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# The immunology of parasite infections in immunocompromised hosts

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## Summary

Immune compromise can modify the severity and manifestation of some parasitic infections. More widespread use of newer immnosuppressive therapies, the growing population of individuals with immunocompromised states as well as the prolonged survival of these patients have altered the pattern of parasitic infection. This review article discusses the burden and immunology of parasitic infections in patients who are immunocompromised secondary to congenital immunodeficiency, malnutrition, malignancy, and immunosuppressive medications. This review does not address the literature on parasitic infections in the setting of HIV-1 infection.

### Keywords

cancer; chemotherapy; HTLV-1; immunocompromised; steriods; transplantation

## Introduction

Parasitic diseases continue to be a major cause of morbidity and mortality, with more than 3 billion people infected worldwide. Many of these infections occur in the developing world, where improved measures to prevent infection require considerable investments in the public health infrastructure. The segment of the population with significant defects in the immune system continues to grow. This population includes the malnourished, those with acquired or congenital immunodeficiencies, as well as patients receiving a wide array of immunosuppressive regimens, including corticosteroids, and the ever growing list of increasingly aggressive immunosuppressive agents used in haematopoietic and solid transplant patients, as well as agents to combat collagen-vascular diseases. In many instances, the ability to successfully combat parasitic infections requires that the host mount an effective inflammatory response against the parasite, while limiting potential tissue damage to the host. Acquisition of infection, clinical severity and outcome of a parasitic disease often depends on innate and acquired host immunity. Immunosuppression, either at



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the humoral or cellular level, has different consequences for the host depending on its magnitude, and will alter the range of pathogens to which they are susceptible.

## Metazoan Infections

### Nematodes

**Strongyloides stercoralis—***Strongyloides stercoralis*, the causative agent of strongyloidiasis, is an intestinal nematode found worldwide in moist soil contaminated by human faeces (1,2). Occupational exposure to contaminated faeces can result in transmission of this disease. This organism currently infects approximately 100 million people worldwide. Unique among the human parasitic nematodes, *S. stercoralis* has an autoinfective cycle that allows infection to persist in the host indefinitely without the need for an external environment. In the immunocompetent host, this nematode can cause a chronic, well-regulated, and occasionally life-long parasitosis (3,4). During chronic uncomplicated infections and disseminated hyperinfections, *S. stercoralis* filariform larvae may migrate to the skin, causing a variety of lesions. Common skin manifestations of strongyloidiasis include (i) a migratory, pruritic, raised, linear rash called ‘creeping eruption’ or ‘larva currens’ and (ii) crops of urticarial eruptions that appear to be manifestations of immediate hypersensitivity reactions to migrating worms.

One of the major stages of the development cycle of *S. stercoralis* within the human body is the transformation of rhabditiform larvae into invasive filariform larvae in the gut (5). This event is referred to as an autoinfectious cycle. Corticosteroids may reduce local inflammation, thus impairing the ability of the gut to contain the parasites. With increased numbers of larvae completing the autoinfection cycle, large numbers of worms can enter the systemic circulation producing a hyperinfection syndrome associated with sepsis or meningitis with enteric organisms causing significant morbidity and mortality in immunocompromised patients (6). Glucocorticoid treatment and human T-lymphotropic virus type 1 (HTLV-1) infection are the two conditions most specifically associated with triggering hyperinfection (7,8).

Disseminated infection has been reported in people with a broad array of immune defects. This population includes individuals with haematopoietic malignancies or connective tissue disease being treated with immunosuppressive therapies and hosts with congenital or acquired hypogammaglobulinaemia. Patients on corticosteroid therapy, hepatic transplantation, renal transplant recipients or patients with renal deficiency, patients with systemic lupus erythematosus, asthma, chronic dermatosis, chronic infections (lepromatous leprosy, tuberculoid leprosy, and tuberculosis) as well as those with neoplastic conditions (lymphoma, leukaemia, and solid tumours), protein-calorie malnutrition, chronic alcoholism, AIDS and achlorhydria, are at higher risk for strongyloidiasis (7–10). Eosinophilia is frequently absent in disseminated infections and in patients receiving corticosteroids (11).

**Immunology—**In both immunocompetent and immunocompromised patients with chronic active infection, high immunoglobulin (Ig) G antibody titres to *Strongyloides* filariform larval antigens have been demonstrated (11,12). Most patients also have specific serum IgA responses against filariform larval antigens. The role of serum IgA antibodies in this disease is unclear, as the magnitude of the antibody response correlates poorly with clinical disease (13). Immediate hypersensitivity is a prominent component of the immune response to *Strongyloides* infection and may play a role in the pathogenesis of disease as well as in protection. Exacerbation of *Strongyloides stercoralis* infection has been associated with infection with human T lymphocyte virus-1 (HTLV-1) (14). HTLV-1-infected hosts appear to have a virally induced Th1 immune system bias. HTLV-1 infection results in increased interferon-gamma (IFN-γ) production from peripheral blood mononuclear cells, and

decreased levels of interleukin (IL) 4 and IgE (15,16). The low total serum levels of IgE may represent selective immunosuppression by the retrovirus, creating a permissive environment for nematode proliferation (17,18).

## Protozoan Infections

### Toxoplasma gondii

*Toxoplasma gondii* is a ubiquitous, obligate intracellular coccidian protozoan parasite of humans and other warm-blooded animals. *Toxoplasma gondii* exists in three forms: tachyzoite, bradyzoites (tissue cysts), and oocysts (the sexual stage which only develops in the intestine of cats) (19). Infections are transmitted by the ingestion of tissue cysts in meat, oocysts contaminating food or water, transplantation of infected organs, or accidental inoculation (20,21). This parasite has a predilection for the brain, heart, lungs, pericardium, and lymphoid tissues (22). Chronic infection of the immunocompetent results in protective immunity (23,24). Congenital toxoplasmosis occurs when seronegative pregnant women are infected, and is characterized by neonatal disease ranging from subclinical to prenatal death or stillbirth depending on the timing of maternal acquisition (25). Immunocompromised pregnant women with chronic infection (26,27) can have reactivation associated with congenital infection (28). While persistence of *Toxoplasma* cysts within host tissues may contribute to maintenance of immunity against reinfection, their presence also represents a risk for reactivation of infection in immunocompromised patients (20). Immunocompromised hosts will often fail to generate a specific antibody response to acute infection, or this response will be delayed (29). In non-AIDS patients, the majority of cases occur in those with haematopoietic malignancies during chemotherapy (especially regimens including corticosteroids), where disease is typically the result of the reactivation of latent infection in the absence of a limiting immune response; and in organ and haematopoietic transplant recipients where disease is generally due to dissemination from the transplanted organ. Additionally, a recent case report describes the reactivation of cerebral toxoplasmosis in a patient with rheumatoid arthritis when humanized monoclonal anti-TNF-α (tumour necrosis factor-alpha) antibody (infliximab) was added to an existing immunosuppressive regimen (30).

**Immunology—**Immunity to toxoplasmosis is largely T-cell mediated. Specific deficiencies in the cell-mediated immune responses towards *Toxoplasma* lysate antigens (TLA) may account for the significant organ damage observed in infants and children with congenital toxoplasmosis (31). While $CD4^+$ and $CD8^+$ cytotoxic T lymphocytes are known to act synergistically in the immune response to *T. gondii* infection (32), astrocytes, a subset of glial cells dominant in the central nervous system (CNS), may also be important in resistance to *T. gondii* (33). Using a murine model of *T. gondii* encephalitis, Gazzinelli *et al.* demonstrate that the down-regulation of IFN-γ and TNF-α results in decreased macrophage or microglial cell activation with subsequent reactivation of *T. gondii* (34).

$CD4^+$ T cells are heterogeneous with regard to cytokine secretion (35). Infection of mice with *T. gondii* elicits both a protective Th1 and immune down-regulatory Th2 cytokine response (36). The Th1 cells preferentially secrete IL-2 and IFN-γ, whereas Th2 cells predominantly produce IL-4, IL-5 and IL-10 (37). Interferon-γ, IL-2, and IL-12 have all proven to be important in host protection against infections with obligate intracellular parasites (38,39). In illustration, using wild-type (wt) and IFN-γ knockout (gko) mice exposed to *T. gondii*, Scharton-Kersten *et al.* demonstrate that the production of IL-12 precedes and initiates the synthesis of IFN-γ, while the latter directly controls parasite growth and diminishes the contributions of Th2 producing T-cell subsets (40). Natural killer (NK) cells (40) and $CD8^+$ T lymphocytes (41) have both been shown to play a central role in the endogenous production of IFN-γ. Additionally, oral infection of IFN-γ receptor-deficient

(IFN-γ R0/0) mice with low-virulent toxoplasms reveal the absolute requirement of IFN-γ for efficient macrophage activation in the defence against toxoplasmosis (42).

Gamma-delta (γδ)T cells appear to play an important role in the early host immune response to infection with *T. gondii*. The adoptive transfer of γδT cells from TCR-αβ deficient mice challenged with UV-irradiated parasites into microglobulin-β2-deficient mice depleted of both $CD4^+$ and NK cells prolonged survival in infected mice (43). Additionally, Nagasawa *et al.* have shown that in mice, the induction of intracellular and surface heat shock protein 65 (hsp65) (a known γδ T-cell ligand) correlates closely with protection against *Toxoplasma* infection (44).

Experimental evidence in a murine model suggests that exogenously administered recombinant IL-2 (rIL-2) is protective against a lethal challenge of *T. gondii* (45). The increased survival rate in IL-2-treated mice is likely the result of potentiated NK-cell activity against *Toxoplasma* tachyzoites (46). Interieukin-15 (IL-15), a cytokine that is biologically similar to IL-2, is secreted by activated monocytes/macrophages (47) and stimulates a number of cell types including NK cells, γδ T cells, and B cells (48,49). Recombinant IL-15 administered in conjunction with soluble *Toxoplasma* lysate Ag (TLA) generated toxoplasmacidal Ag-specific $CD8^+$ T cells, which exhibited long-term memory cytotoxic T lymphocyte (CTL) activity against infected target cells (50). Although this and other studies appear to reveal the importance of IL-15 in the maintenance of $CD8^+$-dependent T-cell memory for *T. gondii* (51), recent work demonstrates that IL-$15^{-/-}$ mice subjected to intraperitoneal infection with *T. gondii* are capable of developing long-term protective antitoxoplasma immunity. Additionally, IL-$15^{-/-}$ mice demonstrated an infection-induced expansion of splenic NK and $CD8^+$ T cells (52).

Another cytokine implicated in host protection against infection with *Toxoplasma gondii* is IL-7. Produced by fetal thymus and bone marrow stromal cells, this monomeric protein induces the proliferation of $CD4^+$ and $CD8^+$ T cells, pro-B lymphocytes, and enhances the cytotoxicity of NK cells and CTL (53,54). When given at the time of infection with a lethal dose of *T. gondii*, IL-7 treatment resulted in murine survival. Phenotypic analysis of treated mice identified an expansion of splenic NK and $CD8^+$ T-cells. Additionally, cytokine analysis revealed a role for IL-7 in the reversal of the parasite-mediated down-regulatory response on IL-2 and enhancement of the IFN-γ response.

During the response of naive Th cells, the presence of IL-4 causes precursors to develop into a population comprised largely of Th2-like effectors. Additionally, IL-4 down-regulates the production of IFN-γ by the Th1 subset of $CD4^+$ T cells (55). Using a murine model of acute *Toxoplasmosis*, oral infection with *T. gondii* tissue cysts revealed an exacerbative role for IL-4, as IL-$4^{-/-}$ mice were found to be more resistant to infection than WT mice. Additionally, plasma IL-12 and IFN-γ levels were higher in IL-$4^{-/-}$ mice. While the exacerbatory role of IL-4 in the intestine was not associated with increased parasite burdens, it was related to comparative expression of IL-10 (56). Demonstrating the intricate balance between Th1 and Th2 responses to infection, Gazzinelli *et al.* have demonstrated an important *in vivo* role for IL-10 in preventing host immunopathology through the down-regulation of monokine and IFN-γ responses to acute intracellular infection (57).

Mononuclear phagocytes are potent mediators in the host defence against a number of intracellular protozoa (58,59). Successful phagocytic activity requires the participation of reactive oxygen metabolites, which are generated during the oxidative metabolic burst under a number of stimulatory conditions (60,61). Phagocytes with substantial activity against *T. gondii* have been shown to contain granule peroxidase, and possess the capacity to generate

a vigorous respiratory burst (62). Additionally, IFN-γ has been shown to activate human macrophage oxidative metabolism and antimicrobial activity (63).

The roles of antibody and complement in the killing clearance of *T. gondii* remain uncertain, although the combination can kill extracellular trophozoites. While the humoral response to *T. gondii* infection includes the production of IgA, IgM, IgG and IgE antibodies, the cellular immune response appears significantly more important for the development of protective immunity (64,65).

## Leishmania spp

*Leishmania* encompasses a broad genus of flagellate protozoa with a worldwide distribution. *Leishmania* exhibit two morphologic forms in their complex life cycle: the amastigote, found intracellularly in vertebrates, and the promastigote, found in the digestive tract of invertebrate hosts. Human infection is initiated by the bite of an infected phlebotomine sandfly. Organisms enter macrophages at the site of the bite and replicate within phagolysosomes. Complement activation may assist in the invasion of the host cell by the parasite (66).

The organisms that cause cutaneous and mucocutaneous leishmaniasis include *Leishmania braziliensis*, *Leishmania major*, *Leishmania mexicana*, *Leishmania tropica*, *Leishmania peruviana*, and *Leishmania aethiopica. Leishmania donovani* (India and Africa), *Leishmania infantum* (Mediterranean), and *Leishmania chagasi* (South America) can all cause visceral leishmaniasis (Kala-azar). Leishmaniasis has been recognized in a broad spectrum of both normal and immunocompromised individuals (67). Cutaneous leishmaniasis is characterized by the development of cutaneous papules that evolve into nodules that ulcerate. Healing leads to the production of depressed scars (68). Local inflammation is primarily lymphocytic and granulomatous, with necrosis of the skin occurring early. In the mucocutaneous form of the disease, organisms spread via the bloodstream or lymphatics to the mucosal surfaces of the nose, mouth, pharynx, and larynx (69). In visceral leishmaniasis, a chronic, and if untreated, highly lethal disease, infected macrophages from the skin serve as a reservoir for organisms that infect spleen, lymph nodes, liver, bone marrow, and intestinal mucosa. This infection causes hyperplasia of focal lymphoid tissue with granulomata. Ulceration of mucosal surfaces may occur. Parasitization of macrophages and Kupffer cells results in enlargement of the liver and spleen.

Recovery from leishmaniasis appears to be followed by a long-lasting immunity, and in immunocompetent persons, second infection is rare (70). There is nearly uniform detection of antibodies against a broad range of *Leishmania* antigens in immunocompetent individuals and in non-AIDS immunocompromised patients with visceral disease. Murine studies suggest that following infection, *Leishmania* amastigotes remain viable, virulent, and are capable of inducing progressive disease under conditions of immunosuppression (71). In addition to AIDS, underlying disorders that predispose to visceral leishmaniasis include lymphoreticular neoplasias, renal transplantation, protein-calorie malnutrition, systemic lupus erythematosus, and corticosteroid therapy (72,73). In endemic areas malnutrition is probably the most important immunosuppressive mechanism predisposing to severe visceral leishmaniasis (73,74). In solid organ transplant recipients, pulse-dose steroids, antilymphocyte antibodies, and intensified immune suppression may accelerate disease.

**Immunology—**Coordinated innate and acquired immune responses influence global outcome of infection. All species of *Leishmania* are intracellular parasites of macrophages. For this reason, the functional status of T lymphocytes and of cytokines affecting macrophage function determines the extent to which organisms are able disseminate within the host (75,76). It has recently been shown that dendritic cells (DC) and macrophages use

different receptors to recognize and ingest *L. major*. Additionally, the authors demonstrated the importance of B-cell-derived, parasite-reactive IgG and DC Fc (77) receptors for optimal development of protective immunity (78).

Resolution of leishmaniasis is dependent on the cell-mediated immune responses (79). In both murine and human infections, effective Th1 responses have been associated with healing. Conversely, strong Th2 responses have been associated with active disease (76,80). In immunocompetent hosts, $CD4^+$ T lymphocytes respond to *Leishmania* antigens by proliferation and production of lymphokines, such as IFN-γ, IL-3, granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor (M-CSF). This results in the activation of microbicidal systems in the macrophages, and the inhibition of intracellular parasite replication (76,81). Several cytokines such as IL-4, IL-I0, and transforming growth factor (TGF)-β are capable of disabling Th1-cell mechanisms, which support chemotherapy (80).

In the immunocompetent individual with cutaneous leishmaniasis, strong delayed hypersensitivity and *in vitro* proliferative responses take place both during the disease and after healing (76). Patients lacking immune responsiveness to the parasite may develop diffuse cutaneous leishmaniasis (DCL), which is characterized by significant *Leishmania*-specific antibody production in the absence of T-cell proliferation or delayed hypersensitivity response to the parasite (76). In visceral leishmaniasis the host is completely lacking a cellular immune response to leishmanial antigens and parasitization of the reticulo-endothelial system is uncontrolled. Despite high levels of circulating antibodies in immune complexes, disease may spread rapidly without therapy (82). Skeiky *et al.* have described the cloning and expression of an *L. braziliensis* gene homologous to the eukaryotic ribosomal protein eIF4A (LeIF). Recombinant LeIF was shown to elicit IL-12 production in normal human peripheral blood mononuclear cells (PBMC), as well as IL-12 production and Th1-type responses in patients with mucosal and self-healing cutaneous disease (83).

All *Leishmania* species express a surface glycocalyx, composed of related glycolipids, including lipophosphoglycan and glycoinositol phospholipids. Components of this surface coat are likely involved in the activation of innate and adaptive immune response against *Leishmania* infection. Group 1 CD1 molecules have been shown to present mycobacterial lipids and glycolipid to specific T cells. Dendritic cells can initiate antimicrobial responses by CD1-mediated presentation of pathogen-derived glycolipids. Amprey *et al.* have demonstrated that infection with *Leishmania donovani* inhibits CD1 expression on human DCs, and prevents activation of CD1-restricted T cells by DCs (84). Natural killer (NK) T cells are activated by synthetic or self-glycolipids and implicated in innate host resistance to a range of viral, bacterial, and protozoan pathogens. Amprey *et al.* also described a *Leishmania*-induced CD1-dependent activation of NKT cells. The elicited response was rapid, Th1 polarized, and independent of IL-12. Additionally, NKT-cell-deficient CD1 (−/−) mice were more susceptible to *Leishmania donovani* infection than their wild-type counterparts. These data suggest an important role for the CD1–NKT-cell immune axis in the early response to visceral *Leishmania* infection (85).

## Trypanosoma cruzi

*Trypanosoma cruzi*, the causative agent of Chagas' disease, is transmitted by the reduvid bug. Approximately 18 million people are infected, the majority residing in the endemic areas of Central and South America. Ten to thirty per cent of infected individuals develop clinical disease associated with congestive heart failure or mega syndromes of various hollow organs (e.g. oesophagus, colon or ureter). Numerous reports of severe forms of Chagas' disease exist in the immunocompromised patient. These most frequently include

meningo-encephalitis and acute myocarditis (86,87). Individuals with lymphoreticular neoplasias receiving immunosuppressive therapies, as well as renal, bone marrow, and cardiac transplant patients appear to be at greatest risk for severe clinical manifestations (88). These disease manifestations typically result from the reactivation of chronic infections, although acute forms resulting from blood transfusions have also been reported (89). Experimental models of chronic infection with *T. cruzi* demonstrate reactivation of the disease with an increase in parasitaemia, exacerbation of myocarditis and myositis, as well as increased mortality in mice submitted to a number of different immunosuppressive regimens (90,91).

**Immunology—**The survival of *T. cruzi* in the vertebrate host depends on its evasion from and suppression of immune effector mechanisms. *Trypanosoma cruzi* has established mechanisms to subvert the host complement system (92). In both acute and chronic disease, the immune suppression caused by *T. cruzi* is characterized by reduced T-cell proliferative responses to polyclonal activators or recall antigens (93–95). It is also associated with decreased secretion of IL-2 (96), and activation-induced T-cell death (97). This immune suppression is believed to contribute to pathogenicity, and manifests clearly in experimental models (93). Several studies suggest that suppression is mediated by parasitic antigens, which cross-react with host antigens at the B- or T-cell level (93,94). In a murine model of *T. cruzi* infection, elevated splenic levels of the negative T-cell regulatory molecule CTLA-4 represented a marker of severe disease (98). Although still under debate, there is evidence that the pathology of chronic Chagas' disease depends on the continuous presence of parasites (99).

## Plasmodium spp

Interestingly, this important worldwide pathogen has not emerged as a major opportunistic pathogen in immunocompromised hosts. As a result, we will not discuss the *Plasmodium* spp. in this review and refer readers to the article dedicated to the topic of malaria appearing in this issue.

## Babesia spp

*Babesia* spp. cause a zoonotic disease that is transmitted by the ixodid tick. It is a zoonotic disease. Several species of *Babesia* cause human disease, including *Babesia microti* and *Babesia divergens*. These piroplasms replicate in host erythrocytes. The spectrum of disease can range from a silent infection, to a fulminant malaria-like illness. Clinical manifestations depend on the age and immunocompetence of the host, as well as the infecting species (100). Abnormal T-lymphocyte function is associated with the development of severe disease (100). In particular, splenectomy is an important risk factor for the development of severe babesiosis (101). Babesiosis has occasionally been seen as a complication of blood transfusion or in organ transplantation. In animal models, the level of parasitaemia is markedly enhanced by the administration of corticosteroids (102).

**Immunology—**In murine models, macrophage depletion (103) or inhibition (102) abolished the protection of mice immunized with *Babesia rodhaini*. Adoptive transfer of macrophages from immune animals has been shown to confer protection on naïve mice challenged with *B. microti* (104). Reactive oxygen and nitrogen intermediates, and TNF-α from stimulated macrophages, appear to mediate parasite death. Levels of NK-cell activity correlate with resistance to *B. microti* in inbred mouse strains. Studies have demonstrated high NK-cell activity in the early stages of infection (105), as well as during peak parasitaemia and the recovery phase (106).

Humoral immunity is considered of limited importance in protection against babesia infections. While transfer of immune serum can delay the onset of *B. rodhaini* parasitaemia in a murine model (107), it does not appear to be able to prevent the development of infection, confer the ability to resolve infection, or alter mortality (107,108). In fact, it has been suggested that *Babesia* species may subvert the humoral immune response by using host IgM (109) and complement (110) to facilitate infection.

The importance of cell-mediated immunity in resistance to *Babesia* infections is illustrated by the significant correlation of splenectomy with severe babesiosis. Matsubara *et al.* have developed a model of murine babesiosis using a mouse-adapted substrain of *Babesia microti*. Mice with severe combined immunodeficiency (SCID), as well as nude mice, demonstrated high levels of persistent parasitaemia, but the adaptive transfer of thymocytes from BALB/c mouse resulted in SCID and nude mice being able to control the infection (108). The transfer of purified T lymphocytes from immune animals has the ability to confer immunity to *B. microti* in naïve mice (111). *In vivo* depletion studies suggest $CD4^+$ T helper cells are the subpopulation of T cells mediating protection. IFN-γ liberated from activated $CD4^+$ T cells may be directly toxic to free and intracellular parasites, and likely plays an important role in clearance of the pathogen from an infected host (112).

## Giardia spp

Giardiasis is an important cause of enteric disease worldwide. Infection with *Giardia lamblia* is caused by ingestion of food or water contaminated with cysts. Patients may develop diarrhoea, malabsorption, and weight loss. Several reports of giardiasis in immunocompromised patients exist (113). Malnutrition, hypogammaglobulinaemia and dys-gammaglobulinaemias are associated with an increased risk of symptomatic disease (114).

**Immunology—**Secretory IgA antibodies play a central role in antigiardial B-cell-dependent host defences (115). In murine models, T cells appear to be important in the intestinal elimination of the parasite (116). However, patients with marked T-cell deficiencies do not exhibit increased susceptibility to giardiasis (117). Experimental evidence also suggests a role for IL-6 in the early control of murine disease (118).

## Cryptosporidium spp

*Cryptosporidium* spp. are important worldwide causes of morbidity and mortality (119). In humans *Cryptosporidium parvum*, considered a zoonotic disease, and *Cryptosporidium hominis* are the most common species described. Infective oocysts are transmitted by faecal–oral contamination of food or water or occasionally by inhalation. Large epidemics have been associated with contaminated public water reserves, as well as fruits and vegetables washed with contaminated water (119).

These organisms cause a moderate self-limited gastroenteritis in the immunocompetent host. In patients with AIDS this organism can cause severe enteritis. A similar syndrome can be seen in patients with the entire range of immune dysfunction. Susceptible immunocompromised patients include neutropenic hosts, haematopoietic and solid organ transplant recipients and individuals with primary immunoglobulin deficiencies (120). In these populations *Cryptosporidium* spp. is associated with a prolonged, severe gastrointestinal infection. Mead *et al.* have developed murine models of chronic cryptosporidial infections in congenitally SCID and nude mice with features similar to that of persistent infections observed in immunodeficient patients (121). The relative absence of effective therapy for this pathogen increases its impact (122,123).

The molecular mechanism and specific proteins involved in the initial interaction between *Cryptosporidium* sporozoites and the intestinal epithelial cells are not known. *C. parvum* sporozoites exhibit surface-associated haemagglutination (lectin) activity (124). These surface-associated lectins have the potential to adhere to host cell receptors in the initial interaction between parasite and host (125).

**Immunology—**The exacerbation of infection by immune suppression reflects the role of the immune system in controlling replication. Both humoral and cellular immune mechanisms appear to be necessary for protection against *Cryptosporidium*, although humoral immunity is incompletely protective. In contrast to the immunocompetent host, immunocompromised patients with cryptosporidiosis fail to develop a significant serologic response to the organism (126,127). The ability to resolve infection depends on reversal of immune compromise in addition to therapy (119). IFN-γ has been shown to mediate an important protective innate response against *C. parvum* in animal models. Treatment of both immunocompetent and immunodeficient mice with IL-12 prior to inoculation with cryptosporidial oocysts prevented or greatly reduced the severity of infection through an IFN-γ-dependent mechanism (128). NK cells in the intestine are likely an important source of this T-cell-independent IFN-γ production (129).

Following infection with *C. muris*, SCID mice develop chronic infections and excrete large numbers of oocysts. Adoptive transfer of total, $CD4^+$ or $CD8^+$ depleted gut intraepithelial lymphocytes (IEL) from immune animals into *C. muris*-infected SCID mice reveal the importance of protective $CD4^+$ cells in the gut epithelium to control infection (130). Additional studies in knockout mice suggest that αβT cells are important for resistance to *C. parvum*, while γdT cells have a less critical role (131). While experimental murine models of *C. parvum* infection reveal only a minor role for $CD8^+$ T cells in the control of infection (132), bovine models suggest an important role for these cells in immune animals (77). There is a correlation between the development of immunity to *C. muris* infection and Th1 and Th2 cytokine production by murine splenocytes (133). This and other studies reveal the Th response against *Cryptosporidium* to be a dynamic one, with the generation of both Th1 and Th2 protective elements (134).

Acute cryptosporidiosis has been associated with production of IgM and IgG serum antibodies against the parasite (135). Reports of chronic cryptosporidiosis in children with congenital immunoglobulin deficiency but intact cellular immunity highlight the importance of antibodies in the immune response against *Cryptosporidium* (136). A number of polyclonal and monoclonal antibodies capable of neutralizing the infectivity of cryptosporidial sporozoites and merozoites have been produced (137–139). Langer *et al.* have found that neutralizing monoclonal antibodies protected against C. *parvum* infection by inhibiting sporozoite attachment and invasion (138). Immunotherapeutic approaches towards treatment of this infection include the use of cow's milk globulin and hyperimmune bovine colostrums (HBC) (140–142). Although the active ingredient(s) of HBC are unknown, bovine $IgG_1$ may play a role in protection, as it is very closely related to human IgA (143). Results of human studies have shown conflicting results in the effectivity of HBC in the control of cryptosporidial infection (144,145).

Sero-epidemiologic studies have indicated that between 30% and 80% of healthy adults will produce serum antibody to *Cryptosporidium*. As a result, commercially available human serum immune globulin likely contains substantial amounts of antiparasitic IgG antibody (146). This therapy has proven effective in at least one paediatric patient who experienced a prolonged cryptosporidial infection while receiving maintenance therapy for acute leukaemia (146).

### Cyclospora spp

Originally described as 'cyanobacterium-like bodies', worldwide reports have confirmed the association of diarrhoeal illness with the coccidian protozoa *Cyclospora cayetanensis* (147). Evidence suggests a faecal–oral route (directly or via contaminated water) of transmission. It is not known if this is a zoonosis. Several foodborne outbreaks implicating contaminated raspberries, black berries and blueberries have been described (148,149). Diarrhoea due to this pathogen is often intermittent and associated with significant systemic symptoms such as fatigue and weakness.

While evidence of high recurrence after treatment is confirmed in patients with leukaemia or cirrhosis, these conditions do not appear to correlate with a more severe course of diarrhoea (150).

Data on the immune response to *C. cayetanensis* is lacking. Previous exposure may confer some resistance against challenge infection (151).

### Primary amoebic meningoencephalitis

Free-living amoebae are widely distributed in soil and water, particularly members of the genera *Acanthamoeba* and *Naegleria*. They have been recognized as opportunistic pathogens that are capable of causing infections of the CNS in both immunocompetent and immunocompromised hosts. *Naegleria fowleri* is the causal agent of a fulminant CNS condition, primary amoebic meningoencephalitis; *Acanthamoeba* spp. (*Acanthamoeba castellani*, *Acanthamoeba hatchetti*, *Acanthamoeba griffini*, *Acanthamoeba divonensis*, *Acanthamoeba palestinensis*, *Acanthamoeba culbertsoni*, *Acanthamoeba astronyxis* and *Acanthamoeba rhysodes* (152)) are responsible for a more chronic and insidious infection of the CNS termed granulomatous amoebic encephalitis, as well as amoebic keratitis. *Balamuthia* spp. have been recognized in the past decade as another amoeba implicated in CNS infections. Primary amoebic meningoencephalitis (PAM) is an uncommon infection of the CNS produced by the amoebae *Naegleria* and *Acanthamoeba* and rarely *Balamuthia mandrillaris*. Other than corneal disease, granulomatous amoebic encephalitis due to *Acanthamoeba* is generally restricted to debilitated individuals or those with immune defects. These defects include individuals with AIDS, diabetes mellitus, cirrhosis, corticosteroid therapy, cancer chemotherapy and in renal, hepatic, and bone marrow transplant recipients (153).

**Immunology—**In patients suffering from PAM, and in corresponding animal models, the brain undergoes a massive inflammatory response, followed by haemorrhage and severe tissue necrosis. Rat microglial cells have been shown to undergo time-dependent necrotic cell death when exposed to *N. fowleri* trophozoites. Additionally, microglial cells co-cultured with *N. fowleri* trophozoites secrete the pro-inflammatory cytokines, TNF-α, IL-1β and IL-6 (154).

### Entamoeba histolytica

*Entamoeba histolytica* is a pseudopod-forming protozoan of the family Endamoebidae (155). While *E. histolytica* is morphologically identical to the nonpathogenic *Entamoeba dispar*, the two can be distinguished by their antigenic, enzymatic, and genetic differences. Infection with *E. histolytica* is common in tropical regions, making amoebiasis the third leading cause of mortality due to parasitic infection, following malaria and schistosomiasis. While the majority of individuals infected with *E. histolytica* remain asymptomatic, under appropriate conditions this pathogen invades the intestinal mucosa, causing dysentery, mass lesions (amoeboma), or extraintestinal lesions including liver abscesses. Among compromised hosts, patients receiving chemotherapy, corticosteroid therapy, or

immunosuppression for organ transplantation are at a greater risk for the development of fulminant colitis (156,157). The mechanism by which amoebiasis is exacerbated in immune suppression is not understood. Host genetic factors and nutritional status, as well as the infecting strain of *E. histolytica*, are important determinants in the outcome of infection (158,159).

**Immunology—**The success of this pathogen is due, in part, to its ability to circumvent the host immune response. Innate mechanisms are responsible for initial resistance to *E. histolytica*. When successful, these mechanisms avoid invasion of the pathogen and limit infection. Physical barriers include the host intestinal mucous layer and structures of the colonic epithelium. The complement pathway is of limited defence for the host, particularly the alternative pathway as pathogenic strains of *E. histolytica* are resistant to killing by the C5b-C9 membrane attack complex (MAC). One mechanism through which the organism evades complement-mediated lysis is through expression of a galactose and N-acetyl-D-galactosamine (Gal/GalNAc)-specific lectin which has antigenic cross-reactivity with human CD59 (a leucocyte antigen that prevents the assembly of the C5b-C9 MAC) (160,161). Additionally, extracellular cysteine proteinases of *E. histolytica* are capable of degrading the complement anaphylatoxins C3a and C5a (162).

The development of a humoral immune response to *E. histolytica* is independent of clinical disease. *E. histolytica* infection elicits mucosal IgA and serum IgG response to the lectin protein. The mucosal IgA response directed at the carbohydrate-recognition domain of the Gal/GalNAc lectin has shown to be protective against infection (163,164). Adult patients cured of acute infection have been shown to produce high levels of intestinal antilectin IgA antibodies that persisted for over 18 months. Such patients are also immune to infection by *E. dispar* (163), which contains functional lectin molecules that are antigenically cross-reactive with the *E. histolytica* lectin (163). Epitope-specific mouse monoclonal antibodies against the cysteine rich region of the Gal/GalNAc lectin heavy subunit have been shown to inhibit adherence to target cells (163,165,166).

Intestinal epithelial cells initiate an inflammatory response to *E. histolytica* infection. Activation of nuclear factor κB and production of pro-inflammatory cytokines has been demonstrated to play a significant role in both tissue damage and host defence against *E. histolytica* trophozoites (167). Specifically, *in vitro* studies suggest an important synergistic role for IFN-γ and TNF-α in murine macrophage (168) and human neutrophil (169) enhancement of amoebicidal activity, as well as increased neutrophil resistance to amoebic contact-dependent killing (169).

## Infections Due to Protists Related To Fungi

### Pneumocystis jirovecii

*Pneumocystis* spp. display a range of host-specific genetic characteristics (170). The *Pneumocystis* species that infects humans (previously termed *Pneumocystis carinii)* has been renamed *Pneumocystis jirovecii* (171). On the basis of molecular taxonomic studies, pneumocystis was reclassified as an ascomycetous fungus in 1988 (172–174). The morphologic appearance, chemical composition, and responsiveness to antiprotozoal drugs of these organisms, however, have important similarities with the protozoan parasites (172–174). Pneumocystis exists primarily as a non-invading alveolar pathogen. Infrequently, pneumocystis disseminates in the setting of overwhelming infection or severe underlying immunosuppression (175). Person-to-person transmission is the most likely mode of acquiring new infections, although acquisition from environmental sources such as soil may also occur (171,176).

*Pneumocystis jirovecii* has been implicated as a cause of pneumonia in a wide array of non-AIDS immunocompromised patients (170,177). Risk factors for the development of pneumocystis pneumonia (PCP) include AIDS, prematurity, severe malnutrition, long-term corticosterioid therapy, chemotherapy, radiation therapy, organ transplantation, malignancy (especially haematopoietic), congenital immune deficiency diseases (cellular, humoral, combined), collagen vascular disease, haematologic disorders (178–182) and low-dose methotrexate therapy for rheumatoid and psoriatic arthritis (183–185). Protein-calorie malnourished or corticosteroid-treated individuals appear to have greater susceptibility to infection with *P. jirovecii* than do patients with other induced immune deficiencies (186). Mouse models of *P. jirovecii* pneumonitis confirm the association of immune suppression and protein-calorie malnutrition in the development of disease (187). When compared to patients with AIDS, individuals with PCP related to other forms of immunosuppression typically present with a shorter median duration of symptoms and lower median room air arterial oxygen tension (188). Additionally, mortality rates in this population are reportedly as high as 60%. This is significantly higher than in patients with AIDS (182).

**Immunology—**Following entry into the lung, pneumocystis organisms are embedded in protein-rich alveolar exudates containing abundant host fibronectin, vitronectin, and surfactant proteins (189,190). Surfactant proteins interact with components of the pneumocystis surface to mediate the aggregation of organisms, as well as their attachment to integrin receptors on the alveolar epithelium (191–193). One such component of the pneumocystis surface is a heavily glycosylated glycoprotein termed glycoprotein A, or major surface glycoprotein. This molecule is immunogenic and antigenically distinct in every form of pneumocystis infecting mammalian hosts (194,195). Another important component of the cyst cell wall is beta-1,3-glucan (196). In association with chitins and other complex polymers, this glucan provides the pneumocystis cell wall with stability, and plays a role in the marked inflammatory response in the lungs of the infected host (197).

In infected tissues, type I pneumocytes with adherent pneumocystis appear eroded (198). Studies of cultured alveolar epithelial cells have shown that the adherence of pneumocystis alone does not disrupt their metabolic, structural, or barrier function (199). Rather, the inflammatory response of the host is primarily responsible for the epithelial derangements characteristic of *P. jirovecii* pneumonia. Exuberant lung inflammation promotes pulmonary injury during infection, and correlates more closely with diffuse alveolar damage, impaired gas exchange, and clinical outcome than with the organism burden (200).

Pneumocystis cannot be easily propagated in culture. For this reason, experimental studies typically employ the infected-animal model of pneumocystis pneumonia. Intricate interactions between cellular immune effectors and soluble factors characterize the immune response to pneumocystis. *In vivo* depletion of $CD4^+$ T cells predisposes mice to infection with pneumocystis (201,202) and the passive transfer of T lymphocytes can cure this infection in nude mice (203). Severe combined immunodeficiency (SCID) mice lack functional T and B lymphocytes and develop spontaneous pneumocystis infection by 3 weeks of age (204). Immune reconstitution with $CD4^+$ T cells restores the ability of SCID mice to effectively clear infection (205). In patients with the human immunodeficiency virus (HIV) type 1, PCP is unlikely to develop with a $CD4^+$ T cell count above 200 cells/$mm^3$ (206).

$CD8^+$ T cells are required for the positive therapeutic effect of IFN-γ gene transfer on experimental pneumocystis in CD4-deficient mice (207). However, activated $CD8^+$ T cells have also been associated with substantial pulmonary inflammation and injury in PCP (208). TNF receptor signalling has been shown to be required for maximal $CD8^+$ T-cell activity (209). A recent murine study identifies the IFN-γ secreting T cytotoxic-1 (Tc1) cells as the

CD8 subpopulation associated with protection. Conversely, the non-Tc1 CD8 population appears to be associated with tissue damage (210).

$CD4^+$ T cells proliferate in response to pneumocystis antigens and generate cytokine mediators, including lymphotactin and IFN-γ (205). Lymphotactin, a chemokine, acts as a potent chemoattractant for lymphocyte recruitment in pneumocystis pneumonia (211). In an analogous fashion, the chemokine IL-8 is strong neutrophil chemoattractant, and has been implicated in the pulmonary inflammatory response to infection (212). Neutrophils recruited into the lungs during infection with pneumocystis are postulated to directly mediate alveolar epithelial cell injury through the release of reactive oxidant species (ROS) and other agents of inflammation (171,198). However, using murine models with significant deficiencies in the production of reactive oxygen species, nitric oxide production, and accumulation of intra-alveolar neutrophils, Swain *et al.* suggest that while the presence of neutrophils correlates strongly with lung damage during infection with pneumocystis, neither neutrophils nor ROS appear to be the causative agent of tissue damage (213).

Alveolar macrophages also play an important role in the host defence against pneumocystis. Koziel *et al.* demonstrate that functional impairment of alveolar macrophage mannose receptor-mediated binding and phagocytosis of pneumocystis is seen in cells from HIV-positive individuals, and is greatest in cells from those with $CD4^+$ counts below 200 cells/$mm^3$ (214). An additional role for alveolar macrophages is the release of pro-inflammatory cytokines such as TNF-α following macrophage activation by components of the parasitic beta-glucan cell wall (197). These events lead to the recruitment of a number of immune effector cells and mediate clearance of the pneumocystis. As previously mentioned, this immune response also results in significant host pathology.

Human serologic studies demonstrate nearly 100% seropositivity to pneumocystis in tested populations by 2 years of age (215). Passive immunization with monoclonal antibodies is partially protective against *P. jirovecii* infection suggesting that humoral immunity plays a role in the host response against this pathogen. Mice deficient in B cells are highly susceptible to infection with pneumocystis. However, experiments by Lund *et al.* suggest that the major protective effect of B cells is through the activation of $CD4^+$ T cells, as opposed to their ability to produce *P. jirovecii*-specific IgG (216).

## Microsporidia

The Microsporidia are obligate intracellular, spore-forming, protists. Several genera of Microsporidia (*Enterocytozoon*, *Encephalitozoon*, *Brachiola*, *Pleistophora*, *Nosema*, *Trachipleistophora* and *Microsporidium*) have been associated with human infections. Many of these organisms are zoonotic. Transmission is probably from food or water containing spores, although insect vectors, sexual transmission and respiratory transmission have also been reported (217,218). While gastrointestinal infection is common, these pathogens have also been associated with systemic infections involving almost every organ system (219). *Enterocytozoon bieneusi* is currently the most commonly recognized microsporidian species in humans and is found predominantly in patients with AIDS (220,221). *E. bieneusi* and other microsporidia have also been isolated from immunocompetent patients, such as travelers and contact lens wearers, and from and immunocompromised patients such as those with organ transplantation or receiving immunosuppressive medications (such as corticosteroids and anti-TNF-α) (222–224). The clinical manifestations of microsporidiosis may vary depending on the infecting species, mode of infection, age of the host at the time of infection, and the competence of the host's immune response (224). In solid organ transplant recipients (heart, lung, liver, kidney and pancreas) and bone-marrow transplant recipients, microsporidial diarrhoea, pneumonitis, keratitis, and encephalitis have been observed.

**Immunology—**Cell-mediated immunity is critical for protection against the Microsporidia (217). *Encephalitozoon cuniculi* is able to persist in its animal host despite an active immune response; however, latent infection remains asymptomatic as long as parasite multiplication and the host immune response are balanced. In murine *E. cuniculi* infection, corticosteroid treatment can perturb this balance, resulting in disease reactivation (225). In humans, microsporidiosisis is predominantly associated with $CD4^+$ T cell deficiency. Immunodeficient murine models have proven useful to the study of the host immune response to *E. cuniculi*. In contrast to the chronic infection established in immunocompetent mice, athymic and SCID mice develop lethal disease following infection with *E. cuniculi* (226,227). Adoptive transfer of sensitized, T-cell enriched splenocytes to infected athymic mice confers resistance to lethal disease (226). Similar immune reconstitution can be seen in SCID mice (226). An effective Th1 cytokine response is important in the immune response to microsporidia. *In vivo* treatment of *E. cuniculi*-infected mice with antibodies to IFN-γ or IL-12 rendered them susceptible to infection (228). *E. cuniculi* infection has also been shown to induce a strong $CD8^+$ CTL response, restricting parasite growth by perforin-dependent lysis of infected cells (229). The induction of $CD8^+$ CTLs is at least partially regulated by γδT cells (230).

*In vitro*, murine peritoneal macrophages can be activated by incubation with lipopolysaccharide (LPS) and murine recombinant IFN-γ to kill *E. cuniculi* (231). However, the ability of mice deficient in inducible nitric oxide synthase ($NOS2^{-/-}$) to resist infection suggests a lesser role for reactive nitrogen intermediate-induced killing in the control of microsporidial infections (228).

The role of humoral immune responses in microsporidial infections is yet to be fully understood. However, evidence to date suggests that as in other human opportunistic protozoal infections, microsporidian-specific antibodies alone may not be protective (226,230,232). In animals, microsporidial infection activates antibody production, and persistence of antibodies reflects latent infection with the parasite. Immune serum from sensitized euthymic mice transferred to athymic mice does not stop or delay the progression of the infection (226). Microsporidia can evade intracellular killing and successfully reside within macrophages. *In vitro* experiments by Niederkorn *et al.* on the ability of mononuclear peritoneal macrophages to phagocytose *E. cuniculi* suggest a role for antibody enhancement of phagocytosis and intracellular killing in host defence against microsporidiosis in rabbits (233).

## Summary

The purpose of this review was to discuss the burden of the major parasitic infections in the immunocompromised patient. Within this context, we discuss the complex immunological interplay between the host and pathogen, and where possible, discuss published research on the immunology of these pathogens using animal models of immunosuppression. Immunosuppression can affect the presentation of a parasitic disease, the susceptibility of the host to various pathogens, and the efficacy of therapy for these diseases. As the population of immunosuppressed patients increases in regions of endemicity for parasitic infections, we can expect that new manifestations of these diseases in this specialized patient population will be discovered.

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