A looming shadow: Impact of parasitic infections in hematopoietic stem cell transplantation: A comprehensive review

Review Article

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ABSTRACT

Parasitic infections have a significant impact on recipients of hematopoietic stem cell transplantation (HSCT), posing considerable risks of morbidity and mortality. They cause a diverse array of clinical syndromes, ranging from asymptomatic to severe disseminated disease. The incidence and range of parasitic infections vary according to geographic region, transplant type, conditioning regimen (the high dose of chemotherapy and radiotherapy to suppressive bone marrow), and immunosuppressive therapy. Early recognition of parasitic infections in HSCT recipients is challenging due to possible nonspecific clinical manifestations and overlapping symptoms with other infectious, and non-infectious complications. This calls for a high index of suspicion and a systematic diagnostic approach for timely diagnosis and appropriate management. Current diagnostic methods, such as microscopy, serological assays, molecular tests, and imaging studies, have limitations in sensitivity and specificity, highlighting the need for improved diagnostic tools. Treatment requires a specific approach based on the pathogen, clinical syndrome, immune status and transplant-related factors, often involving antiparasitic agents combined with supportive care. Despite advances, gaps remain in optimizing management, necessitating further research into diagnostic technologies, host-pathogen interactions, treatment strategies, and preventive measures. A multidisciplinary approach leveraging emerging technologies is essential for improving outcomes in HSCT recipients with parasitic infections. This review discusses broadly the clinical presentations, diagnostic approaches, treatment strategies, and preventive measures for parasitic infections in HSCT recipients.

Keywords: clinical presentation; diagnosis; hematopoietic stem cell transplantation; parasitic infections; prevention; treatment.

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Abbreviations: GVHD: Graft-versus-host disease; **HSCT:** Hematopoietic stem cell transplantation; **NRM:** Non-relapse mortality; **SHS:** *Strongyloides* hyper-infection syndrome.

INTRODUCTION

The introduction of HSCT is an accomplished therapeutic mean for a variety of hematological malignancies and disorders. It involves replacing the patient's diseased or dysfunctional bone marrow with healthy stem cells from either a donor (allogeneic HSCT) or the patient themselves (autologous HSCT). In fact, HSCT treats certain cancers such as leukemia, lymphoma, and multiple myeloma, severe aplastic anemia, and genetic diseases like thalassemia[1]. It is increasingly implemented worldwide, and the incidence of diseases requiring HSCT influences its epidemiological applications[2]. While HSCT apparently promises curing various hematologic disorders, its application holds significant risks, particularly due to the extreme immunosuppression associated with myeloablative conditioning regimens. Besides, it leads to a prolonged period of aplasia, lasting for an average of three weeks, during which HSCT recipients are highly susceptible to variable infections[3]. Evidently, the immune response status of HSCT recipients is significantly compromised due to several factors. Firstly, post-transplant immune reconstitution is slow, lasting for months to years for full recovery, particularly for T-cells, rendering patients vulnerable to infections[4]. Secondly, both innate and adaptive immune functions are reduced; while natural killer (NK) cells and neutrophils recover relatively quickly, T-cell and B-cell functions remain deficient for an extended period[5].

Parasitic infections pose an increased risk among HSCT recipients due to several reasons including 1) the intensive chemo- or radiation therapy used to eradicate diseased bone marrow

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results in immunosuppression; 2) post-transplant, patients receive immunosuppressive drugs to prevent graft-versus-host disease (GVHD)[5,6], which further weakens their immune system; 3) the preparative regimen for HSCT can damage mucosal barriers in the gastrointestinal tract, facilitating easier invasion by intestinal parasites[7]. These factors collectively heighten susceptibility to infections among HSCT recipients, necessitating cautious monitoring and preventive measures. It is worth mentioning that parasitic infections themselves can further suppress the already compromised immune system of HSCT recipients, rendering them more susceptible to secondary bacterial, fungal, or viral infections. These secondary infections can significantly increase morbidity and mortality[8].

The present review aims to present the possible parasitic infections associated with HSCT recipients, their clinical presentations, diagnostic approaches, treatment strategies, and preventive measures.

Prevalence of parasitic infections among HSCT recipients

Parasitic diseases remain significantly under-researched compared to other infections associated with HSCT. The immunocompromised status of HSCT recipients predisposes them to opportunistic pathogens or the reactivation of latent parasitic infections. Understanding their range and impact is crucial for improving patient outcomes[9].

It has been reported that parasitic infections following HSCT occur at a frequency ranging from 0.31% to 10%, which appears to be lower compared to bacterial and viral infections[10]. The concerned reviewers analyzed 30 records from which 126 cases were chosen. Toxoplasmosis emerged as the most prevalent parasitic infection among allogeneic HSCT recipients, with 85 reported cases. Leishmaniasis followed with 21 patients, while a few instances of *Plasmodium* spp. (two patients) and *T. cruzi* infection (one patient) were identified, often linked to the endemic country of either the donor or recipient. Additionally, in the United States and France, there were three reported cases of *Acanthamoeba* spp. infection. Among enteric pathogens, detected infections were by *S. stercoralis* (five patients), *Microsporidium* spp. (six patients), *Cryptosporidium* spp. (one patient), *G. lamblia* (one patient), and *Blastocystis* spp. (one patient)[10]. It seems that quantifying the exact detection rates of parasitic infections in HSCT is challenging due to several factors:

- **Variations in diagnostic methods:** Standardized testing protocols for parasitic infections are not always implemented in healthcare institutions. This inconsistency in diagnostic approaches fails to disclose a clear picture of the true burden of parasitic infections in HSCT patients.
- **Geographic disparities:** The prevalence of parasitic infections varies significantly depending on the geographical location of the transplant center. Endemic parasitic diseases are more prevalent in tropical and subtropical regions, leading to a higher risk for HSCT recipients in these areas.
- **Asymptomatic presentation:** Parasitic infections can sometimes be asymptomatic, particularly in the early stages or latent conditions (e.g., *T. gondii*). This lack of symptoms can hinder timely detection and treatment, potentially leading to complications.

Clinical manifestations

Unlike immunocompetent individuals, HSCT recipients might present with atypical and non-specific symptoms, rendering diagnosis a difficult task. Parasitic infections involve a diverse range of organisms, each able to produce a variety of clinical manifestations in the recipients. Symptoms such as fever, fatigue, diarrhea, and abdominal pain are common in various post-transplant complications such as GVHD, thus challenging the diagnosis. For instance, diarrhea associated with intestinal amebiasis may be mistaken for GVHD. Differentiating between diarrhea due to giardiasis and GVHD is vital, due to similarity of presentations. In their report of amoebic colitis[11], symptoms, e.g., diarrhea, bloating, abdominal disturbance, fever, nausea, vomiting, fatigue and weight loss were observed before HSCT and became worse after the procedure, highlighting the importance of considering parasitic infections in allogeneic HSCT recipients. Blastocystosis and cryptosporidiosis have been identified in HSCT recipients initially presenting as GVHD, emphasizing the need for heightened awareness regarding parasitic infections in these cases[12,13].

The following are some of the common presentations based on the type of parasite:

1. **Intestinal parasites:** Species of *Blastocystis*, *Cryptosporidium* and *Microsporidia* (mainly *E. bieneusi* and *E. intestinalis*) as well as *G. lamblia*, and *E. histolytica* frequently cause chronic diarrhea, abdominal pain, nausea, and vomiting. In severe cases, they cause prominent weight loss in children due to dehydration and malnutrition compromising the health of HSCT recipients further[9,11,14].
2. **Hematologic parasites:** Although uncommon in non-endemic countries, cases of post-HSCT malaria, predominantly involving *P. falciparum* or *P. vivax*, were reported[15]. Post-HSCT malaria often occurs in allogeneic HSCT recipients, frequently from related donors, but also from blood transfusions, or recurrence in the recipient. The onset of symptoms varies, with fever and pancytopenia being common, although some asymptomatic patients receive treatment due to risk factors or positive tests. In a few instances, the diagnosis

of malaria was preceded by the rare occurrence of hemophagocytic syndrome[16]. Moreover, *B. microti* can adversely affect the red blood cells, leading to symptoms like fever, chills, fatigue, anemia, and potential premature hemolysis of red blood cells[17].

3. **Tissue/visceral parasites:** Latent toxoplasmosis invades the central nervous system causing encephalitis[18]. Symptoms of toxoplasmic encephalitis include headache, confusion, seizures, focal neurological deficits, and brain abscess formation, often appearing within the initial two months post-transplantation[19]. Leishmaniasis and Chagas' disease affect a variety of organs with symptoms ranging from fever, fatigue, and lymphadenopathy in addition to organ-specific manifestations depending on the organ affected[9,15]. *Acanthamoeba* spp. and *B. mandrillaris* can result in skin infections and long-lasting granulomatous amebic encephalitis. In contrast, *N. fowleri* causes a rapid and severe form of primary amebic meningoencephalitis[20]. *Acanthamoeba* keratitis primarily affects healthy individuals, often associated with the use of contact lenses[21]. Diagnosis requires alertness, because recipients of autologous HSCT may face an elevated risk of free-living amebic reactivation[12].
4. **Disseminated parasitic infections:** In immunocompromised individuals, parasitic infections frequently extend beyond the primary site of infection, i.e., disseminated disease. This highlights the importance of considering parasitic infections as a differential diagnosis even for apparently unrelated symptoms.
   - **Strongyloidiasis:** It is crucial to recognize the significance of *S. stercoralis*, responsible for hyper-infection, leading to parasite dissemination. The immune response, particularly the T-helper 2 cell–mediated response, plays a crucial role in controlling infection by the larvae stage. However, in HSCT recipients, there's a heightened risk of autoinfection leading to *Strongyloides* hyper-infection syndrome (SHS). Factors such as use of immunosuppressive drugs, including corticosteroids and T cell–depleting agents, and human T-lymphotropic virus type I co-infection also increase the risk of SHS in transplant recipients. On the other hand, cyclosporine-based treatments showed efficacy in preventing *Strongyloides* reactivation among transplant recipients due to the drug's anti-parasitic properties[12,22]. In allogeneic HSCT recipients, the highest risk period for parasitic reactivation typically occurs when GVHD develops and steroid treatment is initiated with discontinuation of cyclosporine[12]. Notably, SHS is characterized by a heavy parasite burden, leading to prominent clinical symptoms primarily affecting the lungs and gastrointestinal tract in addition to larvae dissemination to several organs. Symptoms include fever, rash, gastrointestinal discomfort, diarrhea, coughing of blood, dyspnea, wheezing, and central nervous system involvement manifested as headache, disturbed consciousness, seizures and coma[23].
   - **Microsporidiosis:** *Microsporidia* spp., namely *Encephalitozoon* spp., typically cause disseminated infections involving multiple organs such as the kidneys, lungs, eyes, brain, and others. Clinical presentations encompass interstitial nephritis, bronchitis, keratoconjunctivitis, encephalitis, sinusitis, hepatitis, cholecystitis, osteomyelitis, and myositis[12,14].

Delayed diagnosis and treatment

Overcoming diagnostic difficulties in HSCT recipients involves several challenges including non-specific symptoms and atypical presentations in immunocompromised individuals. To discover the causative parasite, a multifaceted approach is essential. This includes 1) obtaining a detailed medical and travel history to identify potential exposure to endemic diseases, and 2) maintaining a high clinical suspicion for parasitic infections, particularly in patients with unexplained symptoms or those from high-prevalence regions[15,24,25].

Several challenges confront the implementation of treatment of HSCT recipients. One major issue is the immunocompromised state induced by HSCT, which hampers the effectiveness of antiparasitic medications as a functional immune system is often crucial for optimal efficacy[26,27]. In some cases, reduction of immunosuppressive therapy is required to restore immunity for successful treatment, particularly in toxoplasmosis[15]. Additionally, drug interactions pose a significant challenge; antiparasitic medications can interact with immunosuppressive drugs, potentially reducing their effectiveness or increasing side effects[28,29], making careful selection and dose adjustments crucial. Moreover, limited treatment options further complicate the situation as not all antiparasitic medications are safe or effective for HSCT recipients. Some may have severe side effects detrimental to an already compromised immune system, and the emergence of drug-resistant parasites aggravates these difficulties[30].

Impact of parasitic infections on non-relapse mortality (NRM) in HSCT recipients

Although HSCT is life saving for patients battling various hematological malignancies and disorders, its success depends on controlling post-transplantation immunosuppression. While relapse of the underlying disease is the primary concern, parasitic infections can significantly impact NRM in HSCT recipients. De Oliveira *et al*.[31] claimed that NRM exacerbation by parasites may occur due to either the ripple effect or organ dysfunction. First, parasitic infections in HSCT can, lead to complications that ultimately contribute to NRM. Early diagnosis, prompt treatment, and effective supportive care are crucial to minimize

this impact and improve patient outcomes. Second, disseminated parasitic infections can invade various organs, leading to dysfunction and potentially life-threatening complications. For instance, leishmaniasis causes damage to the liver, spleen, and kidneys, while toxoplasmosis affects the central nervous system, increasing the risk of NRM[31].

On the other hand, the careful selection of antiparasitic medications to immunosuppressed HSCT recipients may avoid interactions with immunosuppressive drugs. This can limit treatment options and potentially delay the initiation of effective therapy, leading to worse outcomes and increased NRM[32].

Strongyloides stercoralis

The diagnosis of strongyloidiasis is typically established through detection of rhabditiform larvae or serological assays. However, cross-reactivity with other helminthic infections may occur. In immunocompromised individuals, false negatives can occur due to the overall state of immunosuppression. Serological assays sensitivity and specificity reported range from 42.9-100% and 42.6-100% respectively[33]. Because of the limited sensitivity of serological assays in immunocompromised hosts, a combination of diagnostic methods is necessary to diagnose strongyloidiasis in transplant recipients. Examination of several stool samples increases sensitivity of diagnosis and can reach nearly 100% with the examination of seven serial stool samples because of the low parasite load and the irregular excretion of larvae. Furthermore, identifying eggs in fecal matter is difficult[34]. Stool culture in strongyloidiasis is important to promote growth of free-living stages and to confirm diagnosis. The Baermann, Harada-Mori filter, and agar plate culture methods are considerably more sensitive than single stool smears, but they are seldom employed as routine procedures in clinical parasitology laboratories[34]. The agar plate method is noted for its high sensitivity in detecting larvae in stool especially in endemic areas as documented by Hailu *et al*.[35], the authors investigate its efficacy in comparison to formal ether concentration technique and spontaneous tube sedimentation techniques[35].

Recent advancement in immunodiagnostic methods improves specificity and shortens result-processing times. These innovations include a new commercial ELISA and a luciferase immunoprecipitation system utilizing recombinant antigens (LIPS-NIE), which are designed to avoid cross-reactivity with antigens of other helminths. Furthermore, rapid diagnostic methods such as point-of-care cassettes and dipstick tests were developed to enhance diagnosis of strongyloidiasis[33]. Molecular techniques are considered a promising approach for diagnosing and identifying strongyloidiasis, offering the potential for enhanced sensitivity and specificity. It can provide confirmation by overcoming the limitations of parasitological methods, which often have low sensitivity, and immunological methods, which can lack specificity. Given the rapid progress in molecular technology, it is becoming a cornerstone for detecting strongyloidiasis[33].

Because managing complete eradication of the infection in immunocompromised HSCT recipients is difficult, it is recommended to prolong treatment until neutrophil counts recover, clinical symptoms resolve, and larvae are undetectable[36]. Ivermectin is the drug of choice for strongyloidiasis, with albendazole as an alternative. In severe cases resistant to standard therapy or when oral ivermectin is not feasible, rectal or subcutaneous ivermectin has been suggested[37].

Seropositive candidates should receive treatment before transplantation to prevent SHS. Ongoing monitoring is necessary for high-risk patients to detect and manage hyper-infection or disseminated strongyloidiasis, with long-term follow-up to ensure complete eradication[3].

Entamoeba histolytica

Different techniques are available for diagnosing amebiasis, including microscopy, nucleic acid detection, antigen detection, serology and colonoscopy. Notably, molecular methods considered the gold standard with high sensitivity of 92% to 100% and specificity of 89% to 100%, in addition there was a different PCR method targeting different genes especially those encoding 18SDNAr, being 100 times more sensitive than fecal antigen tests and it specifically targets *E. histolytica*. Besides, it differentiates between pathogenic *E. histolytica* and non-pathogenic *E. dispar*. Antigen detection assays are easier than microscopy but less sensitive than PCR, providing specificity for *E. histolytica* and indicating active infection[38,39]. Colonoscopy aids diagnosis by revealing characteristic ulcers and occasionally cysts or trophozoites. Serology detects IgG antibodies against *E. histolytica*, but it lacks specificity for recent exposure and can produce false negatives, especially in immunosuppressed individuals[15,40].

The treatment strategy consists of employing amoebicidal medications, specifically metronidazole, chloroquine, emetine, or tinidazole, which are effective against the invasive trophozoite forms. Subsequently, a luminal agent, such as paromomycin, diloxanide furoate, iodoquinol, and nitazoxanide is administered to eradicate the cyst[41].

Free living amoeba

In nearly all instances of infections with free living amoebae, tissue diagnosis is imperative. This typically involves examining tissue biopsies stained to identify trophozoites or cysts. Further diagnostic assays include indirect immunofluorescent antibody or immunohistochemical staining of tissue, along with PCR testing[42]. Brain biopsy with tissue examination remains the gold standard for identifying trophozoites and cysts[43]. For *N. fowleri*, microscopic examination should be conducted and if immediate examination is

not feasible, cerebrospinal fluid (CSF) should be stored aseptically at ~25°C[15]. Brain radiographic studies often reveal generalized edema but lack specificity to distinguish from other causes[44].

The ideal antimicrobial regimen for primary amoebic meningoencephalitis and granulomatous amoebic encephalitis remains unclear in the medical literature. While combination ofantimicrobial therapy is commonly used, there is limited evidence indicating the superiority of any specific treatment combinations[20]. For *Acanthamoeba* spp., treatment often includes a combination of pentamidine, fluconazole, and miltefosine administered orally, with additional options such as trimethoprim sulfamethoxazole (TMP/SMX), metronidazole, and azithromycin. In case of *B. mandrillaris*, a regimen of albendazole, pentamidine, fluconazole, and oral miltefosine is typically used. For *N. fowleri*, a common treatment approach involves a combination of amphotericin B, rifampin, fluconazole, azithromycin, and oral miltefosine[20].

For preventing acanthamoebiasis, cotrimoxazole was utilized though its effectiveness remains uncertain[9]. To evaluate potential donors, laboratory analysis should be carried out to detect *Acanthamoeba* cysts and trophozoites in fixed and stained brain tissue through indirect immunofluorescence or immunofluorescent assays. Alternatively, PCR testing can be used to identify *Acanthamoeba* DNA in cerebrospinal fluid or in unfixed brain tissue[10]. To prevent *N. fowleri* infection, it is advised to avoid exposure and, if nasal sinus irrigation is required, boiled, filtered, or distilled/sterile water is used[9].

Blastocystis spp.

Blastocystosis is diagnosed by observing cysts microscopically in stool samples; but this approach can be hindered by technical challenges and limited sensitivity. Using additional trichrome staining methods, and PCR panels aid in diagnosis[15].

Blastocystosis is generally managed using metronidazole, iodoquinol, and nitazoxanide, although there is currently no documented evidence indicating the comparative efficacy of these treatments specifically in HSCT recipients[12].

Giardia lamblia

The conventional method to diagnose giardiasis involves microscopic examination of stool samples to detect cysts or trophozoites, yet this approach has drawbacks of low sensitivity and the need for specialized skills especially in immunocompromised patients. Various antigen detection assays are commercially accessible, such as direct immunofluorescent assays, immunochromatographic assays, and enzyme-linked immunosorbent assays, offering higher sensitivity and faster results compared to stool microscopy[15]. Available PCR assays for detecting *G. lamblia* in stool samples, demonstrate high sensitivity and specificity[45]. Nevertheless, in certain instances, further confirmation through duodenal biopsy and aspiration may be necessary for patients experiencing persistent gastrointestinal symptoms[46].

Giardiasis is commonly managed using medications such as metronidazole, tinidazole, nitazoxanide, mebendazole, albendazole, and paromomycin[47]. Studies involving HSCT recipients have demonstrated favorable outcomes with metronidazole treatment[48]. In instances of resistance, a combination therapy involving metronidazole and quinacrine can be considered effective[49].

Leishmania spp.

Diagnosing visceral leishmaniasis involves identification of amastigotes by microscopic examination or culture of bone marrow aspirate/biopsy or splenic aspirate, especially in immunocompetent individuals[50]. However, due to the potential risk of severe bleeding associated with splenic aspirates, bone marrow aspirates are preferred as a safer alternative, despite having slightly lower sensitivity[51]. The PCR offers higher sensitivity in immunocompromised individuals and represents a non-invasive diagnostic alternative, particularly recommended for HSCT recipients[51]. Additionally, serology testing by ELISA is utilized cautiously in HSCT recipients due to impaired antibody production[12,51].

Amphotericin B is the primary drug used to treat leishmaniasis, in addition patients who do not respond to initial treatment with this drug should be treated with another therapy (pentavalent antimonials or miltefosine) or with a longer drug course[52]. However, several factors, such as the *Leishmania* species, patient characteristics, drug availability, disease severity, and prior treatments, can influence their effectiveness. International guidelines currently favor amphotericin B due to its lower risk of severe side effects that are associated with antimonials, and the emergence of resistant strains[53].

To minimize the risk of infections, both HSCT donors and recipients should receive health education about avoiding activities that could lead to exposure. Donors should refrain from donating if there is any suspicion of an active infection. Recipients who have a history of visceral leishmaniasis before the transplant, as well as those receiving grafts from donors with a history of the disease, should be monitored closely after the transplant. This includes regular testing if any symptoms of reactivation appear[3].

Trypanosoma cruzi

Diagnosis of acute Chagas disease involves direct microscopic examination of samples (e.g., fresh blood or concentrated specimens using methods like the Strout technique or microhematocrit), aiming to identify trypomastigotes in blood, body

fluids, or tissues, or utilizing PCR assays for parasite detection. In chronic cases, diagnosis primarily relies on serological tests detecting IgG antibodies against *T. cruzi* antigens[54].

If replication or evident disease is identified, treatment using benznidazole or nifurtimox is recommended[55]. Infection prevention involves educating both recipients and donors about minimizing exposure to triatomine bugs, especially in areas where Chagas disease is prevalent or when visiting such regions. It is crucial to screen stem cell and blood donors, as well as recipients, for Chagas disease to assess exposure risks. If an infection is identified in either a recipient or donor, ongoing monitoring using PCR and parasitological blood tests is required. To avert the reactivation of *T. cruzi* or a new infection from the donor, treatments like benznidazole is used to eradicate the parasite before symptoms appear[3].

Plasmodium spp.

Malaria diagnosis traditionally relies on microscopy, specifically the examination of thick and thin blood films is considered the gold standard. However, this method is time-consuming, possesses low sensitivity, and is not suitable for donor blood screening as it fails to detect asymptomatic cases with low parasitemia[9,12]. As a complementary diagnostic tool, rapid diagnostic tests (RDTs) detecting circulating *Plasmodium* antigens are employed. The RDTs may identify one or more antigens, with the possibility of antigen persistence in the bloodstream for over a month post-treatment. False-negative outcomes may arise in cases of extremely low or high parasitemia (prozone effect)[56]. The PCR-based techniques exhibit high sensitivity and specificity, especially for detecting mixed parasitemia. While PCR results aren't typically available on the same day in most transplant facilities, they offer early detection of subclinical malaria in donor-derived transmission and aid in accurately identifying mixed infections involving *P. ovale* or *P. vivax*[16].

Treatment selection depends on the species of *Plasmodium* involved and malaria severity. In instances where malaria is confirmed but the species is unknown, prompt initiation of effective treatment against *P. falciparum* is essential. Uncomplicated *P. falciparum* malaria typically calls for oral artemisinin-based combination therapy (ACT) or atovaquone-proguanil. Severe cases of *falciparum* malaria and any complicated or severe malaria cases require intravenous artesunate. Chloroquine is effective against other strains of *Plasmodium*, while chloroquine-resistant infections, such as those caused by *P. vivax, P. ovale, P. malariae*, or *P. knowlesi*, should be treated with ACT. Primaquine should be added to the primary treatment for cases of *P. vivax* and *P. ovale* to prevent relapse[12,29]. In HSCT recipients, it is crucial to consider the interaction between anti-malarial drugs and immunosuppressive therapy, particularly the interaction between quinine and calcineurin inhibitors[28,29].

To reduce the risk of infection, recipients residing in or traveling to malaria-endemic areas should be advised to avoid mosquito bites and use prophylactic medications when visiting these regions. Donors who live in or visit malaria-endemic areas should be screened for infection, and it is preferable to postpone their donation for one year or even up to three years if they are current or former residents of these areas or have had a previous malaria infection[3].

Babesia microti

In patients living in or visiting endemic regions and displaying suggestive clinical symptoms, a diagnosis of babesiosis should be considered. Confirmation entails microscopic examination of blood smears (detecting intraerythrocytic parasites) or amplifying parasite DNA via PCR testing[57].

The standard treatment usually involves a combination of atovaquone with azithromycin or clindamycin with oral quinine, administered for 7-10 d. However, a study of immunocompromised patients who had B cell lymphoma, asplenia, or were undergoing rituximab therapy, revealed that the treatment duration needed to be extended to at least 6 w to achieve a cure. The study highlighted the severity of babesiosis in this group, with a mortality rate of 21%, emphasizing the critical role of blood smears in monitoring the treatment's effectiveness and checking for relapse after the treatment[57]. Exchange transfusion should be considered as part of the treatment for patients with high-level parasitemia (>10%) or severe illness[58].

To prevent tick exposure, transplant recipients should wear appropriate protective clothing and apply repellants. Prospective donors should refrain from high-risk activities in endemic areas for several weeks before donation[9].

Toxoplasma gondii

Diagnosing toxoplasmosis in the context of HSCT poses challenges due to vague clinical and radiological signs[15,59]. Serological tests are often unreliable in immunosuppressed patients and may not detect the infection early post-HSCT. Its diagnosis, whether acute, latent, or reactivated, relies on finding the parasite or its DNA in body fluids or tissues of high-risk HSCT recipients[60].

The severity of toxoplasmosis in immunocompromised patients, especially HSCT recipients, necessitates prompt and effective treatment due to high mortality rates of 38% to 67%[61]. Treatment protocols for transplant patients follow guidelines for HIV-infected individuals because comparative trials are lacking[62,63]. Effective treatments target parasite replication but not cysts. Though prophylaxis substantially reduces toxoplasmosis risk, drug effectiveness can be impeded by pharmacokinetic

challenges like gastrointestinal intolerance or impaired gut absorption due to GVHD, or early discontinuation due to myelotoxicity[15]. The preferred treatment for toxoplasmosis involves a combination of pyrimethamine/sulfadiazine and folinic acid to avoid pyrimethamine myotoxicity. Treatment duration should extend for 6 weeks after symptom resolution, with the possibility of continuation as chronic maintenance therapy[64], while an increasingly popular alternative regimen is TMP/SMX, known also for its clinical efficacy[65]. For high-risky patients intolerant to sulfadiazine, clindamycin plus pyrimethamine and folinic acid are recommended as the first alternative prophylactic regimen. Other options like atovaquone, clarithromycin, and azithromycin are available[66]. Successful treatment may require reducing or discontinuing immunosuppressive therapy to allow for immune restoration that should occur depending on the risk of rejection or GVHD[15].

Efficacy is monitored through clinical examination, with radiologic improvement potentially delayed. In patients with positive *Toxoplasma* blood PCR at diagnosis, successful therapy should result in PCR tests turning negative[15]. For prevention, primary prophylaxis is advised for all allogeneic recipients with positive serology pre-transplant, with TMP/SMX as the preferred choice post-engraftment for at least 6 months. Prolonged prophylaxis may be necessary for highly immunocompromised recipients, such as those experiencing GVHD requiring intensive immunosuppression[67]. Additionally, individuals should refrain from handling cat litter or encountering potentially contaminated soil[68].

***Cryptosporidium* spp.**

The diagnosis of cryptosporidiosis requires acid-fast staining of stool cysts, although immunofluorescence microscopy is considered a more sensitive and specific method for stool examinations. Additionally, real-time PCR and ELISA assessment of antigens are alternative diagnostic tools[69]. However, in HSCT recipients, the similarity in presentation between cryptosporidiosis and gastrointestinal GVHD led to diagnosis only of cryptosporidiosis in a biopsy, after undergoing colonoscopy[70].

Management primarily relies on supportive care and immune support. While oral rehydration stands as the preferred approach, severe cases may necessitate intravenous fluids containing various electrolytes like sodium and potassium. In addition, nitazoxanide, approved by the Food and Drug Administration, demonstrated effectiveness in reducing diarrhea severity and duration in immunocompetent individuals by impeding parasite replication; its efficacy in immunocompromised patients remains uncertain. Ongoing investigations explore alternative drugs such as paromomycin, azithromycin, and nitazoxanide derivatives potentially offering new therapeutic avenues[71]. Notably, combining high-dose nitazoxanide with rifaximin and azithromycin, alongside optimizing tacrolimus levels, has shown resolution of cryptosporidiosis-associated diarrhea in a case report of a renal transplanted patient[72]. Additionally, reducing immunosuppressive therapy to enhance $CD3^+/CD4^+$ cell activity, emerges as an important therapeutic strategy in HSCT recipients for cryptosporidiosis recovery[68].

***Microsporidia* spp.**

Transmission electron microscopy, is considered the gold standard for detecting *Microsporidia* initially, but routine diagnosis relies more practically on light microscopy of stained samples. Common staining methods include Ryan's modified trichrome stain and various others such as Ziehl-Neelsen, silver stain, periodic acid-Schiff, Giemsa, and Gomori methenamine silver stain[73,74]. Alternative PCR is highly sensitive for species identification, followed by sequence analysis to confirm results, and for species detection[73,75].

Albendazole is often regarded as the primary treatment and is best used in conjunction with minimization of immunosuppression when possible. This combined approach helps to ensure a more effective and complete cure[12]. Another alternative drug is fumagillin and nitazoxanide[14].

CONCLUDING REMARKS

1. Parasitic infections pose a significant threat to HSCT recipients, causing morbidity, mortality, and delayed recovery. Accurate quantification is challenging due to variations in diagnostic methods, geographic disparities, and asymptomatic cases.
2. The HSCT recipients often exhibit atypical, non-specific symptoms that complicate diagnosis. Increased awareness, improved diagnostic strategies, and a comprehensive approach are essential to mitigate this risk and improve outcomes.
3. Parasitic infections significantly impact survival by causing organ dysfunction, exacerbating immunosuppression, and increasing susceptibility to secondary infections.
4. Accurate diagnosis requires a comprehensive approach, including detailed medical and travel histories, clinical suspicion, and appropriate diagnostic tools. Collaboration between healthcare professionals is essential.
5. Pre-transplant screening, stricter prophylactic regimens based on geographic considerations, and tailored chemoprophylaxis can reduce infection risk. Specific preventive measures include avoiding exposure to known sources of infection, emphasizing hygiene, and using safe drinking water.
6. Treatment is complicated by the immunocompromised state of patients and potential drug interactions. Supportive care, drug combinations, and prolonged treatment are often necessary.
7. Research into new, safer, and more effective antiparasitic medications with minimal interactions

with immunosuppressive drugs is ongoing. Exploring immunomodulatory therapies to enhance the immune system's ability to fight off parasitic infections is another promising area of investigation.

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