Special Article

Parasitic Infections in Solid Organ Transplantation

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Introduction

As organ transplantation is carried out more regularly around the world and immigration and travel to and from developing countries becomes more common, infections with parasitic diseases are more frequently identified in recipients of organ transplantation. This increase in identification of parasitic infection and recognition of new infections being transmitted through organ transplantation presents the transplant community with new issues regarding donor and recipient screening, as well as, management of infections posttransplantation. Although recent years show an increase in the number of published papers on parasitic infections in transplant recipients it still remains the most understudied of all infections related to organ transplantation with very few prospective trials and no randomized studies that can be accounted for in this field. Recommendations are based primarily on expert opinion (III) unless otherwise stated.

Since publication of the last update of these guidelines in 2009, Balamuthia has been identified as a protozoa transmitted through organ transplantation. Guidelines from several groups have provided recommendations on the management of *Trypanosoma cruzi* infection in the transplant setting. Some helpful new insights on the risks of strongyloides infection and updates on treatment have been published. Slowly, some new treatment options for parasitic diseases are being developed (most are not currently FDA approved) and newer diagnostic assays for parasitic infections are being developed.

Common features of parasitic infection in the transplant recipient

Parasitic diseases may affect transplant recipients as a result of either recrudescence of latent infections in the previously infected recipient or "*de novo*" infection by means of natural infection or transmission by transplanted organ into a naïve recipient. The incidence of parasitic infection is expected to grow in solid organ transplant (SOT) recipients due to multiple factors:

- Many geographic areas where parasitic infections are prevalent now have active organ transplant programs.
- Donors and recipients from endemic areas, with latent or asymptomatic infections, are sometimes referred to transplant centers in Western countries.
- Some patients from developed countries undergo transplantation in endemic areas ("transplant tourism") and return home with either donor derived or naturally acquired infection(s).
- Immigrants to Western countries, unaware of their infectious status, are accepted for organ donation without further evaluation for diseases that are prevalent in their countries of origin.
- With the recent increase in leisure tourism, transplant recipients travel to endemic areas and enhance their risk of exposure.
- The decrease in cyclosporine-based immunosuppressive regimens and the increased use of newer drugs that lack the antiparasitic effects of cyclosporine metabolites may result in higher rates of parasitic infection.

Tissue and Blood Protozoa

Toxoplasmosis
Epidemiology and risk factors: Toxoplasmosis is a zoonotic illness due to infection with the protozoa *Toxoplasma gondii*. Infection in transplant recipients can occur

through ingestion of contaminated food or water, after receiving an infected allograft, or by reactivation of latent infection. Cardiac transplant recipients who are seronegative for toxoplasmosis and receive an organ from a seropositive donor have a 57–75% risk of developing symptomatic infection without prophylaxis, usually within 3 months after transplantation (1,2). Latent infection in the donor myocardium during cardiac transplantation is the most common method of donor transmission, although it has been transmitted through transplantation of other organs (3,4). However, among noncardiac, SOT-related cases of toxoplasmosis are more varied in origin (4).

Toxoplasmosis gondii infection occurs worldwide but it is more common in patients from endemic regions, including France and the moist tropical areas of Latin America and sub-Saharan Africa, when the prevalence may approach 90%. In the United States, 10–40% of people are seropositive for *T. gondii* (5,6). Risk factors for primary infection include ingestion of cysts in under cooked meat or contaminated soil, contact with oocysts in feline feces, maternal-fetal transmission, or via blood or SOT (7). Water-borne transmission of *T. gondii* has been considered uncommon but has been reported (8). A large review of 15 800 SOT recipients at one center found 22 cases of toxoplasmosis disease. Notably, 90% of recipients were seronegative at the time of transplant. Morbidity was high, and the crude mortality rate was 3/22 (13.6%; Ref.3).

Diagnosis: Transplant patients with toxoplasmosis can present with fever, myocarditis, lymphadenopathy, hepatosplenomegaly and meningitis, brain abscess, chorioretinitis, pneumonitis, hepatitis, pancytopenia or disseminated disease. Symptoms often present within 3 months posttransplant, however, later presentations can be seen, particularly after discontinuation of chemoprophylaxis (3,4,9). Definitive diagnosis requires the identification of tachyzoites on histopathology of tissue, seroconversion or amplification of toxoplasma DNA by PCR of infected tissues (10).

The presence of multiple ring-enhancing lesions in the basal ganglia or cerebrum on neuro-imaging, especially in the presence of anti-*Toxoplasma* IgG seropositivty, is suggestive of CNS toxoplasmosis and is sufficient to start presumptive treatment. Stem cell transplant recipients often show a variable enhancement pattern, with the lesion enhancement inversely correlated with the severity of immunosuppression; the radiographic appearance in SOT recipients has not been well described (11). Brain biopsy should be considered in nonresponding patients, as the radiographic differences with other infections or malignancies are neither sufficiently specific nor sensitive. Cerebrospinal fluid (CSF) may have a mild mononuclear pleocytosis and/or an elevated protein. Identification of toxoplasma DNA by PCR in the CSF of patients with HIV/AIDS has a high specificity (96–100%) but the sensitivity is more limited (52–98%; Refs.12–14). Rarely tachyzoites can

be seen on centrifuged CSF samples after Giemsa staining (10).

Myocarditis may present with heart failure; the diagnosis is made by seeing tachyzoites on myocardial biopsy. Chorioretinitis often presents with scotoma, blurred vision, pain or photophobia. On fundoscopic examination raised, yellow-white, cottony lesions in a nonvascular distribution (unlike the perivascular exudates of CMV retinitis) are seen and vitreal inflammation may be present. Pulmonary disease often presents with fever, dyspnea and nonproductive cough, and reticulonodular infiltrates on chest imaging. This pattern of disease may be indistinguishable from *Pneumocystis jiroveci* pneumonia but toxoplasma tachyzoites are identified in bronchoalveolar lavage (BAL) fluid. Although rare, cutaneous toxoplasmosis has been seen after hematopoietic stem cell transplantation (15).

Treatment: Optimal treatment after SOT has not been well studied. However, an extensive literature exists on treatment of toxoplasmosis in patients with HIV/AIDS, which serves as a guide for treatment of the transplant population. The drugs routinely used in the treatment of toxoplasmosis treat the proliferative form (tachyzoites) found during the acute phase of infection but do not eradicate the encysted form of the parasite. Treatment for active toxoplasmosis includes induction therapy with pyrimethamine (plus leucovorin) and sulfadiazine to combat the tachyzoites, followed by chronic suppressive therapy (secondary prophylaxis) to prevent recrudescence of disease (16). Induction therapy is usually given for at least six weeks depending on response to therapy. Chronic suppressive therapy in HIV/AIDS patients is usually provided as reduced doses of the induction therapy until reconstitution of the patient's immune system. A similar strategy is appropriate in transplant recipients, however because the transplant population requires life-long immune suppression, chronic suppressive therapy with reduced toxicity medication, such as trimethoprim/sulfamethoxazole (TMP/SMX) may be considered (Refs.17,18; see Table 1).

Prevention/prophylaxis:

Screening: Pretransplant screening for prior toxoplasmosis exposure is generally done before heart transplant, and is less frequently done before other organ transplants. One retrospective cohort study of 1006 SOT recipients at a single center identified a pretransplant *Toxoplasma* seroprevalence rate of 13% in donors and 18% in recipients, with an incidence of *Toxoplasma* donor-recipient mismatch of 10%, of whom only 39% of mismatched recipients received TMP/SMX prophylaxis. Only four patients seroconverted, of whom two had received prophylaxis, and there were no cases of clinical disease (19). These data suggest that in transplant centers with low *Toxoplasma* seroprevalence, routine screening in SOT donors and recipients might not be necessary, particularly in the era of routine TMP/SMX prophylaxis. In areas of high seroprevalence, routine screening may be indicated.

Table 1: Therapy for common parasitic infections in SOT recipients

Organism	Preferred therapy	Alternative therapy
Blood and tissue protozoa		
Babesia	Atovaquone 750 mg (pediatric: 20 mg/kg/dose) po bid plus azithromycin 600 mg (pediatric 12 mg/kg) a day (if able to take oral medications) to ≥2 weeks beyond clearance of parasitemia (≥6 weeks minimum total treatment; Ref. 123)	Clindamycin 600 mg (pediatric: 20–40 mg/kg/day divided) po tid or 1.2 g IV q12 hours plus quinine 650 mg (pediatric: 30 mg/kg/day divided) po tid (or quinidine IV) to ≥2 weeks beyond clearance of parasitemia (≥6 weeks minimum total treatment; Ref. 123)
Leishmania		
Visceral disease	Liposomal amphotericin B given 3 mg/kg IV on days 1 through 5, 14, and 21. Consider secondary prophylaxis with intermittent dosing in patients at high-risk for relapse	Amphotericin B deoxycholate 1.0 mg/kg daily for 15–20 days **OR** pentavalent antimony compound Consider secondary prophylaxis with intermittent dosing in patients at high-risk for relapse
Cutaneous or mucocutaneous disease	A pentavalent antimony compound (stibogluconate or meglumine antimoniate) at 20 mg/kg IV/IM daily. Duration: cutaneous disease, 21 days and mucocutaneous disease, 28 days	Liposomal amphotericin B, amphotericin B deoxycholate, miltefosine, paromomycin, pentamidine, and fluconazole can be considered based on species and availability
Toxoplasma gondii	*Induction therapy*: Pyrimethamine 200 mg po x1 then 50 mg (<60 kg) to 75 mg (≥60 kg) (pediatric 2 mg/kg/day) PO daily plus sulfadiazine 1.0 (<60 kg) 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 *Chronic suppressive therapy:* Pyrimethamine 25 mg (< 60 kg) to 50 mg (≥ 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 q6h **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) *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 (pediatric <12 years: 10 mg/kg) divided bid for 60 days	Nifurtimox∗ 8–10 mg/kg/day divided three times daily 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)
Intestinal protozoa		
Blastocystis hominis	Nitazoxanide 500 mg po bid for 3 days (pediatric: 12–47 months 100 mg/dose bid)	Metronidazole 1.5 grams x 1 daily for 10 days **OR** Iodoquinol 650 g po tid x 20 days, **OR** TMP/SMX DS bid x 7 days
Cryptosporidium	Nitazoxanide 500 mg po bid x 14 days (same as for HIV+) (pediatric: 12–47 months of age, 100 mg PO bid 4–11 years of age, 200 mg PO bid ≥12 years of age – see adult dosing) Reduce immunosuppression if possible	Paromomycin or azithromycin; consider combination therapy
Cyclospora	TMP/SMX DS qid x 10 days then tid (pediatric: TMP 5 mg/kg/SMX 25 mg/kg/day divided bid)	Ciprofloxacin 500 mg po bid x 7 days, then three times a week x 2 weeks
Entamoeba histolytica	Metronidazole 750 mg (pediatric 35–50 mg/kg/day divided) po tid x 10 days **OR** Tinidazole 2 gram (pediatric >3 years 50 mg/kg) po once daily x 3 days followed by	Nitazoxanide: *intestinal amoebiasis*: 500 mg po bid x 3 days and for *extraintestinal (hepatic) amoebiasis* 500 mg po bid x 10 days followed by paromomycin or iodoquinol as per preferred therapy

Table 1: Continued

Organism	Preferred therapy	Alternative therapy
	Paromomycin 500 mg (pediatric 25–35 mg/kg/day divided) potid x 7 days **OR** Iodoquinol 650 mg po (pediatric 30–40 mg/kg/day divided) tid x 20 days to eliminate cysts.	
Giardia	Tinidazole 2 gram x 1, or Nitazoxanide 500 mg po bid x 3 days (pediatric: 12–47 months 100 mg PO bid 4–11 years 200 mg PO bid ≥12 years—see adult dosing)	Metronidazole 500–750 mg po (pediatric 15–30 mg/kg/day divided) tid x 5 days; **OR** Paromomycin 500 mg po qid x 7 days; *refractory disease:* Metronidazole 750 mg tid plus quinacrine 100 mg tid both for 3 weeks
Cystoisospora belli	*Immunocompromised host*: TMP/SMX DS qid x 10 days then bid x 3 weeks (same as for HIV+) (pediatric: TMP 5 mg/kg/SMX 25 mg/kg/day divided bid)	Ciprofloxacin 500 mg po bid x 7 days **OR** pyrimethamine 75 mg po a day with folinic acid 10 mg a day for 14 days
Microsporidia	Albendazole 400 mg (Pediatric 15 mg/kg/day divided) po bid x 3 weeks or Fumagillin 200 mg po tid	
Helminths		
Strongyloides	Ivermectin 200 microgram/kg/day x 2 days; repeat in 2 weeks (3 mg tablets) (longer for hyperinfection)	Albendazole 400 mg po bid x 10–14 days (longer for hyperinfection)
	Hyperinfection: Treat until document clearance – then 7–14 days longer	Off-Label alternatives if oral therapy not an option:
	HTLV-1 co-infection: Treat until document clearance – then 7–14 days longer. Expect persistent infection. Monitor and retreat as needed.	(a) Per rectum ivermectin (b) Subcutaneous ivermectin
Schistosoma	Praziquantel 20 mg/kg/dose po bid x 1 day if *S. hematobium* or *S. mansoni)*	Oxamniquine and artemether (anti-malarial)
	Praziquantel 20 mg/kg/dose po tid x 1 day if *S. japonicum* or *S. mekongi*	
Echinococcus	Albendazole 400 mg po bid (pediatric 15 mg/kg/day divided bid) for 1–6 months plus possible surgery or PAIR procedure)	Off-Label preprocedure or presurgical use:albendazole (+/- praziquantel in combination) to reduce the chance of secondary seeding

Therapy for Common Parasites.

Note:There are no prospective trials for any regimen in transplantation. Very few drugs interactions with standard transplant-related medications have been reported, and may be underappreciated.

● In the United States, these drugs must be obtained from the Centers for Disease Control at 404–639-3670 (emergency after hours 404–639-2888).

● Pediatric doses are included where available.

Primary prophylaxis: The routine use of TMP/SMX for post-SOT prophylaxis has decreased the risk of toxoplasmosis (20–23) and is currently the most common prophylaxis against this parasite. Multiple studies support the efficacy of primary prophylaxis with TMP/SMX, although the optimal dose and duration of TMP/SMX remains unclear. Many studies showed successful prophylaxis using TMP/SMX (160 mg of TMP, 800 mg of SMX) thrice weekly for varying durations (range 3 months to lifelong; Refs.21–23). In patients with HIV/AIDS, TMP/SMX (160 mg of TMP, 800 mg of SMX) one tablet daily is recommended as first line prophylaxis (16). Reports of toxoplasmosis in high-risk patients after stopping prophylaxis have been described (24). An alternative to TMP-SMX that has been well studied in patients with HIV/AIDS is dapsone plus pyrimethamine (plus leucovorin; Refs.25–27). Atovaquone with or without pyrimethamine (plus leucovorin) has not

been well studied but is considered a likely effective alternative regimen as well (16). Some transplant centers have reported using pyrimethamine with or without sulfadiazine for prophylaxis of toxoplasmosis infection in high-risk cardiac recipients (22,23,28).

To avoid primary infection, transplant recipients should avoid contact with undercooked meat, soil, water or animal feces that might contain toxoplasmosis cysts.

Recommendations (iii)
Pretransplant screening:

● All heart transplant candidates and donors should be tested for *Toxoplasma* IgG pretransplant.

- The benefit of screening nonheart transplant recipients and donors is not well established but could be considered in high prevalence areas.

Diagnosis:

- Acute toxoplasma infection can be identified by histopathological results, seroconversion, or molecular testing (PCR).
- Initiation of empiric therapy (particularly of CNS infection) should be considered based on clinical and radiographic findings manifestations while awaiting results.

Treatment:

- Pyrimethamine plus sulfadiazine is recommended as first-line therapy of acute toxoplasmosis infection.
- Chronic suppressive therapy after induction therapy is recommended.

Prevention:

- Among toxoplasma seropositive heart transplant recipients and seronegative heart transplant recipients receiving organs from seropositive donors, prophylaxis against toxoplasma infection is recommended with TMP/SMX. The optimal dose and duration of prophylaxis posttransplant has not been determined, but many transplant centers give life-long prophylaxis with TMP/SMX double strength (160 mg of TMP, 800 mg of SMX) one tab three times weekly or TMP/SMX single strength (80 mg of TMP, 400 mg of SMX) one tab daily.

Chagas Disease (American Trypanosomiasis)

Epidemiology and risk factors

Chagas disease is caused by the protozoan parasite, *T. cruzi* and infection is transmitted to humans primarily by contaminated feces of a triatomine insect vector (29). However, *T. cruzi* infection has also been transmitted by blood transfusion, infected mother to fetus, oral ingestion, and organ transplantation. Chagas disease is endemic in most Latin-American countries where 8–9 million people are currently living with infection and 2–5 million people have Chagasic cardiomyopathy. Because of recent immigration it is estimated that between 0.3 and 1 million *T. cruzi* infected people are living in the United States (30–32).

Human disease has two distinct phases: the acute phase and the chronic infection. In the normal host, the acute disease usually resolves spontaneously even if untreated; but without specific treatment the infection persists in spite of strong evidence of immunity and patients become chronically infected with the parasite (29). The indeterminate phase (clinical latency) can last 10–30 years or lifelong. In approximately 30% of patients the chronic phase will evolve into irreversible disease of the heart (27%), the esophagus and the colon (6%) and the peripheral nervous system (3%; Ref.33). In transplant recipients there are three distinct scenarios that will be focused on in this section (1) heart transplant recipients with chronic *T. cruzi* infection who are at risk of reactivation posttransplantation, (2) noncardiac transplant recipients with chronic *T. cruzi* infection who are at risk of reactivation posttransplantation and (3) uninfected organ transplant recipients who received organs or blood from *T. cruzi* infected donors.

Patients with chagasic cardiomyopathy: Chagasic cardiomyopathy is the third leading cause for heart transplantation in Brazil (21.9% of all heart transplants; Ref.34). Posttransplant outcomes do not differ significantly from heart transplant for other causes (34–36). Reactivation after transplantation has been reported to occur in 27% (34) to 43% (37) of recipients and risk factors may include treatment of rejection, mycophenolate mofetil use and development of neoplasms (34) although other studies have not found the same associations (37). Clinical manifestations range from asymptomatic parasitemia to fevers, cutaneous manifestations and myocarditis (that may both clinically and histologically appear similar to rejection; Ref.38). Skin manifestations include a rash, which may look more like panniculitis rather than a macular drug rash; a skin biopsy may show trypanosomes. Early diagnosis, careful monitoring and good response to treatment allow for an adequate survival (37).

Patients with chronic T. cruzi infection undergoing nonheart organ transplant: Most of the experience outside of heart transplantation is related to kidney transplantation (39). Reactivation has been described mainly within the first year posttransplant. The most frequent reactivation feature is asymptomatic parasitemia, but fever, panniculitis or other cutaneous involvement, myocarditis, and encephalitis have also been reported (38–40).

Uninfected organ recipients receiving organs or blood from T. cruzi infected donors: *Trypanosoma cruzi* seronegative recipients of seropositive donors may develop acute *T. cruzi* infection posttransplantation (41–43). Transmission rates from seropositive donors to seronegative recipients are approximately 20% for kidney transplants (39,44) and 22–29% of liver transplants (44,45). Because of the tropism of *T. cruzi* for cardiac tissue, rates would likely be higher for heart transplants and several cases of severe acute *T. cruzi* infection in heart transplant recipients have been described (41–43). Transmission rates for other organs (lung, pancreas and intestine) are not well defined. Clinical manifestations of infection can include fever, malaise, anorexia, hepatosplenomegaly and acute

myocarditis with a mean time to symptom onset of 112 days (range 23–240 days; Refs.39,41–43,46–51).

Diagnosis
Diagnosis of chronic T. cruzi infection in organ recipients and donors: Diagnosis of chronic infection is made by detection of antibodies to *T. cruzi* antigens, most commonly by the EIA or IFA methods. Different countries have unique approved testing assays. No single test has sufficient sensitivity or specificity to be relied on alone for clinical diagnosis. Therefore, two serological tests based on different antigens and/or techniques should be used to increase the accuracy of the diagnosis (52). When discordant testing occurs, a third test should be used.

Diagnosis of acute T. cruzi infection posttransplantation: In organ transplant recipients with acute infection and those with chronic *T. cruzi* infection where there is a concern for reactivation, serological testing has limited utility. Direct parasitological test methods for diagnosis include microscopy of the fresh buffy coat preparations, Giemsa-stained peripheral blood smears, and PCR of whole blood or tissue from a biopsy. PCR techniques provide the most sensitive testing and can often identify positive results days to weeks before circulating trypomastigotes are detectable by microscopy of peripheral blood smear and buffy coat preparations (53). Patients with chronic *T. cruzi* infection may have positive PCR in the absence of disease reactivation and may not be helpful. PCR is not commercially available in the United States but can be obtained through the Centers for Disease Control and Prevention (CDC, see contact details below). Hemoculture is of limited utility because of its prolonged turn around time (2–8 weeks).

Monitoring for infection after transplant of an organ from a seropositive donor to a seronegative recipient and after transplantation in a recipient with chronic *T. cruzi* infection is recommended so that treatment can be initiated before the development of clinically significant disease. Monitoring can be accomplished by checking PCR of blood for *T. cruzi* DNA (when available) and review of peripheral blood for parasitemia weekly for 2 months posttransplant, every two weeks for the third month, then monthly afterwards for a period to be determined by the specific clinical scenario. Additional testing is recommended in the setting of intensified immunosuppression, unexplained febrile illness, or episodes of suspected graft rejection (44).

Treatment
Treatment is recommended for patients with evidence of reactivation of chronic infection or acute infection posttransplantation. Two drugs are available for treatment of Chagas disease, nifurtimox and benznidazole (Refs.54,55); see Table 1). Neither drug is approved by the FDA, but they are both available in the United States via the CDC through their investigational drugs protocols. Both drugs have significant side effect profiles; benznidazole is frequently associated with rash and a dose-dependent peripheral neuropathy while nifurtimox is associated with gastrointestinal symptoms (anorexia, weight loss and nausea) and central nervous system symptoms (irritability, insomnia and tremors). Benznidazole is better tolerated among transplant recipients and has fewer drug interactions when compared to nifurtimox and therefore, benznidazole is generally preferred for first-line treatment.

Prevention
Screening of organ donors for T. cruzi infection: Donor and recipient screening should be considered in Latin America (South America, Central America or Mexico). In lower prevalence areas (e.g. United States), universal screening of at-risk populations should be considered based on local epidemiology and targeted screening in all populations is recommended (44). Targeted screening may be accomplished for individuals who answer yes to the following question, "Was the potential donor or recipient born in Latin America (South America, Central America or Mexico)?" In a recent survey of all United States organ procurement organizations, 19% were performing either universal or targeted donor screening for *T. cruzi* infection (56).

Transplantation of organs from T. cruzi seropositive donors to seronegative recipients: Donor-derived *T. cruzi* infection has been described and organ specific rates of transmission are limited but several sets of guidelines have recently been published (44,57,58). Transplantation of kidneys and livers from *T. cruzi* infected donors can be considered with close monitoring posttransplant. However, transplantation of hearts from *T. cruzi* infected donors is not recommended given the tropism of *T. cruzi* for cardiac tissue. Limited data are available on transplantation of other organs (lung, pancreas and small bowel) and can be considered with caution based on anticipated degree of immunosuppression.

Prophylactic treatment to prevent T. cruzi transmission or reactivation of chronic infection: Systematic data are lacking for the efficacy of prophylactic treatment and may mask signs of transmission. Confirmation of infection (or its absence) has important implications for long-term management of the patient. Taking these considerations and potential for drug toxicity, most experts would prefer careful monitoring posttransplant to the use of and not recommend prophylactic treatment.

Consultation for suspected cases of T. cruzi infection
In the United States consultation about known or suspected *T. cruzi* infections, confirmatory testing, monitoring and treatment of transplant recipients should be directed to the Division of Parasitic Diseases and Malaria,

CDC. Phone 770–488-7775. E-mail: parasites@cdc.gov. CDC Emergency Operator (after business hours and weekends): 770–488-7100.

Recommendations
Pretransplant screening:

- Screening for *T. cruzi* infection should be performed in heart transplant candidates.
- Universal organ donor and recipient screening for *T. cruzi* infection should be considered in Latin America (South America, Central America, and Mexico).
- Targeted donor screening in all populations is recommended but universal donor screening for *T. cruzi* in lower prevalence areas should be considered based on local epidemiology.

Diagnosis:

- Chronic infection: Because of insufficient sensitivity or specificity of a single assay, two serological tests based on different antigens and/or techniques should be used to increase the accuracy of the diagnosis of chronic *T. cruzi* infection.
- Acute infection or reactivation of chronic infection: PCR of blood or tissue and review of peripheral blood smear for parasitemia are the preferred techniques for diagnosing active T. cruzi infection posttransplantation.

Treatment:

- In the setting of active *T. cruzi* infection, benznidazole is the preferred treatment in organ transplant recipients with nifurtimox as an alternative.

Prevention:

- Posttransplant anti-*T. cruzi* prophylaxis is not recommend in recipients of organs from seropositive donors or previously infected recipients at risk for reactivation. A strategy of preemptive monitoring and treatment following evidence of active infection is preferred.
- In organ transplant recipients with acute *T. cruzi* infection and those with chronic *T. cruzi* infection where there is a concern for reactivation screening for active infection by serum PCR and peripheral blood for parasitemia is recommended.

Leishmaniasis

Epidemiology and risk factors
Leishmaniasis is caused by a heterogeneous group of protozoan parasites, belonging to the genus *Leishmania* and presents with a variety of different clinical syndromes. The infection is acquired primarily through the bite of an infected female sandfly. It is estimated that 350 million people are at risk of acquiring the infection and that 12 million may be infected (59). Leishmaniasis is found in tropical and subtropical climates and is endemic in the Mediterranean countries in Europe. More than 90% of the world's cases of visceral leishmaniasis occur in India, Bangladesh, Nepal, Sudan and Brazil (60). The disease may appear as late as 30 years after the initial infection, therefore, even distant exposure needs to be considered for differential diagnosis. Leishmaniasis can be classified three ways, (1) geographically into New World and Old World disease; (2) clinically by syndrome into visceral, cutaneous, or mucocutaneous disease and (3) by subgenus, complexes and species based upon taxonomy (59,61).

Derangement of host cellular immunity is a significant risk factor for the development of symptomatic and severe infections and for increased mortality in patients infected with leishmaniasis (61). In most immunocompetent hosts, infection with *Leishmania* spp. is asymptomatic; however, viable organisms remain latent for life of the host (62). Therefore, it is not surprising that severe disease has become more frequently reported in organ transplant recipients who have lived or visited endemic regions. The three main potential mechanisms of acquisition of leishmaniasis in organ transplant recipients are (1) primary infection after transplantation, (2) reactivation of latent infection after transplantation or (3) receipt of an infected organ during transplantation (63,64). Most cases of leishmaniasis in organ transplant recipients have occurred in kidney transplant recipients (65–92) although reports have included liver (88,100), heart (88,102), lung (93) and kidney-pancreas (94). Diagnosis is often encountered late posttransplant with a median time of 18 months (95).

Clinical manifestations of disease vary based on the infecting organism and host immune response. Visceral leishmaniasis is caused by *L. donovani* complex (*L. donovani*, *L. infantum* and *L. chagasi*) and the clinical features are similar to what is seen in immunocompetent patients. Patients suffer from fever, hepatosplenomegaly and pancytopenia (96). Median time to onset was 30 days posttransplant (range of 7 days to 5 months) in one systematic review (95) but other reports have described reactivation as far out as 55 and 96 months posttransplantation (97,98). Cutaneous and mucocutaneous presentations are most often due to species of the *L. mexicana* complex and subgenus Viannia in the New World and *L. major*, *L. tropica* and *L. aetheopica* in the Old World. Cutaneous and mucocutaneous leishmaniasis are less commonly reported on in organ transplant recipients and have a protracted time interval between transplantation and disease manifestations (95,99).

Diagnosis
Visceral leishmaniasis: Direct visualization of amastigotes on histopathology or culture revealing promastigotes remain the gold standards for diagnosis of visceral leishmaniasis. This is most frequently accomplished by bone

marrow or splenic aspiration. In an immunocompetent cohort, splenic biopsies had a greater sensitivity than bone marrow aspirate (96% vs. 70%) for diagnosing visceral leishmaniasis (100). However, in organ transplant patients, bone marrow biopsy has been reported to have a sensitivity of 98% (95). Occasionally the diagnosis can be made from biopsy of other tissues such as lymph node or intestine. Serological testing for visceral leishmaniasis is highly sensitive in organ transplant recipients with 45/49 (92%) of patients testing positive in one systematic review (95). However, serology cannot distinguish between prior exposure and active infection and may cross-react with other protozoa. A urinary antigen test and serum PCR show high sensitivity for the diagnosis of visceral leishmaniasis and may be useful where available (101,102).

Cutaneous and mucocutaneous leishmaniasis: When cutaneous or mucosal leishmaniasis is suspected, a biopsy specimen for histopathological examination and culture should be obtained. After a parasite has been identified, speciation can be performed through isoenzyme analysis or species-specific monoclonal antibodies. Quantitative or semiquantitative PCR assays have shown a high diagnostic sensitivity when applied to histopathological specimens (103). Antileishmanial antibodies can be detected in the serum of patients with cutaneous and mucocutaneous disease but is not used routinely for diagnosis.

Contacting the CDC for diagnostic assistance with leishmania
In the US, information about CDC leishmania serology and PCR, or to obtain NNN (Novy-MacNeal-Nicolle) culture media can be made by contacting the Division of Parasitic Disease, CDC. Phone 770-488-4475. Additional helpful information can be found at www.dpd.cdc.gov.

Treatment
Visceral leishmaniasis: Drugs with efficacy in the treatment of visceral leishmaniasis include amphotericin B, pentavalent antimony, paromomycin, and miltefosine. Pentavalent antimony had previously been the primary treatment for visceral leishmaniasis but resistance rates have been increasing in some regions and there is significant toxicity associated with treatment. Liposomal amphotericin B has been shown to be the most efficacious drug for treatment of this disease and is the only drug licensed for the treatment of visceral leishmaniasis in the United States (104). Cure rates with amphotericin B in immunocompromised patients approach the same success seen in immune competent hosts. However relapsed disease was diagnosed in 24% of cases in organ transplant recipients as early as 1 month and as late as 5 years (77,95,105). Secondary prophylaxis with intermittent dosing of amphotericin may be useful for preventing relapse and is supported by a randomized control trial performed on patients with both HIV/AIDS and visceral leishmaniasis (106). Successful use of secondary prophylaxis has been reported in three cases of

visceral leishmaniasis in organ transplant recipients using different regimens including weekly amphotericin B (107), daily fluconazole (63) and monthly meglumine antimoniate (105).

Cutaneous and mucocutaneous leshmaniasis: Pentavalent antimony compounds are the recommended therapy for most cases of cutaneous and mucocutaneous leshmaniasis. Varying quality studies have also evaluated the efficacy amphotericin B, pentamidine, miltefosine and many other intravenous, oral and topical preparations. In transplant recipients with cutaneous and mucocutaneous disease, treatment with both amphotericin B and pentavalent antimony compounds have been described with mixed results (99,108).

Prevention
Data are lacking to determine if screening potential organ transplant recipients for visceral leishmaniasis 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 (109).

Recommendations (iii)
Pretransplant screening:

- Serologic screening of recipients with a history of potential exposure to *Leishmania* may be considered pretransplant in patients who have spent time in endemic regions.

Diagnosis:

- Bone marrow biopsy should be used over splenic biopsy as first line diagnostic method to obtain histopathology and/or culture to confirm the diagnosis in suspected cases after organ transplantation. Serological testing also has a high sensitivity and may be a useful test in certain cases.
- In organ transplant recipients with cutaneous or mucocutaneous leishmaniasis, skin or mucosal biopsy for histopathology and/or culture remains the gold standard. Serological testing has little role in evaluation of cutaneous disease.

Treatment:

- Liposomal amphotericin B should be considered first line therapy for patients with visceral leishmaniasis when available and secondary prophylaxis may be of benefit in select cases to prevent relapse.
- Pentavalent antimony compounds should be considered first line therapy for most patients with severe cutaneous or mucocutaneous.

Prevention:

- Patients with known prior visceral leishmaniasis or recipients of organs form donors with visceral leishmaniasis should be clinically monitored for evidence of infection after organ transplantation.

Malaria

Epidemiology and risk factors

Malaria poses an immense health problem in developing countries where it is the cause of more than 300 million acute cases and over 1 million deaths per year. It is transmitted to humans mostly through the bite of the female *Anopheles* mosquito; blood transfusions and organ transplantation are responsible for some cases in endemic areas and occasionally in countries with large immigrant populations (110). The disease does not produce protective immunity, but some degree of resistance to clinically severe hyperinfection is achieved through successive exposure and through persistence of plasmodia in the liver, the microvasculature and the blood stream. This incomplete acquired immunity is unable to completely eradicate the infection but explains the lack of detectable parasitemia and the higher incidence of asymptomatic disease in adults from endemic regions. This poses a problem at the time of blood or organ donation when the epidemiological background is not thoroughly investigated.

Many cases of malaria have been described in transplant recipients. It is not always possible to determine the mode of infection but transmission via the graft has been reported (111), although ultimately, some cases were traced to blood or blood products transfused to the recipient, even well before transplantation (112). In developed countries the disease is seldom seen but it should be considered when caring for a transplanted patient who has resided or visited areas where the disease is endemic (or has received an organ from a donor who has been in endemic areas) and presents with an unexplained febrile illness. The four different main plasmodia species that infect humans, *Plasmodium ovale, P. vivax, P. malariae* and *P. falciparum*, have all been diagnosed in SOT. Clinical manifestations have occurred in the early posttransplant period and have been described in kidney, liver and heart recipients (111–113). Fever has been reported as the most frequent presenting symptom, but it did not always have the typical paroxysmal or cyclic pattern (114,115).

Diagnosis

Malaria is classically diagnosed by microscopic observation of thick or thin blood smears. Rapid diagnostic tests are available by using dipsticks and allow the detection of specific plasmodia antigens in clinically significant malarial infections (116). Alternative diagnostic techniques that are recommended in some circumstances to screen blood donors include enzyme-linked immunoabsorbent assay for *P. falciparum* antigens; immuno-fluorescent-assay techniques for species-specific enzymes, DNA hybridization and DNA and mRNA amplification using PCR. In most posttransplant cases, the diagnosis was made by the identification of the parasite in blood smears in febrile patients with unexplained hemolysis and thrombocytopenia (117).

Treatment

Specific treatment of malaria relies on the use of anti-plasmodium drugs. The identification of plasmodia species, the knowledge of their geographical distribution and of their sensitivity patterns is essential. *P. vivax, P. malariae, P. ovale* and uncomplicated *P. falciparum* infection in chloroquine-susceptible regions should be treated with chloroquine. However, resistance to chloroquine has been described from Oceania for *P. vivax*. Uncomplicated *P. falciparum* infection acquired in a chloroquine resistant region can be treated with an artemisinin combination therapy, atovaquone-proguanil, quninine-based regimen, or mefloquine. Severe cases of *P. falciparum* infection 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) followed by doxycycline, atovaquone-proguanil or mefloquine. When artesunate is not available, intravenous quinine or quinidine plus doxycycline, tetracycline or clindamycin should be given. Primaquine should be used to prevent relapse of *P. vivax* and *P. ovale* (after checking for G6PD deficiency).

Malaria is potentially fatal in the transplant recipient. Early diagnosis and conventional specific treatment usually results in prompt and uneventful recovery. *P. falciparum* infection (111), drug toxicity and other infections may hamper the outcome. Special attention is needed when quinine is used for treatment because it may interfere with cyclosporine metabolism, decreasing its blood levels (118).

Prevention

Screening of donors who have recently spent time (preceding 3 years) in malarious regions should be considered. Potential screening methods should include thick and thin smear stained with Geimsa, Wright or Field stains. Rapid diagnostic tests detecting the HRP2 antigen can also be considered when expert review of thick and thin smears is not possible. Recipients traveling to malarious regions should be given appropriate chemoprophylaxis to prevent infection during travel. Chloroquine can potentiate levels of cyclosporine and appropriate dose adjustments should be made.

Recommendation (iii)
Pretransplant screening:

- Consider both donor and recipient testing for malaria with thick and thin smear if epidemiologically at high-risk for infection.

Diagnosis:

- Microscopic observation of thick or thin blood smears remains the gold standard for diagnosing malaria.
- Rapid diagnostic tests can be considered when microscopic evaluation by trained personal is not available.

Treatment:

- Treatment of patients should be performed via standard guidelines provided by the CDC (http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf) and WHO (http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf) based on species and severity of disease.

Prevention

- Organ transplant recipients traveling to malarious regions should be given appropriate chemoprophylaxis and instructed to perform other risk-reducing measures to prevent infection.
- Consultation with a travel medicine expert prior to international travel is highly recommended and valuable to reduce risks of illness. Providers with expertise can be found at www.istm.org and www.astmh.org.

Babesia

Epidemiology and risk factors

Babesiosis is a tick-borne, zoonotic protozoal illness that occurs after infection with *Babesia* spp., which invade and lyse red blood cells. Several species of babesia cause human disease and include *B. microti* primarily in the northeastern United States, *B. divergens* in Europe, *B. duncani* in the western United States, and an unnamed strain, designated MO-1, in Missouri. *B. divergens*, appears to be more virulent than others. Transmission to humans occurs via ticks of the *Ixodes* genus or rarely through blood transfusion. *Ixodes scapularis* is responsible for transmission of *B. microti* in northeastern United States and also may carry *Borrelia burgdorferi* and *Anaplasma phagocytophilum*. All three reports of babesiosis in transplant recipients were transfusion related and include two kidney transplant recipients and one heart transplant recipient (119–121). No current FDA licensed *Babesia* test is available for screening donated blood products.

Risk factors for severe babesiosis include asplenia, immunocompromised state and older age. Clinical manifestations range from asymptomatic to life threatening disease. Early symptoms may be fever and malaise, which can progress to severe hemolytic anemia (potentially manifesting as a posttransplant hemolytic-uremic or hemophagocytic syndromes), adult respiratory distress syndrome, multi-organ system failure and even death. Blood tests may show hemolytic anemia, thrombocytopenia and conjugated hyperbilirubinemia. Disease severity correlates with degree of parasitemia.

Diagnosis

Babesiosis can be diagnosed by microscopic visual review of peripheral blood smear or by PCR of blood. Diagnostic confusion between *Plasmodia* spp. (malaria) and *Babesia* spp. can occur due to similarity in morphology on microscopy when infecting red blood cells. Specific epidemiologic exposures and DNA testing (PCR) can aid in differentiating the diseases. For babesiosis bone marrow biopsy may reveal hemophagocytosis and marrow histiocytosis.

Treatment

Babesiosis is a potentially life threatening infection in immunocompromised hosts and antimicrobial treatment should begin immediately. There are no studies of babesiosis treatment in transplant recipients. Exchange transfusion should be considered in cases of greater than 10% parasitemia, severe hemolysis, severe renal and/or hepatic and/or pulmonary compromise (122). Reduction in immunosuppressive regimen should be considered. Atovaquone plus azithromycin can be used in those able to take oral medications. Clindamycin plus quinine is alternative regimen. In a prospective, nonblinded, randomized trial of the two regimens in 58 normal hosts, atovaquone and azithromycin was as effective as clindamycin and quinine with fewer adverse reactions (15% vs. 72%). The most common adverse effects with atovaquone and azithromycin were diarrhea and rash (8% each), while clindamycin and quinine common adverse effects were tinnitus (39%), diarrhea (33%) and decreased hearing (28%; Ref.123). Azithromycin may increase the serum concentration of tacrolimus and patients should be monitored for toxicity. Sirolimus and tacrolimus metabolism may be slowed by the CYP3A4 inhibitor quinidine.

The optimal antimicrobial or combination therapy in transplant recipients is not clear; persistent relapsing illness has been well described in other immunocompromised hosts. In one series of 14 immunocompromised subjects, most of whom had B-cell lymphoma and were asplenic or had received rituximab, antibabesial treatment was required for at least 6 weeks to achieve cure. Resolution of persistent infection occurred in 11 patients when antibiotic treatment was continued ≥2 weeks after documenting negative blood smears (124). Three (21%) subjects died, highlighting the severity of disease in this population and the need for longer treatment and prolonged monitoring compared to normal hosts (124). Though rare, resistance to the atovaquone/azithromycin regimen can occur, more commonly in immunocompromised hosts (125). Blood smears should be used for monitoring response to therapy and for relapse after completion of treatment, PCR can be considered when available.

Prevention

When visiting endemic areas, transplant recipients should avoid tick exposure by using permethrin repellants on clothing, DEET or Picaridin repellants on skin, and general protective clothing (126). Frequent tick checks and prompt removal is valuable, because early removal decreases the chance of transmission.

Recommendations (iii)
Pretransplant screening:

- Prospective living organ donors should avoid high-risk exposures in endemic regions in the weeks prior to donation.
- Living donors with a prior diagnosis of *Babesia* infection should report this and document they are clear of infection prior to donation.
- No *Babesia* tests are currently licensed for screening U.S. blood and organ donors.

Diagnosis:

- Direct visual microscopy is the most common diagnostic method. Rapid nucleic acid based tests are available through the CDC, and can aid in differentiation from malaria, as well as between various *Babesia* spp.
- Screen or monitor for tick-borne co-pathogens *Borrelia burgdorferi* and *Anaplasma phagocytophilum* in cases of babesiosis, because all three can co-infect an *Ixodes* spp tick.

Treatment:

- Atovaquone/azithromycin is preferred over clindamycin/quinine for babesiosis.
- Consider treatment of infection for 6 weeks, or at least 2 weeks after smear negative, to achieve full eradication. Relapse is common and posttreatment monitoring is recommended.

Prevention:

- Transplant recipients should be educated on how to reduce tick exposure when traveling to endemic regions.

Balamuthia

Epidemiology and risk factors

Balamuthia mandrillaris is a free-living amoeba that has been identified as a cause of human disease in the last two decades (127,128) and more immediately recognized as a cause of donor-derived infection through organ transplantation (129,130). Balamuthia infection is relatively rare (<200 cases reported) and has been identified to cause

disease in both immunocompetent and immunocompromised hosts. Unlike the other two free-living amoeba commonly associated with meningoencephalitis, *Naegleria* and *Acanthamoeba*, that are associated with fresh water exposure, *Balamuthia* is found in soil. Reported clinical manifestations of infection include chronic granulomatous skin lesions and a chronic granulomatous meningoencephalitis (127,128).

Two episodes of donor-derived transmissions of Balamuthia have been reported. The first transmissions occurred from a single donor in 2009 after a previously healthy 4-year-old with a slowly progressive (3 week) neurological decline died from presumed acute disseminated encephalomyelitis and became an organ donor (129). The two kidney recipients developed central nervous system abnormalities 20 days posttransplant and one died and the other had significant neurological deficits despite treatment. The liver and heart transplant recipients were given prophylactic antimicrobials and have remained asymptomatic. The second report of transmission occurred in 2010 when a 27-year-old male died of an apparent stroke (130). He had a chronic skin lesion for 6 months before his death. The recipients of the liver and kidney–pancreas both developed central nervous system symptoms 17 days posttransplant and ultimately died of *Balamuthia* infection. A kidney and a heart transplant recipient were treated with prophylactic antimicrobials and have remained asymptomatic. To date, no infections have been identified in organ transplant recipients from environmental exposure posttransplant or progression of subclinical pretransplant infection.

Diagnosis

Diagnosis of *Balamuthia* infection is unfortunately often made postmortem after histopathological examination of infected tissue. Most frequently brain or skin tissue are identified to have trophozoites or cysts present among granulomatous inflammation and necrosis. An indirect immunofluorescent assay is used to stain the tissue to confirm the diagnosis. Neither serum nor CSF studies are helpful for the diagnosis of *Balamuthia* infection at this time.

Treatment

Given the rarity of the disease, there is very little data on treatment of Balamuthia infection. Reported treatments have included a number of different antimicrobials, often in combination with often unsuccessful results, including amphotericin B, azoles, paromomycin, albendazole, pentamidine, macrolides, metronidazole, sulfadiazine, and miltefosine (127,128,131,132). Experts agree that treatment should include a multidrug regimen for a prolonged period of time yet the best combination of drugs is unclear at this time. Consultation with experts is strongly recommended (131).

Prevention

Because *Balamuthia* is thought to be ubiquitous in the environment, mechanisms for prevention of infection are not known. Early diagnosis and treatment of infection may improve prognosis. Caution should be made when considering transplanting organs from a donor with unexplained meningoencephalitis or unexplained chronic granulomatous skin infections.

Recommendation (iii)
Pretransplant screening:

- Not routinely recommended in asymptomatic patients.

Diagnosis:

- Diagnosis is most often made by identifying cysts or trophozoites in infected tissue. An indirect immunofluorescent assay is used to stain the tissue to confirm the diagnosis.

Treatment:

- Combination therapy is used for treatment and consultation with experts is strongly recommended.

Prevention:

- Caution should be made when considering transplanting organs from a donor with unexplained meningoencephalitis or unexplained chronic granulomatous skin infections.

Acanthamoeba and Naegleria

Epidemiology and risk factors

Acanthamoeba are protozoan parasites found in dust, soil, water, contact lens fluid, air conditioners, sewage, and may colonize the nose and throats of healthy individuals. A recent seroprevalence study found more than 80% of 55 healthy volunteers in Texas had antibodies to *Acanthamoeba* antigens, suggesting that exposure and undiagnosed infections are common (133). This disease can be seen in a variety of solid organ transplant recipient types—kidney, liver, lung and others (134). *Acanthamoeba* can cause either focal disease (usually keratitis, granulomatous amoebic encephalitis, brain abscess, pulmonary lesions, cutaneous lesions, or sinusitis) or disseminated acanthamebiasis which is often fatal in transplant recipients (135).

Naegleria are amoeba found in warm fresh water, heated contaminated tap-water, and soil. It grows best at higher temperatures (∼46°C). Infection can occur from swimming in contaminated water and recently has been contracted by using nasal sinus irrigation using neti pots with contaminated water (136). Use of organs from donors unknown to be infected with *Naegleria fowleri* at the time of transplantation has occurred on at least five occasions without infection of the recipients (137).

Diagnosis

Cutaneous lesions may be the initial manifestation of infection and should be biopsied as early diagnosis diagnosis is imperative to optimize the chance of survival. A direct examination of CSF should also be performed. *Acanthamoeba* can be cultured on agar plates coated with Gram-negative bacteria; it may take up to two weeks of culture before, the amoeba appear as track marks within the bacterial growth. Immunofluorescent tests may be used for species confirmation; DNA and RNA probes can also be used, but are not widely available. Serology is only useful for seroprevalence studies but not for diagnosis.

Treatment

Optimal treatment regimens for *Acanthamoeba* infections remain unknown. Drug sensitivities of free-living amebic infections differ between genera, species, and strains. Combinations of amphotericin B products with rifampin or imidazoles have been tried, as have combinations of sulfonamide antibiotics, azithromycin, caspofungin and flucytosine. Pentamadine has some *in vitro* activity. Central nervous system disease, diagnosed in a liver transplant recipient was cured after partial lobectomy, reduced immunosuppression, and 3 months of trimethoprim-sulfamethoxazole and rifampin (138). Another case of *Acanthamoeba* sinusitis with concomitant *Aspergillus* in a lung transplant recipient was successfully treated with surgical debridement and initial intravenous amphotericin, followed voriconazole and caspofungin (139). Others have reported successful treatment of *Acanthamoeba* after transplantation using amphotericin B and miltefosine in combination with other drugs (134,140). While some drugs are effective *in vitro* against *Naegleria*; nearly all infections are fatal. Prevention is the most important defense against this infection at the moment.

Prevention

How best to prevent the rare infections due to *Acanthamoeba* is not clear, as the amoeba are fairly ubiquitous and seroprevalance rates are high. Trimethoprim-sulfamethoxazole has been used in treatment regimens; it is not known whether its common use in prophylaxis may be able to prevent infections. *Naegleria* prevention includes avoiding exposure. If nasal sinus irrigation is important, use boiled water, filtered (≤1 μm) water, or distilled/sterile water.

Recommendations (iii)
Pretransplant screening:

- Not routinely recommended in asymptomatic patients.

Diagnosis:

- Diagnosis is made by identifying cysts or trophozoites in infected tissue. An indirect immunofluorescent assay is used to stain the tissue to confirm the diagnosis.

Treatment:

- Combination therapy is used for treatment and consultation with experts is strongly recommended.

Prevention:

- If nasal sinus irrigation is important, use boiled water, filtered ($\leq$ 1 m) water, or distilled/sterile water.

Intestinal Parasites

Intestinal parasitic infections are prevalent in developing regions of the world. Accordingly, with increasing travel to and from endemic regions, intestinal parasites may have an increasingly significant role in transplant candidates and recipients. Moreover, relevant parasites including *Strongyloides*, *Giardia*, *Cryptosporidium* and *Entamoeba* have a worldwide distribution. A careful pretransplant social history can identify at-risk individuals who may benefit from focused screening for persistent parasitic infection (141). Parasitic infections are often asymptomatic before transplantation but flourish under immunosuppression, becoming clinically evident. Eosinophilia, gastroenteritis and other clinical manifestations of parasite infections prior to transplant should also trigger an appropriate workup.

Intestinal Protozoa

Cryptosporidium/Cystoisospora belli/Cyclospora, Microsporidia/Blastocystis hominis/Giardia
Epidemiology and risk factors: Cryptosporidium, Cystoisospora belli, Cyclospora, Microsporidia, *Blastocystis hominis* and *Giardia* can all cause significant, and sometimes protracted, gastroenteritis in transplant recipients. While the use of mycophenolate mofetil is the most common cause of chronic diarrhea in transplant recipients, these fastidious organisms can mimic such colitis. *Cryptosporidium* and *Giardia* are among the most common parasitic pathogens seen in transplant recipients, given worldwide distribution. Transmission is more common in the developing world, with rates of infection as high as 20%, and can occur from contaminated food and water, person-to-person spread and zoonotic exposures (142). *Cryptosporidium* transmission in the developed world is facilitated by chlorine resistant oocytes and the 3–7 μm diameter of *Cryptosporidium* that can bypass many municipal water filtration and treatment systems. Moreover, infected individuals produce up to 100 million oocysts per day, while

as few as 10–30 oocysts may cause infection in healthy persons.

Intestinal protozoa have also been reported as donor-derived infections with intestinal transplantation. Most reports of intestinal protozoa in transplant recipients have been in case reports or small series from individual institutions. Biliary disease occurs in 10–15% of HIV-positive patients with cryptosporidiosis (143) and could occur in transplant recipients as well. Extra-intestinal disease is very rare but can occur in the brain or kidney (especially with Microsporidia).

Diagnosis
Standard examination for ova and parasites may be helpful but are time consuming. Concentration of stool and subsequent special stains may be more sensitive for certain pathogens; many laboratories use a trichrome stain to diagnose microsporidial infections or Safranin stain for *Cyclospora*. ELISA of stool may help rapidly diagnose *Cryptosporidium* and *Giardia*. Direct immunofluorescence tests for Giardia and *Cryptosporidium* are also available. Nucleic acid detection studies may also be helpful when available. Electron microscopy of bowel biopsies may also be helpful in diagnosing these infections.

Treatment
Cryptosporidium can be treated with nitazoxanide, paromomycin, azithromycin, or potentially with combinations of these drugs. *Cyclospora* and *Cystoisospora belli* are usually treated with trimethoprim/sulfamethoxazole (DS tablets BID), potentially using the higher doses (DS tablets QID) as recommended for HIV patients (122). Ciprofloxacin or nitazoxanide are potential alternatives in the setting of significant sulfa allergy. *Cystoisospora belli* can also be treated with pyrimethamine combined with folinic acid. Microsporidia treatment depends on the site of infection; albendazole and fumagillin can be effective. *Blastocystis hominis* can be treated with nitazoxanide, metronidazole, iodoquinol, or TMP/SMX. In a cases series of two transplant recipients with microsporidiosis due to *Enterocytozoon bieneusi*, fumagillin was effective but resulted in drug-induced thrombocytopenia (144). *Giardia* can be treated with tinidazole, nitazoxanide, metronidazole, or paromomycin; refractory disease can be treated with metronidazole plus quinacrine (145).

Intestinal protozoa can be difficult to eradicate. Reduction in immunosuppressive regimen may hasten clearance of these durable pathogens. Tacrolimus levels may rise in the setting of diarrhea and should be carefully monitored. Diarrhea may be augmented and/or prolonged by the concomitant use of mycophenolate mofetil. There are no comparison studies of various treatments in transplant recipients.

Prevention

Intestinal protozoa infections are primarily acquired from contaminated food and water. Transplant recipients should avoid untreated well or lake water, and preferentially drink treated municipal water or bottled water. There are no data to support the use of bottled water over treated municipal water for transplant recipients. Person-to-person and zoonotic transmission can occur; transplant recipients should be aware of the potential risks.

Recommendations (iii)
Pretransplant screening:

- Not routinely recommended in asymptomatic patients.

Diagnosis:

- Stool microscopy for ova and parasite is the mainstay for diagnosis and may require special staining such as modified acid-fast stains. Stool ELISA testing enhances sensitivity for the diagnosis of *Giardia* and *Cryptosporidium* infection.

Treatment:

- Conventional therapies should be used as first-line although relapse rate for many infections may be high and repeated, high-dose, and alternative treatment strategies may be required.

Prevention:

- Transplant recipients should avoid untreated well or lake water. They should avoid inadvertent swallowing of water when swimming in lakes.
- Chlorination does not sterilize *Cryptosporidium* making prevention more difficult.
- If concerns of ongoing *Cryptosporidium* exposure exist, installation and proper maintenance of 1-μm secondary household water filters can reduce exposure.

Entamoeba histolytica

Epidemiology and risk factors

Entamoeba histolytica infection can result in asymptomatic carriage, amebic colitis, liver abscess and more rare manifestations including pulmonary, cardiac or brain involvement. It is unknown if the clinical presentations are altered in transplant recipients. *Entamoeba histolytica* tends to occur in regions with limited sanitation. Sexual transmission, especially among men who have sex with men, is more common in industrialized countries.

Diagnosis

Entamoeba histolytica can be diagnosed via stool examination for ova and parasites, although this is less sensitive than stool assays using *Entamoeba* antigen testing or PCR; the latter two methods are species-specific, which can help distinguish between *E. histolytica* and *E. dispar* or *E. moshkovskii*. Only *E. histolytica* is considered pathogenic. Serology may be positive with extra-intestinal disease and can be helpful for screening and diagnosis in low prevalence, nonendemic regions.

Treatment

Treatment of amoebiasis generally involves the use of metronidazole or tinidazole against the active trophozoite stage (tissue amoebicide), followed by the use of paromomycin or iodoquinol to eliminate cysts (luminal agent). There is one case report of successful treatment of amoebiasis with metronidazole in a liver transplant recipient (146). Asymptomatic persons infected with *Entamoeba histolytica* can be treated with a luminal agent alone to prevent transmission and invasive disease (122). Nitazoxanide has shown cure rates of greater than 90% in some studies (147).

Prevention/prophylaxis and infection control issues

These infections are primarily acquired from contaminated food and water. Transplant recipients should avoid untreated well or lake water, and preferentially drink treated municipal water or bottled water. Sexual transmission can occur; transplant recipients should be aware of the potential risks.

Recommendations
Pretransplant screening:

- Not routinely recommended in asymptomatic patients.

Diagnosis:

- Direct microscopy is the most common diagnostic method but does not differentiate *Entamoeba histolytica* from nonpathogenic species.
- Antigen testing, or nucleic acid testing of stool samples can be used to identify active infection while serology can identify present or prior infection.

Treatment:

- Except for asymptomatic carriers, it is important to treat with both a tissue amoebicide (metronidazole or tinidazole) and a luminal agent (paromomycin) to fully eradicate the organism.
- Hepatic amoebiasis typically requires more prolonged treatment.

Prevention:

- Avoidance of contaminated food and water is the best method of prevention.

Intestinal Nematodes

Strongyloides

Epidemiology and risk factors: *Strongyloides stercoralis* infects approximately 100 million persons worldwide (148). The parasite is endemic in the tropics and subtropics, and has been reported from temperate areas such as southern and Eastern Europe, the Caucasus, Belgium, the United Kingdom and southeastern United States (149). *Strongyloides stercoralis* is able to complete its life cycle both in the environment and in the human host. As a consequence, the parasite has an "auto-infective" cycle that produces long-term persistent infections. The rate of autoinfection is regulated by the immune response of the host; the severity of the disease correlates with worm burden. The major reservoir of the parasite is soil contaminated with human feces that harbor *Strongyloides* larvae. The filariform larvae penetrate the intact skin, enter the circulatory system, migrate to the lung, penetrate alveolar spaces, and move to the pharynx/trachea where swallowing allows access to the duodenal mucosa where they become adult parasites. Significant tissue phases of the life cycle accentuate blood eosinophilia. Adult females reproduce asexually (parthenogenesis) and sexually, laying eggs that become either rhabditiform larvae—which are eliminated with the stools completing the parasite life cycle—or filariform larvae that penetrate intestinal mucosa and perpetuate the infection. The molting of rhabditiform larvae into filariform larvae is accelerated under immunosuppression, allowing a massive number of larvae from the intestinal lumen or the perianal skin to autoreinfect the host. As a result, a great number of adult worms are found in the intestinal lumen. This can lead to lung involvement or the disseminated form of the disease.

Clinical syndromes include acute infection; chronic infection with parasite persistence and autoinfection; hyperinfection syndrome (HIS) and disseminated disease (DD). Hyperinfection syndrome is characterized by accelerated larvae production, migration and elevated parasite burden with evident clinical manifestations; but the larvae are restricted to pulmonary and gastrointestinal systems. DD includes the components of HIS with additional larva spread to other organs (150). Risk factors for HIS and DD have been linked to the immune status of the host and are mainly related to corticosteroids or other immunosuppressive agents. HTLV-I co-infection is also a known risk factor for progression to HIS/DD.

Strongyloidiasis has been well described in organ transplant recipients and has been attributed both to reactivation of latent disease as well as donor-derived infection (151,152). The common use of high-dose corticosteroid preconditioning of deceased donors can increase rates and intensity of strongyloides transmission (153).

Strongyloidiasis can be a devastating disease in transplant recipients; the mortality rate approaches 50% in hyperinfection syndrome and 70% in disseminated infection (151). The clinical disease may present with pulmonary involvement, bacterial sepsis or bacterial meningitis with Gram-negative rods from intestinal flora carried on the surface of the parasite during tissue migration. Gastrointestinal presentations include acute and severe abdominal disease, bloody diarrhea, adynamic ileus, intestinal obstruction, and gastrointestinal hemorrhage, caused by larval damage inflicted as they penetrate through the gut wall. This is most likely to occur in the initial months after transplantation when immunosuppression is most intense. Yet, diagnoses associated with SOT at varied stages in some individuals (hypogammaglobulinemia, malnutrition and lymphoma) may facilitate progression to hyperinfection/disseminated disease at later dates (154).

Diagnosis: Eosinophilia can be found in patients with *Strongyloides* acute infection. However, patients with chronic infection, hyperinfection syndrome, disseminated disease and immunocompromised patients may have normal eosinophil counts. Absence of eosinophilia does not rule out disease in recipient or donors (153,155). Definitive diagnosis is achieved by identification of larvae in clinical specimens mainly in stool (typically only HIS/DD have enough larva to allow detection consistently) and duodenal aspirate samples (156). However, in the course of the disseminated disease larvae can be found in respiratory secretions, CSF, peritoneal fluid, urine, pleural effusion, blood and other tissue specimens. Larvae are often accidentally found when searching for other pathogens as causes of the severe disease. In uncomplicated cases, stool larvae density is low and elimination intermittent (direct observation sensitivity 0–14%). Duodenal fluid aspirate, while more sensitive than direct stool examination has only 76% sensitivity and involves an invasive procedure.

Serological testing is often more sensitive for diagnosis of infection, although cannot distinguish active and prior infection, and may not be available worldwide. Enzyme-linked immunosorbent assay (ELISA) is highly sensitive (80–95%) and specific (90%) in normal hosts (157). In immunocompromised patients sensitivity is reduced to 68%, with retained specificity at 89% (158,159). Small series using a combination of methods in immunocompromised patients, improved the sensitivity back toward 90% (160,161). False-positive results are mostly related to the presence of other helminthic infections; thus, local epidemiology is important when considering the positive predictive value. A gelatin particle indirect agglutination (GPIA) has a published 98.2% sensitivity and 100% specificity (155).

Though donor serotesting (when historical factors warrant) may have delayed results, these data remain useful to focus recipient evaluation and treatment. Living donors with potential exposure profiles should be screened well ahead of donation.

Treatment: Ivermectin is the treatment of choice for strongyloidiasis (145,155) and is effective at eradicating adult parasites and larvae from the intestine in normal hosts (122,145,162,163). A repeated dose at two weeks is designed to treat the less susceptible forms by life cycle stage, when they have progressed to a more susceptible phase. Adverse effects are infrequent and usually mild. Albendazole has a primary cure rate of only 45–75% making it a second-line therapy (163,164). Thiabendazole, is the agent with the most clinical experience, although the least satisfactory of all available drugs, due to frequent relapses and toxicities (149).

The experience with ivermectin for the treatment of hyperinfection or disseminated disease in transplant recipients is limited and reports describing clinical failure have been published (165). Cases with heavy parasitic burden require daily doses until clearance; with additional doses for 7–14 days to reduce the risk of relapse (154). Anecdotal experiences lead some to advocate combination or sequential ivermectin and albendazole treatment. Severe strongyloidiasis with concomitant malabsorption is a serious challenge to oral treatment. Off-label rectal ivermectin can be effective in patients unable to tolerate or absorb oral therapy (166). A parenteral veterinary formulation of ivermectin has been used subcutaneously with some success (153,167). In the United States the veterinary formulations require emergency investigational new drug approval from the Food and Drug Administration (Division of Special Pathogens, 301-796-1600).

S. stercoralis and HTLV-1 co-infection typically requires protracted therapy because no treatment reliably cures strongyloidiasis. Treatment recommendation is (typically daily ivermectin) until visible organisms are cleared and then for 7–14 additional days, followed by retreatment if significant symptoms or eosinophilia return–often at weekly to monthly intervals (144).

Prevention: Organ transplant recipients should be educated to wear closed footwear in endemic environments to reduce risk of primary infection. To reduce the risk of disseminated strongyloidiasis in asymptomatic or paucisymptomatic patients; expanded screening with detailed history, parasitological studies and serology facilitate necessary treatment of infection before transplantation is needed (141). In addition to asking about international travel, it is important to inquire about work, volunteer, or military service abroad which many patients do not consider "travel." If not feasible, consider empiric treatment before initiation of immunosuppressive therapy for trans-

plant candidates with unexplained eosinophilia, a history of parasitic infection and/or residence in or travel to, endemic areas even in the remote past (168). Because strongyloidiasis can be transmitted via the graft, information about a donor's epidemiologic risk might trigger further serologic evaluation, or even initiation of pre-emptive treatment for the recipient (151–153,169,170). All infected living donors should be adequately treated prior to transplant. Recipients of untreated infected donors should receive empiric therapy posttransplant as well as monitoring for posttransplant infection.

Recommendations (iii)
Pretransplant screening:

- Evaluation for strongyloidiasis should be strongly considered in transplant candidates with epidemiological risk factors or unexplained eosinophilia during pretransplant evaluation.
- Evaluation for strongyloidiasis should be strongly considered in living donors, and where feasible, deceased donors with epidemiological risk factors or unexplained eosinophilia during pretransplant evaluation.

Diagnosis:

- When evaluating potential living donors and recipients pretransplant at risk for strongylodiasis, a combination of serology and stool examination is recommended.
- In the setting of hyperinfection and disseminated disease, in addition to stool, larvae may be identified in respiratory fluids, skin biopsies and many other fluids and tissues.
- Patients with strongyloidiasis should be tested for HTLV-1, because co-infection affects approaches to treatment, duration of treatment, and clinical monitoring.

Treatment:

- Ivermectin is the drug of choice for treatment of strongylodiasis. Hyperinfection and disseminated disease may require protracted therapy. Nonoral routes of administration can be considered when absorption is poor. Treatment is recommended until visible organisms are cleared and then for 7–14 additional days with close monitoring for relapse.
- *S. stercoralis* and HTLV-1 co-infection typically requires protracted therapy because no treatment reliably cures strongylodiasis.

Prevention:

- All organ transplant recipients and living donors with strongylodiasis should be adequately treated prior to transplant. Organ recipients of untreated infected

donors should receive empiric therapy posttransplant as well as monitoring for posttransplant infection.

- Organ transplant recipients should be educated to wear closed footwear in endemic environments to reduce risk of primary infection.

Trematodes

Schistosomiasis

Epidemiology and risk factors: *Schistosoma* species are found throughout much of the warmer climates; species vary by region, and specific clinical disease varies by species. Schistosomiasis is primarily a fresh-water-borne infection in endemic rural regions. *S. mansoni* and *S. japonicum* can lead to intestinal and hepatic complications, while *S. haematobium* predominantly leads to renal and bladder sequelae. Less common, *S. mekongi* and *S. intercalatum* can lead to intestinal and/or liver disease. At 700 million infected individuals, schistosomiasis is the second most prevalent tropical disease (171).

Chronic, heavy infection with *S. mansoni* can lead to pipe-stem fibrosis, a characteristic pipe-shaped fibrosis around the hepatic portal veins, associated with large numbers of schistosome eggs in the hepatic tissues and can lead to portal hypertension. Studies are mixed on whether schistosomiasis worsens clinical outcomes with hepatitis C infection. Intestinal schistosomal disease usually presents with chronic or intermittent abdominal pain, anorexia and diarrhea. Urinary schistosomiasis may cause hematuria (microscopic or macroscopic), dysuria and urinary frequency. Chronic infection may result in fibrosis and calcification of the bladder and ureters, with ensuing hydroureter and hydronephrosis. Schistosomal nephropathy eventually leads to end-stage renal failure. Mahmoud et al. showed treated *Schistosoma* infection had no significant impact on patient or graft outcomes but they did have a higher incidence of acute and chronic cyclosporine nephrotoxicity, a higher rates of urinary tract infection and urological complications, with no evidence of schistosomal re-infection (172). It is not clear whether the SOT and accompanying immunosuppression alter the clinical course of schistosomiasis. Recurrence of schistosomiasis after liver transplant is rare but several cases have been reported, possibly resulting from reactivation of previous infection as a consequence of immunosuppressive therapy (173,174).

While schistosomes can be transmitted by organ transplant, adult schistosomes do not replicate within the host so only transmission of nonreplicating adult worms occurs. Acute schistosomiasis is often asymptomatic. Chronic schistosomiasis is seen in up to 60% of infected individuals, yet extensive liver disease is only seen in 4–8% of cases (171). Hence both donors and recipients may be unaware of background infection. Adult worms tend to die after 3–5 years.

There are several case-reports describing the successful use of *Schistosoma*-infected donors in SOT (172–177). It is not clear whether transplant recipients with donor-derived infections are at risk for the systemic hypersensitivity reaction associated with primary infection (Katayama fever). Immunosuppression may mask these symptoms, or they may be confused with other clinical entities such as acute graft rejection.

Diagnosis

Schistosomiasis may be diagnosed by tissue biopsy, serology (of serum or CSF), or examination of stool or urine for ova and parasites. Many serologic assays are based primarily on *S. mansoni* antigens and may cross-react with other species. Antibody levels do not correlate with intensity of infection and should not be monitored for response to therapy. Seroconversion may not occur for several months after primary infection and may be delayed in organ transplant recipients.

Treatment

Praziquantel is the usual treatment for schistosomiasis. Oxamniquine and the anti-malarial artemether may be available outside the United States. Case reports of several transplant patients who were treated with praziquantel with good outcomes have been published (173,174) *S. japonicum* and *S. mekongi* require higher doses (Table 1). Altered efficacy or toxicity with treatment has not been well-studied or documented in transplant recipients. Cyclosporine may decrease the metabolism of praziquantel, resulting in higher drug levels and great potential for toxicity; potential interactions with other immunosuppressive agents have not been noted. Cyclosporine has been shown *in vitro* and in animals to have anti-schistosomal properties, especially with *S. mansoni*; similar effects with other immunosuppressive agents have not been reported, and this effect has never been confirmed in humans.

Prevention

Primary schistosomiasis infection can be prevented by avoiding contact with fresh water in endemic regions. Donor-derived and relapsing infections could be prevented by screening donors and recipients from endemic regions, and treating those with positive results.

Recommendations (iii)
Pretransplant screening:

- Consider screening and treatment of living organ donors and potential recipients with epidemiological risk factor for schistosomiasis.

Diagnosis:

- Direct visual microscopy of stool or urine for eggs is an important testing method but can be falsely negative in light infection.

- Serological testing has enhanced sensitivity but can be falsely negative early postinfection and cannot distinguish past and prior infection.

Treatment:

- Praziquantel is the drug of choice, dosing varies some by species.

Prevention:

- Organ transplant recipients should avoid contact with freshwater in areas of endemicity.

Cestodes

Echinococcosis (hydatid-alveolar cyst disease)
Epidemiology and risk factors: Echinococcosis is caused by the ingestion of eggs of either the cestode *Echinococcus granulosus* or *E. multilocularis. Echinococcus granulosus* is a parasite of domestic dogs that causes hydatid or unilocular cyst disease, while *E. multilocularis* is a parasite of wild canines that causes alveolar cyst disease. Humans are intermediate hosts. Hydatid cysts are usually asymptomatic. Symptoms can occur, however, from the mass effect of the enlarging cyst or from the leakage, rupture, or bacterial superinfection of the cyst. Liver failure can result from hydatid cyst growth or from treatment-related complications. Liver transplantation has been performed in terminal liver failure related to hydatid disease, and, although the patients did not receive antiparasitic drugs or intracystic scolicidal agents, no recurrences or deaths related to hydatid disease were reported (178,179). One report in a heart transplant recipient noted the growth rate of the hydadid liver cysts was not enhanced by immunosuppression suggesting that the detection of hydatid cysts in a candidate is not necessarily a contraindication to transplantation (180).

In *E. multilocularis* infection, larvae proliferate making alveolar cysts grow indefinitely and mimic a slow-growing cancer that requires wide surgical resections. Alveolar echinococcosis is similar to hepatobiliary cancer in its clinical behavior. It is lethal in approximately 10 years from diagnosis unless it is promptly identified and radically excised by surgery (181). Liver transplantation should be considered early on for patients with hilar involvement, recurrent biliary infections, secondary biliary cirrhosis and ascites, variceal bleeding caused by portal hypertension and for those with lesions that are invading the hepatic veins and the inferior vena cava. Avoidance of multiple abdominal surgeries favors better results after liver transplantation. Because the disease may spread to the lung and to the brain, patients should be evaluated for extrahepatic involvement before transplantation. Only central nervous system involvement should be considered as an exclusion criteria for transplantation (182). In the 45 cases reported by

a collaborative study from 16 European transplant centers the main indications for transplant were biliary disease related to parasitic involvement of the hilum and a huge parasitic lesion (182). Survival without recurrence was 77% at 1 year and 45% at 10 years. In a series of five liver transplant recipients in China with alveolar echinococcosis of the liver, major technical difficulties were noted, but liver transplantation for otherwise incurable disease was felt to be feasible (183). Best results were achieved if transplantation was performed before blood vessel involvement occurred (184). Immunosuppression can enhance the parasitic growth and the risk of recurrence; therefore, immunosuppression should be reduced to a minimum as early as possible.

Diagnosis
E. granulosus infection (hydatid disease) is often an incidental finding on routine imaging. Radiographic studies such as X-ray, CT scan, ultrasonography and MRI often reveal characteristic cystic lesions. These findings together with a positive epidemiological exposure lead to presumptive diagnosis. Serology may be used to help confirm diagnosis. Available serologic tests have a sensitivity of 60–95%. *E. multilocularis* infection needs to be differentiated from hepatic malignancy. Liver biopsy is considered the gold standard for diagnosis. However, its use is limited due to the high risk of spreading infection. Diagnosis is therefore best achieved by imaging and antibody detection using recombinant antigens. These diagnostic tests are not widely available at all medical facilities. ELISA to measure anti-*E. granulosus* immunoglobulin G titers is considered useful for predicting recurrence (185).

Treatment
The presence of hydatid disease in a potential organ recipient should be recognized and treated with the surgical removal of the cysts and albendazole therapy before transplantation (186). Presurgical administration of albendazole for 7–10 days may reduce the risk of secondary seeding in the event of any cyst contents spillage at the time of surgery. In the event of intra-operative spillage, many experts would prescribe a course of praziquantel as well.

Donors from endemic areas may have unrecognized hydatid cysts that are found at the time of organ procurement. In an effort to reduce the organ shortage, some have suggested that livers with hydatid cysts be used for transplantation provided that the cyst is single and calcified (187), that it does not communicate with the biliary tree, and that a closed resection of the cyst is feasible without damaging the main vascular and biliary structures (188). Treatment with albendazole is recommended for a minimum of 2 years after transplantation even in cases of apparently curative surgery (182). The use of PAIR (percutaneous puncture, aspiration, injection and re-aspiration) technique can be used to obliterate a cyst before full surgical removal.

Although radical surgical excision is necessary for the treatment of *E. multilocularis* infection, recent reports provide evidence that long-term treatment with benzimidazole may slow the progression of the disease (181).

Prevention

Primary prevention involves avoiding contact with dog fecal material that may be contaminated with echinococcal eggs. Dogs involved in the care of sheep, or dogs fed sheep offal, are at greatest risk to be infected with *E. granulosus*. Good hand hygiene after sheep dog grooming reduces the risk of exposure. Because wild animals are the definitive hosts for *E. multilocularis* direct contact and acquisition of disease is rare.

Recommendations (iii)
Pretransplant screening:

- Not routinely recommended in asymptomatic patients.

Diagnosis:

- Preliminary diagnosis is often made by identifying the characteristic appearance of echinococcal cyst(s) on radiographic imaging and can be confirmed with serological testing.
- Serum echinococcal antibody sensitivity varies (60–95%), hence is not definitive for screening donors and evaluating suspicious cysts in livers of potential donors.
- Definite diagnosis can be made through microscopic evaluation of aspirated cyst contents or removed cyst wall.

Treatment:

- Before transplantation in a potential recipient, complete surgical resection of echinococcal cyst, followed by a prolonged course of albendazole is preferred.
- Preprocedure albendazole may reduce the risk of secondary seeding in the event of any cyst contents spillage at the time of surgery or PAIR.

Prevention:

- Avoiding infected sheep dog fecal matter minimizes the risk of acquiring echinococcus.
- Prolonged treatment after surgery or percutaneous treatment is commonly used in SOT recipients due to a concern of higher risk of relapse.

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