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Importance of Nonenteric Protozoan Infections in Immunocompromised People

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INTRODUCTION

A previous report by Stark et al. (533) reviewed the clinical significance of various enteric protozoa in immunocompromised (IC) patients. While enteric protozoan infections are important in IC groups, there is also a large number of nonenteric protozoa capable of causing significant morbidity and mortality, particularly in IC patients. The clinical significance of tissue protozoa in HIV-infected patients has been reviewed previously by others (308), although due to recent developments, an update is warranted. This paper reviews the scientific literature obtainable mostly from the last decade pertaining to protozoan infections in IC patients. The role of certain tissue protozoan infections in human pregnancy is also discussed.

Several nonenteric protozoa are capable of infecting multiple cell/tissue types. Furthermore, virtually every human cell/tissue type is capable of hosting a number of parasitic and potentially parasitic protozoa. This is particularly true for IC patients, whose reduced immunity allows these infections to progress to full capacity without challenge.

The majority of protozoa discussed here have completely adapted to a parasitic life and are unable to survive in the absence of their preferred host(s). The nonenteric microsporidia, the trypanosomatids (*Leishmania* spp., *Trypanosoma* spp., and most lower trypanosomatids), *Toxoplasma gondii*, *Neospora caninum*, *Plasmodium* spp., and *Babesia* spp. are all among the true parasites that will be discussed herein. While many of these protozoa are responsible for zoonoses, some have a limited host range that does not usually include humans under normal circumstances. However, in cases of severe immunosuppression, parasites that rarely infect humans may do so to cause life-threatening disease. This is true for the microsporidia and some lower trypanosomatids whose host range is usually restricted to a few lower vertebrates and invertebrates.

The coccidian parasite *T. gondii* is capable of infecting virtually all warm-blooded organisms (180, 274) but can complete the sexual component of its life cycle only in the intestine of cats (178, 274). Human contact with *Toxoplasma* is common (2, 13, 622), with one-third of the human population believed to be infected (599). Despite this, *Toxoplasma* infections are typically benign (599), with clinically apparent toxoplasmosis occurring almost exclusively in severely IC patients (405, 599).

The role of the coccidian *N. caninum* in IC patients is vague, although recent research suggests a role for *N. caninum* as an opportunistic organism in IC groups. *Neospora* is closely related to *Toxoplasma*, although *Neospora* is best known as a pathogen of veterinary significance. While no human infections with *N. caninum* have been confirmed, the high incidence of *N. caninum* antibodies in patients with HIV compared to non-HIV-infected groups suggests a potential role for *Neospora* as an opportunistic organism in IC patients (361).

Members of the genus *Babesia* have a broad host range, which includes various rodents and ruminants (56, 75, 307). Several *Babesia* species are capable of infecting humans, although *Babesia microti* and *Babesia divergens* are most often

associated with human infection (106). While some *Babesia* spp. have the ability to cause clinical disease in immunocompetent (ICT) humans, there are a number of IC groups that are predisposed to a more severe form of babesiosis.

Several parasitic protozoa have evolved to cause a potentially fatal disease in ICT humans. Several species of *Leishmania*, *Trypanosoma*, and *Plasmodium* are among this group of potentially lethal protozoa. In IC patients infected with these protozoa, disease progression is often more rapid and severe than that in ICT patients. Immunocompromised patients may also present with unusual clinical signs. The reduction in the immune capacity observed for HIV-infected patients also means that the complete eradication of these protozoa is unlikely and the risk of disease relapse is high. The human-infecting species of *Leishmania* and *Trypanosoma* are also zoonoses (93, 123, 202, 418, 445), and the existence of animal reservoirs makes the control of these organisms particularly difficult.

Plasmodium falciparum, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi* are the only five malaria parasites known to infect humans. *Plasmodium knowlesi* is thought to be the only zoonotic malaria parasite, with the ability to cause disease in some nonhuman primates (350, 415). *Plasmodium falciparum* causes the most severe form of malaria, killing approximately 2.7 million people each year (546). *Plasmodium falciparum* is probably an obligate human parasite without any animal reservoirs, as it lacks the ability to infect gorillas and chimpanzees (412).

According to the World Health Organization (WHO), malaria and HIV are among the two most important global health problems of our time (603). Malaria is a huge economic burden in tropical and subtropical countries. The disease is believed to cost Africa alone approximately $12 billion U.S. annually (603). While the topic is of great significance, the importance of *Plasmodium*-HIV coinfections will not be discussed here in any further detail. This topic is thoroughly covered in the scientific literature, and there is a wealth of current resources available (46, 63, 109, 276, 308, 439, 557, 566, 570, 591, 597). The WHO Regional Office for South-East Asia website (http://www.searo.who.int/index.htm) also covers this topic in great detail. One document available from the WHO website is particularly relevant (603).

Some species of protozoa are not parasitic under normal circumstances but will invade the tissues of other organisms if an opportunity is presented. These organisms have no specific adaptations that enable them to parasitize mammalian tissues and normally survive freely in the environment. However, human and animal infections do occur on rare occasions. Infections with these protozoa are almost always fatal (456, 568, 594). These organisms are free-living amoebae, and the most clinically important of these include *Acanthamoeba* spp., *Naegleria* spp., *Balamuthia mandrillaris*, and *Sappinia pedata*.

The clinical importance of these pathogenic tissue protozoa in IC patients is reviewed. Immunocompromised groups discussed in this paper include transplant patients and pregnant women, although particular attention is paid to those infected with HIV.

NONENTERIC PROTOZOA IN PREGNANCY

The importance of tissue protozoa in pregnancy is a well-discussed topic in the scientific literature. This topic is also relevant to the focus of this paper because in the strictest sense, pregnant women are also IC. This controlled state of immunosuppression enables the pregnant mother to accommodate fetal antigens that would otherwise be considered foreign (618). As such, this section has been included in the manuscript as an introduction to the topic. More detailed information pertaining to the importance of various tissue protozoa (including *Plasmodium* spp.) in pregnancy was reported previously (43, 63, 70, 72, 73, 161, 192, 195, 203, 342, 432, 482, 499, 564, 565, 600, 616, 624). For information regarding malaria in pregnancy, the WHO website is useful (see http://www.who.int/features/2003/04b/en/).

During pregnancy, the maternal immune system is shifted to favor a T helper 2 (T_H2) immune response, while the T helper 1 (T_H1) response is downregulated (436, 618). This downregulation of the inflammatory T_H1-type immune response allows the mother to tolerate fetal antigens. However, the T_H1 response is essential for gamma interferon (IFN-γ) production and cytotoxic-T-cell activation, which are paramount to the eradication of intracellular pathogens such as *Leishmania*, *Trypanosoma cruzi*, and *T. gondii* (236, 421, 435, 436, 556). The production of IFN-γ is of particular importance to the control of *Toxoplasma* infections (289, 429, 435). Generally, a healthy mother will keep these infections in check for the duration of the pregnancy. However, the immature immune system of the fetus means that it is vulnerable to infections that may be able to cross the uterine-placental barrier.

In a normal pregnancy, the fetal and maternal circulations are partitioned by a layer of trophoblast cells, which prevent the direct mixing of the two (236). Large blood components such as lymphocytes and erythrocytes do not cross this partition. However, oxygen, nutrients, certain proteins, and endocrine molecules are allowed passage by means of active or passive transport (34). This means that intracellular parasites with limited host cell specificity, such as *Leishmania* (macrophages, neutrophils, and dendritic cells), *Babesia* (erythrocytes), and the extracellular parasite *Trypanosoma brucei*, are unlikely to pose a direct threat to fetal tissues for the duration of the pregnancy. However, at the time of birth a small amount of blood is exchanged between mother and neonate when the placenta separates from the uterine wall (236). This could allow the transfer of *T. brucei*, *Babesia*, or *Leishmania* infections from mother to neonate. Even so, congenital infections with *Babesia* (515), *Leishmania* (52), and *T. brucei* (480) are uncommon compared to congenital infections with *Toxoplasma* and *T. cruzi*.

For intracellular protozoa with a broad range of potential host cells, congenital transmission is reported more frequently. *Toxoplasma gondii* and *T. cruzi* are able to infect virtually all cell types and by these means have the ability to cross the placental-uterine barrier.

Chagas' Disease and Pregnancy

The transplacental transmission of Chagas' disease occurs with an efficiency of around 5% to 6% for infections acquired

in certain regions of Bolivia, Chile, and Paraguay (71, 465, 553). In other areas where the disease is endemic, an efficiency of 1 to 2% or lower has been reported (465). Recently, due to an increase in migration, congenital Chagas' disease has become an increasing public health concern in countries where the disease is not endemic (70, 223, 399, 615). Approximately 26% of all new *T. cruzi* infections are thought to be the result of congenital transmission (42).

Congenital Chagas' disease is thought to occur exclusively in pregnant woman who have lesions on their placenta (71). These lesions cause damage to the trophoblast partition, allowing trypanosomes to enter the fetal circulation (71). Most congenital infections are asymptomatic or cause nonspecific illness in neonates (42). However, a portion of these infections can result in abortion, low birth weight, hepatosplenomegaly, meningoencephalitis, respiratory insufficiency, anemia, and premature birth (42, 71, 553). Congenital infections with *T. cruzi* have a mortality rate of around 14% (71). Speculatively, as with *Toxoplasma* infections, the outcome for the fetus may be dependent on the time during gestation at which trypanosomes begin to parasitize fetal tissues.

Toxoplasmosis and Pregnancy

Toxoplasma gondii is the most significant protozoan pathogen in human pregnancy. Unlike *T. cruzi*, *T. gondii* has a worldwide distribution and a broad host range, which includes most warm-blooded animals. Approximately one-third of the entire human population is thought to be infected with *Toxoplasma*. Furthermore, the efficiency of congenital *Toxoplasma* transmission in humans was reported to be as high as 19.8% in one study (270). However, Innes et al. (290) suggested that the vertical transmission of *Toxoplasma* is not so efficient. Regardless, the importance of *Toxoplasma* to human pregnancy is significant.

In primary *Toxoplasma* infections, the control of the parasite is dependent on a strong T_H1 immune response characterized by the activation of cytotoxic T cells and the production of IFN-γ (436). This T_H1 response suppresses the replication and spread of *Toxoplasma* tachyzoites, which eventually leads to a benign infection. However, the T_H1-type response is downregulated during pregnancy. If the mother was infected with *Toxoplasma* prior to her pregnancy, the risk to the fetus is low. This is due to the development of immunological memory in the mother prior to pregnancy. In this case, the maternal immune system is able to suppress infections before they spread to the trophoblast cells of the placental-uterine partition (435). However, if the mother acquires a primary infection before 20 weeks of gestation, severe fetopathies can result. These can include any combination of the following: chorioretinitis, hydrocephalus, intracranial calcification, and convulsions (538). The overproduction of IFN-γ due to a primary *Toxoplasma* infection early in a pregnancy may also lead to abortion (435). If infection occurs after 20 weeks of gestation, mild fetopathies (if any) may be observed (538). The fetus can produce antigen-specific responses from around 20 to 22 weeks of gestation (300). This reduction in the severity of *Toxoplasma*-related fetopathies after 20 weeks coincides with the appearance of the fetal immune system after approximately 20 weeks of gestation.

Other Protozoa in Pregnancy

Given the close relationship between *Toxoplasma* and *Neospora* and the high prevalence and efficiency of congenital *Neospora* transmission in cattle (607), *Neospora* may also present a risk in human pregnancies. Furthermore, data from experimental infections carried out with nonhuman primates suggest that transplacental transmission is also possible in humans (30). However, the role of *N. caninum* in human pregnancy is yet to be elucidated.

To our knowledge, cases of congenital transmission of all other tissue protozoa discussed in this paper (the microsporidia, nonhuman *Trypanosoma*, lower trypanosomatids, and free-living amoebae) have never been reported.

TISSUE-ASSOCIATED PROTOZOA

Nonenteric Microsporidia

Organism and disease. While the microsporidia are often described as protozoa (25, 363, 577, 578), recent reports indicated that they are actually more closely related to fungi (199, 256, 351, 376). However, in accordance with convention, the microsporidia are described here as protozoa.

The term microsporidia is used as general nomenclature for approximately 1,200 species of obligate intracellular parasites belonging to the phylum Microsporidia. These ancient organisms are ubiquitous in nature but are usually recognized as parasites of invertebrates (531). However, due to the emergence of the global HIV/AIDS pandemic, these organisms are now recognized as opportunistic infectious agents worldwide. The microsporidia are now recognized as significant human pathogens, with infections occurring mainly, but not exclusively, in severely IC patients.

Encephalitozoon spp. are the second most common cause of microsporidial infection in humans after the enteric microsporidian *Enterocytozoon bieneusi*. Three *Encephalitozoon* species are known to cause disease in humans: *Encephalitozoon cuniculi*, *Encephalitozoon hellem*, and *Encephalitozoon intestinalis*, previously known as *Septata intestinalis*. *Encephalitozoon* species are the most common cause of disseminated microsporidiosis (554), and all *Encephalitozoon* species have the propensity to disseminate in IC or immunosuppressed patients (166, 217, 540). *Encephalitozoon intestinalis* is often associated with enteric disease (115, 197) but can infect the kidneys (55), nasal mucosa (167), skin (317), eyes (304), and gallbladder (252). *Encephalitozoon intestinalis* may also be detected in saliva, urine, and bronchoalveolar lavage fluid (167). *Encephalitozoon hellem* can cause pulmonary disease (498), keratitis/keratoconjunctivitis (304), kidney disease, and nasal polyps (252). *Encephalitozoon cuniculi* can infect the intestines, liver, peritoneum, kidneys, and eyes (252, 304). One case study also described an undefined species of *Encephalitozoon* as the cause of sexually transmissible urethritis in an HIV-infected patient (45).

Trachipleistophora species are less frequently encountered than *Encephalitozoon* species. *Trachipleistophora hominis* is known to infect the myocardium and skeletal muscle of HIV-infected patients (132) as well as the conjunctiva, kidneys, and nasal sinuses (252). *Trachipleistophora anthropophthera* is associated with disseminated disease (576).

Nosema ocularum, *Anncaliia* (formerly *Brachiola*) *algerae*,

TABLE 1. Disease spectra observed for humans infected with various tissue-associated microsporidial species

Species of Microsporidia associated with human disease	Disease spectrum and/or tissue(s) involved
Encephalitozoon intestinalis	Disseminated disease, enteric disease; kidneys, nasal mucosa, skin, eyes, and gallbladder; has also been detected in saliva, urine, and bronchoalveolar lavage fluid
Encephalitozoon hellem	Disseminated disease, pulmonary disease, keratitis, keratoconjunctivitis, kidney disease, nasal polyps
Encephalitozoon cuniculi	Disseminated disease, CNS, intestine, liver, peritoneum, kidney, and eyes
Undefined *Encephalitozoon* species	Sexually transmissible urethritis
Trachipleistophora hominis	Myocardium, skeletal muscle, conjunctiva, kidney, and nasal sinuses
Trachipleistophora anthropophthera	Disseminated disease
Nosema ocularum, *Microsporidium ceylonensis*, *Microsporidia africanum*, *Vittaforma corneae*	Keratitis in immunocompetent hosts following eye trauma
Anncaliia (formerly *Brachiola*) *algerae*	Keratitis in immunocompetent hosts following eye trauma; myositis in an immunosuppressed patient
Anncaliia (formerly *Brachiola*) *vesicularum*	Skeletal muscle infections
Pleistophora species	Skeletal muscle infections
Anncaliia (formerly *Brachiola*) *connori*	Disseminated disease infecting the smooth muscle, cardiac muscle, kidney, liver, lungs, and brain

Microsporidium ceylonensis, *Microsporidium africanum*, and *Vittaforma corneae* are causes of keratitis in ICT individuals following eye trauma (168, 586). *Anncaliia algerae* was also reported to cause myositis in an HIV-negative woman receiving a range of immunosuppressive drugs for the treatment of rheumatoid arthritis (82). *Anncaliia* (formerly *Brachiola*) *vesicularum* and *Pleistophora* species are associated with skeletal muscle infections in HIV-infected patients (81, 252, 598). In IC patients, *Anncaliia* (formerly *Brachiola*) *connori* infects the smooth muscle, cardiac muscle, kidneys, liver, lungs, and brain (252, 598). A member of the genus *Nosema* was recently reported to cause keratitis in an ICT patient following bathing in a contaminated water source (133).

Transplant patients and patients suffering from leukocyte malignancies are also predisposed to infections with microsporidia. Pulmonary infection in a leukemia patient by an undefined species of microsporidia has been described (314). An undefined *Encephalitozoon* was described as the cause of disease in the graft of an HIV-negative renal transplant patient, resulting in renal dysfunction (348). Occasionally, the microsporidia may infect immunologically healthy individuals. One such case involved an unusual *E. hellem* infection where spores were being shed in the stool of an HIV-negative, immunologically healthy traveler (398). Table 1 summarizes the disease spectra associated with various species of tissue microsporidia.

The transmission of microsporidiosis is poorly understood, although infection must occur through the direct contact of spores with potential host cells. In cases of ocular infection, transmission results from the direct contact of spores with the eye (304). The inhalation or ingestion of spores from the environment is the probable mode of transmission for some *Encephalitozoon* species (163).

Diagnosis. The diagnosis of microsporidiosis usually relies on microscopy. The use of PCR can be difficult due to the species-specific nature of most PCR assays and the broad range of microsporidia capable of infecting tissues. A PCR-restriction fragment length polymorphism (RFLP) assay is available, which can differentiate between five species of microsporidia (528) and may be useful if applied to DNA extracted from infected tissues or fluids. A PCR method for the differentiation of a number of *Encephalitozoon* species and *E. bieneusi* has also been described, although this method requires downstream processing such as sequencing, RFLP, and/or Southern blot hybridization (212). Real-time PCR assays have been developed for the detection of *E. intestinalis* DNA in stool specimens, which may be adapted to tissue specimens (390, 611). There are several other PCR assays available that may be useful for identifying and/or differentiating various microsporidia (55, 59, 148, 166, 200, 211, 359).

In cases of ocular infection, microscopic examination of corneal scrapings is usually employed for diagnosis (207). Various stains may be applied to fixed corneal scrapings, although a potassium hydroxide-calcofluor white stain was found to be most efficient in one study (303). A PCR assay has also been developed for the detection of *V. corneae* DNA in corneal scrapings (468). Another PCR assay for the detection of *V. corneae* DNA in trichrome-stained smears of corneal scrapings has also been developed (98).

Calcofluor white and a modified trichrome blue stain (165) are useful for the detection of microsporidia in clinical specimens such as bronchoalveolar lavage fluid or urine. Calcofluor white shows greater sensitivity than trichrome blue, although differentiation between calcofluor-stained yeasts and microsporidia may be difficult (165). While it is less sensitive, the trichrome blue stain enables better differentiation between yeast cells and microsporidia (165).

Indirect fluorescent antibody techniques (IFATs) are also available for some *Encephalitozoon* species (529), as are a broad range of non-species-specific stains that can be applied to tissue biopsy specimens and smears (529, 595). If differentiation between species is necessary and PCR or species-specific IFAT is unavailable, transmission electron microscopy (TEM) (Fig. 1) performed on fixed tissue sections may be useful (55). A direct agglutination test (DAT) is also available, which can detect anti-*E. cuniculi* antibodies (302).

Treatment. Albendazole is the drug of choice for the treatment of disseminated microsporidian infections (39). Albendazole demonstrates good antimicrosporidial activity against *Encephalitozoon* species, particularly *E. hellem* (162, 166, 209), *in vivo* and *in vitro*. The drug itraconazole may also be useful

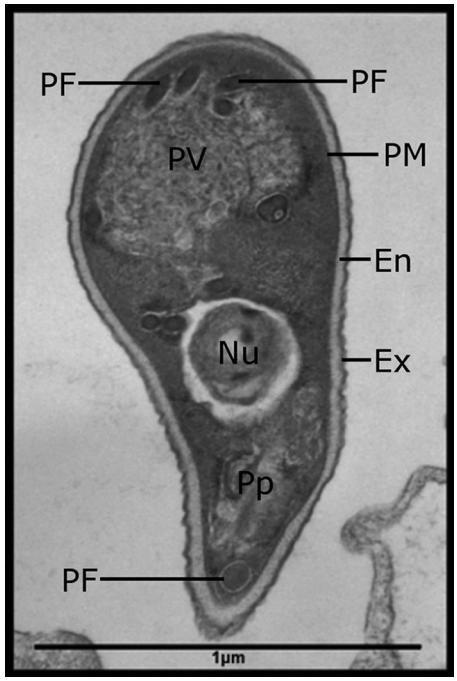

FIG. 1. Transmission electron micrograph of an *Encephalitozoon cuniculi* spore. The main characteristics are labeled, including the polar filament (PF), posterior vacuole (PV), plasma membrane (PM), endospore (EN), exospore (EX), polarplast (Pp), and nucleus (Nu).

when combined with albendazole therapy for infections caused by *Trachipleistophora* or *Anncaliia* (39). Fumagillin is useful for the treatment of ocular microsporidiosis and is applied to the site of infection in the form of eye drops (39). Oral clindamycin therapy may be effective for the treatment of disseminated *E. intestinalis* infection (316, 317). Immune restoration following highly active antiretroviral therapy (HAART) is also necessary for the resolution or remission of microsporidial disease occurring as a result of HIV infection (224, 393).

Given the close relationship between the microsporidia and fungi, it is not surprising that certain antifungal compounds (particularly some benzimidazoles) exhibit good antimicrosporidial activity (164, 233, 489, 491, 532, 617). As such, the future discovery of novel antifungal compounds may also have implications for future antimicrosporidial therapy.

Leishmania

Organism and disease. *Leishmania* spp. are obligate intracellular parasites that cause three major syndromes in humans: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucocutaneous leishmaniasis (MCL) (264). Leishmaniasis is transmitted between hosts via an insect vector, which includes species of sandfly from the genera *Phlebotomus* and *Lutzomyia* (609). Infection occurs when an infected female fly takes a blood meal from an uninfected host, injecting flagellated promastigotes into the bite wound (609). Promastigotes are then phagocytosed by macrophages, neutrophils, or dendritic cells (58, 475). Once inside the host cell phagolysosome, promastigotes transform into nonflagellated amastigotes, where they multiply by binary fission, eventually destroying the host cell (460, 609). While the process of promastigote entry into host cells is generally described as occurring by means of phagocytosis, this process is now thought to be more complex, involving a series of host-parasite cell interactions (324, 408, 475). Infections with visceral *Leishmania* species can also be transmitted via blood transfusion and organ transplantation (379).

Various terrestrial mammals are potential reservoirs of *Leishmania* infection, including rodents and canids (264, 609). Most cases of New World leishmaniasis are the result of zoonotic transmission from either domestic canids or native wildlife (282). In these regions, the recent emergence of zoonotic leishmaniasis is an important public health concern, mostly attributable to poverty, urbanization, and human migration (12, 282).

Approximately 12 million people are thought to be infected with *Leishmania* worldwide (150). *Leishmania* infects 500,000 people annually, resulting in approximately 50,000 associated deaths (374). Approximately 19,000 to 24,000 new cases of VL are reported each year in sub-Saharan Africa alone, with most cases occurring in the East African countries of Sudan, Eritrea, Ethiopia, Kenya, and Somalia (283). In these countries, most cases of VL are caused by *Leishmania donovani*, although *Leishmania infantum* is occasionally identified as the causative agent (283). The highest incidence of VL in sub-Saharan Africa occurs in Sudan, particularly on the Ethiopian border. Old World CL is also endemic to parts of sub-Saharan Africa, where the causative agent is usually *Leishmania major* (283). New World CL and MCL are endemic to parts of Central and South America, where the causal species is usually *Leishmania braziliensis* (218). A list of the clinical syndromes and/or diseases associated with various trypanosomatids (including *Leishmania*) is summarized in Table 2.

(i) Visceral leishmaniasis. Visceral leishmaniasis, resulting from the replication of amastigotes within mononuclear phagocytes of the liver, spleen, and bone marrow, usually results in fever, severe cachexia, hepatosplenomegaly, and pancytopenia (170, 264, 408). The symptoms of VL usually develop after an incubation period of weeks to years (264), and the disease is invariably fatal if left untreated.

(ii) Cutaneous leishmaniasis. CL is characterized by lesions on the surface of the skin resulting from the replication of *Leishmania* amastigotes within mononuclear phagocytes of the skin (Fig. 2 and 3). The morphology of skin lesions can vary greatly. Lesions can exist as ulcers, nodules, plaques, or papules. Ulcerative lesions eventually heal to leave atrophic scars. Patients can have multiple lesions at various localities. Typically, cutaneous lesions appear as well-defined ulcers with raised borders (248). Other unusual lesion morphologies (vegetative, verrucous, crusted, and lupoid) were described by Guimarães et al. (248). Cutaneous leishmaniasis can also present as disseminated skin nodules or papules (Fig. 3) (248). Ulcerative lesions can be painful, and secondary bacterial infections can occur. Cutaneous leishmaniasis can remain subclinical or may become clinically apparent after an incubation period of weeks to months (27, 247, 264, 473).

Usually, lesions undergo complete resolution in ICT individuals. In contrast, lesions in HIV-infected individuals are more severe, larger, and more diffuse and will increase in size without treatment (135, 247). Some cutaneous *Leishmania* spe-

TABLE 2. Disease spectra observed for humans infected with various trypanosomatids

Clinical syndrome or disease spectrum	Species	Distribution	Vector genus	Description
Visceral leishmaniasis	*Leishmania donovani*	Old World; parts of central Asia and East Africa	*Phlebotomus*	These *Leishmania* species may cause other syndromes (such as CL) in IC patients [see "*Leishmania* and HIV. (i) Atypical clinical features"]
	Leishmania infantum[a]	Old World; Mediterranean basin, Central Asia, Middle East, China	*Phlebotomus*	
	Leishmania chagasi[a]	New World; parts of Central and South America	*Lutzomyia*	
	Leishmania tropica	Old World; Mediterranean basin, Middle East, Southwest Asia	*Phlebotomus*	
Cutaneous leishmaniasis	*Leishmania tropica*	Old World; Mediterranean basin, Middle East, Southwest Asia	*Phlebotomus*	These *Leishmania* species may cause other syndromes (such as VL) in IC patients [see "*Leishmania* and HIV. (i) Atypical clinical features"]
	Leishmania major	Old World; Middle East, Southwest Asia, sub-Saharan Africa		
	Leishmania aethiopica	Old World; Ethiopia, Kenya		
	Leishmania killicki	North Africa		
	Leishmania mexicana *Leishmania amazonensis* *Leishmania venezuelensis* *Leishmania braziliensis* *Leishmania panamensis* *Leishmania guyanensis* *Leishmania peruviana* *Leishmania lainsoni* *Leishmania colombiensis* *Leishmania pifanoi* *Leishmania garnhami*	New World; parts of Central America, South America, and the Southern regions of the United States	*Lutzomyia*	
Mucocutaneous leishmaniasis	*Leishmania panamensis* *Leishmania braziliensis* *Leishmania braziliensis* *Leishmania guyanensis*	Parts of Central and South America	*Lutzomyia*	These *Leishmania* species may cause other syndromes (such as VL) in IC patients [see "*Leishmania* and HIV. (i) Atypical clinical features"]
Chagas' disease	*Trypanosoma cruzi*	Parts of Central and South America and South/Southwestern United States	*Triatoma*	In ICT patients, Chagas' disease is often associated with cardiopathies; in IC patients, Chagas' disease can also include CNS manifestations [see "Chagas' disease. (iv) Chagas' disease and HIV"]
African sleeping sickness ("nagana" in animals)	*Trypanosoma brucei rhodesiense* *Trypanosoma brucei gambiense*	Sub-Saharan Africa; Central and West Africa	*Glossina*	There is no evidence to indicate that the clinical course of sleeping sickness is worsened in IC patients
Sleeping sickness-like syndrome ("nagana" in animals)	*Trypanosoma congolense*	Sub-Saharan Africa	*Glossina*	The disease-causing potential of *T. congolense* is not certain, as the patient in this single report was also infected with a *T. brucei* species
Fever, chills, and sensory impairments ("surra" in animals)	*Trypanosoma brucei evansi*	Southeast Asia, Africa, and South America	Any hematophagous fly species and, in South America, vampire bats	*T. b. evansi* relies on mechanical transmission between hosts; therefore, any hematophagous insect or animal is a potential vector; in this single case report, the patient also experienced behavioral changes; the infection was partly attributed to a dysfunctional human trypanolytic factor
Transient fever ("nagana" in animals)	*Trypanosoma brucei brucei*	Sub-Saharan Africa	*Glossina*	In this case, *T. b. brucei* caused transient, self-limiting infection characterized by fever and severe dyspnea; only a single reported case; human infections with *T. b. brucei* are controversial
Fever, anemia, anorexia, and sometimes edema	*Trypanosoma* (*Herpetosoma*) *lewisi*	Malaysia, Africa, and India	Several species of flea	*Trypanosoma lewisi* infection is usually restricted to rodents; children seem to be more susceptible to *T. lewisi* infection than adults
Cutaneous leishmaniasis-like disease	Unnamed, highly divergent member of the genus *Leishmania*	Martinique	Vector unknown or nonexistent	Only 2 reported cases; this organism caused a small cutaneous, ulcerative lesion on the eyebrow of an ICT patient; for an HIV-infected patient, diffuse, cutaneous, nonulcerative lesions were reported
Visceral leishmaniasis-like syndrome	Undefined lower trypanosomatid	Spain	Vector unknown or nonexistent	Only 1 case reported; patient suffered from symptoms similar to those of VL, including pancytopenia and hepatosplenomegaly; the organism was similar to yet morphologically different from *Leishmania*; this species was blunt ended and had a denser kinetoplast
	Leptomonas pulexsimulantis-like organism	Brazil	No vector; a monoxenous trypanosomatid usually infecting fleas	Only 1 case reported; patient suffered from symptoms similar to those of VL, including splenomegaly and fever

[a] It is under debate as to whether *L. chagasi* and *L. infantum* are different species. Some believe that *L. infantum* was originally brought to the New World during the Spanish and Portuguese occupation of South America and that these species are identical.

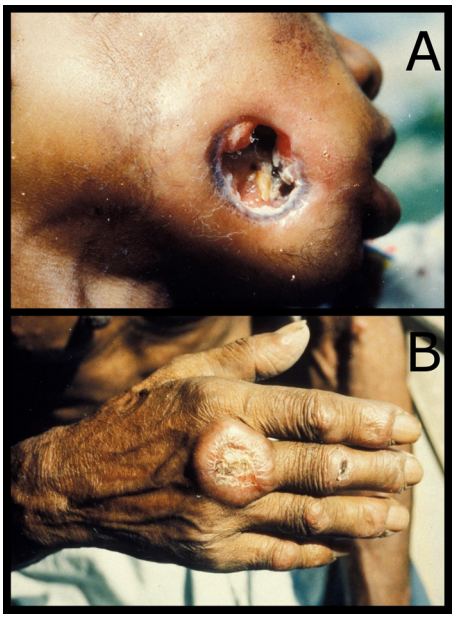

FIG. 2. Clinical presentation of cutaneous leishmaniasis. (A) Ulcerative lesion of the face resulting in complete perforation of the cheek. (B) Partially healed cutaneous lesion of the hand.

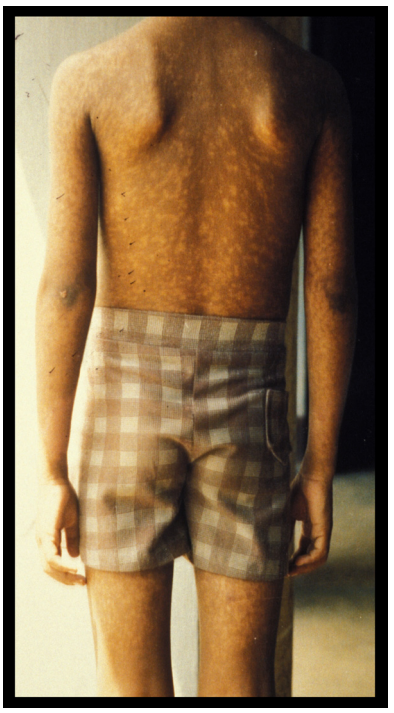

FIG. 3. Diffuse cutaneous leishmaniasis presenting as widespread, nonulcerative plaques.

cies also have the ability to induce T-cell anergy and apoptosis (442).

(iii) Mucocutaneous leishmaniasis. Mucocutaneous leishmaniasis is restricted to the New World and usually follows a cutaneous infection. The species most often associated with MCL is *Leishmania braziliensis*, although *Leishmania panamensis* and *Leishmania guyanensis* may occasionally cause MCL (264, 609). In MCL, *Leishmania* parasites travel from the skin through the lymphatics and/or blood vessels to the mucous membranes of the mouth, nose, throat, and soft palate (219). This results in the destruction of the naso-oropharyngeal membranes, and perforation of the nasal septum can occur (14, 173, 264, 609). Mucocutaneous leishmaniasis can occur concurrently with a cutaneous infection or months to years after cutaneous lesions heal (219). The risk of developing MCL following CL is believed to be less than 5% in ICT individuals (122, 219). While MCL can result in severe disfigurement, the mortality rate is low (219).

***Leishmania* and HIV.** Since the 1980s, *Leishmania*-HIV coinfections (especially infections with *L. infantum*) have become an important public health concern, particularly in European countries surrounding the Mediterranean basin. A study from 1998 reported that 10% of AIDS patients in southern Spain were also infected with *Leishmania* (440). Later studies estimated that 25% to 70% of adult patients with VL in the southern regions of Spain, France, and Italy were also infected with HIV (83). In fact, approximately 90% of all *Leishmania*-HIV coinfections identified by the WHO up to the year 2001 came from Spain, Italy, France, and Portugal (10). Much of the current literature regarding *Leishmania*-HIV coinfection in southern Europe comes from Spain, where *L. infantum* is endemic and VL is the most common syndrome encountered. In Spain, prior to 1985, most patients with VL were ICT children, but after 1998, approximately 80% of patients with VL were IC adults (362). Visceral leishmaniasis is also an important disease in HIV-infected persons in East Africa, South America, and Asia (10, 159).

In HIV-infected patients, the associated reduction in immune function allows latent infections of *Leishmania* to become clinically apparent (605). In one study, the prevalence of clinically apparent VL in HIV-infected patients was 2,320 times greater than that in ICT patients (362). Furthermore, the clinical course of VL is far more severe in HIV-infected patients than in ICT individuals (18).

Intravenous drug use is probably the largest risk factor for obtaining a *Leishmania*-HIV coinfection in southern Europe (83, 440, 449), with some studies reporting 80% to 90% of all coinfected patients being intravenous drug users (11, 362). Furthermore, a more recent report from the WHO stated that 64% of *Leishmania*-HIV coinfections reported in southern Europe between 2001 and 2006 were of intravenous drug users (604). It is probable that the sharing of needles facilitates the concurrent transmission of *Leishmania* and HIV in many of these cases (362).

(i) Atypical clinical features. *Leishmania*-HIV-coinfected patients will often present with atypical clinical features. For example, several studies reported cutaneous or mucocutaneous infections caused by the visceral species *L. infantum* (83, 120, 449). A case of post-kala-azar dermal leishmaniasis was also reported for an HIV-infected patient coinfected with *L. infantum* (534). *Leishmania donovani* can cause cutaneous disease in the presence of HIV (189), while *Leishmania mexicana* can cause visceral disease (463). While MCL usually follows a cutaneous infection, MCL has been reported as the first clinical manifestation of AIDS even before CL or other more

typical AIDS-defining illnesses (135). In a kidney transplant patient, concurrent cutaneous, visceral, and ocular leishmaniases as a result of *L. braziliensis* infection were also described (239). Interestingly, one report noted that 20% to 40% of HIV-infected patients with VL do not exhibit splenomegaly, which is a typical clinical feature of VL in ICT individuals (395).

In other cases of *Leishmania*-HIV coinfection, involvement of the lungs (83, 362, 584), gastrointestinal system (83, 362), pancreas (104), and eye (239) has also been reported.

(ii) *Leishmania* and HIV progression. *Leishmania*-HIV coinfections present a unique problem to clinicians, as *Leishmania* and HIV are thought to complement each other's disease progression. Some studies suggested that *Leishmania* may directly increase the rate of replication of HIV in human macrophages (158, 610, 623). Visceral *Leishmania* species also enhance the progression of HIV infections via the production of certain antigens that induce apoptosis of $CD4^+$ cells (450). Therefore, $CD4^+$ cell counts are an unreliable indicator of the effectiveness of antiretroviral therapy in these patients (17). Human immunodeficiency virus infection is thought to increase the chance of developing VL by 100 to 1,000 times in areas of endemicity (420). The presence of HIV in VL also improves the chances of relapse and reduces the likelihood of a therapeutic response to treatment (420). Cure of clinically apparent leishmaniasis may be achieved temporarily for HIV-infected patients, although it is unlikely that *Leishmania* parasites will be completely eradicated (155, 534).

Diagnosis. Conventional (23, 126, 137, 145, 205, 237) and real-time (91, 154, 396, 569) PCR assays, immunoassays (292, 484, 527), culture systems (17, 53, 527, 535), and microscopy (6, 130, 190) are available for the diagnosis of leishmaniasis. Light microscopy has been described as the method of choice for the diagnosis of leishmaniasis (408, 487). Any of the Romanowsky-based stains, such as a Wright stain (319) or Giemsa stain (130, 466), can be used for the direct microscopic identification of *Leishmania* parasites in tissue sections, smears, or tissue aspirates (Fig. 4B and D) (10). The inoculation of tissue aspirate material onto Novy-MacNeal-Nicolle agar for the cultivation of live *Leishmania* parasites may also be useful for diagnosis but may be impractical for some diagnostic laboratories (487). In Ethiopia, where *L. donovani* VL is endemic and resources are strained, the use of microscopy can also be impractical. In this case, an *L. donovani*-specific DAT is preferred (17). The DAT (and modifications of this test) demonstrate sensitivities of between 89% and 95% (10). The quantitative buffy coat (QBC) tube technique is a rapid and simple technique that is also useful for the diagnosis of VL (356).

Several other serological tests are available, including a commercial IFAT and the rK39 dipstick test (487). The rK39 dipstick test is rapid and inexpensive and displays sensitivities of >90% for the detection of *L. donovani*-associated kala-azar in India. However, sensitivities as low as 20% have been reported for HIV-infected patients with VL in Europe (10). In cases of severe immunodeficiency, enzyme-linked immunosorbent assays (ELISAs) and other serological tests can be of limited use, as antibodies to *Leishmania* may be absent despite an active infection (18, 158). Furthermore, antibodies to some antigenic epitopes of *Leishmania* can cross-react with those of *Trypanosoma* (and other protozoa), which can make the use of some serological tests problematic (10, 79, 381, 581). However, a recently developed latex agglutination test for the detection of *Leishmania* antigen in patient urine samples is available, which demonstrates good sensitivity and specificity (10).

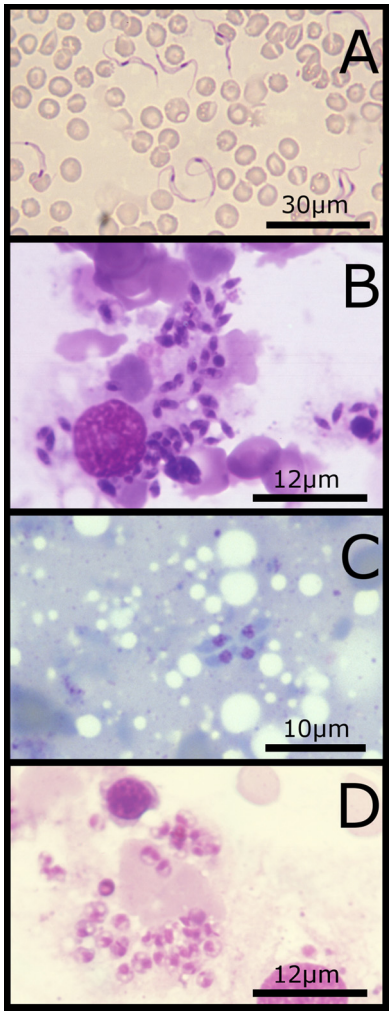

FIG. 4. Microscopic images from clinical samples. (A) *Trypanosoma brucei* trypomastigotes in a blood smear (Leishman stain). (B) Oval-shaped *Leishmania infantum* amastigotes from a bone marrow aspirate (Leishman stain). (C) *Toxoplasma gondii* tachyzoites from CSF (Giemsa stain). (D) Typical round *Leishmania* amastigotes from a bone marrow aspirate (Leishman stain).

PCR performed on DNA extracted from fluids, tissue scrapings, or punch biopsy specimens is a sensitive and specific alternative to serology and antigen detection (438, 527). PCR applied to peripheral blood specimens is useful for the diagnosis of VL in HIV-infected individuals (10). Conventional and real-time PCR assays for the diagnosis of CL have demonstrated greater sensitivity than microscopy or parasite culture (130, 391, 516). PCR performed on DNA extracted from paraffin-embedded tissues is also useful for the diagnosis of CL (490).

To ensure an accurate diagnosis, it is recommended that multiple diagnostic techniques are applied (where possible) when *Leishmania* infection is suspected in HIV-infected patients (143, 170, 441).

Treatment. The antimonial compounds (usually sodium stibogluconate and meglumine antimoniate), miltefosine, and amphotericin B are the mainstay of antileishmanial therapy (10, 17, 158, 239, 464, 488).

In developing countries, the pentavalent antimonial compounds are usually the first line of treatment for leishmaniasis due to their availability and low cost (17, 158). However, these compounds are quite toxic (17, 125, 149, 158, 362). Furthermore, due to their widespread use for over 70 years, resistance has meant that antimonials are virtually useless in parts of India and Nepal (24, 374). In regions of India where antimonial resistance was apparent, pentamidine was once used as an alternative. However, due to severe toxic side effects, the use of pentamidine was abandoned (10, 158). Generally, the pentavalent antimonials are not used in developed countries, where amphotericin B in various forms is favored due to reduced toxic side effects. The comparatively low toxicity of amphotericin B enables treatment with higher dosages and, subsequently, shorter courses of therapy (609).

Liposomal amphotericin B is the treatment of choice for VL (488), although it is expensive and may not be feasible in developing countries (158). In India, oral miltefosine therapy has gained widespread use for the treatment of VL due to its effectiveness and comparatively mild side effects (10). However, as with the antimonials, resistance to miltefosine is likely to become a future problem in India (408). Other drugs that have demonstrated anti-*Leishmania* activity include paromomycin (488), sitamaquine (464), and aminosidine (158), although these drugs have not gained widespread use. Interestingly, the HIV protease inhibitors indinavir and saquinavir have direct leishmaniacidal activity *in vitro* (497).

In Ethiopia, sodium stibogluconate is the first-line treatment for *Leishmania*-HIV-coinfected patients despite severe side effects, including a 33% chance that the patient will die of drug-induced pancreatitis (17). Unfortunately, less-toxic drugs such as amphotericin B and miltefosine are not as accessible in Ethiopia (17). Furthermore, Ethiopian patients with a *Leishmania*-HIV coinfection are less responsive to miltefosine than to antimonials (10).

In a recent study, the efficacy of various regimens for the treatment of American CL and MCL was reviewed (240). The findings of that study indicated that the conventional antimonial drugs (sodium stibogluconate or meglumine antimoniate injected intramuscularly) are efficacious for the treatment of New World CL and MCL (240). Oral allopurinol and oral pentoxifylline were also found to be good adjuvants to antimonial therapy (240). Furthermore, the efficacy of the drug miltefosine was found to be species dependent, being more effective against *L. panamensis* infections than against *L. mexicana* and *L. braziliensis* infections (240).

As with other protozoan-HIV coinfections, HAART resulting in immune reconstitution has greatly reduced the incidence of *Leishmania*-HIV coinfections in symptomatic patients (10, 147, 151, 488).

Trypanosoma

Members of the genus *Trypanosoma* are the causative agents of human African trypanosomiasis (African sleeping sickness) and American trypanosomiasis (Chagas' disease), two blood-borne diseases, each with an insect vector (32). Usually, two species of *Trypanosoma* are associated with human trypanosomiasis. These are *Trypanosoma cruzi* and *Trypanosoma brucei gambiense*/*Trypanosoma brucei rhodesiense*. A broad range of terrestrial mammals, including cattle, dogs, cats, and wild animals, behave as potential reservoir hosts for these species (160, 202, 287, 315).

Both species of *Trypanosoma* infecting humans are transmitted by blood-feeding insects, although they differ fundamentally in their modes of transmission. *Trypanosoma brucei* is transmitted in the salivary secretions of tsetse flies from the genus *Glossina*, while *T. cruzi* is transmitted in the feces of triatomine bugs (1, 127). *Trypanosoma brucei* infection occurs when the tsetse fly takes a blood meal (105, 196). Trypomastigotes from the fly's saliva enter the bite wound and multiply extracellularly in the blood, lymph, or spinal fluid. Humans become infected with *T. cruzi* when a triatomine bug takes a blood meal and defecates on the host's skin. Triatomine salival secretions cause the host to itch and unknowingly rub the triatomine feces (containing trypomastigotes) into the bite wound. Microabrasions caused by host scratching also allow the entry of trypomastigotes into the host (32). *Trypanosoma cruzi* trypomastigotes travel to various host tissues through the blood and lymph. The trypomastigotes eventually enter host cells, where they transform into the amastigote stage and multiply by binary fission until the host cell is destroyed. *Trypanosoma cruzi* may also be transmitted congenitally, via blood transfusion, or via organ transplantation (160, 425). Congenital transmission of *T. brucei* has also been reported although less frequently (105, 313, 413, 427, 480).

Trypanosoma cruzi and *T. brucei* also differ in distribution, with *T. cruzi* being endemic in the Southern/Southwestern regions of the United States and parts of Central and South America (494), while *T. brucei* is confined to parts of Central and Southern Africa (32). African sleeping sickness and Chagas' disease are both potentially fatal in the absence of treatment (32, 103) regardless of the presence of HIV.

Interestingly, human infections with several species of non-human-infecting trypanosomes have also been reported. The non-human-infecting trypanosomes *Trypanosoma brucei brucei*, *Trypanosoma brucei evansi*, *Trypanosoma congolense*, and *Trypanosoma* (*Herpetosoma*) *lewisi* are usually associated with animal disease but are now recognized as the potential agents of a transient, self-limiting illness in ICT humans (138, 299, 305, 495, 521, 560). As most human infections with the non-human-infecting trypanosomes were not associated with immune deficiencies, the role of these organisms in IC patients is yet to be defined. However, given their ability to cause illness in ICT humans, it is likely that these organisms will be recognized in the future as opportunistic agents in IC patients. As such, several case reports of human infection with these trypanosomes are also discussed.

Chagas' disease. Approximately 8 to 9 million cases of Chagas' disease are thought to exist worldwide, with approximately 50,000 cases reported annually (282). *Trypanosoma cruzi* infections in Latin America and the Caribbean are between 5 and 10 times more common than malaria in these regions (282). The Pan-American Health Organization (PAHO) estimates that 7.7 million people in 21 countries where the disease is endemic (including the United States) are infected with *T.*

cruzi (494). In recent years, Chagas' disease has become a public health concern in countries where the disease is not endemic due to immigration from areas where the disease is endemic (293, 294, 502, 601, 615). As such, the screening of solid-organ and blood donors for Chagas' disease has become increasingly important (92, 193, 220, 379). In Canada and some European countries, blood and organ donors are required to fill out a questionnaire in relation to Chagas' disease, and individuals known to be infected are prohibited from donating organs (379, 502). In the United States, screening of blood donors with a recommended enzyme immunoassay has been implemented but is not yet mandatory (502).

The clinical course of Chagas' disease is divided into three stages: the acute, intermediate, and chronic stages (160, 394, 454). At the initial site of infection, inflammation and swelling usually occur. The acute stage begins when symptoms appear 6 to 10 days after the initial infection and continue for up to 2 months (32, 394). Most infections occur during childhood (32).

(i) Acute stage. The acute phase of Chagas' disease often remains unnoticed or misdiagnosed, as the symptoms experienced, including anorexia, fever, malaise, nausea, vomiting, and diarrhea, are not particular to Chagas' disease (160). On rare occasions, death does occur in the acute phase of infection, usually due to myocarditis or meningoencephalitis (32, 457).

(ii) Intermediate stage. The acute phase of Chagas' disease is usually followed by a period of asymptomatic carriage of parasites, which usually remain with the patient for the rest of their life. Approximately 50% of all *T. cruzi*-infected patients are in this intermediate phase of Chagas' disease (454). These patients are generally asymptomatic and unaware of their disease. However, the presence of a *T. cruzi* infection can be demonstrated by serology, PCR, or parasite culture (454).

(iii) Chronic stage. Around 30% of all Chagas' disease patients will develop chronic disease, characterized by severe myopathies and organ and tissue damage after an incubation period of 10 to 30 years (32, 87). During this stage, cardiomegaly, megacolon, and megaesophagus may be observed in patients (543). The damage inflicted on the heart is often permanent and severe to the point where late-stage Chagas' disease patients may require heart transplantation (84, 139). Heart failure and sudden death will usually occur in the absence of treatment (32, 543). An abnormal electrocardiogram (ECG) may be apparent for years prior to the appearance of symptoms such as cardiomegaly. Therefore, an ECG can be used for the early detection of chronic Chagas' disease in patients with a known *T. cruzi* infection (222). Echocardiography and chest radiography are also employed to detect heart abnormalities associated with chronic Chagas' disease (222).

The management of Chagasic heart disease is usually dependent on individual patient circumstances (44, 221, 437, 481). For the treatment of bradyarrhythmias, a pacemaker can be fitted (222). For the treatment of certain ventricular arrhythmias, a cardioverter defibrillator may be implanted (222). Patients with refractory heart failure are usually assessed as candidates for heart transplantation (222). In transplant patients, there is a risk of reactivation of the disease in response to immunosuppressive antirejection therapy (44). There is also a risk of reobtaining a donor-derived infection with *T. cruzi* (222, 330). Chemotherapeutic compounds used for other heart conditions, such as the β-blockers or the drug digoxin, may be prescribed for the treatment of Chagas' disease-associated cardiomyopathies in some cases (44).

The exact pathological mechanisms associated with chronic Chagas' disease are not completely understood (44, 249). Direct tissue damage due to the cycle of host cell infection and destruction is thought to account, to some degree, for the damage inflicted during chronic disease. However, it is now thought that much of the damage associated with chronic Chagas' disease is due to an autoimmune reaction. In most cases, the *T. cruzi* parasite load is disproportionately low compared to the damage inflicted during chronic Chagas' disease (44). As such, the host's own immune system is thought to play a major role in the pathogenesis of chronic disease (44, 249). Several antigens expressed by *T. cruzi* are reported to mimic human proteins, including the cardiac myosin heavy chain and the cardiac muscarinic acetylcholine receptor (44, 131, 353). This results in the development of a cross-reactive autoimmune response (234). As such, the pathogenesis of chronic Chagas' disease is thought to be more a case of postinfectious autoimmunity rather than damage inflicted directly by *T. cruzi* parasites (44, 249).

(iv) Chagas' disease and HIV. In areas of endemicity, reactivated Chagas' disease may be the first presentation of HIV infection (20), and the lethality of *T. cruzi*-HIV coinfection is high (369). In regions where the disease is endemic, reactivation of latent Chagas' disease not only occurs in patients infected with HIV (118, 201, 476, 496) but also has been reported for those with leukemia (9) or lymphoma (208) and transplant recipients (8, 40, 216).

Typically, severe immunosuppression alters the clinical course of Chagas' disease to include central nervous system (CNS) manifestations, which are not usually seen for ICT patients (20). Human immunodeficiency virus-infected patients with Chagas' disease may experience acute meningoencephalitis, fever, headaches, seizures, and vomiting along with myocarditis and other pathologies observed for ICT patients (567). Human immunodeficiency virus-infected patients with Chagas' disease may also present with necrotic brain lesions (349). Unusual pathologies have also been reported. In one case, parasitosis of the cervix uteri was observed for an HIV-infected patient, diagnosed by a cervical biopsy (113). Another unusual case was reported for a kidney transplant patient who developed Chagasic skin lesions (216).

(v) Diagnosis. In HIV-infected individuals, the diagnosis of Chagasic brain pathologies begins with a computed tomography (CT) scan or magnetic resonance imaging (MRI) (20, 174, 369, 567). Meningoencephalitis and myocarditis as seen for *T. cruzi*-HIV coinfection may be easily confused with those observed for *Toxoplasma*-HIV coinfections (20, 522). *Trypanosoma cruzi* necrotic brain lesions are also indistinguishable from those of *Toxoplasma*. Differentiation between these pathogens by PCR or microscopy is essential, as incorrect treatment may result in disease progression and patient death.

A definitive diagnosis can be made by the direct identification of trypomastigotes in stained blood smears or in the buffy coat (20, 543). The QBC tube technique may be a useful diagnostic tool during the acute phase of Chagas' disease (443, 444) but is less useful for diagnosis during the chronic phase of the disease (15). In the acute phase of Chagas' disease, live trypanosomes

may be observable in an unstained blood smear viewed at a ×100 magnification (49). The use of the Romanowsky-based stains (usually a Giemsa, Wright, or Leishman's stain) is suitable for the detection of trypomastigotes in thin blood smears (49, 487). For examination of amastigotes of *T. cruzi* in tissue biopsy specimens, a hematoxylin-and-eosin stain is often employed. The following websites contain excellent images of *T. cruzi* parasites in stained blood smears and heart tissue biopsy specimens: http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/TrypanosomiasisAmerican_il.htm and http://apps.who.int/tdr/publications/tdr-image-library?disease=Chagas+disease&location=&idNumber=&descText=&photographer=&creditSource=&x=19&y=10.

Due to a reduction in $CD4^+$ counts, trypomastigotes may be observed more frequently in the blood of HIV-infected patients than in the blood of ICT individuals (496). In one study, the mean number of *T. cruzi* genome equivalents in patients with chronic Chagas' disease was 25.83 ± 26.32 per ml of blood (62). However, in an HIV-infected patient with cerebral Chagas' disease, 280 *T. cruzi* genome equivalents per ml of blood were detected (74). Both of those studies utilized a quantitative PCR assay (62, 74). Generally, blood microscopy is useful only for detecting trypanosomes in the acute phase of Chagas' disease (160).

In chronic Chagas' disease, serological and molecular techniques should be used preferentially to blood microscopy due to their higher sensitivity. PCR performed on DNA extracted from peripheral blood is useful for the early diagnosis of reactivated Chagas' disease (373) and for monitoring treatment efficacy (74, 171). PCR may also be performed on tissue biopsy specimens for the molecular characterization of strains/isolates (74) or to demonstrate the chronic persistence of trypanosomes in tissues (40). A sensitive real-time PCR assay has also been developed for the detection of *T. cruzi* DNA in blood specimens (446). The diagnosis of congenital Chagas' disease can be made by the microscopic observation of *T. cruzi* parasites in umbilical cord blood specimens, although PCR is a more sensitive alternative (42). Immunological techniques such as ELISA or IFAT can also be useful for the diagnosis of Chagas' disease (99, 100, 160, 238, 372).

A combination of diagnostic tools, including direct detection methods (molecular tools and/or microscopy) and serology, is recommended for an accurate diagnosis of Chagas' disease (160). In the case of the CNS involvement observed frequently for HIV-infected patients, trypanosomes will often be observable microscopically in the cerebrospinal fluid (CSF) (118).

(vi) Treatment. The drugs of choice for the treatment of Chagas' disease are benznidazole and nifurtimox (20, 567). Both drugs are proven to reduce the severity of acute Chagas' disease but are less effective against chronic Chagas' disease (543). These drugs both require extended courses and may cause severe side effects (41, 543). Over 80% of patients are cured of symptoms (20), although trypanosomes will usually persist asymptomatically (543). The drug allopurinol has also demonstrated antitrypanosomal activity (550) and has comparatively few side effects (543). With the completion of the *T. cruzi* and *T. brucei* genome projects, a push toward a more focused identification of new drug targets using bioinformatic approaches has become apparent in recent years (346, 400).

African sleeping sickness. There are four known subspecies of *Trypanosoma brucei*, two of which cause human disease. In Western and Central Africa, *T. brucei gambiense* causes a chronic form of disease, while in Eastern and Southern Africa, *T. brucei rhodesiense* causes an acute form (32, 184, 269). Infection with either subspecies is usually fatal if left untreated (196).

Millions of people from 36 countries in sub-Saharan Africa are at risk of obtaining a *T. brucei* infection. According to the WHO, prevalences of 50% occur in some African communities, including villages in the Democratic Republic of Congo, Angola, and southern Sudan. In these communities, sleeping sickness was considered the first or second cause of mortality even before HIV/AIDS (606). Approximately 50,000 to 70,000 people in sub-Saharan Africa are believed to be infected with *T. brucei*, with approximately 17,000 new cases reported annually (283).

Two stages of African sleeping sickness exist: the early hemolymphatic stage and the successive CNS stage (68, 183). Shortly after the initial infection, a localized inflammatory nodule forms near the bite wound, which may ulcerate (32). This nodule is referred to as a trypanosomal chancre. Trypanosomal chancre does not always occur and its appearance is often dependent on the strain (530) and/or subspecies (32). Trypanosomal chancre occurs in approximately 19% of *T. b. rhodesiense* infections and rarely in *T. b. gambiense* infections (32, 68). Three to four weeks later, the chancre heals while *T. brucei* trypomastigotes spread to the bloodstream and lymphatics (61, 184).

(i) The hemolymphatic stage. During the hemolymphatic stage, patients will usually suffer from headache, arthralgia, weakness, fever, and malaise (315). Patients infected with the *T. b. rhodesiense* subspecies will suffer a more acute form of disease, which can involve anemia, thrombocytopenia, disseminated intravascular coagulation, and heart pathologies (100). Pancarditis and pericardial effusion can occur, eventually leading to heart failure. Pulmonary edema may result in death. Hepatosplenomegaly may also occur (68).

The clinical course of a *T. b. gambiense*-type infection is far more subtle and, as a result, may remain unrecognized or misdiagnosed. In *T. b. gambiense* infections, after several weeks patients will exhibit swollen lymph nodes, often on the posterior of the neck (referred to as Winterbottom's sign) (32).

(ii) The CNS stage. The second stage of African sleeping sickness involves invasion of the CNS by trypomastigotes (196). This second stage occurs within a few weeks in *T. b. rhodesiense* infections but over a matter of months to years in *T. b. gambiense* infections. The clinical manifestations of the CNS stage are quite diverse. Patients will experience the sleeping disorders typical of African sleeping sickness, such as a reversal of sleep-wake cycles and a strong urge to sleep (315). Patients can also experience any range or combination of psychological, motor, and sensory disorders (32, 196, 315). Headache, weight loss, and endocrine disorders such as impotence are also typical (32). If the second stage of African sleeping sickness is left untreated, coma and eventual death will ensue.

(iii) African sleeping sickness and HIV. To our knowledge, there is little association between the occurrence of severe African sleeping sickness and HIV (384). Dedet and Pratlong (141) also described the absence of any significant association between sleeping sickness and HIV. While *T. cruzi* is an intracellular parasite, *T. brucei* is extracellular and exists only in the

lymph, the bloodstream, and, eventually, the CSF. It was suggested that being extracellular, the control of *T. brucei* infection is based on a T-cell-independent immunoglobulin response. Therefore, HIV infection does not place sleeping sickness patients at a significantly increased risk of developing more-severe forms of the disease. As such, the treatment of sleeping sickness patients in the presence of HIV infection is often successful (384). There is little in the literature describing the clinical course of sleeping sickness in HIV-infected patients, although based on current information, the clinical course is similar to that observed for ICT individuals.

(iv) Variable surface glycoprotein. The extracellular life of *T. brucei* means that it is in frequent contact with the humoral immune response. Despite this, *T. brucei* is a successful extracellular parasite capable of inducing chronic infections that can last for several years (100). This is due to its ability to alter the expression of certain immunogenic glycoproteins on its surface. The existence of these variable surface glycoproteins (VSGs) allows *T. brucei* to remain extracellular and still evade the host's humoral immune response.

VSG is the predominant surface antigen in African trypanosomes and covers the entire plasma membrane (585). *Trypanosoma brucei* has approximately 1,250 to 2,000 genes and pseudogenes that control the expression of VSGs (68, 545). During a *T. brucei* infection, specific antibodies to a given VSG are raised by the host. However, *T. brucei* is able to switch on a different VSG gene to express a new VSG that is not recognized by the host immune system. When antibodies are raised to this new VSG, *T. brucei* switches its surface coat once again. This strategy enables *T. brucei* to evade the host immune response. This phenomenon also explains the fluctuation of trypanosome numbers in the blood of the host often observed throughout the course of a *T. brucei* infection (100).

The production of excreted, soluble VSG is another immune evasion strategy employed by *T. brucei* (585). Soluble VSGs divert the host's antibody response by binding circulating anti-VSG antibodies, leaving them unavailable for binding to VSG that is associated with the trypanosome surface. Certain VSGs can also induce the production of autoantibodies by molecular mimicry (585), a phenomenon which is reminiscent of *T. cruzi* infection.

(v) Diagnosis. If neurological symptoms are apparent, an MRI scan of the brain is often used to identify brain abnormalities (315). However, a definitive diagnosis must be made through the use of serology, PCR, or microscopy. The demonstration of trypanosomes in Giemsa- or Wright-Giemsa-stained smears of blood or CSF is useful for a definitive diagnosis (Fig. 4A) (315, 352). This may be more difficult in *T. b. gambiense* infections than in *T. b. rhodesiense* infections due to the low number of parasites circulating in the blood and/or CSF (352). In *T. b. gambiense* infections, parasite loads can vary between 100 and 10,000 trypanosomes/ml; hence, trypomastigotes may be readily observed in blood smears or not at all (100). The following link contains excellent images of *T. brucei* in stained blood smears: http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/TrypanosomiasisAfrican_il.htm.

The concentration and separation of whole-blood constituents by high-speed centrifugation (the microhematocrit centrifugation technique) can allow the direct visualization of live, motile trypanosomes under low-power (magnification of ×100 to ×200) microscopy, and it is more sensitive than stained smears (100). The QBC tube technique can also be used for the diagnosis of *T. brucei* infections. In one study, the QBC tube technique demonstrated a sensitivity of 95% at a blood trypanosome concentration of 450 trypanosomes per ml (16). In that same study, the microhematocrit centrifugation technique displayed a sensitivity of 95% at a blood trypanosome concentration of 7,500 trypanosomes per ml (16).

A number of immunological assays are available for the detection of anti-*T. brucei* antibodies in human sera (194, 352, 561). The card agglutination test for trypanosomiasis (CATT) is the most important serological tool available in areas where *T. b. gambiense* infection is endemic (352). This 5-min test is used extensively in Africa for the screening of populations at risk of obtaining *T. b. gambiense* sleeping sickness (68, 101, 352, 524).

PCR of blood, CSF, or lymph aspirate demonstrates good sensitivity (296, 352). Molecular techniques are useful for both the detection and strain typing of *T. brucei*. Restriction fragment length polymorphism (RFLP) and PCR for *T. brucei* have enabled extensive research into the molecular epidemiology of *T. brucei* sleeping sickness (232, 269, 271). Some molecular techniques can differentiate *Trypanosoma brucei* at the subspecies level and may be useful for determining the most appropriate treatment option (271). A number of sensitive molecular assays are also available for the detection of African trypanosomes. These include a recently developed oligochromatography technique (397), a real-time PCR (36), a loop-mediated isothermic amplification (LAMP) assay (337), and a conventional PCR assay (341).

Determining the protein concentration in CSF can be used to estimate the progression of African sleeping sickness. In sleeping sickness patients, CSF protein concentrations can range from between 100 and 2,000 mg/liter (100). Generally, a CSF protein concentration of >750 mg/liter reflects damage to the blood-brain barrier (100). However, due to various impracticalities such as the need for labile reagents and a lack of standardization, this technique is no longer recommended for field laboratories (100).

Interestingly, experimental *T. b. rhodesiense* infections in vervet monkeys suggested that disease progression and efficacy of treatment can be monitored by measuring the concentrations of serum IgM and interleukin-10 (IL-10) (403). However, this approach is likely to have limitations in the field similar to those of the CSF protein concentration method. Instead, the CSF white blood cell (WBC) count is preferred. Generally, a WBC count of 10 to 20 cells/μl of CSF is indicative of late-stage sleeping sickness and requires timely treatment (100).

(vi) Treatment. The drugs pentamidine, suramin, melarsoprol, eflornithine (DL-α-difluoromethylornithine [DFMO]), and benznidazole are the mainstay of treatment regimens for African sleeping sickness (32). Melarsoprol is widely used for treating late-stage sleeping sickness despite the occurrence of drug-induced, potentially fatal encephalopathies observed for 2 to 12% of patients (51, 61, 225, 233). However, if used under the right regimen, parasitological cure may be achieved with melarsoprol (51). Pentamidine and suramin are used for the treatment of early-stage sleeping sickness (61). Pentamidine is considered the drug of choice for early-stage *T. b. gambiense* infections (68). Eflornithine is used for the treatment of late-

stage *T. b. gambiense* infections but has many adverse side effects and demonstrates limited activity against *T. b. rhodesiense* infections (76, 269). Recently, combination nifurtimox-eflornithine therapy has been proposed as a new treatment option for late-stage *T. b. gambiense* infection because it is as efficacious as eflornithine monotherapy and reduces the likelihood of inducing drug resistance (233, 455).

As with *T. cruzi*, the *T. brucei* genome project has enabled the development of bioinformatic approaches for the selection of new drug targets and the development of new drugs (67, 346, 400). Another recent approach to drug development involves the screening of natural compounds, derived mostly from plants, for the presence of antitrypanosomal activity (225).

Non-human-infecting *Trypanosoma* species. Human infections with non-human-infecting *Trypanosoma* species are rarely reported. However, *T. b. brucei*, *T. b. evansi*, *T. congolense*, and *T. lewisi* infections have been identified in several cases of human disease (138, 285, 299, 305, 311, 495, 521, 560, 573). These trypanosomes infect a range of domestic, feral, and wild animals (124, 261, 262, 371) and probably come into frequent contact with humans.

It is unknown whether immunosuppression is a predisposing factor for infections with the non-human-infecting trypanosomes. One human infection was reported prior to the emergence of HIV (299). In some more-recent cases, patients were HIV negative (285, 305). In other cases, the existence of an immune deficiency was not considered or was simply not discussed (495, 521, 560). While the role of these trypanosomes in IC patients is unknown, infections with these organisms are likely to be reported for IC patients in the future.

(i) Human trypanolytic factor. Due to the coevolution of humans alongside the endemic trypanosomes of Africa, humans and some primates have evolved a non-immune-mediated mechanism designed to specifically eliminate African trypanosomes (365, 423, 424). The human serum components involved in the specific lysis of trypanosomes are referred to as human trypanolytic factor (HTLF) (424). The key components of HTLF are the apolipoprotein L-I and the haptoglobin-related protein (572). These components are found in the serum of all humans (572).

Originally, only two African trypanosomes were thought to be resistant to HTLF: *T. brucei gambiense* and *T. brucei rhodesiense* (424). However, recent reports suggest that certain subtypes of non-human-infecting trypanosomes may also be resistant to HTLF (285, 365, 416). It is plausible that this resistance to HTLF has enabled some human infections with non-human-infecting trypanosomes to occur.

A similar inbuilt antitrypanosomal mechanism does not exist for *T. cruzi*. This is probably due to the comparatively recent arrival of humans in the Americas approximately 9,000 years ago (365).

(ii) *Trypanosoma congolense*. *Trypanosoma congolense* is a pathogen of livestock animals in sub-Saharan Africa, causing weight loss, anemia, and immunosuppression (124). Like *T. brucei*, *T. congolense* has a tsetse fly vector, and so its range is restricted to that of the tsetse fly (124).

A single case of human infection with *T. congolense* was reported for a 50-year-old woman from Cote d'Ivoire who was also infected with a species of *T. brucei* (560). The poor condition of the patient suggested that she was in the later stage of sleeping sickness, although no trypanosomes were identified in the patient's CSF. The woman had a weakly positive CATT result and a negative latex agglutination test. Trypanosomes were identified microscopically but were morphologically different from *T. brucei* and similar to *T. congolense* (comparatively short, with poor motility and lacking a free flagellum).

Species-specific PCR for *T. brucei* spp. and *T. congolense* indicated that the woman was infected with both of these species. The patient was treated with pentamidine and fully recovered (560). Given that the patient in this case was also infected with a *T. brucei* sp., it is impossible to determine whether *T. congolense* contributed significantly to the patient's disease. However, the possible role of *T. congolense* as a human pathogen should not be dismissed.

Recently, Xong et al. (614) found that certain strains of *T. congolense* were completely resistant to HTLF. This finding suggests that more cases of human *T. congolense* infection are likely to be reported in the future.

(iii) *Trypanosoma brucei evansi*. *Trypanosoma brucei evansi* was only recently identified as a subspecies of *T. brucei* (344). *Trypanosoma brucei evansi* is endemic to parts of Southeast Asia, Africa, and South America and causes a potentially fatal disease called "surra" in livestock and companion animals, including horses, dogs, cattle, goats, pigs, and camels (69, 471). *Trypanosoma brucei evansi* exists only as the bloodstream form and lacks the ability to enter the procyclic form in the gut of the tsetse fly (345). As such, *T. b. evansi* relies entirely on mechanical transmission between hosts by means of various species of hematophagous fly and, in South America, by vampire bats (261).

To our knowledge, only a single case of human *T. b. evansi* infection has been reported (305). The patient was a cattle farmer from India who experienced intermittent fever with chills and sweating. The patient later developed signs of sensory deficit and became violent. Giemsa-stained smears enabled the detection of trypanosomes in peripheral blood, although none were observed in the CSF. The patient was treated with a regimen of intravenous suramin as recommended for *T. b. rhodesiense* sleeping sickness, and his symptoms resolved. Three individual PCR assays were employed to identify the causative agent. Surprisingly, the etiological agent was identified as *T. b. evansi* (305).

Interestingly, genetic characterization of this strain of *T. b. evansi* indicated that it was not dissimilar from a number of other *T. b. evansi* reference strains (559). It was therefore hypothesized that the case from India may have been the result of an immunodeficiency in the patient or a deficiency in the patient's HTLF (559). A follow-up study performed by Vanhollebeke et al. (573) confirmed this hypothesis by identifying mutations in both alleles of the patient's apolipoprotein L-I gene, which rendered this patient's major HTLF protein dysfunctional.

While this case appears to be extremely rare and unusual, a recent report by Lai et al. (345) indicated that certain strains of *T. b. evansi* display natural resistance to HTLF. Therefore, as with *T. congolense*, more infections with *T. b. evansi* will probably be encountered in the future.

(iv) *Trypanosoma brucei brucei*. In sub-Saharan Africa, *T. b. brucei* is known as a cause of a potentially fatal animal sleeping

sickness, or "nagana," in livestock (47, 138). *Trypanosoma brucei brucei* is morphologically identical to *T. b. rhodesiense* and *T. b. gambiense*. *Trypanosoma brucei brucei* also infects the same range of vertebrate hosts and relies on the tsetse fly for its transmission. The major difference between these species is that *T. b. brucei* is thought to be sensitive to HTLF and therefore lacks the ability to infect humans (47).

Human infections with *T. b. brucei* are somewhat controversial due to the similarity between *T. b. brucei* and the human-infecting *T. brucei* subspecies (231, 269). Cases of human infection with particular strains of *T. b. brucei* have been identified in the past, although these trypanosomes are now referred to as "*T. b. gambiense* group 2" (138, 231, 558). However, some authors question whether human-infective *T. brucei* isolates are truly different from non-human-infective isolates (269).

Regardless, a recent report identified an atypical human *Trypanosoma* infection, which was eventually attributed to a subtype of *T. b. brucei* (138). In 2003, a 10-month-old child from Ghana was admitted to a local hospital with fever, severe dyspnea, and paleness. The patient's blood was examined for malaria using Giemsa-stained smears. No malarial parasites were identified, although numerous trypanosomes were visible. The necessary drugs were not available for treatment at the time of diagnosis, and the patient did not receive treatment. In an examination 2 years later, no trypanosomes were observed in the patient's Giemsa-stained smears. The child appeared healthy and had a negative CATT result. DNA was extracted from the archived Giemsa-stained slides for species identification by various taxon-specific PCRs. The species was identified as either *T. b. brucei* or *T. b. gambiense* group 2. Based on various unusual aspects of this case, including geographic location and the patient's ability to spontaneously clear the infection, *T. b. gambiense* group 2 infection was considered unlikely. As such, the infection was attributed to *T. b. brucei* (138).

While infections with *T. b. brucei* are controversial, it is possible that certain human-infective subtypes exist that are yet to be identified. In any case, it seems likely that infections with human-infecting *T. b. brucei* subtypes would go mistaken for *T. b. gambiense* or *T. b. rhodesiense*. This error would have little impact on the management of patients.

(v) *Trypanosoma* (*Herpetosoma*) *lewisi*. *Trypanosoma lewisi* is a member of the subgenus *Herpetosoma*, which includes several species of trypanosomes that are usually obligate parasites of rodents (298, 365). *Trypanosoma lewisi* infection is transmitted by various species of flea and has a worldwide distribution (298, 365). Members of the subgenus *Herpetosoma* are morphologically indistinguishable from each other and are often described collectively as *T. lewisi*-like organisms (298). In rodents, *T. lewisi*-like infections are thought to be nonpathogenic and self-limiting due to the organism's limited capacity to alter its surface coat (298, 365). In humans, however, *T. lewisi*-like organisms have been reported to cause a transient disease characterized by fever, anemia, anorexia (285, 299, 495), and, in some cases, generalized edema (285).

To our knowledge, only six cases of *T. lewisi*-like infection in humans have been reported (285, 299, 311, 495, 521). Poor living conditions associated with an infestation of feral rodents are a common characteristic in most cases. Not surprisingly, all reports originate from developing countries, including Malaysia (299), India (311, 521), Thailand (495), and Africa (285). In those reports, the diagnosis of *T. lewisi* infection was based on the morphology of trypanosomes in peripheral blood films, although more-recent reports also utilized molecular techniques (285, 495). While some early reports of *T. lewisi*-like infection were not supported with molecular data (as molecular techniques were not yet available) (299, 521), it should be remembered that human-infecting trypanosomes are not endemic to southeast Asia. As such, these early reports from Malaysia and India are probably accurate in their diagnoses (299, 521).

Generally, *T. lewisi*-like organisms induce a transient infection that is spontaneously cleared by the patient in the absence of specific treatment. In most cases, CNS involvement was not reported. However, in one severe case, trypomastigotes were present in peripheral blood smears and CSF (285). The patient was treated with melarsoprol, and subsequent blood and CSF films were negative for trypanosomes (285).

Unlike some opportunistic infections discussed in this paper, human *T. lewisi* infection is not restricted to patients who are IC. In one case, the patient was confirmed to be HIV negative (285). Another case was reported prior to the emergence of HIV (299). In some cases, immunodeficiency was either not considered or not discussed (495). However, all patients who did not receive treatment spontaneously cleared their infection in a matter of days, which is suggestive of a fully functional immune system. Based on these points, it is unlikely that immunosuppression was a predisposing factor for *T. lewisi*-like infection in these cases. However, given that the majority of infections occurred in infants, it is possible that infants are more susceptible to *T. lewisi*-like infection, perhaps due to an undeveloped immune system (285, 299, 311, 365, 495).

The mechanisms that allow *T. lewisi*-like organisms to infect humans are not understood. It has been speculated that certain subtypes of *T. lewisi* may be resistant to trypanolysis, like some African trypanosomes (365). However, phylogenetic studies based on the small-subunit (SSU) ribosomal DNA (rDNA) indicated that *T. lewisi* and other *Herpetosoma* strains cluster together in a group separate from that of the African trypanosomes (371). Given that HTLF has specific activity against African trypanosomes only (and not *T. cruzi*), it seems logical that infections with *T. lewisi*-like organisms occur (in part) due to the lack of any inherent, protective mechanism against *Herpetosoma* in humans rather than the resistance of *T. lewisi* to HTLF. Unfortunately, no studies exist which explore the effect of normal human serum on *T. lewisi*-like organisms.

Regardless, it is unlikely that immunodeficiency has played a role in the *T. lewisi*-like infections reported. However, given the apparent susceptibility of infants to *T. lewisi* infection, it is plausible that IC patients may be at a greater risk of developing *T. lewisi*-associated disease than ICT individuals.

Lower Trypanosomatids

The "lower trypanosomatids" are a group of trypanosomatid parasites that usually infect invertebrate hosts. These include *Blastocrithidia*, *Crithidia*, and *Leptomonas* species, all of which are considered nonpathogenic to ICT humans. These organisms are known to have only one invertebrate host in their life

cycle and are often referred to as the "monoxenous trypanosomatids."

To our knowledge, only four cases of monoxenous trypanosomatid infection have been reported for humans, and only three of these were HIV-infected patients. However, it should be noted that two of these cases (the infections from Martinique described below) involved an organism that was later identified as a highly divergent member of the genus *Leishmania* (407). As such, this organism may not be considered a true lower trypanosomatid.

HIV-infected patient from Martinique. The earliest case, an HIV-infected patient from Martinique who presented with a disease which resembled diffuse cutaneous leishmaniasis, was reported by Dedet et al. (142). The patient was treated with meglumine antimoniate for suspected *Leishmania* infection and zidovudine for HIV. Skin lesions improved following treatment, although the patient eventually died. Parasites were isolated in culture from skin biopsy material for further study. The patient was negative for *Leishmania* antibodies, and isoenzyme analysis revealed that the parasite was probably not of the genus *Leishmania*. The morphology of these organisms in transmission electron micrographs suggested that they were a species of monoxenous trypanosomatid.

ICT patient from Martinique. A second case report, also from Martinique, identified the same organism as that described above for the previous Martinique case as being the cause of a localized cutaneous lesion in an ICT patient (54). The patient was treated with pentamidine, and the lesion disappeared within 2 months.

In later studies, efforts were made to better characterize this trypanosomatid. Through the use of various molecular techniques and phylogenetic analysis, the organism was identified as a highly divergent member of the genus *Leishmania* (407). DNA sequences from this unnamed species clustered with *Leishmania enriettii* and were basal to all other euleishmania species, although the support for this was low (407). Regardless, these analyses clearly indicated that this organism was a member of the genus *Leishmania*.

Given its relationship to *Leishmania*, it was postulated that this organism, like other *Leishmania* species, would also have a digenetic life cycle (407). It is therefore likely that this organism has a number of vertebrate hosts and a hematophagous insect vector.

Unidentified insect trypanosomatid. The third case of a lower trypanosomatid-HIV coinfection was reported for an intravenous drug abuser from Madrid, Spain (297). Based on clinical findings, including hepatosplenomegaly and pancytopenia, VL was suspected. An immunofluorescent antibody test for the detection of *Leishmania* antibodies was inconclusive. Bone marrow aspirates were negative for amastigotes, although promastigotes were isolated in culture. The patient was treated for 21 days with meglumine antimonite and recovered. After 3 years no relapses had occurred.

The isolated organism was morphologically different from *Leishmania* spp., as it was blunt ended and had a denser kinetoplast. The organism was not infective for BALB/c mice or hamsters. Furthermore, an infection could not be established in the gut of the sandfly *Phlebotomus perniciosus*. As such, the organism was suspected to be a lower trypanosomatid.

Isoenzyme analysis of the cultured organism demonstrated that it was not similar to other *Leishmania* reference strains. DNA cross-hybridization was performed by using DNA from the organism with a range of other lower trypanosomatid species as well as *T. cruzi*. No homology was observed between this organism and all other species tested. As such, this organism was assumed to be a newly discovered non-human-infecting trypanosomatid.

Given that the patient was an intravenous drug user, it was postulated that the infection could have been obtained by washing syringes in water that had been contaminated with insect feces (297). However, other authors suggested that this infection was more likely to have occurred by the accidental inhalation of parasitized insects (140).

***Leptomonas*-like organism.** The most recent report of a lower trypanosomatid-HIV coinfection in a Brazilian male was described by Pacheco et al. (417). The patient presented to a local hospital complaining of weakness and fever. Physical examination revealed an enlargement of the cervical lymph nodes and splenomegaly. The patient was from an area where CL is endemic, and a visceralizing *L. braziliensis* infection was suspected. The patient was positive for *Leishmania* antibodies by IFAT. Promastigote forms similar to those of *Leishmania* were inoculated into a culture from the patient's bone marrow aspirate and cultivated for further study.

Isoenzyme analysis, kinetoplast DNA (kDNA) restriction analysis, and Southern blot hybridization revealed that this organism was not a member of the genus *Leishmania* or *Trypanosoma* or of the subgenus *Sauroleishmania*. However, kDNA restriction analysis demonstrated that this organism was genetically similar to *Leptomonas pulexsimulantis*, a flagellate found in fleas. The patient was treated for 20 days with *N*-methyl-glucantime antimoniate and completely recovered. No relapse was reported for 2 years after treatment.

Additional remarks. The prospect of parasitological cure for patients infected with lower trypanosomatids appears to be quite good, even in the presence of HIV. In all of these cases, patients presented with symptoms similar to those observed for the common *Leishmania* syndromes and responded well to antimonial treatment or pentamidine in one case (54). Therefore, in cases where infection with lower trypanosomatids is misdiagnosed as leishmaniasis and treated as such, therapy is likely to be successful. Infection with these organisms is rare in humans, and consequently, these organisms will be rarely exposed to common anti-*Leishmania* drugs. This makes the development of drug resistance in these organisms highly unlikely. However, the unusual nature of these infections also means that they are likely to go undiagnosed.

Toxoplasma gondii

Organism and disease. *Toxoplasma gondii* is an obligate intracellular parasite with a worldwide distribution and broad host range, which includes most mammals and birds (429). Despite intense debates regarding the phylogeny of this organism (181, 268, 388), *T. gondii* still remains the only species within its genus. The sexual cycle of *Toxoplasma* (the production of oocysts) occurs only in the intestine of cats (178, 274, 599), and human infections usually occur by two routes: either via the ingestion of oocysts shed by a feline definitive host or by the ingestion of meat containing tissue cysts from an interme-

diate host (178). *Toxoplasma* infections are also transmissible via blood transfusion (204), organ transplantation (156), and the congenital route (599). The congenital transmission of *Toxoplasma* may represent the most clinically important route of human infection, although its importance is currently under debate (270, 290).

Toxoplasma tissue cysts occur in both intermediate and definitive hosts and are resistant to the host immune system. These resistant structures harbor the slow-growing bradyzoite form of *Toxoplasma* (599). The rupture of tissue cysts results in the release of bradyzoites, which differentiate into the rapidly multiplying tachyzoite form (178). Tissue cysts can persist in the host indefinitely, presumably due to a cycle of tissue cyst rupture and reinfection of new host cells (599), followed by suppression by the host immune system and the subsequent formation of new tissue cysts. In IC patients, the suppression of this cycle is inadequate. In these patients, tachyzoites are allowed to spread rapidly via the host's circulation to cause widespread tissue damage.

Approximately one-third of the human population is believed to be infected with *T. gondii* (429). In ICT patients, *Toxoplasma* infection is usually subclinical (405, 599). However, in IC patients, *Toxoplasma* causes a range of pathologies. Encephalitis is the most common clinical manifestation of toxoplasmosis in HIV-infected patients (116) and is usually attributable to the reactivation of a latent infection (21, 429, 537). Generally, $CD4^+$ T-lymphocyte counts of less than 100 cells/μl of blood permit the reactivation of toxoplasmosis (328). Prior to the AIDS pandemic, *Toxoplasma* encephalitis was rarely reported but is now considered an important AIDS-defining illness (255).

In humans, close contact with cats and the consumption of rare or undercooked meat increase the risk of acquiring a primary *Toxoplasma* infection (134, 178, 179, 274, 402, 429). As such, the risk of obtaining a primary *Toxoplasma* infection is no higher for IC patients than for ICT individuals (328, 472). Interestingly, one study identified intravenous drug use as a major risk factor for *Toxoplasma* infection (328). As such, the sharing of needles between intravenous drug users may also facilitate the transmission of *Toxoplasma*.

In IC patients, *Toxoplasma* can cause a range of ocular complications (4, 19, 448), pulmonary disease (433, 526), myocarditis (3, 244, 347), cystitis (277), polymyositis (254), pancreatitis (119), and hepatitis (383). Other complications in HIV-infected patients include gastrointestinal disease, panhypopituitarism, diabetes insipidus, orchitis, myositis, and a syndrome characterized by inappropriate antidiuretic hormone secretion (599). Disseminated toxoplasmosis can also occur in IC individuals (22, 422, 562) and may lead to septic shock (364). Bone marrow involvement has also been reported (65). A case of concurrent cerebral toxoplasmosis and Chagas' disease was also reported for an HIV-infected patient (619). A recent case study also reported the unusual localization of a "toxoplasmic abscess" on the spinal cord of an HIV-infected patient (447).

While generally benign, *Toxoplasma* infections in ICT patients can cause polymyositis (254), hepatitis (175), meningoencephalitis (451), and ocular disease (112, 254, 278, 485). *Toxoplasma* is recognized as the most common cause of retinitis in ICT individuals and the second most common cause of retinitis in AIDS patients after cytomegalovirus (339). Transplant patients are also at an increased risk of clinically apparent toxoplasmosis (156, 177, 206, 453).

In sub-Saharan Africa, toxoplasmosis is a significant albeit neglected disease. Due to poor access to HAART, toxoplasmosis remains a common AIDS-defining illness in this region (283). Unfortunately, few studies have been carried out to assess the impact of toxoplasmosis in sub-Saharan Africa. However, a number of serological studies have been performed (419). In a study from Botswana, 6.5% of 46 HIV-infected patients tested positive for anti-*T. gondii* antibodies (602). A study from the town of Nazaret in Ethiopia showed that 39/65 (60%) people tested were positive for *Toxoplasma* by serology (402). This was probably due to the custom of eating raw or undercooked mutton (more than 50% of people in this study admitted to doing this) in these areas and also due to the habit of keeping cats for the control of rats and mice (402). In a study from Burkina Faso, 25.3% of pregnant women were found to be seropositive for *Toxoplasma* (525).

In a recent report, Africa was among the regions associated with a high *Toxoplasma* seroprevalence. Other regions also associated with a high seroprevalence of *Toxoplasma* include the Middle East, parts of Southeast Asia, Latin America, and parts of Eastern/Central Europe (419). Western European countries and the United States were associated with a lower *Toxoplasma* seroprevalence (419).

Diagnosis. The diagnosis of *Toxoplasma* encephalitis usually involves a CT scan or MRI of the brain. However, *Toxoplasma*-associated brain abnormalities may be indistinguishable from AIDS-related cerebral lymphoma (64, 392) or cerebral Chagas' disease (121, 429). Therefore, microscopy, molecular techniques, and/or parasite cultivation should be employed for a definitive diagnosis (428, 583). The direct demonstration of *Toxoplasma* tachyzoites in cerebral tissues is the method of choice for a definitive diagnosis of cerebral toxoplasmosis (429). The microscopic observation of free *Toxoplasma* tachyzoites in stained smears of blood or CSF is indicative of an active infection and is a useful diagnostic tool (Fig. 4C). The cultivation of *Toxoplasma* tachyzoites from CSF can also be useful but may be impractical due to the strict culture requirements of *Toxoplasma*.

The use of certain antibody detection assays is limited, as these assays cannot differentiate between active and benign infections (429). However, ELISAs that detect antibodies against certain excreted/secreted antigens of *Toxoplasma* may be useful. Human immunodeficiency virus-infected patients tend to display higher antibody titers to certain excreted/secreted antigens than patients with a benign infection. As such, these ELISAs may be used as a marker for active *Toxoplasma* infection in IC patients (429). A latex agglutination test (519) and several other ELISAs are also available for the detection of anti-*Toxoplasma* antibodies (2, 338, 519, 613).

PCR performed on CSF can be useful in cases where cerebral toxoplasmosis is suspected but tachyzoites are not visible (541, 621). Several PCR assays are available. One PCR assay exhibited 100% sensitivity and a specificity of 94.4% when applied to DNA extracted from CSF (583). A nested PCR assay demonstrated 33% sensitivity and 100% specificity (108). A multiplex real-time PCR assay that is optimized for the diagnosis of cerebral toxoplasmosis is also available (406). This

assay simultaneously amplifies two *Toxoplasma* genes and displays a specificity of 100% and a sensitivity of 68.8% (406). Other real-time PCR assays are also available (116, 433). Quantitative real-time PCR assays have demonstrated excellent sensitivity (429) and may also be used to monitor a patient's response to anti-*Toxoplasma* therapy. In contrast to antibody techniques, a positive PCR result obtained from peripheral blood or CSF is indicative of an active infection (429). Moreover, HIV-infected patients generally demonstrate a high parasite load in the circulation compared to ICT individuals. In these patients, PCR applied to peripheral blood specimens could eliminate the requirement for invasive CNS biopsy techniques (429). A number of PCR assays have also been optimized for use on amniotic fluid for the diagnosis of congenital toxoplasmosis (188, 404, 409).

As mentioned above in the section on pregnancy, primary *Toxoplasma* infections acquired prior to the commencement of a pregnancy pose little threat to the fetus. Similarly, primary *Toxoplasma* infections obtained after 20 weeks of gestation will result in minimal fetopathies, if any. However, a primary *Toxoplasma* infection obtained prior to 20 weeks of gestation can have serious effects on the fetus. A useful *T. gondii* IgG avidity test is available, which can be used to estimate the time that a *Toxoplasma* infection was acquired relative to a pregnancy (301). This can help to predict the level of potential risk that the infection will pose to the fetus. However, it should also be mentioned that the results of serological tests are often difficult to interpret for pregnant women and neonates (514). For these patients, an interpretation of serological test results requires experience and expertise (514). In the presence of HIV infection, this IgG avidity test may be less useful. In one study, a pregnant mother infected with HIV who acquired a *Toxoplasma* infection while pregnant displayed an antibody profile similar to that of ICT patients with a latent infection (343).

Treatment. The drugs pyrimethamine and sulfadiazine are the mainstays of anti-*Toxoplasma* therapy (39, 429). In cases where patients do not respond to traditional pyrimethamine and sulfadiazine therapy or where patients do not tolerate sulfadiazine, pyrimethamine and clindamycin therapy is an effective alternative (39). The use of the drug leucovorin (folinic acid) in combination with pyrimethamine-sulfadiazine or pyrimethamine-clindamycin therapy is recommended to prevent various hematological side effects associated with the use of pyrimethamine (39, 429). The drug atovaquone (309, 552) and combination azithromycin-pyrimethamine therapy may also be useful for the treatment of cerebral toxoplasmosis in HIV-infected patients (608). In cases of ocular toxoplasmosis, the intravitreal injection of clindamycin can be effective (612). With regard to pregnancy, pyrimethamine and sulfadiazine should be used only after the 20th week of gestation (250). Before the 20th week, spiramycin can be used (250).

Interestingly, there is evidence to suggest that certain antiretroviral drugs have a direct inhibitory effect on *Toxoplasma* (157). As is the case with other protozoa, the availability of HAART has led to a major reduction in AIDS-associated toxoplasmosis (5, 382, 429). In particular, cases of *Toxoplasma* encephalitis have been greatly reduced to the extent that they are now very uncommon in regions with access to HAART (382, 429, 537).

Neospora caninum

The organism. *Neospora caninum* is an apicomplexan parasite closely related to *T. gondii. Neospora* has a canine definitive host and is best known for its veterinary significance. In cattle, *N. caninum* is known as a cause of widespread abortion, resulting in great economic losses (470), and the presence of dogs on cattle farms is a major risk factor for bovine neosporosis (230). The life stages of *Neospora* are morphologically similar to those of *Toxoplasma*. The similarity between *T. gondii* and *N. caninum* is such that some authors question the validity of the genus *Neospora* (280).

Speculatively, close contact with dogs and the consumption of undercooked meat (particularly beef) are probably the most likely risk factors for obtaining an *N. caninum* infection. However, no clinically apparent human infections with *N. caninum* have been reported. Regardless, a reduction in immune capacity as a result of HIV infection could allow infections with *N. caninum* to become clinically apparent. The possibility of such an occurrence is supported by the ability of lower trypanosomatids and the microsporidia, which do not usually infect ICT humans, to do so in the presence of HIV infection.

***Neospora* antibodies in human sera.** Several studies investigated the prevalence of *N. caninum* antibodies in human sera. One study found that 76 women with a history of spontaneous abortion were negative for *N. caninum* antibodies (434). In contrast, another study found 69/1,029 human serum samples obtained from blood donors to be positive for *N. caninum* antibodies (555). In that study, only 27.5% of sera positive for anti-*Neospora* antibodies were also positive for anti-*Toxoplasma* antibodies, which suggests that antigenic cross-reactivity between these organisms did not take place (555). In a later study, anti-*N. caninum* antibodies were detected in patients with HIV and in patients with neurological complaints (361). In that study, an immunoblot analysis was used to differentiate patients with circulating antibodies to *Neospora*, *Toxoplasma*, or both organisms (361). In contrast, an English study found no human exposure to *N. caninum* antigens at all, despite a large study population, which consisted of 3,232 serum samples from the general population and 518 serum samples from a high-risk group (farm workers) (387). However, a recent study from Egypt found a *Neospora* seroprevalence of 7.92% in human serum samples (288). In a study from France, no sera from ICT women were positive for anti-*N. caninum* antibodies, although 4/400 serum samples from HIV-infected patients tested positive for anti-*N. caninum* antibodies (478). However, given the low antibody titers observed by this study, the possibility of low-level cross-reactivity could not be ruled out (478).

Additional remarks. In all studies that reported the detection of anti-*N. caninum* antibodies in human sera, no evidence of clinical disease attributable to *N. caninum* was provided (288, 478, 555). As such, clinically apparent neosporosis is unlikely to occur in ICT humans. However, the results of one of these reports suggest a potential role for *N. caninum* as an opportunistic organism in IC individuals (361). In that study, 23/61 patients infected with HIV tested positive for anti-*N. caninum* antibodies (361). In that same study, 9/50 patients with neurological complaints also tested positive for anti-*N. caninum* antibodies (361). The prevalences obtained for the HIV group and the neurological-complaints group were signif-

icantly higher than the prevalences obtained for the newborn infant group and healthy subjects. This suggests that *N. caninum* may have the potential to infect humans in the presence of HIV and that *Neospora* infections may be linked to neurological complaints (361).

While *N. caninum* has not been linked directly to human disease, the possibility of clinically apparent *N. caninum* infections should not dismissed. In cases where *T. gondii* infections are suspected, *N. caninum* infection may be ruled out through the use of PCR performed on DNA extracted from tissue biopsy specimens or CSF. A number of sensitive PCR assays exist for *N. caninum*, which may be useful (31, 483). The tachyzoite stage of *N. caninum* is morphologically similar to that of *Toxoplasma*. It is quite possible that *N. caninum* could have been mistaken for *Toxoplasma* in CSF smears from IC patients if microscopy alone was used. As such, it is recommended that tissues that are thought to be infected with *T. gondii* should also be tested with a *Neospora*-specific PCR.

BLOOD PROTOZOA

Babesia spp.

Organism and disease. *Babesia* spp. are hemoprotozoan parasites of the order Piroplasmida transmitted by ticks of the genus *Ixodes* (286). Members of the genus *Babesia* share some similarities with the genus *Plasmodium*, including an arthropod vector and the ability to invade erythrocytes. While several species of *Babesia* can infect humans, *Babesia microti* and *Babesia divergens* are the species most often associated with human infection (187, 229, 281). Small mammals (235, 307, 492, 539, 574) and ruminants (275, 354, 501, 542, 574) serve as reservoirs for *Babesia* spp., and humans usually become infected after an infected *Ixodes* tick takes a blood meal. However, transmission via blood transfusion has also been widely reported (50, 86, 246, 272, 366, 379).

Human babesiosis is becoming increasingly common, particularly in IC patients (286). While the prognosis of *Babesia* infection is often good for otherwise healthy ICT individuals (389), *Babesia* infections are more likely to be severe or even life threatening for IC patients (326, 331, 574). Infections of IC patients are also less responsive to treatment (333, 592). In contrast, *Babesia* infections may be self-limiting or subclinical in ICT patients (574). The risk of developing severe babesiosis also increases with age, with individuals over the age of 50 years being predisposed to severe symptoms (263, 334, 389). Other groups predisposed to a severe, potentially lethal form of babesiosis include those with HIV (198, 214, 592), those receiving immunosuppressive therapy (including transplant patients), those with leukocyte malignancies, and those without a spleen (226, 331, 333, 366, 389, 574). The predisposition of splenectomized humans to a more severe form of disease is a feature that is also common to malaria parasites. Immunocompromised individuals are also more likely to suffer a relapse of babesiosis after apparent clinical cure (198).

In ICT patients, the symptoms of babesiosis include fever, sweats, chills, fatigue, and a mild-to-moderate hemolytic anemia (574). Patients who are elderly, IC, or asplenic will experience similar symptoms but with increased severity. An isolated case of splenic rupture due to a *B. microti* infection has also been reported (340). In ICT patients, *Babesia* infections can persist for many months, even if treatment has been initiated (335, 574). While patients suffering from malaria and babesiosis may have similar symptoms, cerebral involvement, as observed for *Plasmodium falciparum* infection, is not known to occur in human *Babesia* infections (582).

A case of babesiosis in a pregnant mother has also been reported, although congenital infection did not occur (467). To our knowledge, only one possible case of congenital *Babesia* infection has occurred (515). As such, congenital *Babesia* infection is an extremely rare event, if it occurs at all.

Nomenclature of human-infecting *Babesia* species. Generally, *B. microti* is associated with human babesiosis in the United States, while *B. divergens* is associated with European babesiosis (187). However, the nomenclature of human-infecting *Babesia* parasites has recently become more complex due to the emergence of new isolates in Europe, the United States, Africa, South America, and Asia. The classification of human-infecting *Babesia* species was initially dependent on morphology and host specificity, although later studies based on molecular techniques indicated that these criteria are inadequate (114, 459).

Human-infecting *Babesia* parasites which could not be classified as either *B. microti* or *B. divergens* were often designated a short acronym to identify them. Examples include WA1, EU1, CA1, MO1, KO, and KY (35, 114, 322, 574). However, based on molecular and immunological evidence, some of these acronyms are now known to represent the same species (114, 574). Furthermore, several studies have demonstrated that these organisms represent previously undescribed species of *Babesia* (265, 279, 547, 574). As such, some of these organisms have recently been allocated species names (114, 265).

(i) *Babesia duncani* (WA1). The first report of a human infection with the WA1 isolate of *Babesia* was described in 1995 by Quick et al. (459) in Washington State. The patient was a 41-year-old ICT male with an intact spleen. The organism was morphologically indistinguishable from *B. microti*. However, molecular and serological studies indicated that this organism was distinct from *B. microti*, *B. divergens*, and several other *Babesia* species (459, 547). Furthermore, the disease caused by WA1 in laboratory rodents was far more severe than that which is typically observed for *B. microti* (459). In 1995, Persing et al. (431) identified four WA1-like infections (one of which was fatal) in splenectomized patients from Northern California. These isolates described by Persing et al. (431) were identified by the acronyms CA1, CA2, CA3, and CA4 (114). Ribosomal DNA sequences from these four isolates were virtually identical (431). Later reports also described infections with WA1-type organisms, which were acquired via blood transfusion in patients from Washington State (267) (isolates WA2 and WA3) and California (327) (isolates CA5 and CA6). Herwaldt et al. (267) PCR amplified sections of the SSU rDNAs from WA2 and WA3, which were found to be identical to each other and to WA1. Kjemtrup et al. (327) later demonstrated that that the SSU rDNAs from CA5 and CA6 were 99.9% similar to that of the WA1 isolate. Using phylogenetic analysis of the SSU rDNAs of various *Babesia* isolates, Kjemtrup et al. (327) also demonstrated that the human

isolates CA1, CA3, and CA4 were extremely similar to *Babesia* isolates from mule deer and the bighorn sheep but distinct from the other WA1-type parasites. In 2006, Conrad et al. (114) confirmed the same phylogenetic relationships by constructing a strict consensus tree based on ITS2 sequences. In that study, Conrad et al. (114) also proposed the species name *Babesia duncani* for the WA1-type isolates (WA1, WA2, WA3, CA5, and CA6). To our knowledge, the organisms CA1, CA2, CA3, and CA4 have not been given a species name.

(ii) *Babesia divergens*-like organisms. In 1996, Herwaldt et al. (263) described a case of fatal babesiosis in a 73-year-old splenectomized man from Missouri. Molecular and immunological characterization of this organism (MO1) revealed that it was similar to *B. divergens* (associated with human babesiosis in Europe) and dissimilar to *B. microti* and WA1 (263). In a later report, a similar organism (KY) was identified as a cause of acute babesiosis in a patient from Kentucky (35). In 2004, Herwaldt et al. (266) reported another *Babesia divergens*-like infection in Washington State in an 82-year-old man without a spleen. The SSU rDNA of this organism was 99.5% similar to that of *B. divergens* (266). Interestingly, Holman (279) found that the SSU rDNA and internal transcribed spacer (ITS) sequences from the KY isolate and a *Babesia* isolate found in cotton-tailed rabbits on Nantucket Island, MA, were 100% identical. However, the ITS1 and ITS2 regions were several bases longer in the KY/rabbit isolates than the ITS regions of *B. divergens* (279). Moreover, studies based on morphology and infectivity in cows demonstrated that these isolates (the KY/rabbit isolates) were distinct from *B. divergens* (279). The KY/rabbit isolate, MO1, and the Washington state *Babesia divergens*-like isolates are now collectively referred to as *B. divergens*-like organisms (574).

(iii) *Babesia venatorum* (EU1). In 2003, Herwaldt et al. (265) identified two non-*B. divergens* infections in two asplenic men from Austria and Italy. This isolate became known as "EU1." PCR and sequence analysis revealed that this organism was not *B. divergens* but was similar to *Babesia odocoilei* (a species known to infect white-tailed deer of the United States) (265). Herwaldt et al. proposed the species name *B. venatorum* for the EU1 isolate (265). In a later study, Haselbarth et al. (253) identified a *Babesia* infection in a 63-year-old splenectomized German patient with nodular lymphocyte-predominant Hodgkin's lymphoma. Sequence analysis of the SSU rDNA of this isolate revealed that it was 99% similar to the EU1 isolates (253). Recently, EU1 *Babesia* parasites have been identified in roe deer from France (56) and in *Ixodes* ticks from Poland (107). To our knowledge, only three human cases of *Babesia venatorum*-like infection have been reported (253, 265).

(iv) Other *Babesia* isolates. Cases of human babesiosis are not as common outside Europe and the United States. However, several cases of human babesiosis have been confirmed in Asia, Central/South America, and Africa. In these cases, species names have not been allocated.

Rios et al. (474) microscopically identified an unknown species of *Babesia* in the blood of a subject from Columbia. Rios et al. also detected anti-*Babesia* antibodies in the sera of several Colombian subjects, although no *Babesia* parasites were observed (474).

Kim et al. (322) identified the first case of human *Babesia* infection in South Korea. Sequencing of the SSU rDNA of this isolate (KO1) determined that it was similar to a *Babesia* parasite isolated from sheep in China (322). In Taiwan, Shih et al. (518) discovered an asymptomatic infection with a species of *Babesia* in a 51-year-old woman. This new isolate (TW1) was antigenically similar to *B. microti* but not identical (518).

A case of transfusion-associated babesiosis has also been reported in Japan (385). The etiological agent from this case (385) was later isolated from the blood donor (493). The rDNA sequence of this organism was 99.2% similar to that of *B. microti*, although serum from the donor was only weakly reactive to *B. microti* isolates from the United States (493). This Japanese isolate became known as the "Kobe strain" (493). Interestingly, a mouse trapped near the residence of the blood donor was infected with a *Babesia* isolate with an rDNA sequence identical to that of the Kobe strain (596). Kobe strain-like *Babesia* isolates have also been detected in field rodents in central Taiwan and Southeastern Mainland China (492).

Cases of human babesiosis have also been reported in South Africa (77), Mexico (326), India (375), and Egypt (191).

Diagnosis. A definitive diagnosis of *Babesia* infection is usually made by the observation of *Babesia* parasites in Giemsa-stained thin blood smears (49, 273, 574). *Babesia* parasites appear as piroplasm or "tear-drop" forms, ring forms, amoeboid forms, and tetrad or "Maltese cross" forms (49, 114). Low-grade infections may be overlooked, where less than 1% of erythrocytes may contain *Babesia* parasites (273, 332). In symptomatic patients, *Babesia* is more readily detectable by microscopy (273). The following website provides excellent images of *Babesia* parasites in Giemsa-stained blood smears: http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/Babesiosis_il.htm.

Babesia parasites can resemble *P. falciparum* in Giemsa-stained smears, which can be problematic for diagnosis (257). In these cases, a patient's travel history can be useful. However, *Babesia* and *Plasmodium* can be distinguished by the presence or absence of pigment deposits (hemozoin) in parasitized erythrocytes. Pigment deposits occur only in *Plasmodium* infections (257).

Other diagnostic techniques are also available. In the past, the inoculation of live laboratory rodents with patient blood specimens was a useful diagnostic tool. One study described rodent inoculation as being as sensitive and specific as PCR (336). However, rodent inoculation may be impractical for some laboratories. Furthermore, the technique can be problematic due to various susceptibilities of different species of rodent to various species of *Babesia*. Diagnosis by live-animal inoculation is also quite slow (273). Due to its limitations, the inoculation of laboratory rodents is not widely used. The QBC tube technique may also be useful for the microscopic diagnosis of *Babesia* infections (102).

PCR is useful for diagnosis of *Babesia* infection (336). Vannier and Krause (574) recommended that PCR be used for diagnosis when *Babesia* infection is suspected and Giemsa-stained blood smears appear negative or ambiguous (574). Molecular techniques are also useful when the identification of the causal species is desired. The sequencing of PCR products has been used widely for phylogenetic analyses of human-infecting *Babesia* species (263, 266, 273).

Serological techniques such as ELISA (360) or IFAT (574)

may also be useful, although IFAT is more frequently used (273). When using IFAT, titers greater than 1:1,024 usually occur for *B. microti* infections in the early, acute phase of infection and may be indicative of a recent and/or active infection (574). Serology is less useful for *B. divergens* infections, as the onset of *B. divergens* babesiosis is more rapid, and disease symptoms become apparent before seroconversion takes place (574).

Treatment. Originally, the standard treatment for *Babesia* infection was clindamycin and quinine therapy (286, 582). However, combination therapy with atovaquone and azithromycin is preferred, as it is just as effective and is associated with fewer adverse reactions (574, 582). In cases of severe babesiosis, aggressive therapy combining large blood transfusions followed by prophylaxis (often an infusion of intravenous clindamycin) is an effective treatment (582).

In a recent animal study, imidocarb diproprionate demonstrated good activity against *Babesia caballi* in horses (510). Imidocarb is not currently licensed for human use, although it has been used under special license to successfully treat some human infections (582). This drug may be useful as an alternative treatment for human babesiosis in the future.

FREE-LIVING AMOEBAE

Acanthamoeba spp.

Organism and disease. *Acanthamoeba* spp. are ubiquitous, free-living amoebae that infect humans opportunistically. These organisms are the etiological agent of fatal granulomatous amoebic encephalitis (GAE), usually associated with IC individuals (511, 593, 594). *Acanthamoeba* exists in a range of environments, including soil, air, freshwater, salt water, and sewage (320). While humans are in frequent contact with environmental sources of *Acanthamoeba* species, this organism infrequently causes disease (320). *Acanthamoeba* can be acquired by washing of the face in pond water, getting sand or dust in the eye, inhalation of contaminated material, or traumatic injection or entry through preexisting wounds or lesions (377, 579). The clinical course of *Acanthamoeba* infection is slow and subtle compared to that of infections with other free-living amoebae (28, 504).

The disease spectrum of *Acanthamoeba* infection is very broad in IC patients. In ICT individuals, *Acanthamoeba* is most often known as a cause of keratitis in contact lens wearers (Fig. 5) (26, 78, 284, 320). Occasionally, ICT individuals will suffer from GAE, although the disease is more common in IC individuals (377, 594). Patients with GAE will often present with seizures, headaches, confusion, and locomotor difficulties (172, 367). GAE is almost always fatal, regardless of immune status, with an approximate survival rate of less than 7% (594). Patients with *Acanthamoeba*-HIV coinfection usually do not survive, particularly patients with disseminated disease (90, 323, 377, 411, 477, 486, 509). In IC patients, *Acanthamoeba* infections also occur in the skin (386) and bones (512). Rhinosinusitis (401, 477), keratitis (251, 318, 358), otitis (185, 513), vasculitis (260, 486), and endophthalmitis (259) have also been reported for *Acanthamoeba*-HIV-coinfected patients. Skin lesions are the most common presenting manifestation of *Acanthamoeba* in AIDS (377) and may be present in the absence of CNS involvement (551).

Acanthamoeba has been reported as a cause of disease in other IC groups. In lung transplant recipients, infections involving the skin, lungs, and brain as well as sinusitis and widely disseminated disease have been reported (176, 411, 571, 580). *Acanthamoeba* has also been reported to cause disease in kidney and liver transplant recipients (215, 536). An unusual case of *Acanthamoeba* infection was reported for a patient who was severely IC ($CD4^+$ cell count of 182 cells/mm^3) due to an infection with *Mycobacterium tuberculosis* (594). In that study, pulmonary and CNS involvements were apparent, with concurrent dermal lesions (594).

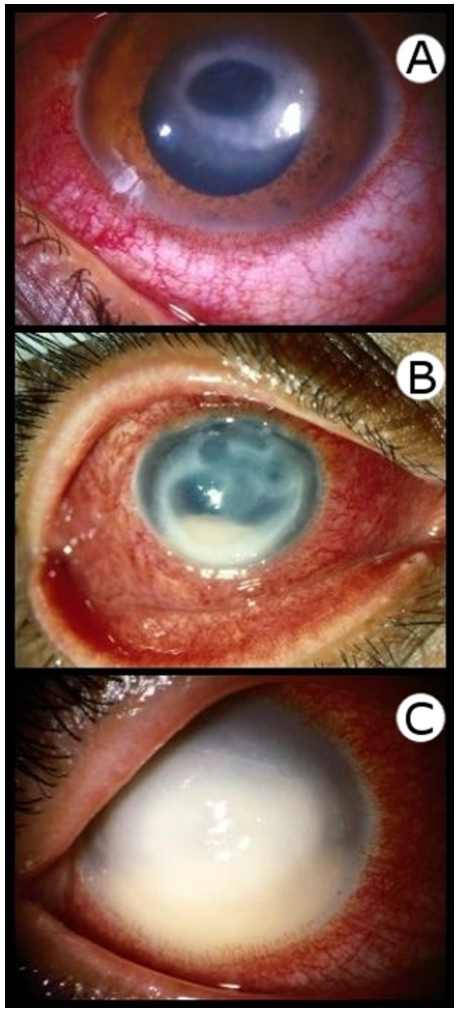

FIG. 5. Clinical presentation of *Acanthamoeba* keratitis. (Courtesy of Paul Badenoch.) (A) Keratitis demonstrating ring-stage infiltrate. (B) Keratitis with multiple ring infiltrates and hypopyon. (C) Keratitis with near-total suppuration.

Diagnosis. The diagnosis of *Acanthamoeba* infection usually requires microscopy of stained tissue sections or wet mounts (377). Giemsa stain, Gram stain, or the fluorescent stain calcofluor white can be used (Fig. 6). The following website provides excellent microscopic images of free-living amoebae: http://www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/FreeLivingAmebic_il.htm.

If CNS involvement is suspected, an MRI is often employed to determine the presence of brain lesions (367, 377). The

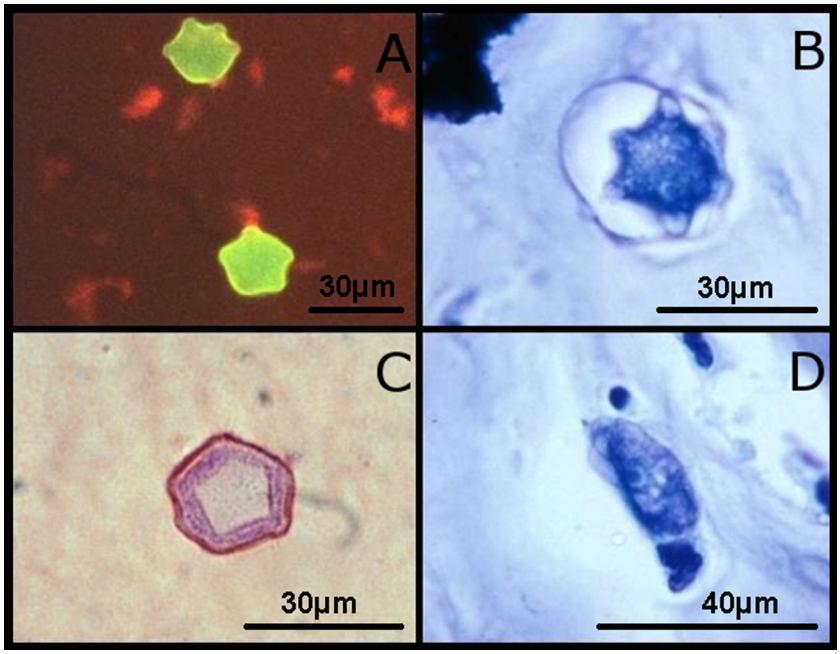

FIG. 6. Fixed, stained sections from corneal scrapings showing cysts and a trophozoite of *Acanthamoeba*. (Courtesy of Paul Badenoch.) (A) *Acanthamoeba* cysts stained with calcofluor white. (B) *Acanthamoeba* cyst stained with a Giemsa stain. (C) *Acanthamoeba* cyst stained with a Gram stain. (D) *Acanthamoeba* trophozoite stained with a Giemsa stain.

cultivation of *Acanthamoeba* from clinical specimens can also be diagnostic. The cultivation of trophozoites from CSF, brain tissue, corneal scrapings, or material from cutaneous/sinus lesions can be achieved by inoculation onto neomycin-nalidixic acid (NNA) agar plates containing a layer of *Escherichia coli* or *Enterobacter aerogenes* cells. Inoculation of biopsy material onto monolayers of cultured mammalian cells can also be performed (377). Immunofluorescent antibody test (377) and PCR (367, 594) are also available for the diagnosis of *Acanthamoeba* infection. In a study performed on a single patient suffering from GAE, PCR was found to be the only technique to return a positive result for four CSF samples, dermal specimens, a bronchoalveolar lavage specimen, lung biopsy specimens, and brain biopsy specimens, while culture, microscopy, and immunofluorescence repeatedly returned negative results (594). Several monoclonal antibodies to surface antigens of *Acanthamoeba* cysts have also been developed, which could be useful for the development of new diagnostic tests in the future (563).

Treatment. A broad range of drugs have been used to treat *Acanthamoeba* infections but with various successes. Drugs that show some anti-*Acanthamoeba* activity include propamidine isethionate, polyhexamethylene biguanide, itraconazole, clotrimazole, pentamidine isethionate, amphotericin B, flucytosine, chlorhexidine gluconate, hydroxystilbamidine, paromomycin, cotrimoxazole, rifampin, polymyxin, sulfadiazine, trimethoprim-sulfamethoxazole, azithromycin, dibromopropamidine, hexamidine, and ketoconazole (215, 377, 401, 411, 579). In one study, propamidine proved to be the most effective anti-*Acanthamoeba* agent against 19 corneal isolates (357). The drug polyhexamethylene biguanide was also effective (357). The drugs pentamidine, hexamidine, chlorhexidine, and chloroxylenol demonstrated intermediate activity, while neomycin, amphotericin B, and povidone-iodine had poor activity (357).

In some cases, surgical intervention may be necessary for the treatment of *Acanthamoeba* infections. In severe cases of sinusitis and rhinosinusitis, sinus debridement surgery may be necessary (401, 580). Surgical intervention may also be necessary for *Acanthamoeba* keratitis where penetrating keratoplasty or complete evisceration of the eye may be required (579).

Despite the broad range of drugs trialed, the most effective treatment for acanthamoebiasis remains undefined, and many drug treatments have shown various efficacies (215, 320, 323, 377, 571, 594). To date, there is no proven regimen for the treatment of *Acanthamoeba* infection (233). As such, once an *Acanthamoeba* infection is confirmed, therapy should be applied rapidly and aggressively.

Balamuthia mandrillaris

Organism and disease. *Balamuthia mandrillaris* is a ubiquitous free-living amoeba that infects humans opportunistically. In humans, *Balamuthia* is known as a cause of lethal granulomatous encephalitis. *Balamuthia* is believed to exist in all environments and has been isolated from environmental soil samples (186, 505) and recreational bathing water (241). Humans become infected either through the inhalation of contaminated material or through cuts or abrasions in the skin. It is also thought that *Balamuthia* can enter the brain through the nose via the olfactory nerves (321). *Balamuthia* infection in animals has also been reported (85, 325). In fact, *B. mandril-*

laris was first isolated in 1993 from a mandrill baboon that had died from meningoencephalitis (590). Approximately 150 cases of human *Balamuthia* infection were reported worldwide between the years 1990 and 2008 (94), with an additional 10 cases reported in California in 2009 (508). The clinical course of *Balamuthia* infection is generally subacute, often extending over a matter of weeks to months and usually concluding with the death of the patient (28, 310, 452, 469, 544).

The disease spectrum of *B. mandrillaris* infection can include skin lesions, rhinitis (588), and disseminated disease (523). However, the most common clinical manifestation of *Balamuthia* infection is GAE, which presents with a clinical picture similar to that of *Acanthamoeba* GAE. Encephalitis resulting from *Balamuthia* infection is often referred to as *Balamuthia* amoebic encephalitis (BAE). Numerous cases of BAE have been reported for ICT and IC persons alike (129, 152, 153, 245, 291, 430, 456). *Balamuthia* amoebic encephalitis is almost invariably fatal (430, 456, 568) regardless of immune status, with most cases being diagnosed postmortem. However, survivals have been reported (144, 306).

Compared to infections with *Naegleria fowleri* (discussed below), the clinical course of *Balamuthia* infection is slow (144, 306). In some of these cases, CNS symptoms are experienced for weeks to months prior to diagnosis and treatment (144, 430). In one patient, CNS involvement did not become apparent until 18 months after the disease presented in the form of a facial lesion (469). In this case, a more timely diagnosis could have improved the outcome (469). While *Acanthamoeba* infection is usually associated with IC individuals (377, 594), *Balamuthia* is known to infect ICT individuals but with a noticeable preference for young children and the elderly (28, 144, 245, 306, 355, 456, 520, 544). Also in contrast to *Acanthamoeba*, *Balamuthia* is not known as a cause of keratitis. Otherwise, the disease spectra associated with these amoebae are similar (588).

Patients infected with *Balamuthia* will often experience fever, headache, nausea, vomiting, stiff neck, and focal neurological signs that accompany brain lesions (380, 430). Other neurological signs can include changes in personality and mental status, seizures, and sleepiness (380). Hydrocephalus may also be experienced (28, 182). Cutaneous lesions have been reported as a presenting feature of *Balamuthia* infection in some cases (153, 456, 469). Susceptibility to *Balamuthia* infection is increased in the presence of cancers, diabetes, drug abuse, alcoholism, organ transplantation, and HIV (380, 426, 430, 587). Several cases of *Balamuthia* infection have been reported for AIDS patients (380, 620). While most *Balamuthia*-HIV coinfections manifest as BAE, disseminated disease due to *Balamuthia*-HIV coinfection has also been reported (523). In one AIDS patient, encephalitis without a granulomatous reaction was observed, along with involvement of the kidneys, adrenal glands, thyroid gland, and liver (523).

Diagnosis. Neurological abnormalities will usually prompt a CT scan or MRI of the brain (291). Brain lesions caused by *Balamuthia* can appear similar to those caused by other protozoa, which may lead to a misdiagnosis and incorrect treatment (523). For a definitive diagnosis, microscopy, PCR, and/or IFAT must be employed. Most *Balamuthia* cases are diagnosed by IFAT (380, 430, 544), which is considered the "gold standard" for the detection of *Balamuthia* (523). Diagnosis by staining and microscopy of fixed tissue sections is also employed but usually after the patient's death (144). For staining of fixed tissue sections, a hematoxylin-and-eosin stain is often used (144, 380, 452). Other alternative stains such as a Gomori's methenamine silver stain or a periodic acid-Schiff stain are also useful (380). Even so, *Balamuthia* may still be inconspicuous in stained tissue sections (430), and laboratories without access to IFAT may underreport the incidence of *Balamuthia* infection (430). As such, *Balamuthia* infection should not be excluded solely on the basis of a negative microscopy result. If IFAT is not available, PCR or electron microscopy may be employed to confirm the presence of a *Balamuthia* infection (380, 452, 544). DNA extracted from deparaffinized brain tissue biopsy specimens can be tested with PCR using *Balamuthia*-specific primers (544). A multiplex PCR assay that can differentiate between infections with *Acanthamoeba*, *Balamuthia*, and *N. fowleri* in a single test has also been developed (462).

Treatment. Treatment regimens for *Balamuthia* infections are poorly defined. *Balamuthia* infections are usually fatal, and in studies which reported "favorable" outcomes (the long-term survival of patients), neurological damage was sometimes permanent and treatment regimens had to be continued for years (144). However, some drugs do demonstrate anti-*Balamuthia* activity. In one *in vitro* study, miltefosine demonstrated anti-*Balamuthia* activity, while the drug voriconazole had virtually no effect (506). In another *in vitro* study, pentamidine and propamidine were shown to be amoebicidal, while amphotericin B was only amoebastatic (507). In the few cases in which patients survived, the treatment regimens employed were as follows: (i) pentamidine (300 mg intravenous once daily), sulfadiazine (1.5 g four times daily), fluconazole (400 mg daily), and clarithromycin (500 mg three times daily) (306) and (ii) fluconazole (400 mg daily), sulfadiazine (1.5 g every 6 h), and clarithromycin (500 mg three times daily) (144).

Usually, the prognosis for BAE patients is very poor, and survival is rare. Further research is required to facilitate the discovery of more effective anti-*Balamuthia* compounds.

Naegleria fowleri

Organism and disease. *Naegleria fowleri* is a free-living amoeboflagellate, first identified as a human pathogen in South Australia by Malcolm Fowler in 1965 (117, 210). *Naegleria fowleri* is recognized as the cause of primary amoebic meningoencephalitis (PAM), an often fatal disease. *Naegleria* infections are obtained exclusively through contact with contaminated bodies of water (29, 33, 48, 60, 89), presumably when the water enters the nasal cavity (117). The protozoa then invade the central nervous system via the olfactory nerve (60). The species *Naegleria italica* and *Naegleria australiensis* are also considered potentially pathogenic members of the genus *Naegleria* (479).

Naegleria species are ubiquitous in wet environments and have recently been identified in domestic water sources (378), cooling waters from power plants (37), and well water (48). Several novel *Naegleria* spp. have recently been isolated from freshwater sediments in Arctic and sub-Antarctic regions (146). However, these species grew only between room temperature and 30°C (146) and therefore probably lack the ability

to parasitize mammalian tissues. Human and animal infections with *Naegleria* are usually associated with temperatures greater than 30°C (95, 117, 136).

Despite the ubiquity of *Naegleria*, infections are comparatively rare, and the estimated risk of becoming infected with *Naegleria* is low (80). However, in one Australian study, an "outbreak" of *N. fowleri* infection was described where 19 cases of probable PAM occurred between 1947 and 1972 (117). These infections were thought to be associated with a contaminated drinking water pipeline from which *N. fowleri* was eventually isolated in 1972. Some patients recalled having water from this source splashed onto their face and in their nose. Furthermore, some of these pipes were in direct contact with sunlight, and temperatures within these pipes were reported to reach 35°C to 45°C in summer. These conditions would have promoted the growth of the vegetative form of *N. fowleri* (117).

Similarly to *B. mandrillaris*, *N. fowleri* infections are associated with healthy ICT persons, often children (111, 128, 258, 410, 517), rather than IC patients (60). In contrast to other free-living amoebae, *N. fowleri* infections are restricted to the CNS (60). To our knowledge, only one case of PAM has been reported for an HIV-infected patient, and parasitic involvement was restricted to the CNS (110). Furthermore, one study described a case where an organ donor had died of PAM, but the single recipient of the kidneys, pancreas, a lung, and liver failed to contract PAM (38, 379).

In the single case of *Naegleria*-HIV coinfection, the patient suffered from a range of neurological symptoms, including headache, somnolence, dysarthria, left hemiparesis, and motor incoordination. The patient died 8 days after admission to the hospital (110).

The progression of PAM is rapid, with death often occurring within a week after the onset of symptoms (29, 89). Survival from PAM is rare, with only 7 reports of survival out of approximately 300 cases reported prior to 2002 (295). *Naegleria fowleri* rapidly destroys the tissues of the CNS, leading to various neurological disturbances, including taste and olfactory impairments, nausea, vomiting, anorexia, headache, dizziness, confusion, and, finally, coma and death (29, 89).

Diagnosis. Primary amoebic meningoencephalitis is usually diagnosed from wet mounts of CSF, where active amoebae may be observed (110, 312, 575). Giemsa- or trichrome-stained CSF smears may aid in the early diagnosis of PAM by enabling the differentiation of amoebae from host cells based on the nuclear structure (589). Fixed hematoxylin-and-eosin stains may also be useful (503).

Since the onset of PAM is extremely rapid (usually less than a week), there is insufficient time for the patients' immune systems to develop a detectable immune response. Therefore, serology is not useful for the diagnosis of PAM (589). The diagnosis of PAM should include PCR (500, 575). A PCR assay with the ability to detect *Naegleria* in formalin-fixed brain sections with a high level of sensitivity was developed (500). A real-time PCR assay that can distinguish between multiple members of the genus *Naegleria* by melting-curve analysis has also been developed (479). This assay could easily be adapted to DNA extracted from the CSF and may be useful in identifying the causal species of a *Naegleria* infection. A recently developed real-time PCR assay is also available for the detection of *N. fowleri* (370, 458). *Naegleria* may also be cultured from fresh CSF onto nonnutrient agar or various other medium formulations for further characterization (97, 312).

Treatment. As with the other free-living amoebae, no proven treatment regimens exist for PAM. However, amphotericin B is probably the drug of choice for the treatment of *N. fowleri* infection due to its successful use in a few cases of PAM (66, 575). Amphotericin B has also demonstrated good anti-*Naegleria* activity *in vitro* (242, 243, 548, 549). However, amphotericin B therapy is not always successful (503). The drugs fluconazole and rifampin have also been used in combination with amphotericin B to successfully treat PAM (575). The drug ketoconazole has also shown anti-*Naegleria* activity in *in vitro* studies (414, 549). Drugs reported to be ineffective against *Naegleria* include trimethoprim (96), penicillin, sulfadiazine, chloramphenicol, oxytetracycline hydrochloride, streptomycin, methotrexate, emetine, quinine, and metronidazole (88).

While survival of patients with *N. fowleri* infection is rare, it has been hypothesized that the prognosis for PAM patients could be improved by a combination of therapies, including multiroute amphotericin B therapy (including the intrathecal route), a range of antimycotic and antibacterial drugs, intrathecal anti-*Naegleria* immunoglobulin, and the anti-inflammatory drug dexamethasone (7). Unfortunately, the rapid course of PAM means that the survival of patients relies on timely and aggressive therapy. Given the lack of any proven treatments for PAM, the prognosis for those diagnosed with the disease is poor. Clearly, more research is required to identify more anti-*Naegleria* compounds and to develop treatment regimens for PAM.

Sappinia pedata

To our knowledge, only a single case of human *Sappinia pedata* infection has been reported (228, 461, 588). This organism is a free-living amoeba that has been isolated from environmental sources such as soil and tree bark (461). Given the existence of this single isolated case, *Sappinia* is mentioned only briefly.

The patient in question was a 38-year-old ICT male who presented with neurological signs, including headache, blurred vision, photophobia, and vomiting, for 2 to 3 days. Magnetic resonance imaging scans revealed a mass in the posterior left temporal lobe, which was later excised. The mass was found to contain trophozoites of an amoeboid organism which was thought to be of the species *Sappinia diploidea* (228). The patient was treated with a range of antiamoebic drugs, including azithromycin, pentamidine, itraconazole, and flucytosine (227). The outcome was favorable, and the patient survived (227, 228). In a later study, three real-time PCR assays were used to ascertain that the etiological agent was more likely to be *S. pedata* than *S. diploidea* (461).

CONCLUSIONS

Protozoan pathogens with the ability to cause disease in human tissues are a major global health concern. In most cases, the prognosis for patients with protozoal disease of solid tissues and/or blood is greatly worsened in the presence of

TABLE 3. Diagnostic techniques available for various blood and tissue protozoan infections

Organism(s)	Techniques	Description
Microsporidia	Light microscopy, TEM, PCR, real-time PCR, IFAT, DAT	Light microscopy is cheap and applicable to any clinical specimen; however, differentiation of species may be difficult by light microscopy; transmission electron microscopy may be useful for differentiation of species, although it can be expensive; several PCR and real-time PCR assays have been developed for detection of various species, although PCR requires a special apparatus; real-time PCR can be more rapid than conventional PCR, as it does not require agarose gel electrophoresis; generally, real-time PCR is more sensitive than conventional PCR; sequencing of PCR products may be necessary for species differentiation; indirect fluorescent antibody tests and DAT are available for some species only
Leishmania	Conventional and real-time PCR, light microscopy, culture systems, serological techniques, DAT, rK39 dipstick test, latex agglutination test, QBC tube technique	Staining of blood films followed by light microscopy is definitive but is less sensitive than molecular techniques; real-time PCR can also be used to monitor patients' responses to therapy but requires a special apparatus; sequencing of PCR products can also allow differentiation of species; culture systems are useful but may be impractical; in Ethiopia DAT is preferred for diagnosis of *L. donovani* infection, as it is cheap, rapid, and sensitive; the rK39 dipstick test is cheap, rapid, and sensitive for diagnosis in ICT patients; however, the rK39 test demonstrated low sensitivities of ~20% in European VL patients infected with HIV; the latex agglutination test is sensitive and noninvasive (applied to urine specimens); enzyme-linked immunosorbent assay and other serological techniques may be of limited use in IC patients, as circulating antibodies may not be detected during an active infection; the QBC tube technique is useful for the diagnosis of VL
Trypanosoma cruzi	Light microscopy, real-time PCR, PCR, ELISA, IFAT, QBC tube technique	Light microscopy is definitive; trypanosomes are more readily observed in peripheral blood specimens in the acute stage and in IC patients; the blood stains are useful for blood stages, and hematoxylin and eosin stains are used for diagnosis of the intracellular stages, as seen in solid tissues; live, motile trypanosomes may be observed microscopically in the buffy coat or CSF (if CNS involvement is apparent); PCR and real-time PCR are sensitive but require a special apparatus; PCR can also be useful for monitoring treatment efficacy; the QBC tube technique is useful for diagnosis during the acute phase of Chagas' disease but is less useful during the chronic phase of the disease
Trypanosoma brucei rhodesiense, *Trypanosoma brucei gambiense*	Light microscopy, PCR, real-time PCR, ELISA, CATT, QBC tube technique	The blood stains are useful for light microscopic diagnosis when applied to blood or CSF; the microhematocrit centrifugation technique also enables the visualization of live motile trypanosomes microscopically; several PCRs and real-time PCRs are also available; PCR is sensitive and can allow differentiation of *T. brucei* subtypes; enzyme-linked immunosorbent assay is also useful; the CATT is available for *T. b. gambiense* sleeping sickness and is the most widely used technique in areas of endemicity, as it is cheap, rapid, and sensitive; a CSF white blood cell count is useful to predict the stage of sleeping sickness; the QBC tube technique has demonstrated greater sensitivity for detection of African trypanosomes than the microhematocrit centrifugation technique
Non-human-infecting *Trypanosoma*	Light microscopy, various molecular techniques	No specific diagnostics are available, as human infections are rare; infections are typically diagnosed by a combination of light microscopy and various molecular techniques
Lower trypanosomatids	TEM, light microscopy, various molecular techniques	As with the non-human-infecting *Trypanosoma* spp., no specific diagnostics are available, as human infections are rare; infections were typically diagnosed by a combination of light microscopy and various molecular techniques; transmission electron microscopy was used in 1 case
Toxoplasma gondii	Light microscopy, PCR, real-time PCR, ELISA, IgG avidity test for pregnancy	Observation of live free tachyzoites in stained smears of blood or CSF is diagnostic of an active infection; enzyme-linked immunosorbent assay can be useful but fails to differentiate between active and benign infections; PCR performed on peripheral blood is also diagnostic for an active *Toxoplasma* infection; real-time PCR assays are available, which are extremely sensitive and specific. The IgG avidity test is useful in pregnancy to predict the risk that a *Toxoplasma* infection poses to the fetus; however, the results of serological tests can be complex and difficult to interpret for pregnant woman and neonates
Neospora caninum	Serology, PCR	Tachyzoites of *Neospora* are virtually indistinguishable from those of *Toxoplasma*; as such, light microscopy cannot differentiate the two; few diagnostics are available for human infections, as human neosporosis has never been reported; however, various serological techniques and PCR assays have been developed, which show good sensitivity and specificity

Continued on following page

TABLE 3—*Continued*

Organism(s)	Techniques	Description
Babesia	Light microscopy, PCR, laboratory rodent inoculation, ELISA, IFAT, QBC tube technique	Microscopic analysis of stained blood smears is useful for diagnosis in the early stages of infection or in IC patients; live-rodent inoculation is sensitive and was once used for diagnosis but has been abandoned due to practicality issues; PCR can be applied to blood specimens and is sensitive and extremely useful for the characterization of new isolates; enzyme-linked immunosorbent assay and IFAT may be useful for diagnosis of *B. microti* infections but are less applicable to *B. divergens* infections; for definitive confirmation of *Babesia* infection at the species level, amplification of the SSU rDNA genes by *Babesia*-specific PCR followed by sequencing of the PCR product can be performed; the QBC tube technique can also be used for the microscopic diagnosis of *Babesia* infection
Acanthamoeba (GAE)	Light microscopy, cultivation, IFAT, PCR	*Acanthamoeba* spp. can be identified in Gram or Giemsa stains of CSF; calcofluor white can also be used for microscopic detection of *Acanthamoeba*; cultivation of trophozoites from CSF or tissue lesions by inoculation of the specimen onto neomycin-nalidixic acid agar plates seeded with a layer of *Escherichia coli* or *Enterobacter aerogenes* cells is a useful diagnostic tool; cultivation of *Acanthamoeba* can also provide the material for downstream molecular characterization; indirect fluorescent antibody techniques and PCR are also available; PCR is probably the most sensitive technique available for diagnosis of *Acanthamoeba* infection
Balamuthia (BAE)	Light microscopy, PCR, IFAT, electron microscopy	Several stains are useful for light microscopic diagnosis, although the hematoxylin and eosin stain is usually applied to fixed tissue sections; however, *Balamuthia* trophozoites may be difficult to see; the use of an immunofluorescent antibody technique is a sensitive and specific alternative to light microscopy and is the gold standard for diagnosis of *Balamuthia* infection; PCR is also useful for diagnosis, as it is sensitive; some PCR assays can distinguish between *Balamuthia* and other free-living amoebae; electron microscopy is useful, although it is expensive
Naegleria fowleri (PAM)	Light microscopy, PCR, real-time PCR, cultivation	As the onset of PAM is rapid, live, motile trophozoites can be readily observed in wet mounts of patient CSF; light microscopy of fixed, stained tissue smears is also useful. PCR and real-time PCR are available; cultivation of *Naegleria* from CSF enables downstream molecular analysis of isolates
Sappinia pedata	Light microscopy, PCR	Only 1 reported case, which was diagnosed by light microscopy; recently, 3 real-time PCR assays were also developed for *Sappinia* spp.

HIV. Due to the debilitation of the immune system seen in HIV infection, organisms such as *Toxoplasma*, which usually cause benign infections, can cause potentially fatal disease. Similarly, the microsporidia and some lower trypanosomatids, which are usually noninfectious to ICT humans, can cause serious disease in HIV-infected patients.

While patients who adhere to antiretroviral therapy may experience a partial and/or temporary reconstitution of the immune system and resolution of some disease symptoms of protozoal origin, HIV infection is also complicated by immune reconstitution disorders (IRDs). Any pathogen capable of causing an opportunistic infection has the potential to cause IRD after the commencement of antiretroviral therapy (213). However, some pathogens have a lower tendency to cause IRDs than others. *Toxoplasma*-associated IRDs are an uncommon event (429), although granulomatous inflammation is often triggered in response to antiretroviral therapy in the presence of *Leishmania* infections (10, 213). Immune reconstitution disorders are characterized by inflammation at the site of a given infection and may be confused as an immunodeficiency-related disease rather than IRD. If a patient has been treated recently for a particular pathogen, IRD may occur in response to dead pathogens still present in the tissues (213). It is important that clinicians be aware of this paradoxical disease syndrome in order to prevent a misdiagnosis of IRD with opportunistic disease. An awareness of IRD is also necessary so that IRD is not mistaken for a failure of antiretroviral therapy.

In IC patients, many tissue-infecting protozoa demonstrate the ability to cause disease states that are atypical. Moreover, different species of parasitic protozoa can cause similar disease states in the presence of HIV. One example of this is the ability of *Toxoplasma* and *T. cruzi* to cause morphologically similar necrotic brain lesions. Atypical disease presentations and the similarity between certain disease states caused by unrelated protozoa in IC patients can make a correct diagnosis challenging. These similarities can lead to misdiagnosis and the inappropriate treatment of patients. It is important that clinicians and diagnostic laboratories are made aware of the pathogenic potential of various protozoa in the presence of HIV and are also aware of the various techniques available for the diagnosis of different protozoal infections. Information relating to the diagnostic techniques available for various tissue protozoa is summarized in Table 3.

Prior to the AIDS pandemic, infections with the microsporidia were rarely observed (169), and only four cases of infections with lower trypanosomatids have been reported to date, three of these in HIV-infected persons. Given the recent identification of the lower trypanosomatids as opportunistic infectious agents in IC individuals, it is not unreasonable to suggest that other opportunistic infectious agents may present themselves in the future. Given the findings of recent serolog-

TABLE 4. Suggested antimicrobial therapy for infections with various blood- and tissue-associated protozoa[a]

Organism	Suggested antimicrobial therapy[c]
Microsporidia	Effective HAART leading to immune restoration can result in clinical cure of microsporidiosis; restoration of $CD4^+$ cell counts of >100 cells/μl should lead to clinical improvement; for treatment of disseminated infections with *Encephalitozoon hellem*, *Encephalitozoon cuniculi*, or *Encephalitozoon intestinalis*, albendazole (400 mg orally twice daily for 3 weeks) can be used; there is no established treatment for *Pleistophora* or *Anncaliia* species infections, although albendazole therapy as described above is recommended; for disseminated infections with *Trachipleistophora*, albendazole (400 mg oral twice daily for 3 weeks) plus itraconazole (400 mg oral daily for 3 weeks) are recommended; clindamycin has also demonstrated some anti-*E. intestinalis* activity (300 mg orally every 6 h)[b]; treatment for ocular infections with *E. hellem*, *E. cuniculi*, *Vittaforma corneae*, or *Nosema ocularum* includes fumigillin (Fumidil B) at 3 mg/ml in saline (final concn of 70 μg/ml fumigillin) in eye drop form plus albendazole (400 mg orally twice daily for 3 weeks)
New World CL and MCL (Mexico, Central America, South America)	Always begin treatment of MCL with antimonial therapy; recommended primary therapy of sodium stibogluconate or meglumine antimoniate (20 mg/kg of body wt/day i.v. for 28 days); in Brazil, antimony and pentoxifylline (400 mg orally 3 times a day for 30 days) are superior to antimonial treatment alone; alternatives are amphotericin B (1 mg/kg i.v. every other day for 20 doses), liposomal amphotericin B (3 mg/kg/day i.v. for 6 days [3 weeks for MCL]), or miltefosine (2.5 mg/kg/day orally for 28 days); oral miltefosine is effective against *L. panamensis*, marginal against *L. mexicana*, and ineffective against *L. braziliensis*
Old World CL and MCL (Europe, Asia, and Africa)	Stibogluconate or meglumine antimoniate (20 mg/kg/day i.v. for 10 days)
Visceral leishmaniasis	Recommended primary therapy of liposomal amphotericin B (3 mg/kg/day i.v. for 5 days followed by 3 mg/kg on days 14 and 21); alternatives are liposomal amphotericin B (10 mg/kg/day i.v. for 2 days), stibogluconate or meglumine antimoniate (20 mg/kg/day i.v. in a single dose for 28 days), miltefosine (1.5-2.5 mg/kg/day orally for 28 days), or standard amphotericin B (1 mg/kg i.v. every other day for 20 days)
Trypanosoma cruzi	For adults, nifurtimox (8-10 mg/kg/day orally [after meals] divided into 4 doses for 120 days); for children 11-16 yr of age, nifurtimox (12.5-15 mg/kg/day orally [after meals] divided into 4 doses for 90 days); for children <11 yr of age, nifurtimox (15-20 mg/kg/day orally [after meals] divided into 4 doses each day for 90 days); an alternative is benznidazole (5-7 mg/kg/day orally divided into 2 doses each day for 30-90 days)
Trypanosoma brucei gambiense sleeping sickness (lymphatic stage)	Recommended therapy is pentamidine (4 mg/kg/day i.m. for 10 days); an alternative is suramin (100-mg i.v. test dose followed by 1 g i.v. on days 1, 3, 7, 14, and 21)
Trypanosoma brucei gambiense sleeping sickness (late CNS stage)	Recommended therapy is melarsoprol (2.2 mg/kg/day i.v. for 10 days); an alternative is eflornithine (100 mg/kg i.v. every 6 h for 14 days)
Trypanosoma brucei rhodesiense sleeping sickness (lymphatic stage)	Suramin (100-mg i.v. test dose followed by 1 g i.v. on days 1, 3, 7, 14, and 21)
Trypanosoma brucei rhodesiense sleeping sickness (late CNS stage)	Melarsoprol (2-3.6 mg/kg/day i.v. for 3 days, repeat after 7 days, and repeat for a third time 7 days after the second course)
Toxoplasma gondii	Treatment is often complex, depending on immune status and the presence or absence of pregnancy; no recommended treatment for immunologically healthy individuals unless there is evidence of severe symptoms or organ damage; treatment of congenital toxoplasmosis is also very complex; for acute infection in pregnancy at <18 wks of gestation, spiramycin (1 g every 8 h orally until delivery) can be used if amniotic fluid is PCR negative; for acute infection in pregnancy at >18 wks of gestation and if amniotic fluid is PCR positive, pyrimethamine (50 mg every 12 h orally for 2 days and then 50 mg/day orally) plus sulfadiazine (75 mg/kg orally for 1 dose and then 50 mg/kg every 12 h orally) plus leucovorin (10-20 mg/day orally) can be used; in cases of chorioretinitis, meningitis, or lowered resistance due to cytotoxic drugs or steroids in non-AIDS patients, pyrimethamine (200 mg/day orally for 1 dose and then 50-75 mg every 24 h) plus sulfadiazine (1-1.5 mg orally 4 times daily) plus leucovorin (5-20 mg orally 3 times per week) can be used (continue for 2 weeks after symptoms subside), and also add prednisone (1 mg/kg/day i.v. in 2 divided doses to reduce CSF protein or vision-threatening inflammation)

Continued on following page

TABLE 4—*Continued*

Organism	Suggested antimicrobial therapy[c]
AIDS-related cerebral toxoplasmosis	For prevention of cerebral toxoplasmosis in AIDS patients (prophylaxis), trimethoprim-sulfamethoxazole DS[e] (1 tablet orally every 24 h) or trimethoprim-sulfamethoxazole SS[f] (1 tablet orally every 24 h); alternatives are dapsone (50 mg orally every 24 h) plus pyrimethamine (50 mg orally per week) plus leucovorin (10-25 mg orally every 24 h) or atovaquone (1,500 mg orally every 24 h); recommended therapy for cerebral toxoplasmosis is pyrimethamine (200 mg orally for 1 dose) followed by pyrimethamine (75 mg/day orally) plus sulfadiazine (1-1.5 g orally every 6 h) plus oral leucovorin (10-20 mg daily) continued for 4-6 weeks after resolution of symptoms or trimethoprim-sulfamethoxazole (10-50 mg/kg/day orally or i.v. divided into 12 hourly doses) for 30 days; alternatives for use in patients with sulfa intolerance are pyrimethamine (200 mg/kg orally for 1 dose) followed by pyrimethamine (75 mg/kg/day orally) plus leucovorin (10-20 mg orally daily) plus one of either (i) clindamycin (600 mg orally or i.v. every 6 h), (ii) clarithromycin (1 g orally twice daily), (iii) azithromycin (1.2-1.5 g orally every 24 h), or (iv) atovaquone (750 mg orally every 6 h), with treatment for 4-6 weeks after resolution of symptoms; for suppression after resolution of cerebral toxoplasmosis, sulfadiazine (500-1,000 mg orally 4 times daily) plus pyrimethamine (25-50 mg orally every 24 h) plus leucovorin (10-25 mg orally every 24 h) (discontinue if $CD4^+$ cell count is >200 for at least 3 mo), clindamycin (300-450 mg orally every 6-8 h) plus pyrimethamine (25-50 mg orally every 24 h) plus leucovorin (10-25 mg orally every 24 h), or atovaquone (750 mg orally every 6-12 h) is recommended
Babesia spp.	Recommended therapy is atovaquone (750 mg orally twice a day for 7-10 days) plus azithromycin (500 mg orally for 1 dose and then 250 mg every 24 h for 7 days); an alternative is clindamycin (600 mg orally 3 times a day) plus quinine (650 mg orally 3 times a day for 7-10 days); adults can receive i.v. clindamycin (1.2 g twice daily); immunocompromised patients should be treated for more than 6 wk
Free-living amoebae	For these organisms no proven treatment regimens exist; these treatment options are based on successful regimens described in case reports
Acanthamoeba spp.	Treatment is a 3-mo course of oral cotrimoxazole plus oral rifampin, a lipid formulation of i.v. amphotericin B plus oral voriconazole, high-dose i.v. amphotericin B plus oral 5-fluorocytosine, or oral trimethoprim-sulfamethoxazole plus oral rifampin plus oral ketoconazole; for treatment of cutaneous lesions, topical chlorhexidine and 2% ketoconazole cream and oral itraconazole are used; for treatment of *Acanthamoeba* keratitis, propamidine (0.1%) and neomycin-gramicidin-polymyxin eye drops, PHMB (0.02%) eye drops, or chlorhexidine (0.02%) eye drops are used
Balamuthia mandrillaris	Pentamidine (300 mg i.v. once a day), sulfadiazine (1.5 g orally 4 times daily), fluconazole (400 mg orally daily), and clarithromycin (500 mg orally 3 times daily) or fluconazole (400 mg oral daily), sulfadiazine (1.5g orally every 6 h), clarithromycin (500 mg orally 3 times daily)
Naegleria fowleri	Intrathecal amphotericin B (1.5 mg/kg/day in 2 divided doses for 3 days); this is followed by intrathecal amphotericin B (1 mg/kg/day for 6 days), followed by intrathecal amphotericin B (1.5 mg/day for 2 days) and then intrathecal amphotericin B (1 mg/day every other day for 8 days)
Sappinia pedata	Azithromycin, pentamidine, itraconazole, and flucytosine therapy[d]

[a] Constructed with the aid of the *Sanford Guide to Antimicrobial Therapy* (233).
[b] See reference 316.
[c] i.v., intravenously; i.m., intramuscularly; PHMB, polyhexamethylene biguanide.
[d] For details, see reference 228.
[e] DS, double strength.
[f] SS, single strength.

ical studies (361, 478), it is possible that *N. caninum* may present itself as an opportunistic infections agent in IC patients in the future. It is recommended that in cases where *Toxoplasma* infection is suspected, PCR for the detection of *N. caninum* DNA should also be used to assess the possible role of *N. caninum* as an opportunistic pathogen in IC patients. Given their ability to infect ICT humans, it is also possible that certain nonhuman *Trypanosoma* species may also become recognized as opportunistic organisms in IC patients.

An awareness of the potential for organisms that rarely infect humans to occasionally cause serious disease is paramount to the survival of patients infected with these organisms. This is true for the free-living amoebae, particularly *N. fowleri*, due to the rapid onset of disease following the appearance of symptoms. In such cases, rapid and aggressive therapy could mean the difference between life and death. Knowledge of the various drugs available for the treatment of numerous protozoal diseases is, of course, paramount to the survival of patients, and clinicians should be aware of the most effective (and current) treatments available. A current list of treatment regimens available for various protozoal infections is summarized in Table 4.

Information regarding neglected tropical diseases caused by the trypanosomes, *Leishmania*, and *Plasmodium* is abundant in

the literature. However, the extent of the HIV problem in some areas of the world (particularly sub-Saharan Africa) allows diseases like toxoplasmosis and microsporidiosis to remain a common health problem in these locations. In Western countries, due to the availability of HAART, these diseases are less frequently encountered. Due to global travel and immigration, nonendemic tropical diseases are increasingly encountered (57, 329, 534). A recent example of this is the diagnosis of cutaneous leishmaniasis in Sydney, Australia (329, 534). As some tissue protozoa are nonendemic in Western countries or are very rarely encountered, many of these protozoa are not a first consideration in the differential diagnosis; hence, diagnostics are often not always available. This is presently being remedied at St. Vincent's Hospital in Sydney.

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