Parasitic Infections in Organ Transplantation

Rashad S Barsoum

More than 340 parasitic species infect more than 3 billion people worldwide with varying morbidity and mortality. The Tropics constitute the main reservoir of infection with the highest clinical impact, owing to favorable ecological factors. Acquisition of infection, clinical severity, and outcome of a parasitic disease depend on innate and acquired host immunity as well as the parasite's own immune response against the host when infection is established. Organ transplant recipients may acquire significant parasitic disease in 3 ways: transmission with the graft, de novo infection, or activation of dormant infection as a consequence of immunosuppression. Malaria, Trypanosoma, Toxoplasma, and Leishmania are the principal parasites that may be transmitted with bone marrow, kidney, or liver homografts, and microsporidia with xenotransplants. De novo infection with malaria and kala-azar may occur in immunocompromised travelers visiting in endemic areas, while immunocompromised natives are subject to superinfection with different strains of endemic parasites, reinfection with schistosomiasis, or rarely, with primary infections such as acanthamoeba. The list of parasites that may be reactivated in the immunocompromised host includes giardiasis, balantidiasis, strongyloidiasis, capillariasis, malaria, Chagas' disease, and kala-azar. The broad clinical syndromes of parasitic infection in transplant recipients include prolonged pyrexia, lower gastrointestinal symptoms, bronchopneumonia, and meningoencephalitis. Specific syndromes include the hematologic manifestations of malaria, myocarditis in Chagas' disease, acute renal failure in malaria and leishmaniasis, and the typical skin lesions of Chagas' and cutaneous leishmaniasis. Many antiparasitic drugs have the potential for gastrointestinal, hepatic, renal, and hematologic toxicity, and may interact with the metabolism of immunosuppressive agents. It is recommended that transplant clinicians have a high index of suspicion of parasitic infections as an important transmission threat, as well as a potential cause of significant posttransplant morbidity.

Key words: *Posttransplant infections, Infections in the immunocompromised, Transmission of donor infections*

The number of solid organ transplantations performed worldwide is more than one million to date. This has yielded a wealth of experience, much of which is regarding infection in the immunocompromised recipient. Interestingly, the microbiological profile of infection in this population differs from that of related conditions that come as the result of congenital or acquired immunodeficiency syndromes, immunosuppression for immune-mediated disorders, and chemotherapy for malignancy. There remains much to learn about the mechanisms involved in these differences.

In this article, parasitic infections reported to occur in organ transplant recipients will be reviewed. Because most of the currently available information is based on small patient cohorts or case reports, the epidemiologic significance of these infections cannot be evaluated. Having mentioned that, compared with other microbial infections, it does not seem that the disease burden of such infections is of a significant magnitude, based on the scarcity of reports.

Cairo University, Egypt
Address reprint requests to: *Rashad S Barsoum, MD, FRCP, FRCPE, Cairo Kidney Center PO Box 91 Bab-El-Louk, Cairo 11513, Egypt*
***Phone**: 00 20 20 5790267 **Fax:** 00 1 310 388 1192 **E-mail:** Rbarsoum@msn.com*

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There are 342 parasitic species that are known to infect humans (Table 1). Billions of people are infected, mostly those in tropical and subtropical regions. Recently, however, there has been a considerable spread of these infections to the rest of the world as a result of travel, immigration, residence of expatriates in the Tropics, and even establishment of endemic foci of infection in the West (vide infra).

Table 1. Clinical classification of human-pathogenic parasites

Circulatory system	21 species
Cavities, organs, and tissues	107 species
Alimentary tract	197 species
Skin and subcutaneous	56 species

Fortunately, morbidity from parasitic infections in the immunocompetent host is limited, varying from nil (eg, ascariasis) to 40% (eg, onchocerciasis). Mortality is also limited from nil to 0.25% (eg, malaria, schistosomiasis). However, both morbidity and mortality are considerably augmented in immunocompromised patients, including transplant recipients.

Parasitic disease affects transplant recipients as a result of transmission with the transplanted organ, recrudescence of a dormant infection, or de novo natural infection. In some instances, it is easy to identify the mode of infection, for example, kala azar in the hepatic macrophages, recrudescence of malaria, or de novo infection with schistosomes. Yet, it is often very difficult to identify the mode of infection in a particular individual.

Only 5% of the known human-pathogenic parasitic infections have been reported in transplant recipients. This certainly does not represent the true prevalence, because only those infections that cause significant morbidity would be expected to find their way into the literature database. These are mostly parasites that live (eg, Plasmodium) or have a transient phase of their life cycle (eg, Leishmania) in the human circulatory system or transplanted organs. On the other hand, disturbance of the host-parasite concomitant immunity may induce recrudescence of alimentary or tissue parasites that may acquire a potentially fatal clinical profile (eg, Strongyloides).

Parasites Inhabiting the Circulatory System

Of 21 human pathogenic species belonging to this category, 3 are relevant to the present topic: malaria, babesiosis, and schistosomiasis.

Malaria

The causative organism of malaria is Plasmodium. The life cycle of this protozoan is ideal for becoming a notorious posttransplant infection. It starts with a mosquito sting that injects the sporozoites into the host's dermis. These are carried in the bloodstream to the liver where they mature in the hepatocytes (extra-erythrocytic cycle) to tissue schizonts that release their merozoites into the hepatic sinusoids. The latter invade the red cells, starting the erythrocytic cycle comprising ring forms, trophozoites, and subsequently, schizonts that contain a new generation of merozoites. The parasitized cells are induced to develop a microtubular system that conveys nutrients to the parasite. They eventually rupture, releasing new merozoites, which repeat the same asexual cycle. A few merozoites are sexually differentiated into male and female gametocytes, which are essential for completion of the sexual cycle in the vector.

Infected red cells constitute an obvious potential means of transmission of the disease with any organ transplant. This has been reported with kidney [1], bone marrow [2], and multiorgan [3] transplantation. Malarial antibodies also have been detected in a recipient of a heart transplant who received his graft from an infected donor [4]. Transmission of malaria has been traced to infected blood transfused to a kidney transplant recipient [5].

Transmission of the disease with an infected liver has been reported [4], although it could not be established whether the infected hepatocytes or blood cells in the hepatic sinusoids were responsible for transmission.

Recrudescence of clinical disease has been reported in recipients previously infected with *P. vivax* [6], *P. malariae* [7] or, peculiarly, *P. falciparum* [8], which does not have the potential of remaining dormant for any length of time.

Primary or reinfection is a distinct risk in exposed transplant recipients. For this reason, chemoprophylaxis has been strongly advocated for travelers visiting endemic areas [9,10]. Unfortunately, infection can still be acquired in nonendemic locations including European or American airports [11] or indigenous malarial foci as those in New York [12] or Georgia [13] in the United States.

The clinical picture of malaria in transplant recipients is usually severe, owing to the impaired immune response. It is characterized by pyrexia,

which may lack the typical periodicity or rigors. Anemia is severe, being typically hemolytic and occasionally hemophagocytic [2]. It is often associated with thrombocytopenia [14]. Hepatosplenic γ-δ lymphoma probably attributed to malarial infection has been described in kidney transplant recipients [15]. Acute graft dysfunction may occur as a consequence of the hemodynamic consequences of falciparum infection [16]. Whether the immune response to malarial infection has an impact on subsequent rejection is unknown.

Diagnosis is confirmed by examination of a Giemsa- or acridine orange-stained peripheral blood smear. In those with low parasitemia, diagnosis can be established by serologic techniques using synthetic peptides [17] or by DNA probes [18].

Antimalarial drugs can be used safely in most patients without problem. However, certain drug-drug interactions must be taken into consideration as those between quinine [19] and chloroquine [20] with cyclosporine. This may be extrapolated to other immunosuppressive agents dependent on cytochrome P450 for their catabolism.

Babesiosis

This rare febrile disease [21] is closely related to falciparum malaria. The causative organisms are protozoa closely similar to plasmodia. *Babesia microti* (Figure 1) and *Babesia divergens* are the two strains responsible for human disease in the United States and Europe respectively. Both are conveyed by *Ixodes dammini*, the same tick that transmits Lyme disease.

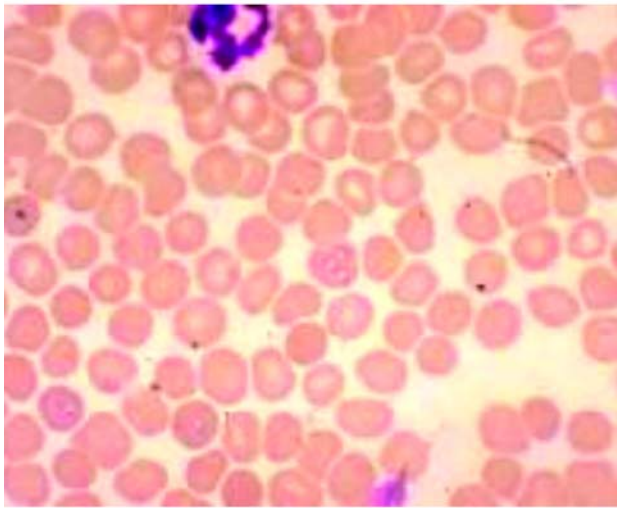

Figure 1. Blood film showing *Babesia microti* in the red cells.

Babesiosis, attributed to transfusion with contaminated blood, has been reported in renal [22] and cardiac [23] transplant recipients. Fever, hemolytic anemia, and impaired graft function dominate the clinical picture in the former; acute respiratory distress in the latter. A hemophagosytic syndrome has been reported in an asplenic renal transplant recipient [24]. Treatment is by a combination of clindamycin and quinine, with therapeutic apheresis in severe cases [25].

Schistosomiasis

Schistosomes are flat worms the inhabit the portal or perivesical veins of humans and several other mammals. They lay eggs, which find their way to the exterior through the rectal or bladder mucosa, which hatch in contact with fresh water releasing miracidia. These infect certain snails where they mature into cercariae, which constitutes the natural infective stage to humans. Upon piercing the skin or mucous membrane of an exposed individual, they further grow into schistosomulae, which migrate through the lymphatics to the bloodstream, and finally the hepatic sinusoids where they are trapped and finally mature into adult worms (Figure 2).

Theoretically speaking, the disease may be transmitted by blood transfusion or organ transplantation only during the short phase of schistosomular migration. Thus far, this has never been reported.

Figure 2. Adult couple of *Schistosoma mansoni* in copulation

On the other hand, transplant recipients may be exposed to new or reinfection if they resume their usual habits of exposure to contaminated water. This has been reported in Egypt [26], where 23% of recipients at high risk were reinfected. The clinical profile in those cases was not significantly different from natural infection in immunocompetent individuals.

Recrudescence of schistosomal glomerulopathy has been reported in an endemic area in South America, where mesangioproliferative glomerulonephritis with schistosomal antigen deposits developed in a recent kidney transplant recipient who originally had been infected with *S. mansoni* [27]. Accordingly, it has been suggested to prophylactically treat patients with such infection before undergoing transplantation, since adult worms often live silently in an infected host for decades and are able to induce glomerular lesions through immune-complex deposits containing schistosomal gut antigens [28].

Parasites Inhabiting Tissues and Cavities

Of 107 species in this category, 3 constitute a significant clinical problem in organ transplant recipients: leishmania, toxoplasma, and Trypanosoma.

Leishmaniasis

Leishmaniasis is acquired through the bite of a female sandfly, introducing the promastigotes of *Leishmania donovani* into the bloodstream. These are carried by the circulating macrophages where they reproduce as amastigotes (Figure 3). The parasitic antigens downregulate the macrophage, thereby inhibiting its ability to destroy them by its powerful proteolytic enzymes and free oxygen radicals. The infected macrophage eventually ruptures, releasing the amastigotes, which infect other macrophages. The latter include both circulating and "fixed" macrophages in different tissues. It is the latter that define the primary site of clinical disease and consequently, the clinical type of leishmaniasis. Infected circulating monocytes are sucked by the vector, where they reproduce as promastigotes, thereby completing the life cycle.

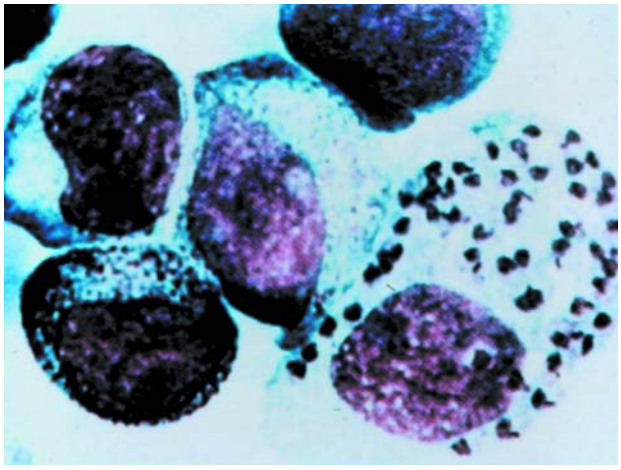

Figure 3. Amastigotes of *Leishmania donovani* in a tissue macrophage

Both visceral (kala-azar) and cutaneous leishmaniasis have been reported in transplant recipients. Recrudescence of dormant infection has been most often blamed following kidney [29,30], liver [31], lung [32], and heart [33] transplants. Transmission with bone marrow transplants also has been suspected in a few cases [34]. De novo infection undoubtedly occurs, but it has not, so far, been reported in the transplant literature.

The disease presents as a pyrexial illness usually by the fourth to the sixth week posttransplant and is associated with splenomegaly and pancytopenia. Acute graft dysfunction may occur in renal transplant recipients. Pentavalent antimonial compounds are the drugs of choice, but they interact with cyclosporine [29] and may carry an increased risk of inducing pancreatitis [35]. Pentamidine, antifungal antibiotics, and other newer agents are promising as effective agents with less adverse effects.

Toxoplasmosis

Toxoplasma gondii is a tissue protozoon that infects man by ingesting oocysts in the excreta of cats, or by eating other mammalian tissue containing bradyzoites in their macrophages. Both the sporozoites released from ingested oocysts and the bradyzoites infect the human intestinal mucosal cells where they rapidly multiply producing tachyzoites (Figure 4), which cause cell death leading to dissemination of the parasite throughout the host's tissues leading to the acute phase of clinical disease. After a few weeks, the parasite divides slowly in response to the host's immunity, producing zoitocysts filled with bradyzoites (Figure 4) that produce limited morbidity. When cats ingest mammalian tissues containing those bradyzoites, they harbor the parasite, which undergoes both sexual and asexual reproduction, forming the infective oocysts and thereby completing the life cycle.

This peculiar scenario contains many spots that permit transmission with blood transfusion or trans-

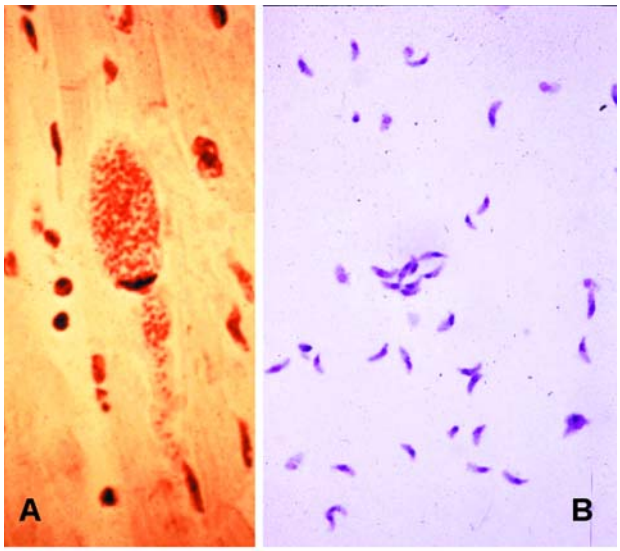

Figure 4. *Toxoplasma gondii*: A. bradyzoites in cardiac muscle; B. tachyzoites in peripheral blood

planted organs. Circulating and tissue macrophages may contain bradyzoites and any tissue may contain tachyzoites, both of which are able to reproduce and cause clinical disease. The same scenario explains the recrudescence of dormant infection as the slow phase of bradyzoite reproduction is switched, through depression of the host's immunity, to the rapid phase of tachyzoite reproduction, which is associated with cellular damage and clinical disease. A study of 31 patients with posttransplant toxoplasmosis has shown that transmission occurred in 10, recrudescence in 2, and the mode of infection remained unknown in 19 [36].

Posttransplant toxoplasmosis has been reported most frequently with heart transplants [37]. It also has been reported with bone marrow [38], stem cell [39], liver [40], kidney [41], simultaneous liver-pancreas, and liver-kidney-pancreas [42] transplants.

The disease is characterized by pyrexia, lymphadenopathy, and multiorgan involvement. Anemia is common, and a hemophagocytic syndrome has been reported in several cases [43]. Encephalitis is a serious and frequent complication [39]. Peripheral neuropathy is common, taking a Guillain-Barré pattern in a recently reported case [44]. Chorioretinitis, similar to that seen in cytomegaloviral infection, is frequently seen [45]. Pulmonary infiltrates, with pleural involvement may occur [40]. Pyrimethamine is the treatment of choice.

Trypanosomiasis

Trypanosoma cruzi (Figure 5), the cause of Chagas' disease, is responsible for a significant proportion of end-stage cardiomyopathy in South America. Resistance to conventional treatment has called for nonconventional therapeutic modalities including intracoronary bone marrow infusion to provide stem cells for myocardial regeneration [46] and cardiac transplantation [47].

The disease is acquired through the bite of a tick that subsequently defecates on the abraded skin, thereby providing access to the metacyclic trypomastigotes to the dermal lymphatics. Rubbing the eyes with contaminated hands is also an established method of exposure to infection. Trypomastigotes multiply in dermal cells and in macrophages producing amastigotes, which are able to induce cell lysis. The released amastigotes infect neighboring cells, while some are transformed into trypomastigotes and remain in the bloodstream. The vector is infected with either the circulating trypomastigotes or the tissue amastigotes, thereby completing the life cycle.

Transmission with transplanted organs, reactivation of dormant infection, as well as de novo infection have all been reported in transplant recipients. In a review of 23 cases, transmission was blamed in 18.7% and recrudescence in 22.7% [48]. In another report, amastigotes from the parenchyma or a renal graft were detected in the recipient 1 month after transplantation, indicating the viability of those forms despite graft perfusion and preservation [49].

Recurrence of cardiomyopathy in recipients of heart transplants has been reported in 28% of patients, with parasitological recrudescence in an additional 33% [50], which shows the magnitude of the problem in endemic areas.

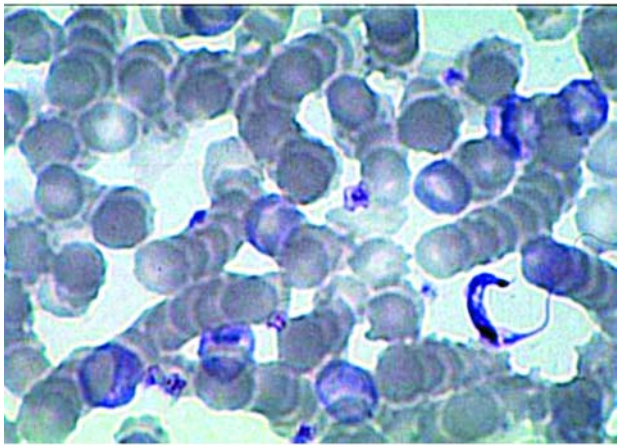

Figure 5. *Trypanosoma cruzi* in a thin blood film

De novo Chagas' disease has been reported in kidney [51] and bone marrow transplant recipients [52] in South America, attributed to transmission from the graft. An alarming report published in 2002 suggests that Chagas' disease was transmitted with grafted organs in the United States [53], but a subsequent retrospective analysis of 1170 donors in the Midwest could not confirm this threat [54].

Like the native disease, Chagas' in transplant recipients manifests with pyrexia, subcutaneous nodules, and cardiomyopathy. Complete heart block was the presenting clinical feature in a patient with reactivation Chagas' [55].

Benznidazole is the treatment of choice [56]. Nifurtimox is an effective alternative.

Alimentary Parasites

Most alimentary parasites are characterized by low morbidity and can exist in the transplant recipient without important clinical sequelae. Intestinal amebiasis, balantidiasis, and giardiasis are examples of protozoal infections that may cause an occasional diarrheal illness or an otherwise unexplained eosinophilia. Several Cestoda (flat worms) and Trematoda (round worms) may have a similar impact.

Certain exceptions to this profile have been reported with such benign infestations as ascariasis, which has caused bile duct obstruction [57], and trichuriasis, which has caused chronic diarrhea [58] in renal transplant recipients. Recurrence of alveolar echinococcosis has been reported after liver transplantation [59].

On the other hand, there are particular alimentary parasites that are notorious for causing serious complications in organ transplant recipients that may indeed be life threatening. These include Strongyloides, Capillaria, Cryptosporidium, Acanthamoeba, and Microsporidia.

Strongyloidiasis

The filariform larvae are the infective stage in the life cycle of *Strongyloides stercoralis*. They penetrate the skin of man exposed to moist soil containing the parasite, migrate into the bloodstream, ultimately reaching the pulmonary capillaries. They penetrate the alveolar walls reaching the bronchioles and bronchi, from which they are coughed up into the pharynx. They are then swallowed to ultimately reach the small intestine where they mature into adult females. Males have never been found in the host's intestine. The females produce eggs that hatch in the intestine producing juveniles that are passed into the exterior with the feces. They live freely in the soil as rhabditiform larvae, which mature into male and female mature worms that produce eggs that hatch producing both rhabditiform (free living) and filariform (infective) larvae, thereby completing the life cycle.

The crucial point in this interesting scenario is the hatching of eggs in the human intestine, thereby being able to start a new wave of infection (autoinfection). The filariform larvae are able to reach the bloodstream probably through the intestinal lymphatics, where they migrate to the lung and repeat the same cycle.

As with other parasitic infections, it is the host immunity that keeps the potential of autoinfection fairly limited. When this immunity is disrupted, the process is dramatically accelerated, hence the term "hyperinfection." This has been described in most immunocompromised states, including patients with HIV infection [60], malignant lymphomas [61], those on immunosuppression for autoimmune disease [62], and kidney [63], heart [64], and stem cell [65] transplant recipients. But since the use of cyclosporine has become a cornerstone in prophylactic immunosuppression, this syndrome has become exceedingly rare owing to the strong parasiticidal effect of the drug, which has been documented in mice [66] and humans [67].

The clinical syndrome of posttransplant strongyloidiasis is characterized by pyrexia, gastrointestinal disturbance, usually a colicky diarrhea, cough, and pneumonitis (Figure 6). Intestinal

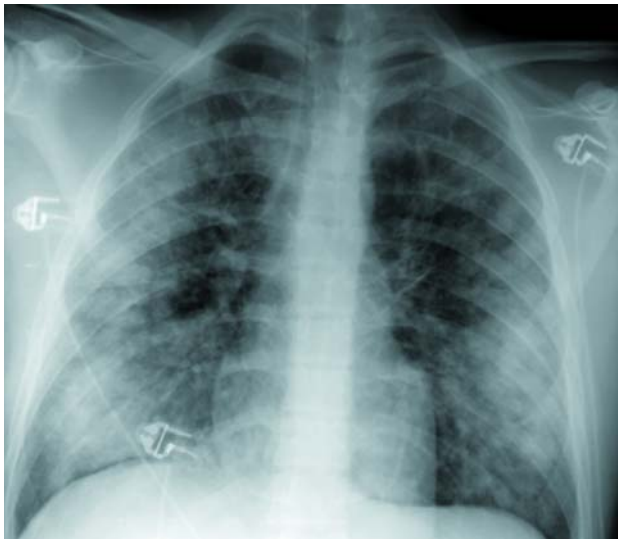

Figure 6. Chest radiograph in strongyloides hyperinfection

obstruction due to the masses of worms in the gut lumen has been described. Respiratory obstruction also has been encountered in many cases, leading to suffocation and death.

Thiabendazole is the treatment of choice. More recently, ivermectin has been increasingly used, being as effective yet better tolerated.

Capillariasis

Capillaria philippinensis is a common intestinal nematode in humans and pets [68]. The disease is acquired by the ingestion of raw or undercooked fish infected with juveniles. The latter mature into adult worms in the host's small intestine. They lay eggs that pass with the feces to be eaten by the fish to complete the life cycle. Like those of strongyloides, the eggs may hatch in the host's small intestine producing infective juveniles that have the potential for autoinfection.

Hyperinfection with Capillaria can occur in immunocompromised patients. We have seen it in one patient on immunosuppression for lupus nephritis and another following a renal transplant (Barsoum, unpublished data). The clinical syndrome was characterized by pyrexia, colicky diarrhea, and eosinophilia. It responded to therapy with albendazole.

Cryptosporidiosis

Cryptosporidium is an intestinal protozoan (Figure 7), which is often a benign commensal in the human intestine that can cause clinical disease in the immunocompromised patient. It is a notorious infection in intestinal transplants [69] but has also been reported as a recrudescence disease in recipients of liver [70], kidney [71], and bone marrow [72] transplants.

It may cause a diarrheal illness that can lead to significant fluid and electrolyte depletion and may be fatal. It can also persist, leading to chronic diarrhea with hepatobiliary involvement [73]. There is no specific treatment, but the most widely used therapy is paromomycin.

Acanthamoebiasis

This is another protozoal disease caused by a free-living amoeba, *Acanthamoeba castellani*, that typically complicates corneal transplantation leading to progressive keratitis, corneal opacities, or perforation [74] (Figure 8). It also has been reported in bone marrow [75] and peripheral stem cell [76] and kidney [77] transplantation.

Disseminated acanthamoebiasis in transplant recipients is associated with gastroenteritis, sclerosing cholangitis [75], encephalitis [76], and osteomyelitis [77]. A fatal outcome has been reported in a few cases where treatment with macrolides was unsuccessful. Other antiprotozoal agents have not been tested in disseminated acanthamoebiasis.

Microsporidiasis

Microsporidia are intracellular spore-forming protozoa that are ubiquitous in the environment and may live in the intestine of insects, birds, and mammals. Human infection has been described most commonly with *Enterocytozoon bieneusi* in patients with HIV disease and only rarely in those with other forms of immunosuppression. Only 12 cases of microsporidiosis have been reported in

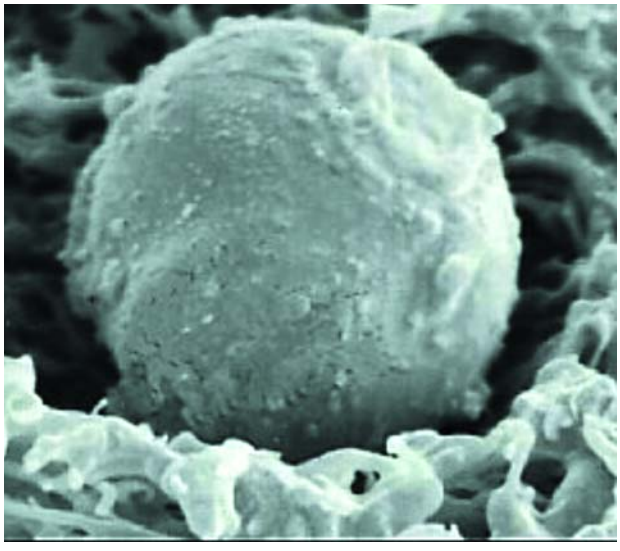

Figure 7. *Cryptosporidium parvum*

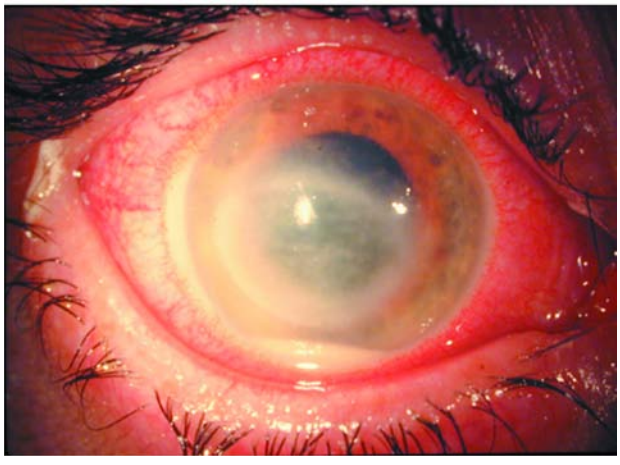

Figure 8. Acanthamoeba keratitis

solid transplant recipients until 2004 [78]. These were recipients of kidney [79] and pancreas-kidney [78] transplants (Figure 9).

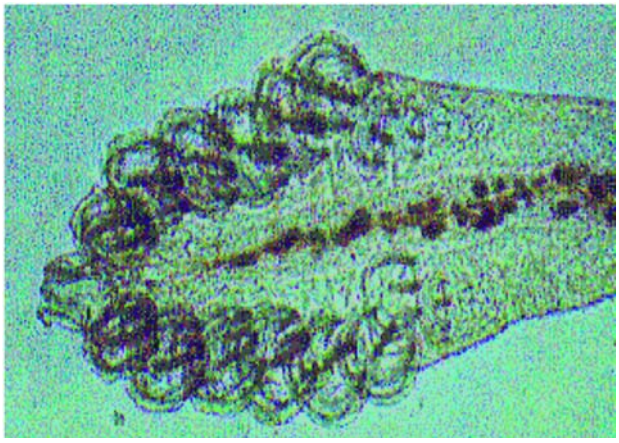

Figure 9. *Enterocytozoon bieneusi*

Infection usually begins with diarrhea and cholangitis. Disseminated microsporidiosis is dominated by a febrile systemic inflammatory response, with rapid development of pneumonia and encephalitis, which is often fatal. The treatment of choice is albendazole.

Skin and Subcutaneous Parasites

Of 56 known parasitic infections of the skin, only cutaneous leishmaniasis and American trypanosomiasis have acquired clinical importance in organ transplant recipients.

Cutaneous Leishmaniasis

Cutaneous leishmaniasis is caused by *L. mexicana* or *L. braziliensis*, depending upon geographic location. Skin lesions also can occur long after recovery from visceral leishmaniasis. They can be localized, diffuse, or mucocutaneous. The skin lesions are basically painless ulcerating nodules (Figure 10) with regional lymphadenopathy.

Recurrence of cutaneous leishmaniasis has been described in immunocompromised patients [80] as well as in organ transplant recipients [81,82]. The skin lesions tend to be diffuse rather than localized and may involve internal organs and the retina [83].

Cutaneous Manifestations of Chagas' Disease

Subcutaneous nodules that rarely ulcerate are often seen in the acute phase of Chagas' disease. They are a prominent feature in posttransplant recrudescence [84] as well as transmitted disease [85]. They have been described as the only manifestation of the disease in a renal transplant recipient [86]. Complete healing has been reported under allopurinol therapy [85].

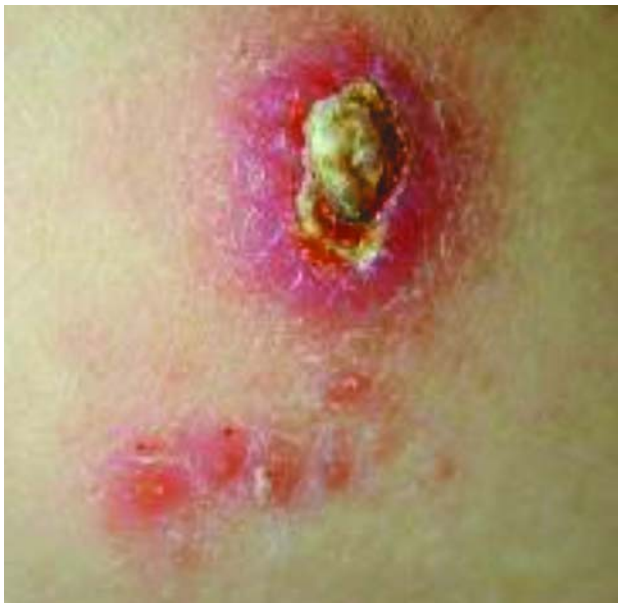

Figure 10. Oriental sore (cutaneous leishmaniasis)

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