Article type : Special Issue-Transplant Infectious Diseases

Tissue and Blood Protozoa including Toxoplasmosis, Chagas disease, Leishmaniasis, Babesia, Acanthamoeba, Balamuthia, & Naegleria in Solid Organ Transplant Recipients – Guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation

RM La Hoz,*[a,*] *MI Morris*[b] *on behalf of the Infectious Diseases Community of Practice of the American Society of Transplantation

[a] ***Division of Infectious Diseases and Geographic Medicine, University of Texas Southwestern Medical Center, Dallas, TX***

[b] ***Division of Infectious Diseases, University of Miami Miller School of Medicine, Miami, FL***

**Corresponding author: Ricardo M. La Hoz, Ricardo.LaHoz@UTSouthwestern.edu*

Keywords:

Parasites, transplant, donor-derived, *Toxoplasma gondii*, *Trypanosoma cruzi*, Leishmaniasis, Malaria, Babesia, *Balamuthia*, *Acanthamoeba*, *Naegleria*.

Abbreviations:

BAL, Bronchoalveolar lavage; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; FDA, Food and Drug Administration; PCR, Polymerase chain reaction; SOT, solid organ transplant; TMP/SMX, trimethoprim/sulfamethoxazole; US, United States;

Abstract

These updated guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation review the diagnosis, prevention and management of tissue and blood protozoal infections in the pre- and post-transplant period. Significant new developments in the field have made it necessary to divide the previous single guideline published in 2013 into two sections, with the intestinal parasites separated from this guideline devoted to tissue and blood protozoa. The current update reflects the increased focus on donor screening and risk-based recipient monitoring for parasitic infections. Increased donor testing has led to new recommendations for recipient management of *Toxoplasma gondii* and *Trypanosoma cruzi*. Molecular diagnostics have impacted the field, with access to rapid diagnostic testing for malaria and PCR testing for *Leishmania*. Changes in *Babesia* treatment regimens in the immunocompromised host are outlined. The risk of donor transmission of free living amebae infection is reviewed. Changing immigration patterns and the expansion of transplant medicine in developing countries has contributed to the recognition of parasitic infections as an important threat to transplant outcomes. Medications such as benznidazole and miltefosine are now available to US prescribers as access to treatment of tissue and blood protozoa is increasingly prioritized.

Introduction

Parasitic infections continue to be recognized as a source of morbidity and mortality in solid organ transplant (SOT) recipients. Bacterial, fungal, and viral infections may dominate the scientific literature in this population, though parasites are increasingly being recognized for their potential to impact transplant outcomes (1). Parasitic infection may be transmitted directly through the donor allograft or the transfusion of blood products. The disease may also occur through reactivation of pre-transplant infection or *de novo* infection post-transplant.

Multiple factors are contributing to the increased importance of parasitic infections in transplantation. Changing worldwide immigration patterns now provide persons born in regions

where parasites are endemic access to transplantation. Furthermore, these immigrants may also become organ donors in developed countries. United States (US) transplant centers in states like California, New York, Florida, and Texas with a high percentage of immigrants have developed screening and management protocols targeting this population. Improved access to medical care and training has supported the establishment of transplant programs in developing countries where parasitic infections are more frequent. Patients from developed countries may also choose to undergo transplantation far from home. Such "transplant tourists" may be exposed to unrecognized local donor-derived or directly transmitted parasitic infections. In addition, recipients transplanted at established centers on stable immunosuppression are generally healthy enough to travel internationally. Trends in exotic and adventure travel facilitate direct exposure of such recipients to emerging tropical diseases, with the potential for unusual manifestations of primary infection months to years post-transplant. In recognition of all of these factors, this expanded guideline encompasses a broad range of parasite species with the potential to cause infection in transplant patients. Improvements in molecular diagnostic testing have made diagnosis of previously neglected diseases feasible through reference laboratories. As more rapid diagnostics become available, access to therapy can be challenging outside of endemic regions. This unmet need may change governmental policy, as with the recent US Food and Drug Administration (FDA) approval of benznidazole for treatment of Chagas disease.

Tissue and Blood Protozoa

Toxoplasmosis

Etiology – description of pathogen

Toxoplasmosis is caused by infection with the parasite *Toxoplasma gondii*. This protozoal infection is generally foodborne, zoonotic, or congenital, though human to human transmission through blood transfusion or organ transplant can occur. Infection can be transmitted through the feces of infected

cats via contact with their litter box or soil and ingestion of infectious oocysts, which can be found in undercooked meat or on the surfaces of vegetables grown in contaminated soil (2).

Epidemiology and risk factors

Toxoplasmosis may be the most prevalent human infection, with an estimated 30-50% of the world's population previously exposed (3). Infection is frequently asymptomatic. Seroprevalence varies geographically, with higher prevalence in South America, the Middle East, and parts of Eastern and Central Europe, Southeast Asia, and Africa. (4). Infection is generally more common in rural areas with lower socioeconomic status (5). Studies have also shown an increased infection rate in lower altitude regions and hot, humid climates. In 2018, the US CDC estimated infection rates vary from 11% of the US population to over 95% of the population in some countries (2). Seroprevalence increases with age.

Screening of all organ donors and recipients is recommended as seronegative recipients of *Toxoplasma* IgG positive donors have the highest risk of infection (D+/R-). The most frequent transmission occurs in D+/R- heart recipients, who have a 57-75% risk of early post-transplant toxoplasmosis unless they receive prophylaxis (6, 7). Although the risk of transmission is significantly lower in non-heart transplant recipients (D+/R-), the morbidity and mortality remains unacceptably high (8). *T. gondii* infection is generally lifelong and asymptomatic in immunocompetent patients. Reactivation of previous infection may occur in the face of transplant immunosuppression and is particularly common in R+ heart transplant recipients though often asymptomatic (7). The majority of clinically significant cases of toxoplasmosis are primary infections in recipients who were seronegative before transplant (9).

Clinical Manifestations

Toxoplasmosis in immunocompromised transplant patients may present with fever but can progress to involve multiple organ systems. Primary infection, generally acquired through the organ allograft

in previously unexposed recipients, presents at a median of 87 days post-transplant, though toxoplasmosis symptom onset has been reported between 12 and 7,097 days after an organ transplant (9). Although more commonly seen in heart recipients, it also occurs in non-heart recipients, and mainly affects recipients in whom trimethoprim/sulfamethoxazole (TMP/SMX) was not instituted or discontinued (8). Common symptoms include fever, dyspnea, cough, headache, confusion, focal neurologic signs, and visual changes, with signs such as hypotension, hepatosplenomegaly, and lymphadenopathy present on exam. Syndromes including pneumonitis, myocarditis, chorioretinitis, meningitis, brain abscesses, and disseminated disease can be seen. Pulmonary infection presents with fever and dyspnea with imaging showing bilateral reticulonodular infiltrates. Myocarditis presents with congestive heart failure and may be mistaken clinically for allograft rejection until tachyzoites are noted on cardiac biopsy. Chorioretinitis should be suspected when visual changes develop sometimes associated with photophobia or pain and yellow-white lesions are seen in the retina in a non-vascular distribution. Central nervous system (CNS) disease is often suspected when multiple ring-enhancing lesions are noted on imaging, often localized to the basal ganglia. Cerebrospinal fluid (CSF) may show increased protein and mononuclear pleocytosis. Most reported cases (82%) were due to primary infection and presented in the first six months post-transplant, often with pulmonary or disseminated infection (9).

Diagnostic Strategies

The clinical presentation of toxoplasmosis is quite varied; infection may be asymptomatic or associated with non-specific signs and symptoms. For this reason, diagnosis depends on laboratory testing. A variety of serologic methods can be used to detect *T. gondii* infection, most of which detect the presence of IgM and IgG antibody with varying sensitivity and specificity (10). Serology results in the immunocompromised transplant patient may be difficult to interpret, and PCR testing can help expedite diagnosis in patients with non-specific febrile illnesses, especially those known to be at increased risk due to discordant donor/recipient toxoplasma IgG status and inability to tolerate

TMP/SMX prophylaxis (11). Toxoplasma IgG donor screening is now mandated by UNOS/OPTN policy. Polymerase chain reaction (PCR) is more sensitive for acute infection and can be performed on blood, cerebrospinal fluid, aqueous humor, bronchoalveolar lavage (BAL) and other body fluids as needed (12). Toxoplasma PCR was positive in 89% of patients with post-transplant toxoplasmosis in a recent case series (13). PCR testing has also been recommended prospectively in the management of stem cell transplant recipients at risk for primary or reactivation toxoplasmosis (14, 15). Serial quantitative PCR testing may be useful to document response to treatment, as parasite loads should decline in the face of effective therapy (13).

Once clinical disease is present, microscopic techniques can be used to diagnose acute toxoplasmosis. The presence of tachyzoites in body fluid or tissue confirms the presence of acute infection. Immunoperoxidase staining of tissue specimens may be more sensitive than conventional stains for detecting the presence of infection. The classic histopathologic changes of toxoplasma lymphadenitis and chorioretinitis in immunocompetent patients are not reliably present in immunocompromised transplant patients. Pathologic diagnosis in transplant is aided significantly by an understanding of recipient risk, ideally based on pre-transplant serologic testing and knowledge of the individual's receipt of appropriate post-transplant antimicrobial prophylaxis.

Recommendations

- For the diagnosis of acute toxoplasmosis in SOT recipients we recommend PCR of blood and body fluids and biopsy of involved tissues to identify tachyzoites. (*strong, low*).

Treatment

Treatment recommendations for acute toxoplasmosis in transplant recipients have primarily been based on studies of disseminated and tissue-invasive *T. gondii* infections in acquired immunodeficiency syndrome (AIDS) patients. Induction therapy with pyrimethamine, sulfadiazine, and leucovorin for a minimum of six weeks is followed by chronic suppressive therapy with the same medications at a reduced dose (Table 1). Treatment is lifelong in chronically immunosuppressed

transplant patients, as medication is effective against the proliferative tachyzoite form but not the encysted parasite. De-escalation to treatment dose TMP/SMX alone may be considered with close follow up in some patients once the infection is controlled and the net state of immunosuppression optimized.

Outcomes vary considerably and are significantly improved with early diagnosis and treatment initiation. In noncardiac transplant recipients with donor-derived tissue invasive infection, diagnosis may be delayed especially in cases where donor and recipient serostatus is unknown. Survival in one case series was 65% but increased to 77% when toxoplasmosis was diagnosed and targeted combination therapy initiated early (16). A review of 20 donor-derived cases in renal transplant recipients reported a 50% mortality, with 30% of cases diagnosed at autopsy; none of the autopsy diagnosed cases had received treatment effective against *T. gondii* (17, 18).

Early diagnosis and effective prophylaxis and therapy may not completely eliminate the impact of *T. gondii* infection on transplant outcomes. Some studies suggest that heart transplant outcomes are worse in D+/R- patients despite appropriate management (19), though other centers report no impact of *Toxoplasma* serostatus on mortality (20).

Recommendations

- For the treatment of Toxoplasmosis in SOT recipient we recommend, induction with pyrimethamine, sulfadiazine, and leucovorin for a minimum of six weeks (*strong, low*).
- Following induction therapy, we recommend lifelong suppression (*weak, low*).

Prevention

Toxoplasma D+/R- organ transplant recipients are at increased risk for infection. They should receive targeted prophylaxis early post-transplant, generally the time of maximal immunosuppression when the majority of transmissions occur. A recent European study of toxoplasmosis in solid organ and stem cell recipients noted infection occurred in 17 of the 87 cases described after chemoprophylaxis had been discontinued, and recommended prophylaxis be continued for $\geq$1 year in mismatched

(D+/R-) SOT recipients (21). Standard TMP/SMX pneumocystis prophylaxis regimens (TMP 160 mg/SMX 800 mg orally three times weekly or TMP 80 mg/SMX 400 mg orally daily) is likely to be efficacious in preventing post-transplant infection, based on efficacy studies in patients with advanced AIDS (22) Atovaquone prophylaxis may not be as effective (23, 24). Transplant specific data on the use of twice-weekly dapsone plus pyrimethamine for toxoplasma prophylaxis is lacking, and use has been based on historical data in HIV/AIDS (22, 25). Since heart transplant recipients are at increased risk, some centers recommend that D+/R- heart recipients be treated with six weeks of pyrimethamine in addition to standard TMP/SMX prophylaxis (6, 26), while other centers report no increased risk of infection with TMP/SMX alone (27, 28). A case report describes the occurrence of disseminated toxoplasmosis in a heart transplant recipient despite prophylaxis with TMP/SMX (29).

Transplant recipients should avoid eating raw or poorly cooked meat and avoid contact with cooking surfaces, utensils, or other food that have been in contact with raw meat until they are cleaned thoroughly. Untreated drinking water should also be avoided. Transplant patients should avoid changing cat litter boxes or wear disposable gloves and wash hands thoroughly after contact. Litter boxes should be changed daily as it takes at least 24 hours for the parasite to become infectious after it is shed in cat feces. Contact with stray cats or kittens should be avoided. Gloves should be worn for all soil and sand contact including gardening, with hand washing after removal (2).

Recommendations

- To minimize the risk of donor derived toxoplasmosis we recommend:
    - Screening all donors and recipients with IgG and use this information to identify patients at high risk (D+/R-) and implement prophylactic strategies (*strong*, *high*).
    - Prophylaxis with TMP/SMX is recommended for D+/R- cardiac recipients (*strong, moderate*
    - Prophylaxis with TMP/SMX should be considered for D+/R- non-cardiac recipients (*weak, very low*).

- Prophylaxis with a regimen of dapsone 50 mg daily, plus pyrimethamine 50 mg weekly plus folinic acid 10 mg weekly can be considered in sulfa-allergic patients after checking for glucose 6 phosphate dehydrogenase deficiency *(weak, low).*
- Lifelong prophylaxis is recommended in high-risk (D+/R-) heart recipients. If prophylaxis is discontinued, ongoing clinical monitoring is recommended with expedited Toxoplasma PCR testing and empiric therapy initiation for signs and symptoms of infection (*weak, low*).

Chagas Disease (American Trypanosomiasis)

Etiology – Description of Pathogen

Chagas disease is a systemic infection caused by the protozoan parasite *Trypanosoma cruzi*, which is transmitted to humans most commonly by large reduviid bugs of the subfamily *Triatominae*. These blood-sucking insects defecate after feeding, releasing infectious trypomastigotes in their feces which enter the host through the bite wound, conjunctiva, or adjacent mucosa. *T. cruzi* infection can also occur through vertical transmission, oral ingestion of contaminated food or drink, as well as via blood transfusion or organ transplantation. Acute symptoms are often mild, but infection is lifelong and can result in severe gastrointestinal and cardiac manifestations (30, 31).

Epidemiology

Vector-borne infection primarily occurs in 21 Latin American countries, with 8-10 million infected (32). International immigration has expanded the impact of Chagas disease worldwide, with over 300,000 infected persons estimated to be living in the United States and over 80,000 in Europe (33, 34). Blood bank screening for *T. cruzi* began in the United States in 2007. In the initial 16 months of screening, 57% of confirmed infections identified were found in two states with large Latin American immigrant populations, California and Florida (35). Blood donor population prevalence may not predict organ donor infection risk; 11 (19%) of 58 US organ procurement organizations (OPOs) have

implemented universal or selective donor screening protocols (36). Infection is generally associated with prolonged stays in rural endemic areas with more primitive housing. In addition, screening serology may have reduced sensitivity in multi-transfused organ donors due to hemodilution and donor-derived Chagas transmission has occurred from serologically negative donors (37).

Recipients of an organ from a donor with Chagas disease are at risk for a donor derived infection, though transmission varies considerably by organ type with heart allografts carrying the highest risk. In cases where donor infection is known before the transplant, candidates should receive appropriate informed consent about transmission risk and the need for post-transplant monitoring as well as the potential need for prolonged treatment and follow up if infection occurs. Donor transmission to kidney recipients has been reported in 13% (38), 18% (32), and 19% (39), of cases. Chagas transmission through the liver allograft was noted in 20-29% of recipients (32, 38). Insufficient data exist to accurately predict the risk of transmission to kidney-pancreas, lung, and intestinal transplant recipients. Cardiac transplant recipients are at increased risk due to the parasite's affinity for heart muscle, with transmission reported in 67-75% of recipients (32, 38). *T. cruzi* infected deceased donors are therefore considered unacceptable heart donors though other organs can be transplanted with appropriate recipient informed consent and post-transplant monitoring.

Chagas cardiomyopathy is now the third most common indication for heart transplantation in South America. Close monitoring for reactivation of infection and immediate therapy initiation when it occurs has led to improvement in outcomes and made transplant a viable management option (40-43).

Clinical Manifestations

Infection often occurs in childhood, with an initial acute phase that is often asymptomatic but may cause a mild febrile illness that resolves after a brief parasitemia. Infection is lifelong without treatment, and chronic disease may manifest years later with cardiac or gastrointestinal

involvement. Most patients do not develop signs or symptoms of visceral involvement and are considered to have the indeterminate form of chronic Chagas disease, with positive IgG serology but no clinical disease. Indeterminate Chagas patients may have minimal abnormalities detected on cardiac or gastrointestinal testing, though the prognostic significance of these findings is unclear (44). About 20-30% of indeterminate Chagas patients ultimately progress to clinical cardiac or gastrointestinal disease (31).

Chronic Chagas infection more commonly involves the heart than the digestive system. Chagas cardiomyopathy is a chronic inflammatory disease associated with early conduction system abnormalities. Inflammation and infection involve all cardiac chambers leading to progressive dilated cardiomyopathy, frequent apical aneurysm formation, and progressive arrhythmias.

Primary gastrointestinal Chagas disease can involve the esophagus or colon. Digestive involvement is more common in patients infected in the southern countries of South America, possibly due to exposure to selected *T. cruzi* genotypes. Esophageal disease can range from mild achalasia, reflux, or dysphagia, to severe megaesophagus. Gastrointestinal infection damages neurons in the wall of the gut and when colonic disease occurs can result in constipation, volvulus, ischemia, and megacolon (45).

Chagas disease can present in transplant recipients as reactivated infection after cardiac transplant for Chagas cardiomyopathy, reactivation in non-cardiac transplant recipients in the face of transplant immunosuppression, or *de novo* infection in recipients who receive organs or blood from donors with prior *T. cruzi* infection (46). Post-transplant Chagas disease presents as an acute febrile illness with associated hepatosplenomegaly and myocarditis. Reactivation of chronic *T. cruzi* in previously exposed recipients may cause unexplained fever as well as more unusual manifestations including painful skin nodules, inflammatory panniculitis, and central nervous system infection (39, 47, 48).

Diagnostic Strategies

In the US, three assays are currently FDA-approved for blood and organ donor screening. These include two EIA assays, Abbott Prism Chagas (Abbott Laboratories, Abbott Park, IL, USA) and ORTHO *T. cruzi* ELISA Test System (Ortho-Clinical Diagnostics, Inc. Raritan, NJ, USA), as well as a multi-step enzyme strip assay, Abbott ESA Chagas (Abbott Laboratories, Abbott Park, IL, USA), which is a more specific confirmatory test that can be run on serum or plasma repeatedly reactive on one of the other two qualitative antibody detection tests (49). Additional serologic tests FDA-cleared for diagnostic use but not screening include the Hemagen Chagas Kit (Hemagen Diagnostics, Inc., Columbia, MD, USA) and Chagatest ELISA Recombinante v.4.0 (Weiner Laboratorios, Rosario, Argentina). There are many other assays available in Latin America for pre-transplant screening. Transplant candidates with positive Chagas serology should have a confirmatory test performed using a different Chagas assay based on a different parasite antigen or technique as no single serologic test is reliable for the diagnosis of *T. cruzi* infection (32). Serologic testing is the preferred modality for patients with chronic Chagas disease in whom parasitemia is unlikely and molecular methods perform poorly.

Confirmatory serologic and molecular testing for Chagas disease is available at the US Centers for Disease Control (CDC). A combination of three real-time PCR assays is used to detect *T. cruzi* DNA in EDTA blood (purple top), heart biopsy tissue, and CSF. Testing is reserved for early detection of infection transmission in immunocompromised hosts and can be shipped directly to the CDC (50).

Prospective clinical and laboratory monitoring of transplant recipients at risk for Chagas transmission from an infected donor or reactivation of chronic or indeterminate Chagas post-transplant is recommended. Molecular testing using PCR methodology should be utilized whenever possible as it is a more sensitive assay modality for the identification of early disease (51, 52). Scheduled systematic testing of blood including WBC buffy coat microscopy and PCR should be coordinated with the US CDC. Outside of the US, the most sensitive available parasite screening tests should be employed to identify infection early (53). Tests should be performed weekly for the first two months

post-transplant, every two weeks in the third month, then monthly afterward for at least six months with the total duration of testing to be determined based on the net state of immunosuppression of the transplant recipient. Augmentation of immunosuppression for the treatment of allograft rejection may predispose to Chagas reactivation in patients with evidence of chronic infection, so more frequent screening tests may be needed. Testing should also be performed in transplant recipients at risk for Chagas reactivation or donor-derived infection who develop unexplained fever at any time post-transplant. After six months of post-transplant monitoring, the interval between laboratory tests may be extended in stable patients with persistently negative screening results (32). Importantly, the myocarditis of Chagas reactivation can easily be mistaken for allograft rejection (54) Cardiac transplant may be indicated for patients with Chagas cardiomyopathy but carries a risk of reactivation (45). Close monitoring post-transplant with rapid initiation of treatment can prevent Chagas reactivation. Heart transplant candidates with Chagas cardiomyopathy should be advised of the significant risk for reactivation which would require close monitoring and potentially toxic medical therapy (43).

Testing should always occur in conjunction with arrangements for immediate initiation of anti-trypanosomal therapy should test results become positive (43).

Recommendations

- To diagnose Chagas infection in transplant candidates with epidemiological risk factors we recommend serological testing. Positive results should be confirmed with a second test using a different assay (*strong, high*).
- To diagnose Chagas reactivation in SOT recipients, with known prior infection, we recommend a combination of a parasitological method and well as PCR testing available through the CDC and treatment promptly initiated if reactivation is confirmed (*strong, moderate*).

- Post-transplant prospective monitoring for recipients of *T. cruzi* infected donor organs should include both a parasitological method as well as PCR and treatment promptly initiated if the diagnosis is confirmed (*strong, moderate*).

Treatment

Antiparasitic therapy should be started as soon as possible after the diagnosis of post-transplant acute or reactivation of Chagas disease. Two antiparasitic agents are available, benznidazole and nifurtimox (Table 1). Both medications have significant associated toxicity, preluding the potential benefit that might be attributed to prophylactic treatment of chronic Chagas patients pre- and post-transplant. In addition, prophylaxis of high-risk heart transplant recipients with dilated cardiomyopathy due to *T. cruzi* infection has not consistently prevented reactivation in the heart allograft and is therefore not currently recommended (42). Although post-transplant prophylaxis with anti-trypanosomal agents is used successfully in countries in which active therapeutic agents are readily available, a strategy of close screening and follow-up of at-risk recipients with preemptive treatment is effective and generally favored (53, 55).

Benznidazole treatment is preferred over nifurtimox in transplant patients as it is generally better tolerated and has fewer drug interactions. Benznidazole (Exeltis USA, Inc. Florham Park, NJ) was FDA-approved in 2017 for use in children 2-12 years of age, but is commonly used to treat adults in the US. It is available in 12.5 mg and 100 mg tablets (56). The recommended adult dose is 5-7 mg/kg/day orally in 2 divided doses for 60 days, with no adjustment for renal or hepatic dysfunction. Common side effects include rash and peripheral neuropathy, both seen in up to 30% of patients. Benznidazole can cause severe skin and subcutaneous reactions, generally within the first ten days of treatment initiation. It can also cause paresthesias, headache, dizziness, and other central and peripheral nervous system effects. Cytopenias have also been reported due to bone marrow suppression by benznidazole. Nifurtimox (Lampit, Bayer 2502) is not approved in the US and must be obtained through the CDC. The recommended adult dose is 10 mg/kg/day orally in 3 divided doses

for 90 days, with no adjustment required for renal or hepatic dysfunction. Gastrointestinal side effects and headache are common, and depression and anxiety may also be associated with therapy (57). In the US, consultation regarding the diagnosis and management of Chagas infection is available through the CDC Division of Parasitic Diseases at 404-718-4745 during business hours and 770-488-7100 for the CDC Emergency Operations Center on weekends and holidays. E-mail inquiries can be directed to chagas@cdc.gov (personal communication, Susan Montgomery).

Recommendations

- For the treatment of *T. cruzi* infection in SOT recipients we recommend:
    - Benznidazole 5-7 mg/kg/day orally in two divided doses for 60 days as the treatment of choice. Patients should be closely monitored for significant rash, cytopenia, and neurologic side effects (*strong, moderate*).
    - Nifurtimox 10 mg/kg/day orally in 3 divided doses for 90 days is an alternative for patients who cannot tolerate benznidazole. Nifurtimox is not approved in the US and must be obtained through the CDC (*strong, low*).

Prevention

Pre-transplant serologic screening of transplant candidates with risk factors for Chagas disease is recommended, targeting patients with a history of prolonged residence in an endemic areas as well as those whose mother is from an endemic region (32). The risk of Chagas disease post-transplant can be predicted and preemptive screening regimens implemented if the transplant recipient risk is identified (58). Prophylactic treatment for all *T. cruzi* patients was recommended in 2005 by the Brazilian Health Ministry and successfully implemented to prevent infection in six liver recipients of Chagas positive donors (59).

PCR can accurately diagnose recipients early enough to permit preemptive anti-trypanosomal therapy and prevent excess toxicity from universal treatment (60). PCR testing has been successfully employed even in the highest risk heart transplantation population undergoing transplant for Chagas

cardiomyopathy (61). Strict adherence to a molecular screening protocol may be more essential in developed countries where more potent post-transplant immunosuppressants such as mycophenolate mofetil are used extensively, as this may contribute to a higher Chagas reactivation rate post-heart transplant (62, 63). Modification of post-transplant immunosuppressive therapy may lower the risk of Chagas reactivation in high-risk heart transplant recipients in whom avoidance of anti-thymocyte globulin and mycophenolate mofetil may be advisable (41, 53, 64).

Recommendations

- We recommend that all SOT recipients with epidemiological risk factors for *T. cruzi* infection (personal or maternal history of residence in endemic areas) be screened using a serological assay. (*Strong, high*).
- We recommend that deceased donors with epidemiological risk factors as above for *T. cruzi* infection be screened using a serological assay (*weak, very low*).
- Heart allografts from *T. cruzi* antibody positive donors should not be transplanted. Other organs can be used at centers where screening for infection transmission can be implemented and timely diagnosis and treatment is available (*Strong, high*).

Leishmaniasis

Etiology-description of the pathogen and epidemiology

Leishmaniasis refers to a variety of clinical syndromes caused by a complex of protozoan parasites belonging to the genus *Leishmania* transmitted through the bite of infected female sandflies (65). Leishmaniasis can be classified three ways, geographically into New World and Old-World disease; clinically by syndrome into visceral (VL), cutaneous (CL), or mucocutaneous (MCL) disease and by subgenus, complexes and species based on taxonomy. Three hundred fifty million people are at risk of acquiring leishmaniasis, twelve million suffer from the disease, and two million new cases occur yearly (66). Approximately ninety percent of the cases of VL occur in India, Nepal, Bangladesh, Sudan, and Brazil. Similarly, ninety percent of the cases of CL occur in Iran, Saudi Arabia, Syria,

Afghanistan, Brazil, and Peru. Finally, ninety percent of the cases of MCL occur in Bolivia, Brazil, and Peru (66).

After inoculation by a sandfly control of the infection relies on activated macrophages and a T helper 1 (Th1) response. As a result, immunosuppression is associated with progression to symptomatic disease and affects disease presentation and response to therapy (67). Leishmaniasis in a SOT recipient can be the result of *de novo* infection, reactivation of pre-existing infection, or donor-derived infection. The majority of cases have been described in kidney transplant recipients. The most common syndrome was VL, followed by CL rarely MCL (68).

Risk Factors and Clinical Manifestations

VL also known as Kala-Azar is caused by *Leishmania donovani* and *L. infantum* (synonym *L. chagasi*) (65). The prevalence of VL amongst SOT recipients in endemic areas is 0.05-0.9%. The only risk factor identified in a series from two endemic countries was the treatment for rejection with high dose steroids in the preceding six months. The median time to presentation was 11 months post-transplantation (range 2-150 months) (69). The classic triad of fever, hepatosplenomegaly, and pancytopenia only occurred in a third of the patients. Thus, the absence of typical signs should not exclude the diagnosis. Secondary bacterial and CMV infection are common occurring in 22 and 14% of SOT recipients diagnosed with VL, respectively (69). CL in the Old World is most frequently caused by *L. major*, *L. tropica*, and *L. aethiopica*; in the New World it is caused by *L. braziliensis*, *L. Mexicana*, *L. panamensis*/*L. guyanensis* (65). Few cases of CL in SOT have been published in the literature (68). The spectrum of CL includes cutaneous ulcers (single or multiple) to diffuse cutaneous leishmaniasis. The cutaneous lesions are chronic, painless and occur in exposed areas of the skin. They typically evolve from a papule to nodules to ulcerative lesions with a central depression and raised indurated borders (65). Patients with diffuse cutaneous leishmaniosis are anergic to *Leishmania*. The disease begins as a localized lesion, but instead of ulcerating, it disseminates to other areas of the skin causing diffuse nodular disease. In about 2-5% patients infected with *L. braziliensis* (or rarely other

species), mucosal involvement of the nose, oral cavity, pharynx or larynx can occur years after the skin lesion has healed; this syndrome is known as MCL (65).

Diagnostic Strategies

Visceral leishmaniasis:

Multiple diagnostic tests are recommended to maximize the diagnostic yield. They include the demonstration of amastigotes in smears or tissue, isolating promastigotes in culture, PCR and serology (70). The first three techniques can be performed on splenic aspiration, whole blood buffy coat, and bone marrow aspirate or liver biopsy. Although splenic aspiration is considered the highest yield diagnostic method, bone marrow aspiration is the preferred diagnostic sample as the former is associated with complications. The Wright-Giemsa stain is used to visualize amastigotes in clinical specimens, the sensitivity in a bone marrow aspirate for SOT recipients is 80-98%. This technique can also be applied to a whole blood buffy coat and has a reported sensitivity of 75% (68, 69, 71). A culture of clinical specimens can be inoculated in one of several culture media (Novy-MacNeal-Nicolle, Scheinder's modified media, and others) and incubated for four weeks with the objective of identifying promastigotes. The sensitivity of cultures in SOT recipients is 56-82% and 33% in bone marrow and whole blood buffy coat respectively (68, 69, 71). PCR has also been used in the diagnosis of VL with a reported sensitivity of 75 and 67% in bone marrow aspirate and whole blood buffy coat and respectively (68, 69, 71). The most common serological assays used are ELISA, indirect immunofluorescent assay (IFAT), and direct agglutination tests (DAT). Despite the concern that serological assays lack sensitivity in SOT recipients due to the net state of immunosuppression, these assays have a sensitivity of 76-92% (68, 69, 71).

Cutaneous and mucocutaneous leishmaniasis:

The definitive diagnosis of CL and MCL requires demonstration of amastigotes in tissue (Wright-Giemsa stain), promastigotes in culture or by PCR. To maximize the diagnostic yield performing all

three diagnostic tests is recommended. Specimens should be collected from the base and margins of active ulcerative lesions after removing eschars and exudates and thorough cleaning. Samples can be collected by scraping, aspiration or biopsy (70). Identification to the species level is warranted as treatment is species dependent. This can be performed once promastigotes are identified in culture by isoenzyme electrophoresis, PCR or matrix-assisted laser desorption/ionization (72-74). PCR is the most sensitive diagnostic test and can be performed in tissue and culture (75). Serologic testing is not recommended as they are neither sensitive nor specific (70).

Contacting the CDC for diagnostic assistance with Leishmanial

In the US, CDC offers leishmaniasis testing including serology, culture and PCR. For questions about issues related to diagnosing leishmaniasis, including how to obtain culture medium, contact the CDC Division of Parasitic Diseases and Malaria reference diagnostic laboratory at 404-718-4175 or DPDx@cdc.gov.

Recommendations

I. For the diagnosis of VL in SOT recipients we suggest:

- Collecting tissue aspirates or biopsies specimens for smears, histopathology, culture, and PCR *(strong, moderate).*
- Bone marrow aspirate is the preferred source of a diagnostic sample. Liver biopsy and whole blood buffy coat are other potential sources *(strong, moderate).*
- Using multiple diagnostic tools to maximize the likelihood of a positive *Leishmania* result *(strong, low).*
- Clinicians contact the CDC before specimen collection and submission *(strong, very low).*

II. For the diagnosis of CL in SOT recipients we suggest:

- Obtaining a sample from the base and margins of ulcerative lesions after removal of eschars and exudates and thorough cleaning. Samples can be collected by scraping, aspiration or biopsy *(strong, low)*.
- Submitting specimens for smears, histopathology, culture, and PCR *(strong, low)*.
- Using multiple diagnostic tools to maximize the likelihood of a positive *Leishmania* result. *(strong, low).*
- Identification to the species level as treatment is species dependent. This can be performed once promastigotes are identified by culture by isoenzyme electrophoresis, PCR or matrix-assisted laser desorption/ionization *(strong, low)*.
- Clinicians should contact the CDC before specimen collections and submission *(strong, very low).*

Treatment

Visceral leishmaniasis

Therapeutic options for VL include amphotericin B, pentavalent antimony, miltefosine, and paromomycin (Table 1). The first consideration in the treatment of VL is the feasibility of reduction of immunosuppression (71). Liposomal amphotericin B (L-AmB) was approved by the FDA in 1997 for the treatment of VL and is considered first-line therapy. Although there is wide variation in the dosing schedules, the FDA approved dose for immunosuppressed patients consists of 4 mg per kg daily on days 1–5, 10, 17, 24, 31, and 38 (total dose of 40 mg/kg) (71, 76, 77). Pentavalent antimonial (Sb^V) compounds have traditionally been considered first-line therapy for VL. However, due to adverse effects and the development of resistance in some areas, it is now considered second-line therapy in SOT recipients (68, 70, 71, 76). Two Sb^V compounds have been used to treat VL: sodium stibogluconate and meglumine antimoniate. Although there are no trials comparing the efficacy and safety of this drugs they are considered interchangeable. Only sodium stibogluconate is available in the US through the CDC under an IND protocol approved by the FDA. Miltefosine has been used in

India for the treatment of VL although recent reports describe high failure rates (70). In 2014 the FDA approved miltefosine for treatment of VL caused by *L. donovani*, in adults and adolescents who are not pregnant or breastfeeding. There is insufficient data describing the efficacy and safety of miltefosine in SOT (78).

After completion of therapy SOT recipients with VL should be monitored for a minimum of 1 year and ideally lifelong to monitor for relapse as they occur in 24-35% of the cases (68-70). Although, secondary prophylaxis is recommended in HIV + patients with CD4 counts <200 cells/mm^3 (70, 79-82), this practice is not recommended in SOT recipients without a relapse (70, 76).

Cutaneous and mucocutaneous leishmaniasis:

Multiple factors are considered to determine the optimal approach to therapy of CL in immunocompetent patients. CL lesions can be classified as simple or complex. All CL lesions in SOT recipient are considered complex and thus warrant systemic therapy via the parenteral or oral route (70). Parenteral therapies include Sb^V (historically the drug of choice), amphotericin and pentamidine. Oral agents include miltefosine or azoles (Table 1). Therapy for SOT recipients with CL should be individualized in consultation with an infectious disease expert (70).

Recommendations

I. For the treatment of VL in SOT recipients we recommend:
   - Reduction of immunosuppression if possible *(strong, very low)*.
   - Liposomal amphotericin B 4 mg per kg daily on days 1-5, 10, 17, 24, 31, and 38 (total dose of 40mg/kg) *(strong, low)*.

II. For the treatment of CL in SOT recipients we recommend:
   - Systemic therapy via parenteral or enteral route as all CL lesions in SOT recipients are considered complex *(strong, low)*.
   - The antimicrobial agents used should be individualized considering multiple factors, in consultation with an infectious diseases expert *(strong, low)*.

Prevention

Data are lacking to determine if screening potential organ transplant recipients for VL would be beneficial. However, those known to be seropositive at the time of transplant should be monitored closely for signs and symptoms of reactivation of infection. Given the limited data on potential donor-derived infection, donor screening cannot be recommended.

SOT recipients visiting areas endemic for leishmaniasis should minimize outdoor activities, especially from dusk to dawn when the sand flies are the most active. Standard protective measures include long sleeves and trousers, applying insect repellent (N,N-Diethyl-meta-toluamide or diethyltoluamide [DEET]), and using pyrethroid-impregnated bed nets.

Recommendations

- We recommend SOT recipients visiting endemic areas minimize outdoor activities, especially from dusk to dawn *(weak, very low)*.
- Standard protective measures include long sleeves and trousers, applying insect repellent (DEET) and using pyrethroid-impregnated bed nets are warranted in endemic areas *(strong, low)*.

Malaria

Etiology-description of pathogen, epidemiology and risk factors

Malaria is the most important parasitic disease in humans and endemic throughout most of the tropics. It is estimated that the disease is found in 108 countries, home to roughly three billion people. In 2010 malaria caused 655,000 deaths (83). While malaria is a rare event in SOT recipients in Latin America, due to the low transplant volume in areas of endemicity, programs in Asia and Africa reported a higher incidence (84, 85). Malaria is caused by five species of the genus Plasmodium (*P. falciparum*, *P. vivax*, *P. ovale, P. malariae*, and *P. knowlesi*) and mainly transmitted by *Anopheles* mosquitos. Other routes of acquisition include blood transfusions, vertical transmission and a via organ transplantation.

The life cycle of the malaria parasite involves two hosts, the *Anopheles* mosquito and human. When the female mosquito bites, sporozoites are injected, infecting the liver after gaining access to the bloodstream. Merozoites are released from the liver and infect the red blood cells; this event correlates with the onset of symptoms. Some *P. vixax* and *P. ovale* intrahepatic forms remain dormant (hypnozoites) and their reactivation may account for relapses.

The disease does not produce protective immunity, but some degree of resistance to clinically severe hyperinfection is achieved through successive exposure. This incomplete acquired immunity is unable to eradicate the infection entirely but explains the lack of detectable parasitemia and the higher incidence of asymptomatic disease in adults from endemic regions (86). This poses a problem at the time of blood or organ donation when the epidemiological background is not thoroughly investigated.

Clinical Manifestations

In SOT recipients malaria infection can be the consequence of *de novo* acquisition, reactivation of hypnozoites (*P. vivax* and *P. ovale*), the recrudescence of persistent asymptomatic infection (in endemic areas), or a donor-derived infection. The median time to presentation of probable cases of a donor-derived infection is 29 days (range 8-157) and the crude mortality 15.6% (5/32) (84). In many of these published cases differentiating between a derived donor event, blood acquisition and recrudescence was not possible. Uncomplicated malaria presents as a nonspecific acute febrile illness. Although fever is the most commonly reported symptom, the absence of a paroxysmal or cyclic pattern should not exclude the diagnosis. The incubation period is 7-30 days for *de novo* acquisition but can be delayed, by weeks to months, with antimalarial prophylaxis. A small case-control study involving renal transplant recipients and patients without chronic kidney disease from Sudan, failed to identify a difference in the incidence of malaria in these two populations (85). Manifestations of severe malaria include altered consciousness (with or without seizures), acute

respiratory distress syndrome, shock, metabolic acidosis, renal failure, disseminated intravascular coagulation, severe anemia (hemoglobin < 7g/dL) and high-grade parasitemia.

Diagnostic strategies

Tools utilized for the diagnosis of malaria include microscopy (visualization of parasites in stained blood smears), rapid diagnostic tests (RDT) and PCR. Detection of parasites by light microscopy on Giemsa stained peripheral smears is the gold standard for diagnosis. These should be prepared as soon as possible after blood collection to avoid degradation of the parasite morphology. Three sets of thick and thin smears every 12 to 24 hours are recommended. Microscopy is labor intensive, requires training and expertise, and lacks sensitivity to detect low-level parasitemia. In endemic areas, RDT that detect malaria antigens (HRP2, pLDH, and aldolase) are increasingly utilized due to ease of use. Limitations include lack of sensitivity for low-level parasitemia and inter-assay variability in diagnostic performance. In contrast to microscopy these assays are semi-quantitative and thus not useful to assess response to therapy (87). PCRs for malaria detection have been developed, targeting the 18S ribosomal RNA sequence; these can be genus or species specific. Nested PCR technology is the most sensitive and available via the CDC (88, 89).

Recommendations

- To diagnose malaria in transplant recipients, we recommend three sets of thick and thin smears every 12 to 24 hours (*strong, high*).
- When microscopic evaluation by trained personnel is not available, we recommend rapid diagnostic tests (*strong*, *moderate*).

Treatment

Factors determining the choice of antimicrobials for malaria treatment consist of severity, *Plasmodium* species, geographic resistant patterns, exposure to chemoprophylaxis cost, and drug availability (83). This guideline is based on US recommendations for the treatment of malaria (Table

1). *P. vivax* (exceptions are Papua New Guinea and Indonesia), *P. malariae*, *P. ovale* and uncomplicated *P. falciparum* infection acquired in chloroquine-susceptible regions should be treated with chloroquine. After checking for G6PD deficiency, primaquine should be used to prevent relapse of *P. vivax* and *P. ovale*. For uncomplicated chloroquine-resistant *P. falciparum* atovaquone-proguanil is the treatment of choice. Severe cases of *P. falciparum* infection require admission to an intensive care unit and should be treated with intravenous artesunate (available as an investigational new drug in the U.S. via the CDC Malaria Hotline: (770) 488-7788 or (855) 856-4713 toll-free Monday–Friday 9 am to 5 pm EST – (770) 488-7100 after hours, weekends and holidays). Intravenous artesunate can be de-escalated to atovaquone-proguanil once the patient can tolerate oral medications. Treatment response should be monitored using clinical parameters, as well as serial microscopy.

Recommendations

- For the treatment of malaria in SOT recipients, we recommend an individualized approach considering severity, *Plasmodium* species, geographic resistant patterns, exposure to chemoprophylaxis and drug availability, in consultation with an infectious diseases expert (*strong, moderate*).

Prevention

The first step to prevent a malaria donor-derived event is to take an epidemiological history from candidates and deceased and living donors. Birthplace, a history of long-term residency in a malaria-endemic area, travel history with the use of malaria prophylaxis as well as a history of malaria are essential to stratify the risk. Long-term residents from endemic areas may have asymptomatic low-level parasitemia. Without exposure, infection with *P. falciparum* resolves in two years, *P. vivax* and *P. ovale* in three, while *P. malariae* can persist indefinitely (86). We recommend against using donors with a history of *P. malariae* infection (84). Screening of transplant candidates and donors

exposed to malaria in the past 2-3 years should be considered. The optimal approach for non-endemic areas is unclear and should be based on transplant urgency, available diagnostic tests, and risk of asymptomatic low-level parasitemia. PCR is most sensitive to detect low-level parasitemia, and with limited availability including the US CDC, and the turnaround time precludes its use in deceased donors. Liver donors with risk factors or history of *P. vivax* and *P. ovale* infection are particularly challenging as current diagnostic tools will not detect the presence of hepatic hypnozoites.

Recipients traveling to malaria endemic areas should seek travel advice. Prevention usually involves a multi-intervention approach that involves chemoprophylaxis and personal protective measures. Standard protective measures include long sleeves and trousers, applying insect repellent (N,N-Diethyl-meta-toluamide or diethyltoluamide [DEET]), and using pyrethroid-impregnated bed nets.

Recommendations

- To prevent reactivation, the recrudescence of low-level parasitemia and malaria donor-derived events we recommend screening all transplant donors and candidates with a comprehensive epidemiological history (*weak*, *very low*).
- To prevent *de novo* infection in travelers to endemic areas, we recommend a multi-intervention approach that involves chemoprophylaxis and personal protective measures (*strong*, *moderate*).

Babesia

Etiology - description of pathogen

Babesia species are protozoan parasites transmitted through tick vectors, though congenital infection and transmission through blood transfusion and organ transplantation also occur.

Epidemiology and Risk Factors

In the US, *Babesia microti* is endemic in the Northeast and upper Midwest; *B. duncani* has caused sporadic infections in the Pacific coastal states. *Babesia divergens* is the most common cause of human babesiosis in Europe, though infections with this species have been seen in the US. *B. venatorum* is found in northeastern China, though infections with both *B. microti* and *B. divergens* have been reported from China. Asymptomatic infection is common. Babesiosis cases have been identified in other countries in Asia, as well as in South America, Africa, and Australia. The *Ixodes* tick vectors and animal reservoirs vary by species and region. The presentation of babesiosis in nonendemic areas or outside the usual season should raise concerns for transfusion or organ donor-transmitted infection in patients at risk (90).

Healthy people infected with *Babesia* may clear the parasite without treatment, but the resolution of infection depends on both the innate and adaptive immune systems. *Babesia* infection is more severe in persons with immune deficits, asplenic patients, and those infected with selected species like *B. divergens (91)*. Transplant recipients with babesiosis are likely to have a severe and even fatal course despite adequate therapy (92, 93). Transplant candidates may have early or unrecognized infection after tick exposure that presents clinically after receipt of immunosuppressive therapy post-transplant (94).

Clinical Manifestations

Symptoms of *Babesia* infection typically present between one and four weeks after an infected tick bite. Patients develop malaise and fatigue followed by the onset of fevers, chills and night sweats as well as headache, myalgias, arthralgias, and anorexia. Localizing signs of pharyngitis, hepatosplenomegaly, and jaundice may occur. Most patients develop hemolytic anemia, frequently associated with thrombocytopenia. Symptoms improve in one to two weeks, though chronic fatigue lasting months can occur. Immunocompetent patients may be asymptomatic or develop only mild symptoms. Older patients, those with prior splenectomy, patients with cancer or HIV infection and

recipients of immunosuppressive medications are at risk for more severe disease. Severe babesiosis may be complicated by pulmonary edema, adult respiratory distress syndrome or disseminated intravascular coagulation. It can mimic the clinical presentation of severe sepsis, albeit with negative cultures (95). Splenic rupture, heart failure, renal failure, and coma may occur. Persistent or relapsing infection despite adequate therapy is also more commonly seen in immunocompromised patients with babesiosis (96). Mortality approaches 21% in immunosuppressed patients and ranges from 6-9% in immunocompetent patients who require hospitalization (91).

B. microti is the most common infection transmitted through blood transfusion in the US (97). Symptoms generally develop within one to nine weeks of transfusion but have been seen up to 6 months later. Transfusion-associated babesiosis is associated with a 19% mortality rate (98). Many cases of babesiosis seen after SOT are transfusion-related transmissions, as the trauma patient who receives blood containing *Babesia* before becoming a potential donor may have active parasitemia at the time of organ procurement (99). *B. microti* lack an exoerythrocytic tissue phase, making direct transmission via an infected organ far less likely than infection through blood products transfused to the donor or candidate pre-transplant or the recipient in the peri-transplant period (100-102).

Diagnostic Strategies

The clinical suspicion for babesiosis should be based on symptoms in a patient with hemolytic anemia and recent exposure in an endemic area or transfusion within the preceding six months. Many infected patients do not recall tick exposure. Initial testing includes thin blood smears stained with Giemsa or Wright stain looking for intraerythrocytic parasites. *B. microti* and *B. duncani* trophozoites appear as ring forms; merozoites of these species may group to form a pathognomonic Maltese cross formation within red blood cells. *Babesia* ring forms can resemble *Plasmodium falciparum* on smear. However, the exposure history and clinical presentation of babesiosis should be easily distinguishable from malaria. Low-level parasitemia is common early in infection. Therefore significant time must be allocated for the review of multiple thin smears (91). PCR testing is more

sensitive but generally only available in reference laboratories, sometimes delaying diagnosis. Available serologic tests include indirect immunofluorescence, ELISA, and Western blot. Serial IgM and IgG testing may be helpful to confirm the diagnosis. Serology is less sensitive in immunocompromised patients and may be negative early in infection. Antibody response may be species-specific, which can be less helpful in non-endemic areas where transfusion transmission from an unknown donor is suspected (103).

There are currently no licensed tests for *Babesia* screening of blood donors (97). Both false positive and false negative results have been documented with serology and PCR methodologies. Even targeted screening of blood donors from highly endemic areas may not be cost effective nor is it currently sensitive enough to detect low-level parasitemia capable of transmitting infection (97).

Recommendations

- In SOT recipients with a compatible clinical presentation and exposure to *Babesia*, we recommend:
    - Multiple Wright-Giemsa stained thin blood smears to identify intraerythrocytic ring forms (*Strong, high*).
    - PCR testing is more sensitive than blood smears but still may not detect infections with very low-level parasitemia (*Strong, moderate*).

Treatment

Babesiosis treatment requires combination therapy with one of 2 regimens, either atovaquone plus azithromycin or clindamycin plus quinine (Table 1). The atovaquone plus azithromycin regimen is associated with fewer adverse effects and has similar efficacy in mild to moderate disease (104). Immunocompetent patients should receive an initial course of 7-10 days, but longer courses are recommended in immunocompromised patients including transplant recipients. Adult dosing is atovaquone 750 mg every 12 hours orally plus azithromycin 500-1000 mg day one followed by 250 mg daily orally daily. Immunocompromised patients should continue azithromycin 600-1000 mg daily for the duration of therapy. Adults treated with clindamycin and quinine should receive

clindamycin 600 mg every 8 hours orally plus quinine 650 mg every 6-8 hours orally. For patients with severe babesiosis, a regimen of clindamycin intravenously at a dose of 300-600 mg every 6 hours and quinine orally has been recommended by guidelines. However, a recent study reported good responses to atovaquone plus azithromycin therapy in this population (105, 106). Exchange transfusion is indicated for patients with parasitemia of 10% or more, severe hemolysis, or significant associated kidney, liver, or respiratory dysfunction (105).

In highly immunocompromised patients with *B. microti* infection, antimicrobial resistance may develop during treatment (107). Based on case reports describing both successful and failed regimens, immunocompromised patients should receive a minimum of two weeks of therapy with the regimen selected, with treatment duration extended for at least two weeks after clearance of parasitemia on thin blood smears or achievement of negative *Babesia* PCR (94, 96, 102). Treatment courses of up to six weeks may be required to ensure clearance of infection.

Recommendations

- For the treatment of *Babesia* in SOT recipients we recommend atovaquone and azithromycin as first line therapy (*strong, moderate*). Clindamycin and quinine is an alternative (strong, moderate).
- We suggest monitoring of SOT recipients during therapy for *Babesia* to ensure clearance of the infection. Treatment should be extended for two weeks after resolution of parasitemia (*strong, moderate*).

Prevention

Transplant candidates and recipients should avoid tick exposure whenever possible. Residents of endemic areas with unavoidable exposure should wear long pants and long-sleeved shirts and use permethrin repellant on clothing and DEET-containing repellants on the skin when outdoors. After returning indoors, immediate bathing and a skin check for the presence of ticks is recommended.

Transplant recipients residing in high-risk areas may consider environmental insecticide treatment around their homes as well as interventions to limit intrusion by local animal reservoirs such as deer and mice.

Recommendations

- To prevent *Babesia* infection, we recommend:
    - Transplant candidates and recipients avoid tick exposure whenever possible (*weak, very low*).
    - Residents of highly endemic areas use tick repellants on skin and clothing and be vigilant for tick exposure especially between late spring and fall (*weak, very low*).

Free Living Ameba Infections (Acanthamoeba, Balamuthia, & Naegleria)

Acanthamoeba

Etiology - description of pathogen

Acanthamoeba are free-living environmental parasites that can cause localized human infections of the eye, skin, and CNS, with the potential for fatal disseminated infection, especially in immunocompromised hosts. Several species of *Acanthamoeba* can cause disease, though the high prevalence of antibodies (40-82%) on screening suggests asymptomatic exposures are common in healthy individuals (108). The parasite life cycle includes a vegetative trophozoite and a cyst form.

Epidemiology and Risk Factors

Infection occurs through contact with soil and water, including sand and potting soil as well as freshwater lakes and rivers. Infections associated with medical water sources involving humidifiers, heating systems, and dialysis units have occurred. Numerous outbreaks of *Acanthamoeba* keratitis have been reported in healthy contact lens users. Organisms can enter the body through the eyes or

be inoculated directly through a break in the skin. Airborne cysts may infect the nasal mucosa or lungs.

Clinical Manifestations

Immunocompromised patients are at increased risk for CNS infection resulting in granulomatous amebic encephalitis. Patients generally have low-grade fever and weeks to months of headache. Subtle neurologic changes including alterations in vision or behavior or focal deficits may occur. These may be associated with nodular or ulcerating granulomatous skin lesions, which if present can help lead to the diagnosis (109, 110). The encephalitis usually progresses slowly to generalized seizures, coma, and death, though cases of acute fulminant infection have been reported (111, 112). Transplant recipients may present with localized skin lesions without CNS involvement or disseminated disease (113). *Acanthamoeba* can also cause sinusitis, pneumonitis, and cerebral abscesses in transplant patients (114, 115).

Diagnostic Strategies

Patients with signs or symptoms of encephalitis may have lymphocytic pleocytosis in the CSF with high protein and low or normal glucose. Trophozoites are sometimes seen on Giemsa stain of CSF or BAL fluid. Organisms can also be cultured on agar plates coated with enteric bacteria. Cysts can be found in skin or brain biopsy tissue with hematoxylin and eosin stain. Immunofluorescent stains or PCR of tissue biopsies can also be diagnostic, with access to molecular tests like PCR obtained through the CDC in the US and limited to specialty or research laboratories. Radiologic imaging of patients with granulomatous amebic encephalitis typically shows multiple ring-enhancing brain lesions often involving the temporal and parietal lobes.

Recommendations

- In SOT recipients with a clinical presentation compatible with *Acanthamoeba* infection we recommend:
    - A lumbar puncture with CSF analysis and microscopy with Wright-Giemsa stain (*strong, low*).
    - Biopsies of affected organs (brain and skin) to identify *Acanthamoeba* cysts *(strong, high*).
    - PCR of CSF and affected organs can also aid in the diagnosis (*strong, low*).

Treatment

Initial treatment of infections in the immunocompromised transplant recipient should include the reduction in immunosuppression if feasible, as well as surgical resection of localized abscesses when present. Combination therapy is preferred, though there are no studies comparing the efficacy of various agents. Most recommendations are based on case reports with successful outcomes. Regimens that include miltefosine, fluconazole and pentamidine plus additional agents have been recommended (116). Other medications with potential for efficacy in treating *Acanthamoeba* include pyrimethamine, sulfadiazine, amphotericin B and voriconazole. Some reports suggest that trimethoprim/sulfamethoxazole prophylaxis decreases the risk of infection and that azole prophylaxis does not (111, 117).

Recommendations

- For the treatment of *Acanthamoeba* infection in SOT recipients we recommend combination therapy though the preferred regimen is still not well defined. Consultation with CDC experts is advised (*weak, low*).

Prevention

Unlike other free-living amebae, there have been no reported transmissions of *Acanthamoeba* infection through SOT, Transplant recipients should exercise caution when engaging in occupations or recreational activities that expose them to untreated freshwater.

Recommendations

- The risk of donor-derived infection in patients with CNS infection due to *Acanthamoeba* is unknown at this time. Most published cases have been in immunocompromised patients at increased risk for disseminated *Acanthamoeba*. It is essential to distinguish skin or CNS disease due to *Acanthamoeba* from *Balamuthia* infection, which is a contraindication to organ donation. Transplant programs considering the use of organs from confirmed *Acanthamoeba* donors should seek expert consultation and obtain informed consent from the recipient (weak, very low).
- To prevent *Acanthamoeba* infection we suggest that SOT recipients avoid direct skin or mucosal contact with untreated or inadequately treated water or soil. (*weak, very low*).

Balamuthia

Etiology - description of pathogen

Balamuthia mandrillaris is the only species known to infect humans. Like *Acanthamoeba*, the parasite has a vegetative trophozoite stage and a dormant cyst form and can cause granulomatous amebic encephalitis.

Epidemiology and Risk Factors

Infections are most commonly reported in the southern United States and South America. Most cases occur in males under age 16, often associated with occupational or recreational exposure to soil (118). Hispanic ethnicity appears to be a risk factor for infection with this organism (119). A

recent history of organ transplant is a risk factor for infection, and unlike *Acanthamoeba*, *Balamuthia* infections have been transmitted through organ donation (120-122).

Clinical Manifestations

Balamuthia enters the body through the skin or airways and then disseminates from the site of entry hematogenously. Infection may present with a localized skin lesion, often a painless nonulcerated plaque following trauma involving the central face or extremities, followed by the gradual onset of neurologic symptoms over weeks to months or years (123). There are rare cases with cutaneous involvement only. Patients may also present initially with neurologic symptoms with no antecedent rash. The neurologic manifestations generally include a subacute presentation with initial fever and fatigue followed by headache, nausea, and vomiting. *Balamuthia*, like *Acanthamoeba*, is a cause of granulomatous amebic meningoencephalitis (GAE). Meningeal signs may develop after the first few weeks of mild symptoms and ultimately progresses to coma and death. The reported mortality rate of *Balamuthia* encephalitis is 90-95% (124).

Diagnostic Strategies

In patients with cutaneous involvement, biopsy of the skin lesions demonstrates trophozoites in two-thirds of cases when stained with hematoxylin and eosin (125). Immunofluorescent staining may be more sensitive but is not readily available. Both trophozoite and cyst forms are present on brain biopsy, with significant vascular and perivascular involvement and evidence of thrombotic angiitis. CSF shows an aseptic meningitis pattern with mononuclear pleocytosis, low glucose, and elevated protein; *Balamuthia* parasites are rarely seen in CSF. PCR testing ,available thru the CDC, of CSF and brain tissue can be diagnostic. Serology testing using indirect immunofluorescence and ELISA is available, though healthy persons may test positive (126). The seroprevalence of *B. mandrillaris* antibodies limits the utility of serology in screening potential organ donors, though high antibody titers may correlate with infection and might be useful in exposed recipients (124, 127).

Neuroimaging of GAE cases often reveals multiple ring-enhancing lesions in the temporal, frontal, occipital, and parietal lobes (128).

Recommendations

- In SOT recipients with a presentation compatible with *Balamuthia* infection we recommend:
    - Skin biopsies, as it often demonstrates trophozoites (*strong, low*).
    - Brain biopsy for those with CNS involvement, to assess for the presence of trophozoite and cyst forms (*strong, moderate*).
    - PCR of CSF or brain tissue (*strong, moderate*).

Treatment

The high mortality rate of neurologic involvement with *Balamuthia* reflects the lack of an identified and reliable curative treatment. Early diagnosis and initiation of combination antimicrobial therapy with a regimen including albendazole, pentamidine, flucytosine, amphotericin, miltefosine, an azole, a macrolide, and a sulfonamide is recommended. Miltefosine containing regimens may be superior (116, 129).

Recommendations

- For the treatment of *Balamuthia* infection in SOT recipients we recommend early initiation of combination therapy with albendazole, pentamidine, flucytosine, amphotericin, miltefosine, an azole, a macrolide, and a sulfonamide (*weak, very low*).

Prevention

Balamuthia mandrillaris infection is more commonly associated with soil exposure, and thus it is unclear if avoidance of freshwater sources will be protective. Precautions to avoid direct skin contact with warm soil including potting soil, as well as warm freshwater, may decrease risk.

Organs from deceased donors with documented *Balamuthia* infection should not be accepted for transplantation. Deceased organ donors with undefined neurologic illnesses must be carefully

evaluated for evidence of infectious encephalitis. The US Organ Procurement and Transplantation Network have developed a guidance document that outlines the recommended approach to potential organ donors to aid in the identification of CNS infections (130). If a donor-derived infection is suspected in a transplant recipient, prompt reporting is required, and all recipients of organs from the same donor should be promptly identified, evaluated, and treated (122).

Recommendations

- To prevent acquisition of *Balamuthia* infection we recommend SOT recipients avoid high-risk soil and warm freshwater exposure, especially during defined outbreaks (*weak, very low*).
- To prevent a *Balamuthia* donor-derived event, we recommend:
    - Carefully screening deceased organ donors for evidence of CNS infection (*strong, moderate*).
    - Organs from donors with known or suspected *Balamuthia* infection should not be transplanted (*strong, low*).
    - All recipients of deceased donors with possible *Balamuthia* infection should be urgently evaluated and offered empiric treatment (*Strong, low*).

Naegleria

Etiology - description of pathogen

Naegleria fowleri, the only human pathogen of this species, is found worldwide in warm freshwater lakes and rivers, as well as humanmade water sources including underchlorinated pools, hot springs, and spas as well as infected tap water. This thermophilic protozoan can live in warm water and soil up to 45°C. The life cycle includes trophozoites, flagellates, and cysts; the disease is caused by the reproducing trophozoites.

Epidemiology and Risk Factors

The majority of infections occur in the summer, with male children disproportionately affected. Most US infections occur in southern states and are often associated with recreational water sports or contact with mud. Many reported cases have a history of recent exposure to warm freshwater lakes or rivers where amebae are ubiquitous (131). Outbreaks have also occurred after nasal sinus irrigation with infected tap water. It is unclear why so few human infections have occurred given the frequency of exposure to this common environmental parasite.

Unlike *Balamuthia* infection, which is an absolute contraindication to donation, the risk of transmission of *Naegleria* infection from infected organ donors is not well defined. Scientific data suggest that spread outside the CNS is possible. However, organs from deceased donors who died from *Naegleria* infection have been successfully transplanted (132, 133). At least five donors provided organs to 21 recipients with no serologic or clinical evidence of infection (134). Expert consultation including a careful assessment of donor risk and potential recipient benefit is recommended when considering the use of such organs.

Clinical Manifestations

Primary amebic meningoencephalitis develops after the nasal mucosa is infected by water containing *Naegleria fowleri*. Amebae migrate through the nasal mucosa and the cribriform plate and along the olfactory nerve to the brain where they cause a fulminant and usually fatal meningoencephalitis. Primary amebic meningoencephalitis due to *Naegleria* is an acute hemorrhagic infection that clinically resembles bacterial meningitis. Infection typically occurs in healthy immunocompetent individuals who present with fever, headache, photophobia, and early alterations of smell and taste possibly related to the nasal route of entry. Nausea and vomiting, as well as seizures, occur with progressive alteration in mental status. Early physical exam reveals light sensitivity, meningismus, and focal cranial nerve palsies with later obtundation and coma. The case fatality rate approaches 99%.

Diagnostic Strategies

Like acute bacterial meningitis, primary amebic meningoencephalitis is associated with peripheral leukocytosis. Initial CNS imaging demonstrates leptomeningeal enhancement typical of meningoencephalitis, with later findings of cerebral edema, herniation, and necrosis as the disease progresses. Hemorrhagic CSF with neutrophilic leukocytosis, high protein, and low glucose develops, though more normal findings can be present early. CSF is diagnostic, with motile trophozoites visible by microscopy of a centrifuged wet mount specimen. CSF wet mounts should be performed in purulent CSF specimens with negative bacterial gram stain. *Naegleria* will grow in culture on bacteria coated non-nutrient agar plates. Multiplex PCR testing of CSF that can simultaneously detect *Acanthamoeba*, *Balamuthia*, and *Naegleria* is available (135).

Recommendations

- For the diagnosis of *Naegleria* infection in SOT recipients we suggest:
    - Considering the diagnosis in patients presenting with purulent hemorrhagic CSF with hypoglycorrhachia typical of bacterial meningitis but with negative gram stain or those with leptomeningeal enhancement and progressive edema (*weak, very low*)
    - A CSF wet mount should be prepared, In those with a compatible clinical presentation (*strong, low*).
    - A CSF multiplex PCR for *Acanthamoeba*, *Balamuthia* and *Naegleria,* in In those with a compatible clinical presentation, (*strong, very low*).

Treatment

Naegleria infection responds poorly to treatment, but case reports from survivors indicate that high dose amphotericin B deoxycholate (1.5 mg/kg/day) combined with medications such as intrathecal amphotericin, rifampin, fluconazole, miltefosine, azithromycin, sulfisoxazole, miconazole

intravenous and intrathecal, voriconazole, and ceftriaxone may be efficacious. High dose steroids are used to control cerebral edema.

Recommendations

- For the treatment of *Naegleria* infection we recommend aggressive combination therapy given the poor outcomes. High dose amphotericin B deoxycholate is the backbone of therapy with multiple other antimicrobials frequently prescribed along with dexamethasone for cerebral edema (*weak, very low*).

Prevention

Transplant recipients should consider avoiding all warm freshwater and soil exposure in the summer months. Traumatic nasal exposure such as jumping, dunking, or diving during water activities is likely particularly high risk. All recipients should avoid nasal irrigation with tap water. Use boiled or filtered water for nasal irrigation and clean all irrigation devices with boiled, filtered, or sterilized water (136).

Organs from transplant donors with *Naegleria* infection can be considered for use with expert evaluation of the individual recipient risks and benefits and appropriate informed consent.

Recommendations

- To prevent *Naegleria* infection in SOT recipients we suggest:
    - Avoiding direct nasal mucosal exposure to warm freshwater or soil, especially during summer months in areas where free-living ameba are known to be present (*weak, very low*).
    - Avoiding using tap water for nasal or sinus irrigation (strong, low).
- Transplant programs considering the use of organs from donors with *Naegleria* infection should seek expert consultation and obtain informed consent from the recipient (weak, very low).

Research and Future Areas of Investigation

The tissue and blood protozoa reviewed are all important human pathogens with the potential to cause devastating infection in immunocompromised transplant patients. The risk of severe disease in Toxoplasma IgG D+/R- recipients and heart transplant candidates with Chagas cardiomyopathy may be mitigated with prophylaxis, however research is needed to understand the optimal agent and duration in transplant patients. Greater access to rapid molecular diagnostics should improve early recognition of tissue and blood protozoal infections. Protocols for targeted donor screening in high risk regions could prevent transmission of infections with Leishmania, Plasmodium, and Babesia species. Greater availability of multiplex PCR to diagnose free living ameba infections could mitigate the risk of donor transmission Studies to identify the optimal treatment regimen for immunocompromised populations will benefit from the improved availability of accurate diagnostics and provide information to enhance post-transplant management. This may require the development of new therapies for pathogens like the free-living ameba, as current treatment outcomes are poor even in immunocompetent patients. Identification of specific exposure risks will provide the basis for risk avoidance strategies that can be targeted to pre- and post-transplant patients. Increased reporting from transplant centers in endemic areas may provide guidance for the optimal management and prevention of some geographically restricted parasitic infections.

Acknowledgments

This manuscript was modified from the Guideline included in the 3rd Edition of the AST Infectious Diseases Guidelines written by Brain S. Schwartz and Steven D. Mawhorter published in the American Journal of Transplantation 2013;13 (Suppl 4): 280-303, and endorsed by the American Society of Transplantation.

Disclosures

RML has no conflicts of interest to disclose. MIM has received research support from Chimerix and Merck and is an advisory board member for Astellas Pharma, Chimerix and ViraCor-IBT.

Table 1. Therapy for Common Parasitic Infections in SOT recipients (Adapted from Schwartz BS, Mawhorter SD. Parasitic infections in solid organ transplantation. Am J Transplant. 2013 Mar;13 Suppl 4:280-303. Table 1)(46)

Organism	Preferred therapy	Alternative therapy
Blood and tissue protozoa		
Babesia	Atovaquone 750mg (pediatric: 20 mg/kg – maximum 750 mg dose) PO BID plus azithromycin 600-1000 mg (pediatric 12 mg/kg) PO daily (if able to take oral medications) for ≥2 weeks beyond clearance of parasitemia. Increased or IV dosing and longer treatment duration recommended for severe infections.	Clindamycin 600mg (pediatric: 20-40 mg/kg/day divided) PO q 8h or plus quinine 650mg (pediatric: 30 mg/kg/day divided) PO q 6-8h to ≥2 weeks beyond clearance of parasitemia. Increased or IV dosing and longer treatment duration recommended for severe infections.
Leishmania		
Visceral disease	Liposomal amphotericin B given 4 mg/kg IV on days 1-5, 10, 17, 24, 31 and 38 (total dose 40mg/kg).	Pentavalent antimony compound (20 mg Sb^V kg/day) for 28 days8 OR Amphotericin B deoxycholate 1.0 mg/kg IV daily for 15 to 20 days
Cutaneous or mucocutaneous disease	Antimicrobials should be individualized considering multiple factors, in consultation with an infectious diseases expert.	
Malaria	Antimicrobials should be individualized considering severity, *Plasmodium* species, geographic resistant patterns, exposure to chemoprophylaxis and drug availability, in	

	consultation with an infectious diseases expert	
Toxoplasma gondii	*Induction therapy*: Pyrimethamine 200 mg PO x1 then 50 mg (< 60 kg) to 75mg (≥ 60 kg) (pediatric 2 mg/kg/day) PO daily plus sulfadiazine 1.0 (< 60kg) to 1.5 gm (≥ 60 kg) (pediatric 100-200 mg/kg/day divided) PO q6h plus leucovorin 10-25 mg PO daily for at least 6 weeks followed by chronic suppressive therapy. *Chronic suppressive therapy:* Pyrimethamine 25 mg (< 60 kg) to 50mg (≥ 60 kg) PO daily plus sulfadiazine 2.0 gm (< 60 kg) to 4.0 gm (≥ 60 kg) PO daily (in 2-4 divided doses) plus leucovorin 10-25 mg PO daily.	*Induction therapy*: Pyrimethamine (same dosing as preferred therapy) plus clindamycin 600 mg IV/PO q6-8h OR TMP-SMX (10 mg/kg TMP-50 mg/kg SMX) IV/PO divided BID OR Atovaquone 1500 mg PO BID plus either pyrimethamine and leucovorin (same dosing as preferred therapy) or sulfadiazine (same dosing as preferred therapy) OR azithromycin 900-1200 mg PO daily plus pyrimethamine and leucovorin (same dosing as preferred therapy) for at least 6 weeks followed by chronic suppressive therapy. *Chronic suppressive therapy:* Pyrimethamine (same dosing as preferred therapy) plus clindamycin 600 mg PO q8h OR TMP-SMX 1 DS tab q12h OR atovaquone 750 mg PO q6-12h +/- either pyrimethamine and leucovorin (same dosing as preferred therapy) or sulfadiazine (same dosing as preferred therapy) OR azithromycin 900-1200 mg PO daily plus pyrimethamine and leucovorin (same dosing as preferred therapy)
Trypanosoma cruzi	Benznidazole 5-7 mg/kg/day PO (pediatric < 12 years 10 mg/kg) BID for 60 days	Nifurtimox 8-10 mg/kg/day PO divided TID for 90 days (pediatric: 1-10 years: 15-20 mg/kg /day divided qid; 11-16 years: 12.5-15 mg /kg/day divided qid)

Note: there are no prospective trials for any regimen in transplantation. Very few drug interactions with standard transplant-related medications have been reported, but data in this population are limited.

References

1. Silvia F, Simona F, Fabrizio B. Solid Organ Transplant and Parasitic Diseases: A Review of the Clinical Cases in the Last Two Decades. Pathogens. 2018;7(3):E65.
2. Centers for Disease C. Parasites - Toxoplasmosis 2018 [Available from: https://www.cdc.gov/parasites/toxoplasmosis/gen_info/faqs.html.
3. Flegr J, Prandota J, Sovickova M, Israili ZH. Toxoplasmosis--a global threat. Correlation of latent toxoplasmosis with specific disease burden in a set of 88 countries. PLoS One. 2014;9(3):e90203.
4. Gourishankar S, Doucette K, Fenton J, Purych D, Kowalewska-Grochowska K, Preiksaitis J. The use of donor and recipient screening for toxoplasma in the era of universal trimethoprim sulfamethoxazole prophylaxis. Transplantation. 2008;85(7):980-5.
5. Pappas G, Roussos N, Falagas ME. Toxoplasmosis snapshots: global status of Toxoplasma gondii seroprevalence and implications for pregnancy and congenital toxoplasmosis. Int J Parasitol. 2009;39(12):1385-94.
6. Wreghitt TG, Hakim M, Gray JJ, Balfour AH, Stovin PG, Stewart S, et al. Toxoplasmosis in heart and heart and lung transplant recipients. J Clin Pathol. 1989;42(2):194-9.
7. Luft BJ, Naot Y, Araujo FG, Stinson EB, Remington JS. Primary and reactivated toxoplasma infection in patients with cardiac transplants. Clinical spectrum and problems in diagnosis in a defined population. Ann Intern Med. 1983;99(1):27-31.
8. Dhakal R, Gajurel K, Montoya JG. Toxoplasmosis in the non-orthotopic heart transplant recipient population, how common is it? Any indication for prophylaxis? Curr Opin Organ Transplant. 2018;23(4):407-16.
9. Fernandez-Sabe N, Cervera C, Farinas MC, Bodro M, Munoz P, Gurgui M, et al. Risk factors, clinical features, and outcomes of toxoplasmosis in solid-organ transplant recipients: a matched case-control study. Clin Infect Dis. 2012;54(3):355-61.
10. Liu Q, Wang ZD, Huang SY, Zhu XQ. Diagnosis of toxoplasmosis and typing of Toxoplasma gondii. Parasit Vectors. 2015;8:292.
11. Assi MA, Rosenblatt JE, Marshall WF. Donor-transmitted toxoplasmosis in liver transplant recipients: a case report and literature review. Transplant Infectious Disease. 2007;9(2):132-6.
12. Montoya JG. Laboratory diagnosis of Toxoplasma gondii infection and toxoplasmosis. J Infect Dis. 2002;185 Suppl 1:S73-82.
13. Robert-Gangneux F, Sterkers Y, Yera H, Accoceberry I, Menotti J, Cassaing S, et al. Molecular diagnosis of toxoplasmosis in immunocompromised patients: a 3-year multicenter retrospective study. J Clin Microbiol. 2015;53(5):1677-84.
14. Martino R, Bretagne S, Einsele H, Maertens J, Ullmann AJ, Parody R, et al. Early detection of Toxoplasma infection by molecular monitoring of Toxoplasma gondii in peripheral blood samples after allogeneic stem cell transplantation. Clin Infect Dis. 2005;40(1):67-78.
15. Gajurel K, Dhakal R, Montoya JG. Toxoplasma prophylaxis in haematopoietic cell transplant recipients: a review of the literature and recommendations. Curr Opin Infect Dis. 2015;28(4):283-92.
16. Campbell AL, Goldberg CL, Magid MS, Gondolesi G, Rumbo C, Herold BC. First case of toxoplasmosis following small bowel transplantation and systematic review of tissue-invasive toxoplasmosis following noncardiac solid organ transplantation. Transplantation. 2006;81(3):408-17.
17. Martina MN, Cervera C, Esforzado N, Linares L, Torregrosa V, Sanclemente G, et al. Toxoplasma gondii primary infection in renal transplant recipients. Two case reports and literature review. Transpl Int. 2011;24(1):e6-12.
18. Wolfe C, Wilk A, Tlusty S, Sifri C, Morris M, Mehta A, et al. Donor-Derived Toxoplasmosis in Solid Organ Transplant 2008-2015: Opportunities for Improvement. Am J Transplant. 2016;16(Suppl 3).

19. Chehrazi-Raffle A, Luu M, Yu Z, Liou F, Kittleson M, Hamilton M, et al. Toxoplasma gondii Serology and Outcomes After Heart Transplantation: Contention in the Literature. Transplant Proc. 2015;47(6):1949-53.
20. van Hellemond JJ, van Domburg RT, Caliskan K, Birim O, Balk AH. Toxoplasma gondii serostatus is not associated with impaired long-term survival after heart transplantation. Transplantation. 2013;96(12):1052-8.
21. Robert-Gangneux F, Meroni V, Dupont D, Botterel F, Garcia JMA, Brenier-Pinchart MP, et al. Toxoplasmosis in Transplant Recipients, Europe, 2010-2014. Emerg Infect Dis. 2018;24(8):1497-504.
22. Podzamczer D, Salazar A, Jimenez J, Consiglio E, Santin M, Casanova A, et al. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of Pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. Ann Intern Med. 1995;122(10):755-61.
23. Gajurel K, Gomez CA, Dhakal R, Vogel H, Montoya JG. Failure of primary atovaquone prophylaxis for prevention of toxoplasmosis in hematopoietic cell transplant recipients. Transpl Infect Dis. 2016;18(3):446-52.
24. Mendorf A, Klyuchnikov E, Langebrake C, Rohde H, Ayuk F, Regier M, et al. Atovaquone for Prophylaxis of Toxoplasmosis after Allogeneic Hematopoietic Stem Cell Transplantation. Acta Haematol. 2015;134(3):146-54.
25. Girard PM, Landman R, Gaudebout C, Olivares R, Saimot AG, Jelazko P, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against Pneumocystis carinii pneumonia and toxoplasmosis in HIV infection. The PRIO Study Group. N Engl J Med. 1993;328(21):1514-20.
26. Montoya JG, Giraldo LF, Efron B, Stinson EB, Gamberg P, Hunt S, et al. Infectious complications among 620 consecutive heart transplant patients at Stanford University Medical Center. Clin Infect Dis. 2001;33(5):629-40.
27. Baran DA, Alwarshetty MM, Alvi S, Arroyo LH, Lubitz S, Pinney S, et al. Is toxoplasmosis prophylaxis necessary in cardiac transplantation? Long-term follow-up at two transplant centers. J Heart Lung Transplant. 2006;25(11):1380-2.
28. Munoz P, Arencibia J, Rodriguez C, Rivera M, Palomo J, Yanez J, et al. Trimethoprim-sulfamethoxazole as toxoplasmosis prophylaxis for heart transplant recipients. Clin Infect Dis. 2003;36(7):932-3; author reply 3.
29. Davila V, Roncancio-Villamil G, Correa LA, Restrepo C, Madrid CA, Gonzalez JM. Disseminated toxoplasmosis in a heart transplant patient despite co-trimoxazole prophylaxis: A case report. Biomedica. 2017;37(3):303-7.
30. Bern C, Montgomery SP, Herwaldt BL, Rassi A, Jr., Marin-Neto JA, Dantas RO, et al. Evaluation and treatment of chagas disease in the United States: a systematic review. JAMA. 2007;298(18):2171-81.
31. Rassi A, Jr., Rassi A, Marin-Neto JA. Chagas disease. Lancet. 2010;375(9723):1388-402.
32. Chin-Hong PV, Schwartz BS, Bern C, Montgomery SP, Kontak S, Kubak B, et al. Screening and treatment of chagas disease in organ transplant recipients in the United States: recommendations from the chagas in transplant working group. Am J Transplant. 2011;11(4):672-80.
33. Bern C, Montgomery SP. An estimate of the burden of Chagas disease in the United States. Clin Infect Dis. 2009;49(5):e52-4.
34. Organization WH. Control and prevention of Chagas disease in Europe. WHO Informal Consultation; December 17-18; Geneva, Switzerland2009.
35. Bern C, Montgomery SP, Katz L, Caglioti S, Stramer SL. Chagas disease and the US blood supply. Curr Opin Infect Dis. 2008;21(5):476-82.
36. Schwartz BS, Paster M, Ison MG, Chin-Hong PV. Organ donor screening practices for Trypanosoma cruzi infection among US Organ Procurement Organizations. Am J Transplant. 2011;11(4):848-51.

37. Kun H, Moore A, Mascola L, Steurer F, Lawrence G, Kubak B, et al. Transmission of Trypanosoma cruzi by heart transplantation. Clin Infect Dis. 2009;48(11):1534-40.
38. Huprikar S, Bosserman E, Patel G, Moore A, Pinney S, Anyanwu A, et al. Donor-Derived Trypanosoma cruzi Infection in Solid Organ Recipients in the United States, 2001-2011. American Journal of Transplantation. 2013;13(9):2418-25.
39. Riarte A, Luna C, Sabatiello R, Sinagra A, Schiavelli R, De Rissio A, et al. Chagas' disease in patients with kidney transplants: 7 years of experience 1989-1996. Clin Infect Dis. 1999;29(3):561-7.
40. Benatti RD, Oliveira GH, Bacal F. Heart Transplantation for Chagas Cardiomyopathy. J Heart Lung Transpl. 2017;36(6):597-603.
41. Bacal F, Silva CP, Pires PV, Mangini S, Fiorelli AI, Stolf NG, et al. Transplantation for Chagas' disease: an overview of immunosuppression and reactivation in the last two decades. Clin Transplant. 2010;24(2):E29-34.
42. Bocchi EA, Bellotti G, Mocelin AO, Uip D, Bacal F, Higuchi ML, et al. Heart transplantation for chronic Chagas' heart disease. Ann Thorac Surg. 1996;61(6):1727-33.
43. Gray AEB, La Hoz RM, Green JS, Vikram HR, Benedict T, Rivera H, et al. Reactivation of Chagas disease among heart transplant recipients in the United States, 2012-2016. Transpl Infect Dis. 2018:e12996.
44. Perez-Molina JA, Perez AM, Norman FF, Monge-Maillo B, Lopez-Velez R. Old and new challenges in Chagas disease. Lancet Infectious Diseases. 2015;15(11):1347-56.
45. Bern C, Kjos S, Yabsley MJ, Montgomery SP. Trypanosoma cruzi and Chagas' Disease in the United States. Clinical Microbiology Reviews. 2011;24(4):655-81.
46. Schwartz BS, Mawhorter SD, Practice ASTIDCo. Parasitic infections in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:280-303.
47. Riganti J, Maqueda MG, Pinero MC, Volonteri VI, Galimberti RL. Reactivation of Chagas' disease: cutaneous manifestations in two immunosuppressed patients. Int J Dermatol. 2012;51(7):829-34.
48. Marchiori PE, Alexandre PL, Britto N, Patzina RA, Fiorelli AA, Lucato LT, et al. Late reactivation of Chagas' disease presenting in a recipient as an expansive mass lesion in the brain after heart transplantation of chagasic myocardiopathy. J Heart Lung Transplant. 2007;26(11):1091-6.
49. FDA. Complete List of Donor Screening Assays for Infectious Agents and HIV Diagnostic Assays [Available from: https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm080466.htm#anti_Tcruzi_Assays.
50. Centers for Disease C. DPDx - Laboratory Identification of Parasites of Public Health Concern 2018 [Blood Specimens]. Available from: https://www.cdc.gov/dpdx/diagnosticProcedures/blood/index.html.
51. da Costa PA, Segatto M, Durso DF, Moreira WJD, Junqueira LL, de Castilho FM, et al. Early polymerase chain reaction detection of Chagas disease reactivation in heart transplant patients. J Heart Lung Transpl. 2017;36(7):797-805.
52. Diez M, Favaloro L, Bertolotti A, Burgos JM, Vigliano C, Lastra MP, et al. Usefulness of PCR strategies for early diagnosis of Chagas' disease reactivation and treatment follow-up in heart transplantation. Am J Transplant. 2007;7(6):1633-40.
53. Pinazo MJ, Miranda B, Rodriguez-Villar C, Altclas J, Brunet Serra M, Garcia-Otero EC, et al. Recommendations for management of Chagas disease in organ and hematopoietic tissue transplantation programs in nonendemic areas. Transplant Rev (Orlando). 2011;25(3):91-101.
54. de Souza MM, Franco M, Almeida DR, Diniz RV, Mortara RA, da Silva S, et al. Comparative histopathology of endomyocardial biopsies in chagasic and non-chagasic heart transplant recipients. J Heart Lung Transplant. 2001;20(5):534-43.
55. Bern C. Chagas disease in the immunosuppressed host. Curr Opin Infect Dis. 2012;25(4):450-7.

56. Exeltis USA I. Benznidazole Package Insert 2017 [Available from: http://www.benznidazoletablets.com/assets/pdf/Prescribing_Information.pdf.
57. Pierrotti LC, Carvalho NB, Amorin JP, Pascual J, Kotton CN, Lopez-Velez R. Chagas Disease Recommendations for Solid-Organ Transplant Recipients and Donors. Transplantation. 2018;102(2S Suppl 2):S1-S7.
58. Chagas' Disease Argentine Collaborative Transplant C, Casadei D. Chagas' disease and solid organ transplantation. Transplant Proc. 2010;42(9):3354-9.
59. D'Albuquerque LA, Gonzalez AM, Filho HL, Copstein JL, Larrea FI, Mansero JM, et al. Liver transplantation from deceased donors serologically positive for Chagas disease. Am J Transplant. 2007;7(3):680-4.
60. Cura CI, Lattes R, Nagel C, Gimenez MJ, Blanes M, Calabuig E, et al. Early Molecular Diagnosis of Acute Chagas Disease After Transplantation With Organs From Trypanosoma cruzi-Infected Donors. American Journal of Transplantation. 2013;13(12):3253-61.
61. Kransdorf EP, Czer LSC, Luthringer DJ, Patel JK, Montgomery SP, Velleca A, et al. Heart Transplantation for Chagas Cardiomyopathy in the United States. American Journal of Transplantation. 2013;13(12):3262-8.
62. Campos SV, Strabelli TM, Amato Neto V, Silva CP, Bacal F, Bocchi EA, et al. Risk factors for Chagas' disease reactivation after heart transplantation. J Heart Lung Transplant. 2008;27(6):597-602.
63. Bacal F, Silva CP, Bocchi EA, Pires PV, Moreira LF, Issa VS, et al. Mychophenolate mofetil increased chagas disease reactivation in heart transplanted patients: comparison between two different protocols. Am J Transplant. 2005;5(8):2017-21.
64. Benatti RD, Al-Kindi SG, Bacal F, Oliveira GH. Heart transplant outcomes in patients with Chagas cardiomyopathy in the United States. Clin Transplant. 2018;32(6):e13279.
65. Herwaldt BL. Leishmaniasis. Lancet. 1999;354(9185):1191-9.
66. World Health O. Control of the leishmaniases. World Health Organ Tech Rep Ser. 2010(949):xii-xiii, 1-186, back cover.
67. van Griensven J, Carrillo E, Lopez-Velez R, Lynen L, Moreno J. Leishmaniasis in immunosuppressed individuals. Clin Microbiol Infect. 2014;20(4):286-99.
68. Antinori S, Cascio A, Parravicini C, Bianchi R, Corbellino M. Leishmaniasis among organ transplant recipients. Lancet Infect Dis. 2008;8(3):191-9.
69. Clemente W, Vidal E, Girao E, Ramos AS, Govedic F, Merino E, et al. Risk factors, clinical features and outcomes of visceral leishmaniasis in solid-organ transplant recipients: a retrospective multicenter case-control study. Clin Microbiol Infect. 2015;21(1):89-95.
70. Aronson N, Herwaldt BL, Libman M, Pearson R, Lopez-Velez R, Weina P, et al. Diagnosis and Treatment of Leishmaniasis: Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). Am J Trop Med Hyg. 2017;96(1):24-45.
71. Clemente WT, Mourao PHO, Lopez-Medrano F, Schwartz BS, Garcia-Donoso C, Torre-Cisneros J. Visceral and Cutaneous Leishmaniasis Recommendations for Solid Organ Transplant Recipients and Donors. Transplantation. 2018;102(2S Suppl 2):S8-S15.
72. de Almeida ME, Steurer FJ, Koru O, Herwaldt BL, Pieniazek NJ, da Silva AJ. Identification of Leishmania spp. by molecular amplification and DNA sequencing analysis of a fragment of rRNA internal transcribed spacer 2. J Clin Microbiol. 2011;49(9):3143-9.
73. Kreutzer RD, Christensen HA. Characterization of Leishmania spp. by isozyme electrophoresis. Am J Trop Med Hyg. 1980;29(2):199-208.
74. Mouri O, Morizot G, Van der Auwera G, Ravel C, Passet M, Chartrel N, et al. Easy identification of leishmania species by mass spectrometry. PLoS Negl Trop Dis. 2014;8(6):e2841.
75. Boggild AK, Ramos AP, Espinosa D, Valencia BM, Veland N, Miranda-Verastegui C, et al. Clinical and demographic stratification of test performance: a pooled analysis of five laboratory diagnostic methods for American cutaneous leishmaniasis. Am J Trop Med Hyg. 2010;83(2):345-50.

76. Clemente WT, Mourao PHO, Aguado JM. Current approaches to visceral leishmaniasis treatment in solid organ transplant recipients. Expert Rev Anti Infect Ther. 2018;16(5):391-7.
77. Meyerhoff A. U.S. Food and Drug Administration approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. Clin Infect Dis. 1999;28(1):42-8; discussion 9-51.
78. Perez-Jacoiste Asin MA, Carrasco-Anton N, Fernandez-Ruiz M, San Juan R, Alonso-Moralejo R, Gonzalez E, et al. Experience with miltefosine for persistent or relapsing visceral leishmaniasis in solid organ transplant recipients: A case series from Spain. Transpl Infect Dis. 2017;19(1).
79. Diro E, Ritmeijer K, Boelaert M, Alves F, Mohammed R, Abongomera C, et al. Use of Pentamidine As Secondary Prophylaxis to Prevent Visceral Leishmaniasis Relapse in HIV Infected Patients, the First Twelve Months of a Prospective Cohort Study. PLoS Negl Trop Dis. 2015;9(10):e0004087.
80. Lopez-Velez R, Videla S, Marquez M, Boix V, Jimenez-Mejias ME, Gorgolas M, et al. Amphotericin B lipid complex versus no treatment in the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. J Antimicrob Chemother. 2004;53(3):540-3.
81. Pintado V, Martin-Rabadan P, Rivera ML, Moreno S, Bouza E. Visceral leishmaniasis in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients. A comparative study. Medicine (Baltimore). 2001;80(1):54-73.
82. Ribera E, Ocana I, de Otero J, Cortes E, Gasser I, Pahissa A. Prophylaxis of visceral leishmaniasis in human immunodeficiency virus-infected patients. Am J Med. 1996;100(5):496-501.
83. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. Lancet. 2014;383(9918):723-35.
84. Pierrotti LC, Levi ME, Di Santi SM, Segurado AC, Petersen E. Malaria Disease Recommendations for Solid Organ Transplant Recipients and Donors. Transplantation. 2018;102(2S Suppl 2):S16-S26.
85. Elsharif ME, Malik EM, Imam ME, Omran MO, Elsharif EG. Malaria incidence among kidney-transplanted recipients in an endemic malaria area, Sudan. Saudi J Kidney Dis Transpl. 2012;23(5):1099-103.
86. Bousema T, Okell L, Felger I, Drakeley C. Asymptomatic malaria infections: detectability, transmissibility and public health relevance. Nat Rev Microbiol. 2014;12(12):833-40.
87. Mouatcho JC, Goldring JP. Malaria rapid diagnostic tests: challenges and prospects. J Med Microbiol. 2013;62(Pt 10):1491-505.
88. Rougemont M, Van Saanen M, Sahli R, Hinrikson HP, Bille J, Jaton K. Detection of four Plasmodium species in blood from humans by 18S rRNA gene subunit-based and species-specific real-time PCR assays. J Clin Microbiol. 2004;42(12):5636-43.
89. Snounou G, Viriyakosol S, Jarra W, Thaithong S, Brown KN. Identification of the four human malaria parasite species in field samples by the polymerase chain reaction and detection of a high prevalence of mixed infections. Mol Biochem Parasitol. 1993;58(2):283-92.
90. LeBel DP, 2nd, Moritz ED, O'Brien JJ, Lazarchick J, Tormos LM, Duong A, et al. Cases of transfusion-transmitted babesiosis occurring in nonendemic areas: a diagnostic dilemma. Transfusion. 2017;57(10):2348-54.
91. Vannier E, Krause PJ. Human babesiosis. N Engl J Med. 2012;366(25):2397-407.
92. Lubin AS, Snydman DR, Miller KB. Persistent babesiosis in a stem cell transplant recipient. Leuk Res. 2011;35(6):e77-8.
93. Berman KH, Blue DE, Smith DS, Kwo PY, Liangpunsakul S. Fatal case of babesiosis in postliver transplant patient. Transplantation. 2009;87(3):452-3.
94. Mascarenhas TR, Silibovsky RS, Singh P, Belden KA. Tick-borne illness after transplantation: Case and review. Transpl Infect Dis. 2018;20(2):e12830.
95. Ather I, Pourafshar N, Schain D, Gupte A, Casey MJ. Babesiosis: An unusual cause of sepsis after kidney transplantation and review of the literature. Transpl Infect Dis. 2017;19(5).

96. Krause PJ, Gewurz BE, Hill D, Marty FM, Vannier E, Foppa IM, et al. Persistent and relapsing babesiosis in immunocompromised patients. Clin Infect Dis. 2008;46(3):370-6.
97. Levin AE, Krause PJ. Transfusion-transmitted babesiosis: is it time to screen the blood supply? Curr Opin Hematol. 2016;23(6):573-80.
98. Herwaldt BL, Linden JV, Bosserman E, Young C, Olkowska D, Wilson M. Transfusion-associated babesiosis in the United States: a description of cases. Ann Intern Med. 2011;155(8):509-19.
99. Brennan MB, Herwaldt BL, Kazmierczak JJ, Weiss JW, Klein CL, Leith CP, et al. Transmission of Babesia microti Parasites by Solid Organ Transplantation. Emerg Infect Dis. 2016;22(11).
100. Kitt E, Keaton AA, Graf EH. The Brief Case: Probable Transfusion-Transmitted Babesiosis in a Transplant Recipient. J Clin Microbiol. 2016;54(11):2632-4.
101. Meissner EG, McGillicuddy JW, Squires J, Skipper D, Self S, Wray D, et al. Across state lines: Fulminant Babesia microti infection in a liver transplant recipient. Transpl Infect Dis. 2017;19(5).
102. Lux JZ, Weiss D, Linden JV, Kessler D, Herwaldt BL, Wong SJ, et al. Transfusion-associated babesiosis after heart transplant. Emerg Infect Dis. 2003;9(1):116-9.
103. Vannier EG, Diuk-Wasser MA, Ben Mamoun C, Krause PJ. Babesiosis. Infect Dis Clin North Am. 2015;29(2):357-70.
104. Krause PJ, Lepore T, Sikand VK, Gadbaw J, Jr., Burke G, Telford SR, 3rd, et al. Atovaquone and azithromycin for the treatment of babesiosis. N Engl J Med. 2000;343(20):1454-8.
105. Wormser GP, Dattwyler RJ, Shapiro ED, Halperin JJ, Steere AC, Klempner MS, et al. The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2006;43(9):1089-134.
106. Kletsova EA, Spitzer ED, Fries BC, Marcos LA. Babesiosis in Long Island: review of 62 cases focusing on treatment with azithromycin and atovaquone. Ann Clin Microbiol Antimicrob. 2017;16(1):26.
107. Wormser GP, Prasad A, Neuhaus E, Joshi S, Nowakowski J, Nelson J, et al. Emergence of resistance to azithromycin-atovaquone in immunocompromised patients with Babesia microti infection. Clin Infect Dis. 2010;50(3):381-6.
108. Chappell CL, Wright JA, Coletta M, Newsome AL. Standardized method of measuring acanthamoeba antibodies in sera from healthy human subjects. Clin Diagn Lab Immunol. 2001;8(4):724-30.
109. Young AL, Leboeuf NR, Tsiouris SJ, Husain S, Grossman ME. Fatal disseminated Acanthamoeba infection in a liver transplant recipient immunocompromised by combination therapies for graft-versus-host disease. Transpl Infect Dis. 2010;12(6):529-37.
110. Akpek G, Uslu A, Huebner T, Taner A, Rapoport AP, Gojo I, et al. Granulomatous amebic encephalitis: an under-recognized cause of infectious mortality after hematopoietic stem cell transplantation. Transpl Infect Dis. 2011;13(4):366-73.
111. Satlin MJ, Graham JK, Visvesvara GS, Mena H, Marks KM, Saal SD, et al. Fulminant and fatal encephalitis caused by Acanthamoeba in a kidney transplant recipient: case report and literature review. Transpl Infect Dis. 2013;15(6):619-26.
112. Epperla N, Olteanu H, Hamadani M. Think outside the box: Acanthamoeba encephalitis following autologous haematopoietic stem cell transplantation. Br J Haematol. 2016;175(5):758.
113. Walia R, Montoya JG, Visvesvera GS, Booton GC, Doyle RL. A case of successful treatment of cutaneous Acanthamoeba infection in a lung transplant recipient. Transpl Infect Dis. 2007;9(1):51-4.
114. Vernon SE, Acar BC, Pham SM, Fertel D. Acanthamoeba infection in lung transplantation: report of a case and review of the literature. Transpl Infect Dis. 2005;7(3-4):154-7.
115. Fung KT, Dhillon AP, McLaughlin JE, Lucas SB, Davidson B, Rolles K, et al. Cure of Acanthamoeba cerebral abscess in a liver transplant patient. Liver Transpl. 2008;14(3):308-12.

116. Aichelburg AC, Walochnik J, Assadian O, Prosch H, Steuer A, Perneczky G, et al. Successful treatment of disseminated Acanthamoeba sp. infection with miltefosine. Emerg Infect Dis. 2008;14(11):1743-6.
117. Juan A, Alonso L, Olive T, Navarro A, Sulleiro E, Sanchez de Toledo J, et al. Successful Treatment of Sinusitis by Acanthamoeba in a Pediatric Patient After Allogeneic Stem Cell Transplantation. Pediatr Infect Dis J. 2016;35(12):1350-1.
118. Centers for Disease C, Prevention. Balamuthia amebic encephalitis--California, 1999-2007. MMWR Morb Mortal Wkly Rep. 2008;57(28):768-71.
119. Schuster FL, Yagi S, Gavali S, Michelson D, Raghavan R, Blomquist I, et al. Under the radar: balamuthia amebic encephalitis. Clin Infect Dis. 2009;48(7):879-87.
120. Centers for Disease C, Prevention. Balamuthia mandrillaris transmitted through organ transplantation --- Mississippi, 2009. MMWR Morb Mortal Wkly Rep. 2010;59(36):1165-70.
121. Centers for Disease C, Prevention. Notes from the field: transplant-transmitted Balamuthia mandrillaris --- Arizona, 2010. MMWR Morb Mortal Wkly Rep. 2010;59(36):1182.
122. Farnon EC, Kokko KE, Budge PJ, Mbaeyi C, Lutterloh EC, Qvarnstrom Y, et al. Transmission of Balamuthia mandrillaris by Organ Transplantation. Clin Infect Dis. 2016;63(7):878-88.
123. Bravo FG, Alvarez PJ, Gotuzzo E. Balamuthia mandrillaris infection of the skin and central nervous system: an emerging disease of concern to many specialties in medicine. Curr Opin Infect Dis. 2011;24(2):112-7.
124. Siddiqui R, Khan NA. Balamuthia amoebic encephalitis: an emerging disease with fatal consequences. Microb Pathog. 2008;44(2):89-97.
125. Siddiqui AA, Berk SL. Diagnosis of Strongyloides stercoralis infection. Clin Infect Dis. 2001;33(7):1040-7.
126. Jackson BR, Kucerova Z, Roy SL, Aguirre G, Weiss J, Sriram R, et al. Serologic survey for exposure following fatal Balamuthia mandrillaris infection. Parasitol Res. 2014;113(4):1305-11.
127. Gupte AA, Hocevar SN, Lea AS, Kulkarni RD, Schain DC, Casey MJ, et al. Transmission of Balamuthia mandrillaris through solid organ transplantation: utility of organ recipient serology to guide clinical management. Am J Transplant. 2014;14(6):1417-24.
128. Ong TYY, Khan NA, Siddiqui R. Brain-Eating Amoebae: Predilection Sites in the Brain and Disease Outcome. J Clin Microbiol. 2017;55(7):1989-97.
129. Schuster FL, Guglielmo BJ, Visvesvara GS. In-vitro activity of miltefosine and voriconazole on clinical isolates of free-living amebas: Balamuthia mandrillaris, Acanthamoeba spp., and Naegleria fowleri. J Eukaryot Microbiol. 2006;53(2):121-6.
130. OPTN/HRSA. Guidance for recognizing central nervous system infections in potential deceased donors 2012 [updated February 1, 2014. Available from: https://optn.transplant.hrsa.gov/resources/guidance/guidance-for-recognizing-central-nervous-system-infections-in-potential-deceased-organ-donors/.
131. Centers for Disease C, Prevention. Primary amebic meningoencephalitis--Arizona, Florida, and Texas, 2007. MMWR Morb Mortal Wkly Rep. 2008;57(21):573-7.
132. Kramer MH, Lerner CJ, Visvesvara GS. Kidney and liver transplants from a donor infected with Naegleria fowleri. J Clin Microbiol. 1997;35(4):1032-3.
133. Carroll JF, Benante JP, Kramer M, Lohmeyer KH, Lawrence K. Formulations of deet, picaridin, and IR3535 applied to skin repel nymphs of the lone star tick (Acari: Ixodidae) for 12 hours. J Med Entomol. 2010;47(4):699-704.
134. Roy SL, Metzger R, Chen JG, Laham FR, Martin M, Kipper SW, et al. Risk for transmission of Naegleria fowleri from solid organ transplantation. Am J Transplant. 2014;14(1):163-71.
135. Qvarnstrom Y, Visvesvara GS, Sriram R, da Silva AJ. Multiplex real-time PCR assay for simultaneous detection of Acanthamoeba spp., Balamuthia mandrillaris, and Naegleria fowleri. J Clin Microbiol. 2006;44(10):3589-95.
136. Diaz JH, Boudreaux JP. Emerging trends in free-living amebic infections of the brain: implications for organ transplantation. J La State Med Soc. 2013;165(6):314-8.