**Name of Journal: *World Journal of Transplantation***

**ESPS Manuscript NO: 24806**

**Manuscript Type: Review**

***Cryptosporidium* infection in solid organ transplantation**

Florescu DF *et al*. *Cryptosporidium* in transplantation

**Diana F Florescu, Uriel Sandkovsky**

**Diana F Florescu, Uriel Sandkovsky,** Transplant Infectious Diseases Program, Division of Infectious Diseases, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE 68198-5400, United States

**Diana F Florescu,** Division of Transplant, Department of Surgery, University of Nebraska Medical Center, Omaha, NE 68198-3285, United States

**Author contributions:** Florescu DF and Sandkovsky U contributed equally in the design, data collection, interpretation, drafting and final approval of the article.

**Conflict-of-interest statement:** Dr. Diana Florescu received a grant from Chimerix Inc.; grant from CLS Behring; consulting for Chimerix Inc. and CLS Behring. Dr. Uriel Sandkovsky received a research grants from from CLS Behring, ViiV healthcare, GSK, Pfizer; consulting for Rib-X pharmaceuticals.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to: Diana F Florescu, MD,** Transplant Infectious Diseases Program, Division of Infectious Diseases, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE 68198-5400, United States. dflorescu@unmc.edu

**Telephone:** +1-402-5598650

**Fax:** +1-402-5595581

**Received:** February 10, 2016

**Peer-review started:** February 12, 2016

**First decision:** April 15, 2016

**Revised:** April 22, 2016

**Accepted:** June 14, 2016

**Article in press:**

**Published online:**

**Abstract**

Diarrhea is a common complication in solid organ transplant (SOT) recipients and may be attributed to immunosuppressive drugs or infectious organisms such as bacteria, viruses or parasites. *Cryptosporidium* usually causes self-limited diarrhea in immunocompetent hosts. Although it is estimated that cryptosporidium is involved in about 12% of cases of infectious diarrhea in developing countries and causes approximately 748000 cases each year in the United States, it is still an under recognized and important cause of infectious diarrhea in SOT recipients. It may run a protracted course with severe diarrhea, fluid and electrolyte depletion and potential for organ failure. Although diagnostic methodologies have improved significantly, allowing for fast and accurate identification of the parasite, treatment of the disease is difficult because antiparasitic drugs have modest activity at best. Current management includes fluid and electrolyte replacement, reduction of immunosuppression and single therapy with Nitazoxanide or combination therapy with Nitazoxanide and other drugs. Future drug and vaccine development may add to the currently poor armamentarium to manage the disease. The current review highlights key epidemiological, diagnostic and management issues in the SOT population.

**Key words:** *Cryptosporidium*; Solid organ transplantation; Diarrhea; Nitazoxanide; Antiparasitic drugs

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Diarrhea caused by *Cryptosporidium* is a serious and underrecognized cause of diarrhea in solid organ transplant recipients. The most important diagnostic challenge is low index of suspicion, since many new diagnostic methods have improved detection of the parasite. Treatment can be challenging as the disease may cause severe dehydration and antiparasitic drugs have modest activity. Electrolyte and fluid replacement, reduction of immunosuppression and antiparasitic therapy are the cornerstones of management. Newer antiparasitic drugs and vaccines may help manage the disease in the future.

Florescu DF, Sandkovsky U. *Cryptosporidium* infection in solid organ transplantation. *World J Transplant* 2016; In press

**INTRODUCTION**

*Cryptosporidium* is a parasitic protozoan causing a gastroenteritis syndrome[[1](#_ENREF_1)]. It is a common intestinal pathogen, not detected by routine ova and parasite evaluation. Because testing for *Cryptosporidium* is not routinely sought, the infection is often underdiagnosed, posing important epidemiological problems. In immunocompetent persons, cryptosporidiosis is usually a self-limited disease lasting between just a few days up to 10-14 d[[1](#_ENREF_1),[2](#_ENREF_2)]. In immunocompromised patients, clinical presentation can vary from asymptomatic to acute gastroenteritis, chronic diarrhea or even extra-intestinal manifestations[[1](#_ENREF_1),[3-24](#_ENREF_3)]. The parasite binds on the apical surface of the intestinal epithelium fostering its own reproduction and causing direct injury of the epithelial cells and a local inflammatory response, leading to impairment of the absorption and secretory function of the intestine[[1](#_ENREF_1),[25](#_ENREF_25)].Several *Cryptosporidium spp.* have been associated with human disease, of which *Cryptosporidium parvum* (*C. parvum*) and *Cryptosporidium hominis* (*C.* *hominis*) account for > 90% of the cases[[26-28](#_ENREF_26)]. In this review, we examine the current epidemiology of Cryptosporidium in solid organ transplant (SOT) recipients, review its pathogenesis and clinical manifestations, diagnostic approach, discussion-available treatment options and possible future approaches.

**EPIDEMIOLOGY**

The incidence and prevalence of cryptosporidiosis varies according to socioeconomic status in both developed and developing countries. In the United States, it is estimated that 748000 cases occur every year[[29](#_ENREF_29)], but prevalence in patients with diarrhea can be as high as 12% in developing countries. In SOT recipients are largely unknown (Table 1). Cryptosporidiosis is most likely underreported in SOT, with most of the data being confined to case reports and case series, many of them from endemic areas such as Brazil, India and Middle East[[3](#_ENREF_3),[10](#_ENREF_10),[30](#_ENREF_30),[31](#_ENREF_31)]. In a study from Brazil, *Cryptosporidium* infections were more common in renal transplant recipients (35%) and hemodialysis patients (25%) compared to the control group (17.4%)[[30](#_ENREF_30)]. Similarly, in a study from Turkey, the prevalence of cryptosporidiosis in kidney transplant recipients was found to be significantly higher than in healthy immunocompetent patients (21.2% *vs* 3.0%, *P =* 0.01)[[10](#_ENREF_10)]. A recent study from India, shows that cryptosporidiosis accounts for the majority of infectious diarrhea (28.5%) in adult transplant recipients[[3](#_ENREF_3)]. Children and immunocompromised patients are disproportionately affected, especially in developing countries[[32](#_ENREF_32)]. Between 1.8% and 3.8% of immunocompetent children in child-care settings in the United States, United Kingdom, Spain, and France have been found to be asymptomatic carriers for *C. hominis*[[31](#_ENREF_31),[33](#_ENREF_33),[34](#_ENREF_34)]. This proportion may be underestimated as up to 70% seroprevalence was found in children living in the United States-Mexican border[[35](#_ENREF_35)]. Bandin *et al*[[8](#_ENREF_8)] reported that *Cryptosporidium* infections were diagnosed in 3.5% of the new pediatric kidney recipients, and was responsible for 18% of the cases of infectious diarrhea over a period of 3 years. This marked heterogeneity in the prevalence of cryptosporidiosis in SOT from different studies (Table 1) is probably the result of different inclusion criteria used in each study, the geographical distribution, the sensitivity and specificity of the diagnostic tests used, type of induction and maintenance immunosuppression regimen[[3](#_ENREF_3),[11](#_ENREF_11)].

Epidemiological studies, animal models and human case reports show that *Cryptosporidium* is transmitted from person to person spread *via* fecal-oral route, including sexual transmission and possibly *via* respiratory secretions[[28](#_ENREF_28),[35-40](#_ENREF_35)]. Infectivity depends on the number of oocysts and *Cryptosporidium* species and subtypes[[41](#_ENREF_41),[42](#_ENREF_42)]. Outbreaks of cryptosporidiosis in developed countries have been described in daycare centers[[43](#_ENREF_43),[44](#_ENREF_44)] in association with animal petting farms[[45](#_ENREF_45),[46](#_ENREF_46)] and recreational water use[[47](#_ENREF_47),[48](#_ENREF_48)]. During the last few decades, several waterborne outbreaks have been reported after ingestion of contaminated recreational water or drinking water, one of these was thought to affect more than 400000 people[[49-58](#_ENREF_49)].Risk factors in SOT recipients reported in the literature are described in Table 2*. Cryptosporidium* oocysts are resistant to chlorine disinfection and can survive for days in treated recreational water despite adequate chlorination[[36](#_ENREF_36),[59](#_ENREF_59)]. *Cryptosporidium* can be eliminated by boiling the water or just heating it to 62°C for few seconds and by filtration through < 1 µm filters[[40](#_ENREF_40)]. Transmission of cryptosporidiosis *via* respiratory secretions is less common; isolation of *Cryptosporidium* DNA in the sputum of children with intestinal cryptosporidiosis and cough supports the respiratory route of transmission of this organisms[[60](#_ENREF_60)]. Even more, all of the life stages of *Cryptosporidium* have been described in the microvillus border of epithelial cells and within the bronchial mucus glands[[61](#_ENREF_61)]. Cryptosporidiosis has also been reported as a donor-derived infection after intestinal transplantation[[14](#_ENREF_14)].

**VIRULENCE IMMUNOPATHOGENICITY**

The severity and duration of illness (from asymptomatic shedding of oocyts to severe life-threatening disease) depends on the infecting species, virulence of the parasite and the host immune response (the degree of the immunodeficiency that impacts mainly T cell function), and the incubation period can range from 2 d up to 2 wk[[1](#_ENREF_1),[2](#_ENREF_2)].

*Cryptosporidium* significantly affects intestinal cells with consequent alterations in absorptive and secretory functions. This may be either caused by direct cell injury or alternatively by activation of the immune system with release of pro-inflammatory cytokines[[1](#_ENREF_1)]. Toll-like receptors (TLR2 and TLR4) play an important part in initiating immune activation following mucosal injury by the parasite[[62-64](#_ENREF_62)] and inducing cytokine release (IL-12, IL-15, IL-18, TNF-α and IFN-α/β) followed by activation of the NF-KB cells with IFN-γ production, mononuclear cell infiltration in the lamina propria, crypt cell hyperplasia, villous atrophy and blunting[[65-67](#_ENREF_65)]. Toll-like receptors also have a role in establishing immunity to infection[[62](#_ENREF_62)]. Innate immunity controls infection, but elimination of the parasite seems to require adaptive immunity[[62](#_ENREF_62)]. IFN-γ is an important cytokine determining CD4+ T cell response to infection, including memory response against *Cryptosporidium* infection in the intestine[[62](#_ENREF_62),[68](#_ENREF_68),[69](#_ENREF_69)] (remove 63, add Pantenburg Infection and immunity). The role of the T cell function is supported by severe and prolonged cryptosporidiosis in patients with AIDS and CD4 count < 50 cells/mm3, and improvement of the symptoms after introduction of highly active antiretroviral therapy[[70](#_ENREF_70)] (Change reference for more recent one) or after decreasing immunosuppression in transplant recipients that allows recovery of the immune system. Antibodies have a minor role in elimination of the infection, being more an indirect marker of the cellular immune response[[68](#_ENREF_68)]. All these changes at the level of the epithelium lead to malabsorption and secretory diarrhea[[12](#_ENREF_12),[65](#_ENREF_65)].

In SOT the type of immunosuppression might play an important role in development of cryptosoridiosis. A recent study showed that patients on a tacrolimus-based immunosuppressive regimen had a significantly higher risk of *Cryptosporidium* infection compared to the patients on a cyclosporine-based regimen. Being on cyclosporine seemed to protect against infection (OR: 0.35; 95%CI: 0.17-0.72). Those on tacrolimus who developed cryptosporidium also had graft dysfunction, likely due to dehydration and increased tacrolimus levels[[3](#_ENREF_3)].

**CLINICAL PRESENTATION**

* Most of the *Cryptosporidium* infections in the SOT population have been reported in renal transplant recipients (Table 1). *Cryptosporidium* can cause asymptomatic infection in transplant recipients and because of that, many cases may be missed[[30](#_ENREF_30),[71](#_ENREF_71)]. A relatively high prevalence of oocyst excretion in asymptomatic transplant population might be detected in the stool with random stool screening[[71](#_ENREF_71)]. When clinically evident, SOT recipients typically present with profuse and prolonged watery diarrhea, sometimes associated with nausea, vomiting, abdominal pain and fever[[1](#_ENREF_1),[4-10](#_ENREF_4),[12-24](#_ENREF_12)]. Other nonspecific symptoms have been described in immunocompetent and immunocompromised patients such as malaise, generalized weakness, myalgia, anorexia and headache[[1](#_ENREF_1),[5](#_ENREF_5),[17](#_ENREF_17)]. Persistent vomiting and diarrhea can lead to dehydration and wasting and have been associated with increased morbidity[[4](#_ENREF_4),[7](#_ENREF_7),[8](#_ENREF_8),[17](#_ENREF_17)]. Several study described acute renal failure, most likely secondary to dehydration, hypotension and sometimes tacrolimus toxicity[[3-5](#_ENREF_3),[7-9](#_ENREF_7),[16](#_ENREF_16),[23](#_ENREF_23)]. Atypical manifestations such as respiratory tract disease, pancreatitis, cholangitis and urinary tract infection, have been reported in patients with immune deficiencies, mainly AIDS[[72-75](#_ENREF_72)]. Biliary involvement with *Cryptosporidium* inducing sclerosing cholangitis has been reported in few SOT recipients[[12](#_ENREF_12),[15](#_ENREF_15),[18](#_ENREF_18)]. However, elevated liver enzymes should not be equivalent to the diagnosis of sclerosing cholangitis as they can be abnormal in the settings of hypotension or high tacrolimus levels[[11](#_ENREF_11)]. Radiologic findings in support of the diagnosis of sclerosing cholangitis: abdominal ultrasound can show dilation of the biliary duct; Technetium 99m iminodiacetic scan might show biliary stasis, irregularity of the biliary ducts, focal strictures[[18](#_ENREF_18)]; endoscopic retrograde cholangiography or MRCP could demonstrate dilation and/or irregularity of the biliary ducts[[15](#_ENREF_15),[76](#_ENREF_76)].

Infection of the biliary tree in immunocompromised patients could represent an extra-intestinal reservoir that would allow the organism to avoid certain antiparasitic agents (paromomycin) and would lead to relapses. Drugs with biliary excretion such as nitazoxanide should be preferred in these patients[[2](#_ENREF_2),[77](#_ENREF_77)]. Relapse rates in cryptosporidiosis are high (up to 40%-60%) due to incomplete eradication of the oocysts, especially from the biliary tree and possibly due to inadequate intestinal drug levels in patients with severe diarrhea[[12](#_ENREF_12),[14](#_ENREF_14)]. Respiratory cryptosporidiosis can present as an upper or lower respiratory tract infection manifested by nasal discharge, voice change, cough, dyspnea and hypoxemia[[78-81](#_ENREF_78)].

**DIAGNOSIS**

Stool microscopy is the main and cheapest method for diagnosis, however all microscopic methods are labor intensive and have low sensitivity unless a high concentration of oocysts are being released in stool. The size of the oocysts is also important (between 3-7 𝜇m) as they can be confounded with yeast, so modified staining with Ziehl-Neelsen or fluorescent techniques such as auramine-rhodamine can be employed to improve detection. The sensitivity of these stains still remains low[[82](#_ENREF_82),[83](#_ENREF_83)], requiring about 500000 oocysts/mL in formed stools for detection[[35](#_ENREF_35)]. The most commonly used test by microbiology laboratories is currently direct immunofluorescence which may be either a standalone test or a combined Cryptosporidium/Giardia diagnostic kit[[35](#_ENREF_35)]. There are several ELISA kits available with sensitivities ranging from 66%-100% but excellent specificity and have the advantage of being more automated when compared to conventional staining methods[[41](#_ENREF_41),[84-89](#_ENREF_84)]. Immunochromatographic tests have lower sensitivity compared to other molecular or other antigen tests and are not as sensitive to detect species other than *C. parvum or C. hominis* but are easy to perform, correlate well with EIA/ELISA tests and provide results in a matter of minutes[[89](#_ENREF_89),[90](#_ENREF_90)]. Molecular methods provide the highest diagnostic sensitivity and are the preferred methods for diagnosis given their superior sensitivity and specificity. There are several multiplex PCR test that can detect different gastrointestinal pathogens including viruses, parasites and bacteria however, these may not available in all laboratories[[91](#_ENREF_91)]. These tests usually have high sensitivity to detect Cryptosporidium, although speciation may require further testing and carry a higher cost[[26](#_ENREF_26),[41](#_ENREF_41),[42](#_ENREF_42),[92-94](#_ENREF_92)].

Tissue histopathology is a useful method for diagnosis, especially when intestinal biopsies are obtained. Parasites may appear lining epithelial surfaces or in the lumen. When hematoxylin is used to stain the tissue, intracellular parasites appear blue or purple[[2](#_ENREF_2),[16](#_ENREF_16),[17](#_ENREF_17),[20](#_ENREF_20)]. Intestinal transplant recipients may have negative stool examinations but the parasite may be readily seen on graft biopsies, highlighting the importance of endoscopic examination even in cases where diarrhea persists and routine stool examinations are negative[[11](#_ENREF_11),[16](#_ENREF_16),[17](#_ENREF_17)].

Detection of Cryptosporidium in respiratory sample specimens is usually achieved with acid-fast, modified acid-fast staining or and indirect immunofluorescence[[28](#_ENREF_28),[74](#_ENREF_74)] although PCR testing may also be possible[[28](#_ENREF_28)]. Histopathology may show parasites lining the mucosal epithelium of trachea, bronchi or lung; tissue biopsies may also show intra or extracellular organisms[[28](#_ENREF_28)].

**TREATMENT**

The main treatment approach is oral rehydration whenever possible, however intravenous fluids that include sodium, potassium, glucose and bicarbonate may be required in severe cases. A lactose free diet is recommended since Cryptosporidium destroys mature epithelial cells that are located in the villi resulting in loss of enzymes such as lactase. The disease is associated with high intestinal transit that may interfere with fluid, electrolyte, and drug absorption. Antimotility agents may be used once other causes of diarrhea such as *Clostridium difficile* or dysentery are ruled-out.

The first step in SOT patients is an attempt to restore immune function by adjusting or switching immunosuppressive therapy, because severity of disease is likely related to the degree of immunosuppression and CD4 cell counts[[3](#_ENREF_3),[10](#_ENREF_10),[13](#_ENREF_13),[19](#_ENREF_19),[37](#_ENREF_37),[74](#_ENREF_74),[82](#_ENREF_82),[95](#_ENREF_95)]. This example was illustrated in a renal transplant recipient with enteritis and sclerosing cholangitis, where an accidental reduction of immunosuppression resulted in clearance of the disease[[15](#_ENREF_15)]. Mycophenolate, a commonly used immunosuppressive agent may have some antiparasitic activity against Cryptosporidium by inhibiting folate metabolism[[4](#_ENREF_4)]. Cryptosporidium induced diarrhea may also result in increased tacrolimus levels[[37](#_ENREF_37)] as evidenced in two recently published case series[[4](#_ENREF_4),[5](#_ENREF_5)]. The pathophysiology is not entirely clear but it is likely a combination of factors including reduced cytochrome 3A activity during inflammation[[96](#_ENREF_96)], interaction with other drugs, and reduced renal function due to fluid depletion[[4](#_ENREF_4)]. Increased tacrolimus may in turn worsen renal function, and prolong immunosuppression[[3](#_ENREF_3)]. Cholecystectomy may be indicated for cases with acalculous cholecystitis and sclerosing cholangitis usually needs endoscopic retrograde pancreatography with possible papillotomy and stenting[[97](#_ENREF_97)]. To date, there has not been a highly effective agent to treat cryptosporidiosis in immunocompromised individuals[[98](#_ENREF_98)]. A meta-analysis of seven trials including 130 patients with AIDS found no evidence for effective agents against cryptosporidiosis, although significant heterogeneity and flaws of individual trials may have influenced the negative results[[95](#_ENREF_95)]. Moreover, whether any drug may have partial effect or the use of combination therapy were not investigated in this meta-analysis. To date, no randomized clinical trial with antiparasitic drugs has been conducted in SOT recipients with cryptosporidiosis and most experience is extrapolated either from data in immunocompetent hosts, patients with HIV infection[[37](#_ENREF_37)] or case series and case reports (Table 3)[[3-19](#_ENREF_3),[21](#_ENREF_21),[23](#_ENREF_23),[24](#_ENREF_24),[30](#_ENREF_30),[99](#_ENREF_99),[100](#_ENREF_100)]. Several antiparasitic drugs such as paromomycin, nitazoxanide or azithromycin have been used with variable success. Nitazoxanide is the only FDA approved drug for treatment of cryptosporidiosis, it is available in tablets and suspension , it has no significant drug-drug interactions or dosing requirements in renal or hepatic failure[[98](#_ENREF_98)]. Its activity, including the one of its metabolites has previously been shown *in vitro*[[101](#_ENREF_101)] and it is believed to interfere with the pyruvate: ferredoxin oxidoreductase enzyme-dependent electron transfer reaction, which is essential to anaerobic energy metabolism[[102](#_ENREF_102)]. Nitazoxanide has been effective in 3 randomized clinical trials among immunocompetent adults and children, showing reduction in duration of diarrhea and eradication of cysts from stool[[103](#_ENREF_103),[104](#_ENREF_104)]. Its effectiveness in immunocompromised patients has been variable with some clinical trials showing positive results whereas in other trials the drug was no better than placebo. In a randomized study of nitazoxanide in HIV infected patients with cryptosporidiosis treated with either 500 mg twice a day or 1 gram twice a day *vs* placebo, good responses to nitazoxanide were seen in those with CD4 cell counts > 50/mm3 although no difference to placebo was seen in the subgroup with CD4 < 50/mm3[[105](#_ENREF_105)]. Nitazoxanide effectiveness was also questioned in a randomized double-blind trial in children with HIV infection who received the drug for 28 d and there was no difference with placebo for clinical and parasitological cure or mortality[[106](#_ENREF_106)]. One difference with patients with HIV infection when compared to SOT recipients is in many cases the ability to more readily manage and adjust immunosuppression, whereas in HIV infection restoration of the immune system with antiretroviral therapy is key and may take longer time[[98](#_ENREF_98)]. The recommended nitazoxanide dose in SOT recipients is 500 mg twice daily for 14 d[[37](#_ENREF_37)], however data from randomized trials in SOT recipients is lacking and longer courses of therapy are sometimes employed[[3](#_ENREF_3),[4](#_ENREF_4),[8](#_ENREF_8)].

Paromomycin, a non-absorbable aminoglycoside has limited activity against the parasite, probably the doses used in clinical practice are not enough to achieve the high concentrations needed to inhibit parasitic activity[[97](#_ENREF_97)]. It was useful reducing oocyst excretion in a small clinical trial[[107](#_ENREF_107)]. Because paromomycin has not been shown to be useful as a standalone agent, combination therapy with other antiparasitice agents such as azithromycin and Nitazoxanide may be an attractive option[[5](#_ENREF_5),[7](#_ENREF_7),[9](#_ENREF_9),[11](#_ENREF_11),[14](#_ENREF_14),[16](#_ENREF_16),[23](#_ENREF_23),[108](#_ENREF_108)].

Macrolide antibiotics such as azithromycin, clarithromycin or spiramycin also have activity against cryptosporidium[[98](#_ENREF_98)], and were shown to reduce duration of symptoms and oocyst shedding in a clinical trial of treatment of children with cryptosporidiosis[[109](#_ENREF_109)], but these findings were not replicated on a subsequent randomized trial[[110](#_ENREF_110)]. Several clinical trials and case series evaluating the use of azithromycin in immunocompetent and immunocompromised patients with cancer and also HIV infection have shown mixed results in clinical response including duration of symptoms, and oocyst shedding[[110-114](#_ENREF_110)]. Several case reports and case series have described successful use of spiramycin and azithromycin either alone, or in combination therapy with paromomycin or Nitazoxanide in SOT patients[[5](#_ENREF_5),[7](#_ENREF_7),[9](#_ENREF_9),[11](#_ENREF_11),[13](#_ENREF_13),[14](#_ENREF_14),[16-18](#_ENREF_16),[23](#_ENREF_23)]. Drug-drug interactions between macrolides and immunosuppressive agents such as tacrolimus or cyclosporine should be considered before treatment is initiated and may further limit prolonged use of these antibiotics[[99](#_ENREF_99)].

Rifamycins also have antiparasitic activity. Rifabutin was shown to decrease cell infection by Cryptosporidium[[115](#_ENREF_115)] and rifaximin has also been shown to be active *in vitro*[[98](#_ENREF_98)]. Interestingly, the incidence of cryptosporidiosis was dramatically decreased in patients with advanced HIV infection who used rifabutin as part of *Mycobacterium avium* chemoprophylaxis[[116](#_ENREF_116),[117](#_ENREF_117)]. To date, there have been no randomized clinical trials to evaluate its efficacy in SOT recipients or other immunocompromised hosts. Drug-drug interactions with rifabutin may also be an important issue in those who take tacrolimus or cyclosporine[[15](#_ENREF_15),[99](#_ENREF_99)]. Tacrolimus levels are not affected by rifaximin, however an elevation of rifaximin levels may be seen as a result of P-glycoprotein inhibition.

Because individual drugs lack full activity against the parasite, use of combination therapy may be a more attractive option. Current guidelines recommend starting with nitazoxanide alone as preferred therapy, although combination therapy is listed as an alternative option[[37](#_ENREF_37)]. Our review of the literature showed some authors have used nitazoxanide as standard therapy, while others have used this approach in relapsed or refractory cases, usually with long courses advocated[[3-5](#_ENREF_3),[8](#_ENREF_8),[9](#_ENREF_9),[23](#_ENREF_23)]. Azithromycin has been combined with either nitazoxanide or paromomycin also with reported success[[5](#_ENREF_5),[82](#_ENREF_82),[115](#_ENREF_115),[118](#_ENREF_118)]. Caution should be exercised though, because large studies using combination therapy including nitazoxanide have not been carried out to date. Current data on combination therapy is derived from case reports and case series, which may only reflect positive outcomes, while negative results may not be necessarily reported.

**PREVENTION**

Transplant recipients should be cautious about swimming in streams or lakes and if possible avoid untreated well or lake water. Drinking water should either be treated municipal, filtered by < 1 µm filters or bottled water. Contact with anyone who has diarrhea should be limited, (food and water may be contaminated by those infected) and hand-washing for everyone, especially all household members is strongly encouraged. Moreover, all surfaces should be cleaned with running water and soap[[37](#_ENREF_37),[119](#_ENREF_119)]. Safe sexual practice using condoms is also encouraged for anal intercourse, since it increases the risk of transmission as well[[119](#_ENREF_119)].

**PERSPECTIVE**

Oral bovine immunoglobulin (hyperimmune colostrum) seemed an attractive alternative for treatment although it has not been effective at conventional doses and at higher doses oocyst excretion was decreased but diarrhea increased and clinical symptoms were not reduced[[120](#_ENREF_120)]. More recently, monoclonal or polyclonal antibodies have shown to reduce oocyst shedding and improve clinical symptoms[[121](#_ENREF_121)]. Thus, although still controversial, using oral bovine immunoglobulin or monoclonal antibodies along with antiparasitic agents may be a strategy to consider in immunocompromised individuals with recurrent or recalcitrant disease[[121](#_ENREF_121)].

The genome of both *C. parvum* and *C. hominis* has been decoded and this should also help develop antiparasitic drugs against specific targets such as calcium-dependent protein kinases, microtubule formation inhibitors, hexokinase, lactate dehydrogenase, inosine-5ʹ-monophosphate dehydrogenase, and fatty acylCoA binding inhibitors among others[[82](#_ENREF_82),[122](#_ENREF_122)].

Despite this, the full understanding of *Cryptosporidium* immunopathogenesis remains unclear[[35](#_ENREF_35),[68](#_ENREF_68)].

Declines in infection rates with increasing age among children in developing countries points to possible acquisition of immunity against the parasite, although immune responses that may lead to protective immunity are not well understood[[35](#_ENREF_35),[82](#_ENREF_82)]. A study conducted in healthy volunteers who were challenged with *Cryptosporidium*, showed that after second re-challenge episodes of diarrhea were similar but clinical severity was milder and fewer subjects were shedding oocysts[[123](#_ENREF_123)]. Both IgG and IgA antibodies increased after exposure, however there was no correlation with infection[[123](#_ENREF_123)]. Vaccination may be a viable alternative and vaccine has been evaluated in a mouse model[[124](#_ENREF_124)]. The two most common species causing human disease, C.parvum and C. hominis share > 95% of their genome so it may be possible to have one vaccine for both species (Mead 2015). Several parasitic antigens such as gp15 and gp40 have been evaluated in vaccine development. Both elicit an immune response and production of interferon gamma by mononuclear cells in patients previously infected with cryptosporidium. A vaccine trial in Bangladesh using IgA against gp15 showed the antibody was not species specific and resulted in shorter duration of illness[[82](#_ENREF_82)]. There are other targets being investigated including a recombinant DNA vaccine using vaccinia, Salmonella or Lactobacillus as DNA vectors[[82](#_ENREF_82)]. A successful vaccine would first have to be proven effective in immunocompetent hosts before moving on to immunocompromised patients, although the latter are the ones who would most likely benefit from vaccination.

**CONCLUSION**

Diarrhea caused by *Cryptosporidium* is a serious clinical syndrome in SOT recipients and diagnosis may be delayed if the infection is not routinely suspected or investigated. Advances in diagnostic methodologies has improved the sensitivity of detection, however, treatment remains problematic, especially in immunocompromised patients. Aggressive fluid and electrolyte replacement, reduction in immunosuppression along with antiparasitic therapy are the mainstay of therapy, but few partially active drugs are available and the infection may follow a protracted course with many relapses. Combination therapy with nitaxoxanide and paromomycin or macrolides may be the best approach, especially in SOT recipients. New therapies in the horizon such as hyperimmune colostrum, monoclonal antibodies, and vaccination may help increase the armamentarium to manage the disease.

**REFERENCES**

1. **Bouzid M**, Hunter PR, Chalmers RM, Tyler KM. Cryptosporidium pathogenicity and virulence. *Clin Microbiol Rev* 2013; **26**: 115-134 [PMID: 23297262 DOI: 10.1128/CMR.00076-12]
2. **Chalmers RM**, Davies AP. Minireview: clinical cryptosporidiosis. *Exp Parasitol* 2010; **124**: 138-146 [PMID: 19545516 DOI: 10.1016/j.exppara.2009.02.003]
3. **Bhadauria D**, Goel A, Kaul A, Sharma RK, Gupta A, Ruhela V, Gupta A, Vardhan H, Prasad N. Cryptosporidium infection after renal transplantation in an endemic area. *Transpl Infect Dis* 2015; **17**: 48-55 [PMID: 25620388 DOI: 10.1111/tid.12336]
4. **Krause I**, Amir J, Cleper R, Dagan A, Behor J, Samra Z, Davidovits M. Cryptosporidiosis in children following solid organ transplantation. *Pediatr Infect Dis J* 2012; **31**: 1135-1138 [PMID: 22810017 DOI: 10.1097/INF.0b013e31826780f7]
5. **Bonatti H**, Barroso LF, Sawyer RG, Kotton CN, Sifri CD. Cryptosporidium enteritis in solid organ transplant recipients: multicenter retrospective evaluation of 10 cases reveals an association with elevated tacrolimus concentrations. *Transpl Infect Dis* 2012; **14**: 635-648 [PMID: 22340660 DOI: 10.1111/j.1399-3062.2012.00719.x]
6. **Frei P**, Weber A, Geier A, Mertens JC, Kohler S, Rogler G, Müllhaupt B. Lessons from a transplant patient with diarrhea, cryptosporidial infection, and possible mycophenolate mofetil-associated colitis. *Transpl Infect Dis* 2011; **13**: 416-418 [PMID: 21615846 DOI: 10.1111/j.1399-3062.2011.00653.x]
7. **Rodríguez Ferrero ML**, Muñoz P, Valerio M, Bouza E, Martín-Rabadán P, Anaya F. [Cryptosporidium parvum infection in a kidney transplant recipient]. *Nefrologia* 2010; **30**: 476-477 [PMID: 20651893 DOI: 10.3265/Nefrologia.pre2010.Apr.10366]
8. **Bandin F**, Kwon T, Linas MD, Guigonis V, Valentin A, Cassaing S, Carol A, Garnier A, Baudouin V, Decramer S. Cryptosporidiosis in paediatric renal transplantation. *Pediatr Nephrol* 2009; **24**: 2245-2255 [PMID: 19714369 DOI: 10.1007/s00467-009-1274-y]
9. **Hong DK**, Wong CJ, Gutierrez K. Severe cryptosporidiosis in a seven-year-old renal transplant recipient: case report and review of the literature. *Pediatr Transplant* 2007; **11**: 94-100 [PMID: 17239130 DOI: 10.1111/j.1399-3046.2006.00593.x]
10. **Arslan H**, Inci EK, Azap OK, Karakayali H, Torgay A, Haberal M. Etiologic agents of diarrhea in solid organ recipients. *Transpl Infect Dis* 2007; **9**: 270-275 [PMID: 17511817 DOI: 10.1111/j.1399-3062.2007.00237.x]
11. **Ziring D**, Tran R, Edelstein S, McDiarmid SV, Gajjar N, Cortina G, Vargas J, Renz JF, Cherry JD, Krogstad P, Miller M, Busuttil RW, Farmer DG. Infectious enteritis after intestinal transplantation: incidence, timing, and outcome. *Transplantation* 2005; **79**: 702-709 [PMID: 15785377 DOI: 10.1097/01.TP.0000154911.15693.80]
12. **Tran MQ**, Gohh RY, Morrissey PE, Dworkin LD, Gautam A, Monaco AP, Yango AF. Cryptosporidium infection in renal transplant patients. *Clin Nephrol* 2005; **63**: 305-309 [PMID: 15847259 DOI: 10.5414/CNP63305]
13. **Udgiri N**, Minz M, Kashyap R, Heer M, Gupta CS, Mohandas K, Minz RW, Malla N. Intestinal cryptosporidiasis in living related renal transplant recipients. *Transplant Proc* 2004; **36**: 2128-2129 [PMID: 15518772 DOI: 10.1016/j.transproceed.2004.08.107]
14. **Pozio E**, Rivasi F, Cacciò SM. Infection with Cryptosporidium hominis and reinfection with Cryptosporidium parvum in a transplanted ileum. *APMIS* 2004; **112**: 309-313 [PMID: 15233648 DOI: 10.1111/j.1600-0463.2004.apm11204-0513.x]
15. **Abdo A**, Klassen J, Urbanski S, Raber E, Swain MG. Reversible sclerosing cholangitis secondary to cryptosporidiosis in a renal transplant patient. *J Hepatol* 2003; **38**: 688-691 [PMID: 12713884 DOI: 10.1016/S0168-8278(03)00055-2]
16. **Delis SG**, Tector J, Kato T, Mittal N, Weppler D, Levi D, Ruiz P, Nishida S, Nery JR, Tzakis AG. Diagnosis and treatment of cryptosporidium infection in intestinal transplant recipients. *Transplant Proc* 2002; **34**: 951-952 [PMID: 12034256 DOI: 10.1016/S0041-1345(02)02712-4]
17. **Gerber DA**, Green M, Jaffe R, Greenberg D, Mazariegos G, Reyes J. Cryptosporidial infections after solid organ transplantation in children. *Pediatr Transplant* 2000; **4**: 50-55 [PMID: 10731059 DOI: 10.1034/j.1399-3046.2000.00087.x]
18. **Campos M**, Jouzdani E, Sempoux C, Buts JP, Reding R, Otte JB, Sokal EM. Sclerosing cholangitis associated to cryptosporidiosis in liver-transplanted children. *Eur J Pediatr* 2000; **159**: 113-115 [PMID: 10653343 DOI: 10.1007/s004310050023]
19. **Ok UZ**, Cirit M, Uner A, Ok E, Akçiçek F, Başçi A, Ozcel MA. Cryptosporidiosis and blastocystosis in renal transplant recipients. *Nephron* 1997; **75**: 171-174 [PMID: 9041537 DOI: 10.1159/000189527]
20. **Current WL**, Garcia LS. Cryptosporidiosis. *Clin Lab Med* 1991; **11**: 873-897 [PMID: 1802526]
21. **Clifford CP**, Crook DW, Conlon CP, Fraise AP, Day DG, Peto TE. Impact of waterborne outbreak of cryptosporidiosis on AIDS and renal transplant patients. *Lancet* 1990; **335**: 1455-1456 [PMID: 1972222 DOI: 10.1016/0140-6736(90)91478-S]
22. **Tzipori S**. Cryptosporidiosis in perspective. *Adv Parasitol* 1988; **27**: 63-129 [PMID: 3289331 DOI: 10.1016/S0065-308X(08)60353-X]
23. **Acikgoz Y**, Ozkaya O, Bek K, Genc G, Sensoy SG, Hokelek M. Cryptosporidiosis: a rare and severe infection in a pediatric renal transplant recipient. *Pediatr Transplant* 2012; **16**: E115-E119 [PMID: 21320246 DOI: 10.1111/j.1399-3046.2011.01473.x]
24. **Vajro P**, di Martino L, Scotti S, Barbati C, Fontanella A, Pettoello Mantovani M. Intestinal Cryptosporidium carriage in two liver-transplanted children. *J Pediatr Gastroenterol Nutr* 1991; **12**: 139 [PMID: 2061770 DOI: 10.1097/00005176-199101000-00026]
25. **Okhuysen PC**, Chappell CL. Cryptosporidium virulence determinants--are we there yet? *Int J Parasitol* 2002; **32**: 517-525 [PMID: 11943224 DOI: 10.1016/S0020-7519(01)00356-3]
26. **Bouzid M**, Tyler KM, Christen R, Chalmers RM, Elwin K, Hunter PR. Multi-locus analysis of human infective Cryptosporidium species and subtypes using ten novel genetic loci. *BMC Microbiol* 2010; **10**: 213 [PMID: 20696051 DOI: 10.1186/1471-2180-10-213]
27. **Elwin K**, Hadfield SJ, Robinson G, Chalmers RM. The epidemiology of sporadic human infections with unusual cryptosporidia detected during routine typing in England and Wales, 2000-2008. *Epidemiol Infect* 2012; **140**: 673-683 [PMID: 21733255 DOI: 10.1017/S0950268811000860]
28. **Sponseller JK**, Griffiths JK, Tzipori S. The evolution of respiratory Cryptosporidiosis: evidence for transmission by inhalation. *Clin Microbiol Rev* 2014; **27**: 575-586 [PMID: 24982322 DOI: 10.1128/CMR.00115-13]
29. **Scallan E**, Hoekstra RM, Angulo FJ, Tauxe RV, Widdowson MA, Roy SL, Jones JL, Griffin PM. Foodborne illness acquired in the United States--major pathogens. *Emerg Infect Dis* 2011; **17**: 7-15 [PMID: 21192848 DOI: 10.3201/eid1701.091101p1]
30. **Chieffi PP**, Sens YA, Paschoalotti MA, Miorin LA, Silva HG, Jabur P. Infection by Cryptosporidium parvum in renal patients submitted to renal transplant or hemodialysis. *Rev Soc Bras Med Trop* 1998; **31**: 333-337 [PMID: 9662959 DOI: 10.1590/S0037-86821998000400001]
31. **Davies AP**, Chalmers RM. Cryptosporidiosis. *BMJ* 2009; **339**: b4168 [PMID: 19841008 DOI: 10.1136/bmj.b4168]
32. **Kotloff KL**, Nataro JP, Blackwelder WC, Nasrin D, Farag TH, Panchalingam S, Wu Y, Sow SO, Sur D, Breiman RF, Faruque AS, Zaidi AK, Saha D, Alonso PL, Tamboura B, Sanogo D, Onwuchekwa U, Manna B, Ramamurthy T, Kanungo S, Ochieng JB, Omore R, Oundo JO, Hossain A, Das SK, Ahmed S, Qureshi S, Quadri F, Adegbola RA, Antonio M, Hossain MJ, Akinsola A, Mandomando I, Nhampossa T, Acácio S, Biswas K, O'Reilly CE, Mintz ED, Berkeley LY, Muhsen K, Sommerfelt H, Robins-Browne RM, Levine MM. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet* 2013; **382**: 209-222 [PMID: 23680352 DOI: 10.1016/S0140-6736(13)60844-2]
33. **Cordell RL**, Addiss DG. Cryptosporidiosis in child care settings: a review of the literature and recommendations for prevention and control. *Pediatr Infect Dis J* 1994; **13**: 310-317 [PMID: 8036049 DOI: 10.1097/00006454-199404000-00012]
34. **Davies AP**, Campbell B, Evans MR, Bone A, Roche A, Chalmers RM. Asymptomatic carriage of protozoan parasites in children in day care centers in the United kingdom. *Pediatr Infect Dis J* 2009; **28**: 838-840 [PMID: 19684527 DOI: 10.1097/INF.0b013e31819d646d]
35. **Shirley DA**, Moonah SN, Kotloff KL. Burden of disease from cryptosporidiosis. *Curr Opin Infect Dis* 2012; **25**: 555-563 [PMID: 22907279 DOI: 10.1097/QCO.0b013e328357e569]
36. **Avery RK**, Michaels MG. Strategies for safe living after solid organ transplantation. *Am J Transplant* 2013; **13** Suppl 4: 304-310 [PMID: 23465022 DOI: 10.1111/ajt.12121]
37. **Schwartz BS**, Mawhorter SD. Parasitic infections in solid organ transplantation. *Am J Transplant* 2013; **13** Suppl 4: 280-303 [PMID: 23465021 DOI: 10.1111/ajt.12120]
38. **Vandenberg O**, Robberecht F, Dauby N, Moens C, Talabani H, Dupont E, Menotti J, van Gool T, Levy J. Management of a Cryptosporidium hominis outbreak in a day-care center. *Pediatr Infect Dis J* 2012; **31**: 10-15 [PMID: 22094626 DOI: 10.1097/INF.0b013e318235ab64]
39. **Chappell CL**, Okhuysen PC. Cryptosporidiosis. *Curr Opin Infect Dis* 2002; **15**: 523-527 [PMID: 12686887 DOI: 10.1097/00001432-200210000-00012]
40. **Dillingham RA**, Lima AA, Guerrant RL. Cryptosporidiosis: epidemiology and impact. *Microbes Infect* 2002; **4**: 1059-1066 [PMID: 12191656]
41. **Chalmers RM**, Katzer F. Looking for Cryptosporidium: the application of advances in detection and diagnosis. *Trends Parasitol* 2013; **29**: 237-251 [PMID: 23566713 DOI: 10.1016/j.pt.2013.03.001]
42. **Xiao L**. Molecular epidemiology of cryptosporidiosis: an update. *Exp Parasitol* 2010; **124**: 80-89 [PMID: 19358845 DOI: 10.1016/j.exppara.2009.03.018]
43. **Artieda J**, Basterrechea M, Arriola L, Yagüe M, Albisua E, Arostegui N, Astigarraga U, Botello R, Manterola JM. Outbreak of cryptosporidiosis in a child day-care centre in Gipuzkoa, Spain, October to December 2011. *Euro Surveill* 2012; **17**: pii: 20070 [PMID: 22321139]
44. **Centers for Disease Control (CDC)**. Cryptosporidiosis among children attending day-care centers--Georgia, Pennsylvania, Michigan, California, New Mexico. *MMWR Morb Mortal Wkly Rep* 1984; **33**: 599-601 [PMID: 6434936]
45. **Gormley FJ**, Little CL, Chalmers RM, Rawal N, Adak GK. Zoonotic cryptosporidiosis from petting farms, England and Wales, 1992-2009. *Emerg Infect Dis* 2011; **17**: 151-152 [PMID: 21192888 DOI: 10.3201/eid1701.100902]
46. **Lange H**, Johansen OH, Vold L, Robertson LJ, Anthonisen IL, Nygard K. Second outbreak of infection with a rare Cryptosporidium parvum genotype in schoolchildren associated with contact with lambs/goat kids at a holiday farm in Norway. *Epidemiol Infect* 2014; **142**: 2105-2113 [PMID: 24308502 DOI: 10.1017/S0950268813003002]
47. **Cantey PT**, Kurian AK, Jefferson D, Moerbe MM, Marshall K, Blankenship WR, Rothbarth GR, Hwang J, Hall R, Yoder J, Brunkard J, Johnston S, Xiao L, Hill VR, Sarisky J, Zarate-Bermudez MA, Otto C, Hlavsa MC. Outbreak of cryptosporidiosis associated with a man-made chlorinated lake--Tarrant County, Texas, 2008. *J Environ Health* 2012; **75**: 14-19 [PMID: 23210393]
48. **Hlavsa MC**, Roberts VA, Kahler AM, Hilborn ED, Wade TJ, Backer LC, Yoder JS. Recreational water-associated disease outbreaks--United States, 2009-2010. *MMWR Morb Mortal Wkly Rep* 2014; **63**: 6-10 [PMID: 24402466]
49. **Baldursson S**, Karanis P. Waterborne transmission of protozoan parasites: review of worldwide outbreaks - an update 2004-2010. *Water Res* 2011; **45**: 6603-6614 [PMID: 22048017 DOI: 10.1016/j.watres.2011.10.013]
50. **D'Antonio RG**, Winn RE, Taylor JP, Gustafson TL, Current WL, Rhodes MM, Gary GW, Zajac RA. A waterborne outbreak of cryptosporidiosis in normal hosts. *Ann Intern Med* 1985; **103**: 886-888 [PMID: 4062089 DOI: 10.7326/0003-4819-103-6-886]
51. **Fournet N**, Deege MP, Urbanus AT, Nichols G, Rosner BM, Chalmers RM, Gorton R, Pollock KG, van der Giessen JW, Wever PC, Dorigo-Zetsma JW, Mulder B, Mank TG, Overdevest I, Kusters JG, van Pelt W, Kortbeek LM. Simultaneous increase of Cryptosporidium infections in the Netherlands, the United Kingdom and Germany in late summer season, 2012. *Euro Surveill* 2013; **18**: [PMID: 23324424]
52. **Hayes EB**, Matte TD, O'Brien TR, McKinley TW, Logsdon GS, Rose JB, Ungar BL, Word DM, Pinsky PF, Cummings ML. Large community outbreak of cryptosporidiosis due to contamination of a filtered public water supply. *N Engl J Med* 1989; **320**: 1372-1376 [PMID: 2716783 DOI: 10.1056/NEJM198905253202103]
53. **Insulander M**, Lebbad M, Stenström TA, Svenungsson B. An outbreak of cryptosporidiosis associated with exposure to swimming pool water. *Scand J Infect Dis* 2005; **37**: 354-360 [PMID: 16051572 DOI: 10.1080/00365540410021072]
54. **Karanis P**, Kourenti C, Smith H. Waterborne transmission of protozoan parasites: a worldwide review of outbreaks and lessons learnt. *J Water Health* 2007; **5**: 1-38 [PMID: 17402277 DOI: 10.2166/wh.2006.002]
55. **Mac Kenzie WR**, Hoxie NJ, Proctor ME, Gradus MS, Blair KA, Peterson DE, Kazmierczak JJ, Addiss DG, Fox KR, Rose JB. A massive outbreak in Milwaukee of cryptosporidium infection transmitted through the public water supply. *N Engl J Med* 1994; **331**: 161-167 [PMID: 7818640 DOI: 10.1056/NEJM199407213310304]
56. **McLauchlin J**, Amar C, Pedraza-Díaz S, Nichols GL. Molecular epidemiological analysis of Cryptosporidium spp. in the United Kingdom: results of genotyping Cryptosporidium spp. in 1,705 fecal samples from humans and 105 fecal samples from livestock animals. *J Clin Microbiol* 2000; **38**: 3984-3990 [PMID: 11060056]
57. **Painter JE**, Hlavsa MC, Collier SA, Xiao L, Yoder JS. Cryptosporidiosis surveillance -- United States, 2011-2012. *MMWR Suppl* 2015; **64**: 1-14 [PMID: 25928581]
58. **Widerström M**, Schönning C, Lilja M, Lebbad M, Ljung T, Allestam G, Ferm M, Björkholm B, Hansen A, Hiltula J, Långmark J, Löfdahl M, Omberg M, Reuterwall C, Samuelsson E, Widgren K, Wallensten A, Lindh J. Large outbreak of Cryptosporidium hominis infection transmitted through the public water supply, Sweden. *Emerg Infect Dis* 2014; **20**: 581-589 [PMID: 24655474 DOI: 10.3201/eid2004.121415]
59. **Korich DG**, Mead JR, Madore MS, Sinclair NA, Sterling CR. Effects of ozone, chlorine dioxide, chlorine, and monochloramine on Cryptosporidium parvum oocyst viability. *Appl Environ Microbiol* 1990; **56**: 1423-1428 [PMID: 2339894]
60. **Mor SM**, Tumwine JK, Ndeezi G, Srinivasan MG, Kaddu-Mulindwa DH, Tzipori S, Griffiths JK. Respiratory cryptosporidiosis in HIV-seronegative children in Uganda: potential for respiratory transmission. *Clin Infect Dis* 2010; **50**: 1366-1372 [PMID: 20377408 DOI: 10.1086/652140]
61. **Moore JA**, Frenkel JK. Respiratory and enteric cryptosporidiosis in humans. *Arch Pathol Lab Med* 1991; **115**: 1160-1162 [PMID: 1747035]
62. **McDonald V**, Korbel DS, Barakat FM, Choudhry N, Petry F. Innate immune responses against Cryptosporidium parvum infection. *Parasite Immunol* 2013; **35**: 55-64 [PMID: 23173616 DOI: 10.1111/pim.12020]
63. **Santaolalla R**, Fukata M, Abreu MT. Innate immunity in the small intestine. *Curr Opin Gastroenterol* 2011; **27**: 125-131 [PMID: 21248635 DOI: 10.1097/MOG.0b013e3283438dea]
64. **Pantenburg B**, Dann SM, Wang HC, Robinson P, Castellanos-Gonzalez A, Lewis DE, White AC. Intestinal immune response to human Cryptosporidium sp. infection. *Infect Immun* 2008; **76**: 23-29 [PMID: 17967863 DOI: 10.1128/IAI.00960-07]
65. **Farthing MJ**. Clinical aspects of human cryptosporidiosis. *Contrib Microbiol* 2000; **6**: 50-74 [PMID: 10943507 DOI: 10.1159/000060368]
66. **McDonald V**. Host cell-mediated responses to infection with Cryptosporidium. *Parasite Immunol* 2000; **22**: 597-604 [PMID: 11123751 DOI: 10.1046/j.1365-3024.2000.00343.x]
67. **McDonald V**, Smith R, Robinson H, Bancroft G. Host immune responses against Cryptosporidium. *Contrib Microbiol* 2000; **6**: 75-91 [PMID: 10943508 DOI: 10.1159/000060371]
68. **Kothavade RJ**. Challenges in understanding the immunopathogenesis of Cryptosporidium infections in humans. *Eur J Clin Microbiol Infect Dis* 2011; **30**: 1461-1472 [PMID: 21484252 DOI: 10.1007/s10096-011-1246-6]
69. **Pantenburg B**, Castellanos-Gonzalez A, Dann SM, Connelly RL, Lewis DE, Ward HD, White AC. Human CD8(+) T cells clear Cryptosporidium parvum from infected intestinal epithelial cells. *Am J Trop Med Hyg* 2010; **82**: 600-607 [PMID: 20348507 DOI: 10.4269/ajtmh.2010.09-0590]
70. **Flanigan T**, Whalen C, Turner J, Soave R, Toerner J, Havlir D, Kotler D. Cryptosporidium infection and CD4 counts. *Ann Intern Med* 1992; **116**: 840-842 [PMID: 1348918 DOI: 10.7326/0003-4819-116-10-840]
71. **Roncoroni AJ**, Gomez MA, Mera J, Cagnoni P, Michel MD. Cryptosporidium infection in renal transplant patients. *J Infect Dis* 1989; **160**: 559 [PMID: 2668434 DOI: 10.1093/infdis/160.3.559]
72. **Ditrich O**, Palkovic L, Stĕrba J, Prokopic J, Loudová J, Giboda M. The first finding of Cryptosporidium baileyi in man. *Parasitol Res* 1991; **77**: 44-47 [PMID: 1825238 DOI: 10.1007/BF00934383]
73. **Hayward AR**, Levy J, Facchetti F, Notarangelo L, Ochs HD, Etzioni A, Bonnefoy JY, Cosyns M, Weinberg A. Cholangiopathy and tumors of the pancreas, liver, and biliary tree in boys with X-linked immunodeficiency with hyper-IgM. *J Immunol* 1997; **158**: 977-983 [PMID: 8993019]
74. **Hunter PR**, Nichols G. Epidemiology and clinical features of Cryptosporidium infection in immunocompromised patients. *Clin Microbiol Rev* 2002; **15**: 145-154 [PMID: 11781272 DOI: 10.1128/CMR.15.1.145-154.2002]
75. **Kocoshis SA**, Cibull ML, Davis TE, Hinton JT, Seip M, Banwell JG. Intestinal and pulmonary cryptosporidiosis in an infant with severe combined immune deficiency. *J Pediatr Gastroenterol Nutr* 1984; **3**: 149-157 [PMID: 6694044 DOI: 10.1097/00005176-198401000-00028]
76. **Azizi L**, Raynal M, Cazejust J, Ruiz A, Menu Y, Arrivé L. MR Imaging of sclerosing cholangitis. *Clin Res Hepatol Gastroenterol* 2012; **36**: 130-138 [PMID: 22306050 DOI: 10.1016/j.clinre.2011.11.011]
77. **Baishanbo A**, Gargala G, Duclos C, François A, Rossignol JF, Ballet JJ, Favennec L. Efficacy of nitazoxanide and paromomycin in biliary tract cryptosporidiosis in an immunosuppressed gerbil model. *J Antimicrob Chemother* 2006; **57**: 353-355 [PMID: 16361328 DOI: 10.1093/jac/dki456]
78. **Dupont C**, Bougnoux ME, Turner L, Rouveix E, Dorra M. Microbiological findings about pulmonary cryptosporidiosis in two AIDS patients. *J Clin Microbiol* 1996; **34**: 227-229 [PMID: 8748314]
79. **Giang TT**, Pollack G, Kotler DP. Cryptosporidiosis of the nasal mucosa in a patient with AIDS. *AIDS* 1994; **8**: 555-556 [PMID: 8011262 DOI: 10.1097/00002030-199404000-00021]
80. **Harari MD**, West B, Dwyer B. Cryptosporidium as cause of laryngotracheitis in an infant. *Lancet* 1986; **1**: 1207 [PMID: 2871438 DOI: 10.1016/S0140-6736(86)91181-5]
81. **Pellicelli AM**, Palmieri F, Spinazzola F, D'Ambrosio C, Causo T, De Mori P, Bordi E, D'Amato C. Pulmonary cryptosporidiosis in patients with acquired immunodeficiency syndrome. *Minerva Med* 1998; **89**: 173-175 [PMID: 9676183]
82. **Checkley W**, White AC, Jaganath D, Arrowood MJ, Chalmers RM, Chen XM, Fayer R, Griffiths JK, Guerrant RL, Hedstrom L, Huston CD, Kotloff KL, Kang G, Mead JR, Miller M, Petri WA, Priest JW, Roos DS, Striepen B, Thompson RC, Ward HD, Van Voorhis WA, Xiao L, Zhu G, Houpt ER. A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for cryptosporidium. *Lancet Infect Dis* 2015; **15**: 85-94 [PMID: 25278220 DOI: 10.1016/S1473-3099(14)70772-8]
83. **Khurana S**, Sharma P, Sharma A, Malla N. Evaluation of Ziehl-Neelsen staining, auramine phenol staining, antigen detection enzyme linked immunosorbent assay and polymerase chain reaction, for the diagnosis of intestinal cryptosporidiosis. *Trop Parasitol* 2012; **2**: 20-23 [PMID: 23508690 DOI: 10.4103/2229-5070.97234]
84. **Chalmers RM**, Atchison C, Barlow K, Young Y, Roche A, Manuel R. An audit of the laboratory diagnosis of cryptosporidiosis in England and Wales. *J Med Microbiol* 2015; **64**: 688-693 [PMID: 25976007 DOI: 10.1099/jmm.0.000089]
85. **Chalmers RM**, Campbell BM, Crouch N, Charlett A, Davies AP. Comparison of diagnostic sensitivity and specificity of seven Cryptosporidium assays used in the UK. *J Med Microbiol* 2011; **60**: 1598-1604 [PMID: 21757501 DOI: 10.1099/jmm.0.034181-0]
86. **Garcia LS**, Shimizu RY. Evaluation of nine immunoassay kits (enzyme immunoassay and direct fluorescence) for detection of Giardia lamblia and Cryptosporidium parvum in human fecal specimens. *J Clin Microbiol* 1997; **35**: 1526-1529 [PMID: 9163474]
87. **García-Bujalance S**, García-Gil V, Baquero-Artigao F. [Microbiological diagnosis of Cryptosporidium spp. and Giardia intestinalis in paediatrics]. *Enferm Infecc Microbiol Clin* 2013; **31**: 193-194 [PMID: 22763114 DOI: 10.1016/j.eimc.2012.04.005]
88. **Johnston SP**, Ballard MM, Beach MJ, Causer L, Wilkins PP. Evaluation of three commercial assays for detection of Giardia and Cryptosporidium organisms in fecal specimens. *J Clin Microbiol* 2003; **41**: 623-626 [PMID: 12574257 DOI: 10.1128/JCM.41.2.623-626.2003]
89. **Helmy YA**, Krücken J, Nöckler K, von Samson-Himmelstjerna G, Zessin KH. Comparison between two commercially available serological tests and polymerase chain reaction in the diagnosis of Cryptosporidium in animals and diarrhoeic children. *Parasitol Res* 2014; **113**: 211-216 [PMID: 24221885 DOI: 10.1007/s00436-013-3645-3]
90. **Weitzel T**, Dittrich S, Möhl I, Adusu E, Jelinek T. Evaluation of seven commercial antigen detection tests for Giardia and Cryptosporidium in stool samples. *Clin Microbiol Infect* 2006; **12**: 656-659 [PMID: 16774562 DOI: 10.1111/j.1469-0691.2006.01457.x]
91. **Khare R**, Espy MJ, Cebelinski E, Boxrud D, Sloan LM, Cunningham SA, Pritt BS, Patel R, Binnicker MJ. Comparative evaluation of two commercial multiplex panels for detection of gastrointestinal pathogens by use of clinical stool specimens. *J Clin Microbiol* 2014; **52**: 3667-3673 [PMID: 25100818 DOI: 10.1128/JCM.01637-14]
92. **Elwin K**, Robinson G, Hadfield SJ, Fairclough HV, Iturriza-Gómara M, Chalmers RM. A comparison of two approaches to extracting Cryptosporidium DNA from human stools as measured by a real-time PCR assay. *J Microbiol Methods* 2012; **89**: 38-40 [PMID: 22366300 DOI: 10.1016/j.mimet.2012.02.006]
93. **Hadfield SJ**, Robinson G, Elwin K, Chalmers RM. Detection and differentiation of Cryptosporidium spp. in human clinical samples by use of real-time PCR. *J Clin Microbiol* 2011; **49**: 918-924 [PMID: 21177904 DOI: 10.1128/JCM.01733-10]
94. **Bouzid M**, Heavens D, Elwin K, Chalmers RM, Hadfield SJ, Hunter PR, Tyler KM. Whole genome amplification (WGA) for archiving and genotyping of clinical isolates of Cryptosporidium species. *Parasitology* 2010; **137**: 27-36 [PMID: 19765343 DOI: 10.1017/S0031182009991132]
95. **Abubakar I**, Aliyu SH, Arumugam C, Hunter PR, Usman NK. Prevention and treatment of cryptosporidiosis in immunocompromised patients. *Cochrane Database Syst Rev* 2007; **(1)**: CD004932 [PMID: 17253532 DOI: 10.1002/14651858.CD004932.pub2]
96. **Maezono S**, Sugimoto K, Sakamoto K, Ohmori M, Hishikawa S, Mizuta K, Kawarasaki H, Watanabe Y, Fujimura A. Elevated blood concentrations of calcineurin inhibitors during diarrheal episode in pediatric liver transplant recipients: involvement of the suppression of intestinal cytochrome P450 3A and P-glycoprotein. *Pediatr Transplant* 2005; **9**: 315-323 [PMID: 15910387 DOI: 10.1111/j.1399-3046.2005.00315.x]
97. **Clinton White A**. Cryptosporidiosis (Cryptosporidium Species). In: Bennett JF, Dolin R, Blaser MJ. Mandell, Douglas, Bennett's, Principles and practice of infectious diseases: Expert Consult Premium Edition 8 Ed. Philadelphia, PA: Curchil Livingstone, 2015: 3173-3183
98. **Cabada MM**, White AC. Treatment of cryptosporidiosis: do we know what we think we know? *Curr Opin Infect Dis* 2010; **23**: 494-499 [PMID: 20689422 DOI: 10.1097/QCO.0b013e32833de052]
99. **Trofe-Clark J**, Lemonovich TL. Interactions between anti-infective agents and immunosuppressants in solid organ transplantation. *Am J Transplant* 2013; **13 Suppl 4**: 318-326 [PMID: 23465024 DOI: 10.1111/ajt.12123]
100. **Franco A**, Rocamora N, Merino E, Paya A. [Cryptosporidiosis. A rare infection in renal transplantation]. *Nefrologia* 2006; **26**: 753-754 [PMID: 17227259]
101. **Gargala G**, Delaunay A, Li X, Brasseur P, Favennec L, Ballet JJ. Efficacy of nitazoxanide, tizoxanide and tizoxanide glucuronide against Cryptosporidium parvum development in sporozoite-infected HCT-8 enterocytic cells. *J Antimicrob Chemother* 2000; **46**: 57-60 [PMID: 10882689 DOI: 10.1093/jac/46.1.57]
102. **Smith HV**, Corcoran GD. New drugs and treatment for cryptosporidiosis. *Curr Opin Infect Dis* 2004; **17**: 557-564 [PMID: 15640710 DOI: 10.1097/00001432-200412000-00008]
103. **Rossignol JF**, Ayoub A, Ayers MS. Treatment of diarrhea caused by Cryptosporidium parvum: a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. *J Infect Dis* 2001; **184**: 103-106 [PMID: 11398117 DOI: 10.1086/321008]
104. **Rossignol JF**, Kabil SM, el-Gohary Y, Younis AM. Effect of nitazoxanide in diarrhea and enteritis caused by Cryptosporidium species. *Clin Gastroenterol Hepatol* 2006; **4**: 320-324 [PMID: 16527695 DOI: 10.1016/j.cgh.2005.12.020]
105. **Rossignol JF**, Hidalgo H, Feregrino M, Higuera F, Gomez WH, Romero JL, Padierna J, Geyne A, Ayers MS. A double-'blind' placebo-controlled study of nitazoxanide in the treatment of cryptosporidial diarrhoea in AIDS patients in Mexico. *Trans R Soc Trop Med Hyg* 1998; **92**: 663-666 [PMID: 10326116]
106. **Amadi B**, Mwiya M, Sianongo S, Payne L, Watuka A, Katubulushi M, Kelly P. High dose prolonged treatment with nitazoxanide is not effective for cryptosporidiosis in HIV positive Zambian children: a randomised controlled trial. *BMC Infect Dis* 2009; **9**: 195 [PMID: 19954529 DOI: 10.1186/1471-2334-9-195]
107. **White AC**, Chappell CL, Hayat CS, Kimball KT, Flanigan TP, Goodgame RW. Paromomycin for cryptosporidiosis in AIDS: a prospective, double-blind trial. *J Infect Dis* 1994; **170**: 419-424 [PMID: 8035029 DOI: 10.1093/infdis/170.2.419]
108. **White AC**, Cron SG, Chappell CL. Paromomycin in cryptosporidiosis. *Clin Infect Dis* 2001; **32**: 1516-1517 [PMID: 11317257 DOI: 10.1086/320171]
109. **Sáez-Llorens X**, Odio CM, Umaña MA, Morales MV. Spiramycin vs placebo for treatment of acute diarrhea caused by Cryptosporidium. *Pediatr Infect Dis J* 1989; **8**: 136-140 [PMID: 2652084]
110. **Wittenberg DF**, Miller NM, van den Ende J. Spiramycin is not effective in treating cryptosporidium diarrhea in infants: results of a double-blind randomized trial. *J Infect Dis* 1989; **159**: 131-132 [PMID: 2642518 DOI: 10.1093/infdis/159.1.131]
111. **Allam AF**, Shehab AY. Efficacy of azithromycin, praziquantel and mirazid in treatment of cryptosporidiosis in school children. *J Egypt Soc Parasitol* 2002; **32**: 969-978 [PMID: 12512828]
112. **Blanshard C**, Shanson DC, Gazzard BG. Pilot studies of azithromycin, letrazuril and paromomycin in the treatment of cryptosporidiosis. *Int J STD AIDS* 1997; **8**: 124-129 [PMID: 9061412 DOI: [10.1258/0956462971919543](http://dx.doi.org/10.1258/0956462971919543%22%20%5Ct%20%22_blank)]
113. **Hicks P**, Zwiener RJ, Squires J, Savell V. Azithromycin therapy for Cryptosporidium parvum infection in four children infected with human immunodeficiency virus. *J Pediatr* 1996; **129**: 297-300 [PMID: 8765631 DOI: 10.1016/S0022-3476(96)70258-5]
114. **Nachbaur D**, Kropshofer G, Feichtinger H, Allerberger F, Niederwieser D. Cryptosporidiosis after CD34-selected autologous peripheral blood stem cell transplantation (PBSCT). Treatment with paromomycin, azithromycin and recombinant human interleukin-2. *Bone Marrow Transplant* 1997; **19**: 1261-1263 [PMID: 9208124 DOI: 10.1038/sj.bmt.1700826]
115. **Giacometti A**, Cirioni O, Barchiesi F, Ancarani F, Scalise G. Activity of nitazoxanide alone and in combination with azithromycin and rifabutin against Cryptosporidium parvum in cell culture. *J Antimicrob Chemother* 2000; **45**: 453-456 [PMID: 10747821 DOI: 10.1093/jac/45.4.453]
116. **Fichtenbaum CJ**, Zackin R, Feinberg J, Benson C, Griffiths JK. Rifabutin but not clarithromycin prevents cryptosporidiosis in persons with advanced HIV infection. *AIDS* 2000; **14**: 2889-2893 [PMID: 11153670 DOI: 10.1097/00002030-200012220-00010]
117. **Holmberg SD**, Moorman AC, Von Bargen JC, Palella FJ, Loveless MO, Ward DJ, Navin TR. Possible effectiveness of clarithromycin and rifabutin for cryptosporidiosis chemoprophylaxis in HIV disease. HIV Outpatient Study (HOPS) Investigators. *JAMA* 1998; **279**: 384-386 [PMID: 9459473 DOI: 10.1001/jama.279.5.384]
118. **Smith NH**, Cron S, Valdez LM, Chappell CL, White AC. Combination drug therapy for cryptosporidiosis in AIDS. *J Infect Dis* 1998; **178**: 900-903 [PMID: 9728569 DOI: 10.1086/515352]
119. **Centers for Disease Control (CDC)**. Cryptosporidium Prevention and Control. Available from: URL: http: //www.cdc.gov/parasites/crypto/gen\_info/prevention-general-public.html
120. **Okhuysen PC**, Chappell CL, Crabb J, Valdez LM, Douglass ET, DuPont HL. Prophylactic effect of bovine anti-Cryptosporidium hyperimmune colostrum immunoglobulin in healthy volunteers challenged with Cryptosporidium parvum. *Clin Infect Dis* 1998; **26**: 1324-1329 [PMID: 9636857]
121. **Mead JR**. Challenges and prospects for a Cryptosporidium vaccine. *Future Microbiol* 2010; **5**: 335-337 [PMID: 20210541 DOI: 10.2217/fmb.09.115]
122. **Miyamoto Y**, Eckmann L. Drug Development Against the Major Diarrhea-Causing Parasites of the Small Intestine, Cryptosporidium and Giardia. *Front Microbiol* 2015; **6**: 1208 [PMID: 26635732 DOI: 10.3389/fmicb.2015.01208]
123. **Okhuysen PC**, Chappell CL, Sterling CR, Jakubowski W, DuPont HL. Susceptibility and serologic response of healthy adults to reinfection with Cryptosporidium parvum. *Infect Immun* 1998; **66**: 441-443 [PMID: 9453592]
124. **Costa LB**, Noronha FJ, Roche JK, Sevilleja JE, Warren CA, Oriá R, Lima A, Guerrant RL. Novel in vitro and in vivo models and potential new therapeutics to break the vicious cycle of Cryptosporidium infection and malnutrition. *J Infect Dis* 2012; **205**: 1464-1471 [PMID: 22454464 DOI: 10.1093/infdis/jis216]

**P-Reviewer:** **S-Editor:** Kong JX **L-Editor: E-Editor:**

**Table 1 Cases and case series of cryptosporidiosis in solid organ transplant recipients**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **No. of patients** | **Incidence** | **Median/mean (range/SD) age (years)** | **Allograft** | **Immuno-****suppression regimen** | **Symptoms** | **Acute renal failure** | **Abnormal LFTs** |
| Abdo *et al*[15] | 1 | NA | 40 (NA) | Kidney | TAC+AZA+S | Abdominal pain, D | No | Yes |
| Acikgoz *et al*[23] | 1 | NA | 6 | Kidney | TAC+MMF+S | N, V, D | Yes | No |
| Arslan *et al*[10] | 43 | 7/43 (16.28%) | 32.9 ± 12.2 | Kidney (40)1Liver (3)1 | MMF, TAC, AZA, CsA, S | D | N/A | N/A |
| Bandin *et al*[[8](#_ENREF_8)] | 38 | 7/38 (18%) | 8.93(4.5-14) | Kidney | MMF+TAC+S(3)1MMF+TAC (2)1MMF+CsA+S (2)1 | D (7)1, V (4)1, abdominal pain (7)1, hTN (4)1 | Yes (7) | No |
| Bhadauria *et al*[3] | 119 | 34/119 (28.5) | 33.96 ± 11.13 (15-52) | Kidney | CsA+MMF+STAC+MMF+S | D(12) #, F(11) #, malaise(25) #, V(18) #, abdominal pain (17) #, weight loss (9) #, dehydration (15) #, hypotension (8) # | Yes (12) # | N/A |
| Bonatti *et al*[5] | 10 | NA | 51(34-57) | Kidney (8)1Liver (1)1Lung (1)1 | TAC+MMF+S (8)1CsA+AZA+S (1)1TAC+S (1)1 | D (10)1, V (5)1, malaise (4)1, F (1)1 | Yes | N/A |
| Campos *et al*[18] | 3 | NA | 3.92 (1.25-7) | Liver | TAC+S (2) # | V(1) #, D(3)#, F(1)#, abdominal pain (2) # | No | Yes (2) # |
| Chieffi *et al*[30] | 23 | 17.2 | N/A | Kidney | N/A | N/A | N/A | N/A |
| Clifford *et al*[21] | 3 | 3/28(10.7) | N/A | Kidney | CsA+AZA+S | D(2) | No | No |
| Delis *et al*[16] | 4 | NA | 20.21(0.83-34) | Intestine | TAC+P(3)1TAC+MMF+S (1)1 | D (4)1, abdominal pain (1)1, F (1)1 | Yes (4)1 | N/A |
| Franco *et al*[100] | 1 | NA | 60 | Kidney | CsA+MMF+S | D, N, V, malaise, weight loss, | Yes | NA |
| Frei *et al*[6] | 1 | NA | 34 (NA) | Liver | MMF | D | N/A | N/A |
| Gerber *et al*[17] | 1160 | 4/1160 (0.34%) | NA | Liver (3)1Intestine (1)1 | CsA+S (1) #TAC+S (3) # | D (4)1, lethargy (1)1, weight loss (1)1 | No | Yes (1)1 |
| Hong *et al*[9] | 1 | NA | 7 (NA) | Kidney | TAC+MMF+S | N, V, D | Yes | No |
| Krause *et al*[4] | 6 | NA | 3.7(1.1-6.6) | Kidney (4)1Liver-Kidney (1)1Heart (1)1 | TAC+MMF+STAC+AZA+STAC+MMF | D (6)1, F (2)1, V (1)1, abdominal pain (1)1, weight loss (4)1 | Yes (5/6)1 | Yes (4/6)1 |
| Ok *et al*[19] | 69 | 13/69 (18.8%) | N/A | Kidney | N/A | Asymptomatic, D | N/A | N/A |
| Pozio *et al*[14] | 1 | NA | 13 (NA) | Intestine | TAC+S | None (1st episode)D (2nd episode) | N/A | N/A |
| Rodríguez Ferrero*et al*[7] | 1 | NA | 78 | kidney | MMF+TAC | D, hTN | Yes | No |
| Tran *et al*[12] | 1 | NA | 59 | Kidney | TAC+sirolimus+S | N, V, D, abdominal pain | No | No |
| Udgiri *et al*[13] | 60 | NA | 35.07( ± 9.22) | Kidney | CsA+AZA+S (47)1CsA+MMF+S (13)1 | D (2)1 | N/A | No |
| Vajro *et al*[24] | 2 | NA | 1.49; 10 | Liver | CsA+S | F | No | No |
| Ziring *et al*[11] | 33 | 2/33 (6.06%) | 2.83 (0.83-48.75) | Intestine ± Liver | TAC+MMF+S | N/A | N/A | N/A |

1Number of patients; NA: Not applicable; N/A: Not available; N: Nausea; V: Vomiting; D: Diarrhea; F: Fever; hTN: Hypotension; TAC: Tacrolimus; MMF: Mycophenolate mofetil; CsA: Cyclosporine A; AZA: Azathioprine; S: Steroids.

**Table 2 Risk factors, diagnosis and co-morbidities in *Cryptosporidium* Infections**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Exposure** | ***Cryptosporidium spp.*** | **Diagnosis** | **Co-infection** | **Tacrolimus levels (early on admission)** |
| Abdo *et al*[15] | N/A | *C. parvum* | N/A | No | No |
| Acikgoz *et al*[23] | Petting animals | N/A | ELISAModified acid fast staining | No | Increased |
| Arslan *et al*[10] | N/A | N/A | Modified acid fast staining | N/A | N/A |
| Bandin *et al*[[8](#_ENREF_8)] | Swimming pool (3)rTraveler diarrhea (1)1 | N/A | Zielh-Nielsen stainingAuramine stainingMicroscopyBiopsy | No | N/A |
| Bhadauria *et al*[3] | N/A | N/A | Modified acid fast staining | CMV (8) | Increased |
| Bonatti *et al*[5] | Travel (water exposure) (4)1Camping (1)1Restaurant (1)1Well water/farm animals (1)1 | *C. jejuni* (1/10)1 | MicroscopyEnzyme immunoassay | N/A | Increased |
| Campos *et al*[18] | N/A | N/A | N/A | No | N/A |
| Chieffi *et al*[30] | N/A | *C. parvum* | Carbol-fuchsin staining | N/A | N/A |
| Clifford *et al*[21] | Public water supply | N/A | N/A | No | No |
| Delis *et al*[16] | N/A | N/A | MicroscopyBiopsy | No | Increased |
| Franco *et al*[100] | N/A | N/A | Gastric and small bowel biopsies and hematoxillin staining. | No | N/A |
| Frei *et al*[6] | N/A | N/A | Modified Ziehl-Neelsen staining | No | N/A |
| Gerber *et al*[17] | N/A | N/A | Micriscopy (2)1Biopsy (3)1 | No | N/A |
| Hong *et al*[9] | Swimming pool | N/A | Modified acid-fast stainingDFA | N/A | Increased |
| Krause *et al*[4] | None | N/A | Immunochromatographic test | No | Increased (5/6) |
| Ok *et al*[19] | N/A | N/A | N/A | *Blastomycsis hominis, Giardia intestinalis, Dientamoeba fragilis, Entamoeba coli* | N/A |
| Pozio *et al*[14] | AllograftN/A | *C. hominis**C. parvum* | MicroscopyBiopsy | No | N/A |
| Rodríguez Ferrero*et al*[7] | N/A | N/A | Modified Kinyoun stain | No | No |
| Tran *et al*[12] | N/A | N/A | Modified acid fast stainingMicroscopyBiopsy | No | No |
| Udgiri *et al*[13] | N/A | N/A | Modified acid fast stain | *Giardia spp.* (7)1*Entamoeba butschili* (1)1 | N/A |
| Vajro *et al*[24] | N/A | N/A | Monoclonal antibody fluorescein-conjugated stain | No | NA |
| Ziring *et al*[11] | Nosocomial (1)1 | N/A | Direct immunofluorescent assay | N/A | N/A |

1Number of patients; DFA: Direct fluorescent antibody; N/A: Not available.

**Table 3 Management of *Cryptosporidium* infections**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Ref.** | **Treatment regimen (length)** | **Changes in immunosuppression** | **Resolution of symptoms** | **Graft loss** | **Death** |
| Abdo *et al*[15] | Rifampin (3 wk) | Temporary lower level of TAC | Resolved | No | No |
| Acikgoz *et al*[23] | Spiramycin+NTZ+PAR (4 wk) | Switch from MMF o AZA | Resolved | No | No |
| Arslan *et al*[10] | N/A | N/A | N/A | N/A | N/A |
| Bandin *et al*[[8](#_ENREF_8)] | NTZ (4 wk) (2)fffffNTZ (2 wk) (5)1 | MMF switched to AZA (3)1MMF reduced (3)1TAC switched to sirolimus (1)1 | Resolved | No | No |
| Bhadauria *et al*[3] | NTZ (13) #(16-60 d)NTZ+fluoroquinolone (21) #(16-60 d) | MMF🡪AZA (3) #TAC 🡪 CsA (8) #Reduction of immunosuppression (11)# | Resolved microbiologically (83%) | Yes (3) |  |
| Bonatti *et al*[5] | AZM (14-21 d) (2)1AZM+NTZ (6-18 d) (2)1NTZ (14-16 d) (2)1AZM(5d)+NTZ+TMP/SMX(14d)(1)1AZM+PAR(14d) (1)1 | MMF stopped (4)1MMF reduced (1)1 | Resolved | No | No |
| Campos *et al*[18] | Spiramycin 🡪 PAR (6 mo)PAR(2) # | N/A | Resolved | No | No |
| Chieffi *et al*[30] | N/A | N/A | N/A | N/A | N/A |
| Clifford *et al*[21] | N/A | N/A | Resolved | No | No |
| Delis *et al*[16] | AZM (7 d) + PAR (21 d) (2)1PAR (14 d) (1)1PAR (21 d) (1)1 | S stopped (1/4)1TAC reduced (1/4)1 | Resolved | No | No |
| Franco *et al*[100] | Spiramicin 10 d | MMF🡪AzaStopped Aza | Resolved | No | No |
| Frei *et al*[6] | PAR (4 wk) | No | Resolved | No | No |
| Gerber *et al*[17] | AZM (3 wk) (1)1PAR (2-3 wk) (2)1 | No | Resolved | No | No |
| Hong *et al*[9] | NTZ (4 wk)PAR +AZM (5 wk),oral human immunoglobulin (5 d) | TAC reducedMMF stopped and AZT started | Resolved | No | No |
| Krause *et al*[4] | NTZ (5-24 d) | No | Resolved | No | No |
| Ok *et al*[19] | N/A | N/A | N/A | N/A | N/A |
| Pozio *et al*[14] | AZM (1 wk)+PAR(3 wk)AZM+PAR (1yr7 mo) | N/A | Resolved | No | No |
| Rodríguez Ferrero*et al*[7] | AZM + PAR (14 d)NTZ (6 d) | MMF and TAC reduced | Resolved | No | No |
| Tran *et al*[12] | PAR (4 wk) | Sirolimus discontinued | Resolved | No | No |
| Udgiri *et al*[13] | Spiramycin (10 d) (2)1 | No | Resolved | No | No |
| Vajro *et al*[24] | None | No | Resolved | No | No |
| Ziring *et al*[11] | PAR+AZM | N/A | Resolved | No | No |

1The number of patients; TAC: Tactolimus; MMF: Mycophenolate mofetil; AZT: Azathioprine; S: Steroids; AZM: Azithromycin; NTZ: Nitazoxanide; PAR: Paromomycin; N/A: Not available; TMP/SMX: Trimethoprim/sulphamethoxazole.