Systematic Review

COMBINATION THERAPIES FOR CRYPTOSPORIDIOSIS IN IMMUNOCOMPROMISED PATIENTS

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ABSTRACT

Cryptosporidium sp. is a gastroenteritis-causing pathogen that may increase mortality and morbidity in immunocompromised patients. Diarrhea is a common problem among acquired immunodeficiency syndrome (AIDS) patients, with 30–60% of patients in developed countries and 90% in developing countries affected. The prevalence of cryptosporidiosis is 3–5% of the global population, with 14.42% of those affected being immunocompromised. There is currently no vaccine available to prevent cryptosporidiosis, while nitazoxanide monotherapy is ineffective in eradicating the organism in immunocompromised hosts and malnourished children. This study aimed to determine the most effective combination therapy for cryptosporidiosis in immunocompromised patients. This study used a systematic review design and implemented eligibility criteria for the literature search across PubMed, ScienceDirect, Epistemonikos, Google Scholar, Nature, Springer, and John Wiley databases. The search utilized specific keywords and Boolean operators, i.e., "*Cryptosporidium*," OR "cryptosporidiosis," AND "combination therapy," OR "combination treatment," AND "immunocompromised." Two cohort studies and two case reports were selected, three of which used a nitazoxanide and azithromycin combination as the intervention, whereas only one cohort study used a nitazoxanide and fluoroquinolone combination. The studies comprised 54 samples from post-kidney transplantation patients and one sample from an acute lymphoblastic leukemia (ALL) patient. The nitazoxanide and fluoroquinolone combination showed superior outcomes than the nitazoxanide and azithromycin combination. The stool clearance was significantly lower with nitazoxanide monotherapy than the nitazoxanide and fluoroquinolone combination (OR=0.65, 95% CI=0.34–0.92, p=0.01). However, it was non-significantly lower with the nitazoxanide and azithromycin combination compared to monotherapy (OR=0.27, 95% CI=0.01–5.77, p=0.24). Nitazoxanide monotherapy exerted a significantly lower effect than the nitazoxanide and fluoroquinolone combination in stopping diarrhea symptoms (OR=0.45, 95% CI=0.21–0.81, p=0.004). In conclusion, a combination therapy using nitazoxanide and fluoroquinolone for cryptosporidiosis in immunocompromised patients offers more favorable outcomes compared to monotherapy, particularly in stopping diarrhea and enhancing stool clearance.

Keywords: Cryptosporidiosis; immunocompromised; nitazoxanide; combination therapy; human immunodeficiency

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Highlights:
1. This study was conducted to review which combination therapy offers greater advantages for immunocompromised patients facing challenges due to the ineffectiveness of nitazoxanide monotherapy.
2. This study concluded that the combination therapy using nitazoxanide and fluoroquinolone for cryptosporidiosis in immunocompromised patients yields more favorable outcomes than the other combination therapy.

INTRODUCTION

Waterborne infectious diseases are major causal aspects of morbidity and mortality around the world. Protozoa have been identified as the cause of various waterborne epidemics over the last three decades. The World Health Organization (WHO) places *Cryptosporidium* sp. as one of the top protozoan parasites responsible for waterborne infectious diseases. *Cryptosporidium* sp. is an obligate enteric intracellular parasite that infects the gastrointestinal tract. This parasite is an opportunistic pathogen harmful for immunocompromised patients (Meidani et al. 2014, Tang et al. 2022). In patients with compromised immune systems, cryptosporidiosis may present as a critical illness. Dehydration, severe diarrhea, and wasting syndrome are among the persistent symptoms present in immunocompromised patients with cryptosporidiosis (Bouzid et al. 2013, Ali et al. 2014, Florescu & Sandkovsky 2016, Certad et al. 2017, Pumipuntu & Piratae 2018, Gerace et al. 2019, Mohebali et al. 2020, Deltombe et al. 2020).

The prevalence of cryptosporidiosis in humans is approximately 3–5% of the world population, with 14.42% of the affected individuals having a compromised immune system. The impact of cryptosporidiosis extends beyond the physical aspect, as it can also cause social and economic losses. The largest cryptosporidiosis outbreak occurred in Milwaukee, USA, in 1993, with an infection incidence exceeding 400,000 people. The total losses amounted to 96.2 million USD, comprising 31.7 million USD in medical costs and 64.6 million USD in lost productivity. Currently, no vaccine is available to prevent the protozoan disease caused by *Cryptosporidium* sp. (Efstratiou et al. 2017, Ahmadpour et al. 2020). Therefore, it is important to continuously research prospective treatments and preventive measures for cryptosporidiosis, particularly in immunocompromised individuals, to fulfill the global and national commitments under the Sustainable Development Goal (SDG) 3, which aims to improve people's well-being through healthy and prosperous lives.

The most effective therapy so far for cryptosporidiosis in immunocompromised patients includes rehydration, antimotility agents, antiparasitics, nutritional therapy, and reversal therapy. Nitazoxanide (NTZ) is the only drug approved by the U.S. Food and Drug Administration (FDA). However, this drug does not effectively eradicate the organism in immunocompromised hosts and malnourished children (Esmat et al. 2022). Thus, combination therapy is a potential treatment for immunocompromised patients. Prior research has demonstrated that the combination of nitazoxanide and fluoroquinolone (FQ) is more effective than monotherapy in kidney transplant patients (Bhadauria et al. 2015). Additionally, Lanternier et al. (2017) have shown the effectiveness of combining nitazoxanide with azithromycin (AZR) to treat cryptosporidiosis in immunocompromised patients. The purpose of this systematic review was to discover the most effective combination therapy for treating cryptosporidiosis in immunocompromised patients. Given the limited information regarding the treatment of cryptosporidiosis, it is necessary to review the effectiveness of combination treatments used in previous studies.

MATERIALS AND METHODS

This study used a systematic review design and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with ID number CRD42024579886, entitled "Combination Therapy for Cryptosporidiosis in Immunocompromised Patients: A Systematic Review" (https://www.crd.york.ac.uk/PROSPERO/#CRD42024579886). The method used in this study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al. 2021). The literature was collected from PubMed, ScienceDirect, Epistemonikos, Google Scholar, Nature, Springer, and John Wiley databases. The literature search used the following keywords along with Boolean operators: "*Cryptosporidium*," OR "cryptosporidiosis," AND "combination therapy," OR "combination treatment," AND "immunocompromised."

The literature search was limited to papers from certain locations, involving human samples, written in English, subjected to peer review, and available in full text. Forty-five resources were selected according to these inclusion criteria. Articles in languages other than English were excluded. Only articles utilizing combination therapy for cryptosporidiosis were considered, whereas papers presenting study designs other than cohort studies and case reports were eliminated. The publication time of the studies was limited from January 2007 to December 2023. This study employed the Population, Intervention, Comparison, Outcome, Study design (PICOS) framework as outlined by Amir-Behghadami & Janati (2020). The details were as follows: (1) Population: Immunocompromised patients with cryptosporidiosis; (2) Intervention: Combination therapy using nitazoxanide with either fluoroquinolone or azithromycin; (3) Comparison: Nitazoxanide monotherapy; (4) Outcomes: Cryptosporidiosis; (5) Study design: Cohort studies and case reports. Figure 1 displays the PRISMA

flowchart for the article selection process.

RESULTS

The literature search yielded 99 articles that were published from January 2007 to December 2023. A total of 54 articles were omitted due to duplications. The remaining 45 articles were analyzed for inclusion in this study according to the eligibility criteria. Finally, 41 papers were excluded, resulting in the inclusion of four articles in this systematic review. The four articles consisted of two cohort studies and two case reports. Among the selected articles, one cohort study and two case reports demonstrated a combination therapy using nitazoxanide and fluoroquinolone as the intervention. The other cohort study reported a combination therapy using nitazoxanide and fluoroquinolone as the intervention. A total of 54 samples from post-kidney transplantation patients and one sample from an acute lymphoblastic leukemia (ALL) patient were involved in the selected studies. Three out of the four studies were conducted in India, while the other one took place in France.

Four studies were included in the systematic review, as shown in Table 1. Three of the four studies reported kidney transplantation cases, in which the subjects consumed immunosuppressants. The other study documented acute lymphoblastic leukemia cases, in which the subjects did not take immunosuppressants. A total of 54 samples from post-kidney transplantation patients and one sample from an acute lymphoblastic leukemia (ALL) patient were involved in the selected studies. Three out of the four studies were conducted in India, while the other one took place in France.

Table 1. Characteristics of the included studies.

Studies	Location	Study design	Conditions associated with being immunocompromised	n
Bakliwal et al. (2021)	India	Case report	Acute lymphoblastic leukemia	1
Priyamvada et al. (2014)	India	Case report	Kidney transplantation	2
Bhadauria et al. (2015)	India	Cohort	Kidney transplantation	34
Lanternier et al. (2017)	France	Cohort	Kidney transplantation	18

The two case reports discussed the duration required for the cessation of diarrhea after administering immunosuppressant therapy. All subjects in the case reports were immunocompromised due to kidney transplantation and acute lymphoblastic leukemia, and they received immunosuppressive drugs. The immunosuppressive drugs administered were tacrolimus, mycophenolate mofetil, and corticosteroids. Bakliwal et al. (2021) demonstrated that the administration of combination therapy resulted in the resolution of the diarrhea by day 13. Furthermore, there were no oocysts found in the samples microscopically examined using modified Ziehl-Neelsen acid-fast staining. Priyamvada et al. (2014) reported that the administration of combination therapy in the first sample resulted in the clearance of oocysts after 28 days. At the same time, the negative oocyst examination indicated that feces were identified on day 28, as shown in Table 2. However, on day 35, diarrhea reoccurred, prompting the continuation of combination therapy until day 42.

Table 2. Systematic review of the included case reports.

Author	Intervention	Required duration for diarrhea cessation	Required duration for stool clearance	Immunosuppressants
Bakliwal et al. (2021)	NTZ and AZR	13 days	13 days	None
Priyamvada et al. (2014)	NTZ and AZR	21 days	28 days	Tacrolimus, prednisolone, and, mycophenolate mofetil
		42 days	28 days	Tacrolimus, prediniosolone, and azathriopine

Legends: NTZ=nitazoxanide; AZR=azithromycin.

Two cohort studies carried out by Bhadauria et al. (2015) and Lanternier et al. (2017) analyzed the duration of interventions for each therapy using Fisher's exact test. The odds ratio (OR) was assessed to determine the effectiveness of nitazoxanide monotherapy compared to combination therapies according to the number of diarrhea cases resolved. The two cohort studies reported an OR effect size of less than one, suggesting an inverse OR. One of the cohort studies showed an OR of 0.65 (p=0.001) for stool clearance and 0.45 (p=0.004) for diarrhea resolution. The other study yielded an OR of 0.27 for both stool clearance and diarrhea cessation (p=0.24), indicating a lack of statistical significance due to the small sample size. The detailed results are presented in Table 3.

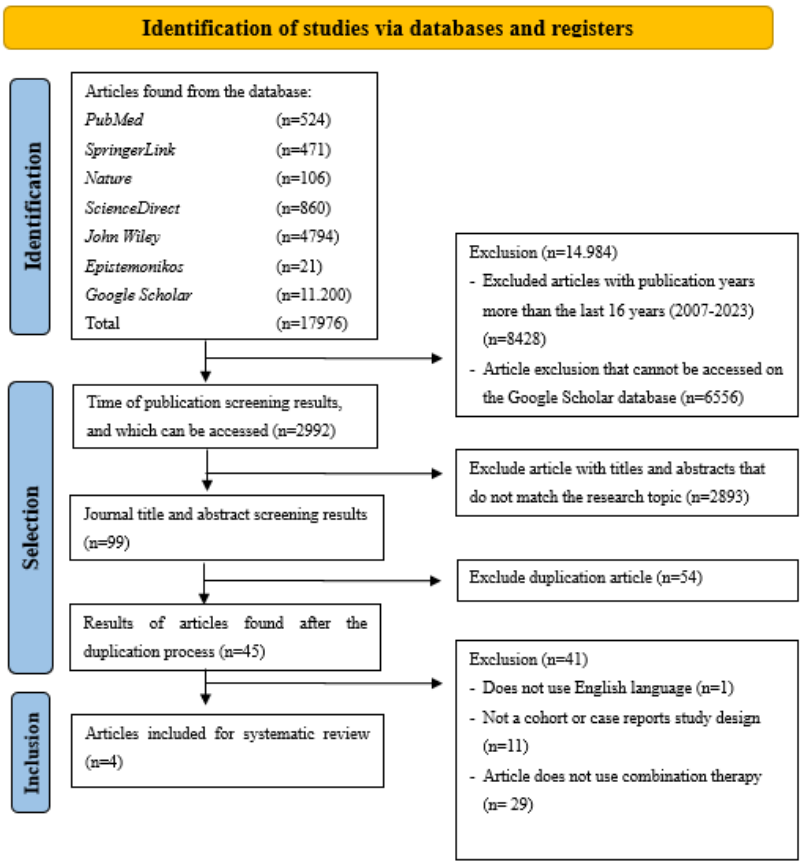

Figure 1. PRISMA flowchart depicting the studies included and excluded at each screening stage.

Table 3. Systematic review of the included cohort studies.

Author	Intervention	Diarrhea cessation (%)		Stool clearance (%)		Immunosuppressants	OR	p
		I	C	I	C			
Bhadauria et al. (2015)	NTZ and FQ	85.71	38.46	95.23	61.53	Prednisolone, tacrolimus, and mycophenolate mofetil	S: 0.45 D: 0.65	S: 0.004 D: 0.01
Lanternier et al. (2017)	NTZ and AZR	66	91	66	91	Tacrolimus, prednisolone, and mycophenolate mofetil	0.27	0.24

Legends: OR: I=intervention group; C=control group; OR=odds ratio; NTZ=nitazoxanide; FQ=Fluoroquinolone; AZR=azithromycin; S=stool clearance; D=diarrhea cessation.

DISCUSSION

Human cryptosporidiosis is known as an intestinal protozoan infection with different clinical characteristics between immunocompetent and immunosuppressed individuals. Although it is self-limiting in immunocompetent people, it poses a potential life-threatening risk for those with immune deficiency (Utami et al. 2020). We conducted a systematic review analysis of two case reports and two cohort studies about cryptosporidiosis in immunocompromised patients. The reviewed studies were undertaken in India and France between 2014 and 2021. The immunocompromised samples consisted of patients with acute lymphoblastic leukemia and those who had undergone renal transplant. The results reported in this study were the types of drugs, drug doses, the duration of monotherapy and combination therapy, as well as the types and doses of immunosuppressant therapy administered alongside the cryptosporidiosis therapy. This study also included the statement and duration of oocyst-negative recovery (stool clearance) and the resolution of clinical diarrhea symptoms of diarrhea after the administration of combination therapy, along with p and OR values that indicated the significance of the nitazoxanide monotherapy compared to the combination therapy intervention.

Bakliwal et al. (2021) administered nitazoxanide and azithromycin to a 3-year-old boy with cryptosporidiosis and acute lymphoblastic leukemia. The patient reported diarrhea cessation and stool clearance on day 13 after consuming the combination therapy. Nitazoxanide, in combination with azithromycin, may contribute to multiple opportunistic pathogen prophylaxis (MOPP) in immunocompromised individuals, leveraging the advantages of agents that are effective against a variety of opportunistic pathogens. Azithromycin exhibits effectiveness against various Gram-positive bacteria, Gram-negative bacteria, mycobacteria, and T. gondii. The mechanism underlying the additive anticryptosporidial effect of the nitazoxanide and azithromycin combination appears to be complex. Nitazoxanide inhibits the enzyme pyruvate ferredoxin oxidoreductase (PFOR), hence obstructing the energy production and metabolism of anaerobic parasites. Azithromycin can inhibit protein synthesis by binding to the transpeptidation site of the larger ribosomal subunit. The combination of nitazoxanide and azithromycin may produce a cumulative inhibitory effect. Nitazoxanide as a monotherapy can suppress parasite activity by 56.1%. However, its combination with additional agents can achieve an 83.9% reduction. The cytotoxicity of this drug in monotherapy ranges from 8.9% to 11.2%, but in combination therapy, it is around 6.5% to 8.4%. The studies imply that the combination therapy exhibits a lower cytotoxicity in comparison to monotherapy, resulting in minimized diarrhea as a side effect (Certad et al. 2017, Lee et al. 2017).

Priyamvada et al. (2014) reported the varying durations required to achieve diarrhea resolution using immunosuppressants. Tacrolimus and steroids inhibit the proliferation and cytokine production of cluster of differentiation 4^+ ($CD4^+$) T cells by suppressing interleukin 2 (IL-2) production. Mycophenolate mofetil has antiproliferative effects on T and B lymphocytes. Tacrolimus and mycophenolate mofetil consumption increase the incidence of $CD4^+$ helper defects, but a tacrolimus and azathioprine combination may provide an opposite effect (Jurdi et al. 2023). The varying durations of diarrhea cessation may be attributed to the immune system of a specimen, specifically the activity of $CD4^+$ cells in regulating innate and adaptive immunity. $CD4^+$ T cells play an important role in establishing and maximizing the immune response. These cells lack cytotoxic or phagocytic activity, rendering them incapable of directly killing infected cells or clearing pathogens. However, they "mediate" the immune response by directing other cells to perform these tasks and regulate the type of immune response that develops. Impaired immunity complicates the elimination of the parasite and increases the risk of reinfection. The opportunistic nature of the pathogen facilitates infection, resulting in prolonged diarrhea and delayed stool clearance in the first sample (Laurent & Lacroix-Lamandé 2017).

The combination of nitazoxanide and fluoroquinolone plays a role in the prophylaxis of multiple opportunistic pathogens. Fluoroquinolone is active against Gram-positive and Gram-negative bacteria, which can stop diarrhea in cases of opportunistic infections (Bhadauria et al. 2015, Rizk et al. 2018). The antimicrobial activity of fluoroquinolone arises from its ability to inhibit topoisomerase II, also known as deoxyribonucleic acid (DNA) gyrase, and topoisomerase IV, hence actively obstructing the replication of *Cryptosporidium* sp. parasite DNA and killing pathogenic bacteria. Nitazoxanide demonstrates its antiparasitic activity by inhibiting the metabolism of anaerobic parasites (Hooper & Jacoby 2016, Fief et al. 2019). In this study, the effect of nitazoxanide monotherapy on stool clearance was significantly lower compared to the combination therapy (OR=0.65, 95% CI=0.34–0.92, p=0.01). The inverse OR (<1) indicated that nitazoxanide monotherapy is 1.65 times less effective in achieving stool clearance in comparison to combination therapy. The effect of nitazoxanide monotherapy on diarrhea resolution was significantly lower compared to the

combination therapy (OR=0.45, 95% CI=0.21–0.81, p=0.004). The inverse OR implied that nitazoxanide monotherapy is 2.2 times less effective in stopping diarrhea compared to combination therapy (Higgins & Thomas 2022).

Lanternier et al. (2017) have shown that macrolides may increase plasma levels of tacrolimus, which is metabolized by cytochrome P4503A (CYP3A). In addition, an increase in the blood concentration of calcineurin inhibitors during a diarrheal episode and cryptosporidiosis interferes with parasite elimination. This creates a burden on both innate and adaptive immunity systems, thereby increasing the risk of reinfection (Ali et al. 2014, Laurent & Lacroix-Lamandé 2017). Combination therapy may be more beneficial than monotherapy in terms of the durations required for stool clearance and diarrhea cessation. However, the level of tacrolimus should be closely monitored when administered along with other drugs that are metabolized by CYP3A in order to appropriately adjust the level of immunosuppression during diarrheal episodes and cryptosporidiosis (Tuano et al. 2021). This study demonstrated that the combination therapy had a lower effect on stool clearance compared to monotherapy (OR=0.27, 95% CI=0.01–5.77, p=0.24), despite not being statistically significant. The non-significant result might be because the sample used in this study was too small or did not meet the minimum size. Statistical tests with a more extensive sample size would yield more significant results. A sample size that is too small reduces the power of the research and increases the margin of error.

Strength and limitations

This study is unprecedented, as no other systematic review has addressed the topic discussed here. One notable limitation of this study is the tendency to use samples from patients devoid of confounding variables, such as human immunodeficiency virus (HIV) or other conditions. Drug interactions are particularly critical in immunocompromised patients, including those who have undergone organ transplantation. Another limitation of this study is the lack of resources, comprising only four publications in total, and the fact that only one person conducted the review process, which might increase the risk of bias.

CONCLUSION

Combination therapies may provide more favorable outcomes compared to monotherapy for immunocompromised patients with cryptosporidiosis. Specifically, a combination therapy using nitazoxanide and fluoroquinolone demonstrates significant improvement of cryptosporidiosis clinical symptoms, including diarrhea cessation and stool clearance. This combination therapy can be administered together with immunosuppressive drugs, such as tacrolimus.

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Conflict of interest

None.

Ethical consideration

None.

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None.

Author contribution

WSU contributed to the conception and design, analyzed and interpreted the data, critically revised the article for important intellectual content, and provided final approval of the article. MSIR drafted the article, provided statistical expertise, and collected and assembled the data. LI analyzed and interpreted the data, drafted the article, and provided final approval of the article as well as administrative, technical, or logistic support. CA and BH drafted the article, critically revised the article for important intellectual content, and provided final approval of the article.

REFERENCES

Ahmadpour E, Safarpour H, Xiao L, et al. (2020). Cryptosporidiosis in HIV-positive patients and related risk factors: A systematic review and meta-analysis. Parasite 27**,** 27. doi: 10.1051/parasite/2020025.

Ali S, Mumar S, Kalam K, et al (2014). Prevalence, clinical presentation and treatment outcome of cryptosporidiosis in immunocompetent adult patients presenting with acute diarrhoea. The Journal of the Pakistan Medical Association 64**,** 613–618. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25252476.

Amir-Behghadami M, Janati A (2020). Population, intervention, comparison, outcomes and study (PICOS) design as a framework to formulate eligibility criteria in systematic reviews.

Emergency Medicine Journal 37, 387–387. doi: 10.1136/emermed-2020-209567.

Bakliwal A, Nath UK, Mohanty A, et al (2021). Life-threatening cryptosporidium diarrhea in a child on induction chemotherapy for acute lymphoblastic leukemia. Cureus. doi: 10.7759/cureus.18340.

Bhadauria D, Goel A, Kaul A, et al (2015). Cryptosporidium infection after renal transplantation in an endemic area. Transplant Infectious Disease 17, 48–55. doi: 10.1111/tid.12336.

Bouzid M, Hunter PR, Chalmers RM, et al (2013). Cryptosporidium pathogenicity and virulence. Clinical Microbiology Reviews 26, 115–134. doi: 10.1128/CMR.00076-12.

Certad G, Viscogliosi E, Chabé M, et al (2017). Pathogenic mechanisms of cryptosporidium and giardia. Trends in Parasitology 33, 561–576. doi: 10.1016/j.pt.2017.02.006.

Deltombe C, Lefebvre M, Morio F, et al (2020). Cryptosporidiosis and microsporidiosis as causes of diarrhea in kidney and/or pancreas transplant recipients. Médecine et Maladies Infectieuses 50, 407–413. doi: 10.1016/j.medmal.2019.07.010.

Efstratiou A, Ongerth JE, Karanis P (2017). Waterborne transmission of protozoan parasites: Review of worldwide outbreaks - An update 2011–2016. Water Research 114, 14–22. doi: 10.1016/j.watres.2017.01.036.

Esmat M, Abdel-Aal AA, Shalaby MA, et al (2022). Efficacy of clofazimine and nitazoxanide combination in treating intestinal cryptosporidiosis and enhancing intestinal cellular regeneration in immunocompromised mice. Food and Waterborne Parasitology 27, e00161. doi: 10.1016/j.fawpar.2022.e00161.

Fief CA, Hoang KG, Phipps SD, et al (2019). Examining the impact of antimicrobial fluoroquinolones on human DNA topoisomerase IIα and IIβ. ACS omega 4, 4049–4055. doi: 10.1021/acsomega.8b03428.

Florescu DF, Sandkovsky U (2016). Cryptosporidium infection in solid organ transplantation. World Journal of Transplantation 6, 460–471. doi: 10.5500/wjt.v6.i3.460.

Gerace E, Presti VDM Lo, Biondo C (2019). Cryptosporidium infection: Epidemiology, pathogenesis, and differential diagnosis. European Journal of Microbiology and Immunology 9, 119–123. doi: 10.1556/1886.2019.00019.

Higgins J, Thomas J (2022). Cochrane handbook for systematic reviews of interventions. Cochrane. Available at: https://training.cochrane.org/handbook/archive/v6.3.

Hooper DC, Jacoby GA (2016). Topoisomerase inhibitors: Fluoroquinolone mechanisms of action and resistance. Cold Spring Harbor perspectives in medicine. doi: 10.1101/cshperspect.a025320.

Jurdi N El, Hoover A, O'Leary D, et al (2023). Phase II study of myeloablative 7-8/8-matched allotransplantation with post-transplantation cyclophosphamide, tacrolimus, and mycophenolate mofetil. Transplantation and Cellular Therapy 29, 576.e1-576.e5. doi: 10.1016/j.jtct.2023.06.008.

Lanternier F, Amazzough K, Favennec L, et al (2017). Cryptosporidium spp. infection in solid organ transplantation. Transplantation 101, 826–830. doi: 10.1097/TP.0000000000001503.

Laurent F, Lacroix-Lamandé S (2017). Innate immune responses play a key role in controlling infection of the intestinal epithelium by Cryptosporidium. International Journal for Parasitology 47, 711–721. doi: 10.1016/j.ijpara.2017.08.001.

Lee S, Harwood M, Girouard D, et al (2017). The therapeutic efficacy of azithromycin and nitazoxanide in the acute pig model of Cryptosporidium hominis ed. Yeruva L. PLoS One 12, e0185906. doi: 10.1371/journal.pone.0185906.

Meidani M, Naeini AE, Rostami M, et al (2014). Immunocompromised patients: Review of the most common infections happened in 446 hospitalized patients. Journal of Research in Medical Sciences : The Official Journal of Isfahan University of Medical Sciences 19, S71-3. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25002900.

Mohebali M, Yimam Y, Woreta A (2020). Cryptosporidium infection among people living with HIV/AIDS in Ethiopia: A systematic review and meta-analysis. Pathogens and Global Health 114, 183–193. doi: 10.1080/20477724.2020.1746888.

Page MJ, McKenzie JE, Bossuyt PM, et al (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJn71. doi: 10.1136/bmj.n71.

Priyamvada PS, Parameswaran S, Morkhandikar S, et al (2014). Successful eradication of cryptosporidium in kidney transplant recipients – Two case reports. Indian Journal of Transplantation 8, 22–24. doi: 10.1016/j.ijt.2014.01.013.

Pumipuntu N, Piratae S (2018). Cryptosporidiosis: A zoonotic disease concern. Veterinary World 11, 681–686. doi: 10.14202/vetworld.2018.681-686.

Rizk MA, AbouLaila M, El-Sayed SA, et al (2018). Inhibitory effects of fluoroquinolone antibiotics on Babesia divergens and Babesia microti, blood parasites of veterinary and zoonotic importance. Infection and Drug Resistance 11, 1605–1615. doi: 10.2147/IDR.S159519.

Tang W, Akakulu W, Desai K (2022). Pneumatosis intestinalis caused by Cryptosporidium colitis in a non-immunocompromised patient. IDCases 27, e01372. doi: 10.1016/j.idcr.2021.e01372.

Tuano KS, Seth N, Chinen J (2021). Secondary

immunodeficiencies. Annals of Allergy, Asthma & Immunology 127**,** 617–626. doi: 10.1016/j.anai.2021.08.413.

Utami WS, Murhandarwati EH, Artama WT, et al (2020). Cryptosporidium infection increases the risk for chronic diarrhea among people living with HIV in Southeast Asia: A systematic review and meta-analysis.Asia Pacific Journal of Public Health 32**,** 8–18. doi: 10.1177/1010539519895422.