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PROTOZOA (R MEJIA, SECTION EDITOR)

Epidemiology of Cryptosporidiosis and Giardiasis: What Pediatricians Need to Know

Luther A. Bartelt[1] · **Elizabeth Attias**[2] · **Jimmy Black**[2]

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Abstract Diarrheal illness in the USA is a significant contributor to adverse morbidity in children and has a major impact economically, including the utilization of healthcare resources. Viral and bacterial pathogens account for the majority of cases that have an infectious cause; however, intestinal protozoan parasites are important but often under-recognized etiologic agents for infectious diarrhea. *Cryptosporidium spp*. and *Giardia lamblia* are the most common intestinal protozoal infections in both resource-limited and resource-abundant countries and predominately affect children, usually those between ages 1–9 years and most often in children less than 4 years of age. Both *Cryptosporidium* and *Giardia* are ubiquitous in the environment and transmit primarily through the fecal-oral route after ingestion of oocysts/cysts in contaminated water or food or direct person-to-person contact. Both are environmentally hardy. The chlorine-tolerant *Cryptosporidium* oocysts in particular have led to more diarrheal outbreaks due to treated recreational water exposure than any other pathogen. Despite notifiable diseases in the USA, reporting is very low and thus general awareness of epidemiology and clinical manifestations is limited. Underdiagnosis can further contribute to under-reporting, especially in asymptomatic patients and where specialty consultation and reliable diagnostics are absent. Once a diagnosis of cryptosporidiosis or giardiasis has been confirmed, in addition to appropriate case reporting and treatment considerations, it is essential to provide educational support to children and their parents or caregivers to prevent further transmission of the disease within the household and throughout the community.

Keywords *Cryptosporidium* · Epidemiology · *Giardia* · *Giardiasis* · *Cryptosporidiosis*

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✉ Jimmy Black
jblack@atomstrategic.com

[1] Division of Infectious Diseases and International Health, University of Virginia, Charlottesville, VA, USA

[2] Atom Strategic Consulting, 40 Market Street, Suite 423, Morristown, NJ 07960, USA

Introduction

It has been estimated that around 200–375 million episodes of diarrheal illness occur annually in the USA [1], which results in considerable morbidity and has a major impact economically, including the utilization of healthcare resources [2]. Although viral and bacterial pathogens account for the majority of cases that have an infectious cause, intestinal protozoan parasites are important etiologic agents for infectious diarrhea. Globally, intestinal protozoa are estimated to cause 58 million cases of diarrhea per year, and the direct costs for management of childhood protozoal diarrhea worldwide have been estimated at US$150 million [3]. *Cryptosporidium spp*. and *Giardia lamblia* (syn. *G. intestinalis or G. duodenalis*) constitute the most prevalent intestinal protozoal infections in both resource-limited and resource-abundant countries. These protozoa predominately affect children, usually those between ages 1 to 9 years and most often in children less than 4 years of age. Collectively, giardiasis and cryptosporidiosis in the USA account for an estimated US$80 million in hospitalization costs alone [4] and 1.2 million and 750,000 cases, respectively, per year [5, 6]. Despite being notifiable diseases in the USA, only about 15,000 cases of giardiasis and less than 10,000 cases of cryptosporidiosis are reported annually to the Centers for Disease Control and Prevention (CDC) [6, 7]. Underdiagnosis further contributes to under-reporting,

especially in asymptomatic patients and where specialty consultation and reliable diagnostics are absent. The aim of the current article is to provide an overview on the epidemiology of *Cryptosporidium spp*. and *G. lamblia* gastrointestinal infection in children for general pediatricians practicing in North America.

Prevalence and Transmission Patterns of *Cryptosporidium* and *Giardia*

Estimating childhood prevalence of *Cryptosporidium* and *Giardia* infection is challenging since many episodes may be asymptomatic, conventional microscopy lacks adequate diagnostic sensitivity, and national surveillance systems, where available, rely upon either voluntary clinician reporting or water quality monitoring rather than active surveillance for case detection. These factors collectively contribute to a likely underestimated burden of these infections. In the USA, *Giardia* has been demonstrated in 4–7 % of submitted stool specimens and infection is nearly universal in resource-poor countries [8, 9]. *Cryptosporidium* prevalence also varies geographically and is subject to diagnostic methodology used. Surveillance of *Cryptosporidium* in stool specimens has reported rates of 2.2–2.5 % in diarrheal specimens in Europe and North America [10–12] and up to 18.7–25 % in parts of South America, India, and sub-Saharan Africa [13]. Seroprevalence studies, however, have indicated higher exposure rates of 25–55 % in North America [14–17] and up to 75–90 % in parts of South America and India [13]. Comparisons between stool studies and seroprevalence estimate approximately 50 % of *Cryptosporidium* infections are missed by stool examination [13]. Since *Giardia* and *Cryptosporidium* can be found in surface waters of all continents except Antarctica, the potential for transmission exists in every country.

Several factors account for the high transmissibility of *Cryptosporidium* and *Giardia*. Both are ubiquitous in the environment and transmit primarily through the fecal-oral route [18, 19] after ingestion of oocysts/cysts in contaminated water or food [20–24] or direct person-to-person contact. The life cycle of *Cryptosporidium* spp. consists of a sporozoite stage which invades the apical surface of ileum enterocytes. *Cryptosporidium* reproduces via either an asexual cycle via merozoites or a sexual cycle that leads to oocysts that can either directly re-infect or be excreted in feces [25]. Infected persons can shed ~1 billion oocysts in a single diarrheal specimen [26, 27]. The life cycle of *G. lamblia* consists of a non-invasive flagellate trophozoite stage in the duodenum and a cyst stage which is passed in feces. The numbers of cysts excreted in feces can be highly variable and intermittent: however, up to 10 billion cysts can be excreted daily and shedding can last for several months [28, 29]. *Cryptosporidium* oocysts can remain viable for at least 6 months if kept moist and for at least 10 days even in properly chlorinated recreational water venues [30]. *Giardia* cysts also survive well in the environment, particularly in cold water [31, 32]. Oocysts/cysts are immediately infectious upon shedding, and as few as only 10–100 oocysts/cysts may be sufficient to cause infection [33–35].

Within the USA, these intestinal protozoa are most notorious for causing water-borne outbreaks. The largest water-borne diarrheal outbreak in the USA occurred in 1993 when the Milwaukee, Wisconsin, public water supply was contaminated with *Cryptosporidium,* leading to ~400,000 infections in local residents [36, 37]. A review of all published water-borne protozoal outbreaks that occurred worldwide between 2004 and 2010 included 199 outbreaks of human disease [38]. Reports were most frequently from Australia (47 %), North America (31 %), and Europe (16 %), and in almost all the outbreaks, the etiological agent was either *Cryptosporidium* spp. (60 %) or *Giardia lamblia* (35 %). Outbreaks in endemic resource-poor countries were generally under-reported in the literature, in part due to the lack of surveillance systems and the likely more continuous pattern of transmission.

There is a seasonal peak of reported cases in North America in late summer to early fall months [5, 6, 39] that is coincident with increased human outdoor activity and temporally associates with outbreaks from recreational water sources (i.e., water parks, swimming pools, rivers, and lakes) [40, 41]. Water-borne *Giardia* outbreaks are commonly related to consumption of fecal-contaminated untreated surface water or water treated by a faulty purification system or by inadequate chlorination [37, 42]. *Cryptosporidium* is extremely chlorine-tolerant, even at CDC-recommended water chlorination levels, and is thus the diarrheal pathogen most associated with *treated* recreational water exposure (i.e., swimming pools and water parks) accounting for 42 % of US, treated, recreational water outbreaks in 2009–2010 [7, 41, 43]. Despite major pathogens in water-associated disease outbreaks in the USA [41], only 1.4 % of *Giardia* and 5.5 % of *Cryptosporidium* cases reported to the CDC were associated with a detected outbreak [5, 6]. These statistics imply that a substantial number of sporadic cases also occur.

Few studies have evaluated sporadic transmission of *Giardia* and *Cryptosporidium* in the USA. Person-to-person transmission contributes to case incidence, particularly as a means of secondary spread following a primary water-borne outbreak [30], and has been reported among children attending play groups and day care centers [44, 45]. Contact with children ages 2–11 years with diarrhea has been found to be a major risk factor for cryptosporidiosis in North America [46], and day care workers, siblings, and mothers of children with giardiasis have higher rates of infection [47]. The overall prevalence of protozoal infections in day care settings in North America has not been rigorously studied and is likely lower

than that in day care centers in countries with limited resources. However, since many children in day care settings could harbor asymptomatic or undetected infections [11, 48, 49], infants and children in day care can represent an important nidus for further spread within the community [47].

Travel to or emigration from endemic settings is another risk factor of giardiasis and cryptosporidiosis [7, 50]. *Giardia* is the most commonly identified pathogen among returning international travelers presenting with gastrointestinal illness [51]. Food-borne transmission also contributes to infection [52–55]. Finally, the vast environmental distribution of *Cryptosporidium* and *Giardia* is also influenced by animal reservoirs. Zoonotic transmission may occur either through direct contact with infected pets or farm animals [56, 57] or contamination of runoff surface water [7]. *C. parvum* is of particular concern in the US beef industry, and contact with cattle is a risk factor for human cryptosporidiosis [46]. Most information indicates that zoonotic transmission of *Giardia* is of minimal influence in North America [8, 58, 59]; however, since zoonotic-related outbreaks have been reported [60], this potential route of transmission should not be excluded, particularly in children with close contact with pets or farm animals.

Childhood Susceptibility to *Cryptosporidium* and *Giardia*

The increased susceptibility of children to *Cryptosporidium* and *Giardia* infection is likely multifactorial. Children are in general more susceptible to enteric pathogens, in part due to increased exposure to contaminated sources. Veterinary practice and experimental animal models demonstrate that primary infection with either *Giardia* [61] or *Cryptosporidium* [62] occurs more readily in neonates than in older individuals, suggesting that immature intestinal mucosal defenses also confer increased susceptibility. Malnutrition in field studies and experimental models [63, 64] further predisposes young hosts to more severe intestinal protozoal infection, as do select primary immunodeficiencies such as agammaglobulinemia and common variable immunodeficiency for *Giardia* [9] and T-cell deficiencies (i.e., hyper IgM/CD40L deficiency syndrome) [13] and IL21R mutations for *Cryptosporidium* [65]. In endemic settings, there is an age-related decrease in disease incidence for both pathogens [66, 67], invoking development of protective adaptive immunity. Also, previously exposed individuals in temporally distinct but geographically overlapping giardiasis outbreaks demonstrated reduced susceptibility to re-infection [68]. In contrast, individuals with acquired immunodeficiencies such as untreated infection with HIV or treatment with anti-rejection medications after organ transplantation have increased vulnerability to intestinal protozoa [69]. Indeed, pediatric transplant recipients are notably susceptible to cryptosporidiosis and delayed treatment can result in serious complications [70–72].

A Clinical Approach to Detecting Pediatric *Cryptosporidium* and *Giardia* Infections

Pediatric gastroenteritis from *Cryptosporidium* and *Giardia* spp. are more frequent than commonly perceived, and both infections have been insufficiently studied and under-reported [73]. Partially accounting for under-reporting are the unique clinical and laboratory challenges facing the general pediatrician in the diagnosis of cryptosporidiosis and giardiasis. In this regard, it is important to emphasize that, while hallmark clinical features are commonly ascribed to certain pathogens (i.e., fever with bacterial gastroenteritis, respiratory symptoms with viral gastroenteritis, and greasy stools with giardiasis), no single symptom is pathognomonic for a specific etiology and only targeted microbiological testing will identify the culprit pathogen [2].

General Considerations

In the assessment of gastroenteritis, the general pediatrician will most commonly see a child with acute illness, usually within 1–4 days of onset. Viral infections (e.g., rotavirus, norovirus), followed by bacteria (e.g., *Salmonella* spp. *Shigella spp*., *Campylobacter jejuni*, *Escherichia coli*), account for most infectious etiologies (>90 %) in the acute setting in North America [2]. Since viral and bacterial etiologies of acute diarrhea are usually transient, self-limited, and typically respond rapidly (within 3–4 days) to appropriate symptomatic therapy (i.e., rehydration and nutritional therapy), microbiological testing is seldom performed in the acute setting [2]. However, it has recently been recognized that *Cryptosporidium* is second only to rotavirus as a leading cause of acute moderate-severe diarrhea in children <5 years of age in resource-limited settings [74] and a major attributable cause of community-associated diarrhea in similar field sites [75]. Thus, a careful epidemiological history should be performed in any child with acute gastroenteritis to identify any of the aforementioned epidemiological risk factors for intestinal protozoal infection (on-going outbreak of unknown etiology, known local protozoal outbreak, day care or institutional exposure, recreational water exposure [particularly in late summer and early fall], a sibling with diarrhea [particularly if <2 years of age], travel to an endemic region, and/or contact with farm animals and pets). Furthermore, a severely ill child with diarrhea, one who is immunocompromised, or one who lives with or is in frequent contact with someone with an immunocompromised condition warrants an early search for an etiologic agent, including evaluation for *Cryptosporidium* and/or *Giardia*.

A presentation with diarrhea for >7 days and notably failure of symptomatic and/or specific antibiotic therapy more strongly implicates a parasitic infection that would prompt specific testing. In all cases of pediatric diarrhea, adequate fluid and electrolyte replacement therapy should be instituted to ensure adequate hydration.

Cryptosporidiosis

Cryptosporidiosis is caused by a range of *Cryptosporidium* spp. and has only been recognized as a major source of parasite-induced infection in recent decades. The most common species are *C. hominis* and *C. parvum* in humans, although other species can be involved such as *C. meleagridis*, *C. felis*, *C. canis*, *C. andersoni*, *C. suis*, *C. baylei*, and *C. muris* [76, 77]. Crytposporidiosis is classically characterized by profuse, watery diarrhea with or without crampy abdominal pain, which may be intermittent or continuous and may include vomiting or low-grade fever [25, 78]. Although *Cryptosporidium* species are morphologically indistinct, clinical manifestations between different species and subtypes within a species can differ. For example, *C. parvum* symptoms are most often limited to diarrhea, whereas *C. hominis* can associate with diarrhea, nausea, vomiting, and malaise [79]. Molecular diagnostics demonstrate that the quantitative burden of *Cryptosporidium* in a stool specimen correlates with severity of disease [80]. Host immune status also influences severity of infection, with the potential for cholera-like voluminous diarrhea in the severely immunocompromised host [13]. Although generally considered a self-limited illness, symptoms can last 1–4 weeks and relapses can occur [81]. Furthermore, in children <5 years of age in resource-limited settings with acute moderate-severe diarrhea, *Cryptosporidium* associates with increased mortality [74]. Asymptomatic shedding of *Cryptosporidium* spp. can also occur [82–85]. Whether symptomatic or asymptomatic, *Cryptosporidium* has been associated with persistent growth delays in children [86].

The conventional diagnosis of cryptosporidiosis is usually undertaken using routine fecal parasite testing for identification of oocysts in stool samples. However, identification using light microscopy and staining can be unreliable in practice for routine diagnostic laboratories [19, 87]. Patients should therefore submit several stool samples over several days for testing [88]. The use of direct fluorescent-antibody assays with fluorescence microscopy or antigen detection by immunoassays improves the sensitivity and specificity of detection [59], but requires specific requests since routine parasite testing of stool specimens may not include methods to detect this parasite [88]. PCR and other DNA-based techniques provide even greater sensitivity [89] and are necessary for genotyping in the outbreak setting [59]. Currently, DNA-based technologies are only used in specialist reference laboratories, but *Cryptosporidium* is included in most multiplex molecular-based high-throughput platforms that are becoming increasingly available.

Giardiasis

G. lamblia generally causes a self-limited, but often persistent illness that is initially characterized by diarrhea, flatulence, greasy/floating stools, bloating, abdominal cramps, and dehydration and eventual possible weight loss and malabsorption [90]. *Giardia* more frequently associates with persistent than acute diarrhea [91]; however, volume depletion resulting in need for hospitalization can occur, and as many as 18 % of children <5 years of age with *Giardia* present with failure to thrive [92]. Asymptomatic shedding of *G. lamblia* has also been demonstrated [84, 93]. The consideration of bacterial and/or viral co-infection should be made in symptomatic children who have traveled or emigrated from endemic regions [94, 95]. Unlike *Cryptosporidium*, the quantity of *Giardia* cysts excreted in feces does not appear to correlate with symptoms [80] and therefore abundance of parasites seen microscopically should not influence treatment considerations.

The diagnosis of giardiasis is usually based on routine fecal parasite testing for cysts (or rarely trophozoites) using fresh or preserved stool specimens. However, this can give false negative results and may necessitate repeat testing to confirm diagnosis. Detection of cysts can be difficult using light microscopy, and low numbers may be present due to intermittent excretion of cysts. Thus, multiple stool collections, i.e., three stool specimens collected on separate days, increase diagnostic sensitivity [96, 97]. Specific antigen detection immunoassays can provide more reliable results in routine diagnostic laboratories, and like *Cryptosporidium, Giardia* is included on most multiplex rapid diagnostic PCR-based platforms. DNA-based assays are also available in reference laboratories for specific genotyping [8, 59], although this is not required for routine diagnosis.

Conclusions

Cryptosporidium spp. and *G. lamblia* are intestinal protozoa that are ubiquitous in the environment and are important but under-reported agents of gastroenteritis in children [73]. Once a diagnosis of cryptosporidiosis or giardiasis has been confirmed, it is essential to provide educational support to children and their parents or caregivers to prevent further transmission of the disease in the household and in the community. Appropriate medical treatment of parasite-induced diarrhea in children, including anti-parasitic medications and consultation with Infectious Disease experts, should be considered not only to treat the individual patient but also to limit the potential for transmission to others within the community. The potential

role of antiparasitic agents to limit duration of shedding/transmission in outbreak circumstances deserves further study [45]. To prevent transmission throughout the community, children should be advised to remain at home and not attend day care, educational centers, and public venues during the infectious period and at least until treatment is completed. As with all agents of infectious diarrhea, the key role of rigorous handwashing with soap and hot water at regular intervals and particularly with high-risk activities such as toileting, diaper changing, food handling, etc., in the prevention of person-to-person transmission from fecal-oral contamination should be emphasized to parents/caregivers and also for children of a suitable age. Specific counseling to direct families to the use of appropriate anti-protozoal surface disinfectants (such as hydrogen peroxide rather than bleach) is advised. Adherence to such basic hygiene should also continue after resolution of gastrointestinal symptoms as *Giardia* cysts and *Cryptosporidium* oocysts can continue to be excreted for a considerable time following symptom resolution. Notably, children with cryptosporidiosis should abstain from swimming or participating in water-based recreational activities until at least 2 weeks after their diarrhea has completely resolved [98], and this 2-week restriction still applies to children who have been treated with a course of nitazoxanide [88].

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Compliance with Ethical Standards

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