

Cryptosporidiasis: Clinical and Public Health

Helen Maiara Gunsch de Lucas^{1*}, Natan Soares Silveira², Rafael Vinícius Lôndero Quintino dos Santos², Luca Erdmann Bini Cordeiro², Felipe Ximenes Barreto², Mayara de Lima Bueno² and Pedro Henrique Martins de Oliveira²

¹Médica formada pelo Centro Universitário Serra dos Orgãos, Teresópolis, Brazil

²Acadêmico do curso de Medicina do Centro Universitário Serra dos Orgãos, Teresópolis, Brazil

*Corresponding author: Helen Maiara Gunsch de Lucas, Médica formada pelo Centro Universitário Serra dos Orgãos (UNIFESO), Teresópolis (RJ), Brazil, Tel: (21)968253808; E-mail: helen_maiara_g@hotmail.com

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Abstract

Cryptosporidiasis is an infection of the gastrointestinal tract caused by a coccidian protozoan of the genus *Cryptosporidium*. There are several species of *Cryptosporidium* described that infect birds, mammals, amphibians, reptiles and fish. But only *C. parvum*, *C. hominis* and *C. meleagridis* are capable of infecting humans. Research carried out in Peru, India, Brazil and Bangladesh showed that *C. hominis* was the main cause of diarrhea in children. In particular, "*C. meleagridis*" is an exclusively avian species and the only one with zoonotic potential in these animals. Representing in some countries an important part of the occurrence of infection in humans, similar or superior than the infection by *C. parvum*. The discussion was based on the Cochrane, Lilacs, Pubmed, Scielo, and Scielo Brazil databases.

Keywords: Cryptosporidiasis; Protozoan infections; Public health

Introduction

Cryptosporidiasis is an infection of the gastrointestinal tract caused by a coccidian protozoan of the genus *Cryptosporidium* [1].

It was first described in 1907 as a parasite that inhabited the gastric mucosa of mice [2]. In 1976 it was discovered that it was capable of causing infection in humans [3]. Up to 1985 only seven cases had been recorded, however, between 1982 and 1983 there was a sudden increase in cases [2]. Subsequently,

Cryptosporidium has been found to be a pathogen that frequently causes self-limited diarrhea in immunocompetent individuals and is also responsible for persistent diarrhea in children and immunocompromised individuals, especially individuals with Acquired Immune Deficiency Syndrome (AIDS) [4].

The parasite belongs to the phylum Apicomplexa, order Eucoccidiiida, suborder Eimeriina, family Cryptosporiidae. The significance of *Cryptosporidium* is "hidden sporocysts", since its oocyst does not have sporocysts [1].

"*Cryptosporidium* was classified as a parasite of the subclass Coccidia, class Coccidiomorpha. Recently it was re-classified as subclass Cryptogregarina and class Gregarinomorpha. This change was based on genomic, biochemical, microscopic and molecular information that demonstrated the similarity between the gregarines and the *Cryptosporidium*. *Cryptosporidium* is the only representative of this class and subclass which includes epicellular parasites of vertebrate animals that have a feeder organelle, but without an apicoplast [5,6]."

There are several species of *Cryptosporidium* described that infect birds, mammals, amphibians, reptiles and fish [5]. But only *C. parvum* and *C. hominis* are capable of infecting humans. Research carried out in Peru, India, Brazil and Bangladesh showed that *C. hominis* was the main cause of diarrhea in children [3].

It is an intestinal pathogen with a greater capacity for contagion. This is due mainly to two factors: chlorine resistance and low dose of oocysts required to cause infection, making it important from a clinical and epidemiological point of view.

Etiology

Morphological Aspects

As previously mentioned, the main infectious form in humans is *Cryptosporidium parvum*, however, the human infection by *C. hominis* species is already well documented.

Infection occurs through ingestion of minute oocysts (3 to 6 micrometers) by water or contaminated food. These oocysts are activated in the stomach and proximal portions of the small intestine, producing serine and cysteine - protease and aminopeptidase - allowing it to be sporulated, releasing four sporozoites [4]. These sporozoites have substances in their apical membrane that allow the invasion of intestinal epithelial cells [4]. When invading the cell there is formation of a vacuole below the epithelial membrane, in this way the parasite is intracellular but extra cytoplasmic [1]. This process takes approximately twelve hours.

Within these vacuoles, differentiation occurs in unicellular trophozoites and in 48 to 72 hours the cells hatch releasing merozoites. This process occurs by merogony, that is, asexual multiplication. Merozoites that are mobile bind to and infect other cells of the intestinal epithelium and generate macrogametes (female sexual stage) and microgametes (male sexual stage), these fertilize and form the zygote which will give rise to the oocysts that will be released in the feces [1].

By being able to reproduce itself in a complete cycle within the host (monoxene cycle), *Cryptosporidium* perpetuates its infection spontaneously. It is worth mentioning that *Cryptosporidium* produces distinct oocysts, being one of thick walls that resist chlorine, iodine, acid and temperatures below 65°C, making it extremely resistant in the environment. And the other that consists of thin walls has the purpose of hatching in the intestinal lumen in order to spread the infection [3].

Immunology and Pathology

It is known that humoral and cellular immunity are important for the control of cryptosporidiasis. Countless changes in the innate response can lead to severe infections with *Cryptosporidium*. Mannose binding lectin, is a plasma protein that activates the complement lectin pathway and leads to the elimination of pathogenic microorganisms, without the production of antibodies. In adults and children who have mannose-binding lectin polymorphisms, *Cryptosporidium* infection is more severe and recurrent [3].

Toll-like surface receptors generate the trigger for the production of defensins that prevent pathogenic invasion. In vitro and in vivo research have shown that TLR / MyD88 gene deficiency causes lower defensin production and culminates in increased parasite burden [3].

Interferon γ (INF - γ) is the main mediator of the acquired immune response to *Cryptosporidium*. Inactivation of INF - γ causes more infection, independent of CD4 cell depletion. In rats and cattle, the INF- γ that was expressed in the intestinal cells led to the control of the peak expression of the oocysts. In addition, depletion of IL-12, which is a strong stimulator of INF- γ , is also related to severe infections and chronicity of diarrhea [4].

Hyper immunoglobulin M syndrome (IgG, IgE, IgA deficiency) causes a defect in the CD40 ligand, (CD40LG) causing an increase in the frequency and severity of *Cryptosporidium* infection. In addition, the syndrome is associated with deficiency of IL-12 and TNF- α , both of which stimulate the production of INF- γ [3].

Humoral immunity also demonstrates importance in the control and prevention of the disease. The high concentration of antibodies specific to *Cryptosporidium* correlates with cryptosporidiosis of less duration and less elimination of oocysts, and breast milk antibodies are related to infant protection [3]. However, the importance and efficacy of these antibodies are controversial in the literature [4].

In addition to the immunological factors mentioned, the key to the control of *Cryptosporidium* infection is CD4 T cells, since they are also located in the intestinal lamina propria [7]. In patients with HIV, CD4 dosage correlates with the presentation of the disease. In those with satisfactory levels, (≥ 180 cells / ml) the disease tends to be self-limited. While in individuals with CD4 depletion, the disease is chronic and fulminant [4] CD8 T cells have less relevance in *Cryptosporidium* infection, although they are important for the production of INF- γ .

The infection occurs in the small intestine; in immunocompetent individuals it occurs initially in the terminal ileum and proximal colon, while in immunodeficient the pathogen was found along the intestine and also extra intestinal as: biliary tree and bronchial tree [4].

The anatomopathological changes are non-specific [1]. In children with persistent *Cryptosporidium* there is atrophy of the villi and slight increase of the lymphocytes of the basal layer. In severe and chronic cases of the disease there is crypt hyperplasia associated with atrophy, fusion and loss of villi in addition to important infiltration of the lamina propria with lymphocytes, plasma cells, neutrophils and macrophages [4]. This process leads to the clinical presentation of the disease that is marked by diarrhea and malabsorption [1].

Initially, it was believed that the cause of diarrhea was based on a secretory mechanism mediated by a toxin, as occurs in cholera for example, however, current research corroborates the belief that the mechanism that leads to *Cryptosporidium* diarrhea is mediated by the response inflammatory activity [7].

Infection of the intestinal cells activates the nuclear factor kappa B that has pro-inflammatory action and inhibits apoptosis. The proinflammatory action is mediated by tumor necrosis factor alpha (TNF- α), interleukin-1 β (IL-1 β), interleukin-8 and lactoferrin [4]. A study conducted with Haitian children shows those fecal levels of TNF- α remained high during the six months following infection, suggesting that there is persistent systemic inflammation, which may explain malnutrition and dwarfism in children who had cryptosporidiasis [7].

In addition, the cytokines and chemokines cited increase the expression of cyclooxygenase type 2 (COX 2) and, consequently, prostaglandins. The increase in prostaglandins has a dubious effect: it increases the production of mucin that impairs cell invasion by sporozoites and, on the other hand, alters chloride secretion [7]. In pigs and cattle, it increases sodium secretion [4].

There is also increased production of substance P, a neuropeptide produced by inflammatory cells. This has been shown in research to correlate with the severity of diarrhea [8]. In addition to perpetuating the inflammatory response, chloride secretion also increases [7].

In short, the inflammatory process that causes diarrhea characteristic of *Cryptosporidium* causes sodium malabsorption, increased chloride secretion, increased intestinal permeability, decreased glucose absorption and decreased lactase. In this way, it generates massive diarrhea [1,4].

Clinical Aspects

Human Disease

Natural history: The incubation period of the disease varies from one to thirty days and such variation depends on the dose of oocysts to which the person was exposed and the organic response to infection. The clinical manifestations of *Cryptosporidium* are variable and depend on the immune status of infected persons. In healthy individuals, the infection may be asymptomatic and may lead to self-limited, bulky diarrhea (3 to 10 bowel movements/day with loss of 1 to 3 liters of water per day) with an average duration of 3 to 14 days. Additionally, it may be accompanied by abdominal pain, anorexia, nausea, flatulence, fever and headache. Therefore, abdominal pain and diarrhea are exacerbated with food [4].

In children beyond the mentioned frame there may be weight and growth retardation that may not be overcome after the disease has been eliminated [4], and may lead to malnutrition. It is known that in Brazil, children up to two years of age who had *Cryptosporidium* had impairment of cognitive function and physical constitution after four years of age [7]. In addition, the child is predisposed to other intestinal infections that cause diarrhea. This is due to the loss of intestinal barrier function [2].

In those who have immune compromise, such as AIDS, *Cryptosporidium* is markedly differentiated by chronicity. However, it is worth emphasizing that the clinical presentation has an intimate relationship with CD4 levels. In individuals with counts greater than 180 cells/ml, the condition tends to be self-limiting; in people with lower levels of CD4, the disease can lead to more severe diarrhea with water losses reaching as high as 15 liters/day (cholera like), in addition to chronic diarrhea (≥ 4 weeks) [4].

In some cases, immunodeficient patients may present extra-intestinal manifestations. The disease in the biliary tree occurs along with enteritis. The way the parasite in the gallbladder and biliary tract occurs is unknown; however, it is said that this

infection can contribute to the chronicity of the disease and the difficulty of eradicating the parasite. (Dirce, 2015). Clinically, it may manifest as acalculous cholecystitis, sclerosing cholangitis, and bile duct stenosis [1].

The manifestations of pulmonary cryptosporidiosis include chronic cough, fever, dyspnea and there may be pulmonary interstitial infiltrates. The dissemination to this tract occurs by luminal route. It is noteworthy that there are divergences among researchers as to the real possibility of lung infection by *Cryptosporidium* to generate a respiratory issue, in fact. Diagnosis is confirmed by the Ziehl Neelsen sputum staining test [2].

Differential Diagnosis

Cryptosporidium, *Isospora belli* and *Cyclospora cayentanensis* are the main parasites included in this context [9]. In addition, cytomegalovirus, Rotavirus, Salmonella, Shigella, Campylobacter, *E. histolytica* and *Mycobacterium avium* infections should also be considered as causing epidemics of diarrhea, especially in underdeveloped countries [10].

Disease in dogs (cat, wild animals and etc ...)

Although *Cryptosporidium* has several species (*C. baileyi*, *C. muris*, *C. serpentis*, *C. wrairi*, *C. parvum*, *C. felis*, *C. meleagridis*, *C. saurophilum*) that infect animals such as birds, mammals, reptiles and amphibians, the transmission between man and animal does not occur. In addition, in most animals, the infection is asymptomatic [4].

The occurrence of *C. parvum* and *C. muris* was evaluated in three wilderness areas in southeastern Brazil, being Itatiaia National Park, Serra da Bocaina and Serra da Fartura; in the samples of wild animals captured, with confirmation of the presence of *C. parvum* oocysts in 5.1% of samples and 5.1% of *C. muris*. These results show that wild animals can serve as reservoirs of the disease [11].

Laboratory Diagnosis

Clinically the disease is indistinguishable from other causes of diarrhea. Therefore, in immunocompetent patients who have acute diarrheal disease, laboratory investigation is not necessary. On the other hand, in immunocompromised patients with chronic diarrhea, the etiological investigation is important because it allows adequate treatment [3].

The laboratory diagnosis through the identification of oocyst in stool sample is the cheapest exam, with a widely diffused and available technique. However, it has a sensitivity of 70% to 80%, varying according to the staining technique used [3]. Ideally, it should be done by collecting multiple samples. The coloration of carbol fuchsin leaves the parasite with a light cyst on a red background which is visualized under light microscopy. Ziehl-Neelsen and methylene blue techniques are also employed [2,12].

Immunological diagnosis uses direct immunofluorescence techniques: antibodies are labeled with fluorescence and, in stool samples, identify the oocysts. It is a fast and easy way to read method, and has good accuracy. Its use is limited to epidemiological studies to identify asymptomatic infections [12], however, this diagnostic method does not allow the identification of the species, only the presence of the disease.

Polymerase chain reaction (PCR) technique is an excellent screening test for *Cryptosporidium* and has been used in laboratories. Its disadvantages are the high cost and need of a trained professional to carry it out [3]. They are able to increase several times the DNA of the parasite, being able to detect concentrations of oocysts below 103 micrometers/gram of feces [13].

In cases in which the fecal examination is not enlightening, a biopsy of the terminal ileum made by High Digestive Endoscopy with material stained with hematoxylin-eosin is used. The sensitivity and specificity of the test are excellent [13].

Evaluation by complementary methods (Radiology, ECG, etc.)

Imaging tests are of little use in cases of chronic diarrhea because they present nonspecific alterations that do not permit the development of a specific etiologic agent. Radiological changes are characterized by prominence of mucous folds and thickening of the intestinal wall [14].

Treatment

In acute diarrheal immunocompetent conditions, the approach is based on the traditional approach to hydration, nutrition and electrolyte support. Medications, when employed, aim to promote symptomatic comfort without having an influence on the duration of the disease. That is, it promotes substrate for the immune system to stop the disease [3,4,14].

In immunocompromised individuals, the diagnostic and therapeutic approaches are more comprehensive and include, in addition to the measures cited above, the use of antiparasitic medications. Furthermore, antiretroviral therapy is the mainstay of treatment in people with AIDS, in order to reestablish the CD4 levels so that the immune system is able to interrupt the situation [3].

The drugs used in *Cryptosporidium* have low efficacy and several regimens have been used over the years. Research has shown that piramycin, azithromycin, and immunoglobulin are not effective. Paromomycin has little effect on symptomatology and low efficacy in oocyst elimination. Nitazoxanide is the drug that has shown the best results in research and has been approved for the treatment of *Cryptosporidium* [3].

Somatostatin analogs for diarrhea control (Octreotide), and antiarrheals (Loperamide) may also be used.

The schemes used in Brazil according to Dirce (2015) are:

- Paromomycin 500mg, orally, three times a day for 14 to 28 days.
- Paromomycin 1g, orally, twice a day, associated with azithromycin 500mg, orally for 4 weeks and then only paromomycin for 8 weeks.
- Roxithromycin 300mg per day, for a variable time.
- Nitazoxanide 500mg twice daily (immunocompetent)
- Nitazoxanide 1g, oral, Twice daily for 14 days to 8 weeks.

Several investigations have been directed towards the development of new drugs against cryptosporidia (Alejandro Castellanos-Gonzalez et al., 2013). Calcium-dependent protein kinase inhibitors are promising drugs. In addition, other pathways have been proposed such as blocking the formation of microtubules of *Cryptosporidium* and inhibitors of hexokinase and lactate dehydrogenase [3].

Nursing Care for Patients with Cryptosporidia

The nurse must perform the Systematization of Nursing Care (SAE) closing the nursing diagnoses with possible interventions. The main nursing diagnoses, according to the NANDA-North American Nursing Diagnosis Assay [15] taxonomy, are: "Diarrhea related to the infectious process", with the main interventions being: Observe and note the quantity and appearance of faeces, offer and guide diet according to prescription, observe and note state of consciousness; "Diarrhea related to liquid stool dehydration more than three times a day", having as nursing interventions: installation and maintenance of oral or parenteral rehydration, besides water control, observation, recording and balance of fluids administered, ingested and eliminated every 24 hours [16] "Nausea related to gastrointestinal infections, evidenced by skin pallor" with the main nursing interventions as follows: Reporting reflexes of nausea and emesis; Record characteristics of the emesis; Maintain headboard 180°; "Acute pain in the right hypochondrium and jaundice" may indicate biliary disease, especially in immunocompromised individuals [17], main nursing interventions: Observe and note the state of consciousness [16]. Noting characteristics of pain; Communicate to the doctor signs of pain; Observe and note state of consciousness; "Altered Nutrition: Ingestion Minor Than Body Needs". Nursing interventions will be: avoid foods that increase diarrhea, such as those rich in fiber, milk derivatives, and gas builders. "Nursing care also includes verification of vital signs, especially axillary temperature and blood pressure - by the possibility of hypotension secondary to volume reduction.

Ecology and Epidemiology

Cryptosporidium is a global distribution parasite, except in Antarctica and is more common in moist months. Recent research shows that 15% to 25% of children with diarrhea had *Cryptosporidium* identified by PCR technique. This information

indicates that the parasite was underestimated as the frequency of its occurrence in immunocompetent children [3].

Cryptosporidium is considered a pathogen of cosmopolitan distribution however, it is more prevalent in tropical and subtropical regions where in addition to humidity, sanitary conditions help in its perpetuation. The prevalence of cryptosporidia in Brazil in HIV infected patients varies from 6.4% to 9.1% [18].

The main form of *Cryptosporidium* contagion is contaminated water, contaminated food and oral fecal transmission. For this reason, in Brazil, it is established by the Ministerial Order No. 518 of March 25, 2004, of the Ministry of Health to investigate pathogenic organisms such as enterovirus, *Giardia* spp cysts and *Cryptosporidium* spp oocysts in the water offered to the population. However, this monitoring does not occur routinely in Water Treatment Stations under the justification of methodological, financial and lack of trained human resources [19].

Prophylaxis and Control

Because the main forms of transmission of cryptosporidia are water and contaminated food- in addition to person-to-person transmission - purification of drinking water is essential. Since the *Cryptosporidium* oocyst resists chlorine, the main form of water treatment must be through filtration and flocculation [4,19].

Swimming pool water is also a frequent source of outbreaks of cryptosporidia. When the water treatment of the pool occurs, it should be done by aggressive measures with closure of the pool until the extinction of the oocysts [4,9].

Individual or family measures include hand washing, especially before meals, adequate stool fate, environmental and sanitary education, filtration of water into filters of 1 µm or less and boiling of the same [20-22].

In the hospital environment, the decontamination of the materials used by contaminated patients is essential. In addition, the identification and treatment of contaminated persons is important to reduce oocyst disposal in the environment [8,23].

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