Protozoan Infections

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Definitions

Parasites are generally subdivided into three categories: protozoans, or single-cell nucleated organisms; helminths, which are metazoan wormlike organisms; and arthropods such as ticks and insects. This chapter focuses on protozoan pathogens [see Figure 1]; helminths are discussed elsewhere [search ACP Medicine for information on helminthic infections].

Parasitism can lead to four different host-parasite states: (1) symbiosis, which is the association of two organisms that cannot exist independently; (2) mutualism, an association in which both organisms benefit; (3) commensalism, in which the parasite benefits and the host is unaffected; and (4) disease, in which the parasite benefits and the host is harmed.

Parasites can be ectoparasites that live on the outside of the host, where they cause an infestation, or endoparasites that live within the host, where they cause an infection. Hosts are classified by the forms of parasites found in them. There are five categories of hosts: definitive, reservoir, incidental, intermediate, and carrier. A definitive host harbors the adult or sexual form of the parasite. Definitive hosts can be reservoir hosts (animals that harbor the same parasite species as humans) or incidental hosts (unnecessary for the maintenance of the parasite in nature). Intermediate hosts harbor a developing larval or asexual form of the parasite. Carrier hosts harbor larval or asexual forms of the parasite without development.

Vectors are objects or organisms responsible for transmitting parasites between hosts. A vector may be biologic, in which the parasite multiplies or develops, or mechanical, in which the parasite is transmitted unchanged from host to host.

In general, protozoa are classified by their organelles of locomotion [see Figure 1]. Sporozoa, including Plasmodium, Toxoplasma, and Cryptosporidium, have no evident organelles of locomotion. Microsporidia also lack evident organelles of locomotion. Ciliates, such as balantidia, move with cilia; flagellates, such as the trypanosomes Giardia, Leishmania, and Trichomonas, move with flagella; and Sarcodina, or amebae, move by means of pseudopodia extension of the cytoplasm.

Only the sporozoa have a clearly identified sexual phase. Other protozoa appear to divide simply by binary mitosis.

Malaria

Introduction
Four *Plasmodium* species cause human malaria: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae* [see Table 1]. *P. vivax* and *P. falciparum* are the most prevalent worldwide, and falciparum malaria is the form of malaria responsible for most deaths. Malaria is transmitted by anopheline mosquitoes. In the United States, malaria transmission is uncommon. Worldwide, however, malaria mortality is rising and rose by an estimated 19.9% since 1990 to 1.17 million deaths in 2010.¹ ² Malaria is resurgent because of multiple factors, including mosquito vector resistance to insecticides, inability of governmental programs to control mosquito vector populations, increased opportunities for breeding of vector mosquitoes, and increasing resistance of *Plasmodium* to chemotherapeutic agents.

### Etiology and Epidemiology

Malaria is endemic in many countries [search ACP Medicine for health advice for the international traveler]. Most cases of malaria in the United States are imported. In 2010, 1,691 cases of malaria—nine of them fatal—were reported to the Centers for Disease Control and Prevention (CDC). Of these cases, 898 occurred in US civilians.¹ ³ *P. falciparum* accounted for 58% of cases and *P. vivax* for 19%. Among patients with a recorded reason for travel, the majority (56%) who acquired malaria while abroad were traveling to visit friends and relatives. This has been the most difficult group to educate about the need for malaria prophylaxis. Along with infections acquired abroad, less common means of transmission are by blood transfusion, by sharing of contaminated needles, by organ transplantation, and congenitally in infants who are born of infected mothers.¹ ³ In addition, because species of *Anopheles* mosquitoes that can transmit malaria are endemic in the United States, isolated cases of autochthonous malaria have developed in persons in the United States who have been bitten by local mosquitoes that fed on persons with imported malaria.⁴ A final means of introduction of malaria into the United States is so-called airport malaria, which arises when an infected mosquito enters the country on an aircraft from a malarious area and transmits the infection in the area around the airport.⁵

### Pathogenesis

Malaria is normally acquired through the bite of an infected female *Anopheles* mosquito [see Figure 2]. Sporozoites inoculated into the bloodstream during the blood meal travel to the liver and infect hepatocytes; this is the preerythrocytic stage of infection. Notably, only two species of *Plasmodium*—*P. vivax* and *P. ovale*—cause persistent infections within the liver; the dormant intrahepatic sporozoites are termed hypnozoites. Within the hepatocytes, the sporozoites transform into merozoites. In the erythrocytic stage of malarial infection, merozoites released from infected hepatocytes and later from infected erythrocytes interact with specific erythrocyte membrane proteins and invade the red blood cells. (The Duffy blood group antigen is the requisite erythrocyte receptor for *P. vivax*. Absence of the Duffy blood group—a genetic trait found in many West Africans and their descendants—confers resistance to that species of *Plasmodium*.) Within the infected cells, malarial parasites undergo schizogony to form new merozoites, which are then released to reinfect other erythrocytes. A few parasites differentiate into sexual stages (gametocytes) capable of infecting mosquitoes [see Figure 3]. Male and female gametocytes transform and reproduce in the midgut of the mosquito, leading to the production of new sporozoites that localize in the mosquito’s salivary glands.

![Figure 1. Taxonomy of pathogenic protozoans.](image)

Because malarial parasites can multiply in an infected human, intense infections can develop from minimal inocula of sporozoites. Travelers have developed malaria after being bitten by mosquitoes during brief layovers at airports in malarious areas and during flights on airplanes that have stopped in malarious regions. Consequently, malaria prophylaxis is warranted for even the most limited exposures to mosquitoes in malarious regions.
Infected persons remain asymptomatic during the time between the infecting mosquito bite and the erythrocytic stage of infection, a period that may range from about 1 to 4 weeks for deadly *P. falciparum* infection. Because most malaria chemoprophylaxis does not prevent malaria but, rather, treats erythrocytic-stage infection, most chemoprophylactic medication must be continued for the full 4 weeks after a return from a malarious area. Failure to do so permits the development of *P. falciparum* infection. An exception to this is with so-called causal prophylactic medication, such as atovaquone-proguanil, which also kills liver-stage parasites. This form of prophylaxis can be discontinued a week after leaving a malarious area. Prophylaxis generally does not prevent late emergence of *P. vivax* or *P. ovale* from incubating liver hypnozoites.

Immune responses develop to malarial infections. Development of antibodies to the most indolent and chronic malarial species, *P. malariae*, may lead over years to the onset of immune complex-mediated nephrotic syndrome. Repeated infections with other *Plasmodium* species can elicit a partially protective immunity that will limit the severity of infection but not prevent it. Of note, residents of malarious areas may lose their relative immunity after staying several years in a nonmalarious region; such persons may be fully susceptible to malarial infection upon their return.

**Table 1. Differentiating Features of Malaria Species**

**Figure 2.** The life cycle of malaria. All four human malaria species—*P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*—may be transmitted by *Anopheles* mosquito bites or, rarely, introduced by blood (e.g., congenitally, through transfusion, and by sharing of needles). Once in the bloodstream, *Plasmodium* sporozoites travel to the liver and infect hepatocytes. This is the preerythrocytic stage of infection. Only two species of *Plasmodium*, *P. vivax* and *P. ovale*, cause persistent infections within the liver, which can lead to later recrudescence of malaria. Within the hepatocytes, the sporozoites transform into merozoites. In the erythrocytic stage of malarial infection, merozoites released from infected hepatocytes and later from infected erythrocytes interact with specific erythrocyte membrane proteins and invade the red blood cells. Within the infected cells, malarial parasites undergo schizogony to form new merozoites, which are then released to reinfect other erythrocytes. A few parasites differentiate into sexual stages (gametocytes) capable of infecting mosquitoes. Symptoms develop with infection of erythrocytes (erythrocytic cycle) about 1 or more weeks after a mosquito bite; malaria therapy is directed toward the erythrocytic stage. *P. falciparum* causes more severe disease because it is able to invade all stages of red blood cells (RBCs); thus, the parasitemia is higher. In addition, late trophozoites and schizonts of *P. falciparum* adhere to endothelia, causing end-organ damage such as cerebral malaria or placental malaria in pregnancy.

**Diagnosis**

Malaria should be considered a cause of any febrile illness in immigrants from malarious areas and in persons who have traveled or worked in malarious areas. Febrile illness in recipients of transfused blood or transplanted organs and in neonates of potentially infected mothers should be considered possible acquired malaria. Finally, even in US residents, the diagnosis of malaria may need to be considered in febrile patients with compatible illnesses that may have developed from the uncommon autochthonous transmission of malaria.

Infections with the four human malarial species of *Plasmodium* produce distinct clinical syndromes,
in part because of the different interactions of each species with erythrocytes. The four species of malaria can be distinguished by their characteristics on blood smears [see Figure 3]. *P. vivax* and *P. ovale* infect young red blood cells only, which helps limit the intensity of infection. It also explains why enlarged red blood cells are characteristic of *P. vivax* and *P. ovale* infections in speciation of malaria on blood films. In contrast, *P. falciparum* infects erythrocytes of all ages. This capacity of falciparum malaria, the greater numbers of merozoites produced by this species, and especially the great propensity of falciparum-infected erythrocytes to adhere to the microvascular endothelium help make falciparum malaria distinctly more severe than other forms of malaria. Erythrocytes infected with *P. falciparum* develop unique surface knobs that mediate binding and adherence to endothelial cells in capillaries and venules. Sequestration of infected erythrocytes in these small vessels results in local anoxia and can lead to severe complications, including cerebral malaria and pulmonary edema [see Table 1].

**Figure 3.** Identification of species of malaria based on forms seen on blood smears. During the ring stage, multiple parasites are more likely to be seen within the red blood cell in *Plasmodium falciparum* infection. The late trophozoites and schizonts of *P. falciparum* are not usually seen on smears because of their propensity to adhere to the endothelia of the peripheral organs. *P. falciparum* infects mature red blood cells, whereas *P. vivax* and *P. ovale* commonly infect only reticulocytes, which are larger and slightly bluish when stained. Schizonts of *P. vivax* often have more than 14 nuclei, which distinguishes them from other malarial species. The trophozoites of *P. malariae* often have a bandlike appearance across the red blood cell. The spots in late trophozoites are hemozoin deposits; these cells can sometimes be mistaken for granulocytes. Banana-shaped gametocytes are pathognomonic for *P. falciparum* infection but are seen only after 10 to 14 days of erythrocytic infection.

**Clinical Features**

Symptoms of malaria develop about 1 to 4 weeks after infection and typically include fever and chills. Virtually all patients with acute malaria have episodes of fever. At the outset, fever may occur daily; over time, the paroxysms may take on the typical pattern of fevers every other day (*P. vivax, P. ovale, P. falciparum*) or every third day (*P. malariae*) [see Table 1]. The paroxysms of fever, which may reach as high as 41.5°C [106.7°F], and chills (with or without rigors) may be irregular, however—especially in falciparum malaria. Other possible symptoms are headache, increased sweating, back pain, myalgias, diarrhea, nausea, vomiting, and cough. The constellations of symptoms are nonspecific and may suggest diagnoses other than malaria. With time, anemia and splenomegaly develop.

Because of the distinct capacity of falciparum-infected erythrocytes to cause microvascular blockade, potentially fatal organ involvement can develop rapidly in patients with falciparum malaria. Cerebral involvement may lead to delirium, focal disorders (e.g., seizures), and coma. Pregnant women are at special risk for death and fetal loss from falciparum infections. Careful studies have shown that patients infected with HIV are at increased risk for worse outcomes with malaria infection. Splanchnic involvement of malaria may cause protracted nausea, vomiting, diarrhea, melena, and abdominal pain; this syndrome can be readily mistaken for traveler's diarrhea. Lung involvement may cause pulmonary edema and acute respiratory distress syndrome. There may be severe hypoglycemia. A rare syndrome known as blackwater fever reflects hemoglobinuria and acute renal failure from massive intravascular hemolysis.

*P. malariae* organisms can persist in the blood as an indolent, even asymptomatic, infection for years or even decades.

**Laboratory Findings**
The white blood cell count is usually in the normal range in malaria patients. Anemia develops but may not be prominent on presentation, especially if the patient is dehydrated. Thrombocytopenia may develop; disseminated intravascular coagulation sometimes occurs in falciparum malaria. Liver enzyme levels may be elevated.

The specific diagnosis and speciation of malaria depend on the recognition of parasites in properly stained smears of peripheral blood [see Figure 3]. Thick smears are more sensitive than thin smears, but the layering of cells necessitates greater expertise in examining morphology. Smears should be taken repeatedly for several days because of the cyclic nature of the parasitemia. This is especially important in suspected *P. falciparum* infections, in which infected cells may be sequestered in the microvasculature and in which late trophozoites and schizonts are generally not seen. The morphologic features of the parasites (and the infected host erythrocytes) are useful in species identification and in distinguishing *Plasmodium* species from the morphologically similar *Babesia microti*, which causes babesiosis. It is very important to identify and treat *P. falciparum* infection rapidly because of its potential for swift progression if left untreated or if treated improperly. In the absence of a skilled microscopist, the clinician is advised to presumptively treat falciparum malaria when malarial forms are identified on a blood smear. The quantitative buffy coat (QBC) technique is sensitive in identifying plasmodial parasitemia but does not identify the species. Dipstick antigen-capture assays are available and have the potential to help clinicians detect falciparum infections, particularly where no specialized laboratories are available, but sensitivity may vary widely. DNA probes, polymerase chain reaction (PCR) tests, and serologic tests exist but are not usually immediately available for diagnosis of acute malaria at presentation. Thus, examination of blood smears is still the standard in assessing, first, whether a patient has malaria and, second, whether the malaria is caused by *P. falciparum*.

**Treatment**

Treatment of patients with acute malaria requires consideration of the *Plasmodium* species involved and, in cases of falciparum malaria, the likelihood of resistance to antimalarial medications.

Chloroquine is the mainstay of treatment for all malarial species except those strains of *P. falciparum* that are resistant to the drug [see Table 2]. Notably, chloroquine-resistant *P. falciparum* (CRPF) malaria is now widespread in all countries where *P. falciparum* is endemic, except Haiti, the Dominican Republic, areas of Central America west of the Panama Canal, and parts of the Middle East [search ACP Medicine for health advice for international travelers]. For *P. falciparum* infections acquired in countries with chloroquine-resistant strains, alternative therapies must be used [see Table 2]; the typical regimen in such cases remains quinine or quinidine combined with a tetracycline. Mefloquine-resistant strains of *P. falciparum* have been identified at the Thailand-Myanmar border. Isolated strains of *P. vivax* resistant to chloroquine have been reported in Africa, Central and South America, Oceania, and Asia. Generally, chloroquine is no longer recommended for treatment of vivax malaria from Papua New Guinea and Indonesia. Isolates of *P. malariae* resistant to chloroquine have now been reported as well.

Acute attacks caused by all species except CRPF are treated with oral chloroquine phosphate at an initial dose of 1 g (600 mg base), followed by 500 mg (300 mg base) at 6 hours and again at 24 and 48 hours. For suspected CRPF malaria, several alternative regimens are available. The CDC recommends atovaquone-proguanil as the first choice. This drug is available as a fixed-dose combination tablet (Malarone) containing 250 mg atovaquone and 100 mg proguanil. The treatment dose for adults is four tablets by mouth once daily for 3 days. The second choice of treatment is artemether-lumefantrine, which is available as the fixed-dose combination (Coartem) containing 20 mg artemether and 120 mg lumefantrine. Dosing for adults (weighing 35 kg or more) is an initial dose of four tablets by mouth followed by a second four-tablet dose 8 hours later; four tablets are administered orally twice daily for the next 2 days (total of six doses over 3 days). The third choice of treatment for malaria is quinine sulfate. A dose of 542 mg base (= 650 mg salt) is administered orally three times daily for 3 days (7 days for infection acquired in Asia) together with doxycycline, 100 mg orally twice daily for 7 days [see Table 2].
Until very recently, the drugs of choice for malaria patients who are too ill to take oral therapies were intravenous quinidine gluconate and quinine dihydrochloride; these are effective against all species of *Plasmodium*.\textsuperscript{11} Quinidine is effective and well tolerated when appropriate precautions are used; these include hemodynamic and electrocardiographic monitoring. A loading dose of 10 mg/kg (maximum 600 mg) of quinidine in normal saline is infused slowly over 1 to 2 hours, followed by continuous infusion of 0.02 mg/kg/min. Parenteral therapy should be continued until oral therapy can be tolerated; in most cases, oral therapy can be substituted within 48 to 72 hours.

Artesunate, which is derived from the sweet wormwood plant (*Artemisia annua*), has been in worldwide use for treatment of severe malaria for many years and became available in the United States in June 2007 under a Food and Drug Administration (FDA) Investigational New Drug (IND) protocol.\textsuperscript{13} Studies comparing quinine with artesunate have demonstrated better outcomes in the artesunate-treated groups,\textsuperscript{14} perhaps because of the very rapid clearance of parasites after artesunate therapy. Artesunate is not FDA approved in the United States and can be obtained only through the CDC. The CDC now has artesunate stockpiled for release for treatment of severe malaria. Physicians can enroll patients in the artesunate IND protocol by calling the CDC Malaria Hotline (770-488-7788, Monday through Friday, 9 am to 5 pm Eastern time; call 770-488-7100 after hours ask to speak with a CDC Malaria Branch clinician). To minimize delay in antiparasitic therapy, physicians should give immediate quinidine therapy while requesting artesunate. Artesunate therapy must be followed with a course of another antimalarial agent; the CDC recommends atovaquone-proguanil (Malarone), doxycycline (clindamycin in pregnant women), or mefloquine for this purpose.

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<tr>
<th>Table 2. Antimalarial Drugs\textsuperscript{11}</th>
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<td>For fulminant falciparum malaria (e.g., parasitemia &gt; 10%, cerebral malaria), exchange transfusion can be an adjunct to chemotherapy but has not been convincingly shown to decrease mortality.\textsuperscript{15} Patients with moderate to severe falciparum malaria and any pregnant individual with falciparum malaria should be hospitalized and monitored for hypoglycemia and other complications, as well as response to therapy.</td>
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<tr>
<td>With the exception of atovaquone-proguanil, each of the chemotherapeutic agents above is active only in the erythrocytic stage of infection. Because <em>P. vivax</em> and <em>P. ovale</em> have persisting hepatic stages that may cause relapses of malaria after chloroquine use, an agent that is active against the exoerythrocytic cycle should be administered after a course of chloroquine. Primaquine is the sole agent used to eradicate hepatic involvement; the dosage is 26.3 mg (15 mg base) orally every day for 2 weeks. <em>P. vivax</em> from Oceania and Tanzania has been reported to be primaquine tolerant, and 1.5 to 2 times the normal dose is given for 2 to 3 weeks if primaquine-tolerant strains are suspected.\textsuperscript{11} Because primaquine may induce hemolysis in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency, patients should be screened for the disorder before treatment. If only mild G6PD deficiency is found, primaquine may be given at a dosage of 79 mg (45 mg base) orally once a week for 8 weeks.</td>
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**Advice for Travelers**

Most US residents lack immunity to malaria and are at risk for the morbidity and mortality associated with the disease, especially the falciparum form, if they visit countries where malaria transmission occurs. Among the 898 cases in US civilians for whom information on chemoprophylaxis use and travel area was known, 45 (5%) reported that they had followed and adhered to a chemoprophylactic drug regimen recommended by the CDC for the areas to which they had traveled.\textsuperscript{1} It is imperative that travelers receive appropriate advice on reducing their risk of
acquiring malaria, including the use of appropriate chemoprophylactic regimens [search ACP Medicine for health advice for international travelers]; up-to-date information can be found on the CDC Web site (http://wwwn.cdc.gov/travel/). Current alternatives, depending on the area of travel, the length of travel, and the characteristics of the traveler, include chloroquine, mefloquine, doxycycline, atovaquone-proguanil, and primaquine. Also, a common approach to malaria prevention is to follow the "A, B, C, D" rule: Awareness of risk, Bite avoidance, Compliance with chemoprophylaxis, and prompt Diagnosis in case of fever.16,17

Babesiosis

Introduction

Babesia organisms are intraerythrocytic protozoan parasites that produce a malarialike illness. Most cases of babesiosis have been reported in the northeastern United States, but cases have also occurred in the upper Midwest, the West Coast, and other regions of the United States, as well as in Europe and elsewhere.18

Etiology and Epidemiology

Several species of Babesia have been recognized as causes of human disease. The first to be recognized was Babesia divergens, a parasite of cattle that has caused several fatal infections in splenectomized persons. Most of these cases have occurred in Europe, although a related species, designated MO1, caused a fatal case in a splenectomized man in Missouri.19

Babesia microti is the principal cause of babesiosis in the eastern and central United States. This parasite of white-footed mice is transmitted by deer ticks and is prevalent on the islands off Massachusetts, New York, and Rhode Island and in focal areas in Connecticut, Wisconsin, and Minnesota. The risk of Babesia infection is not increased by splenectomy, but the disease is more serious in persons who have undergone splenectomy, have HIV infection, or have other immunocompromising conditions.18,20 Many infected persons have subclinical infections, as evidenced by serologic surveys in endemic areas. Recrudescence of symptomatic infection may occur in patients with subclinical infection who undergo splenectomy. Because nymphal ticks are the most efficient at transmitting infection, most cases develop between May and August, when nymphal ticks are most abundant.18

Another form of babesiosis develops from infection with an organism found in states along the Pacific coast and designated as WA1.21 The vector and the reservoir of this emerging Babesia species are not yet known. Infections have been recognized in asplenic persons and less commonly in normal hosts; serologic surveys in rural and semirural California indicate that subclinical infection with WA1 may have developed in up to 20% of the population.18

Babesiosis may also be acquired perinatally and through blood transfusions.18,21

Diagnosis

Clinical Features

Many persons infected with B. microti or WA1 remain asymptomatic. In those who have symptoms, illness develops gradually in the weeks after being bitten by a tick or undergoing blood transfusion. Malaise, anorexia, and fatigue are followed by the onset of myalgias, fevers, and sweats. Emotional lability, depression, nausea, vomiting, and headache are common. Symptoms tend to abate over several weeks, although fatigue and malaise may persist for months. Splenomegaly is occasionally present. Infections may become more fulminant and persistent in asplenic patients, elderly patients, and patients with HIV infection or other immunocompromising conditions. Intravascular hemolysis, hemoglobinuria, and renal failure may develop. On blood smears, parasitemia is usually less than
1%, but parasites may be present in as many as 85% of red blood cells; this level of parasitemia can be fatal, especially in asplenic persons.

**Laboratory Findings**

Laboratory findings may include hemolytic anemia, normal to low leukocyte counts, and abnormal liver function test results. The diagnosis is based on the finding of ring forms and pleomorphic intraerythrocytic organisms on Giemsa-stained blood smears [see Figure 4]. Occasionally, extracellular merozoites are seen. Unlike malarial parasites, *Babesia* organisms do not produce pigment in red blood cells. In some patients, a parasitemia level of 5% or higher and the presence of several ring forms in a single red blood cell might suggest *P. falciparum* infection; the absence of gametocytes and intracellular pigmentation will help distinguish babesiosis from malaria. Serologic testing is of value for diagnosing chronic infections with *B. microti* and WA1 when parasites are not detectable on blood smears.

**Figure 4.** Blood smear showing *Babesia* parasites in erythrocytes (arrows).

**Treatment**

The treatment of choice for babesiosis is a combination of atovaquone (750 mg p.o., b.i.d., for 7 to 10 days) plus azithromycin (500 to 1,000 mg on day 1, then 250 to 1,000 mg on days 2 to 10). In a minority of patients who improve symptomatically, parasitemia may nevertheless persist. Occasionally, pulmonary edema may develop after initiation of therapy for babesiosis, as also may occur with malaria. Exchange transfusion can be an adjunct to chemotherapy in cases of fulminant babesiosis.

The tick vector of babesiosis may simultaneously transmit *Borrelia burgdorferi*, the agent of Lyme disease [search ACP Medicine for information on Lyme disease and other spirochetal zoonoses], and *Anaplasma (Ehrlichia)* species, the agents of anaplasmosis [search ACP Medicine for information on infections due to Rickettsia, Ehrlichia, and Coxiella]. Because of the high rate of coinfection, patients from endemic areas who are diagnosed with babesiosis should also receive doxycycline for presumptive Lyme disease and anaplasmosis.

**Toxoplasmosis**

**Introduction**

*Toxoplasma gondii*, the cause of toxoplasmosis, is an intracellular protozoan parasite of worldwide distribution. *T. gondii* can infect nearly all animals and birds, making it one of the most widely distributed parasites. Cats are the definitive hosts of *T. gondii*, because only felines harbor the sexual forms; however, humans can develop toxoplasmosis in ways other than exposure to cats.

Humans acquire *T. gondii* infections by the oral and transplacental routes and, less commonly, from blood transfusion and organ transplantation. Infection via the oral route is caused by the ingestion of *T. gondii* tissue cysts in undercooked food or the ingestion of *T. gondii* oocysts, which are found in cat feces [see Figure 5]. After ingestion, bradyzoites (from tissue cysts) or sporozoites (from oocysts) invade surrounding cells and develop into tachyzoites, a rapidly dividing form that may disseminate and invade any nucleated cell type. With time and the development of immunity, the parasite will form tissue cysts containing many bradyzoites. Tissue cysts may remain viable for decades without causing disease. Loss of immunity, however, allows reactivation from the latent tissue cysts and the generation of many invasive tachyzoites.
Although toxoplasmosis is extremely common, most acquired and congenital infections are subclinical and are revealed only by the presence of antibodies. The prevalence of infection varies greatly in different population groups and geographic regions. In the United States, serologic evidence of *Toxoplasma* infection varies regionally in prevalence from 3 to 30%.

**Clinical Syndromes**

Toxoplasmosis can be divided into five major clinical syndromes: primary toxoplasmosis, toxoplasmosis in immunosuppression, toxoplasmosis in AIDS, congenital toxoplasmosis, and ocular toxoplasmosis.

**Primary Toxoplasmosis**

An immunocompetent person usually experiences subclinical illness after acquisition of a primary toxoplasmosis infection. Painless lymphadenopathy is the most common symptom. Lymphadenopathy may be localized or generalized and may persist for many months. Isolated cervical lymphadenopathy is the most frequent finding. Enlarged nodes may be the only manifestation; less often, fever, malaise, myalgias, and sore throat are also present. Fatigue and weakness may be pronounced. In addition to lymphadenopathy, physical findings may include pharyngitis, maculopapular rash, and, in a minority of patients, hepatosplenomegaly. Atypical lymphocytosis may be present. The major differential diagnosis includes infectious mononucleosis, cytomegalovirus infection, and lymphoma; less often, sarcoidosis, cat-scratch disease, and other infectious processes may resemble toxoplasmosis. Serologic testing is the key to diagnosis.

Although symptoms of acquired lymphadenopathic toxoplasmosis can persist for weeks or months, the process is almost always self-limited and does not require specific therapy. In severe or protracted cases, pyrimethamine and sulfonamides may be helpful. Chemotherapy should also be used for the rare complications that can occur in the normal host, including chorioretinitis, pericarditis, myocarditis, pneumonitis, myositis, and meningoencephalitis.

**Toxoplasmosis in Immunosuppression**

In an immunosuppressed person with defective cell-mediated immunity, *T. gondii* can cause devastating neurologic or disseminated disease. Usually, this process develops from reactivation of latent infection and not from a primary infection. Seronegative recipients of organs (especially hearts) transplanted from seropositive donors are at particular risk as are patients with Hodgkin disease, hairy-cell leukemia, and other malignant disorders.

Neurologic abnormalities predominate in at least 50% of these patients. The clinical picture is highly variable and may take the form of a diffuse encephalitis, a meningoencephalitis, or a cerebral mass lesion. The cerebrospinal fluid (CSF) often shows a mild lymphocytic pleocytosis and an elevation of protein levels; glucose levels, however, remain normal. Pneumonitis may occur in immunosuppressed patients with toxoplasmosis. Fever and dyspnea are present, but cough is absent, and no sputum is produced. Chest radiographs typically reveal diffuse bilateral pulmonary infiltrates. In a few cases, the diagnosis has been established by the presence of organisms in the fluid obtained from bronchoalveolar lavage. Other manifestations of disseminated toxoplasmosis in immunosuppressed patients include myocarditis, pericarditis, peritonitis, and lymphadenitis. Many of these immunosuppressed patients have simultaneous infections with other opportunistic pathogens, especially herpesvirus and cytomegalovirus.

Appropriate serologic titers will support the diagnosis of toxoplasmosis; however, antibody levels may be low in these patients, and, therefore, brain, lung, or lymph node biopsy may be required for diagnosis. An aggressive diagnostic approach is warranted because pyrimethamine and sulfonamides can be effective in these infections, which are usually fatal if left untreated.
**Figure 5.** Life cycle of *Toxoplasma gondii*. Felines, which acquire infection by carnivorism, are the definitive hosts; they are the only species supporting the sexual cycle that leads to oocyst excretion in feces. The oocysts must mature in the environment for at least several days to become infectious to intermediate hosts such as humans. Humans and other carnivores become infected by ingestion of mature oocysts or by ingestion of tissue cysts in undercooked meat. Within the host, both oocysts and tissue cysts convert to rapidly proliferating tachyzoites (a); tachyzoites can invade and grow in almost any cell. They form tissue cysts (b), which persist in a latent form and can reactivate to proliferate and cause clinical disease if the host becomes immunosuppressed. Reactivation can occur even decades after infection.

**Toxoplasmosis in AIDS**

Toxoplasmosis is a particularly severe problem in patients with AIDS; clinically apparent toxoplasmosis develops in 3 to 40% of these patients. Although any of the manifestations of disseminated toxoplasmosis may occur in patients with AIDS, central nervous system (CNS) abnormalities predominate. Most cases of toxoplasmosis in patients with AIDS result from reactivation of latent *Toxoplasma* cysts acquired before infection with HIV; reactivation is particularly likely when the CD4+ T cell count falls below 100 cells/μL. All HIV-infected persons should be tested for antibodies to *T. gondii*. Those who are *Toxoplasma* negative should be cautioned to minimize exposure by cooking meat to an internal temperature of 150°F, washing their hands after contact with raw meat or soil, washing fruits and vegetables before eating them, and avoiding contact with cat feces or contaminated litter (or wearing gloves if these materials must be handled).

In AIDS patients, toxoplasmosis most often presents as necrotizing encephalitis. Symptoms include focal abnormalities (e.g., hemiparesis, sensory loss, visual abnormalities, tremor, cranial nerve palsy, and focal seizures) and generalized neurologic abnormalities (e.g., headache, personality changes, confusion, stupor or coma, and seizures). Although a CSF lymphocytic pleocytosis is consistent with the diagnosis of cerebral toxoplasmosis, computed tomographic (CT) or magnetic resonance imaging (MRI) scans are the crucial diagnostic tests in most cases. Typical findings include single or multiple rounded mass lesions; when a contrast agent is administered, more than 90% of these lesions display ring or nodular enhancement. MRI scans may reveal lesions that were not visualized by CT scanning. Positron emission tomography (PET) may prove useful for distinguishing lesions of toxoplasmosis, which are hypometabolic, from lymphomas, which are hypermetabolic.

Serum antibody tests are useful for screening AIDS patients for cerebral toxoplasmosis; such tests are usually positive because most cases of cerebral toxoplasmosis in patients with AIDS arise from reactivation of latent infection. Although negative findings on antibody testing suggest a diagnosis other than toxoplasmosis, a few seronegative cases have been reported. However, serum antibody tests cannot be relied on in the diagnosis of primary toxoplasmosis in patients with AIDS; antibody titers do not reach the high levels typical of immunocompetent patients with toxoplasmosis, nor are IgM antibodies always present in patients with AIDS. Antibodies against *Toxoplasma* are present in the CSF in nearly two thirds of AIDS patients with cerebral toxoplasmosis; their detection may assist in the diagnosis [see Diagnosis, below].

In addition to toxoplasmosis, CNS lesions caused by fungi, mycobacteria, lymphomas, Kaposi sarcoma, metastatic tumors, multifocal leukoencephalopathy, or HIV itself may develop in patients with AIDS. Despite this broad differential diagnosis, empirical treatment of toxoplasmosis is often preferable to early brain biopsy if the clinical and radiologic picture is compatible with the diagnosis and if serum anti-*Toxoplasma* antibodies are present. Because toxoplasmosis is the most common and most treatable cause of cerebral lesions in patients with AIDS, empirical therapy using a combination of sulfonamides and pyrimethamine or the combination of clindamycin and
pyrimethamine can be initiated; if the diagnosis is correct, clinical and radiologic improvement is often observed within 1 to 2 weeks. If patients respond poorly to treatment and are seronegative or belong to population groups at high risk for tuberculosis (e.g., Haitians, Africans, or intravenous drug abusers), biopsy should be strongly considered.  

**Congenital Toxoplasmosis**

Congenital toxoplasmosis arises almost exclusively when the mother develops a primary infection during gestation. Congenital infection almost never develops from latent toxoplasmosis acquired before pregnancy, and the few recognized cases have developed mainly in pregnant women with reactivation of toxoplasmosis secondary to immunosuppressive therapy or HIV infection. The risk of fetal infection depends on when maternal infection occurs, rising from 10% during the first trimester to 60% during the third trimester. The consequences of fetal infection also depend on when infection occurs: fetal infections early in gestation are most likely to result in severe damage.

The clinical spectrum of congenital toxoplasmosis varies widely. About 85% of infected babies appear normal at birth; without treatment, however, about 85% of these infants will experience chorioretinitis, hearing loss, or developmental delay. The clinical spectrum of symptomatic congenital toxoplasmosis includes fetal death, neurologic damage (i.e., cerebral calcification, seizures, retardation, hydrocephalus, or microcephaly), chorioretinitis, fever, hepatosplenomegaly, and rash. The differential diagnosis includes congenital infection with cytomegalovirus, herpes simplex, rubella, or syphilis. Congenital toxoplasmosis can be diagnosed by serologic methods, by a PCR test performed on amniotic fluid, or by identification of the organism in the placenta or fetal tissues. Infants with congenital toxoplasmosis may benefit from prolonged treatment with pyrimethamine and sulfonamides.

The prevention of congenital toxoplasmosis is of major importance. Pregnant women should minimize contact with cats, especially strays or cats that eat raw meat; they should wash their hands after contact with cats and should have another person empty the litter box daily. In addition, pregnant women should wash all fruits and vegetables before eating them and should not eat undercooked meat. Serologic screening of pregnant women is advisable.

**Ocular Toxoplasmosis**

Toxoplasmosis may account for about 30% of cases of retinochoroiditis. Many cases result from the reactivation of congenital infection; hence, ocular toxoplasmosis is most common in older children and young adults. Retinochoroiditis may also develop as a manifestation of primary infection. Impairment of vision is the most common symptom, but pain and photophobia may accompany intense inflammation. Typical lesions appear as yellow-white fluffy exudates clustered in the posterior pole. Although a positive *Toxoplasma* serology is needed for the diagnosis of ocular toxoplasmosis, most patients have relatively low titers because the initial infection was acquired years earlier. In most cases, therefore, ocular toxoplasmosis is a clinical diagnosis that depends on the morphology of the lesions. Other conditions considered in the differential diagnosis include tuberculosis, sarcoidosis, syphilis, histoplasmosis, and candidiasis.

**Diagnosis**

Serologic testing is important in evaluating patients with potential toxoplasmosis. Many tests are available; the most widely used are the indirect fluorescent antibody test and the Sabin-Feldman dye test. Many other tests are used by reference laboratories. Tests that measure IgG antibodies show positive results 1 to 3 weeks after infection and continue to show positive results for many years after infection. Diagnoses of recently acquired toxoplasmosis, especially pertinent during pregnancy, and of congenital toxoplasmosis in the newborn require assays of IgM anti-*Toxoplasma* antibodies. Some commercial IgM assays have been noted to generate false positive results and to detect IgM antibodies persisting for over 1 year, potentially confounding the reliability of these assays to detect
only recent infections. Positive IgM test results may necessitate confirmation by alternative testing assays, such as avidity testing; IgM, IgG, and IgG Western blot testing to detect new bands bound by infant but not maternal antibodies; and PCR.

Because tissue cysts may be present in tissues for years, definitive evidence of active toxoplasmosis within tissue biopsy specimens requires the detection of tachyzoites. These forms are not readily seen with conventional pathologic stains. Application of immunofluorescent or peroxidase-antiperoxidase antibody staining is needed. Tachyzoites are not usually detectable in biopsy specimens from lymph nodes, although characteristic histopathologic features can support the diagnosis. PCR methods are highly sensitive for detecting the organism in amniotic fluid in congenital infections, but neither PCR nor direct culturing of the organisms from blood or tissues has been widely used in diagnosing other forms of toxoplasmosis.

Treatment

Primary and AIDS-Associated Toxoplasmosis

Although the majority of patients with primary lymphadenopathic toxoplasmosis do not require treatment, chemotherapy should be considered for patients with unusually prolonged or severe illness. Patients with active chorioretinitis, CNS involvement, or disseminated toxoplasmosis should also be treated, as should immunosuppressed patients with toxoplasmosis, including patients with AIDS.

Combined administration of pyrimethamine and sulfonamides (sulfadiazine or trisulfapyrimidines) is the treatment of choice. Other sulfonamides are less active against T. gondii and therefore should be avoided. In adults, a loading dose of 200 mg of pyrimethamine is given on the first day of treatment, followed by the usual dosage of 50 to 75 mg/day for 3 to 6 weeks. Sulfadiazine or trisulfapyrimidines are usually given to adults in a loading dose of 4 g, followed by 1 to 1.5 g four times daily for 3 to 6 weeks. The most common toxic effect of pyrimethamine is marrow suppression; leukocyte, red blood cell, and platelet counts should be monitored twice weekly, and 10 to 15 mg of folic acid should be administered daily. Trimethoprim (5 mg/kg) plus sulfamethoxazole (25 mg/kg) twice daily (given intravenously or orally) is a commonly used alternative regimen.

For AIDS patients who are intolerant of sulfonamides, clindamycin at a dosage of 600 mg orally or intravenously four times a day in combination with pyrimethamine has been effective in treating CNS toxoplasmosis. Atovaquone plus pyrimethamine is also effective for sulfa-intolerant patients.

Patients with AIDS who have been treated for toxoplasmosis and those who have not experienced active toxoplasmosis infection but have positive Toxoplasma serologies and CD4+ T cell counts below 100/µL are at risk for reactivation of toxoplasmosis and require prolonged suppressive therapy. A variety of regimens are available for toxoplasmosis prevention in AIDS patients. A regimen consisting of sulfadiazine (500 to 1,000 mg four times a day) and pyrimethamine (25 to 50 mg/day) plus folic acid (5 mg/day) is most effective. Dapsone-pyrimethamine is also effective for patients intolerant of sulfonamides. Some regimens used for the prevention of Pneumocystis pneumonia also provide primary prophylaxis for toxoplasmosis; examples include trimethoprim-sulfamethoxazole, dapsone-pyrimethamine, and, for sulfa-intolerant patients, atovaquone. If the CD4+ T cell count rises above 200/µL for 3 months, secondary prophylaxis for toxoplasmosis can be stopped.

Congenital Toxoplasmosis

Newly acquired toxoplasmosis documented during pregnancy presents difficult choices. Pyrimethamine is teratogenic and should be avoided in the first trimester. Spiramycin, given at a dosage of 3 to 4 g/day, can diminish the risk of transplacental infection. The FDA has designated
spiramycin as an orphan drug; it is available in the United States from the Palo Alto Medical Foundation Toxoplasma Serology Laboratory (650-853-4828), U.S. National Collaborative Treatment Trials study (773-834-4152), or the FDA (301-796-1600). If in utero infection is documented, therapy with pyrimethamine and sulfadiazine should be initiated. Therapeutic abortion might be considered if infection is acquired early in pregnancy; ultrasonography can be used to detect hydrocephalus, intracranial calcifications, and other signs of fetal damage. Children who are born with serologic or clinical evidence of congenital toxoplasmosis should be treated for a year with pyrimethamine and sulfadiazine.\textsuperscript{42}

**Ocular Toxoplasmosis**

Pyrimethamine and sulfonamides are the mainstays of therapy for ocular toxoplasmosis, but results are unpredictable, and relapses commonly occur. When there is a threat of visual loss, the patient should receive corticosteroids in combination with antimicrobials.

**Intestinal Protozoan Infections**

**Introduction**

The human intestinal tract may serve as a host for several protozoan parasites. The intestinal protozoa *Entamoeba coli*, *Entamoeba hartmanni*, *Endolimax nana*, and *Iodamoeba butschlii* are nonpathogenic and do not require therapy. Pathogenic intestinal protozoan parasites include five groups: (1) the flagellates (*Giardia lamblia* and *Dientamoeba fragilis*); (2) the amebae, or *Sarcodina* (*Entamoeba histolytica* and, possibly, *Blastocystis hominis*); (3) coccidia (*Cryptosporidium*, *Isospora*, *Cyclospora*); (4) a ciliate (*Balantidium coli*); and (5) microsporida.

**Giardiasis**

*G. lamblia* inhabits the proximal small intestine; manifestations of *G. lamblia* infections can vary from no symptoms to profound malabsorption. *G. lamblia* and *Cryptosporidium* are the most common pathogenic intestinal protozoan parasites in the United States.\textsuperscript{54}

**Etiology and Epidemiology**

*G. lamblia* exists in two morphologic forms: the trophozoite and the cyst [see Figure 6]. The trophozoite is a pear-shaped, multistagellated organism that measures 9 to 15 μm long, 5 to 15 μm wide, and 2 to 4 μm thick. It is bilaterally symmetrical and contains two prominent nuclei. On the ventral surface is an adhesive disk with which the trophozoite attaches to the mucosal surface of the duodenum and jejunum. During passage in the bowel, the trophozoite usually encysts. The cysts measure 8 to 12 μm long by 7 to 10 μm wide, have a well-defined outer wall, and contain four nuclei when mature [see Figure 6].

Trophozoites may be seen in duodenojejunal fluid and in loose stools but generally are not found in formed stools [see Diagnosis, below]. Trophozoites are not resistant to external environmental stresses. In contrast, cysts are harder and may survive in water for at least several months; decreased water temperature enhances their survival. Although infection can occur if trophozoites are ingested in quantities of food that are sufficient to buffer their transit through the stomach, the cyst stage is principally responsible for human infections. In studies, ingestion of as few as 10 cysts has resulted in human infection.

**Figure 6.** *Giardia lamblia* trophozoites (a) and cysts (b).
foodborne or waterborne transmission. Direct person-to-person transmission accounts for a heightened prevalence of giardiasis in several settings. In institutions where there is fecal incontinence and poor hygiene, giardiasis may be hyperendemic. Particularly in child day care centers, giardiasis can be a cause of intestinal disease. The risk of acquisition and transmission is greatest for young children not yet toilet trained, who may be a source of additional secondary cases within their families. Person-to-person transmission is also responsible for the prevalence of giardiasis in men who have sex with men (MSM). Sexual practices, including anilingus, can allow direct transfer of infectious cysts.

Waterborne transmission is a major source of giardiasis. Because filtration of water through soil removes Giardia cysts, deep well water is usually safe. In contrast, surface water, such as mountain streams and reservoirs, can harbor Giardia cysts, which are hardy in water and resistant to routine levels of chlorination. Coliform counts are not a reliable measure of giardial contamination. In addition, water-dwelling mammals, such as beavers, can become infected and then serve as continuing sources of water contamination, although whether giardiasis is a zoonotic disease is currently controversial. It may be difficult to recognize a water supply as the common source of giardiasis because the resultant infection is often asymptomatic.

G. lamblia is widely distributed throughout the world. Travelers to many countries, including those in developed areas, may acquire giardiasis.

Pathogenesis

After G. lamblia cysts have been ingested and have passed through the stomach, they liberate trophozoites that proliferate by binary fission. Trophozoites, which localize in the duodenum and the proximal jejunum, may attach to the microvillus border of intestinal epithelial cells by means of their ventral adhesive suckers. They may also reside in the unstirred layer above the epithelium, move around in the luminal contents, or, uncommonly, invade the space between the epithelial cells. Functional changes in the absorptive capabilities of the small bowel may develop. The activities of epithelial brush-border enzymes are diminished, leading to deficiencies in disaccharidases, including lactase deficiency. Jejunal biopsies of patients with giardiasis usually reveal no pathologic findings. The pathogenetic mechanisms of these functional alterations in the small bowel remain uncertain. With both types of alterations, specific anti­giardial therapy is effective, albeit return to normal occurs slowly in some patients. Hypochlorhydria predisposes persons to infection. Giardiasis often occurs with greater severity in patients with cystic fibrosis and in those with immunoglobulin deficiencies, possibly because of deficiencies in secretory IgA.

Diagnosis

Clinical features The clinical manifestations of giardiasis may be quite varied. A significant number of persons with giardiasis are asymptomatic. Indeed, in one well-studied outbreak of waterborne giardiasis, two thirds of those infected were asymptomatic. In contrast, others with the infection experience typical acute giardiasis. After a 1- to 3-week incubation period, the acute onset of the illness is marked by watery diarrhea; abdominal cramping (and other, frequently epigastric, discomfort); nausea (less commonly, vomiting); and systemic symptoms. Fever has been reported but is extremely unusual. Increased intestinal gas production leads to malodorous flatulence and sulfurous eructation. Impaired fat absorption and steatorrhea are common in symptomatic giardiasis. Stools are usually greasy and malodorous and float in water. Blood and mucus in stool are uncommon. These symptoms may be prominent for more than a week, diminishing in intensity over the ensuing weeks. Clinical findings that have helped identify cases of giardiasis in epidemiologic studies include a duration of illness lasting 7 or more days, with at least two of the following six symptoms: diarrhea, flatulence, foul-smelling stools, nausea, abdominal cramps, and excessive fatigue.

A chronic phase of giardiasis may follow the acute phase or may become manifest without an antecedent acute illness. This chronic phase is characterized by loose, but usually not diarrheic,
stoools that are soft and greasy. Increased abdominal gassiness with cramping, borborygmi, flatulence, and burping occurs. Fever is uncommon, but malaise, fatigue, and depression may ensue. Lactose intolerance can develop with the infection and augment intestinal symptoms after ingestion of milk products. The course can be remitting; asymptomatic periods may alternate with exacerbations of symptoms. For a small number of patients, particularly children, the persistence of infection is associated with moderate to marked malabsorption and weight loss.60

Uncommonly, G. lamblia spreads from the duodenum to the biliary and pancreatic ducts. Cases of cholecystitis, cholangitis, and granulomatous hepatitis have been reported. Impaired exocrine pancreatic function, manifested by diminished secretion of trypsin and lipase, has been noted.

**Laboratory findings** Leukocytosis and eosinophilia do not occur in giardiasis. Fecal fat excretion is increased (see above), and the results of other laboratory tests of malabsorption may also be abnormal. An upper gastrointestinal (GI) series usually shows no significant radiologic changes.

Definitive diagnosis of giardiasis requires the morphologic identification of the cyst or trophozoite of the parasite [see Figure 6]. Fecal examinations are usually positive in acute giardiasis; evaluation of three sequential daily fecal samples can detect more than 90% of infections. Cysts, which may be present in either loose or formed stools, are hardy, so the search for them does not necessitate prompt analysis of stools. In contrast, examinations to detect trophozoites should be performed on fresh stools or stools preserved in polyvinyl alcohol or merthiolate-iodine-formaldehyde (MIF). Substances that interfere with fecal microscopic evaluations, such as barium, antacids, and mineral oil, should be avoided before stool examinations. Immunologic assays detect giardial antigens in stool with greater sensitivity than a single stool examination.61

In chronic giardiasis, the frequency of detection of giardial forms on stool examination diminishes. If three or more stool examinations are unrevealing, the upper intestinal contents should be sampled by duodenojjunal aspiration. Alternatively, a biopsy of the small bowel can be performed. Recognition of trophozoites in biopsy specimens may require diligent searching of processed tissue; direct examination of mucosal imprint smears from a biopsy specimen can increase detection.

**Differential Diagnosis**

Other infectious agents that cause gastroenteritis must be considered early in the course of acute giardiasis. Because most of these agents produce illness of short duration, the persistence of symptoms after a week and the prominence of symptoms of malabsorption (i.e., flatulence, lactose intolerance, burping) suggest a giardial etiology. However, chronic giardiasis is difficult to distinguish from other chronic small bowel infections, such as Cyclospora or Cryptosporidium. Chronic giardiasis may resemble other diseases associated with malabsorption.62

**Treatment**

Tinidazole, given as a single 2 g oral dose, is highly effective for the treatment of giardiasis.63 Nitazoxanide is also effective; it is given for 3 days (in adults, 500 mg b.i.d.; in children 4 to 11 years of age, 250 mg b.i.d; and in children 1 to 3 years of age, 150 mg b.i.d.). A randomized trial showed that for the treatment of symptomatic giardiasis in children, the efficacy of nitazoxanide is comparable to that of metronidazole.64 An alternative agent for children is furazolidone, which is available as a suspension; it is effective and well tolerated.11

Both tinidazole and nitazoxanide are approved by the FDA for the treatment of giardiasis. Metronidazole, although not approved for the treatment of giardiasis, has been the principal agent used to treat this infection11,64,65 because quinacrine, the first effective drug for giardiasis, is no longer distributed in the United States. The usual dosage of metronidazole is 250 mg orally three times a day for 5 days, although this may lead to recurrences in up to 40% of cases, or 500 to 750 mg orally three times a day for 10 days, which is effective in 60 to 95% of cases.63 Administration of 2 g of metronidazole once daily for 3 consecutive days is associated with the highest cure rates,
with an efficacy of 93 to 100%. Refractory cases can be cured by a combination of quinacrine (available through compounding pharmacies) and metronidazole. Side effects of metronidazole include nausea, headache, and a metallic taste in the mouth; less commonly, dark urine, paresthesias, and dizziness occur. Metronidazole may have a disulfiram-like effect, so alcohol consumption should be avoided when metronidazole is used.

Treatment of giardiasis in pregnancy can be difficult. Metronidazole is often avoided, although studies have not documented teratogenic risks of metronidazole during pregnancy. If symptoms of giardiasis are minimal, therapy can be withheld until delivery. If symptoms are bothersome, one approach is to administer a nonabsorbable aminoglycoside, paromomycin, 25 to 35 mg/kg/day orally in three divided doses for 7 days. This regimen may provide at least symptomatic relief. If giardiasis in pregnancy is associated with dehydration, malabsorption, or severe symptoms, therapy with metronidazole is warranted.

In any patient, resolution of malabsorptive symptoms may require months for regeneration of functioning intestinal mucosa after effective antiparasitic therapy. Lactose intolerance may remain indefinitely.

**Prevention**

Attention to hygiene is necessary to prevent person-to-person transmission of giardiasis. The risks and benefits of treating asymptomatic infected children in day care centers have not been fully defined; however, treatment of asymptomatic persons who pass cysts is indicated to prevent the spread of infection. Boiling water or heating it to at least 70°C (158°F) for 10 minutes renders water noninfectious. For hikers and campers, iodine-based water treatments are more effective than chlorine-based treatments; iodine disinfection must be carried out for at least 8 hours to be 99.9% effective. High-quality water filtration units are effective for *Giardia* cyst removal.

**Dientamoeba Fragilis Infection**

The large-intestine parasite *D. fragilis* has only a trophozoite stage and no cyst stage [see Figure 7]. Although previously grouped with the amebae, histologic and antigenic examination and ribosomal RNA homology have demonstrated that it is closely related to the trichomonad flagellates. Because the trophozoite is not resistant to gastric acid, it is not clear how humans acquire infection. The eggs of the pinworm, *Enterobius vermicularis*, might transmit *D. fragilis* trophozoites because the two infections frequently coincide. *D. fragilis* can cause an illness characterized by abdominal pain, anorexia, and loose stools. As with *Isospora* infections, but not other protozoan infections, eosinophilia may accompany infection with *D. fragilis*. The trophozoite stage is not hardy and is difficult to detect; to ensure detection, stool samples must be preserved in polyvinyl alcohol fixative, sodium acetate-acetic acid-formalin fixative, or Schaudinn fluid and must be examined after permanent staining. *D. fragilis* infection can be treated with iodoquinol (650 mg t.i.d. for 20 days), paromomycin (25 to 30 mg/kg/day in three doses for 7 days), or metronidazole (500 to 750 mg b.i.d. for 10 days).

**Amebiasis**

Infection with the ameba *E. histolytica* is responsible for human amebiasis. These infections may be limited primarily to the colon. Infections range in severity from asymptomatic to markedly dysenteric and may involve extraintestinal sites, of which the liver is the most common.

**Etiology and Epidemiology**

*E. histolytica* is distinguishable morphologically from the other nonpathogenic intestinal amebae, including *E. coli* and *E. hartmanni* [see Figure 8]. *E. histolytica* exists in two forms: as a trophozoite and as a cyst. The trophozoite, which usually measures 10 to 20 μm in diameter but may be larger in
dysenteric stools, is motile and possesses a single nucleus and a granular cytoplasm [see Figure 9]. Trophozoites are passed in loose stool, but this form is not hardy and does not survive outside the body. In contrast, the cyst stage, which arises within the colon from the trophozoite, can survive environmental stresses and passage through the acid of the stomach. Cysts measure 10 to 20 μm in diameter and contain one to four nuclei, which have small, centric karyosomes and a pattern of fine peripheral chromatin.

**Figure 7.** *Dientamoeba fragilis* trophozoite. Note double nuclei.

**Figure 8.** *Entamoeba histolytica*, which causes amebiasis, is distinguishable morphologically from nonpathogenic intestinal amebae such as *Entamoeba coli*; on this photomicrograph, the cyst of *E. histolytica* is visibly larger than the cyst of *E. coli*.

It has long been recognized that not all strains of *E. histolytica* are pathogenic. Nonpathogenic strains can be isolated from asymptomatic patients and have been prevalent in promiscuous male homosexuals in the United States and England. Pathogenic and nonpathogenic strains cannot be distinguished by microscopy, except that pathogenic trophozoites often phagocytose erythrocytes. On the basis of biochemical, immunologic, and genetic data, *E. histolytica* has been redescribed. A new species, *Entamoeba dispar*, now represents the nonpathogenic isolates and is apparently never invasive in humans, whereas *E. histolytica* includes only the potentially pathogenic strains. 

Because not all potentially pathogenic *E. histolytica* strains invariably produce disease, other processes undoubtedly influence amebic virulence.

**Figure 9.** Trophozoite form of *Entamoeba histolytica*.

An immunoassay to distinguish *E. histolytica* from *E. dispar* has been developed on the basis of *E. histolytica*-specific N-acetyl-D-galactosamine lectin. Currently, no other method is available for a commercial diagnostic laboratory to readily distinguish one organism from the other [see Diagnosis, below], although these organisms can be distinguished by differences in isoenzymes, restriction fragment patterns, repetitive DNA, and riboprinting.

Cysts passed in human feces are primarily responsible for human infections. Acquisition of infection represents fecal-oral contamination and may occur by waterborne or foodborne transmission, as well as by person-to-person transmission. The latter accounts for the heightened prevalence of *E. histolytica* infection among MSM and in institutions where there is fecal incontinence and poor hygiene. Amebiasis is more common in lower socioeconomic groups than in the general population because of poor sanitation and overcrowding. In the United States, cases are seen in persons who have returned from international travel or have immigrated from areas where amebiasis is endemic.

**Pathogenesis**

Ingested cysts are carried into the intestine, where they excyst to liberate trophozoites that proliferate by binary fission within the colon [see Figure 9]. Trophozoites are cytolytic and may invade the bowel wall, resulting in local necrosis. The resultant ulcers are flask shaped, with a
narrow neck through the mucosa and a broader submucosal base. Unless colonic involvement is extensive, intervening areas of bowel are normal. The areas most frequently affected are the cecum and the ascending colon, followed in frequency by the rectosigmoid, the appendix, the descending and transverse colon, and the terminal ileum [see Figure 10].

The severity of colonic involvement in patients with amebiasis is quite varied and may range from mild or negligible disease to diffuse and extensive tissue invasion and necrosis. Most persons who harbor *E. histolytica* experience no significant colonic invasion. The determinants of severity are not well understood but may include the inoculum size of *E. histolytica*, the coexisting colonic microbial flora, and the nutritional and physiologic state of the host. Corticosteroid use and pregnancy both diminish host resistance. Complications of colonic involvement include hemorrhage and peritonitis, the latter developing more commonly from transmural leakage across involved colonic tissue than from frank perforation. With chronicity, a granulomatous tissue response can develop at a site of infection (most commonly in the cecum) and can produce a mass lesion termed an ameboma. Colonic strictures may also develop.

Amebiasis may spread hematogenously from the bowel to involve any organ in the body. The liver is most commonly affected, followed in frequency by the lungs, which are principally affected as a result of transdiaphragmatic spread from the liver [see Figure 10]. Trophozoites carried via the portal venous system produce necrosis in the liver and cause abscesses. About 90% of abscesses are in the right lobe, especially in the superior and anterior aspects. Although multiple abscesses can occur, a solitary abscess ranging in size from a few centimeters to 20 cm in diameter is more common. Amoebic liver abscesses are seven to nine times more common in men than in women; in children, the sex distribution is equal. Uncommonly, an abscess may develop concomitantly with amebic colitis. Depending on the reported series, 50 to 70% of patients with amebic-hepatic abscesses have no history of amebic colitis. Rupture of a right lobe abscess may result in extension of infection into the chest, producing an amebic empyema, pneumonia, or a bronchopleural fistula. Extension into the peritoneal cavity is less common. Rupture from a left lobe abscess can result in extension into the pericardium, frequently with fatal consequences.

**Figure 10.** Amebiasis from *Entamoeba histolytica* may be limited to the colon—most often, the proximal or terminal portions—or may spread by direct extension or hematogenously to any organ in the body. The liver is most commonly affected, followed by the lungs, but brain or spleen abscess may also occur, as may cutaneous involvement.

The role of immunity in protection of disease from *E. histolytica* has been controversial, but studies in children in endemic regions suggest that development of intestinal IgA antibodies to an *E. histolytica* N-acetyl-D-galactosamine lectin is highly associated with the development of acquired immunity. This lectin appears essential for cell binding and pathogenesis by *E. histolytica*, and, presumably, blocking its function in vivo leads to protection.

**Diagnosis**

**Clinical features** Most persons with colonic amebiasis experience no symptoms. Fecal cyst excretion in these asymptomatic individuals is detected only by serendipity. In persons who do experience symptoms, the illness may range from mild diarrhea to fulminant dysentery. The former presentation is common, and most patients are able to continue daily activities as they experience mild diarrhea that may alternate with constipation. The course of illness can be remitting, with subsequent symptomatic relapses. Abdominal discomfort, tenesmus, dull sacral pain, and flatulence are common, but systemic symptoms and fever are less prominent than what is common with bacterial colitis. Blood and mucus are frequently noted in stools. Abdominal findings reflect the severity of the colonic involvement. Tenderness may be absent or mild over the involved areas. In some cases, however, prominent abdominal tenderness, together with high fever and systemic
toxicity, is a consequence of extensive colonic disease. Amebomas may be palpable as tender abdominal masses.

In patients with amebic liver abscess, presenting symptoms usually include malaise, fatigue, anorexia, abdominal pain, fever, and weight loss; the duration is usually 1 week to several weeks or, less commonly, many months. The abdominal pain is usually dull and aching and localized over the right upper quadrant or right chest. At times, there is referred pain to the right shoulder. A presentation with pleuritic chest pain, cough, and dyspnea may mistakenly suggest an intrapulmonary infection. An abscess in the left lobe may produce midepigastric or left upper quadrant pain. On examination, hepatomegaly and hepatic punch tenderness or focal tenderness over the abscess are frequent. Frank jaundice is rare. On chest examination, dullness at the right lung base as a result of diaphragmatic elevation and pleural effusion formation can be appreciable. Rales may be heard.

Cutaneous amebiasis, resulting in ulcerative or fungating lesions, most commonly develops on the perineum and genitalia. Lesions arise from invasion by trophozoites derived from fecal contamination or sexual transmission. The lesions can be distinguished from neoplastic, tuberculous, and syphilitic processes by the presence of trophozoites in exudate or tissue biopsy specimens.

**Laboratory findings** In symptomatic amebic colitis, a mild to moderate leukocytosis may develop. Mild anemia and mild elevations of liver enzyme levels (which are not usually indicative of incipient abscess formation) may occur. Feces usually contain frank or occult blood.

Leukocytosis, anemia, and an elevated erythrocyte sedimentation rate are common with an amebic liver abscess. In more than two thirds of patients, alkaline phosphatase levels are one to four times higher than normal. Elevated aminotransferase levels occur in fewer than 50% of patients. Bilirubin levels may be elevated, but usually to no more than 2.5 mg/dL. Chest x-ray often shows elevation of the right diaphragm and may reveal a pleural effusion. An isotopic liver scan will reveal a space-occupying lesion; an ultrasound scan will show a round to ovoid hypoechoic lesion. In addition, ultrasonography can reveal transdiaphragmatic pleural involvement. CT or MRI also can document the abscess and any local extension.

For intestinal amebiasis, definitive diagnosis requires morphologic or antigenic identification of the cysts or trophozoites of *E. histolytica* [see Figure 8 and Figure 9]. Unformed stool should be examined immediately for motile trophozoites. Formed stools may be examined directly or after application of concentration techniques for cysts. Stools may also be preserved in polyvinyl alcohol or MIF for subsequent examination. Fecal leukocytes and nonpathogenic amebae are easily confused with *E. histolytica*; thus, definitive speciation should be performed on stained samples by experienced personnel. Antimicrobial agents, cathartics, antacids, and barium interfere with microscopic detection. Testing of a single stool has only 33 to 50% sensitivity, so multiple stools should be examined when the diagnostic suspicion is high. Because the excretion rate of cysts varies daily, three or more stool samples from different days should be examined. About half of patients with symptomatic amebic colitis have rectosigmoid involvement; thus, aspirates, scrapings, or biopsies of mucosal lesions obtained at sigmoidoscopy can be examined for trophozoites. A fecal antigen detection test for *E. histolytica* has been introduced that is based on a monoclonal antibody to a specific lectin on this organism.71

Serologic tests for amebiasis are infrequently positive in asymptomatic persons who pass cysts, but the rates of seropositivity rise with increasing extent and duration of amebic colonic involvement. Such tests can be an adjunct to the diagnosis of acute amebic disease and can be especially helpful in the etiologic assessment of chronic colitis. Serologic tests, performed by a variety of methods, may remain positive for months to years after infection; this fact should be considered when interpreting a positive test result.

Serologic tests are positive in 90 to 95% of patients with extraintestinal amebiasis; titers increase with the duration of the disease. A positive titer, together with compatible clinical findings and tests demonstrating a cystic hepatic lesion, allows for the diagnosis of amebic hepatic abscess. The results
of stool examinations, either negative or positive, are not etiologically pertinent in such cases. Trophozoites are rarely demonstrable in aspirated abscess fluid, which usually has an anchovy paste or chocolate-brown appearance.

**Differential Diagnosis**

In cases of mild intestinal amebiasis, the diagnosis of irritable bowel syndrome, diverticulitis, or regional enteritis may be suggested by the duration and symptoms of the infection. For more severe intestinal amebiasis with an acute presentation, infections with *Shigella*, *Salmonella*, *Escherichia coli* O157:H7, and *Campylobacter* can be distinguished by positive stool cultures and by the presence of large numbers of fecal leukocytes, which are not found in amebic colitis. Ulcerative colitis and Crohn disease are to be considered in the differential diagnosis for chronic amebic colitis [search ACP Medicine for information on inflammatory bowel disease]. Lesions on sigmoidoscopy and barium enema findings may be identical in amebic colitis and ulcerative colitis. It is critical to distinguish between these two conditions because corticosteroid therapy, which may be indicated for ulcerative colitis, would aggravate amebic colitis; therefore, amebic serologic tests and examinations of feces and mucosal lesions for amebae are of cardinal importance. A therapeutic trial of metronidazole cannot be relied on to identify the etiology, because metronidazole may have a salutary effect on inflammatory bowel disease as well as on amebic colitis.

An ameboma may simulate an adenocarcinoma or another granulomatous process. A positive amebic serology and resolution of the mass with metronidazole therapy support the diagnosis of an ameboma. If resolution is not complete, a biopsy is indicated to exclude a coincidental lesion of nonamebic cause.

The differential diagnosis of amebic hepatic abscess is guided by two observations: (1) an isotopic liver scan that shows a space-occupying lesion and (2) an ultrasound, CT, or MRI scan that shows a cystic lesion. Although hepatic cysts and echinococcal cysts are usually not associated with fever and the other symptoms of an amebic lesion, they should be considered in the differential diagnosis. Pyogenic abscesses should be considered as well. A positive amebic serology supports an amebic etiology. In contrast to echinococcal cysts, amebic abscesses calcify very rarely. Imaging studies of echinococcal cysts often demonstrate complicated cysts with internal daughter cysts, which are not seen in amebic abscesses. An amebic abscess and a pyogenic abscess may respond alike to metronidazole therapy. Amebic abscesses are uncommonly infected secondarily. If uncertainty persists about the bacterial or amebic etiology of an abscess, diagnostic aspiration of abscess fluid for bacterial cultures and Gram stain may be necessary.

**Treatment**

For symptomatic intestinal disease or extraintestinal disease, oral metronidazole (750 mg t.i.d. for 10 days) is usually highly effective and is the preferred therapy.11 Alternatively, oral tinidazole (2 g daily for 5 days) can be given.11 Information about the side effects of metronidazole and precautions about its use have been presented in the discussion of giardiasis (see above). Occasional failures in the treatment of hepatic abscesses with metronidazole have been noted. Because relapses of intestinal disease may infrequently occur in the absence of reinfection, follow-up is indicated for a number of months. Chemotherapy may be unnecessary for many asymptomatic persons who pass cysts because such persons often harbor nonpathogenic *E. dispers*. If speciation of *Entamoeba* is not available, asymptomatic persons who pass cysts should be treated if they handle food or if they are receiving corticosteroids; they should also be treated in the setting of an amebiasis outbreak.70 In asymptomatic patients, concentrations of metronidazole in the colonic lumen may be inadequate to eradicate amebae, and either paromomycin or iodoquinol, which are luminal amebicides, should be used.11 Paromomycin is given in a dosage of 25 to 35 mg/kg/day in three doses for 7 days. The dosage of iodoquinol is 650 mg three times a day for 20 days; it is important not to exceed this dosage because of the potential for causing optic neuritis. Iodoquinol is contraindicated for patients with optic neuropathy or thyroid disease. A course of iodoquinol is recommended for patients treated for symptomatic intestinal or extraintestinal amebiasis.11 Another alternative is nitazoxanide, which
in one study showed 96% efficacy for elimination of cyst passage. A placebo-controlled trial showed efficacy of nitazoxanide for *E. histolytica* GI infections, although there was no comparator to metronidazole. Nonetheless, nitazoxanide looks promising for the treatment of amebiasis.

Therapeutic aspiration is usually not necessary for amebic hepatic abscess, although diagnostic aspiration may be useful in certain cases [see Differential Diagnosis, above]. Drainage, which can be achieved by percutaneous aspiration, is indicated for those lesions that fail to respond to initial medical therapy or that are in imminent danger of rupturing.

**Prevention**

Prevention of amebiasis relies on personal hygiene to prevent person-to-person transmission. In areas where amebiasis is endemic, the provision and use of adequate toilet facilities can decrease the spread of disease. Avoidance of vegetables that grow close to the ground (e.g., lettuce) is advisable because of potential contamination by human feces. Water can be rendered safe by boiling or by use of iodine-based water treatment tablets.

**Blastocystis Hominis Infection**

*B. hominis* was previously considered to be a nonpathogenic yeast. Most investigators now consider this organism to be a protozoan that is distantly related to ameba or that perhaps belongs in its own phylogenetic group. Whether *B. hominis* is capable of causing intestinal illness is controversial. Support for the belief that this organism may be pathogenic stems from the finding of large numbers of *B. hominis* organisms in the feces of patients with diarrhea for which no other cause has been identified. Other investigators, however, have failed to confirm this finding. They have found no concordance between the numbers of fecal organisms and the extent of the diarrhea and have seen no resolution of symptoms after therapy for *Blastocystis* infection. Until the issue of the pathogenicity of *B. hominis* is settled, patients with a diarrheal illness who are excreting this organism in their feces should be studied for other parasitic, bacterial, or viral infections or other reasons for illness, such as irritable bowel syndrome or inflammatory bowel disease. Stool samples typically reveal the vacuolated form of *B. hominis*, although several other forms can be seen as well [see Figure 11]. If diarrheal symptoms are sufficient to warrant therapy and other causes for diarrhea have been ruled out, iodoquino, 650 mg three times a day for 20 days, or metronidazole, 750 mg three times a day for 10 days, can be used.

**Figure 11. Blastocystis hominis** on a trichrome stain.

**Coccidiosis**

Coccidia, which are found in the intestines of many domestic and wild animals, are unicellular parasites that reproduce by asexual and sexual cycles in gut epithelium. Three coccidial organisms—*Cystoisospora belli* (formerly known as *Isospora belli*), *Cryptosporidium*, and *Cyclospora cayetanensis*—have been documented to be pathogenic as enteric parasites for humans; humans serve as the definitive host and pass infectious cysts in stool [see Figure 12]. Contact with infected cattle may result in infection with *Cryptosporidium*, and contaminated water or food sources transmit *C. belli*, *Cryptosporidium*, and *C. cayetanensis*. All three coccidial parasites have been identified as opportunistic pathogens in patients infected with HIV.

**Cystoisosporiasis (Formerly Known as Isosporiasis)**
**Diagnosis** Illness from *C. belli* infection usually begins abruptly. Fever and malaise appear first, followed by abdominal pain, diarrhea, and weight loss. In most cases, the illness is self-limited, although chronic infections may last several weeks to several months. Severe diarrhea, steatorrhea, and hepatic involvement may ensue; in rare instances, severe disease results in death. In patients with AIDS, infection with *C. belli* causes chronic watery diarrhea and weight loss that is indistinguishable from such symptoms produced by Cryptosporidium.

Histologic examination of mucosal lesions in patients who have cystoisosporiasis shows shortened villi, crypt hypertrophy, and infiltration with eosinophils, neutrophils, lymphocytes, and plasma cells. Blood eosinophilia, which is not seen with other protozoan infections except *D. fragilis*, may develop with *C. belli* infections. The presence of oocysts in the stool establishes the diagnosis. Although routine stool examinations may fail to detect oocysts, they can be demonstrated with acid-fast staining. If oocysts in the feces are few, incubation of stool at room temperature for 24 to 48 hours can encourage oocyst maturation, and the zinc sulfate concentration technique can be used before examining the stool. Parasite forms may also be detected in biopsy specimens of intestinal tissue and in intestinal contents.

**Treatment** *C. belli* infections are treated with double-strength trimethoprime-sulfamethoxazole (160 mg of trimethoprime and 800 mg of sulfamethoxazole) given orally four times a day for 10 days and then twice a day for 3 weeks. Because recurrences of infection are likely in patients who have AIDS, the initial 10-day course of trimethoprime-sulfamethoxazole should be followed by long-term maintenance therapy with either one double-strength tablet of trimethoprime-sulfamethoxazole three times a week or the combination of 25 mg of pyrimethamine and 500 mg of sulfadoxine once a week in those patients. In patients who are intolerant of sulfa drugs, pyrimethamine (50 to 75 mg daily in divided doses plus leucovorin 10 to 25 mg/day) or ciprofloxacin (500 mg b.i.d. for 7 days) has been successful; a maintenance dosage of 50 to 75 mg/day of pyrimethamine or 500 mg orally three times a week of ciprofloxacin has prevented relapses of *I. belli* infections.

**Cryptosporidiosis**

*Cryptosporidium* inhabits the brush border of the small intestine mucosa and can cause enterocolitis in both normal and immunocompromised hosts. Infection may be acquired by ingestion of fewer than 100 oocysts. A common means of transmission is by water, including municipal drinking water and recreational water (i.e., water in pools and water slides). Cryptosporidiosis has caused outbreaks of diarrheal disease in day care centers and may be acquired by international travelers. Cryptosporidial infection and cryptosporidiosis have their highest incidences in children of the developing world. Because fecal oocysts are infectious, infection can spread nosocomially, via food handlers, and within households.

**Diagnosis** In normal hosts, illness begins after a mean incubation period of about a week. It consists of watery, nonbloody diarrhea that is accompanied at times by such clinical manifestations as abdominal pain, nausea, fever, anorexia, and weight loss.

The diarrhea is generally noninflammatory in nature, although children in the developing world and small numbers of infected adults have white blood cells and lactoferrin in the stool. Symptoms may persist for 1 to 2 weeks and are usually self-limited. By contrast, in immunocompromised patients, cryptosporidiosis can be persistent and severe. In HIV-infected patients with CD4 T cell levels greater than 180/µL, cryptosporidiosis can be self-limited. With more profound immunocompromise, however, the secretory diarrhea, which is chronic and profuse, is usually unremitting. In these persons, *Cryptosporidium* organisms may cause hepatobiliary disease, including cholecystitis, cholangitis, and papillary stenosis.

*Cryptosporidium* oocysts, which are 4 µm in size, can be detected in fecal smears examined microscopically, either as an iodine wet mount or after staining with a monoclonal antibody or the modified Kinyoun acid-fast reagent (see Figure 12). In addition, direct fluorescent stains and immunoassays of fecal samples can enhance diagnostic yields of *Cryptosporidium*.
**Figure 12.** Cysts of the three coccidial organisms—(a) *Cryptosporidium*, (b) *Cyclospora*, and (c) *Cystoisospora*—with documented pathogenicity as enteral parasites. All are stained with modified Kinyoun (acid-fast) stain. Note that cysts of *Cryptosporidium* and *Cyclospora* can be distinguished only by their size (cysts of *Cryptosporidium* are 4 µm in diameter, and those of *Cyclospora* are 8 µm), whereas *Cystoisospora* cysts are 25 × 15 µm and ovoid in shape.

**Treatment**  In immunocompetent patients, cryptosporidiosis is a self-limited illness and usually requires only supportive therapy. Chemotherapy would be valuable in immunocompromised patients, but an effective regimen for cryptosporidiosis has not been established. If the patient is receiving immunosuppressive drugs, cessation of these agents may lead to resolution of the diarrhea. Similarly, improvement of CD4 T cell levels in HIV-infected patients by highly active antiretroviral therapy has led to the cessation of life-threatening cryptosporidial diarrhea. For some HIV-infected patients, paromomycin may be at least partially beneficial in treating cryptosporidiosis, although small controlled trials were unable to show a difference between paromomycin and placebo. Perhaps a better alternative is nitazoxanide (in adults, 500 mg b.i.d.; in children 4 to 11 years of age, 250 mg b.i.d; in children 1 to 3 years of age, 150 mg b.i.d.); nitazoxanide is approved by the FDA for the treatment of cryptosporidiosis in children only. One randomized trial has shown efficacy in cryptosporidiosis in immunocompetent patients, but a meta-analysis of nitazoxanide therapy failed to show its utility for immunocompromised patients.

**Cyclosporiasis**

*Cyclospora* appears to be widely distributed geographically; illness attributable to this protozoan has been described in the United States, Latin America, Africa, Europe, and Asia. Epidemiologic studies indicate that contaminated water and contaminated produce such as raspberries, blackberries, mesclun, and basil have been sources of infection. The oocysts that are passed in stool require days to weeks outside the host in the right environmental conditions to sporulate and become infectious. For this reason, person-to-person transmission is unlikely. The median incubation period after ingestion of the infectious sporocyst is about 1 week but is possibly as short as 1 to 2 days.

**Diagnosis**  Many patients infected with *Cyclospora* experience prodromal flu-like symptoms, diarrhea, and symptoms common to other small bowel pathogens, including nausea, vomiting, flatulence, and burping. The illness may be confined to a single self-limited episode or may wax and wane, but prolonged diarrhea, anorexia, and upper GI symptoms often occur. Prolonged fatigue and weight loss also frequently occur.

Small bowel biopsies can reveal the parasite in epithelial cells and can demonstrate jejunal inflammation, which is associated with increased numbers of intraepithelial lymphocytes and increased degrees of villous atrophy and crypt hyperplasia. Fecal leukocytes and blood are absent, suggesting that the disease involves a noninvasive mechanism. The diagnosis can be made by detection of oocysts in the stool, which, like *Cryptosporidium* oocysts, are apparent in acid-fast stains. Although *Cyclospora* oocysts, which measure 8 to 10 µm in diameter, are larger than *Cryptosporidium* oocysts, caution is needed to avoid confusing the two distinct protozoan organisms in diagnostic testing [see Figure 12]. Fluorescence microscopy is a rapid and sensitive means of detecting oocysts, which are autofluorescent. *Cyclospora* oocysts have been found in patients infected with HIV; infection in these patients can range from asymptomatic to severe.

**Treatment**  Double-strength trimethoprim-sulfamethoxazole tablets (160 mg/800 mg twice daily for 7 to 10 days) have proved to be effective therapy for cyclosporiasis. HIV-infected patients, however, may require a higher dosage (four times a day for 7 days) and may need long-term
maintenance treatment (three times a week). Ciprofloxacin (500 mg b.i.d. for 7 days, then 500 mg three times a week) has been shown to be less effective than trimethoprim-sulfamethoxazole in HIV-infected persons but can be used in patients who are sulfa intolerant. Like cryptosporidiosis, *Cyclospora* infection must be considered in any patient with prolonged diarrhea, anorexia, and upper GI symptoms.

**Balantidium Coli Infection**

*B. coli* is the only ciliate that causes human disease. *B. coli* is a rare cause of diarrhea and inflammatory colitis. Humans are incidental hosts. Large mammals, such as pigs, and contaminated food or water are the main sources of human infection. The ciliated trophozoite, which is found in diarrheal stools, is usually 60 to 70 μm and ovoid in shape; cysts may also be found [see Figure 13](#image13). Clinical symptoms usually consist of chronic intermittent diarrhea and weight loss, but acute dysentery occurs in about 5% of cases. In these latter cases, superficial and, rarely, deep colonic ulcerations have been observed. Treatment with tetracycline (500 mg q.i.d. for 10 days) or, possibly, metronidazole (500 to 750 mg t.i.d. for 5 days) or iodoquinol (650 mg t.i.d. for 20 days) is effective.

![Figure 13. Balantidium coli cyst.](#image13)

**Microsporidiosis**

Microsporidia, which are obligate intracellular, spore-forming organisms, belong to a distinct phylum of protozoans that includes many genera capable of infecting diverse vertebrate and invertebrate hosts. They are most closely related to fungi, although their exact phylogenetic relationship to other eukaryotes remains unclear. Human microsporidial infections have been recognized in recent years; to date, seven genera of microsporidia—*Enterocytozoon, Encephalitozoon* (including *Septata*), *Vittaforma, Trachipleistophora, Pleistophora, Nosema*, and *Brachiola*—have been identified as causes of human disease, especially in persons infected with HIV. These microsporidia are differentiated by their size, nuclear morphology, and mode of division, as well as by the intracellular site of proliferation (microsporidia multiply either freely in the cytoplasm or within membrane-bound vacuoles). Despite the ubiquity of microsporidia in other host species, how humans become infected is not known. Because almost all microsporidial infections in humans have been identified in immunocompromised hosts, it is not clear how frequently immunocompetent hosts are infected or whether infections that develop in immunocompetent hosts are symptomatic or self-limited.

The spectrum of disease attributable to microsporidia is broad, with the disease state apparently depending on the infecting species and the immune status of the host. The most commonly recognized microsporidial infections are *Enterocytozoon bieneusi* infections in HIV-infected patients, usually those with CD4+ T cell levels below 100/μL. In HIV-infected patients, intestinal *E. bieneusi* and *Encephalitozoon intestinalis* (formerly *Septata intestinalis*) infections are causes of chronic diarrhea, and *E. bieneusi* and *E. intestinalis* may infect the biliary tract, causing cholangitis. *Encephalitozoon* species have caused keratoconjunctivitis marked by a coarse punctate epithelial keratopathy in HIV-infected patients, whereas *Vittaforma* and *Nosema* species have caused stromal keratitis in a few HIV-seronegative patients. *Encephalitozoon* microsporidia have also been associated with peritonitis and hepatitis, as well as nasal and sinus infections and infections in other diverse sites in HIV-infected patients. *Trachipleistophora, Pleistophora*, and *Brachiola* species have caused myositis.

Microsporidia are gram-positive organisms with mature spores that measure only 0.5 to 2 μm by 1 to
4 μm; the small size hinders detection of the parasite. Many microsporidial infections have required electron microscopic tissue evaluation for diagnosis [see Figure 14]. Intracellular spores can also be recognized by light microscopy of tissues that are stained with hematoxylin-eosin, Giemsa, or Gram stain or modified acid-fast stains. Intestinal microsporidia appear to be spottily distributed and may not be detected on examination of tissue biopsy specimens. Chromotrope-based and fluorochrome (Uvitex 2B and Calcofluor) staining methods facilitate detection of microsporidial spores in smears of either feces or duodenal aspirates.93

Figure 14. A transmission electron micrograph shows developing forms of *Encephalitozoon intestinalis* inside a parasitophorous vacuole (red arrows) with mature spores (black arrows).

For intestinal infections with *E. intestinalis*, oral albendazole (400 mg b.i.d. for 21 days) has been beneficial or curative; *E. bieneusi* infections are less responsive, although patients may experience symptomatic improvement without eradication of the infection.95,96 Oral albendazole has also been used for systemic infections with *Encephalitozoon hellem*, *Encephalitozoon cuniculi*, *E. intestinalis*, *Pleistophora*, *Trachipleistophora*, and *Brachiola vesicularum*.11 Oral fumagillin (60 mg daily for 14 days) has been effective in treating *E. bieneusi* infections.11 For keratoconjunctivitis caused by *E. hellem*, topical therapy with fumagillin suspension combined with oral albendazole (400 mg b.i.d.) has been beneficial.11

### Infections from Free-Living Amebae

Although amebae such as *E. histolytica* cannot survive and replicate outside of animal hosts, most amebae are free-living in soil or water. Amebae of the genera *Naegleria*, *Acanthamoeba*, *Balamuthia*, and *Sappinia* can cause acute meningitis, acute meningoencephalitis, or chronic granulomatous meningoencephalitis [see Figure 15 and Figure 16].98-100 *Naegleria* species, notably *Naegleria fowleri*, cause acute meningoencephalitis in immunocompetent hosts; infection has been reported after trauma in warm freshwater in the southeastern United States. Progression of disease is typically rapid and inexorable, although effective therapy has been reported with amphotericin B, miconazole, and rifampin.101

In addition to chronic granulomatous meningoencephalitis, *Acanthamoeba* species have been recognized as a cause of keratitis102 and, in a small number of HIV-infected patients, of disseminated disease with cutaneous manifestations.103 *Acanthamoeba* organisms have been isolated from water, airborne dust, hot tubs, and saline solutions used to clean contact lenses. Factors associated with the development of amebic keratitis include the lack of effective disinfection of contact lenses, a history of minor corneal trauma, and exposure to soil or standing water. The lesions, which are usually chronic and severely painful, consist of variable anterior uveitis, epithelial erosion, scleritis, and an infiltrative stromal keratitis that is often ring shaped. Lesions are refractory to the usual antimicrobial medications and must be distinguished from keratitis caused by herpes simplex virus [search ACP Medicine for information on herpesvirus infections]. The diagnosis can be made by microscopic examination of Giemsa- or trichrome-stained corneal scrapings and by the use of indirect immunofluorescent antibody staining of corneal scrapings. The ameba can be cultured by inoculating corneal tissue into nonnutrient agar seeded with *Escherichia coli*. Acanthamebic keratitis has been treated with topical regimens using chlorhexidine (bis-biguanide) and propamidine or the polymeric equivalent polyhexamethylene biguanide (PHMB). PHMB was originally combined with propamidine but is now combined with hexamidine.102 Topical biguanides are the only effective therapy for the resistant encysted form of the organism. The use of topical steroids is controversial, but probably beneficial, for the management of severe corneal inflammatory complications that have not responded to topical biguanides alone. Therapeutic keratoplasty retains a role for therapy of
some severe complications of acanthamebic keratitis but not for initial treatment.\textsuperscript{104}

**Trichomoniasis**

*Trichomonas vaginalis* is a flagellated protozoan that causes an estimated 3 million vaginal infections a year.\textsuperscript{105} It is a venereal disease, with the highest incidence in women who have multiple sexual partners; thus, persons with *Trichomonas* infection should be screened for other sexually transmitted pathogens, such as *Chlamydia*, *Neisseria gonorrhoeae*, and HIV. *Trichomonas* infection can be passed to neonates, and 2 to 17% of infected women transmit it to their female offspring during birth. It does not have a cyst form but, rather, only the trophozoite form, so that human-to-human transmission is the norm, although *T. vaginalis* can exist outside of the host for several hours if it is in a moist environment. Trichomonads appear to damage genital epithelium by direct contact, and this results in microulcnerations and inflammation. Management of trichomonal infection is discussed in detail elsewhere [search ACP Medicine for information on vaginitis and sexually transmitted diseases].

**Leishmaniasis**

**Introduction**

*Leishmania* organisms are protozoan hemoflagellates that are obligate intracellular parasites in humans. *Leishmania* species produce a wide spectrum of disease, ranging from generalized visceral involvement to diffuse or circumscribed cutaneous or mucocutaneous lesions. Four species complexes of *Leishmania* may infect humans: *Leishmania donovani*, *Leishmania tropica*, *Leishmania mexicana*, and *Leishmania* (subgenus Viannia) *braziliensis*. The resulting patterns of illness arise from the tissue tropism of the leishmanial species and the host's immune response, principally the cell-mediated component of immunity.

![Figure 15.](image) (a) *Acanthamoeba polyphaga* cyst. (b) A histopathologic slide shows *A. polyphaga* infection in a mouse brain. Similar histopathologic features are seen in *Acanthamoeba* meningoencephalitis, which generally occurs in immunocompromised persons.

**Visceral Leishmaniasis**

**Etiology and Epidemiology**

The *L. donovani* species complex includes several species (e.g., *Leishmania infantum* and *Leishmania chagasi*). These species cause visceral leishmaniasis, or kala-azar, which is endemic in areas of India, China, Central and South America, East and West Africa, and the countries surrounding the Mediterranean. *Leishmania tropica* can also cause a viscerotrophic disease involving bone marrow cells.\textsuperscript{106} Sandflies of the genus *Phlebotomus* are the insect vectors that spread *L. donovani*; the species vary in the different areas. In India, no extrahuman reservoirs are known, but in other regions, infection may involve several mammalian species, including dogs, foxes, and wild rodents.

![Figure 16.](image) *Naegleria* meningoencephalitis in a human brain, on hematoxylin-eosin stain.

**Pathogenesis**

The flagellated promastigotes of *L. donovani* are introduced by an insect bite. After entering
macrophages of the reticuloendothelial system, these forms change into amastigotes, which multiply in phagocytic cells. Released amastigotes disseminate hematogenously and invade reticuloendothelial cells in the spleen, liver, lymph nodes, bone marrow, and skin. Prospective studies have demonstrated that the ratio of inapparent infection to disease ranges from greater than 6.5:1 in children younger than 5 years, the most susceptible group, to greater than 18:1 in older children and adults.107 Cell-mediated immunity controls Leishmania infection; compromise of cell-mediated immunity, such as from young age or malnutrition, contributes to susceptibility.

**Diagnosis**

**Clinical features** Symptoms of visceral leishmaniasis usually are of gradual onset, occurring several months after infection; symptoms include weakness, dizziness, weight loss, diarrhea, and constipation. Fever, which almost always develops, may spike twice daily and is sometimes accompanied by chills and sweating. As the disease progresses, the liver and spleen enlarge, the latter often expanding into the iliac fossa. When bone marrow macrophages are parasitized, anemia and leukopenia ensue. Thrombocytopenic patients may bleed from the gingivae, nose, or GI tract, and ecchymoses and petechiae may appear on the skin. Death can result from secondary bacterial infections, severe anemia, or uncontrolled bleeding. Latent infection can become manifest and progressive during immunosuppression, and visceral leishmaniasis can develop as an opportunistic infection in HIV-infected patients. Two thirds of patients with visceral leishmaniasis have typical infections, but leishmanial parasites may localize in unusual sites, including the larynx and throughout the GI tract, and hepatosplenomegaly may be absent.

**Laboratory findings** Anemia, leukopenia, thrombocytopenia, hyperglobulinemia, and hypoalbuminemia suggest visceral leishmaniasis when they are observed in a patient with fever, hepatosplenomegaly, and a history of exposure in endemic areas. The differential diagnosis is wide, including hepatosplenic schistosomiasis, malarial hypersplenism, myeloproliferative diseases, typhoidal *Salmonella* infections, miliary tuberculosis, brucellosis, histoplasmosis, subacute bacterial endocarditis, and infectious mononucleosis. Definitive diagnosis of visceral leishmaniasis requires demonstration of the organism in host tissues cultured on a Novy-MacNeal-Nicolle (NNN) or other medium or detection of Leishman-Donovan bodies (amastigotes) in stained tissue samples. Alternatively, PCR can be performed using genus- or species-specific oligonucleotides. In most cases, the diagnosis can be established by examining bone marrow aspirates. Splenic aspirates have the highest yields, but splenic aspiration is risky. Liver biopsy or aspiration of enlarged lymph nodes can also provide diagnostic material.

**Treatment**

Liposomal amphotericin B (3 mg/kg IV on days 1 to 5, 14, and 21) is the therapy of choice for most cases of leishmaniasis.11 Miltefosine (not available in the United States) and paromomycin have been shown to be effective in India for the treatment of visceral leishmaniasis.108,109 The dosage of miltefosine is 2.5 mg/kg/day in a single dose or, preferably, in two divided doses, orally for 28 days. In one trial, a single infusion of liposomal amphotericin B was not inferior to and was less expensive than conventional therapy with amphotericin B deoxycholate.110

**Cutaneous and Mucocutaneous Leishmaniasis**

**Etiology and Epidemiology**

Old World cutaneous leishmaniasis is caused by three species of *Leishmania* that belong to the *L. tropica* complex: *L. tropica* is present in the Middle East and the Mediterranean littoral; *Leishmania major* is found in the Middle East, Arabia, the former Soviet Union, India, and sub-Saharan Africa; and *Leishmania aethiopica* is found principally in Ethiopia and Kenya. *Phlebotomus* sandflies are the principal vectors, although direct contact with an ill person may, in rare cases, result in infection. Infections that are caused by *Leishmania* can be acquired by travelers, as well as by military and other personnel residing in endemic areas. Military personnel in the Middle East have acquired
New World cutaneous leishmaniasis arises from infection with parasites belonging to the *L. mexicana* group or the *L. braziliensis* (subgenus *Viannia*) group. The *Viannia* subgenus is distinguished from the *Leishmania* subgenus by the differences in development in the sandfly gut. The patterns of illness vary with the nature of the infecting leishmanial organisms, which are found in different regions of North, Central, and South America [see Table 3]. In areas of Central and South America, infection with organisms of the *L. mexicana* group produces cutaneous leishmaniasis. A few autochthonous cases have been found in Texas. Infections with strains of *Leishmania viannia*, which are endemic in various areas of South America, cause cutaneous leishmaniasis and, in a small percentage of those infected, result in the later development of mucocutaneous leishmaniasis. Such mucocutaneous disease (espundia) involves the nasal or oropharyngeal mucosa, or both, and may prove fatal. All of these New World leishmanial parasites are transmitted principally by sandfly vectors, although direct human contact may also bring about infection. Various mammals are naturally infected reservoirs of the organisms.

**Pathogenesis**

Both Old World and New World forms of leishmaniasis are initiated when the bite of an infected sandfly injects promastigotes into the human host. The organisms enter tissue macrophages and capillary endothelial cells, become amastigotes, and multiply. A granulomatous inflammatory response develops at the bite site. With local ischemia, the lesion ulcerates [see Figure 17]; a bacterial infection of the necrotic area may extend the ulceration. Resolution of clinical infection is associated with CD4+ T helper type 1 cells that secrete interferon gamma in response to *Leishmania*. Progression of disease appears to be associated with an immune response dominated by interleukin-10, a cytokine that suppresses other cytokine responses.

**Diagnosis**

**Clinical features** In Old World cutaneous leishmaniasis, after an incubation period of weeks to months, a papule develops at the inoculation site. This area may resolve spontaneously. More frequently, it ulcerates, and a shallow circular lesion appears that is several centimeters in diameter and has a raised margin. Bacterial superinfection may lead to regional lymphadenopathy. The lesions are often solitary, but multiple bites can produce several concurrent lesions. Healing of the lesions is slow, sometimes requiring more than a year.

*L. mexicana* infections produce a single lesion or a few lesions on exposed surfaces of the body such as the face and ear.111 The ulcer usually heals spontaneously over 6 months. An ulcer involving the ear, however, may cause extensive destruction of the pinna. *L. viannia* infection is associated with lesions on the skin or mucous membranes, which may be multiple and may become very large, especially when bacterial superinfection develops. Cutaneous lesions caused by *L. braziliensis* are much less likely to heal spontaneously than those caused by *L. mexicana*.111 *L. viannia braziliensis* species can invade regional lymph nodes and cause progressive ulcerations along the lymphatics or extend locally and involve mucous membranes. Often the infection metastasizes to the nasal or oral mucosa after an intervening period of months to years. Metastatic lesions can erode the nasal septum or the hard palate or soft palate. Some patients die of malnutrition or bacterial infection.

Diffuse cutaneous leishmaniasis occurs in parts of Ethiopia, Venezuela, Brazil, and the Dominican Republic. The initial nodule does not ulcerate; instead, multiple nodules evolve on the body. Leishmanial organisms abound in the lesions. Patients with this form of leishmaniasis have a deficiency of cell-mediated immunity, which is similar to the defective immunity that occurs in patients with lepromatous leprosy.

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**Table 3. New World Cutaneous Leishmaniasis**106
**Laboratory findings** A definitive diagnosis is made by demonstrating amastigotes on stained smears [see Figure 18] of a biopsy or of scrapings from the border of an ulcer. Alternatively, the diagnosis can be made by culturing amastigotes on NNN medium inoculated with lesion material. Use of PCR targeting parasite kinetoplast DNA has allowed detection of organisms that might be missed on histologic section or culturing. Moreover, this technique serves as a rapid method for speciating *L. mexicana* and *L. viannia*. In contrast to *L. tropica* and *L. mexicana* amastigotes, which can be readily cultured and are abundant in lesions, *L. viannia* amastigotes are difficult to culture and are sparse in lesions, especially those of mucocutaneous leishmaniasis. Organisms of these species cannot be distinguished morphologically, and specialized immunologic, enzymatic, or nucleic acid studies may be needed for definitive speciation. Except in diffuse cutaneous leishmaniasis, the leishmanin skin test is usually positive.

**Treatment**

Although the pentavalent antimonial compounds sodium stibogluconate (20 mg/kg/day IV or IM of pentavalent antimonial for 20 days) and meglumine antimoniate are the general treatments of choice for both Old World and New World cutaneous leishmaniasis,11 optimal therapeutic regimens with these or alternative agents have not been rigorously defined. Individual species and geographic strains of *Leishmania* respond differently to treatment and differ in their capacity to cause mucosal disease or to heal spontaneously. Furthermore, it is difficult to distinguish infective species solely on clinical grounds. Therefore, progress in developing rational plans for appropriate treatment has been impeded. Advice on treatment of leishmaniasis is available from the CDC's Division of Parasitic Diseases [see Sidebar Protozoan Infection Information on the Internet]. *Leishmania* organisms have ergosterol in their membrane and are sensitive to amphotericin-containing preparations and azole 14-demethylease inhibitors. Amphotericin B and lipid preparations of amphotericin have been shown to be effective for mucosal leishmaniasis resistant to antimonial compounds. For Old World cutaneous disease with *L. major*, treatment with fluconazole (200 mg daily for 6 weeks) was effective in one trial112; nevertheless, experts do not favor the use of fluconazole for most cases of cutaneous leishmaniasis because of borderline efficacy. Pentamidine and topical paromomycin have been used as alternatives for treatment of cutaneous disease.11

**Trypanosomiasis**

**American Trypanosomiasis (Chagas Disease)**

Infection with the protozoan hemoflagellate *Trypanosoma cruzi* produces American trypanosomiasis, or Chagas disease, which has acute and chronic forms.113

**Etiology and Epidemiology**

Two forms of *T. cruzi* infect mammals: trypanosomes, which are carried in the blood, and amastigotes, which are found in infected cells. The parasite is transmitted by several genera of reduviid or triatomid bugs, commonly called assassin bugs because they prey on other insects or kissing bugs because of their predilection for biting the face [see Figure 19]. Nonhuman reservoirs include cats, dogs, rats and other rodents, raccoons, opossums, and armadillos. The local pattern of transmission of *T. cruzi* infections depends on the species of reduviid bug, the sylvatic and domestic mammalian reservoirs, and housing conditions. Infected animals living around dwellings, usually in rural areas, are likely to transmit the organism to reduviid bugs. These infected bugs inhabit niches in walls and ceilings of poorly constructed houses. At night, they come out and feed on the blood of sleeping humans by biting exposed skin areas such as the face. During their meal, the insects
excrete feces containing infective-stage metacyclic trypansomes, which enter the host through the bite wound, cutaneous abrasions, or mucous membranes of the conjunctiva or lips.

**Figure 17.** An ulcerative lesion of *Leishmania (Viannia) braziliensis* acquired in the jungles of Belize.

Although reduviid vectors are present in the United States and infected mammals have been found in several states, the opportunity for transmission of infections seems limited. Only rare autochthonous cases of Chagas disease have been reported in the United States.\textsuperscript{114,115} In rural areas of Central and South America, human infections are common where conditions favor access of infected bugs to persons.\textsuperscript{113} In addition, infections may be transmitted by blood transfusions, across the placenta, to laboratory workers, and, in rare instances, by ingestion of foodstuffs contaminated with the excreta of infected reduviid bugs.

**Figure 18.** Amastigotes are demonstrated on Giemsa-stained biopsy tissue from an ulcer in a patient with Old World cutaneous leishmaniasis.

**Pathogenesis**

Both acute and chronic forms of Chagas disease are recognized. The acute form, which develops soon after infection, principally affects children in endemic areas.\textsuperscript{113} Within several days of infection, an indurated erythematous lesion termed a chagoma appears at the inoculation site. When the inoculation site is the conjunctiva, unilateral periorbital edema develops, called the Romana sign [see Figure 20]. After about 2 weeks, trypansomes appear in the blood and invade cells, generally those of mesenchymal origin, where they multiply as intracellular amastigote forms. They are even able to proliferate in macrophages, unless the macrophages have been activated by interferon gamma. The resultant intracellular pseudocysts rupture, releasing both trypanosomal and amastigote forms. Both of these forms are infectious to mammalian cells. A combination of humoral and cell-mediated immunity controls high-level parasitemia, but despite this relative immunity, the host remains parasitemic at low levels for life. The reasons *T. cruzi* is able to establish lifelong infection are incompletely understood, but contributors include the following: evasion of complement-mediated cytolysis, intracellular growth in phagocytes, and the display of thousands of antigenically distinct surface proteins that appear to disrupt an effective cell-mediated immune response. Only 10 to 30% of infected persons develop chronic forms of Chagas disease. The reasons some persons develop disease and others do not are poorly understood and may involve the initial parasite burden, continuous inflammation in critical areas, induction of autoimmunity by the chronic infection, or some combination thereof.
CDC Drug Service

http://www.cdc.gov/ncidod/srp/drugs/drug-service.html

Information on special immunobiologic agents and drugs distributed through the CDC Drug Service, Scientific Resources Program, and the Division of Quarantine of the National Center for Infectious Diseases

Emerging Infectious Diseases

http://www.cdc.gov/ncidod/eid

The online edition of the peer-reviewed journal published by the CDC's National Center for Infectious Diseases

http://www.cdc.gov/DiseasesConditions/

World Health Organization

Division of Control of Tropical Diseases

http://www.who.int/ctd

Scientific publications and other information from the WHO's lead program for the control of tropical diseases

Special Programme for Research and Training in Tropical Diseases

http://www.who.int/tdr

Disease information, image library, publications, research guidelines, grant applications, and other information from a scientific collaboration of the United Nations Development Program, UNICEF, the World Bank, and the WHO

Karolinska Institutet: Parasitic Diseases


Figure 19. Triatoma infestans, commonly known as assassin bugs or kissing bugs, are vectors for Chagas disease.

Figure 20. Periorbital edema of the right eye (Romana sign) is evident in a child from Panama with acute Chagas disease.

Diagnosis
Clinical features During the acute phase, the patient may experience intermittent or continuous fever, malaise, an evanescent rubelliform or petechial rash, hepatosplenomegaly, lymphadenopathy, nonpitting edema of the face or extremities, tender subcutaneous nodules termed hematogenous chagomas, and, in infants, diarrhea. In severe cases, fatal myocarditis or meningoencephalitis can develop. The acute phase is usually self-limited: patients eventually become asymptomatic, and parasites can no longer be detected in the bloodstream except by PCR or by having reduviid bugs feed on the patient's blood and then examining the bugs for evidence of infection.

The chronic form of Chagas disease may become manifest either after an acute infection or, more commonly, after a clinically inapparent infection. It usually arises in the second or third decade of life and progresses over subsequent decades. Chronic complications of Chagas disease result from the destruction of autonomic ganglia and from myositis; the pathogenesis of these lesions is not understood. The organ most frequently involved is the heart, which develops biventricular hypertrophy and a mononuclear cell infiltrative myocarditis. Conduction disorders often include right bundle branch block, partial or complete atrioventricular block, and premature ventricular contractions. Sudden death has occurred in patients with Chagas disease, and fatalities have also resulted from complications of heart failure.

The GI tract is the second most frequently involved organ system. The disease causes denervation leading to impaired motility and dilatation, which results in megaesophagus and megacolon. Neurologic disease is the third most frequently observed complication of chronic Chagas disease; it manifests primarily as peripheral neuropathies.

Congenital infections are usually responsible for premature births. Such premature infants may have hepatosplenomegaly, abdominal distention, cardiomegaly, megaesophagus, and meningoencephalitis.

In HIV-infected patients, reactivation of Chagas disease can produce cerebral masses and, in patients with acute infections, necrotizing encephalitis. These CNS infections cannot be distinguished radiographically from toxoplasmosis, and biopsy must be performed in patients with risk factors for both infections.

Laboratory findings In acute Chagas disease, the total leukocyte count often exceeds 18,000 cells/μL (70 to 90% lymphocytes), and parasites are often demonstrable in the blood or in specimens from bone marrow, lymph nodes, CSF, pericardial fluid, or other involved areas. On unstained blood smears, motile trypanosomes may be seen; on Giemsa-stained smears, the organisms appear as C-shaped forms [see Figure 21]. If smears do not reveal the organisms, trypanosomes may be found in stained sediment obtained by centrifuging several milliliters of blood after lysing the erythrocytes. Organisms may be cultured from blood on NNN medium or in blood broth. Alternatively, blood may be injected into a laboratory rodent, whose blood is then monitored for evidence of parasitemia. Xenodiagnosis, which is not readily available, is one of the most sensitive diagnostic techniques to detect parasites. In this procedure, laboratory-reared reduviid insects are allowed to feed on a patient. If the blood ingested by the insects contains trypanosomes, the insects will become infected; such infection can be detected by subsequent examinations of the insects’ feces for excreted parasites. PCR to detect circulating parasites is becoming available in clinical laboratories, is as sensitive as xenodiagnosis, and is easier to implement than xenodiagnosis. Blood containing trypanosomes is infectious and should be handled with care.

In chronic Chagas disease, a chest x-ray may reveal biventricular cardiomegaly and congestive heart failure. Electrocardiographic abnormalities are commonly seen, particularly right bundle branch block. Barium swallow or enema examinations may demonstrate megaesophagus or megacolon disease. Methods other than PCR or xenodiagnosis are rarely capable of detecting organisms in the blood. Similarly, it is difficult to demonstrate parasites in affected tissues; commonly, only mononuclear inflammatory cells or fibrosis is seen in pathologic specimens. Indirect fluorescent antibody and enzyme immunoassay T. cruzi serology tests are performed by the CDC. Both of these tests rely on crude antigens derived from cultured insect forms of T. cruzi; individuals infected with Leishmania may have cross-reactive antibodies that give a false positive result on these tests.
Although these serology tests may be positive, their results may only reflect past infection and fail to establish a link between clinical findings and active Chagas disease.

Increasingly, clinicians are asked to consult on patients found to be seropositive after blood donations. The clinician should verify that the blood bank did both the screening and confirmatory radioimmunoprecipitation assay for diagnosis and that the patient is from an endemic area (this includes the southeastern United States); the clinician should then speak with the CDC’s Division of Parasitic Diseases (770-488-7775; email ncipdbpi@cdc.gov) about the advisability of therapy. More information is available at the CDC’s Chagas disease Web page, [http://www.cdc.gov/chagas/hcp.html](http://www.cdc.gov/chagas/hcp.html).

**Figure 21.** A trypanosomal form of *Trypanosoma cruzi* is visible on this Giemsa-stained blood smear.

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**Treatment**

Optimal therapy for *T. cruzi* infections remains to be established. Nifurtimox (available from the CDC Drug Service) eliminates parasitemia [see Sidebar Protozoan Infection Information on the Internet]. It should be administered to patients with acute disease and to patients with chronic disease and demonstrated parasitemia.\(^{11}\) There is some debate about whether it has efficacy in patients with chronic disease in whom parasitemia has not been demonstrated. Side effects are frequent and include hemolytic anemia in patients with G6PD deficiency, peripheral neuritis, and psychosis. Anecdotal evidence suggests that interferon gamma combined with nifurtimox may shorten the duration of acute disease. Some authors believe that benznidazole is the drug of choice for treating *T. cruzi* infection, but it is not available in the United States and is associated with a variety of toxicities, including granulocytopenia, rash, and peripheral neuropathy.\(^{113}\) Itraconazole and other azoles have activity in blocking the ergosterol synthesis of *T. cruzi*, and itraconazole may have some efficacy against chronic disease.\(^{117}\) Although some small studies have shown benefit of benznidazole or nifurtimox treatment of early chronic Chagas cardiac disease, most experts agree that the cardiovascular and GI complications of chronic Chagas disease should be managed medically. Surgical treatment may be required for megacolon, and balloon dilatation of the lower esophageal sphincter may be needed for megaesophagus. If cardiac transplantation is contemplated, preparations to provide antitrypanosomal therapy should be made because reactivation of latent parasitemia can occur as a complication of the immunosuppressive drugs.

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**African Trypanosomiasis**

*Etiology and Epidemiology*

African trypanosomiasis, or sleeping sickness, is an acute or chronic parasitic disease caused by protozoan hemoflagellates of two *Trypanosoma brucei* subspecies. The disease is prevalent in a broad periequatorial belt across Africa. Two forms occur in humans: West African and East African (or Rhodesian) sleeping sickness. West African trypanosomiasis is present in the tropical forests of West and Central Africa and is caused by *T. brucei gambiense*, a parasite not carried in any major animal reservoir. In contrast, *T. brucei rhodesiense*, which produces East African sleeping sickness, is prevalent in the savanna and woodlands of tropical East Africa and exists in wild animal reservoirs. Visitors to game parks are at risk for acquiring East African trypanosomiasis.\(^{118}\) Both types of African trypanosomiasis are transmitted by species of tsetse flies (genus *Glossina*), with the riverine *Glossina palpalis* group transmitting *T. brucei gambiense* and the savanna *Glossina morsitans* group transmitting *T. brucei rhodesiense*. *T. brucei* species are able to exist as chronic infections in the bloodstream and, later, in the CNS partly because of their ability to undergo sequential antigenic variation of the major variant surface glycoprotein (VSG) that covers the
trypanosome. As antibodies develop to a given VSG, most of the trypanosomes are eliminated from the circulation, but variants expressing an antigenically distinct VSG grow out and continue the infection. The combination of thousands of genes and pseudogenes for VSGs, plus an ability to create new VSG genes by recombination, allows the trypanosome to stay ahead of the immune response.

**Diagnosis**

**Clinical features** Within a few days to a couple of weeks after inoculation of organisms by a tsetse fly, a trypanosomal chancre may develop at the site of the insect bite, which is usually on exposed skin. The chancre initially appears as a papule and, within 2 weeks, evolves into an inflamed, painful nodule that subsequently resolves spontaneously. Trypanosomal chancres commonly occur in non-African patients but usually do not develop in African patients.

During the next phase of African trypanosomiasis, the hemolymphatic phase, trypanosomes invade the bloodstream and lymph nodes. In Africans, the development of symptoms in this phase occurs slowly, over several months; presenting symptoms include fever, lymphadenopathy, headache, and debility. In non-Africans, however, the onset is abrupt and early, often concomitant with the development of the chancre. In non-Africans, episodes of high fever that last 1 to 7 days and recur after afebrile periods are prominent. Associated symptoms include chills, headache, malaise, and anorexia. Soft, nontender lymphadenopathy develops more prominently with West African trypanosomiasis and may include enlargement of posterior cervical nodes (Winterbottom sign). A characteristic rash, which can be observed on light-skinned individuals, occurs about 6 to 8 weeks after infection and may appear as evanescent, circinate, erythematous patches, usually located on the trunk.

The next phase in the evolution of African trypanosomiasis is CNS invasion leading to diffuse meningoencephalitis or meningomyelitis. In West African trypanosomiasis, which is a slowly evolving illness, the symptoms of sleeping sickness may not develop until years after infection. Increasing lassitude and indifference are complicated by progressive neurologic compromise leading to coma and death by inanition or intercurrent infection. In contrast, the pace of East African trypanosomiasis is much more rapid, and CNS involvement may develop earlier. Even before CNS involvement, such manifestations as somnolence, personality changes, and an inability to concentrate may appear. Pancarditis often complicates acute East African trypanosomiasis and may cause death before the onset of CNS disease. Because East African trypanosomiasis may be acquired by visitors to game preserves and is an acute febrile illness, it may be mistaken for malaria and must be considered in the differential diagnosis of a febrile patient returning from an endemic area.

**Laboratory findings** The total leukocyte count is usually normal, but the differential may show mononucleosis of 50 to 70%. Serum IgM levels rise 1 to 2 weeks after parasites appear in the blood and may increase to more than seven times the normal level. The definitive diagnosis is made by detecting trypanosomal organisms in blood, bone marrow, fluid from enlarged lymph nodes, or centrifuged CSF [see Figure 22]. Trypanosomes may be seen moving rapidly on wet mounts of blood or other aspirates. Organisms stained with Wright, Giemsa, or Leishman stain may be found in a chancre 48 hours before they appear in the blood. If examination of peripheral blood is unrevealing, trypanosomes may be found in fluid aspirated from involved lymph nodes or among buffy coat cells. Even in cases in which neurologic symptoms are absent, CNS disease must be excluded by performing a lumbar puncture. Even if trypanosomes are not seen in centrifuged CSF, CNS involvement may still exist, as indicated by elevations of the cell count or of protein or IgM concentrations. Serologic tests for African trypanosomiasis exist, but treatment is generally reserved for parasitologically confirmed cases because the therapy is so toxic.

**Treatment**

Treatment of African trypanosomiasis depends on the infecting species and the stage of disease. Pentamidine is effective therapy for early (hemolymphatic) stage disease caused by *T. brucei gambiense* infections; efornithine is the treatment of choice for the later CNS stages. The early
stage of *T. brucei rhodesiense* infection East is treated with suramin, and the CNS stage is treated with melarsoprol.\textsuperscript{120} Pentamidine is available by prescription in the United States; efornithine, suramin, and melarsoprol must be obtained from the CDC Drug Service [see Sidebar Protozoan Infection Information on the Internet]. Each of these drugs has a variety of toxicities, some of them serious; notably, melarsoprol treatment is itself fatal in 4 to 6\% of patients. Thus, patients must be closely monitored and expert consultation is advised.

**Figure 22.** *Trypanosoma brucei* parasites, the cause of African sleeping sickness, are evident on this Giemsa-stained blood smear.

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