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Cryptosporidium and its public health

Neveen, S. Satour

Parasitology Department, Alexandria Lab.
Animal Health Research Institute (AHRI), Agriculture Research Center (ARC), Egypt.

Review Article

Correspondence author:
Neveen Satour
E.mail: neveen.satour@yahoo.com

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Abstract
The protozoon parasite of the genus *Cryptosporidium* is the source of the food and water-borne zoonotic disease known as cryptosporidiosis. The two main species responsible for infections in both humans and animals are *C. hominis* and *C. parvum*. Both the respiratory and fecal-oral routes might spread the disease, as it's highly resistance to antimicrobials and anticoccidials. There are some drugs used for treatment as halofuginone lactate and nitazoxanide. As a result, proper hygiene practices are therefore essential to preventing and controlling disease. This review aims to provide an overview of the infective stage, life cycle, pathogenesis, epidemiology, diagnosis, treatment and control of cryptosporidiosis.

Keywords: *Cryptosporidium, life cycle, zoonotic disease*

Introduction

Cryptosporidiosis is a parasitic disease caused by genus *Cryptosporidium*, this parasite was discovered in the mice's stomach glands in 1910 by **Edward Ernst Tyzzer**, who gave it the name "kruptos" (which means hidden), since the parasite does not have sporocysts within its oocysts and sporulates while still attached to the host wall **Tyzzer, (1910)**. *Cryptosporidium* is one of the most prevalent waterborne diseases and the main global source of outbreaks of waterborne diseases **Helmy *et al.*, (2017 and Hopkins *et al.*, (2013).** Up to 1.6 million people worldwide have died from diarrheal diseases each year. Due to poor hygiene and contaminated drinking water, a third of these deaths have been recorded among children under the age of five **Dadonaite *et al.*, (2021)**. More than 8 million cases of foodborne illness occur worldwide each year as a result of *Cryptosporidium* **Ryan *et al.*, (2018)**. Oocysts are thought to be one of the causes of waterborne diarrheal outbreaks because of their extreme resistance to standard household disinfectants and their ability to persist in water for more than 140 days **Dillingham *et al.*, (2002) and Gururajan *et al.*, (2021).** The approved treatments for *Cryptosporidium* infections in humans and animals are nitazoxanide and halofuginone. Reducing the incidence of infection, obstructing animal-human transmission pathways and maintaining a good hygienic environment for both humans and animals are the main strategies used to control cryptosporidiosis **Yosra, (2014)**. Information about the route, spread of *Cryptosporidium* and the main subspecies of *Cryptosporidium* that predominate in both humans and animals, is essential to attain successful control. The objective of this review paper is to review available information about *Cryptosporidium* and its significance for public health.

3) Life Cycle of *Cryptosporidium*: -

The life cycle of *Cryptosporidium* is complicated, in which has ability to reproduce asexually and sexually within a single host. The infective stage of *Cryptosporidium* is the sporulated oocyst that contains four sporozoites **Hassan *et al.*, (2020)**. Transmission occurs mainly by ingestion contaminated water and food, then after ingestion the oocysts, each oocyst releases four infectious sporozoites that attach to the apical surface of intestinal epithelial cells, in which they locate in the microvilli in parasitophorous vacuoles between the cell wall and the cytoplasm that intracellular but extracytoplasmic **Current and Reese, (1986).** Sporozites mature into trophozoites inside the vacuole, which undergo three cycles of asexual reproduction, followed by a cycle of sexual stages to produce oocysts with either thin or thick walls that each contain four sporozoites **Current and Reese, (1986) and English *et al.*, (2022)**. The majority of oocysts that are formed have thick walls and can survive very well in the external environment but some have thin walls. Usually, these thin-walled oocysts release their sporozoites in the host's gut lu-

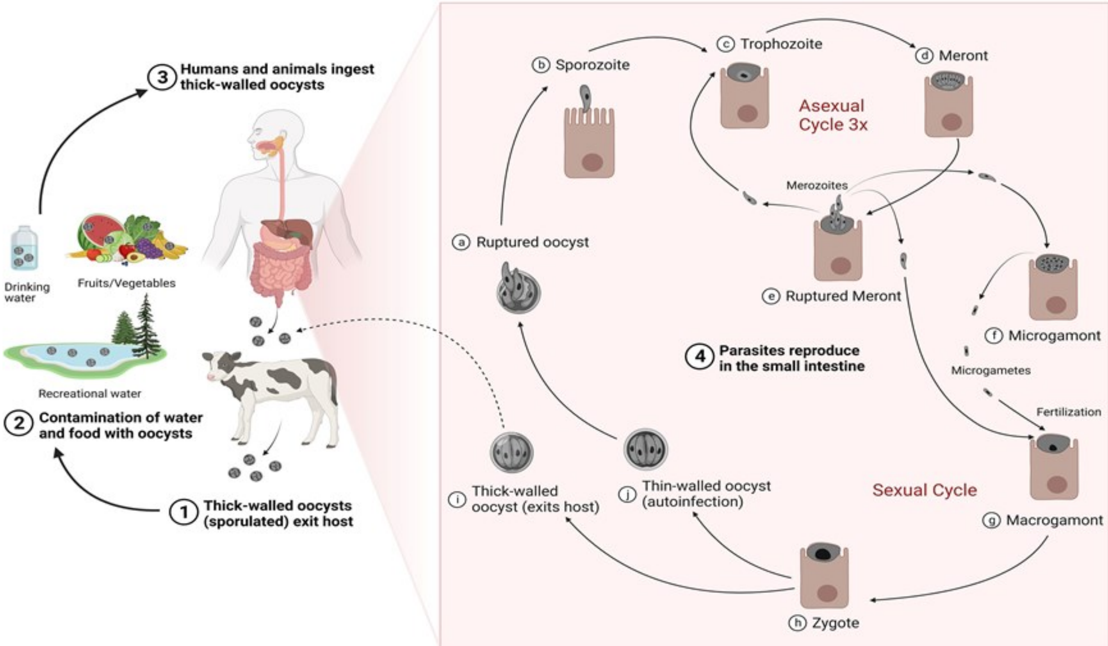

Fig. (1). Life cycle and transmission of *Cryptosporidium* **CDC, (2019)**. Created with BioRender.com.

Pathogenesis of *Cryptosporidium*:

After ingestion of sporulated oocyst with food or water by the host, oocyst rupture and releases sporozoite that attach to the apical surface of epithelial host cells. *Cryptosporidium* infections in calves often occur between one and four weeks of age, although they can also occur in older ages. **Wahba (1994)** when examined histological sections prepared from alimentary tract of experimentally infected mice with *Cryptosporidium* oocysts, found that the most pathological changes were observed to be prevalent in the ileum, stomach, duodenum and caecum. On the other hand, pathological changes in jejunum and large intestine were of a less degree. *Cryptosporidium* oocysts could be noticed on the epithelial surface of intestinal villi and being embedded in the mucosa of stomach and caecum. The lamina propria of the ileum villi was infiltrated with inflammatory cells. Goblet cells were distended and increased in number. In addition, there was necrosis, hyperplasia and vacuolation of the epithelium. There was diffuse atrophy in the villi which was much more obvious in the ilium. The epithelial cells of atrophied villi have been transformed to low columnar or cuboidal-shaped cells. In sections from the duodenum, there was swelling of some villi, some of which were fused together with the formation of synechiae. Vacuolation also appeared in the caecum. Haemorrhages appeared in the lamina propria of ileum and caecum. In the submucosa of stomach and caecum, blood vessels were dilated with phlebitis and formation of thrombi inside. Calves that suffering from diarrhea may be lethargic, anorexica and dehydrated. The diarrhea is a pale yellow color with mucous. In severe cases, calves die from dehydration and cardiovascular collapse. There are some pathogens such as Rotavirus, *Escherichia coli* and coccidia may can also be found in calves during the first month of age, this might cause cryptosporidiosis to appear more severe than it actually is. **Joachim *et al.*, (2003)**.

Epidemiology of *Cryptosporidium*: -

Cryptosporidium is a parasitic infection that infects a wide range of vertebrates, including humans. Millions of people have died from gastroenteritis due to cryptosporidiosis throughout the last quarter of the 20th century and at the beginning of the 21st century, with high death rates among children under the age of five. Risk factors for contracting *Cryptosporidium* infection include those with weakened immune systems, children, those who interact with animals, inadequate social infrastructure, sewage-contaminated water supplies, animal dung contaminating fruits and vegetables and using animal dung as fertilizer in agriculture. **Ramadan *et al.*, (2020).** Cryptosporidiosis is the main cause of chronic diarrhea and is associated with a high mortality rate in immunocompromised people, especially those with an AIDS-defining disease. Members of the genus *Cryptosporidium* are thought to be the second leading cause of diarrhea and mortality in the USA, after retroviruses **Hassan *et al.*, (2020).** There are different species and genotypes of *Cryptosporidium* have been identified. Among these are *C. hominis* and *C. parvum* which represent the 95% of cryptosporidiosis cases in humans. A few cases of *C. meleagridis* infections have also been recorded in humans, as well as *C. canis*, *C. felis*, *C. suis*, *C. muris*, and *C. andersoni* in immunocompromised individuals. A variety of hosts, including fish, birds, reptiles and mammals can become infected with *C. parvum* **CDC, (2022)**.

Diagnosis of *Cryptosporidium*: -

The traditional method of diagnosing cryptosporidiosis is based on presence of oocysts in feces. Fecal flotation, molecular, serological and smear analysis using certain stains are some of the approaches that can be used to identify oocysts.

Parasitological method: -

Numerous techniques are available for identifying *Cryptosporidium* in fecal samples. Microscopy is the most common technique among them to detect oocysts. Fecal samples can be examined directly using the concentration flotation method. **Fayer and Xiao, (2007)**. Detection of *Cryptosporidium* oocysts is usually done by microscopy without any staining and/or by the modified Ziehl-Neelsen stain technique **Henriksen and Pohlenz, (1981)** under light microscopy with oil immersion lens, whereby the oocysts stain purple with green background figure (2). Also, safranin methylene blue **Baxby *et al.*, (1984)**, methylene blue eosin **Cross and Moorhead, (1984)** and Giemsa stain **Pohlenz *et al.*, (1978)**. Another useful technique is immunofluorescence staining techniques. Despite the higher sensitivity of immunofluorescent antibody-based (IFA) procedures, traditional staining techniques like Ziehl-Neelsen stain are still widely used since they are simpler and less expensive **Caccio and Widmer, (2014)**.

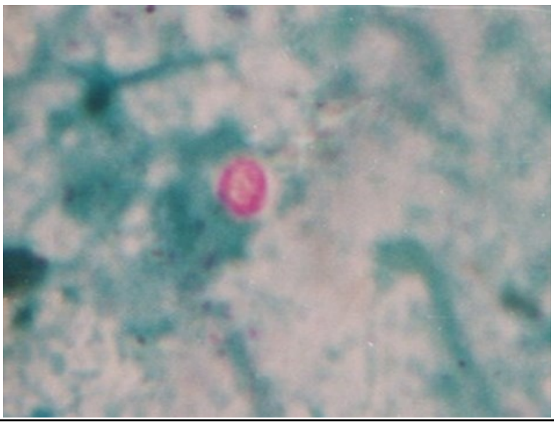

Fig. (2). Faecal smear from diarrheic lamb stained with modified Ziehl-Neelsen stain technique showed *Cryptosporidium parvum* oocyst (x1000) **Ebied and Satour, (2019)**.

Serological method:
Different serological techniques such as enzyme linked immunosorbent assays (ELISA) and immune chromatographic test provide good sensitivity and specificity for detecting of *Cryptosporidium* antigens **Agnamey *et al.*, (2011) and Hawash, (2014).**

Molecular method:
Polymerase Chain Reaction (PCR) technique offers very sensitive, species-specific diagnostics. Compared to traditional microscopical and serological approaches, PCR-based methods for detecting oocysts in faeces are more sensitive in the detection of *Cryptosporidium*. *Cryptosporidium* species oocysts were analyzed by PCR. The 18s rRNA gene sequences used in the PCR process showed positive bands at 1056 bp. However, *Cryptosporidium parvum* subtyping at actin gene sequences reveals positive bands at 400 bps. **Ebied and Satour, (2019)** as shown in figure (3).

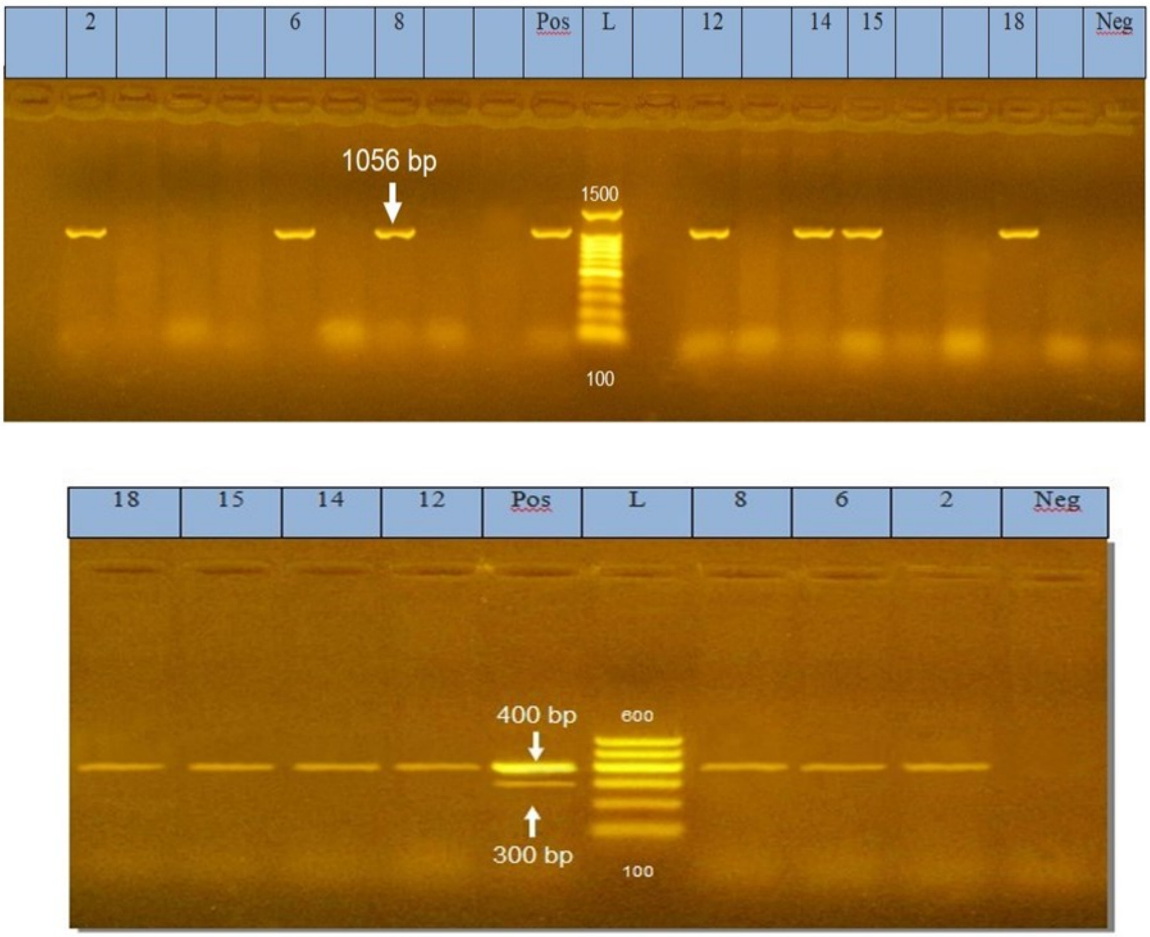

Fig. (3). Sub typing of *Cryptosporidium parvum* at actin gene sequences showing positive bands at 400bp. **Ebied and Satour, (2019)**.

Treatment and control of *Cryptosporidium*:
People with healthy immune systems will recover without treatment. Drinking lots of fluids helps in preventing dehydration, which is one way to manage diarrhea. While intravenous therapy may be required and nutritional support may be helpful, replacing fluids and electrolytes through oral rehydration solutions is the most important aspect of treatment **Zintl *et al.*, (2009).** Pregnant women and small children should drink enough of fluids during illness as they may be more susceptible to dehydration from diarrhea. Diarrhea can cause rapid fluid loss, which can be fatal for infants. Anti-diarrhea medications could be able to reduce diarrhea. Nitazoxanide has been used for treatment of diarrhea caused by *Cryptosporidium* in people with good immune systems **CDC, (2012).** halofuginone lactate has been used in both prevention and treatment of cryptosporidiosis in calves at a dose of 0.10 mg/kg of body weight per day for seven consecutive days. Halofuginone lactate treatment shortens the duration of diarrhea and oocyst discharge but does not entirely prevent or cure disease **Jarvie *et al.*, (2005) and Trotz-Williams *et al.*, (2011).** In order to prevent and control cryptosporidiosis, continuous efforts must be made to prevent the spread of *Cryptosporidium* through food, water and contact with animals and people who are affected. In any setting, practicing good hygiene is important.

Some studies done related to *Cryptosporidium* species in Egypt:
Wahba (1994) when examined faecal samples of different animals with modified Ziehl-Neelsen stain found *Cryptosporidium* oocysts in 6.6% buffalo calves, 8.2% in cattle calves, 5.2% in lambs and 2.5% in kids slaughters at Giza and Kalyobia abattoirs.

According to a study by **El-Seify *et al.* (2012)**, 698 fecal samples were examined with modified Ziehl-Neelsen staining technique for *Cryptosporidium* species oocysts. The prevalence of *Cryptosporidium* spp. was 34.1 %.

Satour (2012), examined 397 domestic birds, the highest infection rate with *Cryptosporidium* species oocysts was that in *Cryptosporidium baileyi* where it reached 23.5% and 13.7% in domestic duck and broiler chicken respectively, followed by *Cryptosporidium meleagridis* was 8.8% and 2.4% in farmed quail and broiler chicken respectively.

Abdel-Hady *et al.* (2014), examined 100 diarrheic fecal samples from calves aged 5 to 90 days to evaluate the presence of bovine corona viral antigen by ELISA method and *Cryptosporidium* oocysts with modified Ziehl-Neelsen staining technique. Ziehl-Neelsen positive specimens for *Cryptosporidium* were confirmed by PCR. Both coronaviral antigen and *Cryptosporidium* were detected in 3 out of 100 tested specimens.

In a study by **Essa *et al.* (2014),** A total of 717 fecal samples from Friesian and buffalo calves were collected for microscopical examination from Minufiya governorate. The results indicated that one-week-old calves had the highest percentage of *Cryptosporidium* (56.32%). The safranin staining method is used to examine these samples.

Mahfouz *et al.* (2014) claimed that a total of 2283 fecal samples were collected from farm animals and examined for detection of *Cryptosporidium* oocysts. The prevalence was 1.29%, 7.07% and 2.50% in buffalo, cattle and sheep respectively.

According to a study by **Ebied and Satour (2019**), by microscopic examination and PCR analysis, the prevalence of *Cryptosporidium parvum* in lambs and goat kids were 14% and 6.2%, and 27.7% and 8.3% respectively.

In study by **Hamza *et al.* (2020)** using Ziehl–Neelsen stain and Multiplex PCR for detection of *Cryptosporidium* spp.in diarrheic buffalo calves. The results revealed that prevalence of *C. parvum*, C.*bovis* and *C. andersoni were* 50%, 35% and 30% respectively. No *C. reyne* was detected in the examined samples.

Elmahallawy *et al.* (2022), examined 608 fecal samples collected from cattle and buffalo in Upper Egypt. The prevalence of *Cryptosporidium* spp. was 38.27% and 28.16% in cattle and buffalo respectively.

Recommendations and conclusion:
- Preventing the transmission of *Cryptosporidium* requires practicing basic good hand hygiene. Hands should be cleansed for at least 20 seconds with soap and water. Alcohol-based hand sanitizers do not completely kill *Cryptosporidium*.

- Avoid drinking untreated water from lakes, rivers, ponds and shallow wells, as well as swallowing the water you swim in.
- Clean any surfaces that have obvious contamination according to manufacturer's instructions. Use normal detergents in a washer/ dryer to clean clothes and bedding.
- Avoid swimming and water activities of any kind (lakes, splashpads, hot tubs and pools) if you've been sick.

Conclusion: *Cryptosporidium* is the second most common cause of moderate to severe diarrhea in infants under two years old and it is also a major global cause of mortality. *Cryptosporidium* is a serious global health concern, especially for immunocompromised individuals and children. The incidence of it varies widely and this wide variation in incidence can be attributed to a variety of factors, including the patient's age, immune status and environmental habitats. Cryptosporidiosis is a dangerous protozoal disease as its sporocysts excreted with faeces to outside the infected host already sporulated and not take a time to be sporulated outside the host like some other protozoa.

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