Infections and Chronic Diarrhea in Children

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Diarrhea is classified, according to its onset and duration, into acute (<7 days), prolonged (7–14 days), persistent or chronic (14 days or more). Although frequently considered as synonymous, "persistent" emphasizes the presence after 2 weeks of an acute-onset diarrheal episode of presumed infectious etiology, whereas, "chronic" diarrhea usually reflects structural and/or inflammatory bowel disorders frequently lasting more than 4 weeks.

Chronic diarrhea etiology varies according to child's age, immune status, socioeconomic factors and clinical setting. Enteric infections are the most frequent cause of chronic diarrhea worldwide, and sequential infections with the same or different pathogens may be responsible for prolonged symptoms. Other etiologies of chronic diarrhea include nutrient malabsorption, inflammatory bowel diseases and functional intestinal disorders.

In the present review, we focus on chronic diarrhea of infectious origin, without any other subclassification.

EPIDEMIOLOGY

The prevalence of chronic infectious diarrhea (CID) in childhood is unknown and significantly varies according to the geographical and clinical setting. In low-income countries, 12–35% of children with acute diarrhea undergo a prolonged course, and 5–7% of cases last >14 days.[1,2] In the United States, 8% of children accessing ambulatory care for loose/watery stools fulfill the definition of CID, with an incidence of 1 of 5 children per year.[3] On the other hand, 1 of 10 children referring to pediatric gastroenterology center for chronic diarrhea in Europe, demonstrated an infectious origin, although routine microbiologic investigations may have lacked sensitivity to detect viral infections in this population.[4]

The etiologic spectrum, clinical features and complications of CID differ among otherwise healthy and immunocompromised children living in high- or low-income settings.

ETIOLOGY

High-income Settings

Although in developed countries CID runs a benign course, it represents a major cause of medical consultation, work-days loss, invasive procedures and hospitalization. Seasonality may affect the incidence rate, peaking in winter. Moreover, travelers from tropical areas may have CID or present diarrhea even 14 days after return.

The etiology of CID in high-income countries is relatively narrow with a primary role of viruses and bacteria, rather than parasites or fungi. A multicenter study in children living in the United States demonstrated that rotavirus, norovirus and sapovirus are significantly associated with CID.[3] *Clostridium difficile*, enteroaggregative and atypical *Escherichia coli* were isolated with similar frequency at baseline and in children with prolonged symptoms, suggesting a low correlation with the persistency of diarrhea.

More recent studies, with sensitive molecular tests, demonstrated that specific enteroaggregative *E. coli* (EAEC) strains expressing a combination of virulence genes involved in biofilm and mucus layer production (lack of *pic*, association of *pic* and *sat* and lack of *aggA* genes), are associated with CID in European children.[5] The pathogenicity of EAEC, still debated in otherwise healthy children or in acute gastroenteritis, is likely based on a mosaic genome that easily adapts virulence factors to the host and environment.

Salmonella, *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*, frequently acquired by contaminated foods, and *C. difficile* are common agents of CID in otherwise healthy children.

Cytomegalovirus (CMV) may cause severe colitis and protein-losing enteropathy particularly in younger infants, characterized by early-onset chronic diarrhea (often before 3 months of age), frequent rectal bleeding and

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possible complications (ie, perforation, strictures). Although most young infants result in IgG-positive, due to mothers' antibodies transfer, the diagnosis may be challenging and is based on a combination of serology (IgM positive < 50% cases), histopathology, immune-chemistry (60% cases), and CMV DNA on blood and tissue (positive < 50% cases). Immunocompetent infants showed a significant rate of spontaneous remission, the frequent need of nutritional support with no associated mortality. Ganciclovir may be considered in severe cases.

Children with underlying chronic conditions are at higher risk of CID, due to mucosal susceptibility, dietary habits and concomitant treatments. In inflammatory bowel diseases, intestinal pathogens may act as primary cause of CID or trigger a relapse of the underlying disease. Selected pathogens have been more frequently isolated in patients with inflammatory bowel diseases, including *C. difficile*, *Campylobacter*, *E. coli* O157:H7, *Aeromonas* or *Plesiomonas*, *Salmonella*, *Shigella*, *Yersinia*, adenovirus and CMV. Parasites (eg, *Giardia*) may affect about 20% of children with underlying chronic diseases or immunodeficiency.

In this setting, if thorough microbiology does not provide a diagnosis in few days, noninfectious etiologies need to be rapidly investigated in accordance with the child's age and clinical conditions (4). In neonates, with the exception of necrotizing enterocolitis which has close relationships with enteric agents, chronic diarrhea is rarely of infectious origin and may be predictive of congenital enterocyte disorders that need specialist management.

Low-income Settings

CID is a major cause of morbidity and mortality in unprivileged areas due to the high-risk of dehydration, weight loss and perpetuation of a vicious cycle with malnutrition. Children often develop stunting and malnutrition, triggering chronic diarrhea and vice versa.

In malnourished children, the findings of pathogens in stools need to be interpreted with caution, since their effective pathogenic role is under debate. *Giardia lamblia* and *Shigella* spp. were most likely to persist into the stools of undernourished children,[6] even after stabilization of the undernutrition status. This finding was associated with increased intestinal inflammation but not with changes in clinical outcome.

Irrespective of nutritional status, children with diarrheal episodes lasting more than 7 days (prolonged diarrhea) have a 6-fold increase of evolving into chronic diarrhea and 2-fold of developing further CID episodes in later childhood.[1]

Enteroadherent *E. coli*, *Giardia* and *Cryptosporidium parvum* have been historically implicated in severe chronic diarrhea in developing countries. However, the use of sensitive molecular techniques may provide new insight similarly to what happened in high-income settings.

The case-controlled Global Enteric Multicenter Study (GEMS), investigated the factors associated with the prolonged duration of diarrhea in children <5 years of age in sub-Saharan Africa and South Asia.[2] In the majority of enrolled children, multiple pathogens (up to 5) were isolated, and *Cryptosporidium* (23%), EAEC (19%), *Campylobacter jejuni* (16%), *Giardia* (16%) and rotavirus (11%) were the most commonly identified agents. Although other factors influenced the duration of diarrhea (ie, stunting and water source), *Cryptosporidium* spp and *C. jejuni* and less closely EAEC and heat-stable enterotoxin producing *E. coli*, were associated with an increased risk of chronic diarrhea.

Immunocompromised Children

Immunodeficient children are exposed to recurrent and chronic diarrhea, opportunistic infections, persistent intestinal damage, invasive infection and sepsis (due to intestinal translocation), with higher risk of surgical complications, prolonged hospitalization and fatality risk. On the other hand, CID is a hallmark of immunodeficiencies in childhood.

In a nationwide cohort of 246 children with primary immunodeficiency, 10% had severe and chronic diarrhea.[7] The clinical pattern of those children varies according to the type of immunodeficiency and the ongoing antimicrobial prophylaxis or therapy. Bacteria (ie, *Salmonella* spp, *Pseudomonas* and *E. coli*) are the main agents of CID in children with severe combined immunodeficiency, predominately antibody deficiencies or phagocyte defects. Parasites (ie, *G. lamblia* and *Cryptosporidium*) are more frequently isolated in X-linked agammaglobulinemia, common variable immunodeficiency and hyper-IgM syndrome.

In about 1 of 3 immunodeficient children, more than one parasite may be found, including *G. lamblia, Blastocystis hominis*, *Entamoeba hartmanni, Enterobius vermicularis* and *Dientamoeba fragilis*.

Viruses, including type A rotavirus, norovirus, CMV, coxsackievirus, may cause CID in children with severe-combined and common variable immunodeficiency or hyper-IgM syndrome.[8] Children receiving chemotherapy, solid organ or hematopoietic stem cell transplant, are exposed to high-risk of norovirus infection with diarrhea prolongation and severe complications including seizures (also afebrile), renal failure, pneumatosis intestinalis or intestinal perforation and need of nutritional support. In a cohort of 116 pediatric transplant recipients, norovirus was identified more frequently than any other pathogen (22% of cases) and was related to CID and hospital admission in more than half of cases and to intensive care unit admission in 27% of cases.[9]

The relationship between CID and HIV infection is well-known. However, chronic diarrhea may have multiple causes in this population, including HIV-induced enteropathy, small-intestinal bacterial overgrowth, malnutrition and antiretroviral treatment itself.

In the era of widespread antiretroviral therapy, the etiology and severity of CID significantly vary according to accessibility and adherence to treatment. *Cryptosporidium*, *Giardia*, *Mycobacterium avium*, CMV and enterotoxigenic *Escherichia coli* have recently been confirmed as the main agents of CID in treatment-naive children. In children under treatment, common pathogens, including viruses or other causes of chronic diarrhea should be investigated.

DIAGNOSTIC WORK-UP AND DIFFERENTIAL DIAGNOSIS

An infectious etiology should always be suspected in any child with chronic diarrhea, and the step-wise diagnostic approach always includes extensive microbiologic investigations.[4] Most children with CID present associated symptoms, including fever, vomiting, abdominal pain, fatigue and weight loss. The latter distinguishes between organic and functional disorders, such as postenteritis diarrhea.

History of recent travels and contact with a potential source of infection such as animals, untreated water and probably tainted food need to be investigated.

Monitoring the stool pattern may help in the diagnosis and drive empirical treatment. Secretory diarrhea with a high number and abundant watery stools are usually related to viral infections (ie, rotavirus, norovirus and astrovirus) or the action of toxins (ie, enterotoxigenic *E. coli* and *C. difficile*) in the ileal tract. On the other hand, a typical pattern of colitis, characterized by frequent evacuations of small amounts with mucus and/or blood and abdominal pain, suggests invasive bacterial infections, *C. difficile* or CMV colitis.

Analysis of stool electrolyte concentration and osmolarity may distinguish an osmotic (stool osmotic gap >100 mOsm) from secretory diarrhea (stool anion gap <50 mOsm). However, in some infections (ie, rotavirus) or when symptoms persist for a long time, a mixed and biphasic mechanism driven by inflammation is found.

Early identification of pathogens may improve a child's quality of life and accelerate

TABLE 1. Characteristics and Therapeutic Options for the Principal Enteric Pathogens Responsible of Chronic Diarrhea

Pathogens Responsible for CID	Characteristics of Diarrhea	Treatment Options	Comments
Virus			
Rotavirus	Watery	Supportive care	Typical in immunocompromised
		Human Ig through oral route	May cause extraintestinal symptoms (ie, seizures)
Norovirus	Watery	Supportive care	Typical in transplant recipients
		Human Ig through oral route	Severe complication (pneumatosis intestinalis and renal failure)
			Persistent vomiting also isolated
Adenovirus	Watery	Supportive care	Typical in immunocompromised
Astrovirus	Watery	Supportive care	Typical in immunocompromised
CMV	Colitis	Ganciclovir followed by valganciclovir in severe colitis, immunocompromised patients and complications (retinitis)	Complicated by protein-losing enteropathy, hypoalbuminemia and intestinal perforation
			Endoscopy typically showed crypt distortion, inflammatory infiltration and CMV inclusion bodies
Bacteria			
Salmonella spp.	Watery or Colits	Ceftriaxone or azithromycin or ciprofloxacin	May cause skin rash and possible invasive infections, abscesses and meningoencephalitis in immunocompromised or young infants
Shigella	Dysentery	Azithromycin or ceftriaxone or ciprofloxacin	–
Campylobacter	Watery or Colitis	Azithromycin	Most episodes are self-limiting
Clostridium difficile	Watery or Colitis	Metronidazole (intravenous or oral)	Complications: pseudomembranous colitis, intestinal perforation or toxic shock
		Vancomycin (oral)	Frequent recurrence: considered
			Fidaxomycin or fecal-microbiota transplantation for treatment
Yersinia	Colitis	TMP-SMX, ceftriaxone or ciprofloxacin	Right lower quadrant pain and clinical features of appendicitis.
			Granulomatous inflammation on biopsies
ETEC	Watery	Ceftriaxone, TMP-SMX, ciprofloxacin, azithromycin	Frequent in developing areas or travelers' diarrhea.
			Increasing resistance pattern
EAEC	Watery	Doubtful (single-case evaluation)	High antibiotic resistance
EPEC	Watery or Colitis	Ceftriaxone, TMP-SMX, ciprofloxacin	Typical of developing areas or travelers' diarrhea.
			Severe course in infants and immunocompromised.
			Increasing resistance pattern
Aeromonas species	Dysentery	Azithromycin or ceftriaxone or ciprofloxacin	Tropical and subtropical areas
Parasites			
Giardia	Initially watery	Metronidazole	May cause bloating, abdominal distention and weight loss
	Later greasy	Nitazoxanide	Typical of HIV-infected or immunocompromised patients and developing countries
Cryptosporidium spp	Watery	Nitazoxanide	Typical of HIV-infected or immunocompromised patients and developing countries
Entamoeba histolytica	Watery and colitis	Metronidazole, tinidazole, paromomycin	Typical of HIV-infected or immunocompromised patients and developing countries
			Responsible of liver abscess
Dientamoeba fragilis	Colitis	Paromomycin	Typical of HIV-infected or immunocompromised patients and developing countries
Cystoisospora belli	Watery	TMP-SMX	Typical of HIV-infected or immunocompromised patients and developing countries
Cyclospora Cayetanensis	Watery	TMP-SMX	Typical of HIV-infected or immunocompromised patients and developing countries
Schistosoma mansoni colitis	Colitis	Praziquantel	Typical of endemic areas of developing countries
Blastocystis hominis	Watery	Albendazole, metronidazole, tinidazole	Frequent in HIV-infected patients. Treatment adjusted to CID4+ level
		TMP-SMX	
Strongyloides	Watery or Colitis	Ivermectin	May cause skin rash.
			Frequent in endemic areas of developing countries
Microsporidium spp.	Watery	Albendazole	Typical in HIV-infected patients
Mycobacterium spp.	Colitis	Antitubercular treatment according to resistances	*M. avium* complex hallmark of HIV-infected and immunocompromised patients. *M. tuberculosis* may affect cecum and ileo-cecal valve. The presence of transversal ulcers to endoscopy and respiratory symptoms may help to differentiate with Crohn's disease.
Other causes of CID related to infectious diseases			
Short intestinal bacterial overgrowth (SIBO)	Watery	Antibiotic cycle based on metronidazole, rifaximin, ciprofloxacin, amoxicill-clavulanate, gentamycin	Responsible for metabolic acidosis in children with short bowel syndrome, motility disorders or postsurgery.
			Lactose free and low-carbohydrate diet suggested
Antibiotic-associated diarrhea (AAD)	Watery and Colitis in case *C. difficile*	Large spectrum antibiotic withdrawal or *C. difficile* treatment	
Postenteritis diarrhea	Watery	No specific treatment, lactose-free diet or probiotics	Follow-up needed to rule out postinfectious functional disorders, mainly demonstrated after *Salmonella* and norovirus infection

CID, chronic infectious diarrhea; CMV, cytomegalovirus; EAEC, enteroaggregative *E. coli*; EPEC, enteropathogenic *E. coli*; Ig, immunoglobulin; iv, intravenous; TMP-SMX, trimethoprim-sulfamethoxazole.

healthcare assistance. A wide microbiologic examination should be performed in any child with chronic diarrhea, including stool culture (enriched for *Yersinia, Aeromonas* and *Plesiomonas*), viral antigens, *C. difficile* toxins and parasites. Antigen detection for *Giardia* and *Cryptosporidium* is more sensitive and specific than routine microscopy.

Polymerase chain reaction assay provides rapid identification of pathogens, but to date has been seldom applied to CID. Paradoxically, those assays are usually not available in settings where infections represent the leading cause of chronic diarrhea. Conversely, in United States populations, about 60–75% of fully assayed stool specimens of children with chronic diarrhea do not demonstrate any pathogen.[3]

The use of gas chromatography has been proposed as a new diagnostic tool for the characterization of volatile compound profiles related to specific pathogens in the stools, including *C. difficile*, *C. jejuni*, *Vibrio cholerae* and *Giardia duodenalis*.[10]

Endoscopy may be used in CID, for differential diagnosis but only few pathogens show typical macroscopic or histopathology features. In CMV colitis, endoscopy typically shows longitudinal deep ulceration, crypt distortion, inflammatory infiltration and viral inclusion bodies (immunohistochemistry). *Yersinia* and *Mycobacteria* may cause granulomatous infiltration.

Other causes of chronic diarrhea should be considered in children with recent intestinal or systemic infections (Table), including:

1. *Postenteritis diarrhea*, in which mucosal damage persists after acute infections, and secondary disaccharidase deficiency, sensitization to foods and changes in gut microflora contribute to the persistence of diarrhea.
2. *Antibiotic-associated diarrhea*, a frequent complication of large-spectrum antibiotic treatment due to dysregulation of microbiota, prokinetic effects of antibiotics or proliferation of toxigenic *C. difficile*.
3. *Small intestinal bacterial overgrowth*, in which diarrhea may be the result of either a direct microorganism/enterocyte interaction or the consequence of deconjugation and dehydroxylation of bile salts, and hydroxylation of fatty acids secondary to abnormal proliferation of bacteria in the proximal intestine.

THERAPEUTIC APPROACH

Chronic diarrhea, associated with impaired nutritional status, may be a serious condition, and therapy should be started promptly. The treatment includes general supportive measures, nutritional rehabilitation, elimination diets and drugs. The latter are frequently introduced empirically, pending stool testing results.

When pathogens are isolated, specific antimicrobial treatments need to be considered (Table).[11] Multidrug-resistant strains seem not directly related to the duration of diarrhea. However, the increasing antibiotic resistance (ie, beta-lactams, aminoglycosides and quinolones) may limit the treatment possibilities, as frequently happens for enteropathogenic *E. coli* isolated in travelers or hospitalized patients.

Empiric antibiotic treatment of suspected small intestine bacterial overgrowth includes metronidazole, rifaximin, ciprofloxacin, amoxicillin-clavulanate and oral gentamycin. Fragile children with rotavirus- or norovirus-induced CID may benefit from a single oral administration of human immunoglobulins (300–400 mg/kg).

Antiviral therapy with ganciclovir for at least 2 weeks, and subsequent valganciclovir, should be considered in infants with severe CMV colitis, immunocompromised children and those with CMV-related comorbidities (ie, retinitis).

CONCLUSION AND FUTURE NEEDS

The role of infections in chronic diarrhea changes according to setting and child's nutritional and immune status. Enteric pathogens are often implicated in chronic diarrhea, but the majority of self-limiting episodes of chronic diarrhea, interpreted as infections, are negative to wide microbiologic assays.

As for the respiratory tract, new molecular assays for the search of stool pathogens are rising issues about the interpretation of results and treatment indications. Up to 5 different stool pathogens have been isolated in children with CID, and distinguish between etiologic agents and by standers may be challenging. A case-controlled approach, as used in the GEMS study, may be the right approach to better set-up appropriate treatment.

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