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REVIEW

Cryptosporidium infection in solid organ transplantation

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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

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.

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INTRODUCTION

Cryptosporidium is a parasitic protozoan causing a gastroenteritis syndrome[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[1,2]. In immunocompromised patients, clinical presentation can vary from asymptomatic to acute gastroenteritis, chronic diarrhea or even extra-intestinal manifestations[1,3-24]. 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[1,25]. 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]. 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], 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[3,10,30,31]. 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]. 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]. A recent study from India, shows that cryptosporidiosis accounts for the majority of infectious diarrhea (28.5%) in adult transplant recipients[3]. Children and immunocompromised patients are disproportionately affected, especially in developing countries[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*[31,33,34]. This proportion may be underestimated as up to 70% seroprevalence was found in children living in the United States-Mexican border[35]. Bandin *et al*[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[3,11].

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[28,35-40]. Infectivity depends on the number of oocysts and *Cryptosporidium* species and subtypes[41,42]. Outbreaks of cryptosporidiosis in developed countries have been described in daycare centers[43,44] in association with animal petting farms[45,46] and recreational water use[47,48]. 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]. 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[36,59]. *Cryptosporidium* can be eliminated by boiling the water or just heating it to 62 ℃ for few seconds and by filtration through < 1 μm filters[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]. 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]. Cryptosporidiosis has also been reported as a donor-derived infection after intestinal transplantation[14].

VIRULENCE IMMUNOPATHOGENICITY

The severity and duration of illness (from asymptomatic shedding of oocyts to severe life-threatening disease)

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

Ref.	No. of patients	Incidence	Median/mean (range/SD) age (yr)	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)[1] Liver (3)[1]	MMF, TAC, AZA, CsA, S	D	N/A	N/A
Bandin *et al*[8]	38	7/38 (18%)	8.93 (4.5-14)	Kidney	MMF + TAC + S (3)[1] MMF + TAC (2)[1] MMF + 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 + S TAC + 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)[1] Liver (1)[1] Lung (1)[1]	TAC + MMF + S (8)[1] CsA + AZA + S (1)[1] TAC + 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)[1] TAC + 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)[1] Intestine (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)[1] Liver-Kidney (1)[1] Heart (1)[1]	TAC + MMF + S TAC + AZA + S TAC + 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)[1] CsA + 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

[1]Number 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.

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[1,2].

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]. Toll-like receptors (TLR2 and TLR4) play an important part in initiating immune activation following mucosal injury by the parasite[62-64] and inducing cytokine release (IL-12, IL-15, IL-18, TNF-α and IFN-α/β) followed by activation of the NF-κB cells with IFN-γ production, mononuclear cell infiltration in the lamina propria, crypt cell hyperplasia, villous atrophy and blunting[65-67]. Toll-like receptors also have a role in establishing immunity to infection[62]. Innate immunity controls infection, but elimination of the parasite seems to require adaptive immunity[62]. IFN-γ is an important cytokine determining $CD4^+$ T cell response to infection, including memory response against *Cryptosporidium* infection in the intestine[62,68,69] (remove 63, add Pantenburg Infection and immunity). The role of the T cell function is supported by severe and prolonged cryptosporidiosis in

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	ELISA Modified 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]	Swimming pool (3) Traveler diarrhea (1)[1]	N/A	Zielh-Nielsen staining Auramine staining Microscopy Biopsy	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)[1] Camping (1)[1] Restaurant (1)[1] Well water/farm animals (1)[1]	*C. jejuni* (1/10)[1]	Microscopy Enzyme 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	Microscopy Biopsy	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)[1] Biopsy (3)[1]	No	N/A
Hong *et al*[9]	Swimming pool	N/A	Modified acid-fast staining DFA	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]	Allograft N/A	*C. hominis* *C. parvum*	Microscopy Biopsy	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 staining Microscopy Biopsy	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

[1]Number of patients; DFA: Direct fluorescent antibody; N/A: Not available. *C. hominis*: *Cryptosporidium hominis*; *C. parvum*: *Cryptosporidium parvum* ; *C. jejuni*: *Cryptosporidium jejuni*.

patients with AIDS and CD_4 count < 50 cells/mm^3, and improvement of the symptoms after introduction of highly active antiretroviral therapy[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]. All these changes at the level of the epithelium lead to malabsorption and secretory diarrhea[12,65].

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].

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[30,71]. A relatively high prevalence of oocyst excretion in asymptomatic transplant population might be detected in the stool with random stool screening[71]. When clinically evident,

SOT recipients typically present with profuse and prolonged watery diarrhea, sometimes associated with nausea, vomiting, abdominal pain and fever[1,4-10,12-24]. Other nonspecific symptoms have been described in immunocompetent and immunocompromised patients such as malaise, generalized weakness, myalgia, anorexia and headache[1,5,17]. Persistent vomiting and diarrhea can lead to dehydration and wasting and have been associated with increased morbidity[4,7,8,17]. Several study described acute renal failure, most likely secondary to dehydration, hypotension and sometimes tacrolimus toxicity[3-5,7-9,16,23]. 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]. Biliary involvement with *Cryptosporidium* inducing sclerosing cholangitis has been reported in few SOT recipients[12,15,18]. 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]. 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]; endoscopic retrograde cholangiography or magnetic resonance cholangiopancreatography could demonstrate dilation and/or irregularity of the biliary ducts[15,76].

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[2,77]. 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[12,14]. Respiratory cryptosporidiosis can present as an upper or lower respiratory tract infection manifested by nasal discharge, voice change, cough, dyspnea and hypoxemia[78-81].

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[82,83], requiring about 500000 oocysts/mL in formed stools for detection[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]. There are several enzyme linked immunosorbent assay (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[41,84-89]. 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[89,90]. Molecular methods provide the highest diagnostic sensitivity and are the preferred methods for diagnosis given their superior sensitivity and specificity. There are several multiplex polymerase chain reaction (PCR) test that can detect different gastrointestinal pathogens including viruses, parasites and bacteria however, these may not available in all laboratories[91]. These tests usually have high sensitivity to detect Cryptosporidium, although speciation may require further testing and carry a higher cost[26,41,42,92-94].

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[2,16,17,20]. 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[11,16,17].

Detection of Cryptosporidium in respiratory sample specimens is usually achieved with acid-fast, modified acid-fast staining or and indirect immunofluorescence[28,74] although PCR testing may also be possible[28]. Histopathology may show parasites lining the mucosal epithelium of trachea, bronchi or lung; tissue biopsies may also show intra or extracellular organisms[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[3,10,13,19,37,74,82,95]. 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]. Mycophenolate, a commonly used

immunosuppressive agent may have some antiparasitic activity against Cryptosporidium by inhibiting folate metabolism[4]. Cryptosporidium induced diarrhea may also result in increased tacrolimus levels[37] as evidenced in two recently published case series[4,5]. The pathophysiology is not entirely clear but it is likely a combination of factors including reduced cytochrome 3A activity during inflammation[96], interaction with other drugs, and reduced renal function due to fluid depletion[4]. Increased tacrolimus may in turn worsen renal function, and prolong immunosuppression[3]. Cholecystectomy may be indicated for cases with acalculous cholecystitis and sclerosing cholangitis usually needs endoscopic retrograde pancreatography with possible papillotomy and stenting[97]. To date, there has not been a highly effective agent to treat cryptosporidiosis in immunocompromised individuals[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]. 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 human immunodeficiency virus (HIV) infection[37] or case series and case reports (Table 3)[3-19,21,23,24,30,99,100]. 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]. Its activity, including the one of its metabolites has previously been shown *in vitro*[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]. 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[103,104]. 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 g twice a day *vs* placebo, good responses to nitazoxanide were seen in those with CD4 cell counts > 50/mm^3 although no difference to placebo was seen in the subgroup with CD4 < 50/mm^3[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]. 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]. The recommended nitazoxanide dose in SOT recipients is 500 mg twice daily for 14 d[37], however data from randomized trials in SOT recipients is lacking and longer courses of therapy are sometimes employed[3,4,8].

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]. It was useful reducing oocyst excretion in a small clinical trial[107]. Because paromomycin has not been shown to be useful as a standalone agent, combination therapy with other antiparasitic agents such as azithromycin and Nitazoxanide may be an attractive option[5,7,9,11,14,16,23,108].

Macrolide antibiotics such as azithromycin, clarithromycin or spiramycin also have activity against cryptosporidium[98], and were shown to reduce duration of symptoms and oocyst shedding in a clinical trial of treatment of children with cryptosporidiosis[109], but these findings were not replicated on a subsequent randomized trial[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]. 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[5,7,9,11,13,14,16-18,23]. 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].

Rifamycins also have antiparasitic activity. Rifabutin was shown to decrease cell infection by *Cryptosporidium*[115] and rifaximin has also been shown to be active *in vitro*[98]. Interestingly, the incidence of cryptosporidiosis was dramatically decreased in patients with advanced HIV infection who used rifabutin as part of *Mycobacterium avium* chemoprophylaxis[116,117]. 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[15,99]. 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]. 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,

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 to AZA	Resolved	No	No
Arslan *et al*[10]	N/A	N/A	N/A	N/A	N/A
Bandin *et al*[8]	NTZ (4 wk) (2) NTZ (2 wk) (5)[1]	MMF switched to AZA (3)[1] MMF reduced (3)[1] TAC 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)[1] AZM + NTZ (6-18 d) (2)[1] NTZ (14-16 d) (2)[1] AZM (5 d) + NTZ + TMP/SMX (14 d) (1)[1] AZM + PAR(14d) (1)[1]	MMF stopped (4)[1] MMF 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)[1] PAR (14 d) (1)[1] PAR (21 d) (1)[1]	Stopped (1/4)[1] TAC reduced (1/4)[1]	Resolved	No	No
Franco *et al*[100]	Spiramicin 10 d	MMF → Aza Stopped Aza	Resolved	No	No
Frei *et al*[6]	PAR (4 wk)	No	Resolved	No	No
Gerber *et al*[17]	AZM (3 wk) (1)[1] PAR (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 reduced MMF 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 (1 yr 7 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

[1]The 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.

usually with long courses advocated[3-5,8,9,23]. Azithromycin has been combined with either nitazoxanide or paromomycin also with reported success[5,82,115,118]. 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[37,119]. Safe sexual practice using condoms is also encouraged for anal intercourse, since it increases the risk of transmission as well[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]. More recently, monoclonal or polyclonal antibodies have shown to reduce oocyst shedding

and improve clinical symptoms[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].

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-5-monophosphate dehydrogenase, and fatty acylCoA binding inhibitors among others[82,122].

Despite this, the full understanding of *Cryptosporidium* immunopathogenesis remains unclear[35,68].

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[35,82]. 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]. Both IgG and IgA antibodies increased after exposure, however there was no correlation with infection[123]. Vaccination may be a viable alternative and vaccine has been evaluated in a mouse model[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]. There are other targets being investigated including a recombinant DNA vaccine using Vaccinia, Salmonella or Lactobacillus as DNA vectors[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.

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