3	Transcription factor
IPEX-like syndrome	Unknown	Unknown	Unknown
Immunodeficiency & autoimmune enteropathy	Unknown	Unknown	Unknown
APS-1	AIRE	21p22.3	Regulation gene transcription
Autoimmune enteropathy & colitis-GAGD	Unknown	Unknown	Unknown