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Parasitic Infections in Solid Organ Transplant Recipients

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Introduction

In spite of the high prevalence of human parasitic diseases that affect billions of people throughout the world, only 5% of over 340 known parasitic infections have been reported in transplant recipients (1). Although the number of published papers has increased in recent years, reflecting an increased number of cases, parasitic infections remain the most understudied of all infections related to organ transplantation with only very few prospective trials and no randomized studies that can be accounted for in this field. Recommendations are based primarily on expert opinion (Grade III) unless otherwise stated.

Common Features of Parasitic Infection in the Transplant Recipient

Parasitic diseases may affect transplant recipients as a result of

(1) Recrudescence of latent infections in the previously infected recipient.
(2) '*De novo*' infection by means of
    (i) Natural infection.
    (ii) Transmission by transplanted organ (or blood product, either before or after transplantation) into a naïve recipient.

For the most part, only those organisms that can complete their life cycle within the human host result in more severe infections in an immunocompromised host. Co-infection is a common feature of parasitic infection in transplantation, and invasive disease may be associated with viral infection (particularly cytomegalovirus) or with disseminated bacterial infection.

The incidence of parasitic infection is expected to grow in solid organ transplant recipients due to multiple factors:

(1) Many geographic areas where parasitic infections are highly prevalent have now active organ transplant programs.
(2) Donors and recipients from endemic areas, with latent or asymptomatic infections, are sometimes referred to transplant centers in Western countries.
(3) Some patients from developed countries undergo transplantation in highly endemic areas (transplant tourism) and return home with either donor derived or naturally acquired infection(s).
(4) 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.
(5) With the recent increase in leisure tourism, transplant recipients travel to endemic areas and enhance their risk of exposure.
(6) The decrease in cyclosporine-based immunosuppressive regimens and the increased use of newer drugs that lack the anti-parasitic effects of cyclosporine metabolites may result in higher rates of parasitic infection.

Protozoa-Nonintestinal

Toxoplasmosis

Epidemiology and risk factors: *Toxoplasma gondii* infection in transplant recipients can be caused by primary infection transmitted by an allograft or by reactivation of latent infection. Symptomatic toxoplasmosis has been well described after solid organ transplantation; cardiac transplant recipients who are seronegative for toxoplasmosis and receive an organ from a seropositive donor have a 50–75% risk of symptomatic infection without prophylaxis, usually within 3 months after transplantation. Latent infection in the myocardium during cardiac transplantation is the most common method of donor transmission, although it has been transmitted through transplantation of other organs. Infection is worldwide but 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* (2,3). Toxoplamosis is a zoonotic illness; 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 solid organ transplantation (4). Water-borne transmission of *T. gondii* has been considered uncommon; a large human outbreak linked to contamination of a municipal water reservoir in Canada by wild felids and the widespread infection by marine mammals in the United States suggest this may be another method of transmission (5). In a recent review of 52 noncardiac SOT-related cases of toxoplasmosis, 86% of patients developed disease within 90 days of transplantation; of these patients, 42% had primary infection, 21% had reactivation or reinfection and 37% had mechanisms that could not be determined (6).

Pretransplant screening for prior toxoplasmosis exposure is generally done before heart transplant, and is less frequently done before other organ transplants. To determine whether donors and recipients for all solid organ transplants should have toxoplasmosis serology, a retrospective cohort study of 1,006 solid organ transplant recipients at a single center was performed to examine the incidence of *Toxoplasma* seroconversion, reactivation, and clinical toxoplasmosis and to evaluate the impact of trimethoprim-sulfamethoxazole (TMP/SMX) prophylaxis (7). Pretransplant *Toxoplasma* seroprevalence was 13% in donors and 18% in recipients, and the incidence of *Toxoplasma* donor–recipient mismatch was 10% during the 14-year study period, 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. This data suggests that in transplant centers with low *Toxoplasma* seroprevalence, routine screening in solid organ donors and recipients might not be necessary, particularly in the era of routine TMP/SMX prophylaxis. In areas of high seroprevalance, routine screening may be indicated.

Diagnosis: Transplant patients with active toxoplasmosis may present with brain abscess, chorioretinitis, pneumonitis or disseminated disease. Definitive diagnosis requires the identification of tachyzoites in biopsy samples or clear seroconversion. Transplant recipients may have a muted serologic response, thus negative serologic results should be viewed cautiously.

The presence of multiple ring-enhancing lesions in the basal ganglia or cerebrum on neuro-imaging, especially in the presence of anti-*Toxoplasma* IgG antibodies, is suggestive of CNS toxoplasmosis and is sufficient to start presumptive treatment for CNS toxoplasmosis. 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 (8). Brain biopsy should be considered in non-responding patients, as the radiographic differences with other infections or malignancies are not sufficiently specific nor sensitive. Cerebrospinal fluid (CSF) may have mild mononuclear pleocytosis and elevated protein hyperproteinorrachia. Identification of anti-*T. gondii* antibodies by enzyme-linked immunosorbent assay (ELISA) in the CSF is a sensitive and specific method. *Toxoplasma* can be detected in CSF by DNA amplification in most AIDS patients with CNS infection; tachyzoites can sometimes be seen on centrifuged CSF samples after Giemsa staining.

Myocarditis may present with heart failure; the diagnosis is made by seeing tachyzoites on myocardial biopsy. Chorioretinitis (a posterior uveitis) usually present with eye pain and decreased visual acuity, and appears as raised yellow-white, cottony lesions in a nonvascular distribution (unlike the perivascular exudates of CMV retinitis). Vitreal inflammation may be present and a significant percent may have concurrent CNS lesions. Pulmonary disease often presents with fever, dyspnea and nonproductive cough, with radiographic reticulonodular infiltrates and an overall clinical picture that may be indistinguishable from *Pneumocystis jiroveci* pneumonia; *Toxoplasma* tachyzoites can be identified in bronchoalveolar lavage (BAL) fluid. Although rare, cutaneous toxoplasmosis has been seen after hematopoietic stem cell transplantation; it may be difficult to diagnose because of the morphologic similarity of *T. gondii* to other organisms, such as *Leishmania* and *Histoplasma* species.

Treatment: Optimal treatment after solid organ transplantation has not been well-studied. In general, the literature in AIDS is much more robust. The drugs routinely employed in the treatment of toxoplasmosis treat the proliferative form (tachyzoites) found during the acute phase of infection but do not eradicate the encysted form (bradyzoites) of the parasite. Treatment for active toxoplasmosis generally includes a prolonged course (4–6 weeks or longer) of pyrimethamine and sulfadiazine with folinic acid (to prevent hematologic toxicity from pyrimethamine), followed by suppressive therapy with TMP-SMX. In sulfa allergic recipients, pyrimethamine and folinic acid can be used with high doses of one of the following: clindamycin, clarithromycin or azithromycin, or atovaquone (Table 1), followed by secondary prophylaxis with one of the agents listed further (9).

Prevention/Prophylaxis: The routine use of TMP/SMX for post-SOT prophylaxis has decreased the risk of toxoplasmosis (10,11) and is currently the most common prophylaxis against toxoplasmosis. Pyrimethamine with sulfadiazine is effective and has been used for high-risk cardiac recipients; this combination does not seem to be essential based on clinical data and experience. Numerous studies suggest that primary prophylaxis with TMP/SMX is sufficient, although the optimal dose of TMP/SMX remains

Table 1: Therapy for common parasites

Organism	Primary treatment	Secondary treatment
Extraintestinal protozoa		
Babesia	Atovaquone 750 mg po bid and azithromycin 600 mg/day (if able to take oral medications) × 7–10 days	Clindamycin 600 mg po tid or 1.2 g IV q12 hours and quinine 650 mg po tid (or quinidine IV) × 7–10 days
Leishmania-New World	Sodium stibogluconate* (USA) or meglumine antimonite (Europe, Latin-America) at 20 mg/(kg day) divided 2× day 28 days or amphoB 1 mg/kg every other day for 20 doses or liposomal amphoB 3 mg/(kg day) for 6 days for cutaneous or 3 weeks for mucocutaneous	Miltefosine 2.5 mg/(kg day) for 28 days
Leishmania-Old World	Sodium stibogluconate or meglumine antimonite at 20 mg/kg/day divided 2× day for 10 days	Fluconazole 200 mg po q day for 6 weeks (*L. major*)
T. gondii	(CNS disease) pyrimethamine 200 mg po ×1 then 75 mg po a day with sulfadiazine 1–1.5 gram po q6 with folinic acid 10–20 mg a day for 4–6 weeks then suppressive therapy or TMP/SMX 10/50 mg/kg per day po or IV divided q12 × 30 days then suppressive therapy	Pyrimethamine with folinic acid and clindamycin or clarithromycin or azithromycin or atovaquone for 4–6 weeks then suppressive therapy
T. cruzi	Nifurtimox* 8–10 mg/(kg day) divided 4× day for 120 days or benznidazole* 5–7 mg/(kg day) divided 2× day for 30–90 days	
Intestinal protozoa		
Blastocystis hominis	Nitazoxanide 500 mg po bid for 3 days	Metronidazole 1.5 grams × 1 daily for 10 days, iodoquinol 650 mg pot id × 20 days, or TMP/SMX DS bid × 7 days
Cryptosporidium	Nitazoxanide 500 mg po bid × 14 days (same as for HIV+)	Paromomycin or azithromycin; consider combination therapy
Cyclospora	TMP/SMX DS qid × 10 days then tiw	Cipro 500 mg po bid × 7 days then tiw × 2 weeks
E. histolytica	Metronidazole 750 mg po tid × 10 days or tinidazole 2 gram a day × 3 days against the active trophozoite stage, followed by paromomycin 500 mg pot id × 7 days or iodoquinol 650 mg pot id × 20 days to eliminate cysts.	
Giardia	Tinidazole 2 gram × 1, nitazoxanide 500 mg po bid × 3 days	Metronidazole 500–750 mg pot id × 5 days; paromomycin 500 mg po qid × 7 days; if refractory disease, metronidazole 750 mg tid plus quinacrine 100 mg tid both for 3 weeks
I. belli	TMP/SMX DS bid × 10 days (normal host) to qid × 10 days then bid × 3 weeks (same as for HIV+)	Cipro 500 mg po bid × 7 days or pyrimethamine 75 mg po a day with folinic acid 10 mg a day for 14 days
Microsporidia	Albendazole 400mg po bid × 3 weeks or fumagillin 200 mg po tid	
Intestinal nematode		
Strongyloides	Ivermectin 200 microgram/(kg day) × 2 days (3 mg tablets) (longer for hyperinfection)	Albendazole 400 mg po bid × 2 days (longer for hyperinfection)
Trematodes		
Schistosoma	Praziquantel 20 mg po bid × 1 day (tid if *S. japonicum* or *mekongi*)	Oxamniquine (*S. mansoni*)
Cestodes		
Echinococcus	Albendazole plus surgery	

Therapy for Common Parasites: 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).

unclear. Baren *et al* reviewed the collective 28-year experience at two urban transplant programs with 596 heart transplant recipients, and found no cases of toxoplasmosis, but all patients received trimethoprim-sulfamethoxazole to prevent *Pneumocystis* pneumonia; they concluded that additional specific anti-toxoplasmosis prophylaxis is unnecessary in heart transplant recipients (12). Baden et al. reviewed 417 heart transplant recipients on 160 mg of TMP/800 mg of SMX three times a week and found one case (0.2%) of toxoplasmosis in the setting of D+R– while

undergoing treatment of acute rejection (10). Muñoz et al. reviewed 315 heart transplant recipients on 160 mg of TMP/800 mg of SMX three times a week, 10% of whom were D+R– and approximately half of whom were given 6 weeks of pyrimethamine, and found no toxoplasmosis in an endemic region (11). Keough et al. reviewed 126 heart transplant recipients on TMP/SMX and found that no toxoplasmosis occurred during prophylaxis, but did occur after prophylaxis was stopped (13).

First line prophylaxis should be TMP–SMX dosed at either a double strength tablet (160 mg of TMP/800 mg of SMX) three times a week or a single strength tablet (80 mg of TMP/400 mg of SMX) a day (Grade II-2). More studies have been done with the three times a week dose, although daily dosing may be sufficient. If D+/R– mismatch is present, a double strength tablet (160 mg of TMP/800 mg of SMX) may be given daily, although previously mentioned data suggest that the preceding doses are adequate. TMP–SMX should be dosed based on renal function. Second line prophylaxis should include either atovaquone or dapsone with pyrimethamine and folinic acid; the choice should be made based on tolerance of regimen, cost and availability. Atovaquone may be costly and unpalatable to some recipients, while dapsone can cause anemia in those with G6PD deficiency and pyrimethamine can cause hematologic toxicity. The optimal duration of prophylaxis is not clear; infection has been seen after cessation of prophylaxis. To avoid primary infection, transplant recipients should avoid contact with undercooked meat, soil, water or animal feces that might contain toxoplasmosis cysts.

Recommendations

(1) All pre-heart transplant recipients and donors should be serotested for *Toxoplasma* (Grade II). It is not clear that other organ transplant recipients and donors need to be tested (7).
(2) After heart transplant, prophylaxis should be given, as outlined earlier. Disease has been seen after cessation of prophylaxis, the optimal duration of prophylaxis has not been determined, and it is given for life at many transplant centers (Grade III).
(3) Acute toxoplasmosis can have protean manifestations and should be included in the differential diagnosis of infectious syndromes after organ transplant.
(4) Treatment of acute toxoplasmosis is not well-studied in solid organ transplant recipients; much of our knowledge comes from the treatment of HIV+ patients.

Chagas disease (American Trypanosomiasis)

Epidemiology and risk factors: This zoonotic disease is caused by a flagellate protozoan parasite, *Trypanosoma cruzi.* It is transmitted to humans in up to 80% of cases by the contaminated feces of a triatomine insect vector that serves as the parasite intermediate host (14). The disease has been transmitted to humans also by unscreened blood transfusion (5–20%), from infected mother to fetus (0.5–8%) (14), by laboratory accidents, by organ transplantation and rarely by the oral route. It is endemic in most Latin-American countries where it affects 16–18 million people and about 100 million are believed to be at risk (15). Due to recent immigration it is estimated that more than 100,000 infected people are living in United States of America (16).

Human disease has two distinct phases: the acute phase and the chronic infection. 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 (14). 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%) (15). Transplant recipients with chronic *T. cruzi* infection are at risk of reactivation. Heart transplant recipients differ from other solid organ transplant patients and will be considered separately. Chagas disease can also be transmitted from infected donors to naive recipients.

Heart transplantation: Chagasic cardiomyopathy is the third leading cause for heart transplantation in Brazil (21.9% of all heart transplants) (17). Posttransplant outcome does not differ significantly from heart transplant for other causes (17,18). Reactivation after transplantation has been reported to occur in 26.5% (17) to 42.9% (19) of recipients and has been linked by some authors, in multivariate analysis, to rejection treatment, to MMF use and the development of neoplasms (17). Others have not found the same associations (19). Reactivation can occur early after transplant; relapses after treatment have also been described. Clinical manifestations range from asymptomatic parasitemia, fevers, sub-cutaneous involvement to more frequently myocarditis that needs to be differentiated from rejection. Skin manifestations include a rash that may look more like a panniculitis rather than a macular drug rash or may appear to look like erythema nodosum; a skin biopsy may be positive for trypanosomes. Early diagnosis, careful monitoring and good response to treatment allow for an adequate survival (19). Prophylactic treatment early after transplantation was of no benefit in a small cohort of patients and did not prevent reactivation (17).

Noncardiac solid organ transplantation: Most of the experience outside of heart transplantation is related to kidney transplantation (20). Reports are very few for other organ transplants. Reactivation has been described mainly within the first posttransplant year. It can reach an incidence of 15–35% with a good response to treatment and good graft and patient survival in long-term follow-up. The most frequent reactivation feature is asymptomatic parasitemia, followed by panniculitis or other manifestations of

sub-cutaneous involvement; myocarditis and encephalitis have also been reported.

Donors with* T. cruzi *infection: Two reports of transmission of acute Chagas infection by organ transplantation from unscreened deceased donors have been published in the United States (21,22). In countries where the disease is endemic, with informed consent, the transplant teams would accept organs from infected donors provided no better donor is available in a reasonable time span, or the patient has been on the waiting list for a long period of time and is deteriorating rapidly. Transmission by infected donors to negative recipients was reported in 1993 in kidney transplant recipients who were prospectively evaluated (23,24). Transmission from positive donors was detected by systematic search for parasitemia in 19% of seronegative recipients in the first 6 months after transplantation and were cured with trypanocidal treatment (20). No new cases were diagnosed on long-term follow-up.

Diagnosis: Diagnosis is achieved by direct parasitological tests, including the examination of whole blood preparations and a concentration method (Strout test) in the acute phase, and with serology tests in the intermediate and chronic stages. The most commonly used are: enzyme immuno-assay (EIA), indirect hemagglutination (IHA) and indirect immunofluorescence (IFA); complement fixation test (CF: Machado Guerreiro test), has been replaced by the former in recent years. All have good sensitivity but less than optimal specificity, and show considerable variation in reproducibility and reliability of results (25). In recent years a new ELISA Test System (Ortho-Clinical Diagnostic) has been licensed by the FDA. It shows a reproducible sensitivity and specificity and no enhanced diagnostic power has been achieved when using simultaneously 'confirmatory' tests such as IFA or radioimmuno-precipitation assay (RIPA) (26). Nevertheless, at the time of writing this text the World Health Organization still recommends that at least two different methods of testing must be positive for a diagnosis of *T. cruzi* infection. Polymerase chain reaction (PCR) based assays, which are now in the final evaluation phase for standardization, have recently been used in clinical research**,** raising new diagnostic and prognostic possibilities and might provide a useful tool for rapid diagnosis.

In chagasic transplant recipients, serology has no utility in diagnosis of reactivation. Direct parasitological tests should be used when searching for reactivation. Also, all available tissue specimens should be evaluated for the presence of amastigotes. PCR-based tests may prove to be beneficial and allow for earlier diagnosis.

Treatment: Two drugs are available for treatment: nifurtimox and benznidazole (16). When either is administered for 30–60 days, parasitic cure is achieved in 60–100% of acute cases. Also, evidence supports that trypanocidal treatment modifies the outcome of indeterminate and chronic infection in 20–60% of immunocompetent patients (27). Similar data do not exist for immunocompromised patients. The adverse side effects of these drugs are significant and include dermatitis, peripheral polyneuropathy, weight loss, gastrointestinal disease, hematologic disorders and an increased incidence of lymphoma. Nifurtimox is no longer available in most Latin-American countries, and it is only available through Bayer in Germany and through the Centers for Disease Control and Prevention (CDC) in the United States. Benznidazole is available in Latin-America but not in the United States except from the CDC, nor in Europe.

Recommendations (Grade III)
Acceptability criteria

(1) Patients with chagasic myocardiopathy are eligible for heart transplant.
(2) Patients with chagasic infection (indeterminate phase) and those with early chronic disease (grade 0–1 Kushnir myocardiopathy) are eligible to receive solid organ transplants.
(3) Patients with Chagas disease and grade $\geq$ 2 Kushnir myocardiopathy should be excluded for nonheart solid organ transplant.

Pretransplant evaluation

(1) All transplant candidates who have lived or traveled extensively in endemic regions, or who were born to mothers from endemic regions or who have received unscreened blood or blood product transfusions should be sero-tested for *T. cruzi* infection. Caution is needed in the interpretation of negative results in patients with high epidemiological risk that have been treated with immunosuppressive drugs.
(2) Active parasitemia should be evaluated in all infected candidates.
(3) Evaluation for other latent endemic pathogens should be considered.

Pretransplant treatment: There is no prospective randomized evidence to support that pretransplant trypanocidal treatment is useful to inhibit or to avoid posttransplant reactivation. Hence, no recommendation based on evidence can be made at this time. The risk of toxicity from trypanocidal drugs, especially in patients with end stage renal disease and liver insufficiency, largely outweighs its potential benefits (28). Hence, trypanocidal treatment should generally be reserved only for those transplant candidates with proven *T. cruzi* parasitemia at the time of evaluation.

Posttransplant follow-up

(1) A diagnosis of reactivation should always be considered with unexplained febrile illness, skin involvement, myocarditis or encephalitis.

(2) Patients should be systematically monitored for asymptomatic parasitemia (i.e. asymptomatic reactivation) for the first posttransplant year and every time immunosuppression regimen is intensified (i.e. after anti-rejection treatment) to allow for early treatment. A possible schedule would include: once every 1–2 weeks for the first 100 days and monthly thereafter.
(3) Biopsies should be performed on all skin/subcutaneous lesions and evaluated for amastigotes.
(4) All endomyocardial biopsies, protocol or otherwise, should be evaluated for amastigotes.
(5) Reactivation should be treated for 30–60 days with nifurtimox or benznidazole.
(6) Serotesting of donors should be performed routinely in regions that have indigenous disease.
(7) Serotesting of donors should be carefully considered in those areas that have a significant immigrant population.
(8) Infected donors are unacceptable for heart transplantation. The allocation of other organs from infected donors, with appropriate informed consent, could be acceptable for
    (i) infected recipients;
    (ii) uninfected kidney recipients;
    (iii) possible use in uninfected lung and liver recipients in emergency situations;
    (iv) these patients need to be monitored for disease transmission and promptly treated if transmission occurs.

Leishmaniasis

Epidemiology and risk factors: Leishmaniasis is caused by a heterogeneous group of protozoan parasites, belonging to the genus *Leishmania* and causes a variety of different clinical syndromes. It is estimated that 350 million people are at risk of acquiring the infection and that 12 million may be infected (29). 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 (30). 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 geographically into New World and Old World disease; clinical syndromes can be divided into visceral, cutaneous, or muco-cutaneous leishmaniasis and finally, separation into subgenus, complexes and species can be based upon taxonomy (29,31).

The infection is acquired through the bite of an infected female sandfly. Each species of *Leishmania* tends to be associated with a single sandfly vector, a major animal reservoir and a major clinical syndrome. Nonetheless, considerable overlap exists (29). In visceral leishmaniasis, liver, spleen and lymph node enlargement are a consequence of the infection of a large number of monocytes in these organs as also bone marrow failure (31). Cutaneous leishmaniasis is the result of parasitization of macrophages in the skin, followed by a necrotizing granulomatous response with lesions healing spontaneously after a variable period of time (usually months**)** (32). A small subset of patients infected with *L. (V.) braziliensis* or, very rarely, by other *Leishmania* species, may develop mucosal disease after months or years.

The final outcome of *Leishmania* infection is the result of the balance between different immune responses. Cell mediated immune mechanisms are ultimately responsible for controlling the infection. Patients with progressive visceral leishmaniasis usually lack a *Leishmania*-specific immune response (33) in spite of high levels of nonprotective antileishmanial antibodies; patients who resolve the infection have been able to mount a Th1-type response. Derangement of cellular immune mechanisms is a risk factor for the occurrence of symptomatic and severe infections and for increased mortality (31). Infections caused by *Leishmania* species have been increasingly reported in transplant recipients since the first case was described in 1979 (34). The clinical picture may simulate other infections, and only a high index of suspicion will lead to the diagnosis. Cutaneous and mucocutaneous presentations are rare and have a protracted time interval between transplantation and disease manifestations (34). Some have occurred in geographical areas where mucosal disease-producing *Leishmania* species are quite infrequent (35–37). Visceral leishmaniasis has been described predominantly in kidney transplant recipients (38–65) but has also been seen in kidney–pancreas (66), liver (55, 67), lung (68) and heart (55,69) transplant recipients. Visceral leishmaniasis should always be considered in the differential diagnosis of patients with fever who live, have lived in and who have traveled extensively to endemic areas, even in the remote past. Visceral leishmaniasis has occurred as early as 3 months (38,57) and as late as 13 years (58) after transplantation. Reactivation of an old infection, possibly induced by immunosuppressive therapy, is the most frequent mechanism involved in the posttransplant disease. The main clinical manifestations are fever, spleen enlargement and pancytopenia (50). The presenting symptoms are often atypical because anemia and leukopenia may be absent and splenomegaly may develop late in the course of an unnoticed infection (39). Patients may present with fever without other signs; malabsorption caused by infiltration of the gastrointestinal tract can occur and presentation with interstitial pneumonitis, fever and pancytopenia has been reported in a splenectomized kidney transplant recipient (41). The diagnosis can be elusive, and the examination of multiple samples may be needed before a diagnosis can be made (50). The mortality rate in transplant recipients can reach 30%: Bacterial superinfections are the immediate cause of death in reported fatalities. Also relapses and recurrence episodes occur in approximately 30%. Repeated measurement of the spleen has been proposed as both a marker of cure and a predictor of recurrence (50). Post-kala azar cutaneous disease may occur in a subset of

patients after treatment of visceral leishmaniasis and has been reported in two transplant recipients (55,70).

Diagnosis: The diagnosis is made by the confirmation of amastigotes in tissue specimens or by the isolation of promastigotes in cultures. Amastigotes in biopsy specimens and aspirates or touch preparations can be observed with the Wright–Giemsa stain (32). The diagnostic yield of skin lesion aspirates, bone marrow aspirates, or aspirates of spleen specimen depends on the parasite species and the culture media. In transplant recipients, the diagnosis is usually made by examination and culture of bone marrow aspirate. In nontransplanted patients, the method's sensitivity approaches 60–80%, but this seems to be higher (approximately 90%) in transplant recipients (50). Repeated sampling may be needed to reach a diagnosis. Liver biopsy; lymph node aspiration or biopsy; and, occasionally, samples from the gastrointestinal tract, lung, or pleura may also lead to diagnosis. When cutaneous and mucosal leishmaniasis are suspected a small wedge or punch biopsy specimen for histopathological examination and culture should be obtained. Touch preparations have a superior diagnostic yield (29). 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 in a limited number of patients: They allow for measurement of blood parasitic load, and could be used as surrogate markers of disease activity and response to treatment (34). Anti-*Leishmania* antibodies have been positive in 92% of transplant recipients with visceral leishmaniasis (34), hence, serology could be used as a first diagnostic approach whenever the disease is suspected. The methods available for antibody detection include the indirect fluorescent antibody test, the ELISA, and a direct agglutination test. Serologic testing cannot differentiate between past or present infections, so results must be carefully interpreted in light of the history and clinical manifestations. ELISA using a recombinant protein antigen (K39) may show a greater specificity (32). Cross reactions with *T. cruzi* can be seen.

Treatment and prevention: Standard treatments for leishmanial infections have been the pentavalent antimony (SbV)–containing drugs, sodium stibogluconate, and meglumine antimonite, at 20 mg SbV per kg body weight for 20–28 days. The common side effects are myalgias, arthralgias, fatigue, malaise, abdominal pain and nephrotoxicity. Serious toxicities are infrequent; they include pancreatitis and cardiac rhythm disturbances (29). Antimonial compounds have an effect on the cytochrome P-450 pathway, so metabolic interactions might lead to high levels of immunosuppressive drugs and close monitoring is necessary to avoid toxicity (44). Most transplant recipients initially treated with pentavalent antimonials have had elevated amylase and lipase levels, with clinical pancreatitis occurring in roughly 25% (51). Liposomal amphotericin B is the only drug licensed for the treatment of visceral leishmaniasis in the United States (71) and is considered the standard of care in Europe. The recommended dose for immunocompromised patients is 4 mg/(kg day) on days 1 to 5, 10, 17, 24, 31 and 38 (32). Miltefosine has efficacy against some *Leishmania* species and is available from the CDC. It's use has not been reported in transplant patients. Due to increased resistance to pentavalent antimony-containing drugs there are recent data on new apparently successful treatment strategies using a sequential combination of liposomal amphotericin and oral miltefosine (72). Liposomal amphotericin B has been used as the first-line treatment in a small number of kidney transplant recipients (total dose administered was 20–40 mg/kg) with optimal results and no significant toxicity or relapes (51). However, toxicity requiring discontinuation has also been reported (69). Other therapeutic alternatives include pentamidine (4 mg/kg every other day for 15 doses), conventional amphotericin B deoxycholate, other lipid-associated amphotericin B compounds, allopurinol in combination with ketoconazole (42, 52) or pentavalent antimonials. Immunosuppression was temporarily reduced during the initial phase of treatment in the reported cases. A successful outcome can be obtained while preserving graft function in kidney transplant recipients.

Recommendations (Grade III)

(1) Serologic studies before transplantation on both donors and recipients with a history of potential exposure to *Leishmania* should be considered, although no specific study on prevention strategy in transplantation candidates has been conducted.
(2) Reducing immunosuppression in the early stages of treatment might be advisable.
(3) Secondary prophylaxis has been suggested as an option to avoid recurrence of the disease but data are inconclusive or lacking thus there is no scientific ground to recommend it at the present time.

Malaria

Epidemiology and risk factors: Malaria is the world's most prevalent parasitic disease and 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 are responsible for some cases in endemic areas and occasionally in countries with large immigrant populations (73). 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, which may pose a problem at the time of blood or organ donation.

Few cases of malaria have been described in transplant recipients. Transmission via the graft seems to be the main mode of acquisition of the disease (74), although some cases have been traced to blood or blood products transfused to the recipient, even well before transplantation (75). In developed countries, the disease is seldom seen but it should be considered when caring for SOT patients with unexplained febrile illness who have resided in or visited endemic areas or who have received an organ from a donor from such areas. The four different main species that infect humans, *Plasmodium ovale, Plasmodium vivax, Plasmodium malariae* and *Plasmodium falciparum,* have all been diagnosed in SOT recipients. Clinical manifestations have occurred in the early posttransplant period and have been described in kidney, liver and heart recipients (74–76). Fever has been reported as the most frequent presenting symptom, albeit not always with the typical paroxysmal or cyclic pattern (77,78).

Diagnosis: Malaria is classically diagnosed by thick and thin blood smears. Rapid diagnostic tests detect specific plasmodia antigens (79,80). Alternative diagnostic techniques that are recommended in some circumstances to screen blood donors, and thus may also be helpful for SOT include DNA hybridization, and PCR for DNA and mRNA amplification. Serology could be of use when investigating the risk from a potential donor, although if the infection is acute, the serology might be negative but parasitemia should be evident in blood smear. 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 (81).

Treatment, prevention and prophylaxis: 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 sensiti vity patterns is essential. *P. vivax, P. malariae* and *P. ovale* should be treated with a 3-day course of chloroquine, bearing in mind that resistance to the drug has been reported from Oceania for *P. vivax*. If the transmission occurred in a chloroquine sensitive region, *P. falciparum* infection should be treated with chloroquine, otherwise, atovaquone-proguanil, an artemensenin-containing combination therapy, quinine in combination with another drug (such as doxycycline, tetracycline or clindamycin), or mefloquine should be used. Geographical distribution of resistance to anti-plasmodium drugs changes over time therefore updated international treatment guidelines need to be checked before starting therapy as well as more specific recommendations for different treatment regimens (82). Severe disease should be treated with intravenous medications such as quinine (quinidine in the United States) or artesunate. Primaquine should be used in addition to standard therapy 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 (74), 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 (83). Transmission of malaria via SOT from infected donors has been documented (74). Donors from endemic regions present a risk, even if they have been away from those areas for a long time as they may still transmit the more indolent species.

Prevention of malaria in transplant patients residing in or traveling to endemic areas is imperative. This is covered in detail in the chapter 'Travel Medicine and the Solid Organ Transplant Recipient'.

Recommendations (III)

(1) Obtain, if possible, a detailed history of geographic exposure and disease.
(2) The utility and cost-benefit ratio of blood testing at the time of organ donation are unknown. With known risk, such testing could be considered.
(3) If blood smears are positive:
    (i) Living donors: Treatment is recommended before donation in an attempt to avoid transmission.
    (ii) Deceased donors: Consider deferring harvest of the organs; or, if after transplant has occurred, treat recipient(s).
(4) If a recipient has received a "risky" organ, a systematical search for parasites in the blood smears should be conducted, even in the absence of clinical symptoms, in order to obtain an early diagnosis and to start specific treatment promptly.
(5) Solid organ transplant recipients who travel to malarious areas should be given medication for malaria prophylaxis and use mosquito avoidance behaviors, including the use of bed nets and mosquito repellants.

Babesia

Epidemiology and risk factors: *Babesia* is a zoonotic malarial-like illness that occurs in certain endemic regions. *Babesia microti* occurs primarily in the northeastern United States, with scattered reports of disease elsewhere, while *Babesia divergens* occurs in Europe. There are more than 100 species of *Babesia*, all of which have an animal reservoir, typically either rodents or cattle; transmission to human occurs via the tick vector, *Ixodes scapularis* (same vector as Lyme disease) and accidentally via transfusion of blood products. Reports of babesiosis in transplant recipients are few, and include two kidney transplant recipients and one heart transplant recipient (all transfusion-related) (84–86). Risk factors for severe babesiosis include asplenia, immunocompromised state and older age. The clinical manifestations are variable and include fever, malaise and hemolytic anemia (potentially manifesting as a posttransplant hemolytic-uremic or hemophagocytic syndromes);

severe cases can proceed to adult respiratory distress syndrome.

Diagnosis: Babesiosis can be diagnosed by a routine peripheral blood smear reviewed under a microscope or by PCR testing of blood for *Babesia* DNA. Diagnostic confusion between malaria and *Babesia* can occur, in which case the diagnosis must be made based on morphology and epidemiologic exposures. DNA testing could also help distinguish between the two diseases. Bone marrow biopsy may reveal hemophagocytosis and marrow histiocytosis. Additional tests may show hemolytic anemia, thrombocytopenia and conjugated hyperbilirubinemia.

Treatment and prevention: Babesiosis can be a life threatening infection in immunocompromised hosts and treatment should begin immediately. There are no studies of babesiosis treatment in transplant recipients. For those with high level parasitemia, or severe ill, exchange transfusion should be considered. Reduction in immunosuppressive regimen might be helpful (Grade III). Atovaquone 750 mg po bid and azithromycin 600 mg a day can be used in those able to take oral medications; alternatively, clindamycin 600 mg po tid or 1.2 g IV q12 hours and quinine 650 mg po tid (or quinidine IV) can be used. In a prospective, nonblinded, randomized trial of the two regimens in 58 normal hosts, atovaquone and azithromycin was as effective as a regimen of clindamycin and quinine and was associated with fewer adverse reactions (15% versus 72%); the most common adverse effects with atovaquone and azithromycin were diarrhea and rash (8% each), while with clindamycin and quinine the most common adverse effects were tinnitus (39%), diarrhea (33%) and decreased hearing (28%) (87). 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 duration of 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, anti-babesial treatment was required for at least 6 weeks to achieve cure, and resolution of persistent infection occurred in 11 patients after 2–10 courses of therapy and 3 subjects died, highlighting the severity of disease in this population and the need for prolonged monitoring and treatment (88).

For prevention, transplant recipients should avoid ticks bites in endemic regions. In the proper clinical context, transplant recipients who receive blood transfusions should have the diagnosis of babesiosis considered.

Recommendations (Grade III)

(1) Numerous cases of *Babesia* have been described in solid organ transplant recipients. It can be transmitted quite readily by ticks in endemic regions, as well as by blood transfusions, potentially in nonendemic regions.
(2) Optimal treatment has not been well-studied in organ transplant recipients. There are potential drug interactions with standard anti-babesial therapy and immunosuppressive agents.
(3) SOT recipients should avoid tick bites by use of DEET, protective clothing, and frequent tick checks.

Acanthamoeba

Epidemiology and risk factors: *Acanthamoeba* are protozoan parasites that have been found in dust, soil, water sources, contact lens fluid, air conditioners, sewage, and may be colonize the nose and throats of healthy individuals. A recent study of seroprevalance among adults in Texas found that more than 80% had antibodies to Acanthamoeba antigens, suggesting that exposure and undiagnosed infections are common (89). *Acanthamoeba* can cause either focal disease (usually keratitis, granulomatous amoebic encephalitis, pulmonary lesions, cutaneous lesions or sinusitis) or disseminated acanthamebiasis and is often fatal in transplant recipients. A case of granulomatous dermatitis has been described in a lung transplant recipient (90).

Diagnosis: Early biopsy of *Acanthamoeba* lesions is imperative to optimize chance of survival, based on review of cases in the literature. Cutaneous lesions may be the initial manifestation of infection and should be biopsied. A direct examination of CSF should also be performed. *Acanthamoeba* can be cultured on agar plates coated with Gram negative bacteria; after up to 2 weeks of culture, the amoeba may 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 and prevention: Optimal treatment regimens for *Acanthamoeba* 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. One case of brain disease in a liver transplant recipient was cured with 3 months of trimethoprim-sulfamethoxazole and rifampin (91). Another case of *Acanthamoeba* sinusitis with concomitant *Aspergillus* in a lung transplant recipient was successfully treated with surgical debridement and intravenous amphotericin, later changed to voriconazole and caspofungin (92). Granulomatous dermatitis was successfully treated in a lung transplant recipient with lipid formulation of amphotericin B and voriconazole, drugs that have not been previously reported to treat Acanthamoeba (90). Miltefosine, an alkylphosphocholine, has been successfully used in an immunocompromised host (93).

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.

Recommendations (Grade III)

(1) Increased awareness of this rare pathogen is warranted. Early biopsy is imperative to optimize chance of survival (Grade III). Cutaneous lesions may be the initial manifestation of infection and should be biopsied.
(2) Optimal treatment in solid organ transplant recipients is not well studied. New therapies are emerging.

Intestinal Parasites

Intestinal parasite infections are highly prevalent in developing regions. However, with the recent significant increase in travel of both humans and foodstuffs to and from endemic regions, intestinal parasites may have an increasingly significant role in transplant candidates. Parasites that are largely asymptomatic before transplantation may flourish and become clinically evident under immunosuppressive treatment. Eosinophilia, gastroenteritis and other clinical manifestations of parasite infections prior to transplant should trigger an appropriate workup.

Protozoa: Cryptosporidium/Isospora Belli/Cyclospora Family Microsporidia/Blastocystis Hominis/Giardia

Epidemiology and risk factors: *Cryptosporidium, I. belli*, *Cyclospora*, Microsporidia, *Blastocystis hominis* and *Giardia* can all cause significant gastroenteritis in transplant recipients. While the use of mycophenolate mofetil is 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, especially in endemic regions; severe cryptosporidiosis has been reported in numerous transplant recipients. Transmission is more common in the developing world, where rates of infection as high as 20% have been noted (94), and can occur from contaminated food and water, person-to-person spread, and zoonotic exposures; intestinal protozoa have also been reported as donor-derived infections with intestinal transplantation. Most reports of intestinal protozoa in transplant recipients occur in cases reports or small series from individual institutions. Biliary disease occurs in 10–15% of HIV-positive patients with cryptosporidiosis (95) and could occur in transplant recipients as well. Extra-intestinal disease is very rare and can occur in the brain or kidney (especially with Microsporidia).

Diagnosis: Specific methods for the diagnosis of protozoan infections are time-consuming, and molecular methods are increasingly being used in laboratories that have appropriate resources. Standard examination for ova and parasites may be helpful. 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*. Enzyme-linked immunosorbent assay (ELISA) of stool may help rapidly diagnose *Cryptosporidium* and *Giardia*. Direct immunofluorescence tests for Giardia and *Cryptosporidium* are 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 and prevention: *Cryptosporidium* can be treated with nitazoxanide, paromomycin, or azithromycin or potentially with combinations of these drugs. *Cyclospora* and *I. belli* are usually treated with trimethoprim/sulfamethoxazole, potentially using the higher doses as with HIV patients, or ciprofloxacin; *I. belli* can also be treated with pyrimethamine 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 recent cases series of two transplant recipients with microsporidiosis due to *Enterocytozoon bieneusi*, fumagillin was effective but resulted in drug-induced thrombocytopenia (96). *Giardia* can be treated with tinidazole, nitazoxanide, metronidazole, or paromomycin; refractory disease can be treated with metronidazole plus quinacrine.

Intestinal protozoa can be difficult to eradicate. Reduction in immunosuppressive regimen may hasten clearance of these durable pathogens (Grade III). 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 (Grade III). There are no comparison studies of various treatments in transplant recipients.

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 (Grade III). 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 (Grade III)

(1) Intestinal protozoan infections are common, especially in endemic regions.
(2) They may be hard to detect and require dedicated diagnostics.

(3) Optimal treatment is not well studied in solid organ transplant recipients.
(4) Infections may relapse and be hard to eradicate in immunocompromised hosts.
(5) Transplant recipients should avoid untreated well or lake water, and preferentially drink treated municipal water or bottled water. They should avoid inadvertent swallowing of water when swimming in such waters. Chlorination does not sterilize again *Cryptosporidium*.

Entamoeba histolytica and amebiasis

Epidemiology and risk factors: *E. histolytica* is very rarely reported in transplant recipients. Amebic colitis, liver abscess and more rare manifestations including pulmonary, cardiac or brain involvement can occur can be seen in normal hosts; it is not known if the clinical presentations are altered in transplant recipients. *E. histolytica* tends to occur in regions with limited sanitation; sexual transmission, especially among male homosexuals, is more common in industrialized countries.

Diagnosis: *E. 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 are species-specific, which can help distinguish between *E. histolytica* and *Entamoeba dispar*, which is considered nonpathogenic. Serology may be positive with extra-intestinal disease.

Treatment: Treatment of amoebiasis generally involves the use of metronidazole or tinidazole against the active trophozoite stage, followed by the use of paromomycin or iodoquinol to eliminate cysts. There is one case report of successful treatment of amebiasis with metronidazole in a liver transplant recipient (97).

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 (Grade III). Sexual transmission can occur; transplant recipients should be aware of the potential risks.

Recommendations (Grade III): Same as for Cryptosporidium/Isospora Belli/Cyclospora FAMILY Microsporidia/ Blastocystis HPominis/Giardia, aforementioned.

Intestinal nematodes

Strongyloides

Epidemiology and risk factors: *Strongyloides stercoralis* infects about 80–100 million persons worldwide (98). 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 (99). *Strongyloides stercoralis* is the only human helminth 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, reach the intestinal lumen, migrate through its mucosa, then reach the lung and finally the duodenal mucosa where they become adult parasites. 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, and a massive number of larvae from the intestinal lumen or the perianal skin autoinfect the host. As a result, a great number of adult worms are found in the intestinal lumen. This can eventually lead to lung involvement or to the disseminated form of the disease.

Clinical syndromes include acute infection; chronic infection with parasite persistence and autoinfection; hyperinfection syndrome with accelerated larvae production and migration, elevated parasite burden with evident clinical manifestations but larvae are restricted to pulmonary and gastrointestinal systems and disseminated disease with larvae spread to other organs (100). Risk factors for hyperinfection syndrome and disseminated disease have been linked to the immune status of the host and are mainly related to corticosteroid use alone or in association with other immunosuppressive agents.

In transplant recipients, the occurrence of severe stongyloidiasis belongs almost entirely either to the immunosuppression era before cyclosporine use or more recently to the cyclosporine-sparing or T-cell depleting immunosuppressive regimens (101–103). Strongyloidiasis has mainly been described in kidney transplant recipients and has been attributed in most cases to reactivation of a latent infection. More recently, a few cases of this disease have been reported in pancreas and intestine transplantation and attributed to transmission from the donated intestine (104). Strongyloidiasis can be a devastating disease in transplant recipients; the mortality rate approaches 50% in hyperinfection syndrome and 70% in disseminated infection (104). The clinical disease may present with pulmonary involvement, bacterial sepsis or bacterial meningitis with Gram negative rods from intestinal flora, and also with acute and severe abdominal disease including bloody diarrhea, adynamic ileus, intestinal obstruction and gastrointestinal hemorrhage. They are caused by the damage inflicted by the larvae that penetrate through the gut wall. This is most likely to occur in the initial months after transplantation when the immunosuppression is most intense.

Diagnosis: Eosinophilia can be found in patients with *Strongyloides* acute infection. People with chronic infection, hyperinfection syndrome, and disseminated disease may have normal eosinophil counts, as might SOT recipients on corticosteroids. Hence, a lack of eosinophilia should not be misleading (105). Definitive diagnosis is achieved by identification of larvae in clinical specimens mainly in stool and duodenal aspirate samples (106). 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, larvae density is low (less than 25/stool g) and elimination is intermittent. Hence, direct observation of stool samples (with a diagnostic sensitivity of 0–52%) can be misleading. Diagnostic sensitivity can be enhanced with different methods (106):

(1) Formalin-ether concentration method: can achieve a sensitivity of 31–55% with 3 sequential samples and 90% with seven sequential samples.
(2) Harada-Mori filter paper culture (sensitivity 13–55%)
(3) Agar plate culture technique: 78–96% sensitive.

All of the aforementioned are more laborious than direct observation and less common in regular microbiology laboratories.

- Duodenal fluid aspirate, while more sensitive than direct stool examination has only 76% sensitivity and involves an invasive procedure

Serological tests may be used for diagnosis of infection. It should be noted, however, that these methods are not available worldwide.

(1) ELISA is highly sensitive (80–95%) and specific (90%) (107). False-positive results are related to the presence of other helminthic infections; thus, local epidemiology is important when considering the positive predictive value of a positive test.
(2) GPIA (gelatin particle indirect agglutination) has 98.2% sensitivity and 100% specificity (105).
(3) The sensitivity and specificity of serologic tests in immunocompromised patients are unknown; however, small series have shown that, when a combination of methods is used in immunocompromised patients, the sensitivity approaches 90% (108,109).

Treatment and prevention

Ivermectin is now considered the treatment of choice for uncomplicated strongyloidiasis (105). A single oral dose of 200 micrograms per kg for 2 days is highly efficacious in eradicating adult parasites and larvae from the intestine in normal hosts (110,111). Some experts re-treat immunocompromised hosts with two more doses given 2 weeks later (Grade III). Adverse effects are infrequent and usually mild. The experience with ivermectin for the treatment of hyperinfection or disseminated disease in transplant recipients is still scarce and reports describing clinical failure have been published (112). With heavy parasitic burden daily doses should be used until clearance occurs; an additional two doses 2 weeks later may be considered. Albendazole (400 mg twice daily for 3 days) has a primary cure rate of 45–75% making it a reasonable alternative to ivermectin (111,113).

Thiabendazole, 25 mg/kg twice daily for a maximum of 3 g/day for 2–3 days and is the agent with the most extensive clinical experience, although it is probably the least satisfactory of all available drugs. Relapses and toxicities are common (as many as 30%) (99). In transplant recipients, an anti-*Strongyloides* treatment course of 5–7 days at usual doses is recommended for disseminated disease; however, patients should be monitored for larvae eradication from the sputum, stool, and duodenal aspirates and treatment should continue for up to a week before treatment ceases. Even in the absence of larvae, monthly 5-day treatment courses for at least 6 months have been suggested before treatment is definitely discontinued (114).

To avoid the risk of disseminated strongyloidiasis an adequate screening with parasitological studies and serology and treatment of the infection before transplantation are needed. If this is not feasible, empiric treatment has been proposed before the initiation of immunosuppressive therapy for transplant candidates with unexplained eosinophilia, with a history of parasitic infection and of residence in or travel to, even in the remote past, endemic areas and in those in whom strongyloidiasis is suspected on clinical grounds (114). Also, because strongyloidiasis can be transmitted via the graft, information about a donor's epidemiologic risk might trigger the initiation of preemptive treatment for the recipient and further serologic evaluation of the donor (104,115,116).

Recommendations (III)
Pretransplant:

(1) Intestinal strongyloidiasis should be actively evaluated in transplant candidates with epidemiological burden or with unexplained eosinophilia, during pretransplant evaluation.
    (i) Serologic evaluation is the most sensitive method. If available, it should be preferentially performed (Grade II).
    (ii) Agar-plate cultures from multiple stool samples should be used together with serological methods.
    (iii) All with confirmed diagnosis should be treated with ivermectin or albendazole as above (Grade II).

(iv) Empiric treatment with ivermectin in areas of high endemicity should be given if an accurate diagnosis cannot be obtained.

(2) Donors of intestine and pancreas who have resided or visited endemic regions should be screened: serology and larvae identification in intestinal biopsy specimens could be used.

Posttransplant:

(1) Intestine (includes pancreas) recipients might benefit from treatment upon confirmation of donor infection before the onset of symptoms.

(2) No recommendation can be made at this time for posttransplant follow-up of pretransplant treated patients except to bear in mind that relapses are a possibility.

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. *Schistosoma mansoni* and *Schistosoma 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 both lead to intestinal and/or liver disease.

Clinical syndromes that may be of significance in solid organ transplant include pipe-stem fibrosis, a characteristic pipe-shaped fibrosis around the hepatic portal veins, which can be seen with chronic heavy infection with *S. mansoni*, and is thought to be induced by the presence of large numbers of schistosome eggs in the hepatic tissues; it leads to portal hypertension. Studies are mixed as to 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, sometimes only at end of void), dysuria and urinary frequency; chronic infection may result in fibrosis and calcification of the bladder and ureters, with ensuing hydroureter and hydronephrosis. Schistosomal nephropathy is a well-known occurrence and eventually leads to end-stage renal failure. Although some earlier studies suggested that *Schistosoma*-specific nephropathy might occur in the transplanted kidney (117), Mahmoud et al. showed that treated *Schistosoma* infection had no significant impact on patient or graft outcomes after renal transplantation, although patients were found to have a higher incidence of acute and chronic cyclosporin nephrotoxicity as well as significantly higher incidence of urinary tract infection and urological complications with no evidence of schistosomal re-infection (118). It is not clear whether the solid organ transplantation and accompanying immunosuppression alters the clinical course of schistosomiasis. Recurrence of schistosomiasis after liver transplant is rare. Several cases of schistosomiasis after liver transplant have been reported, possibly resulting from reactivation of previous infection as a consequence of immunosuppressive therapy (119,120).

While schistosomes can be transmitted by organ transplant, adult schistosomes do not replicate within the host (because they need snails for the intermediate host) so only transmission of nonreplicating adult worms occurs. There are several case-reports describing the successful use of *Schistosoma*-infected donors in the solid organ transplantation (118–123). It is not clear whether transplant recipients with donor-derived infections are at risk for Katayama fever, a systemic hypersensitivity reaction against the migrating parasites, with sudden onset of fever, chills, myalgias, arthralgias, dry cough, diarrhea and headache, often resembling serum sickness; lymphadenopathy and hepatosplenomegaly may be found, with eosinophilia and patchy pulmonary infiltrates. 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. 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.

Treatment and prevention: Praziquantel is the usual treatment for schistosomiasis. Oxamniquine (for *S. mansoni*) may be available outside the United States. Case reports of several transplant patients who were treated with one dose of praziquantel at 40 mg/kg with good outcomes have been published (119,120). 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.

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.

Recommendations (Grade III)

(1) Schistosomiasis is common; the effects of immunosuppression on long-term disease outcomes are not clear.

(2) Screening and treatment of solid organ transplant recipients may prevent long-term sequelae.
(3) Donors with schistosomiasis may be used with caution; there are numerous reports of successful use of organs from such donors, and no adverse reports.

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 *Echinococcus multilocularis*. *E. 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 of the disease. Hydatid cysts are usually asymptomatic. Symptoms can occur, however, from the mass effect of the enlarging cyst or from the leakage, rupture or bacterial infection 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 have been reported (124,125). One report suggests that the detection of hydatid cysts at the time of transplantation is not necessarily a contraindication to transplantation because the growth rate of the liver cysts was not enhanced by the intense immunosuppression used for a heart transplant recipient (126).

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 (127). Liver transplantation should be considered early on for patients with hilar involvement, with recurrent biliary infections, with secondary biliary cirrhosis and ascites, for patients with 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 of 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 exclusion criteria for the procedure (128). 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 (128). Survival without recurrence was 77% at 1 year and 45% at 10 years. In a series of 5 liver transplant recipients in China with alveolar echinococcosis of the liver, major technical difficulties were noted, but OLT for incurable disease was felt to be feasible (129). Best results are achieved if transplantation is performed before blood vessel involvement occurs (130). 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 (hydatic disease) is mostly found by chance on routine imaging exams. Chest X-ray, CT scan, ultrasonography and MRI show a quite characteristic cystic lesion. These findings together with a positive epidemiological exposure lead to presumptive diagnosis. Serology may be used to help confirm diagnosis. Available tests have 60–95% sensitivity but negative results may occur even in active infection if the cyst is not ruptured.

E. multilocularis infection needs to be differentiated from hepatic malignancy. Liver biopsy specimens are considered the gold standard for diagnosis. However, its use is limited due to the high risk of infection spreading. 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 (131).

Treatment and prevention: The presence of hydatid disease should be recognized and treated with the surgical removal of the cysts and albendazole therapy before transplantation (132). 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 unique and calcified (133), 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 (134). Treatment with albendazole (15 mg/(kg day)) is recommended for a minimum of 2 years after transplantation even in cases of apparently curative surgery (128).

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 (127).

Disclosure

The authors have nothing to disclose.

References

1. Barsoum RS. Parasitic infections in organ transplantation. Exp Clin Transplant 2004; 2: 258–267.

2. Israelski DM, Chmiel JS, Poggensee L, Phair JP, Remington JS. Prevalence of Toxoplasma infection in a cohort of homosexual men at risk of AIDS and toxoplasmic encephalitis. J Acquir Immune Defic Syndr 1993; 6: 414–418.
3. Roghmann MC, Faulkner CT, Lefkowitz A, Patton S, Zimmerman J, Morris JG, Jr. Decreased seroprevalence for *Toxoplasma gondii* in Seventh Day Adventists in Maryland. Am J Trop Med Hyg 1999; 60: 790–792.
4. Kotton CN. Zoonoses in solid-organ and hematopoietic stem cell transplant recipients. Clin Infect Dis 2007; 44: 857–866.
5. Dubey JP. Toxoplasmosis—a waterborne zoonosis. Vet Parasitol 2004; 126: 57–72.
6. 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: 408–417.
7. 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: 980–985.
8. Ionita C, Wasay M, Balos L, Bakshi R. MR imaging in toxoplasmosis encephalitis after bone marrow transplantation: Paucity of enhancement despite fulminant disease. AJNR Am J Neuroradiol 2004; 25: 270–273.
9. Ferreira MS, Borges AS. Some aspects of protozoan infections in immunocompromised patients—a review. Mem Inst Oswaldo Cruz 2002; 97: 443–457.
10. Baden LR, Katz JT, Franck L et al. Successful toxoplasmosis prophylaxis after orthotopic cardiac transplantation with trimethoprim-sulfamethoxazole. Transplantation 2003; 75: 339–343.
11. Munoz P, Arencibia J, Rodriguez C et al. Trimethoprim-sulfamethoxazole as toxoplasmosis prophylaxis for heart transplant recipients. Clin Infect Dis 2003; 36: 932–933; author reply 3.
12. Baran DA, Alwarshetty MM, Alvi S et al. Is toxoplasmosis prophylaxis necessary in cardiac transplantation? Long-term follow-up at two transplant centers. J Heart Lung Transplant 2006; 25: 1380–1382.
13. Keogh A, Macdonald P, Richens D, Harvison A, Spratt P. Minidose trimethoprim with sulphamethoxazole prevents pneumocystis and toxoplasmosis infections after heart transplantation. Transplant Proc 1992; 24: 2263.
14. Rodriques Coura J, de Castro SL. A critical review on Chagas disease chemotherapy. Mem Inst Oswaldo Cruz 2002; 97: 3–24.
15. Enfermedad de Chagas: control y eliminación. Organización Mundial de la Salud. 2008:1–4. Available at: http://www.who.int/gb/ebwha/pdf_files/EB124/B124_17-sp.pdf. Accessed November 17, 2009.
16. Bern C, Montgomery SP, Herwaldt BL et al. Evaluation and treatment of chagas disease in the United States: A systematic review. JAMA 2007; 298: 2171–2181.
17. Campos SV, Strabelli TM, Amato Neto V et al. Risk factors for Chagas' disease reactivation after heart transplantation. J Heart Lung Transplant 2008; 27: 597–602.
18. Bocchi EA, Fiorelli A. The paradox of survival results after heart transplantation for cardiomyopathy caused by *Trypanosoma cruzi*. First Guidelines Group for Heart Transplantation of the Brazilian Society of Cardiology. Ann Thoracic Surg 2001; 71: 1833–1838.
19. Diez M, Favaloro L, Bertolotti A 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: 1633–1640.
20. Riarte A, Luna C, Sabatiello R et al. Chagas' disease in patients with kidney transplants: 7 years of experience 1989–1996. Clin Infect Dis 1999; 29: 561–567.
21. Chagas disease after organ transplantation–Los Angeles, California, 2006. MMWR Morb Mortal Wkly Rep 2006; 55: 798–800.
22. From the Centers for Disease Control and Prevention. Chagas disease after organ transplantation–United States, 2001. JAMA 2002; 287: 1795–1796.
23. de Faria JB, Alves G. Transmission of Chagas' disease through cadaveric renal transplantation. Transplantation 1993; 56: 746–747.
24. Vazquez MC, Riarte A, Pattin M, Lauricella M. Chagas' disease can be transmitted through kidney transplantation. Transplant Proc 1993; 25: 3259–3260.
25. Pirard M, Iihoshi N, Boelaert M, Basanta P, Lopez F, Van Der Stuyft P. The validity of serologic tests for *Trypanosoma cruzi* and the effectiveness of transfusional screening strategies in a hyperendemic region. Transfusion 2005; 45: 554–561.
26. Gorlin J, Rossmann S, Robertson G et al. Evaluation of a new *Trypanosoma cruzi* antibody assay for blood donor screening. Transfusion 2008; 48: 531–540.
27. Viotti R, Vigliano C. Etiological treatment of chronic Chagas disease: Neglected 'evidence' by evidence-based medicine. Expert Rev Anti-Infect Therapy 2007; 5: 717–726.
28. Altclas JD, Barcan L, Nagel C, Lattes R, Riarte A. Organ transplantation and Chagas disease. JAMA 2008; 299: 1134; author reply 5.
29. Evans TG. Leishmaniasis. Infect Dis Clin North America 1993; 7: 527–546.
30. Leishmaniasis. 2009. Available from: http://www.dpd.cdc.gov/dpdx/HTML/Leishmaniasis.htm. Accessed January 9, 2009.
31. Pearson RD, De Sousa A, Jeronimo SMB. Leishmania species: Visceral (Kala Azar), cutaneous, and mucosal leishmaniasis. In: Mandell G, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. New York: Churchill Livingstone; 2000:2831–2845.
32. Pearson RD, Jeronimo SMB, De Sousa A. Leishmaniasis. In: Gillespie S, Pearson RD, eds. Principles and Practice of Parasitology Hoboken, NJ, USA: John Wiley and Sons Ltd; 2001:287–331.
33. Holaday BJ, Pompeu MM, Evans T et al. Correlates of Leishmania-specific immunity in the clinical spectrum of infection with Leishmania Chagasi. J Infect Dis 1993; 167: 411–417.
34. Antinori S, Cascio A, Parravicini C, Bianchi R, Corbellino M. Leishmaniasis among organ transplant recipients. The Lancet Infectious Diseases 2008; 8: 191–199.
35. Alrajhi AA, Saleem M, Ibrahim EA, Gramiccia M. Leishmaniasis of the tongue in a renal transplant recipient. Clin Infect Dis 1998; 27: 1332–1333.
36. Borgia F, Vaccaro M, Guarneri F, Manfre C, Cannavo SP, Guarneri C. Mucosal leishmaniasis occurring in a renal transplant recipient. Dermatology (Basel, Switzerland) 2001; 202: 266–267.
37. Iborra C, Caumes E, Carriere J, Cavelier-Balloy B, Danis M, Bricaire F. Mucosal leishmaniasis in a heart transplant recipient. Br J Dermatol 1998; 138: 190–192.
38. Fernandez-Guerrero ML, Aguado JM, Buzon L et al. Visceral leishmaniasis in immunocompromised hosts. Am J Med 1987; 83: 1098–1102.
39. Hussein MM, Mooij JM, Roujouleh HM, Hamour OA, Felemban H. Non-typhoid Salmonella septicemia and visceral leishmaniasis in a renal transplant patient. Transplantation 2001; 71: 479–481.

40. Jimenez M, Ferrer-Dufol M, Canavate C et al. Variability of Leishmania (Leishmania) infantum among stocks from immunocompromised, immunocompetent patients and dogs in Spain. FEMS Microbiol Lett 1995; 131: 197–204.
41. Jokipii L, Salmela K, Saha H et al. Leishmaniasis diagnosed from bronchoalveolar lavage. Scandinavian J Infect Dis 1992; 24: 677–681.
42. Llorente S, Gimeno L, Navarro MJ, Moreno S, Rodriguez-Girones M. Therapy of visceral leishmaniasis in renal transplant recipients intolerant to pentavalent antimonials. Transplantation 2000; 70: 800–801.
43. Mittal R, Saxena S, Guleria S et al. Visceral leishmaniasis: A rare cause of unexplained pyrexia in a renal allograft recipient. Nephron 1995; 70: 123–124.
44. Moulin B, Ollier J, Bouchouareb D, Purgus R, Olmer M. Leishmaniasis: A rare cause of unexplained fever in a renal graft recipient. Nephron 1992; 60: 360–362.
45. Sharma RK, Jha R, Kumar P et al. Visceral leishmaniasis in a renal transplant recipient: Diagnostic and therapeutic problems. Am J Nephrol 1996; 16: 358–360.
46. Oliveira RA, Silva LS, Carvalho VP et al. Visceral leishmaniasis after renal transplantation: Report of 4 cases in northeastern Brazil. Transpl Infect Dis 2008; 10: 364–368.
47. Esteban RJ, Bravo JA, Osuna A, Asensio C. Early antimoniate poisoning in a non-fatal visceral leishmaniasis kidney transplant recipient with renal failure. Nephrol Dial Transplant 1996; 11: 1898.
48. Hueso M, Bover J, Seron D et al. The renal transplant patient with visceral leishmaniasis who could not tolerate meglumine antimoniate-cure with ketoconazole and allopurinol. Nephrol Dial Transplant 1999; 14: 2941–2943.
49. Malek Hosseini SA, Javid R, Salahi H, Nezakatgoo N, Ahmad E, Ghahramani N. A case report of Kala-Azar in a kidney transplant patient. Transplant Proc 1995; 27: 2715.
50. Sabbatini M, Pisani A, Ragosta A, Gallo R, Borrelli F, Cianciaruso B. Visceral Leishmaniasis in renal transplant recipients: Is it still a challenge to the nephrologist? Transplantation 2002; 73: 299–301.
51. Boletis JN, Pefanis A, Stathakis C, Helioti H, Kostakis A, Giamarellou H. Visceral leishmaniasis in renal transplant recipients: Successful treatment with liposomal amphotericin B (AmBisome). Clin Infect Dis 1999; 28: 1308–1309.
52. Halim MA, Alfurayh O, Kalin ME, Dammas S, al-Eisa A, Damanhouri G. Successful treatment of visceral leishmaniasis with allopurinol plus ketoconazole in a renal transplant recipient after the occurrence of pancreatitis due to stibogluconate. Clin Infect Dis 1993; 16: 397–399.
53. Kher V, Ghosh AK, Gupta A, Arora P, Dhole TN. Visceral leishmaniasis: An unusual case of fever in a renal transplant recipient. Nephrol Dial Transplant 1991; 6: 736–738.
54. Orofino L, Marcen R, Gamez C et al. Visceral leishmaniasis in renal transplant patients. Nephrol Dial Transplant 1992; 7: 651.
55. Hernandez-Perez J, Yebra-Bango M, Jimenez-Martinez E et al. Visceral leishmaniasis (kala-azar) in solid organ transplantation: Report of five cases and review. Clin Infect Dis 1999; 29: 918–921.
56. Ghosh AK. Visceral leishmaniasis in kidney transplant recipients. An endemic disease. Transplantation 1995; 59: 453.
57. Portoles J, Prats D, Torralbo A, Herrero JA, Torrente J, Barrientos A. Visceral leishmaniasis: A cause of opportunistic infection in renal transplant patients in endemic areas. Transplantation 1994; 57: 1677–1679.
58. Le Cacheux P, Hurault de Ligny B, Reman O, Ryckelynck JP. [Visceral leishmaniasis of favourable course in a patient with renal transplantation]. La Revue de Medecine Interne/Fondee 1990; 11: 250–251.
59. Lamas S, Orte L, Parras F, Garcia Larana J, Matesanz R, Ortuno J. Non-fatal leishmaniasis in a renal transplant recipient. Nephron 1987; 45: 71.
60. Aguado JM, Bonet F, Plaza JJ, Escudero A. Visceral leishmaniasis in a renal transplant recipient: A diagnostic and therapeutic challenge. J Infect 1986; 13: 301–303.
61. Salva M, Fernandez Fernandez J, Berisa F et al. Visceral leishmaniasis in kidney transplantation: Report of one case. Clin Transplants 1986: 134.
62. Broeckaert-van Orshoven A, Michielsen P, Vandepitte J. Fatal leishmaniasis in renal-transplant patient. Lancet 1979; 2: 740–741.
63. Ma DD, Concannon AJ, Hayes J. Fatal leishmaniasis in renal-transport patient. Lancet 1979; 2: 311–312.
64. Moroni G, Bossi L. Don't forget visceral leishmaniasis in transplant patients. Nephrol Dial Transplant 1995; 10: 563–564.
65. Apaydin S, Ataman R, Serdengect K et al. Visceral leishmaniasis without fever in a kidney transplant recipient. Nephron 1997; 75: 241–242.
66. Torregrosa JV, Ricart MJ, Montesinos M et al. Visceral leishmaniasis-like cause of unexplained fever in a reno-pancreatic graft recipient. Nephron 1993; 65: 318–319.
67. Horber FF, Lerut JP, Reichen J, Zimmermann A, Jaeger P, Malinverni R. Visceral leishmaniasis after orthotopic liver transplantation: Impact of persistent splenomegaly. Transpl Int 1993; 6: 55–57.
68. Morales P, Torres JJ, Salavert M, Peman J, Lacruz J, Sole A. Visceral leishmaniasis in lung transplantation. Transplant Proc 2003; 35: 2001–2003.
69. Frapier JM, Abraham B, Dereure J, Albat B. Fatal visceral leishmaniasis in a heart transplant recipient. J Heart Lung Transplant 2001; 20: 912–913.
70. Roustan G, Jimenez JA, Gutierrez-Solar B, Gallego JL, Alvar J, Patron M. Post-kala-azar dermal leishmaniasis with mucosal involvement in a kidney transplant recipient: Treatment with liposomal amphotericin B. Br J Dermatol 1998; 138: 526–528.
71. Meyerhoff A. U.S. Food and Drug Administration approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. Clin Infect Dis 1999; 28: 42–48; discussion 9–51.
72. Sundar S, Rai M, Chakravarty J et al. New treatment approach in Indian visceral leishmaniasis: Single-dose liposomal amphotericin B followed by short-course oral miltefosine. Clin Infect Dis 2008; 47: 1000–1006.
73. Mungai M, Tegtmeier G, Chamberland M, Parise M. Transfusion-transmitted malaria in the United States from 1963 through 1999. N Engl J Med 2001; 344: 1973–1978.
74. Fischer L, Sterneck M, Claus M et al. Transmission of malaria tertiana by multi-organ donation. Clin Transplant 1999; 13: 491–495.
75. Talabiska DG, Komar MJ, Wytock DH, Rubin RA. Post-transfusion acquired malaria complicating orthotopic liver transplantation. Am J Gastroenterol 1996; 91: 376–379.
76. Pandey D, Lee KH, Wong SY, Tan KC. Malaria after living donor liver transplantation: Report of two cases. Hepatobiliary Pancreat Dis Int 2008; 7: 210–213.
77. Holzer BR, Gluck Z, Zambelli D, Fey M. Transmission of malaria by renal transplantation. Transplantation 1985; 39: 315–316.
78. Lee PC, Lee PY, Lei HY, Chen FF, Tseng JY, Ching YT. Malaria infection in kidney transplant recipients. Transplant Proc 1994; 26: 2099–2100.

79. The Use of Rapid Malaria Diagnostic Tests. 2nd ed. Geneva: World Health Organization; 2006. Available at: http://malaria.who.int/docs/RDT/TheUseOfMalariaRDT (2nd Edition).pdf. Accessed November 17, 2009.
80. White NJ. The treatment of malaria. N Engl J Med 1996; 335: 800–806.
81. Nuesch R, Cynke E, Jost MC, Zimmerli W. Thrombocytopenia after kidney transplantation. Am J Kidney Dis 2000; 35: 537–538.
82. Health Information for International Travel. In: Control CFD, ed. The Yellow Book, 2008.
83. Tan HW, Ch'ng SL. Drug interaction between cyclosporine A and quinine in a renal transplant patient with malaria. Singapore Med J 1991; 32: 189–190.
84. Lux JZ, Weiss D, Linden JV et al. Transfusion-associated babesiosis after heart transplant. Emerg Infect Dis 2003; 9: 116–119.
85. Perdrizet GA, Olson NH, Krause PJ, Banever GT, Spielman A, Cable RG. Babesiosis in a renal transplant recipient acquired through blood transfusion. Transplantation 2000; 70: 205–208.
86. Slovut DP, Benedetti E, Matas AJ. Babesiosis and hemophagocytic syndrome in an asplenic renal transplant recipient. Transplantation 1996; 62: 537–539.
87. Krause PJ, Lepore T, Sikand VK et al. Atovaquone and azithromycin for the treatment of babesiosis. N Engl J Med 2000; 343: 1454–1458.
88. Krause PJ, Gewurz BE, Hill D et al. Persistent and relapsing babesiosis in immunocompromised patients. Clin Infect Dis 2008; 46: 370–376.
89. 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: 724–730.
90. Walia R, Montoya JG, Visvesvera GS, Booton GC, Doyle RL. A case of successful treatment of cutaneous Acanthamoeba infection in a lung transplant recipient. Transplant Infect Dis 2007; 9: 51–54.
91. Fung KT, Dhillon AP, McLaughlin JE et al. Cure of Acanthamoeba cerebral abscess in a liver transplant patient. Liver Transplant 2008; 14: 308–312.
92. 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: 154–157.
93. Aichelburg AC, Walochnik J, Assadian O et al. Successful treatment of disseminated Acanthamoeba sp. infection with miltefosine. Emerg Infect Dis 2008; 14: 1743–1746.
94. Udgiri N, Minz M, Kashyap R et al. Intestinal cryptosporidiasis in living related renal transplant recipients. Transplant Proc 2004; 36: 2128–2129.
95. Vakil NB, Schwartz SM, Buggy BP et al. Biliary cryptosporidiosis in HIV-infected people after the waterborne outbreak of cryptosporidiosis in Milwaukee. N Engl J Med 1996; 334: 19–23.
96. Lanternier F, Boutboul D, Menotti J et al. Microsporidiosis in solid organ transplant recipients: Two Enterocytozoon bieneusi cases and review. Transpl Infect Dis 2008.
97. Palau LA, Kemmerly SA. First report of invasive amebiasis in an organ transplant recipient. Transplantation 1997; 64: 936–937.
98. Genta RM. Global prevalence of strongyloidiasis: Critical review with epidemiologic insights into the prevention of disseminated disease. Rev Infect Dis 1989; 11: 755–767.
99. Liu LX, Weller PF. Strongyloidiasis and other intestinal nematode infections. Infect Dis Clin North Am 1993; 7: 655–682.
100. Keiser PB, Nutman TB. Strongyloides stercoralis in the Immunocompromised Population. Clin Microbiol Rev 2004; 17: 208–217.
101. Khattab A, Pica-Mattoccia L, Klinkert MQ, Wenger R, Cioli D. Cyclosporins: Lack of correlation between antischistosomal properties and inhibition of cyclophilin isomerase activity. Exp Parasitol 1998; 90: 103–109.
102. Nolan TJ, Schad GA. Tacrolimus allows autoinfective development of the parasitic nematode Strongyloides stercoralis. Transplantation 1996; 62: 1038.
103. Schaeffer MW, Buell JF, Gupta M, Conway GD, Akhter SA, Wagoner LE. Strongyloides hyperinfection syndrome after heart transplantation: Case report and review of the literature. J Heart Lung Transplant 2004; 23: 905–911.
104. Patel G, Arvelakis A, Sauter BV, Gondolesi GE, Caplivski D, Huprikar S. Strongyloides hyperinfection syndrome after intestinal transplantation. Transpl Infect Dis 2008; 10: 137–141.
105. Vadlamudi RS, Chi DS, Krishnaswamy G. Intestinal strongyloidiasis and hyperinfection syndrome. Clin Mol Allergy 2006; 4: 8.
106. Siddiqui AA, Berk SL. Diagnosis of Strongyloides stercoralis infection. Clin Infect Dis 2001; 33: 1040–1047.
107. Lindo JF, Conway DJ, Atkins NS, Bianco AE, Robinson RD, Bundy DA. Prospective evaluation of enzyme-linked immunosorbent assay and immunoblot methods for the diagnosis of endemic Strongyloides stercoralis infection. Am J Trop Med Hyg 1994; 51: 175–179.
108. Stone WJ, Schaffner W. Strongyloides infections in transplant recipients. Semin Respir Infect 1990; 5: 58–64.
109. Genta RM, Douce RW, Walzer PD. Diagnostic implications of parasite-specific immune responses in immunocompromised patients with strongyloidiasis. J Clin Microbiol 1986; 23: 1099–1103.
110. Gann PH, Neva FA, Gam AA. A randomized trial of single- and two-dose ivermectin versus thiabendazole for treatment of strongyloidiasis. J Infect Dis 1994; 169: 1076–1079.
111. Marti H, Haji HJ, Savioli L et al. A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of Strongyloides stercoralis and other soil-transmitted helminth infections in children. Am J Trop Med Hyg 1996; 55: 477–481.
112. Ashraf M, Gue CL, Baddour LM. Case report: Strongyloidiasis refractory to treatment with ivermectin. Am J Med Sci 1996; 311: 178–179.
113. Archibald LK, Beeching NJ, Gill GV, Bailey JW, Bell DR. Albendazole is effective treatment for chronic strongyloidiasis. Q J Med 1993; 86: 191–195.
114. DeVault GA, Jr., King JW, Rohr MS, Landreneau MD, Brown ST, 3rd, McDonald JC. Opportunistic infections with Strongyloides stercoralis in renal transplantation. Rev Infect Dis 1990; 12: 653–671.
115. Hoy WE, Roberts NJ, Jr., Bryson MF et al. Transmission of strongyloidiasis by kidney transplant? Disseminated strongyloidiasis in both recipients of kidney allografts from a single cadaver donor. JAMA 1981; 246: 1937–1939.
116. Ben-Youssef R, Baron P, Edson F, Raghavan R, Okechukwu O. Stronglyoides stercoralis infection from pancreas allograft: Case report. Transplantation 2005; 80: 997–998.
117. Falcao HA, Gould DB. Immune complex nephropathy i schistosomiasis. Ann Intern Med 1975; 83: 148–154.
118. Mahmoud KM, Sobh MA, El-Agroudy AE et al. Impact of schistosomiasis on patient and graft outcome after renal transplantation: 10 years' follow-up. Nephrol Dial Transplant 2001; 16: 2214–2221.
119. Ahmed K, Safdar K, Kemmer N, Atiq M, Wang J, Neff GW. Intestinal schistosomiasis following orthotopic liver transplantation: A case report. Transplant Proc 2007; 39: 3502–3504.

120. Hoare M, Gelson WT, Davies SE, Curran M, Alexander GJ. Hepatic and intestinal schistosomiasis after orthotopic liver transplant. Liver Transplant 2005; 11: 1603–1607.
121. Kayler LK, Rudich SM, Merion RM. Orthotopic liver transplantation from a donor with a history of schistosomiasis. Transplant Proc 2003; 35: 2974–2976.
122. Pannegeon V, Masini JP, Paye F, Chazouilleres O, Girard PM. Schistosoma mansoni infection and liver graft. Transplantation 2005; 80: 287.
123. Pungpapong S, Krishna M, Abraham SC, Keaveny AP, Dickson RC, Nakhleh RE. Clinicopathologic findings and outcomes of liver transplantation using grafts from donors with unrecognized and unusual diseases. Liver Transplant 2006; 12: 310–315.
124. Moreno-Gonzalez E, Loinaz Segurola C, Garcia Urena MA et al. Liver transplantation for Echinococcus granulosus hydatid disease. Transplantation 1994; 58: 797–800.
125. Loinaz C, Moreno-Gonzalez E, Gomez R et al. Liver transplantation in liver disease: Echinococcus granulosus. Transplant Proc 1998; 30: 3268–3269.
126. Sobrino JM, Pulpon LA, Crespo MG et al. Heart transplantation in a patient with liver hydatidosis. J Heart Lung Transplant 1993; 12: 531–533.
127. Bresson-Hadni S, Vuitton DA, Bartholomot B et al. A twenty-year history of alveolar echinococcosis: Analysis of a series of 117 patients from eastern France. Eur J Gastroenterol Hepatol 2000; 12: 327–336.
128. Koch S, Bresson-Hadni S, Miguet JP et al. Experience of liver transplantation for incurable alveolar echinococcosis: A 45-case European collaborative report. Transplantation 2003; 75: 856–863.
129. Xia D, Yan LN, Li B et al. Orthotopic liver transplantation for incurable alveolar echinococcosis: Report of five cases from west China. Transplant Proc 2005; 37: 2181–2184.
130. Li F, Yang M, Li B et al. Initial clinical results of orthotopic liver transplantation for hepatic alveolar echinococcosis. Liver Transplant 2007; 13: 924–926.
131. Bresson-Hadni S, Koch S, Beurton I et al. Primary disease recurrence after liver transplantation for alveolar echinococcosis: Long-term evaluation in 15 patients. Hepatology 1999; 30: 857–864.
132. Guidelines for treatment of cystic and alveolar echinococcosis in humans. WHO Informal Working Group on Echinococcosis. Bull World Health Organ 1996; 74: 231–242.
133. Bein T, Haerty W, Haller M, Forst H, Pratschke E. Organ selection in intensive care: Transplantation of a liver allograft, including calcified cyst of Echinococcus granularis. Intensive Care Med 1993; 19: 182.
134. Jimenez Romero C, Moreno Gonzalez E, Garcia Garcia I et al. Successful transplantation of a liver graft with a calcified hydatid cyst after back-table resection. Transplantation 1995; 60: 883–884.