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Cryptosporidiosis in Immunocompromised Population: A Review of Neglected Global Disease

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Abstract

Cryptosporidiosis is a diarrheal disease caused by the protozoan Cryptosporidium spp. and is a major cause of morbidity and mortality in children and individuals with weakened immune systems, such as those with HIV/AIDS, cancer, or organ transplant recipients. This infection is transmitted via the fecal-oral route, primarily through contaminated water or food, with the most common species being C. hominis and C. parvum. Its pathogenesis involves invasion of intestinal epithelial cells, leading to impaired absorption and secretory diarrhea. Clinical symptoms range from asymptomatic to severe chronic diarrhea in immunocompromised patients. Diagnosis is made through microscopic examination, immunofluorescence, or PCR to detect oocysts or parasite DNA, with varying sensitivities. The mainstay of therapy is nitazoxanide, although its effectiveness is still limited in immunocompromised patients. Infection prevention emphasizes clean water, sanitation, and immune system strengthening, including the use of antiretroviral therapy for HIV patients. Thus, cryptosporidiosis remains a global health challenge that requires attention to early diagnosis, environmental control, and the development of more effective therapies in the future.

Keywords: Cryptosporidiosis, Infection, Intestinal epithelial cells, Chronic diarrhea

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INTRODUCTION

Cryptosporidiosis is a parasitic disease caused by the protozoan Cryptosporidium spp. This infection is particularly dangerous for immunocompromised patients, especially those with AIDS, cancer, and organ transplant recipients. In individuals with weakened immune systems, cryptosporidiosis can cause life-threatening chronic diarrhea and complications in other organs such as the bile ducts and lungs.[1,2]

Cryptosporidium infection in humans has a global prevalence of approximately 7.6%, with higher rates found in individuals from low-income countries, those with gastrointestinal disorders, children under five years of age, and populations living in rural or non-urban areas. Approximately 65% of children experience Cryptosporidium infection in their first two years of life. This infection is often associated with severe diarrhea, dehydration, and stunted growth in children under two years of age, particularly in South Asia. Recent studies estimate that Cryptosporidium is responsible for the deaths of more than 200,000 children under five each year in South Asia and sub-Saharan Africa.[2,3]

Cryptosporidium infection in humans is generally asymptomatic in most people, but it often causes gastroenteritis and presents as self-limiting diarrhea in immunocompetent individuals. Conversely, in immunocompromised individuals, the infection can cause severe, potentially fatal diarrhea that does not respond to conventional treatment.[3,4] The primary symptom of Cryptosporidiosis is diarrhea, often accompanied by nausea, abdominal pain, and fever. In immunocompromised patients, symptoms can be longer and more severe than in individuals with normal immune systems. Diagnosis is usually made through stool examination using acid-fast staining or molecular methods such as PCR. Major risk factors include recent chemotherapy, immunosuppressive therapy, hematopoietic stem cell transplantation, and severe neutropenia and lymphopenia.[2]

Treatment of cryptosporidiosis in immunocompromised patients is limited. Nitazoxanide is the primary drug used, but its effectiveness is limited in this patient group. The duration of treatment is generally around 14 days, but may be longer for patients with hematologic malignancies. Response to treatment tends to be poorer in immunocompromised patients than in those with normal immune systems.[2,3]

Prevention of Cryptosporidium infection is crucial for immunocompromised patients. Transmission can occur via the fecal-oral route or by inhalation of contaminated oocysts in droplets or fomites. Therefore, maintaining hand and environmental hygiene, as well as avoiding potentially contaminated water, is highly recommended. The use of antiretroviral therapy in HIV/AIDS patients has shown positive effects in reducing the frequency and severity of infections.[3–5]

In immunocompromised individuals, chronic and severe intestinal Cryptosporidiosis infection can cause long-term morbidity and high medical costs. Evidence regarding effective treatments for Cryptosporidiosis remains very limited. Further research is needed to develop better diagnostic methods, more effective treatment options, and appropriate prevention strategies for immunocompromised patients. Controlled studies with novel agents are needed to determine the optimal management of Cryptosporidiosis in this vulnerable population. Furthermore, a better understanding of the mechanisms of immunity to Cryptosporidium may aid the development of effective immunomodulatory therapies.[3–5]

Cryptosporidiosis is often underrecognized and underdiagnosed. Yet, Cryptosporidium is a cause of moderate to severe diarrhea in children under two years of age and a significant cause of death worldwide. Furthermore, treatment remains suboptimal, and there are currently no robust preventative measures. While most infections are self-limited in individuals with healthy immune systems, they can cause chronic symptoms, malnutrition, and other complications in immunocompromised individuals. This literature review aims to analyze the pathogenesis, diagnostic methods, and treatment of Cryptosporidium infections to provide a comprehensive understanding of the mechanisms of infection and its management, particularly in immunocompromised individuals.[5,6]

RESULTS AND DISCUSSION

Definition of Cryptosporidiosis

*Cryptosporidiosis*Cryptosporidiosis is an infectious disease caused by microscopic parasites of the genus Cryptosporidium in intestinal epithelial cells. This disease has received increased attention in recent years, particularly because of its impact on immunocompromised individuals, including kidney transplant recipients.[6]

Etiology Cryptosporidiosis is primarily caused by two species of Cryptosporidium: C. hominis and C. parvum. These protozoan parasites belong to the phylum Apicomplexa and can infect the gastrointestinal tract of humans and various animals. Transmission occurs via the fecal-oral route, usually through the consumption of contaminated water or food, or through direct contact with infected individuals or animals.[6]

Cryptosporidiosis is now recognized as a significant threat to HIV-infected individuals, with a lifetime risk of infection of approximately 10%. However, it is also responsible for significant outbreaks of waterborne diarrhea in immunocompetent individuals and causes diarrhea in children and the immunocompromised in both developed and developing countries. In immunocompetent individuals, the infection usually causes acute, self-limiting diarrhea, while patients with drug-induced immunodeficiency or AIDS experience more severe and persistent clinical symptoms, which can even become chronic, leading to electrolyte imbalance, wasting, and even death. Since 2004, Cryptosporidiosis has been included in the WHO's 'Neglected Diseases Initiative', in recognition of the importance of this infection in developing countries.[7]

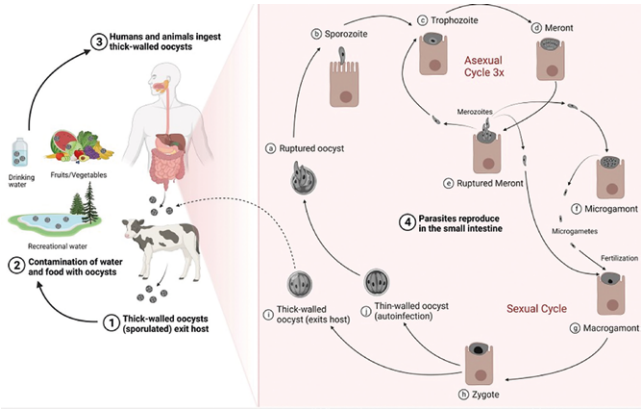

Figure 1. Life Cycle and Transmission of Cryptosporidium[7]

The life cycle of Cryptosporidium involves asexual and sexual stages, with the infectious stage being the oocyst. These oocysts are highly resistant to environmental stressors and common disinfectants, contributing to their persistence in water sources and the environment. This resilience makes Cryptosporidium a significant public health problem, particularly in areas with inadequate water treatment facilities.[6] According to Figure 2.1, infection begins when a person ingests protozoan oocysts that have been shed in the feces of an infected human or animal. The 50% infectious dose (ID_{50}) in an immunocompetent individual is approximately 132 oocysts.[5] The life cycle and transmission of Cryptosporidium proceeds sequentially as follows:

Initially, thick-walled, sporulated oocysts are released in the feces of infected hosts, contaminating food and water sources.

Transmission occurs primarily through consumption of water or food contaminated by the host.

After ingestion, the oocyst ruptures and releases four sporozoites.

These sporozoites have the ability to move (gliding motility), enter the host epithelial cells, and develop into trophozoites.

The trophozoite then undergoes three asexual divisions to produce meronts which will release eight merozoites.

Merozoites from the third asexual cycle will develop into the sexual stage after re-infecting the host cell, namely becoming microgramont (male) and macrogramont (female).

Microgametes released from the microgramont will fertilize the macrogramont and form a diploid zygote.

This zygote undergoes meiosis and sporogony to produce thin-walled or thick-walled oocysts, each containing four haploid sporozoites.

Thick-walled oocysts are released into the intestinal lumen and excreted into the environment, where they are immediately infectious. In contrast, thin-walled oocysts rupture within the host and cause auto-infection.

Epidemiology of Cryptosporidiosis

The epidemiology of cryptosporidiosis has shown significant variation both internationally and within specific regions over the past decade. Recent studies have provided valuable insights into the distribution and transmission patterns of this parasitic infection. Internationally, cryptosporidiosis remains a major cause of diarrheal disease, particularly in low- and middle-income countries. Cryptosporidium hominis is the dominant species infecting humans in most low- and middle-income countries. Five subtype families of C. hominis are commonly found in different regions. In contrast, Cryptosporidium parvum infections in these regions are primarily caused by the anthropotic subtype IIc family rather than the zootic subtype II a family.[7]

Human-to-human transmission can occur among close contacts, such as in childcare settings. Waterborne transmission is very common. Oocysts are not killed by routine chlorination. In conclusion, although specific data on Cryptosporidiosis in Indonesia over the past decade are limited, global trends suggest that the country may face challenges similar to those in other low- and middle-income countries. More targeted research and improved surveillance efforts are needed to fully understand the epidemiology of Cryptosporidiosis in Indonesia and to develop effective prevention and control strategies. [8,7]

Pathogenesis of Cryptosporidiosis

Pathogenesis begins with the entry of Cryptosporidium. Transmission occurs through zoonotic transmission, human-to-human transmission, waterborne transmission, food transmission, and hospital transmission. Zoonotic transmission from livestock is common, particularly in children, including those from urban environments who visit educational farms or rural activity centers. Pets have long been considered a potential source of human Cryptosporidiosis. However, pets are generally infected with host-specific and non-zoonotic Cryptosporidium species; therefore, they are not considered an important reservoir of infection. Cryptosporidiosis is rare in adults in rural areas, likely due to frequent exposure and the development of immunity. [9,10] Human-to-human transmission has been reported among family members, partners (sexual contact involving fecal contact), children in childcare centers, and hospital patients and staff. Outbreaks in childcare centers have been reported in the United Kingdom and the United States, primarily as a result of direct fecal-oral transmission (human-to-human transmission), although the initial infection can be zoonotic. Infected adults may have been infected by young children at home or in their workplace. Cryptosporidium is also a cause of traveler's diarrhea, although not as frequently as Giardia.[3,5]

PathogenesisThe pathophysiology of cryptosporidiosis involves complex interactions between the parasite and the host, leading to intestinal dysfunction and clinical manifestations. Human-to-human transmission can occur among close contacts, such as in childcare settings. Waterborne transmission very general. Oocyst resistant to routine-chlorination. Cryptosporidium *parvum*,The primary causative agent of Cryptosporidiosis initiates infection by attaching to and invading the epithelial cells lining the intestinal tract. This process is mediated by surface glycoproteins, such as gp40 and gp15, encoded by the Cpgp40/15 gene. [9] These proteins play a crucial role in parasite attachment and host cell invasion, with gp40 being particularly important because it binds specifically to host cells and can be neutralized.

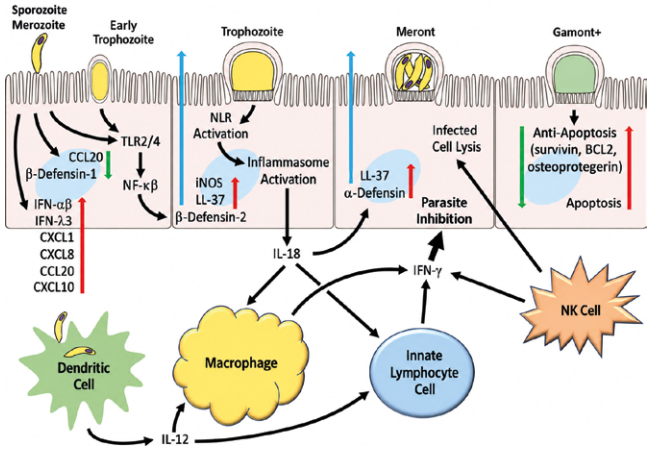

Figure 2. Protective innate response to Cryptosporidium

Figure 2.2 is a general schematic depicting the initial and subsequent host cell responses to Cryptosporidium infection. The progression of the parasite life cycle stages (from left to right) after invasion by sporozoites (and merozoites) is shown representatively, and the schematic pathway is not necessarily restricted to a specific stage. Parasite infection results in suppression of several chemokines (e.g., CCL2) and β-defensin-1. Toll receptors (TLR2 and TLR4) are activated, leading to the production and secretion of antimicrobial peptides (e.g., LL-37 and β-defensin-2). Inflammasome activation occurs, triggering the production of IL-18. Various chemokines (e.g., CCL2, CXCL1, CXCL8, CXCL10), interferons (IFN-α, IFN-β, and IFN-λ), and cytokines are released. Infection by C. parvum induces apoptosis, but this is counterbalanced by the activation of anti-apoptotic genes (such as survivin, BCL2, and osteoprotegerin). Dendritic cells produce IL-12 in response to parasites or parasite antigens, and together with IL-18 released from epithelial cells, it helps activate macrophages to produce IFN-γ. Innate lymphocytes (ILC1) and natural killer cells also produce IFN-γ, which act on epithelial cells to inhibit parasites.[4,9,11]

T cells play a crucial role in the elimination of Cryptosporidium infection. In humans, T cell immunosuppression caused by other infections or chemotherapy

increases susceptibility to infection. Furthermore, severe cryptosporidiosis has been reported in individuals with mutations affecting the costimulatory molecules CD40 or CD40L, which are required for T cell activation. In particular, CD4+ T cells are essential for controlling infection and achieving sterile immunity in adults, while the role of CD8+ T cells is not fully understood. Consistent with these findings, a low CD4+ T cell count (<100 cells/mm^3) indicates a poor prognosis if infection occurs. The most important cytokine in the fight against Cryptosporidium is interferon-γ (gamma interferon), and its primary source is CD4+ T cells. Therefore, a Th1 (T helper 1) immune response appears to play a role in clearing this infection. Interleukin 12 (IL-12), produced by dendritic cells and macrophages upon antigen exposure, plays a key role in activating interferon-γ production by T cells. [9-11]

During infection, antigen-specific antibodies, including IgG, IgA, and IgM, can be detected in serum. If the infection is successfully controlled, IgM levels decline rapidly, while IgG levels may persist for several months. Experimental studies in mouse models and data from AIDS patients suggest that, although antibodies may contribute to a protective immune response against Cryptosporidium, they are not considered a critical component in the development of immunity against this parasite.[10]

Watery diarrhea is a hallmark of non-inflammatory infections of the small intestine, particularly those associated with toxin-producing organisms and enteric viruses. Several mechanisms have been proposed to explain these symptoms, including decreased absorptive capacity, particularly for water and electrolytes, increased secretory capacity due to intestinal crypt hypertrophy, osmotic effects due to loss of enzymes on the surface of microvilli (e.g., disaccharidases) leading to sugar malabsorption, increased chyme osmolality and fermentation of sugars by microbes in the large intestine, which may explain the characteristic foul odor of stool, and toxic activity of parasites or their products.[9-11]

Recent research has also highlighted the potential long-term consequences of Cryptosporidium infection. The parasite has been linked to oncogenesis, suggesting that chronic infection may have broader effects than previously understood. [13] Furthermore, the parasite's ability to modulate host cell gene expression, cytoskeleton rearrangements, and signal transduction pathways suggests a sophisticated level of host manipulation that contributes to its pathogenesis. [14]

Clinical Manifestations of Cryptosporidiosis

*Cryptosporidiosis*It presents with a wide range of clinical manifestations, ranging from asymptomatic infection to severe, life-threatening disease. The severity and duration of symptoms are largely influenced by the host's immune status, with immunocompromised individuals often experiencing more severe and prolonged manifestations.[15]

The most common and characteristic symptom of cryptosporidiosis is diarrhea, which can be acute or chronic. In individuals with healthy immune systems, diarrhea is usually self-limiting, lasting about 1-2 weeks, with a variety of symptoms occurring. Initial symptoms can last from one to several days and include malaise, abdominal pain, nausea, and loss of appetite. Gastrointestinal symptoms usually appear abruptly, with stools described as watery, greenish, containing mucus in some cases, without blood or pus, and having a strong odor. Patients may have more than 20 bowel movements per day, but usually between three and six. Other symptoms include colicky abdominal pain (cramps), especially after eating, loss of appetite, nausea and vomiting, flatulence, and significant weight loss. Systemic flu-like effects, such as malaise, headache, muscle aches, and fever, are also common. Gastrointestinal symptoms generally last about seven to 14 days, but weakness, lethargy, mild abdominal pain, and occasional loose stools may persist for up to a month. Reported complications include pancreatitis (accompanied by severe abdominal pain), toxic megacolon, and reactive arthritis. In patients with normal immune systems, death from cryptosporidiosis is rare. After an incubation period of about 1 week, patients may remain asymptomatic or experience watery, bloodless diarrhea, sometimes accompanied by abdominal pain, nausea, loss of appetite (anorexia), fever, and weight loss lasting 1–2 weeks.[15]

Abdominal pain is another common symptom of cryptosporidiosis. Studies have shown a significant link between Cryptosporidium infection and abdominal pain.16 This discomfort can range from mild cramping to more severe pain, often accompanied by episodes of diarrhea.[15] For patients with chronic conditions, such as those undergoing hemodialysis for chronic kidney disease, cryptosporidiosis can pose additional challenges. These patients may experience a higher prevalence of infection and are more likely to suffer from symptoms such as diarrhea and abdominal pain.[16]

***Update* Diagnosis of Cryptosporidiosis**

The diagnosis of cryptosporidiosis involves a variety of laboratory techniques, each with its own advantages and limitations. Because cryptosporidiosis is a major cause of chronic and persistent diarrhea, particularly in children and immunocompromised patients, accurate diagnosis is crucial for effective management and treatment.[19,20]

Current diagnostic methods in most laboratories worldwide rely heavily on the identification of oocysts in feces, although the parasite can also often be detected in histological sections of intestinal biopsies. Oocysts are typically spherical and measure 4–6 µm. Three commonly used staining methods are auramine staining, modified Ziehl–Neelsen staining, and immunofluorescence using monoclonal antibodies against oocysts. However, these techniques are relatively insensitive. Detection thresholds considered 100% reliable have been found to be 10,000 oocysts/gram in loose stool, 50,000 oocysts/gram in solid stool using immunofluorescence, and 500,000 oocysts/gram in solid stool using acid-fast staining. Conventional stool examination for eggs and parasites cannot detect Cryptosporidium.[19,21] Conventional microscopy using modified Ziehl–Neelsen (ZN) staining remains the common diagnostic method. This technique involves staining stool samples to identify Cryptosporidium oocysts. However, while specific, this technique has limited sensitivity. A study comparing various diagnostic methods found that modified ZN staining detected Cryptosporidium in only 29.4% of AIDS cases with diarrhea, indicating its lower sensitivity compared to other methods.[19] In a direct comparison of seven diagnostic tests, the modified ZN staining had the lowest sensitivity, followed by auramine-phenol fluorescence microscopy, and then immunofluorescence microscopy.[21] Figure 2.3 Stool smear stained with the modified ZN method showing Cryptosporidium parvum oocysts, examined using an oil immersion objective at 100x magnification.[22]

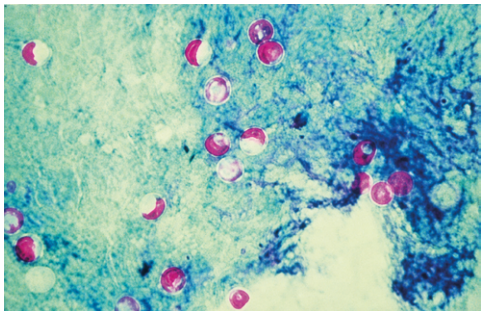

Figure 2. Modified ZN assay for Cryptosporidium[22]

Enzyme-linked immunosorbent assay (ELISA) antigen detection offers better sensitivity than microscopy. In the same comparative study, antigen ELISA detected Cryptosporidium in 67.3% of cases, significantly outperforming modified ZN staining. This method is based on the detection of specific Cryptosporidium antigens in stool samples and offers a more sensitive diagnostic approach.[20]

Molecular techniques, particularly polymerase chain reaction (PCR), have emerged as the most sensitive diagnostic tool for Cryptosporidiosis. In the aforementioned study, nested PCR detected Cryptosporidium in 77.5% of cases, surpassing modified ZN staining and antigen ELISA. PCR-based methods amplify parasite-specific DNA sequences, enabling highly sensitive and specific detection. Although more expensive and time-consuming than microscopy, PCR can be adapted for batch analysis, potentially reducing costs. 19 Multiplex PCR assays have shown promise and are now emerging as the leading diagnostic technique. For large sample sizes, they are more efficient than microscopy. Some more robust PCR assays, such as the ParaGENIE Crypto-Micro Real-Time PCR, allow for the simultaneous diagnosis of multiple parasites, which is particularly helpful in detecting Cryptosporidium spp. and microsporidia, both of which are global public health concerns.[21]

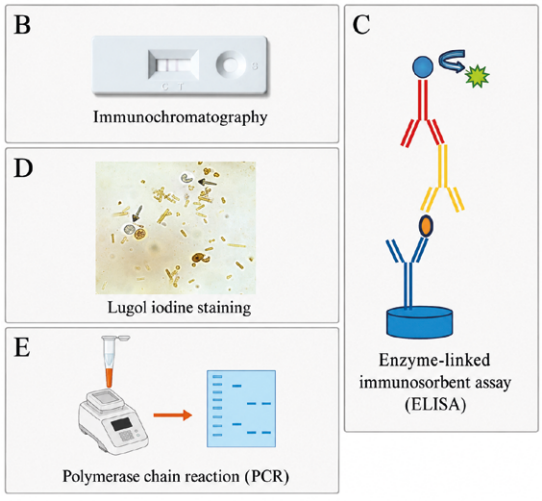

Figure 2. Laboratory examinations to detect Cryptosporidium[7]

Figure 2.4 describes the types of ancillary tests for detecting Cryptosporidium. The primary methods used for detecting Cryptosporidium in stool samples. The first test involves microscopic identification of Cryptosporidium oocysts stained with a

modified Ziehl–Neelsen stain. The top panel shows oocysts appearing bright red against a background of blue-green fecal debris and yeast. The bottom panel shows colorless oocysts associated with a resolving infection. A second test, an immunochromatographic assay, can be used to detect Cryptosporidium oocysts in stool samples. A third test that can be used is an ELISA test for the detection of Cryptosporidium antigens in stool samples, and a rapid strip test is now also available. The fourth test involves detecting colorless Cryptosporidium oocysts (marked with arrows) with Lugol's iodine solution. The oocysts appear similar to yeast but are colorless. The final test involves detecting Cryptosporidium using PCR.[7]

It is important to note that a general stool test is often uninformative for detecting Cryptosporidium oocysts, highlighting the need for specialized diagnostic procedures. In some cases, additional tests, such as blood tests, may be performed to assess the patient's overall health and detect any associated complications.[21]

Diarrhea due to cryptosporidiosis is watery diarrhea without symptoms of dysentery or inflammation. Differential diagnosis of cryptosporidiosis includes diarrhea due to other amebiasis, such as isosporiasis and giardiasis. The absence of blood, pus, cells, or Charcot–Leyden crystals distinguishes cryptosporidiosis from some types of acute bacterial diarrhea, as well as from amebiasis and isosporiasis. In patients with normal immune systems, the symptoms of cryptosporidiosis are similar to those of giardiasis or cyclosporiasis. Severe abdominal pain and cramps are generally more common in cryptosporidiosis, but bloating and weakness tend to be less common. In immunocompromised patients, particularly those with AIDS, isosporiasis is clinically difficult to distinguish from cryptosporidiosis, but it can be diagnosed by identifying the causative organism in the stool, where Charcot–Leyden crystals may also be present. This infection responds to treatment with cotrimoxazole, as does cyclosporiasis.[19,21]

Update on Cryptosporidiosis Management

Management of cryptosporidiosis primarily focuses on supportive care and targeted pharmacological interventions, with strategies varying based on the patient's immune status and symptom severity. For immunocompetent individuals with acute, self-limiting cryptosporidiosis, the primary treatment is supportive care. This includes oral or, in severe cases, intravenous rehydration to replace fluid and electrolyte losses caused by diarrhea. Antimotility agents may be used cautiously to provide symptomatic relief, but should be avoided in cases of severe or bloody diarrhea.[22]

*Nitazoxanide*It is currently the only FDA-approved drug for treating cryptosporidiosis in immunocompetent patients. It has demonstrated efficacy in reducing the duration and severity of diarrhea in this population. The typical course of treatment for adults is 500 mg twice daily for 3 days, with dose adjustments for pediatric patients.[2,23]

Managing cryptosporidiosis in immunocompromised patients, such as those with HIV/AIDS or organ transplant recipients, presents a greater challenge. In these cases, the primary goal is to improve the patient's immune status whenever possible. For HIV patients, this often involves optimizing antiretroviral therapy to increase CD4+ T-cell counts. In transplant recipients, careful adjustment of the immunosuppressive regimen may be necessary to balance infection control with graft preservation.[2,24]

Other treatment that still under study is immunotherapy. Immunoglobulin from bovine colostrum or human serum has shown positive results in uncontrolled studies, but results from randomized, double-blind trials have been disappointing. Second, somatostatin analogs: Like octreotide, are effective in reducing nonspecific diarrhea but do not cure cryptosporidiosis parasitically. Third, HAART (antiretroviral therapy): Highly effective in reducing the incidence and severity of cryptosporidiosis by increasing CD4+ cell counts. This therapy may also directly inhibit Cryptosporidium proteases.[9,32]

Combination therapies, such as azithromycin + paromomycin or azithromycin + nitazoxanide, have shown promising results, especially in immunocompromised patients. Triple therapy has even shown complete cure in kidney transplant patients. Combining antimicrobials with HAART accelerates clinical response in AIDS patients. However, large-scale controlled trials are needed for validation.[32,33]

Cryptosporidiosis in the Immunocompromised

Cryptosporidiosis in immunocompromised patients presents significant clinical challenges, often manifesting as severe and potentially life-threatening disease. This parasitic infection, caused by Cryptosporidium species, particularly affects individuals with weakened immune systems, such as those with HIV/AIDS, organ transplant recipients, and patients undergoing immunosuppressive therapy. In immunocompromised

patients, Cryptosporidiosis often causes prolonged or persistent diarrhea, which can lead to severe dehydration, malnutrition, and wasting. The severity of the infection is closely related to the patient's immune status, with those with CD4 counts below 200 cells/mm^3 being at highest risk for severe disease.[26,27] In fact, an isolate rate of 55.0% was observed in patients with CD4 counts less than 200 cells/mm^3, highlighting the vulnerability of individuals with severely compromised immune systems.[26]

The clinical presentation in immunocompromised patients can be more severe and prolonged than in individuals with a competent immune system. Symptoms can include profuse watery diarrhea, abdominal pain, nausea, vomiting, and weight loss. In some cases, the infection can spread beyond the gastrointestinal tract, leading to biliary tract involvement or even extraintestinal manifestations.[28] Cryptosporidiosis infection in immunocompromised patients can involve various organs, such as the pharynx, esophagus, stomach, duodenum, jejunum, ileum, appendix, colon, rectum, gallbladder, bile duct, pancreatic duct, and respiratory tract. Cryptosporidial cholecystitis (with symptoms of severe pain in the right upper quadrant), sclerosing cholangitis, pancreatitis, hepatitis, and respiratory tract symptoms can occur, with or without diarrhea. The clinical picture may also include other symptoms of HIV infection and there is often co-infection with other pathogens such as Cytomegalovirus, Pneumocystis jiroveci, and Toxoplasma gondii.[33,32]

Research into new treatment options for cryptosporidiosis in immunocompromised patients is ongoing. New approaches, such as fecal microbiota transplantation (FMT), are being explored as potential therapeutic options, particularly in cases refractory to conventional treatments.[34,35]

Recent advances in the management of opportunistic infections in immunocompromised patients have highlighted the importance of integrating improved diagnostic strategies with individualized therapeutic approaches. Early and accurate detection using molecular-based techniques enables timely intervention and may reduce disease severity and complications. In addition, multidisciplinary management strategies, including optimization of immune status and targeted antimicrobial therapy, are essential to improve clinical outcomes in this high-risk population.[36-39]

CONCLUSIONS

Cryptosporidiosis poses a serious threat to immunocompromised patients, particularly those with HIV/AIDS and organ transplant recipients. In these populations, infection can cause severe, life-threatening chronic diarrhea, with the severity closely correlated with the patient's immune status. Diagnosis of the disease is challenging, requiring advanced techniques such as PCR for accurate detection.

Treatment of cryptosporidiosis in immunocompromised patients is challenging, with limited therapeutic options. The primary focus of treatment is improving the patient's immune status, particularly through optimizing antiretroviral therapy in HIV/AIDS patients. Supportive care, such as aggressive rehydration, is also crucial. Prevention through hygiene education and avoiding sources of contamination are crucial aspects of disease management.

To improve treatment, the development of new, more effective drugs, improved screening and early diagnosis, and further research into disease pathogenesis are needed. A multidisciplinary approach and increased access to comprehensive care are essential to optimize clinical outcomes for immunocompromised patients infected with cryptosporidiosis.

Ethics Statement and Conflict of Interest Disclosures

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REFERENCES

1. Hunter PR, Nichols G. Epidemiology and clinical features of Cryptosporidium infection in immunocompromised patients. Clin Microbiol Rev. 2015;15(1):145–54.
2. Mann I and Okhuysen PC. Cryptosporidiosis in Immunocompromised Patients with Cancer Receiving Chemotherapy, CAR-T Cell Therapy and Hematopoietic Stem

Cell Transplantation: A Retrospective Analysis. Open Forum Infect Dis. 2023;10(Suppl 2).
3. Fahmy AM, El-Enain G, Abdou AMH, Elhakeem M. Comparative Study between Wild and Commercial Egyptian Lactobacillus reuteri-Antagonizing Effects in Cryptosporidiosis Models. Adv Anim Vet Sci. 2021; 5-9.
4. Sponseller JK, Griffiths JK, Tzipori S. The evolution of respiratory Cryptosporidiosis: evidence for transmission by inhalation. Clin Microbiol Rev. 2015;27(3):575–86.
5. Kosik-Bogacka D, Łanocha-Arendarczyk N and Korzeniewski K. Cryptosporidium spp. Infection in Adult Kidney Transplant Patients: A Systematic Review and Meta-Analysis. J Clin Med. 2024;13(21).
6. Gerace E, Presti VDML and Biondo C. Cryptosporidium Infection: Epidemiology, Pathogenesis, and Differential Diagnosis. European Journal of Microbiology and Immunology. 2019; 4: 119–23.
7. Yang X, Guo Y, Xiao L, Feng Y. Molecular Epidemiology of Human Cryptosporidiosis in Low- and Middle-Income Countries. Clin Microbiol Rev. 2021;34(2).
8. Nwosu A, Berke O, Trotz-Williams LA, Pearl DL. Exploring the geographical distribution of human cryptosporidiosis in Southern Ontario from 2011 to 2014. Zoonoses Public Health. 2022;69(5):425–38.
9. Diptyanusa and Sari. Treatment of human intestinal cryptosporidiosis: A review of published clinical trials. International Journal for Parasitology: Drugs and Drug Resistance. 2021; 17: 128–138.
10. Khan SM and Witola WH. Past, current, and potential treatments for cryptosporidiosis in humans and farm animals: A comprehensive review. Front Cell Infect Microbiol. 2023: 1-10.
11. Cevallos AM, Zhang X and Waldor MK. Molecular cloning and expression of a gene encoding Cryptosporidium parvum glycoproteins gp40 and gp15. Infect Immune. 2015;68(7):4108–16.
12. Balendran T, Iddawela D, Lenadora S. Cryptosporidiosis in a Zoonotic Gastrointestinal Disorder Perspective: Present Status, Risk Factors, Pathophysiology, and Treatment, Particularly in Immunocompromised Patients. J Trop Med. 2024; 64; 393-75.
13. Sawant M, Benamrouz-Vanneste S and Meloni D. Putative SET-domain methyltransferases in Cryptosporidium parvum and histone methylation during infection. Virulence. 2022;13(1):1632–50.
14. In Genova BM and Tonelli RR. Infection Strategies of Intestinal Parasite Pathogens and Host Cell Responses. Front Microbiol. 2016;7:256.
15. Adamu H, Petros B and Zhang G. Distribution and clinical manifestations of Cryptosporidium species and subtypes in HIV/AIDS patients in Ethiopia. PLoS Negl Trop Dis. 2014;8(4):2831.
16. Ibrahim SS, Hassan M and Ismail MAM. Cryptosporidiosis Prevalence Associated With Gastrointestinal Manifestations Among Hemodialysis Patients With Chronic Renal Disease In Beni-Suef University Hospitals, Beni-Suef, Egypt. J Egypt Soc Parasitol. 2022: 1-2.
17. Prabakaran M, Weible LJ and Champlain JD. The Gut-Wrenching Effects of Cryptosporidiosis and Giardiasis in Children. Microorganisms. 2023;11(9).
18. Insulander M, Silverlås C, Lebbad M, Karlsson L, Mattsson JG, and Svenungsson B. Molecular epidemiology and clinical manifestations of human cryptosporidiosis in Sweden. Epidemiol Infect. 2015;141(5):1009– 20.
19. Khurana S dan Chaudhary P. Laboratory diagnosis of cryptosporidiosis. Trop Parasitol. 2018;8(1):2–7.
20. Uppal B, Singh O, Chadha S dan Jha AK. A comparison of nested PCR assay with conventional techniques for diagnosis of intestinal cryptosporidiosis in AIDS cases from northern India. J Parasitol Res. 2015; 706-105.
21. Germanovich NA dan Kuznetsova N V. Diagnosis and treatment of Cryptosporidiosis in dogs. Leg Regul Vet Med. 2024: 1-2.
22. Saccio SM. Cryptosporidium and cryptosporidiosis. In: Oxford Textbook Medicine Infection. 5th ed. United Kingdom. Oxford University Press; 2015. p. 721-8.
23. Grossman T, Ken-Dror S dan Pavlotzky E. Molecular typing of Cryptosporidium in Israel. PLoS One. 2019;14(9): 219977.
24. Shrateh ON, Jobran A, Zaid MA dan Saleh M. Successful management of life-threatening post-COVID-19 cryptosporidiosis in a renal transplant patient: a case report. Pan Afr Med J. 2023;45:10.
25. da Silva DRR, de Oliveira TCB, Marta B, Baptista CB, Bottaro M dan Bresciani KDS. Vaccine development for cryptosporidiosis: Systematic review. Res Soc Dev. 2021; 1-2.
26. Yunusa T, Kolade-Yunusa dan Oluseyi H. Prevalence of Cryptosporidiosis among HIV Seropositive Patients in a Tertiary Health Institution, Nigeria. In: ; 2015. 1-2.
27. Piazzesi A, Pane S dan Russo A. Case Report: The impact of severe cryptosporidiosis on the gut microbiota of a pediatric patient with CD40L immunodeficiency. Front Cell Infect Microbiol. 2023;13:1281440.
28. Abubakar I, Aliyu SH, Arumugam C, Hunter PR dan Usman NK. Prevention and treatment of cryptosporidiosis in immunocompromised patients. Cochrane database Syst Rev. 2017;(1):4932.
29. Kadappu KK, Nagaraja M V, Rao P V dan Shastry BA. Azithromycin as treatment for cryptosporidiosis in human immunodeficiency virus disease. J Postgrad Med. 2022;48(3):179–81.
30. Cabada MM dan White ACJ. Treatment of cryptosporidiosis: do we know what we think we know? Curr Opin Infect Dis. 2015;23(5):494–9.
31. Jameson JL, Fauci AS, Kasper DL, Hauser SL dan Longo DL. Cryptosporidiosis. In: Harrison's Manual of Medicine. 20th ed. United States. Mc Graw Hill; 2020. p. 855-6.
32. Kelly P dan Siwila J. Intestinal Protozoa, The Coccidia. In: Manson's Tropical Disease. 24th ed. United Kingdom. Elsevier; 2024. p. 692-4.
33. Sinto R, Nelwan EJ dan Shakinah S. Diare Akut Karena Infeksi. In: Buku Ajar Ilmu Penyakit Dalam FK UNAIR. Edisi VII. Jakarta: PIP Interna; 2024. p. 702-5.
34. Beeching N dan Beadsworth M. Gastrointestinal Presentations. In: Tropical Medicine. 7Th Ed. United Kingdom: Wiley Blackwell; 2015. p.7-8.
35. Lemieux MW, Sonzogni-Desautels K dan Ndao M. Lessons Learned from Protective Immune Responses to Optimize Vaccines against Cryptosporidiosis. Pathogens. 2018; 7: 3-4.
36. Baiceanu AM, Spataru TI, Cozma M, Popescu R, Negreanu L. Patient-reported outcomes: a compass through inflammatory bowel disease journey. Medicina Moderna. 2024;31(4):305. https://doi.org/10.31689/rmm.2024.31.4.305
37. Jabbar MF, Aubaid AH. Evaluating the role of biomarkers in catheter-related urogenital infections. Medicina Moderna - Modern Medicine. 2025;32(4):393. https://doi.org/10.31689/rmm.2025.32.4.393
38. Jasim SK, Al-Momen H, Ibrahim HAR, et al. Prevalence of thyroid dysfunction among postmenopausal women in Baghdad Medical City. Medicina Moderna - Modern Medicine. 2025;32(4):411. https://doi.org/10.31689/rmm.2025.32.4.411