Endemic or regionally limited parasitic and fungal infections in haematopoietic stem-cell transplantation recipients: a Worldwide Network for Blood and Marrow Transplantation (WBMT) Review

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There is a scarcity of data on endemic and regionally limited fungal and parasitic infections in recipients of haematopoietic stem-cell transplantation (HSCT) outside western Europe and North America. This Worldwide Network for Blood and Marrow Transplantation (WBMT) Review is one of two papers aiming to provide guidance to transplantation centres worldwide regarding prevention, diagnosis, and treatment based on the currently available evidence and expert opinion. These recommendations were created and reviewed by physicians with expertise in HSCT or infectious disease, representing several infectious disease and HSCT groups and societies. In this paper, we review the literature on several endemic and regionally limited parasitic and fungal infections, some of which are listed as neglected tropical diseases by WHO, including visceral leishmaniasis, Chagas disease, strongyloidiasis, malaria, schistosomiasis, histoplasmosis, blastomycosis, and coccidioidomycosis.

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Introduction

Opportunistic parasitic and fungal infections complicate outcomes in patients who are immunocompromised, particularly patients who are undergoing allogeneic haematopoietic stem-cell transplantation (HSCT). Besides few common parasitic and fungal infections, the majority are rare and uncommon, particularly in non-endemic areas,[1] and many of them are listed as a neglected tropical disease by WHO.[2]

In our first Review, we discussed regionally limited bacterial and viral infections. This Worldwide Network for Blood and Marrow Transplantation (WBMT) second paper discusses the major endemic parasitic (visceral leishmaniasis, Chagas disease, strongyloidiasis, malaria, and schistosomiasis) and fungal (histoplasmosis, coccidioidomycosis, and blastomycosis) infections, combining input from experts around the globe, who reviewed the basic clinical characteristics of these organisms, and their frequency and outcomes in recipients of HSCT. Recommendations are based on expert opinions and were not graded for their level of evidence because of the scarcity of data available for these infections (panel 1; panel 2).

The aim of this Review is to provide HSCT teams with guidance and recommendations on the management of regionally limited parasitic and fungal diseases. We prioritise those pathogens that are described in recipients of HSCT in the literature or those judged as having a clinically significant effect on transplantation outcome, but for which there is a paucity of data available in the medical literature.

Methods

WBMT is a non-profit organisation affiliated with 21 HSCT and cellular therapy organisations, with an aim to provide education and facilitate scientific collaboration between affiliate organisations. One of the main aims of the WBMT is to improve HSCT practices in low-income and middle-income countries. The recommendations in this Review were made in two phases. Phase 1 of the project included the establishment of a core writing committee (MA, INM, CC, and SG). The initial outline of contents and subsequently the first draft was circulated and critically reviewed among the expert group three times. A group of experts (all other authors) was then formed to work on the project writing, including several infectious disease and bone marrow transplantation experts from international and regional WBMT affiliate organisations, with adequate representation from endemic areas. Infectious-disease expert members included in the project writing are affiliated with the European Group for Blood and Marrow Transplantation, the Center for International Blood and Marrow Transplant Research, and the experts in bone marrow are affiliated with the Latin American Bone Marrow Transplantation group, the Eastern Mediterranean Bone Marrow Transplantation group, and Asia Pacific Blood and Marrow Transplantation group. We did not do a systematic review. The network gathered data on selected reported cases and literature on multiple endemic or regionally limited infections that might confer an increased risk for poor outcomes among recipients of HSCT.

Panel 1: **Summary of recommendations for the selected parasitic infections**

Visceral leishmaniasis
- Monitoring symptoms is suggested in recipients with a history of visceral leishmaniasis or recipients of seropositive donors
- No data support the routine screening of donors or recipients

Chagas disease
- Screening of people who receive haematopoietic stem-cell transplantation (HSCT) and donors (stem cells and blood) who are living in, have previously lived in, or are travelling (long-term) to endemic regions
- Stem-cell donation should be avoided, if possible, from seropositive donors
- Recipients who are positive for Chagas disease (or in the case of a positive donor) should undergo active surveillance at regular intervals in the period after transplantation
- Treatment is indicated, if reactivation or a new infection is detected, before symptom onset

Strongyloidiasis
- Screening is recommended for recipients and donors of HSCT living in or travelling to endemic areas or in cases of unexplained eosinophilia
- Treatment is recommended in confirmed cases and can also be initiated prophylactically in highly endemic areas with not enough resources for testing
- Recipients of transplantation at risk of the disease should be screened periodically

Malaria
- Donors with recent travel to endemic areas should not donate for at least a year and a duration of 3 years is suggested for donors who are current or former residents of endemic areas
- Potential recipients in endemic areas should be screened for active disease before transplantation
- When donor deferral is not possible, empiric treatment should be considered

Schistosomiasis
- Donors and recipients who are living in endemic areas are advised to receive treatments in mass treatment programmes
- Evidence to suggest routine screening is not available; however, low threshold for screening and treatment should be maintained in recipients and donors with risk factors
- Deferral of donors with active disease or a history of schistosomiasis is recommended; however, there is not enough evidence related to deferral duration

Panel 2: **Summary of recommendations for the selected endemic fungal infections (histoplasmosis, coccidioidomycosis, and blastomycosis)**

- Donors and recipients should be screened for risk of exposure to endemic fungi (by asking them about place of residence, travel, outdoor activities, occupational risk, etc); no routine screening test is recommended for recipients or donors in endemic areas or with recent travel
- More data are needed to clarify the duration of donor deferral after treating an active infection
- Monitoring of recipients of haematopoietic stem-cell transplantation (HSCT) with a previous history of infection after transplantation is recommended and secondary prophylaxis should be considered
- Education about high-risk activities (ie, those that expose them to dust and soil, including gardening and occupational or recreational outdoor hazards) should be provided to recipients of HSCT living in or travelling to endemic areas, particularly in the early period after HSCT and while they are receiving immunosuppression treatment
- Recommended treatment for recipients of HSCT with severe infection generally involves initial treatment with amphotericin B and then an azole for long-term suppressive therapy

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Parasitic infections

Parasitic infections after HSCT are less frequent compared with other types of infections, and this low frequency might contribute to underdiagnoses.[3] Nevertheless, parasitic infections contribute to the morbidity and mortality of recipients of HSCT, and more research is needed to guide physicians on their diagnosis and treatment (panel 1). In this section, we discuss the microbiological and clinical characteristics of endemic parasites, including leishmaniasis, Chagas disease, strongyloidiasis, malaria, and schistosomiasis, in the context of HSCT (table 1) and provide consensus recommendations related to these infections.

Visceral leishmaniasis

Visceral leishmaniases is an opportunistic infection that can affect both, people who are immunocompetent and immunocompromised, and is the second most common cause of mortality due to parasitic infections after malaria. The infection is transmitted to humans by the adult female sandfly. Visceral leishmaniases is endemic mainly in the Mediterranean region, southeast Asia, and South America. Although infections in humans might be caused by more than 20 species, *Leishmania donovani*, *Leishmania infantum*, and *Leishmania braziliensis* are the most frequent ones. Visceral leishmaniases has an incubation period ranging between 3 to 8 months but longer periods have been reported and relapses could occur, particularly in immunocompromised patients. Patients with visceral leishmaniases can be asymptomatic but usually present with fever, organomegaly (particularly splenomegaly), and weight loss. The constellation of symptoms with systemic involvement constitute visceral leishmaniases, also known as kala-azar. Laboratory findings usually include pancytopenia and hypergammaglobulinaemia. Skin lesion can also occur during or after infection (known as post-kala-azar cutaneous leishmaniasis) and in some patients, the disease can progress and cause multiple organ failure and death. Visceral leishmaniases can be diagnosed via direct methods (histology, culture) and indirect methods including PCR and antigen testing, and splenic or bone marrow aspiration.[4] Patients with visceral leishmaniases should be treated using liposomal amphotericin B (4 mg/kg/day on days 1–5, 10, 17, 24, 31, and 38; total dose 40 mg/kg), or an alternative option and secondary prophylaxis and chronic maintenance therapy might be

	Visceral leishmaniasis	Chagas disease	Strongyloidiasis	Malaria	Schistosomiasis
Most affected areas	South America (particularly Brazil), India, and east Africa	South America but more recently also North America, and other continents	Tropical and subtropical regions, including South America, Europe, Asia, and sub-Saharan Africa	Affects many countries but most cases are from Africa	Middle East, Africa, South America, and east Asia; however, most cases happen in Africa
Incubation period	Up to 8 months (can be years)	Varies based on transmission; can be between 1–2 weeks and 2 months	Up to 4 weeks	Up to 1 month	Up to 2 months
Transmission	Commonly through sandfly bites (mainly female phlebotomine), rarely: through blood products, organ donation, and vertical transmission	Commonly through triatomine insect bites, blood products, consumption of contaminated food, organ donation, and vertical transmission	Commonly through skin contact with contaminated surfaces (ie, soil), rarely: through faecal–oral transmission and person-to-person transmission	Commonly through mosquito bites (mainly female *Anopheles* spp), rarely: through blood products, contaminated needles, organ donation, and vertical transmission	Transmissions commonly occur through skin exposure to contaminated water
Clinical symptoms	Fever, pancytopenia, weight loss, and hepatosplenomegaly	Acute and chronic phase: acute phase has non-specific symptoms, including fever, lymphadenopathy, muscle pain, etc; chronic disease presents with cardiac, neurological, and gastrointestinal manifestations	Most commonly asymptomatic but presents with GI symptoms (including diarrhoea and abdominal pain), skin rash (pruritus, urticaria), and pulmonary (cough) manifestations; also has a chronic phase	Fever and a constellation of non-specific symptoms and signs; however, can present with severe symptoms and multiple organ failure	Acutely and subacutely presents with pruritus (travelers' itch) or Katayama syndrome (fever, fatigue, urticaria, etc); chronic presentation is variable depending on species (hepatic or urinary disease)
Diagnosis of acute infection	Multiple methods include serological testing and splenic or bone-marrow aspiration	PCR and direct microscopic parasitological methods by observing trypomastigotes in the blood or detecting the parasite in other fluids or tissues	Serological testing and microscopic detection in stool testing (under microscope)	PCR, parasitological test through light microscopy of blood smear and antigen detection	Microscopic detection of parasite eggs in urine or stool
Treatment	Liposomal amphotericin B	Benznidazole or, as an alternative, nifurtimox	Ivermectin	Artemisinin-based combination therapies	Praziquantel (prednisone is added in an acute phase)

Table 1: **Epidemiology, clinical features, and treatment of selected parasitic infections**

required until resolution of immunosuppressive state to prevent relapses.[5]

In recipients of HSCT, visceral leishmaniases could be transmitted via sandflies, from blood products, theoretically through the stem cell graft, or occur due to reactivation of the previous infection. Thus far, there are more than ten reported cases after allogeneic or autologous HSCT (table 2).[6–9] Most cases have involved male patients who were on immunosuppression agents at the time of infection. Most of these patients presented with fever, splenomegaly and cytopenia, and subsequently needed bone marrow examination. Liposomal amphotericin B treatment led to the recovery in all patients except one. In a case[6] from southern France (endemic area), diagnosis of visceral leishmaniases was delayed due to initially suspecting more common infectious causes. Furthermore, Drexler and Holbro[8] found visceral leishmaniases in the bone marrow of an asymptomatic patient with progressive pancytopenia. This patient was not living in an endemic area and his travel history was unrevealing, illustrating the importance of keeping broad differentials in approaching recipients of HSCT, particularly after excluding common causes. Atypical presentations resembling gastrointestinal graft-versus-host-disease (GVHD) have also been reported.[7] In all cases, no proven transmission from a donor to a recipient was observed. Few cases were reported after day 100, for instance, Komitopoulou and colleagues[17] reported three cases that were diagnosed more than a year after allogeneic HSCT, two of which had initial recovery to liposomal amphotericin but subsequent recurrence.

Recipients and donors of HSCT should avoid high-risk activities, such as exposure to sandflies (eg, wearing long sleeves) and community-based efforts to control the anthroponotic foci. Donor deferral is recommended if active infection is suspected but no data are available to support deferral in donors with a history of visceral leishmaniases. No data support the routine screening of HSCT donors or recipients. Recipients with a pre-transplantation history of visceral leishmaniases and recipients from positive donors should be monitored after transplantation for reactivations with a low threshold to frequently test in case of suspicious symptoms (many symptoms, such as pancytopenia, are commonly the presenting features of many post-transplantation complications).

Chagas disease

Chagas disease (American trypanosomiasis) is a multisystemic infection caused by the protozoan parasite *Trypanosoma cruzi*. The disease is transmitted to humans most commonly by infected triatomine insects in endemic areas of continental Latin America,[18] but it can also occur both in endemic and non-endemic regions as a result of blood transfusion, organ or stem-cell transplantation, vertical transmission from mother to child, laboratory accidents, or ingestion of contaminated food.[19] Chagas disease has two phases: acute and chronic. Both phases in hosts who are immunocompetent are frequently asymptomatic, although 20–30% of individuals who are infected might develop cardiac, gastrointestinal, or neurological symptoms during the

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	Age in years; sex	Disease (type of HSCT)	Country (time after transplantation)	Presentation	Therapies applied	Outcome
Visceral leishmaniasis						
Sirvent-Von et al, 2004[6]	57; male	AML (allogeneic)	France (>365 days)	Fever	Liposomal amphotericin B	Recovered
Martinez-Losada et al, 2013[7]	49; female	AML (allogeneic)	Spain (160 days)	GI symptoms, fever, odynophagia, and pancytopenia	Liposomal amphotericin B and meglumine antimoniate	Death
Drexler & Holbro 2014[8]	49; male	CML (allogeneic)	Switzerland (300 days)	Pancytopenia	Liposomal amphotericin B	NR
Machado et al, 2009[9]	6; female	MDS (allogeneic)	Brazil (150 days)	Fever and splenomegaly	Liposomal amphotericin B	Death from disease relapse
Chagas disease						
Villalba et al, 1992[10]	20; male	ALL (allogeneic)	Spain (94 days)	Fever, weakness, oedema	Nifurtimox	Death
Angheben et al, 2012[11]	9; female	AML (allogeneic)	Italy (46 days)	Fever, hepatomegaly, pancytopenia	Benznidazole	Death
Guiang et al, 2013[12]	54; female	MM (autologous)	USA (during initial 30 days)	Detected by PCR monitoring	Benznidazole	Recovered
Malaria						
Abdelkefi et al, 2004[13]	25; male	MDS (allogeneic)	Tunisia (donor via transfusion; 17 days)	Fever, pancytopenia, and haemophagocytic syndrome (*Plasmodium falciparum*)	Quinine	Recovered
Inoue et al, 2010[14]	6; male	ALL (allogeneic)	Brazil (26 days)*	Asymptomatic (diagnosed in the donor only; *Plasmodium vivax*)	Chloroquine	Recovered
Ladeb et al, 2018[15]	27; male	SAA (allogeneic)	Tunisia (12 days)†	Febrile neutropenia and haemophagocytic syndrome (*Plasmodium falciparum*)	Quinine	Recovered

Cases were selected as examples that reflect different clinical aspects. ALL=acute lymphocytic leukaemia. NR=not reported. AML=acute myeloid leukaemia. CML=chronic myeloid leukaemia. HSCT=haematopoietic stem-cell transplantation. MDS=myelodysplastic syndrome. MM=multiple myeloma. *Donor with extensive history of malaria. †Received transfusion from a donor in an endemic country.

Table 2: **Selected cases of parasitic infections in recipients of HSCT**

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life-long chronic phase. Acute Chagas disease can be diagnosed by direct microscopic parasitological methods (fresh blood or after concentration techniques such as the Strout method or microhematocrit), observing trypomastigotes in the blood or other fluids or tissues, or detecting the parasite by PCR-based tests. Chronically infected individuals can be diagnosed by IgG-antibodies to *T cruzi* antigens in serological tests.[18] Recipients of HSCT can develop Chagas disease as a consequence of: 1) infection through infused stem cell graft or blood products from an infected donor; 2) reactivation of latent chronic infection; or 3) de-novo infection in the post-transplantation period (as in the general population). Clinical manifestations are frequently non-specific and can be severe in patients who are immunosuppressed (eg, with fever, malaise, anorexia, subcutaneous nodules, hepatosplenomegaly, myocarditis, encephalitis), thus a high index of suspicion should be maintained to identify the disease in patients who are at high risk.[20]

Many case reports of Chagas disease in autologous or allogeneic HSCT have been described in the literature, both in endemic and non-endemic regions,[20,21] occasionally with an initially unsuspected infection and fatal outcome (table 2). Altclas and colleagues[22] described a series of recipients positive for Chagas disease in Argentina including 12 recipients of autologous HSCT, 10 allogeneic HSCT donors, and 4 HSCT donors positive for Chagas disease who were followed with monitoring for reactivation or primary infection, and pre-emptive treatment with benznidazole. Reactivation and primary infection (or a donor-transmitted acute infection) can be detected in the recipient of HSCT through direct microscopic parasitological methods (eg, Strout method) or PCR. Whenever possible, quantitative PCR on blood, showing an increase in the parasitic load, is the method of choice for the identification of reactivation, owing to its high sensitivity and specificity. Microscopy is less sensitive, and serology does not help detect reactivation.[23] Treatment with benznidazole or nifurtimox should be initiated if replication or overt disease is detected.[24]

Key recommendations for transplantation centres regarding the selected parasitic infections are in panel 1. Recipients of HSCT and donors living in endemic areas, or travellers to areas where Chagas disease is endemic, should receive education on minimising the risk of exposure to triatomine bugs and good hygiene practices in food preparation, storage, and consumption. Stem cell donors, blood donors, and recipients living in endemic regions, or people at risk in non-endemic areas (such as residents or migrants from endemic regions, long-term travellers to endemic regions, or people with a history of blood transfusions in an endemic area) should be screened. Donors with previous history or active Chagas disease should be avoided unless no other suitable donors are available. Identification of a recipient (or donor) infection should prompt active surveillance of the recipient after transplantation with PCR and direct parasitological visualisation methods (eg, Strout method) on blood samples. The monitoring should be initiated at regular intervals starting with conditioning therapy. The monitoring schedule might include weekly tests for the first 2 months, then every 2 weeks during the third month,

and then monthly until at least 6 months, or as determined by the degree of immunosuppression. Suggested treatment against reactivation of *T cruzi* (or a donor-derived acute infection) include benznidazole (5–7 mg/kg/day orally for 60 days). Alternatively, nifurtimox (8–10 mg/kg/day orally for 60–90 days) could be considered to eradicate parasitaemia before the onset of symptomatic disease.

Strongyloidiasis

Strongyloidiasis, a chronic parasitic infection caused most commonly by *Strongyloides stercoralis* is acquired by direct contact of intact skin with the filariform larvae in the soil or other contaminated surfaces. During the lifecycle, the larvae can re-enter via the intestinal mucosa and perianal skin of the human host in a process called autoinfection that can result in a protracted course of illness.[25] Strongyloidiasis is widely distributed globally with increased prevalence in rural populations with low socioeconomic status in tropical and subtropical regions, and in immigrants and refugees from endemic areas. The prevalence of strongyloidiasis was estimated at 8·1% of the global population, corresponding to more than 600 million people infected worldwide.[26]

Strongyloidiasis is generally unrecognised in the general population but in immunosuppressed hosts, the larvae in the intestine can initiate a process of uncontrolled proliferation and accelerated infection, called strongyloides hyperinfection syndrome (SHS). Recipients of HSCT are at risk of developing SHS if they have latent strongyloidiasis.[27–29] Cases have been reported in the literature with mortality rates reported to be as high as 83% in recipients of allogeneic HSCT,[30–34] emphasising the importance of screening and implementing preventive strategies.[23]

Clinical symptoms of SHS are related to the presence of the larvae mainly in the gastrointestinal tract, skin, and respiratory system, and fever is usually present. The disease can spread to other organs beyond the usual lifecycle of the parasite such as liver, urinary tract, or CNS in disseminated strongyloidiasis. Concurrent gram-negative bacterial sepsis and meningitis can occur as a result of damage to the intestinal epithelium and translocation of bacteria along with the larvae from the gut to the bloodstream. By contrast with uncomplicated strongyloidiasis, peripheral blood eosinophilia is generally absent.[35]

Asymptomatic chronic infection can be detected in candidates for HSCT with IgG-anti *S stercoralis* serological assays. Microscopic stool tests are a less sensitive alternative but are particularly useful in transplantation recipients who are highly immunosuppressed due to the risk of false-negative results in serology. Stool testing should be repeated at least 3 times to increase sensitivity. In SHS, there is usually a high parasite burden and larvae can be detected by microscopy in stool, sputum, or bronchoalveolar lavage samples, and in other body fluids or tissue biopsies. Ivermectin is the drug of choice for the treatment of *S stercoralis* infection.[1,20,23]

Key recommendations on strongyloidiasis for transplantation centres are in panel 1. Education is recommended to minimise the risk of de novo infection or reinfection with *S stercoralis*, which includes emphasising the need to avoid skin exposure to soil or other surfaces contaminated with human faeces, and to wear shoes and maintain good personal hygiene. Donors in endemic areas and people at epidemiological risk in non-endemic areas (residence or long-term travel to an endemic region, with no time limit since the possibility of exposure) should be screened. In an appropriate clinical setting and the presence of risk factors, the empirical treatment could be considered in resource-limited settings. Although no data support the deferral of donors with a history of infection, people with active infection should avoid donation. Candidates for HSCT in endemic areas and people at epidemiological risk in non-endemic areas (residence or long-term travel in an endemic region, with no time limit since the possibility of exposure) or if they have unexplained eosinophilia should be screened. If resources are scarce or in the presence of risk factors, or in cases where urgent HSCT is needed, empirical treatment could be considered in patients with suggestive features. Seropositive HSCT candidates should receive treatment before transplantation to minimise the risk of SHS in the period after. Surveillance for SHS or disseminated strongyloidiasis in patients at risk should be implemented and long-term follow-up of patients should be performed to confirm complete eradication. Ongoing prophylaxis with ivermectin is mandatory in patients with persistent infection. Suggested treatment includes ivermectin 0·2 mg/kg daily for 2 days, repeated after 2 weeks (a fo ur-dose regimen, covering one auto-infection cycle). A longer course is suggested in cases of overt disease: ivermectin 0·2 mg/kg/day (with or without albendazole).

Malaria

Malaria is the most common parasitic disease worldwide, affecting millions of people each year, with the large majority of cases detected in Africa. Malaria is usually transmitted to humans via the *Anopheles* mosquito with an incubation period ranging from a week to around 30 days. Malaria can present in many ways that include fever and a constellation of non-specific symptoms and signs. Initial laboratory findings can include cytopenias, mild coagulopathy, and renal dysfunction. However, it should be noted that malaria can progress, and in severe forms, multiple organ failure and loss of consciousness is common. The diagnosis of malaria is done by parasitological test through light microscopy of blood smear and PCR. A rapid test kit that detects malaria antigens is used, particularly in endemic countries. Treatment of uncomplicated malaria is dependent on presence of chloroquine resistance and includes first-line

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For an **interactive map on the distribution of visceral leishmaniases** see https://apps.who.int/neglected_diseases/ntddata/leishmaniasis/leishmaniasis.html

For more on the **distribution of Chagas disease** see https://cdn.who.int/media/docs/default-source/ntds/chagas-disease/chagas-2018-cases.pdf?sfvrsn=f4e94b3b_2

For an **interactive map on the distribution of malaria** see https://www.who.int/teams/global-malaria-programme/surveillance/malaria-threats-map

For more on the **worldwide distribution of malaria** see https://www.cdc.gov/malaria/about/distribution.html

For an **interactive map on the distribution of Schistosomiasis** see https://apps.who.int/neglected_diseases/ntddata/sch/sch.html

artemisinin-based combination therapies. In case of sensitivity, chloroquine or hydroxychloroquine can be used. Other options, outside endemic areas in which artemisinin-based combination therapies are occasionally not available, include atovaquone-proguanil, mefloquine, quinine, and tetracycline. For severe or cerebral malaria, intravenous artesunate is preferred.[36,37]

Cases of malaria have been reported in the literature for patients after HSCT (table 2).[38,39] These include both children and adults, with the majority of cases in the allogeneic HSCT setting and high numbers of donor-related transmission via HSCT or blood transfusions, even when donors tested negative before transplantation.[38,39] Current guidelines recommend deferring donors for 1 year in case of recent travel to an endemic country and screening of recipients living in or from endemic areas before HSCT, and then a low threshold for testing if suggestive symptoms develop.[1]

Fever and pancytopenia are among the most reported symptoms and laboratory abnormalities. However, some patients were asymptomatic, yet received treatment due to high-risk factors or positive testing.[14] A less common presentation preceding the diagnosis of malaria has been haemophagocytic syndrome, reported in two cases.[13,15] Because of the high rate of donor-related transmission, most cases have been reported in the first 100 days after HSCT. Of note, most patients recovered with the standard anti-malarial treatment, with no relapse reported in any of the selected cases. All reported cases were caused by either *Plasmodium falciparum* or *Plasmodium vivax;* infections with other plasmodium species have not been reported in the HSCT setting.

Key recommendations for transplantation centres regarding the selected parasitic infections are in panel 1. Recipients of HSCT living in endemic areas or travellers to endemic areas should avoid exposure to mosquitoes and follow general preventive measures, including prophylaxis, when travelling to endemic areas.[36,37] Donors should be screened for the history of malaria if they are from an endemic area. Additionally, donors with recent travel to endemic areas should not donate for 1 year. Whenever possible, donors who are residents (including former residents) of endemic areas or donors with a previous history of malaria should not donate for an extended period (3 years is suggested). However, for transplantations in endemic areas, such a recommendation cannot be made, thus, empirical treatment might be considered. Recipients who are residents (including former residents) of endemic areas should be screened for active disease before transplantation. A low threshold for testing in recipients of HSCT living in endemic areas or travellers to endemic areas is recommended.

Schistosomiasis

Three major disease-causing species of *Schistosoma* include *Schistosoma mansoni*, *Schistosoma japonicum,* and *Schistosoma haematobium*. The highest prevalence of schistosomiasis is reported in Africa, and then the Middle East, Africa, South America, and east Asia. Schistosomiasis transmission occurs through skin exposure to contaminated water.[40] It presents in several forms, acutely as Katayama syndrome in patients with no previous exposure (ie, travellers) 2–8 weeks after infection and with possible several chronic manifestations including intestinal, hepatosplenic, or pulmonary features. Diagnosis is usually made by the detection of parasite eggs in stool (for species causing hepato-biliary disease) or urine (for *S haematobium*, which causes urinary disease).[41] However, serological testing can also be used. Treatment of acute schistosomiasis consists of two courses of praziquantel, with corticosteroids given with the first course. Chronic schistosomiasis, however, can be treated with a single dose of praziquantel.[42]

Very few cases of schistosomiasis have been reported in recipients of HSCT. Mahmoud and colleagues[43] described the increase in the risk of sinusoidal obstruction syndrome (previously known as veno-occlusive disease) in recipients of allogeneic HSCT with schistosomal hepatic periportal fibrosis. Additionally, Yalcin and colleagues[44] reported a 28-year-old man who received allogeneic HSCT and developed portal hypertension and haematuria. The patient was treated with a single dose of praziquantel (40 mg/kg). After 2 days of therapy, shock syndrome evolved and the patient died 39 days after allogeneic HSCT.

Key recommendations for transplantation centres regarding the selected parasitic infections are in panel 1. Recipients and donors must be educated to avoid high-risk activities, including minimising exposure to contaminated water. Donors and recipients should participate in large population-based treatments. Routine screening is not recommended for donors or recipients in endemic areas or with recent travel history to an endemic region. However, a low threshold for performing diagnostic tests or empirical treatment should be maintained. Evidence is scarce for the duration of deferral in donors with a previous history of disease or after the treatment of active infection. This should be discussed with the center's infectious diseases and travel medicine experts, and the deferral duration is up to the discretion of the treating provider. Low threshold should be maintained for testing in recipients of HSCT living in endemic areas or travellers to endemic areas.

Endemic fungal infections

Endemic fungal infections comprise diseases that occur in a restricted geographic area, such as histoplasmosis, blastomycosis, coccidioidomycosis, paracoccidioidomycosis, talaromycosis, emergomycosis, and sporotrichosis.[45] Our discussion in this paper is limited to histoplasmosis, coccidioidomycosis and blastomycosis; however, other rare and endemic fungi have been reported in recipients of HSCT. High suspicion is needed to diagnose such infections because late diagnosis can contribute to mortality and morbidity.

For example, a 52-year-old patient[46] with history of acute myeloid leukaemia and allogeneic HSCT developed neutropenic fever and subsequently skin lesions, which did not improve despite treatment with fluconazole and anidulafungin for presumed candida infection. The patient was later diagnosed with trichosporonosis after skin biopsy, with clinical improvement after starting voriconazole.[46] Additionally, Woo and colleagues[47] reported a case of talaromycosis in a 57-year-old man who presented more than 3 years after allogeneic HSCT complicated with the onset of bronchiolitis obliterans with organising pneumonia, necessitating multiple courses of steroids. The patient was started on treatment with intravenous amphotericin B; however, he died secondary to multiple organ failure. Other endemic or rare fungal infections were reported in recipients of HSCT, such as *Fusarium* spp and *Scedosporium* spp.[48,49]

Histoplasmosis, coccidioidomycosis, and blastomycosis have been reported in recipients of HSCT (table 3). They are diseases caused by dimorphic fungi that exist as moulds in the environment and as yeasts or spherules in the host; infection can occur due to inhalation of aerosolised conidia resulting in asymptomatic infection or pulmonary disease. In recipients of HSCT, cellular immunodeficiency can facilitate progression to disseminated disease after primary infection or as a consequence of reactivation of a latent infection. Diagnosis of endemic mycosis requires a high index of suspicion and relies on a combination of clinical signs and symptoms, epidemiological risk of exposure, radiological findings, and culture-based and non-culture-based diagnostic tests.

In an analysis involving recipients enrolled in the US National Institutes of Health Transplant-Associated Infection Surveillance Network (TRANSNET) of 23 centers between 2001 and 2006, only four cases of histoplasmosis, two of coccidioidomycosis, and no cases of blastomycosis were reported in recipients of HSCT. Four of the six endemic fungal infections reported were in recipients of autologous HSCT, with a median time to infection of 343 days (range 0–4195).[59,60] The incidence of endemic fungal infections was also low in the multicenter Prospective Antifungal Therapy (PATH) Alliance registry in North America, with only one case of histoplasmosis in 234 recipients of HSCT included in this study.[61] No cases of these endemic fungal infections were reported in epidemiological studies of invasive fungal infections in recipients of HSCT from Italy or Brazil,[62,63] although it is worth noting the high incidence of fusariosis in the Brazilian report.

There is a paucity of data and limited clinical experience in the management of endemic fungal infections after HSCT. Therefore, therapeutic recommendations are largely based on expert opinions and previously published guidelines for the management of endemic fungal infections, which have included recommendations for immunosuppressed patients but not specifically targeted at recipients of HSCT.

Histoplasmosis

Histoplasma capsulatum, the causative agent of histoplasmosis, has a worldwide distribution and is mainly found in temperate regions where it grows in nitrogen and phosphate-enriched soils associated with bird and bat guano. The highest incidence is reported in the region of the Americas, particularly in central and eastern USA, and Latin America from Mexico to Uruguay. Other areas considered endemic are central, western, and southern Africa, and some regions in southeast Asia, whereas most of Europe (with the exception of northern Italy) and Oceania are considered of low endemicity.[45]

For more on the **distribution of histoplasmosis** see https://www.cdc.gov/fungal/diseases/histoplasmosis/maps.html

Diagnosis can be rapidly facilitated with *Histoplasma* antigen enzyme immunoassay in serum, urine, or other samples and antigenemia or antigenuria are also useful for monitoring response to treatment. The main limitations are that the test is not widely available and that it might present cross-reactivity with other fungal infections. Identification of the fungus by cytology or histopathology from affected tissue using specific stains can also help to establish the diagnosis. Antibody detection tests are less useful in recipients of HSCT due to low sensitivity in the immunosuppressed population; nucleic acid amplification assays are being developed but still need standardisation and validation. Culture remains the gold standard for diagnosis and, although it is laborious, requires weeks for adequate growth, and has low sensitivity, it should be performed to confirm rapid diagnostic tests results.[64]

Histoplasmosis in recipients of HSCT presented as either pulmonary or progressive disseminated infection, and most cases reported recent use of immunosuppression and GVHD, and presented with fever with a high mortality rate.[50,51] A case was reported during voriconazole prophylaxis[52] and in another case, diagnosis was delayed due to a false positive galactomannan assay.[51]

Treatment in the majority of patients receiving HSCT reported was with amphotericin B; others were treated with itraconazole or voriconazole and in some cases, amphotericin B was given before an azole, with a generally poor outcome. However, no deaths occurred for at least 3 months after the diagnosis in the TRANSNET series.[59,60]

Recommended treatment for severe pulmonary or progressive disseminated disease is with lipid formulation of amphotericin B in adults or amphotericin B deoxycholate in children (and can also be considered in adults at low risk for nephrotoxicity) for 1–2 weeks or until a favourable response is observed, and then itraconazole maintenance for a total of at least 12 weeks should continue as long as significant immunosuppression persists. The addition of corticosteroids should be considered for severe acute pulmonary disease.[65]

Although the risk of histoplasmosis seems to be very low after HSCT, even in endemic areas,[66] itraconazole can be considered in selected cases for primary or secondary prophylaxis. Newer azoles (voriconazole, posaconazole,

	Age in years; sex	Disease at HSCT (type of HSCT)	Country (time after transplantation)	Presentation	Therapies applied	Outcome
Histoplasmosis						
Peterson et al, 1987[50]	20; female	SAA (allogeneic)	USA (35 days)	Fever	Amphotericin B	Death
Jones et al, 2009[51]	30; male	HD (autologous)	USA (around 6 months)	Weight loss, cough	Amphotericin B lipid complex and then itraconazole	Recovered
Agrawal et al, 2020[52]	55; male	DLBCL (autologous)	USA (365 days)	Cough, fatigue, fever	Itraconazole	Recovered
Coccidioidomycosis						
Glenn et al, 2005[53]	42; male	CML (allogeneic)	USA (79 days)	Fever, diarrhoea, skin rash, later dyspnoea	Post-mortem diagnosis	Death
Multani et al, 2019[54]	73; male	AML (allogeneic)	USA (around 8 months)	Fevers, fatigue, cough	Liposomal amphotericin B, voriconzole	Death
Saling et al, 2021[55]	61; female	AML (allogeneic)	USA (around 15 months)	Dyspnoea, fatigue, cough, night sweats, headaches; seroconversion	Fluconazole	Recovered
Blastomycosis						
Winston et al, 1979[56]	27; male	SAA (allogeneic)	USA (210 days)	Fever, dyspnoea, cough	Amphotericin B	Recovered
Torres et al, 2002[57]	49; male	CML (allogeneic)	USA (not reported)	Dyspnoea, cough, fever	Itraconazole, Amphotericin	Recovered
Linder et al, 2016[58]	51; female	CML (allogeneic)	USA (10 months)	Cough, dyspnoea	Voriconazole	Recovered

ALL=acute lymphocytic leukaemia. AML=acute myeloid leukaemia. CML=chronic myeloid leukaemia. DLBCL=diffuse large B-cell lymphoma. HD=Hodgkin lymphoma. HSCT=haematopoietic stem-cell transplantation. MDS=myelodysplastic syndrome. MM=multiple myeloma. SAA=severe aplastic anaemia.

Table 3: **Selected reported cases of endemic fungal infections in recipients of HSCT**

and isavuconazole) are active agents against histoplasmosis but there are less data to support their use.[67]

Coccidioidomycosis

For more on the **distribution of coccidioidomycosis** see https://www.cdc.gov/fungal/pdf/more-information-about-fungal-maps-508.pdf

Coccidioidomycosis is caused by two species of soil-dwelling fungi, *Coccidioides immitis* and *Coccidioides posadasii*. There are many geographical areas of endemicity in the Americas located in arid and semi-arid regions, in southwestern USA; northwestern Mexico; regions of Honduras, Guatemala and Nicaragua in central America; and in South America, mainly in northern Colombia and Venezuela, central and northern Argentina, Bolivia, Paraguay, and northeastern Brazil.[45]

Definitive diagnosis relies on the isolation of *Coccidioides* from cultures of respiratory secretions or other specimens. Direct visualisation by microscopy using various stains and antigen tests, if available, could help to establish the diagnosis in a timely manner. Nucleic acid tests might be helpful but they are only available at reference centres. Serological screening before transplantation in endemic areas might be useful to identify HSCT candidates at risk of reactivation or to detect seroconversion during follow-up but sensitivity is reduced due to impaired immunity.[68]

Coccidioidomycosis in the immunocompetent host is usually asymptomatic and when the disease occurs it presents as pulmonary illness and, uncommonly, disseminates to extrapulmonary locations mainly with meningeal, osteo-articular, cutaneous, or soft tissue manifestations. Dissemination is more common in immunosuppressed patients.[68] Riley and colleagues[69] reported the first 3 recipients of allogeneic HSCT with coccidioidomycosis, including one case of pulmonary disease and two cases of disseminated disease, with two cases having a fatal outcome.

Two cases were described in the TRANSNET analysis and both had localised pulmonary coccidioidomycosis,[59,60] whereas in another retrospective analysis, 11 (3%) of 426 recipients of allogeneic HSCT treated during a 10-year period had coccidioidomycosis.[70] Of these 11 patients, ten were on immunosuppressive agents at the time of diagnosis and three were on anti-fungal prophylaxis. Additionally, most patients presented in the late post-engraftment period and up to 24-months afterward, and five died, highlighting the high mortality rate in these cases.[53–55]

Fluconazole can be used prophylatically or for the treatment of clinically stable recipients of HSCT. For people with severe or rapidly progressing acute pulmonary or disseminated coccidioidomycosis, the suggested treatment is with amphotericin B formulations until the patient has stabilised, and then fluconazole for the duration of immunosuppression. Other azoles (itraconazole, voriconazole, posaconazole, and isavuconazole) are also active but with less clinical experience.[71]

Blastomycosis

For more on the **distribution of blastomycosis** see https://www.cdc.gov/fungal/pdf/more-information-about-fungal-maps-508.pdf

Blastomycosis is caused by two species, *Blastomyces dermatitidis* and *Blastomyces gilchristii*, mainly found in damp soils and decaying vegetation near lakes and rivers. The infection is endemic in central and southeastern

Search strategy and selection criteria

We did not conduct a systematic review. We identified relevant data and references used in this Review using MEDLINE from inception until Dec 31, 2021). Our search method used Boolean logic to identify as many results as possible with terminology such as: "Bone Marrow Transplantation" and "Hematopoietic Stem Cell Transplantation" in combination with disease-specific terms related to infections, including: "Strongyloidiasis", "Malaria", "Chagas disease", "Histoplasmosis", etc. We identified additional references by authors' own files and by manually searching relevant review articles (ie, reference lists). We restricted relevant references to peer-reviewed publications, including case reports and series, observational studies, experimental studies, and guideline papers. We limited articles identified to English language only.

USA; Canadian provinces that border the Great Lakes and St Lawrence river; central, eastern, and southern Africa; and India.[45]

Early diagnosis can be facilitated by antigen detection assays or by detecting yeast forms in fluids or tissue biopsy of stained specimens (most frequently respiratory secretions obtained from bronchoalveolar lavage). The definitive diagnosis is made by culture isolation technique. There is not much benefit for serological testing in recipients of HSCT and nucleic acid detection tests are not routinely available.[72]

Blastomycosis is an infrequent disease in the context of HSCT, and the cases reported presented with respiratory symptoms and isolated pulmonary disease without evidence of dissemination.[56–58] This observation is in contrast with what happens with patients who are immunosuppressed and have not received HSCT,[73] and also with histoplasmosis and coccidioidomycosis in the context of HSCT, in which extrapulmonary dissemination is frequently seen (table 3). The treatment suggested for pulmonary or disseminated blastomycosis in patients who are immunosuppressed consists of a lipid formulation of amphotericin B or amphotericin B deoxycholate for 1–2 weeks or until there is evidence of improvement, and then an azole, generally itraconazole, for at least 12 months. Long-term secondary prophylaxis with itraconazole should be considered as long as significant immunosuppression persists.[74] Newer azoles (voriconazole, posaconazole, and isavuconazole) are active agents against blastomycosis but not enough data support their use.[75] For the recommendations on fungal infections in the HSCT setting see panel 2.

Conclusions

Endemic or regionally limited parasitic and fungal diseases are infrequently found in recipients of HSCT. These diseases should be considered for screening when there are epidemiological risk factors before transplantation or during subsequent follow-up, prophylaxis, or as a causative aetiology of infection when more common pathogens are not identified. There are multiple limitations to our assessment and recommendations, including that the studies and cases reported were limited to the English language and that the current Review is limited to a group of selected organisms and not all endemic infections. Additionally, cases reported are probably patients in whom the infection was identified and treated, leading to bias. Because of the limitations of the current literature, the true incidence and prevalence of these infections cannot be identified. Future research is needed to identify the incidence of these infections, risk factors, and the effect they have in the field of HSCT. Additionally, educational initiatives are needed to increase awareness not only in endemic regions but also in non-endemic ones.

Contributors

INM, SG, DN, MSB, MBCK, CC, MA, MM, AdS, DW, HG, and PL conceptualised the paper. INM, SG, CMM, MBA, MFMS, and RFC contributed to data curation. INM, SG, DN, MSB, MKCB, PL, CC, MA, MFMS, MM, AdS, DW, HG, and REF contributed to the methods. INM, SG, CMM, MBA, RFC, MAKB, YK, SC, YA, JaS, MA, and REF contributed to the resources. INM, SG, MA, and REF wrote the original draft. MA supervised the writing of the paper. All authors reviewed and edited the paper.

Declaration of interests

MBCK declares honoraria from Gilead and an advisory board role at Gilead. RDLC declares honoraria from Gilead. NW: declares honoraria from Novartis, Kite Gilead, Sanofi Genzyme, and Therakos Mallinckrodt; consultancy fees from Novartis; travel fees from Kite Gilead and BMS Celgene; research funding from Sanofi Genzyme; and speaker fees from Therakos Mallinckrodt. EB declares honoraria from Novartis, Astellas, Alexion, Jazz Pharmaceuticals, Gilead, MSD, Keocyt, and Amgen; and travel fees from Novartis, Jazz Pharmaceuticals, and Amgen. JeS declares consultancy fees from Alexion, Sobi, and Takeda; honoraria from Alexion, Sobi, and Takeda; travel fees from Sobi; and an advisory board role at Prevail Therapeutics. JaS declares honoraria from MSD, Glead, TEVA, Atara, and Takeda. DW declares research funding from FATE therapeutics and Incyte. SKH declares honoraria from Pfizer, Novartis, Janssen, Therakos Mallinckrodt, Sanofi, and Roche. All other authors declare no competing interests.

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