Parasitic Infections of the Stem Cell Transplant Recipient and the Hematologic Malignancy Patient, Including Toxoplasmosis and Strongyloidiasis

Driele Peixoto, MD[a,*], Daniel P. Prestes, MD[b,c]

KEYWORDS

• Parasitic infections • Hematopoietic stem cell transplantation • Immunosuppression • Toxoplasmosis • Strongyloidiasis

KEY POINTS

- Parasitic infections are an emerging and potentially serious complication in HSCT.
- Diagnosis of toxoplasmosis can be challenging in the HSCT scenario, and it usually requires a high clinical suspicion as it may present with pleotropic symptoms.
- In the HSCT recipients and hematologic malignancy patients using immunosuppression may lead to severe forms of Strongyloides infection.
- In the setting of HSCT recipients and hematologic malignancy patients unusual parasitic infections such as leishmaniasis, chagas disease, malaria, schistosomiasis and other parasitic infections may occur.

INTRODUCTION

In the past decade, advances in the new antimicrobial agents, expanded immunosuppression protocols, and increased knowledge of immune reconstitution have led to changes in recommendations for prevention of infection in hematopoietic stem cell transplantation (HSCT) recipients. Despite these advances, infection is reported as the primary cause of death in up to 8% of autologous HSCT recipients and ranges from 17% to 20% of allogeneic (allo) HSCT patients.[1]

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[a] São Paulo State Cancer Institute (ICESP), Hospital das Clínicas, Av. Dr. Arnaldo, 251, São Paulo CEP: 01246-000, Brazil; [b] A. C. Camargo Cancer Center, Rua Professor Antonio Prudente, 211, Sao Paulo CEP: 01509-010, Brazil; [c] Emilio Ribas Infectious Diseases Institute, Av. Doutor Arnaldo, 165, Sao Paulo CEP: 01246-900, Brazil
* Corresponding author.
E-mail address: driele.peixoto@yahoo.com.br

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Nevertheless, the proportion of parasitic infections among HSCT patients seems to be lower than that of bacterial and viral infection, with an estimated frequency reported between 0.31% and 10%.[2] However, it is not known whether this small proportion is due to a small number of cases or if there is an underestimated reporting of cases, as parasitic diseases are often neglected and mainly occur in underdeveloped countries where the access to diagnostic methods is underresourced.

Therefore, in view of the increasing number of transplants performed worldwide and the severity of these diseases and their impact on public health, a better knowledge of parasitic infections would help to minimize their potentially fatal outcomes and improve patient care. This article reviews the key aspects of parasitic infections in individuals with hematologic malignancy and recipients of stem cell transplantations.

TOXOPLASMOSIS

Toxoplasma gondii is a ubiquitous intracellular protozoan parasite. Transmission to human host occurs by ingestion of raw or undercooked meat containing tissue cysts, by exposure to oocysts in soil contaminated with cat feces, or transplacentally (Fig. 1).

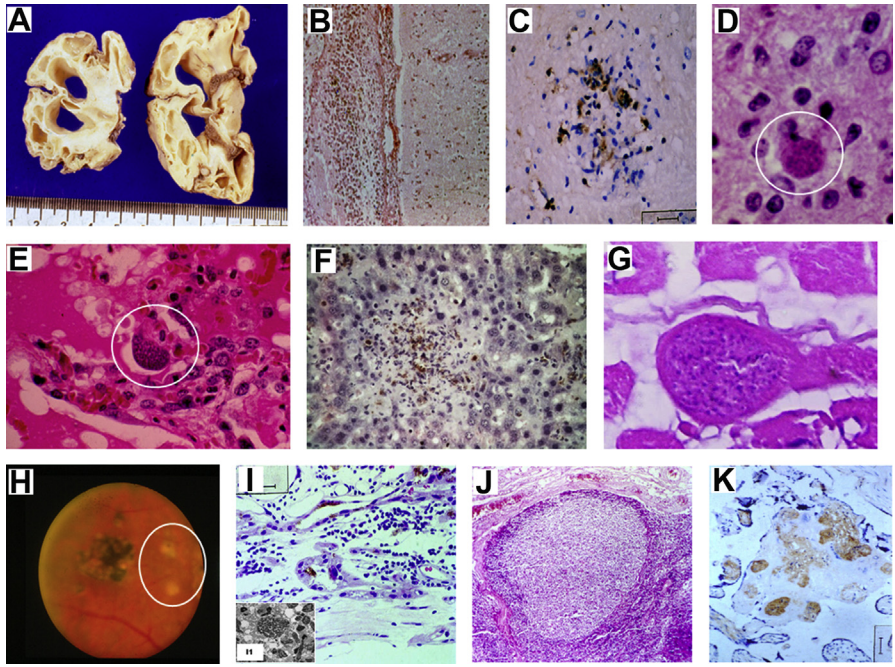

Fig. 1. Toxoplasmosis. (*A*) CNS congenital toxoplasmosis: dilated cerebral ventriculus and thinning of the cortex. (*B*) Histopathologic observation of a *Toxoplasma* meningoencephalitis with a mononuclear and polymorphonuclear infiltrate leading to a meningeal thickening. (*C*) *T gondii* immunohistochemical reaction in a microglial nodule. (*D*) *T cruzi* cyst within a microglial nodule. (*E*) Toxoplasmosis interstitial pneumonia with hemorrhage and a *T gondii* pseudocyst. (*F*) *T gondii* immunohistochemical reaction in the liver acinar cells. (*G*) *T gondii* pseudocyst in the myocardial cell. (*H*) Ocular toxoplasmosis showing whitish thickenings. (*I*) Toxoplasmosis retinitis immunohistochemical reaction showing *T gondii* antigens. (*I1*) Electron microscopy showing a *T gondii* pseudocysts in the retina. (*J*) Reactional lymph node with a lymphoid and germinative center hyperplasia. (*K*) *T gondii* antigens expressed in the placental villi. (*Courtesy of* Dr Maria Irma Seixas Duarte, MD, PhD, Sao Paulo, Brazil.)

Its prevalence varies geographically from less than 15% in the United States to 50% to 80% in Central Europe and some regions in Latin America (**Table 1**). In healthy individuals, primary infection is seldom asymptomatic; it usually manifests as fever and lymphadenopathy and is commonly diagnosed by serology.[3–5]

In immunocompromised patients such as HSCT recipients, toxoplasmosis is usually the result of a reactivation of a latent infection in seropositive patients rather than primary infection.[6] In this setting, *T gondii* presentation may include severe invasive organ disease as well as disseminated forms.[7] Most cases occur within the first 100 days following transplantation. The highest-risk patients are seropositive allo-HSCT recipients who have received cord blood transplant, unrelated donor graft, or T cell–depleted transplants, those with prior high-grade graft-versus-host disease (GVHD), and those who are unable to take trimethoprim-sulfamethoxazole (TMP/SMX) for *Pneumocystis jirovecii* prophylaxis.[8,9]

Several studies have reported an incidence of 0.3% to 8% in the first year after HSCT, depending on the seroprevalence of *T gondii* in the post-transplant toxoplasmosis studied population.[9] Additionally the prognosis of toxoplasmosis is poor, with reported mortality rates of up to 60%, including a considerable proportion of cases diagnosed post mortem, mostly in cases of disseminated disease.[10]

In immunocompromised patients, the clinical presentation may vary from constitutional symptoms such as fever, headache, and lymphadenopathy to symptoms of single-organ invasive disease, and to disseminated disease including myocarditis, pneumonitis, retinitis, and hepatitis (see **Fig. 1**).[7] In the immunosuppression scenario, the most commonly affected organ is the central nervous system (CNS), when clinical manifestations may include headache, altered mental status, peripheral nerve palsy, numbness, and visual changes.

The most common CNS toxoplasmosis neuroimaging findings on computed tomography or MRI studies are ring-enhanced lesions, usually localized in the basal ganglia, sometimes with perilesional edema.[6] Because these lesions are very characteristic, treatment should be started empirically whenever they are present. In general, a follow-up imaging study is recommended after 7 to 10 days to evaluate treatment response. In nonresponding cases brain biopsy should be considered, particularly to evaluate for other causes of similar lesions such as malignancies and other infections.[3] Because immunocompromised patients may lack the typical CNS lesion characteristics owing to immunosuppression,[11] the *T gondii* polymerase chain reaction (PCR) in the cerebrospinal fluid (CSF) can be a valuable confirmatory tool because of its high specificity (96% to 100%).[12]

Diagnosis of toxoplasmosis can be challenging in the HSCT scenario, and usually requires a high clinical suspicion index because it is a disease with pleiotropic symptoms at presentation. It is known that specific anti-*T gondii* antibodies are not a reliable diagnostic tool in the immunosuppression context and they can be absent in the early phase after HSCT.[7,9] Moreover, early diagnosis is of great importance because of its high mortality, particularly when treatment is delayed.[13,14] Thus, molecular techniques have been introduced as a pre-emptive strategy for those high-risk patients after HSCT, and some centers are developing pre-emptive protocols with weekly blood *T gondii* PCR monitoring. These protocols aim to help diagnose toxoplasmosis in an early phase and start treatment before the symptom onset. This might be a valuable option, particularly in high-burden areas, and recent publications have shown a favorable prognosis with a reduction in mortality.[8,15]

The treatment of choice for toxoplasmosis is based on the combination of pyrimethamine/sulfadiazine and folinic acid. Another alternative regimen that has been gaining popularity recently is the use of TMP/SMX, reported to have clinical efficacy similar to

Table 1
Main parasitic diseases in hematopoietic stem cell transplantation, and their distribution and transmission

Disease	Organism	Distribution/ Prevalence	Transmission
Toxoplasmosis	*Toxoplasma gondii*	Worldwide ~60% USA 11% of population (>6 years old)	Foodborne, zoonotic (cats), congenital, blood transfusion, organ transplant
Leishmaniasis NTD	*Leishmania* spp	90 countries in the tropics, subtropics, and southern Europe Cutaneous leishmaniasis 700,000–1.2 million/y Visceral leishmaniasis 100,000/y	Anthroponotic (bite of phlebotomine sand flies)
Chagas Disease NTD	*Trypanosoma cruzi*	Mexico Central America South America ~8 million infected persons	Infected triatomine Contaminated food Congenital Blood transfusion Organ transplant
Malaria	*Plasmodium falciparum* *Plasmodium vivax* *Plasmodium malariae* *Plasmodium ovale* *Plasmodium knowlesi*	Worldwide, tropical 216 million cases of malaria occurred in 2016	Mosquito-borne disease
Babesiosis	*Babesia microti* *Babesia divergens*	*B divergens* (Europe) *B microti* (USA)	Tick bites (*Ixodes scapularis*) Blood transfusion
Free-living amebae (acanthamebiasis)	*Naegleria fowleri* *Acanthamoeba* spp *Balamuthia mandrillaris*	Worldwide in the environment in water and soil	Nasal insufflation, contaminated water, swimming pools, soil Contact lenses
Schistosomiasis NTD	*Schistosoma mansoni* *Schistosoma japonica* *Schistosoma mekongi* *Schistosoma guineensis* *Schistosoma intercalatum*	200 million people infected worldwide	Skin comes in contact with contaminated freshwater (cercaria)
Strongyloidiasis	*Strongyloides stercoralis*	Tropical or subtropical climates 30–100 million infected persons	Skin penetration by contacting contaminated soil autoinfestation
Cryptosporidiosis	*Cryptosporidium hominis* *Cryptosporidium parvum*	Widespread	Fecal-oral route, person-to-person transmission, sexual partners and heath care works, animal to human in contact in farms

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Table 1
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Disease	Organism	Distribution/ Prevalence	Transmission
Microsporidium	*Enterocytozoon bieneusi* *Encephalitozoon* spp	Widespread	Uncertain Water sources? Farm? Animals?
Amebiases	*Entamoeba histolytica*	Widespread	Ingestion of the infectious cyst, mainly through contact with contaminated hands, food, or water, but there is a new appreciation that exposure to fecal matter may occur during sexual contact
Giardiasis	*Giardia duodenalis* or synonymous *G lamblia*	Widespread	Infection is transmitted by ingestion of the cyst, which is found in contaminated water, food, or person to person
Blastocystosis	*Blastocystis* spp	Widespread	Eating food contaminated with feces from an infected human or animal

Abbreviation: NTD, neglected tropical diseases.
Adapted from www.cdc.gov/parasites/index.html. Accessed November 4, 2018.

that of the first-line therapy among AIDS patients with the advantage of a lower number of pills per day.[16] Alternative regimens are presented in **Table 2**. The treatment should be maintained for 4 to 6 weeks after resolution of symptoms; however, it may be continued longer depending on the degree of immunosuppression (**Table 2**).

Primary prophylaxis is recommended for all allogeneic recipients with a positive serology before transplant. In these cases, the first-line option is TMP/SMX (160/800 mg) 3 times per week starting after the engraftment[1] and maintained for at least 6 months. Moreover, prolonged prophylaxis courses may be needed if the recipient remains significantly immunocompromised (eg, the occurrence of GVHD requiring high-dose immunosuppressant). For high-risk patients who are intolerant to TMP/SMX, the first recommended alternative prophylactic regimen may include clindamycin plus pyrimethamine and folinic acid. Therefore, other options such as atovaquone, dapsone, clarithromycin, and azithromycin can be used although the evidence supporting their efficacy is limited.[17] Another alternative approach to prophylaxis is the use of a pre-emptive protocol based on weekly screening quantitative PCR in those high-risk recipients who are unable to take prophylaxis or combined with prophylaxis for high-risk patients requiring longer surveillance because of prolonged periods of immunosuppression.

Despite controversy on the need for widespread use of secondary prophylaxis in HSCT, most services agree on its need in individuals with a high risk of reactivation

Table 2
Recommended treatment of parasitic infections in hematopoietic stem cell transplantation recipients

Disease	Primary Treatment	Secondary Treatment
Toxoplasmosis	CNS disease: pyrimethamine 200 mg PO × 1 then 75 mg PO per day with sulfadiazine 1–1.5 g PO q6 h with folinic acid 10–25 mg per day for 4–6 wk then suppressive therapy or TMP/SMX 10/50 mg/kg per day PO IV divided q12 h × 6 wk then suppressive therapy	Pyrimethamine with folinic acid and clindamycin or clarithromycin or azithromycin or atovaquone for 4–6 wk then suppressive therapy
Leishmaniasis	Cutaneous and mucocutaneous: Sodium stibogluconate or meglumine antimonitate (Glucantime) at 20 mg/kg/d IV/IM × 28 days OR Liposomal amphotericin B 3 mg/kg IV daily with total dose of 20–60 mg/kg Visceral: Liposomal amphotericin B 3 mg/kg IV daily ON DAYS 1–5, 10, 17, 24, 31 and 38 (total of 40 mg/kg)	Fluconazole 200 mg PO daily × 6 wk (*L major* only); ketoconazole 600 mg PO daily for 30 d (*L mexicana*, *L panamensis*, and *L major*) Miltefosine 2,5 mg/kg/d (maximum of 150 mg/d) PO × 28 d
Chagas disease	Benznidazole 5–7 mg/kg/d PO bid, 60 d	Nifurtimox, 8–10 mg/kg/d PO divided 4×/d 90 d
Malaria	Uncomplicated (*P vivax*, *P malariae*, *P ovale*, *P knowlesi*) OR *P falciparum* (chloroquine sensitive): chloroquine phosphate 1 g (600 mg base) PO, then 0,5 g in 6 h, then 0,5 g daily × 2 d PLUS primaquine phosphate 52.6 mg PO once daily × 14 d (for *P vivax and P ovale*) Complicated (Artesunate 2.4 mg/kg IV at 0, 12, 24, 48 h Continue q24h if unable to take oral medication Follow parenteral therapy wiyh a complete oral course of one of: Atovaquone/proguanil × 3 days Artemether/lumefantrine × 3 days Doxycycline 100 mg q12h × 7 days * If severe P. vivax add Primaquine [see uncomplicated P. vivax])	Uncomplicated (*P vivax*, *P malariae*, *P ovale*, *P knowlesi*): none Uncomplicated (*P falciparum*): atovaquone-proguanil 4 adult tablets (100/400 mg) PO in a single dose daily × 3 d (with food) OR quinine sulfate 650 mg PO tid × 3 d PLUS doxycycline 100 mg PO bid
Babesiosis	Atovaquone 750 mg PO bid PLUS azithromycin 500–1000 PO on day 1, then 250–1000 mg/d PO for 7–10 d Treat 6 wk to include 2 wk after blood smear negative for severe cases	Clindamycin 600 mg PO tid PLUS Quinine 650 mg PO tid 7–10 d

Free-living amebae	*Acanthamoeba* sp: no proven therapy, can try: pentamidine + fluconazole + miltefosine 50 mg PO tid. May add TMP/SMX, metronidazole, and azithromycin *Balamuthia mandrillaris*: albendazole + fluconazole or itraconazole + miltefosine 50 mg PO tid + pentamidine. May add TMP/SMX *Naegleria fowleri*: amphotericin B deoxycholate + rifampin 10 mg/kg/d + fluconazole 10 mg/kg/d + miltefosine 50 mg PO tid + azithromycin 500 mg.	
Schistosomiasis	Praziquantel: 20 mg/kg/dose PO bid × 1 d *S mansoni*, *S hematobium*, or *S intercalatum* 20 mg/kg PO tid × 1 d *S japonicum* or *S mekongi*	Oxamniquine and artemether (antimalarial) Oxamniquine (*S mansoni*)
Strongyloidiasis	For disseminated disease with larvae in stool and sputum, repeat treatment every 15 days while stools positive and then 1 more treatment cycle Ivermectin 200 μg/kg/d PO for 2 d (asymptomatic or intestinal disease) For hyperinfection or disseminated disease in immunocompromised patients: Ivermectin 200 μg/kg/d PO per day until stool and/or sputum exams are negative for 2 wk	Albendazole 400 mg PO bid × 7 d for asymptomatic or intestinal disease
Cryptosporidiosis	Nitazoxanide 500 mg PO bid, 14 d	Paromomycin or azithromycin
Microsporidium	Albendazole 400 mg PO bid, 2–4 wk	Fumagillin
Amebiasis Diarrhea	Metronidazole 500–750 mg PO tid, 5–10 d Followed by Paromomycin (25–35 mg/kg/d PO divided 3 doses × 7 d) or iodoquinol (650 mg PO tid × 20 d)	Tinidazole 2 g PO daily 3 d Followed Paromomycin (25–35 mg/kg/d PO divided 3 doses × 7 d) or iodoquinol (650 mg PO tid × 20 d)
Giardiasis	Tinidazole 2 g, 1 day	Nitazoxanide 500 mg PO bid × 3 d Metronidazole 500–750 mg PO tid × 5 d, paromomycin 500 mg PO qid × 10 d
Blastocystosis	Nitazoxanide, 500 mg PO bid for 3 d	Metronidazole 1.5 g × 1 daily for 10 d

Abbreviations: bid, twice daily; IV, intravenously; PO, orally; q, every; qid, every day; SMX, sulfamethoxazole; tid, 3 times daily; TMP, trimethoprim.

Adapted from Gilbert DN, Chambers HF, Eliopoulos GM, et al., editors. Sanford guide to antimicrobial therapy 2018, 48th edition. Sperryville (VA): Antimicrobial Therapy, Inc; 2018; with permission.

after therapy discontinuation. This population includes those with a history of chronic toxoplasmosis and previous infection, and those who develop recurrent GVHD.[14,18]

LEISHMANIASIS

Leishmaniasis is an anthropozoonotic infection caused by protozoans of the genus *Leishmania* (see **Table 1**). It is transmitted to humans by the bite of a mosquito from the genus *Phlebotomus* (New World) or *Lutzomya* (Old World).[19] However, other forms of transmission including donor-derived transmission and incidental transmission by blood transfusion or by needle sharing among intravenous drug users have also been reported.[19–21]

There are 3 major forms of leishmaniasis: visceral (VL), cutaneous (CL), and mucocutaneous. The disease is considered a public health issue because it affects some of the poorest regions of the world. Leishmaniasis is present in 4 continents and it is considered endemic in 88 countries, including 72 developing countries.[19]

In the HSCT setting, the derangement of host cellular immunity caused by the conditioning therapy or GVHD treatment could lead to leishmaniasis reactivation. However, post-HSCT leishmaniasis can also be a result of a primary infection, and the graft itself has been described as another potential source.[22]

The clinical presentation is variable and depends on the form of leishmaniasis as well as the degree of immunosuppression (**Fig. 2**). Among HSCT patients, VL is the form described in most cases, usually presenting with fever, hepatomegaly, splenomegaly, lymphadenopathy, and pancytopenia. Though less common, cutaneous disease has also been described in HSCT recipients and usually presents as single or multiple ulcerating papular lesions.[23] In addition, post-kala-azar dermal leishmaniasis is a cutaneous complication of VL characterized by a macular, maculopapular, and nodular rash, which should be considered in an HSCT patient who has recovered from a VL episode.[24]

Because symptoms of VL form are nonspecific, diagnostic delays are common. However, given mortality rates reaching 100% without specific treatment, clinicians should consider leishmaniasis a possible diagnosis in HSCT recipients from endemic areas who present with fever and pancytopenia.[25]

The proven diagnosis of leishmaniasis is the evidence of the parasite in tissue specimens such as the detection of amastigotes in the bone marrow. However, other methods can be used, including *Leishmania* PCR detection in the bone marrow or blood, which is a very sensitive and specific technique in the VL diagnosis. Among immunocompromised patients, it is also valuable for follow-up of treatment response.[26,27]

The serology tests for leishmaniasis include indirect fluorescent antibody test, enzyme-linked immunosorbent assay (ELISA), and direct agglutination. However, in the HSCT recipient a serology result should be carefully interpreted because there is impairment in the antibody production in these patients.[28] Skin test is considered a marker of previous exposure to *Leishmania* and it is not a valuable diagnostic tool for active infection, especially for patients from high-burden areas.[25]

The 2 most used drugs for treatment of leishmaniasis are pentavalent antimonials and amphotericin B.[25] According to the pharmacologic properties of these drugs, there are many variables that can affect their efficacy such as the *Leishmania* species, patient characteristics, drug availability, disease extent, and previous treatments.[29] Indeed, among HSCT patient data comparing both drugs are lacking and evidence relies mostly on case reports describing VL treatment with liposomal amphotericin B, with a good response.[22,28] Data from other immunocompromised

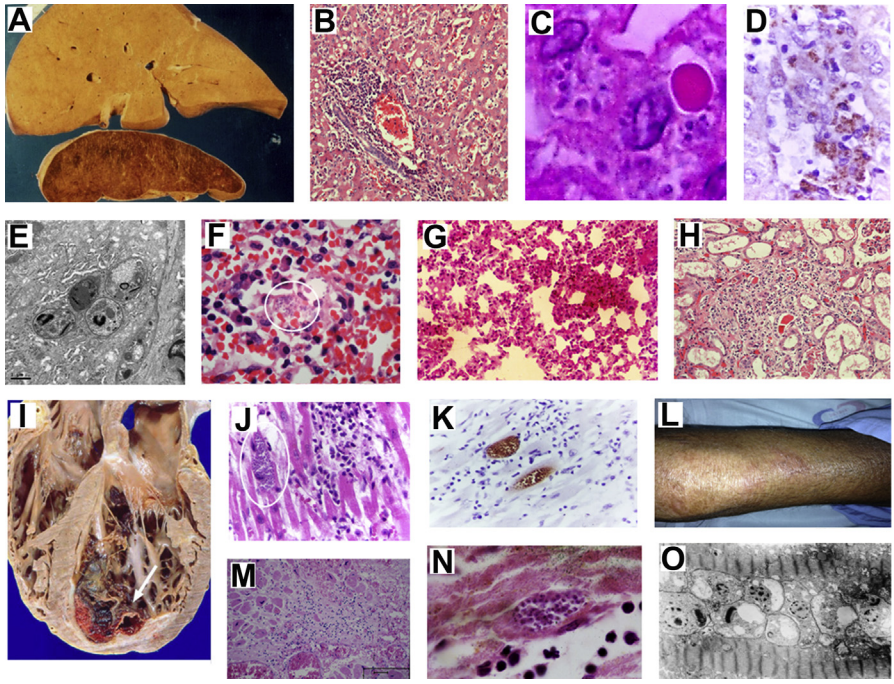

Fig. 2. Leishmaniasis and Chagas disease. (*A*) Visceral leishmaniasis showing a steatosis yellowish enlarged liver and an enlarged parasitized spleen with reticuloendothelial cell hyperplasia. (*B*) Histopathologic observation of a liver showing a mononuclear infiltrate of the portal space and hyperplasia of the Kupffer parasitized cells. (*C*) Kupffer cells cytoplasm containing amastigote parasites. (*D*) Immunohistochemical reaction revealing amastigotes parasitizing Kupffer cells. (*E*) Electronic microscopy illustrating amastigote forms in Kupffer cells' cytoplasm. (*F*) Spleen red pulp with macrophages containing amastigotes. (*G*) Leishmaniasis interstitial pneumonitis with mononuclear cells infiltrate. (*H*) Histopathologic observation of a leishmaniasis interstitial nephritis with mononuclear cells infiltrate. (*I*) Chagas enlarged heart with dilated cavities and a left ventricular thrombosis. (*J*) *T cruzi* amastigotes form parasitized heart myocardial cells with an interstitial mononuclear cells infiltrate. (*K*) Immunohistochemical reaction showing *T cruzi* antigens expressed in the myocardial cells cytoplasm. (*L*) Chagas skin lesions in a renal transplant patient. (*M*) Chronic Chagas myocarditis with an extensive inflammation and fibrosis. (*N*) Myocardial with *T cruzi* amastigotes. (*O*) Electron microscopy showing *T cruzi* amastigotes in the cardiac cell cytoplasm. (*Courtesy of* Dr Maria Irma Seixas Duarte, MD, PhD, Sao Paulo, Brazil.)

populations such as HIV and solid organ transplant patients show similar efficacy of both therapies when used to treat VL (see **Table 2**).[30] However, currently amphotericin B is considered the drug of choice for the treatment of VL according to international guidelines, owing to greater antimonial-related severe side effects when systemically administered, leading to treatment interruptions.[30] Also, the development of resistance of *Leishmania* to pentavalent antimonials is another drawback of these drugs.[31–33]

CHAGAS DISEASE

Chagas disease, also referred to as American trypanosomiasis, is caused by *Trypanosoma cruzi*, a protozoan parasite transmitted by infected triatomine bugs.

Transmission may also occur through oral transmission, contaminated blood transfusion, tissue/organ transplantation, or vertical transmission.[34] Chagas disease is a public health concern in endemic areas in South America, Mexico, and Central America, although more than 200,000 people live with *T cruzi* infection in the United States, mostly immigrants from endemic areas (see **Table 1**).[35]

The disease has acute and chronic phases. In the acute cases symptoms can vary from mild, nonspecific febrile illness to life-threatening myocarditis or meningoencephalitis. The life-long chronic phase has a long latent period, termed the undetermined phase. This phase may include cardiac complications such as heart rhythm abnormalities or dilated cardiomyopathy, and gastrointestinal tract complications such as megaesophagus and megacolon (see **Fig. 2**).[36]

Because a high number of parasites circulating in blood characterizes the acute phase, the diagnosis relies on: (1) direct methods of parasitologic identification using the concentration method (Strout method) or microhematocrit; (2) hemocultures as indirect methods of parasitologic identification; and (3) techniques based on nucleic acid detection such as PCR, which have high sensitivity even among immunocompromised patients.[37]

Chronic infection is characterized by intermittent and extremely low parasitemia; thus, diagnosis relies on positive serology, most commonly ELISA and immunofluorescent antibody test. When results are discordant, a third assay or repeat sampling may be required.[34]

Chagas disease reactivation is defined as an increase in parasitemia that can be detected by direct parasitologic and/or PCR methods, even in the absence of clinical symptoms. In immunocompromised patients, including HSCT, the most common presentation of Chagas disease is reactivation. Particularly for HSCT the risk of reactivation varies from 17% to 40% for autologous or allogeneic HSCT, respectively.[38] The most common presentation in reactivation is febrile illness, subcutaneous nodules (chagoma), panniculitis, myocarditis, meningitis, encephalitis, and stroke. In this clinical scenario, direct parasitologic tests and blood PCR are usually needed, although other specific tests may be performed on skin lesion biopsy samples or on CSF.[37] Additionally a rare presentation of Chagas reactivation with retinitis in HSCT transplant patients, with vitreous biopsy PCR positive for *T cruzi*, was published recently.[39]

Another peculiarity of Chagas management in the immunocompromised population is the need to investigate proactively high-risk individuals, even if asymptomatic, before the use of chemotherapy or conditioning regimens.[37] This higher-risk population includes individuals from endemic areas, those born to mothers from such areas, and those who receive blood transfusion in endemic countries. This investigation can be performed with serologic tests for antibody detection, although caution is needed when interpreting results because false negatives may occur.[40]

Among HSCT candidates, monitoring of possible reactivation during the chemotherapy phase before the transplant is recommended. The recommended follow-up schedule is based on directed parasitologic methods and PCR repeated weekly for 2 months, bimonthly between second and sixth months post transplant, and annually thereafter.[37] This protocol is of importance because early treatment has been shown to reduce the incidence of severe cases and fatal disease.[41]

The treatment of Chagas disease is based on benznidazole and nifurtimox. Because of its better tolerance, benznidazole is considered a first-line treatment.[36] In addition, antiparasitic treatment is indicated for all cases of reactivated Chagas disease (see **Table 2**).[34]

MALARIA

Malaria is an acute parasitic infection caused by 5 human plasmodia species: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*, and *Plasmodium knowlesi*.[42] It is transmitted to humans mostly by the mosquito bite of the female *Anopheles* (see **Table 1**), although it can be acquired through blood product transfusion or grafts in the HSCT scenario.[43,44]

Although successive exposures to malaria do not produce a protective immune response, some degree of tolerance and resistance is achieved through persistence of plasmodia in the liver, the microvasculature, and the bloodstream. This incomplete acquired immunity does not eradicate the infection but elucidates the lack of parasitemia and higher incidence of asymptomatic disease in adults from endemic regions, although it may also pose a problem for blood and organ donation.[45]

The disease has been described after solid organ transplantation, including in recipients of liver, kidney, and heart transplants.[45] Infection following HSCT is considered an unusual infectious complication of the transplant procedure, mainly described by case reports. In this population, fever is the main symptom reported and may be accompanied by pancytopenia.[46]

Classically, definitive diagnosis is made by direct microscopy of thick and thin blood smears by Giemsa or acridine orange stain (**Fig. 3**).[12] This method was most commonly used for diagnosis of febrile patients after HSCT. Nevertheless it is time consuming, has low sensitivity, and is not recommended for donor blood screening, as it is not suitable for detection of asymptomatic cases with low parasitemia. Molecular diagnostic methods, including DNA hybridization and PCR for DNA and mRNA amplification, are more sensitive than direct stains and can detect low levels of parasitemia earlier than examination of blood film.[42] Serology may be useful to investigate a potential donor; however, it might be negative in case of acute disease. Rapid diagnostic tests are available by using dipsticks, allowing the detection of specific plasmodia antigens, although they are not suitable for detecting submicroscopic parasitemia because of their low sensitivity.[12]

In endemic areas, previous episodes of malaria are not considered an exclusion criterion for donation; however, active surveillance is strongly recommended for recipients from these regions, those who had previous malaria infection, and recipients of donors from endemic areas. After a malaria episode the disease can persist for a long period, which can vary from 3 to 40 years depending on the *Plasmodium* species.[42] Therefore, in the transplant setting the parasitized red cells are a potential source of transmission and clinical malaria can emerge from a pre-existent subclinical infection in the donor, which is exacerbated during the immunosuppression period.[2]

The anti-*Plasmodium* treatment is based on the *Plasmodium* species, and takes into account the geographic distribution and sensitivity profile. Special attention is needed to the interaction between antimalarial drugs and immunosuppressive therapy. In brief, individuals in uncomplicated areas should be treated with chloroquine or artemisinin-based combination therapy (ACT). In areas with chloroquine-resistant infections, *P vivax*, *P ovale*, *P malariae*, or *P knowlesi* malaria should be treated with ACT. To prevent relapse, cases of *P vivax* and *P ovale* should have primaquine added to the primary treatment. Uncomplicated *P falciparum* malaria should be treated with one of the ACTs. For severe disease, intravenous treatment with artesunate is recommended (see **Table 2**).

BABESIOSIS

Babesiosis is an infectious disease caused by intraerythrocytic protozoal parasites of the genus *Babesia*. Transmission to humans occurs via ticks or blood transfusion (see

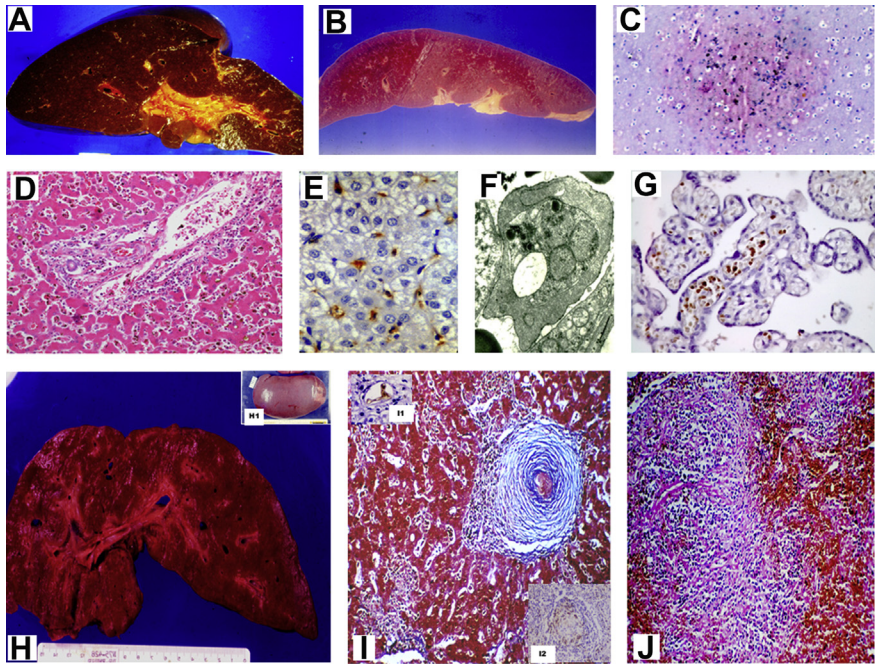

Fig. 3. Malaria and schistosomiasis. (*A*) Malaria enlarged liver with dark-brown color resulting from hemosiderin and malaria pigment deposition. (*B*) Malaria splenomegaly with accentuation of red pulp. (*C*) Histopathologic observation of CNS malaria duck granuloma with mononuclear infiltrate and malaria pigment impregnation. (*D*) Histopathologic aspect of a malaria-affected liver with mononuclear infiltrate confined to the portal space and Kupffer cells hyperplasia. (*E*) Kupffer cells with a malaria-positive immunohistochemical reaction. (*F*) Electron microscopy of cerebral malaria showing *P falciparum* trophozoites clustered into a macrophage cytoplasm. (*G*) Placental villi red blood cells with malaria immunohistochemical positive reaction. (*H*) Enlarged liver showing portal spaces fibrosis. (*H1*) Congestive sclerosis splenomegaly. (*I*) Histopathologic observation of a liver with a granuloma containing *S mansoni* ova. (*I1*,*I2*) Schistosomiasis granuloma with eggs and cells showing an *S mansoni*-positive antigen immunohistochemical reaction. (*J*) Liver biopsy showing hepatosplenic schistosomiasis and histiocytic lymphoma. (*Courtesy of* Dr Maria Irma Seixas Duarte, MD, PhD, Sao Paulo, Brazil.)

Table 1). A case reported in transplant recipients has been tracked back to pretransplant blood transfusion in an HSCT recipient.[47]

The incubation period is typically 1 to 9 weeks post exposure. *Babesia* infection can range from asymptomatic in healthy individuals to life-threatening disease in immunocompromised patients. Symptoms may develop within a few weeks or months after exposure. Early symptoms may be fever and malaise, which can progress to severe hemolytic anemia, adult respiratory distress syndrome, multiorgan failure, and even death.[48] Risk factors for severe babesiosis include anatomic or functional asplenia, immunocompromised state, rituximab use, thrombocytopenia, parasitemia greater than 10%, and older age (>60 years).[49]

Reports of babesiosis in transplant recipients are few; nonetheless babesiosis can be a cause of anemia post HSCT,[50] and hemophagocytic lymphohistiocystosis has been described in immunocompetent patients and splenectomized renal transplant patients.

The babesiosis diagnostic involves the identification of intraerythrocytic parasites in blood smears, indirect immunofluorescence, or the PCR testing of blood for *Babesia* DNA.[51]

The treatment requires a combination of atovaquone plus azithromycin or clindamycin plus oral quinine for at least 7 to 10 days (see **Table 2**). However, in a series of 14 immunocompromised subjects, most with B cell lymphoma, asplenic, or treated with rituximab, the treatment was required for at least 6 weeks to achieve a cure. Three (21%) subjects died, highlighting the severity of disease in this population and the importance of blood smears for monitoring response to therapy and relapse after completion of treatment.[52]

For those patients with high-level parasitemia (>10%) or severely ill patients, exchange transfusion should be considered as part of the treatment. Though rare, resistance to the atovaquone/azithromycin regimen can occur, more commonly in immunocompromised hosts.[53]

FREE-LIVING AMEBAE

Acanthamoeba species are ubiquitous in the environment and infective forms can occur through the eye, the nasal passages to the lower respiratory tract, and ulcerated or broken skin (see **Table 1**). Systemic infection is increasingly reported in immunocompromised hosts,[54] except the *Acanthamoeba* keratitis that occurs in healthy individuals and is associated with contact lens use.[55]

A high index of suspicion is necessary to make this diagnosis, and recipients of autologous HSCT may be at increased risk for amebic reactivation.[54] *Acanthamoeba* spp and *Balamuthia mandrillaris* cause cutaneous infection and chronic granulomatous amebic encephalitis, whereas *Naegleria fowleri* causes an acute, fulminant primary amebic meningoencephalitis.[54,56] Despite the limited data of *Acanthamoeba* encephalitis among HSCT recipients, at least 1 case series of 10 individuals reported 100% lethality, even in adequately treated individuals.[57]

Diagnosis is usually made by the identification of cysts or trophozoites in infected tissue. Cutaneous lesions should be biopsied because early diagnosis is imperative to optimize the chance of survival. Brain computed tomography and MRI can also be helpful in the diagnostic investigation, although its results may be nonspecific, particularly in *Naegleria* cases. Direct examination of CSF should be performed.[58] In *Acanthamoeba* infections, a brain biopsy may be needed to investigate for trophozoites, specific tissue abnormalities, and immunofluorescence. Additionally an increasing number of PCR-based techniques for detection and identification of free-living amebic infections have been described.[59]

Optimal treatment regimens for free-living amebic infections remain unknown.[60] Thus, antimicrobial therapy must have wide spectrum and be aggressive. Related treatments with combinations of drugs have been used with inconsistent results (see **Table 2**).[58,61]

SCHISTOSOMIASIS

Schistosomiasis is a neglected tropical disease caused by trematode worms of the genus *Schistosoma*. The infection affects almost 240 million people worldwide, mostly in tropical and subtropical areas. Six species are responsible for human infection, with diverse geographic distributions: *Schistosoma mansoni* is prevalent in Africa, South America, and the Caribbean islands; *Schistosoma japonicum* in China and the Philippines; *Schistosoma mekongi* in Southeast Asia; *Schistosoma guineensis* and related *Schistosoma intercalatum* in central Africa; and *Schistosoma haematobium* (the species related to urogenital schistosomiasis) in Africa and the Middle East (see **Table 1**).[62]

Intestinal schistosomiasis has a nonspecific clinical presentation that includes abdominal pain, diarrhea, bloody stools, and liver enlargement in advanced cases, whereas urogenital schistosomiasis usually presents with hematuria (see **Fig. 3**).[62]

Schistosomiasis is rare in immunocompromised populations, particularly among hematologic malignancy or stem cell transplanted patients, and most publications are limited to few case reports.[63,64] Nevertheless, for patients coming from endemic areas, routine stool and urine examinations and serologic tests of schistosomiasis should be performed, and proper treatment of schistosomiasis at least 3 to 8 weeks before HSCT is recommended.[65]

Schistosomal periportal fibrosis may thus be added to the known risk factors predisposing to the development of veno-occlusive disease (VOD) in allogeneic transplant recipients, as shown among 89 allogeneic HSCT recipients in whom VOD of the liver was higher in those with schistosomal periportal fibrosis.[66]

In general, stool and/or urine examination for ova is the primary diagnostic method for suspected schistosome infections. The choice of sample to diagnose schistosomiasis depends on the parasite species likely to be causing the infection. Whereas *S haematobium* adult worms are found in the venous plexus of the lower urinary tract and eggs are shed in urine, the other species' eggs are shed in feces. The eggs are shed irregularly, so to increase the sensitivity of the examination multiple samples are needed, and a set of 3 serial samples is usually recommended. The clinical investigation of individuals undergoing chemotherapy is particularly challenging because its use might reduce the amount of excreted eggs, hampering the diagnosis in many cases.[64,67]

The first-line treatment of schistosomiasis is oral praziquantel, a safe drug efficacious against all adult worms' species,[68] infrequently associated with parasite resistance. Patients should be retreated if stool or urine examination remains positive at 4 weeks.[69] Although some other treatments are available, they are rarely needed (see **Table 2**).

STRONGYLOIDIASIS

Strongyloides stercoralis is an intestinal nematode endemic to tropical and subtropical areas and has also been reported in temperate regions of Europe and the southeastern United States (see **Table 1**). The parasite has an autoinfective cycle that allows it to cause long-term persistent infections. This characteristic can be explained by its ability to complete the life cycle either in the environment or in the human host.[45]

The perpetuation of infection by the filariform larvae is limited by the host immunity, especially the T-helper 2 cell–mediated immune response. Thus, in the immunocompromised patient such as the HSCT recipient, autoinfection is facilitated and can culminate in the so-called *Strongyloides* hyperinfection syndrome (SHS).

In the transplant setting, risk factors for SHS are those linked to the use of immunosuppressive drugs such as corticosteroids and T cell–depleting drugs, although cyclosporine-containing regimens have a crucial impact in reducing *Stongyloides* reactivation among the transplant population, as the drug also has an antihelminthic effect.[70] Indeed, among the allogeneic HSCT population, the period of highest reactivation risk is not the immediate post-transplant period but when GVHD develops and steroids are started with cyclosporine discontinuation.[71]

The clinical presentation is variable and the disease can present as: acute infection; chronic infection with autoinfection; SHS with high parasite burden leading to exuberant clinical manifestations, restricted to pulmonary and gastrointestinal symptoms; and disseminated disease characterized by the spreading of the larvae to other organs (**Fig. 4**).[45,70] The main symptoms reported include fever, bacteremia, rash, gastrointestinal pain, diarrhea, hemoptysis, wheezing, and CNS

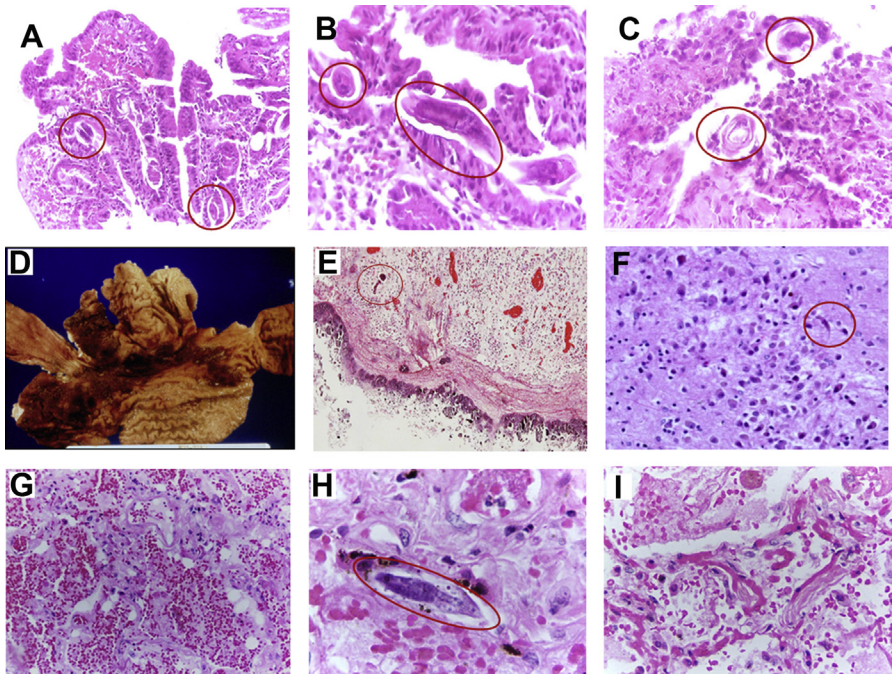

Fig. 4. Strongyloidiasis. (*A*) Duodenitis: histopathologic section with inflammatory infiltrate from *S stercoralis* rhabditoids and adult worms crypt invasion. (*B*) Small bowel with adult worms and eggs in the villi. (*C*) *S stercoralis* worms' transversal segment and eggs on an ulcerated gastric mucosa. (*D*) Hemorrhagic gastritis with edema and mucosal erosion. (*E*) Colonic mucosa showing edema and submucosal inflammation with *S stercoralis* worm. (*F*) CNS parenchymal inflammatory nodule with a filarioid worm. (*G*) *S stercoralis* hemorrhagic pneumonia. (*H*) Filarioid worm within the hemorrhagic area. (*I*) Hemorrhagic pneumonia with diffuse alveolar damage. (*Courtesy of* Dr Maria Irma Seixas Duarte, MD, PhD, Sao Paulo, Brazil.)

manifestations compatible with meningitis caused by gram-negative bacteria from intestinal flora.

The diagnosis of strongyloidiasis should be suspected when there is epidemiologic risk along with clinical signs and symptoms, eosinophilia, or suggestive serologic findings.[72] Eosinophilia is usually mild (5% to 15%); however, it is a nonspecific marker of disease, and patients with chronic infection, SHS, or disseminated disease may have normal or even low eosinophil counts.[73] Definitive diagnosis is made by identification of larvae on direct microscopy from clinical species mainly in stool and duodenal aspirate. In addition, if strongyloidiasis is clinically suspected in a seronegative patient or if serology tests are unavailable, a total of 3 or more stool examinations is recommended to increase the sensitivity of the test.[1]

Serology by ELISA is also available and may be used for diagnosis. It is highly sensitive (88%) and specific (90%) in an immunocompetent host,[72] although the sensitivity may be lower in the setting of immunosuppression.[74] In addition, the *Strongyloides* antibody test can cross-react with other helminth infections, which may result in a false-positive test.[72]

Ivermectin is considered the drug of choice for treatment of uncomplicated strongyloidiasis in the immunocompetent host.[45] Because the complete eradication of *Strongyloides* infection is difficult in immunocompromised patients, some experts

recommend repeating the 2-day treatment 2 weeks later or even treating for longer until neutrophil counts recover.[75]

Albendazole is an alternative, and has been shown to clear stool of *S stercoralis* larvae in 38% to 45% of infected individuals and to normalize serology in chronic infected patients with a negative stool test.[70] Although thiabendazole was routinely used for the treatment of *S stercoralis*, the high rate of adverse events limits its use (see **Table 2**).[70]

The best treatment approach for SHS in immunocompromised patients is unclear, and clinical failure with ivermectin has been reported. Moreover, with high parasite burden it is recommended to continue treatment for a longer period, until the clinical syndrome resolves and larvae are no longer detectable. Also, for severe cases refractory to conventional treatment or for those patients who are unable to take oral ivermectin, there are some case reports advocating the use of subcutaneous ivermectin as a rescue treatment with good overall survival rates and microbiologic "cure."[76]

Strongyloidiasis is considered a devastating complication in the immunosuppression context, with mortality rates reported to range from 50% to 70% in SHS and disseminated infection, respectively. Because of this risk, adequate screening before transplantation is strongly recommended. The current recommendation for HSCT recipients is to screen those with unexplained eosinophilia who were exposed to/living in endemic areas.[1] Moreover, given the limitation of current diagnostics and considering the favorable tolerability of the drug, some authors suggest a pre-emptive therapy with ivermectin for high-risk patients regardless of serology result or eosinophilia.[75]

CRYPTOSPORIDIOSIS

Cryptosporidium is an intracellular protozoan parasite that has emerged as an important cause of diarrheal illness worldwide. Most infections worldwide have been attributed to *Cryptosporidium hominis* and *Cryptosporidium parvum* (see **Table 1**).[77]

Cryptosporidium infection in immunocompetent individuals is self-limited. However, the clinical presentation in immunocompromised patients is highly variable. The spectrum of its presentation may spread from asymptomatic individuals to life-threatening gastrointestinal and biliary tract disease, including cases of transient gastrointestinal symptoms and chronic diarrhea.[78] A Brazilian study of hematologic patients showed a significantly higher frequency of *Cryptosporidium* infection than in the control group with the same age and environmental exposition.[79]

Transmission is usually via the fecal-oral route, as well as person-to-person transmission particularly within households and nurseries, among sexual partners and heath care workers, and animal to human via contact in farms.[80]

Cryptosporidium infection has been reported with a variable prevalence following HSCT. In a study in southern India, its incidence was 4.61%,[81] whereas in a French study where a systematic screening was used, the cumulative incidence of digestive *Cryptosporidium* in allogeneic HSCT reached 9.6% in patients with diarrhea and 4% in all HSCT recipients.[82] In this population the entire gastrointestinal tract can be affected, and the infection may mimic intestinal GVHD.

Detection of *Cryptosporidium* infection is based on analysis of stool samples by use of microscopy with tinctorial and fluorescent stains or via antigen and nucleic acid detection. More sensitive, specialized tests available in reference facilities include PCR and, for maximum sensitivity in exceptional circumstances, immunomagnetic separation with immunofluorescence microscopy.[77] Serologic testing has a limited value for clinical diagnoses because it can remain elevated for more than a year after the infection.

The Food and Drug Administration–approved drug for treatment of *Cryptosporidium* is nitazoxanide,[83] a broad-spectrum antiparasitic with reported use as a deworming agent as well as a treatment of giardiasis and cryptosporidiosis in randomized trials (see **Table 2**).[69] An immunocompromised patient was successfully treated with a combination of azithromycin and nitazoxanide, aiming for a rapid combined action of drugs.[82]

MICROSPORIDIA

Microsporidia is a group of obligatory intracellular parasites currently considered to be related or belonging to the fungi kingdom. The commonest microsporidia in humans are *Enterocytozoon bieneusi* and *Encephalitozoon* spp. The routes of microsporidia infection are still uncertain, but the species that can infect humans have been identified in water sources as well as in farm, domestic, and wild animals (see **Table 1**).[84]

Although traditionally associated with diarrheal illness in patients with AIDS, extraintestinal infections involving various organs have been reported, particularly in immunocompromised hosts.[85] Clinical presentations may include enteropathy, keratoconjunctivitis, sinusitis, tracheobronchitis,[86] encephalitis, interstitial nephritis, hepatitis, cholecystitis, osteomyelitis, and myositis.[87]

Reports on the prevalence of *Microsporidium* in oncologic patients are limited. In a study of 320 patients with cancer, the prevalence of microsporidia infection has been reported to be as high as 11% using staining of the stool samples.[88] High-risk HSCT patients with gastrointestinal complaints should be evaluated for microsporidian pathogens regularly to improve their quality of life and decrease the problems during the treatment period.[89] In addition, microsporidia should be considered in the differential diagnosis of pulmonary infections in immunosuppressed patients.[90,91]

Albendazole is the first-line therapy for most species that infect humans (see **Table 2**).[69] Additionally the reduction of immunosuppression, whenever possible, is essential for clearing the infection. One alternative regimen is oral fumagillin, although its use is limited because of significant bone marrow toxicity.[85]

AMEBIASES

Intestinal amebiasis caused by *Entamoeba histolytica* is a leading cause of severe parasitic diarrhea worldwide, mostly in developing countries with poor sanitary conditions (see **Table 1**).[92]

The transmission of amebiasis occurs after the ingestion of the infectious cyst, mainly through contact with contaminated hands, food, or water, but there is a new appreciation that exposure to fecal matter may occur during sexual contact.[93]

Amebiasis presentation can range from asymptomatic infection, to invasive intestinal amebiasis (dysentery, colitis, appendicitis, toxic megacolon, amebomas), and to invasive extraintestinal amebiasis (liver abscess, peritonitis, pleuropulmonary abscess, cutaneous and genital amebic lesions).[94]

Amebiasis has rarely been reported in patients undergoing HSCT, although it is an extremely common infection worldwide.[95,96] More recently a study demonstrated that patients with either symptomatic or asymptomatic intestinal amebiasis treated with corticosteroid therapy were at higher risk of developing the potentially fatal complication of fulminant amebic colitis. Thus, patients from endemic areas with very high epidemiologic burden might benefit from screening before treatment with corticosteroids.[92]

Amebiasis can be diagnosed by stool examination, colonoscopy, and histologic examination. Antigen kits to detect *Entamoeba* require fresh (not formalin-preserved)

stool for analysis, and stool PCR is a promising new technique. Serum antibodies are useful in a person from a nonendemic country.[97]

Amebic colitis should be treated with metronidazole followed by a luminal agent, such as paromomycin. Treatment with a luminal agent alone is sufficient for patients with asymptomatic intestinal amebiasis (see **Table 2**).[92] The luminal agent usually prescribed is either nitazoxanide or paromomycin, although an allogeneic bone marrow transplanted patient with diarrhea, intestinal amebiasis and acute GVHD was successfully treated with metronidazole in Japan.[98]

GIARDIASIS

Giardia lamblia is a flagellated protozoan and is a common cause of diarrheal disease throughout the world. Infection is transmitted by ingestion of the cyst, which is found in fecally contaminated water, food, or person-to-person transmission (see **Table 1**).[99]

Giardia infections can be asymptomatic, estimated in 5% to 15% of infected people, but typical symptoms include diarrhea flatulence, abdominal pain, and distension. Later the diarrhea becomes more intermittent, with periods of normal bowel function interspersed with diarrhea and malabsorption.

Immunosuppression in patients with *Giardia* can have serious effects, and it may be difficult to distinguish between infection and GVHD.[100–102] An Indian study including 29 renal, 2 liver, and 7 bone marrow transplant recipients documented a prevalence of *Giardia* of 11%,[103] and *Giardia* was a common cause of diarrhea in the Indian HSCT community.[104]

The diagnosis of giardiasis is generally made by the identification of cysts or trophozoites in fecal specimens. Shedding of cysts is somewhat intermittent, so a total of 3 fecal samples over a period of several days is generally recommended. Fecal coproantigen detection using enzyme immunoassays or immunochromatography detection and fluorescent antibody assays of fecal specimens are now used more frequently. Nucleic acid detection methods have also been studied extensively and include conventional and real-time PCR. Nucleic acid methods probably have greater sensitivity, although questions remain regarding their specificity.[99]

The most studied drugs to treat giardiasis are metronidazole, tinidazole, and albendazole (see **Table 2**). The efficacies of metronidazole and tinidazole have been uniformly excellent, whereas some studies of albendazole have shown inferiority to the nitroimidazoles.[99,105]

BLASTOCYSTOSIS

Blastocystis hominis is a protozoan parasite that inhabits the human gastrointestinal tract.[106] It has a worldwide distribution, although it is more frequent in developing countries. Fecal-oral route is the presumed route of transmission (see **Table 1**).[107,108]

The pathogenic role for *B hominis* is uncertain in the immunocompetent host, and in some communities prevalence is as high as 20% in asymptomatic individuals. However, infection has been reported in allogenic bone marrow transplantation with acute GVHD involving the gastrointestinal tract.[109]

In a Turkish study, 201 of 452 bone marrow transplant recipients (44%) experienced one or more episodes of diarrhea from the first day of the conditioning regimen to day 100 following transplantation. In this study, *B hominis* was found to be the only cause of diarrhea in 8 patients, although in 3 patients it was associated with other pathogens.[104]

Blastocystis is detected by standard clinical parasitologic techniques using preparations of fresh stool.[108] However, these methods have a low diagnostic sensitivity

compared with molecular tools, such as PCR assays, and could greatly underestimate the real prevalence of the parasite.[110]

The clinical literature also offers no conclusive evidence as to what constitutes effective treatment for the eradication of *B hominis*. The main drugs that have been used are iodoquinol, metronidazole, and nitazoxanide (see **Table 2**).[108]

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