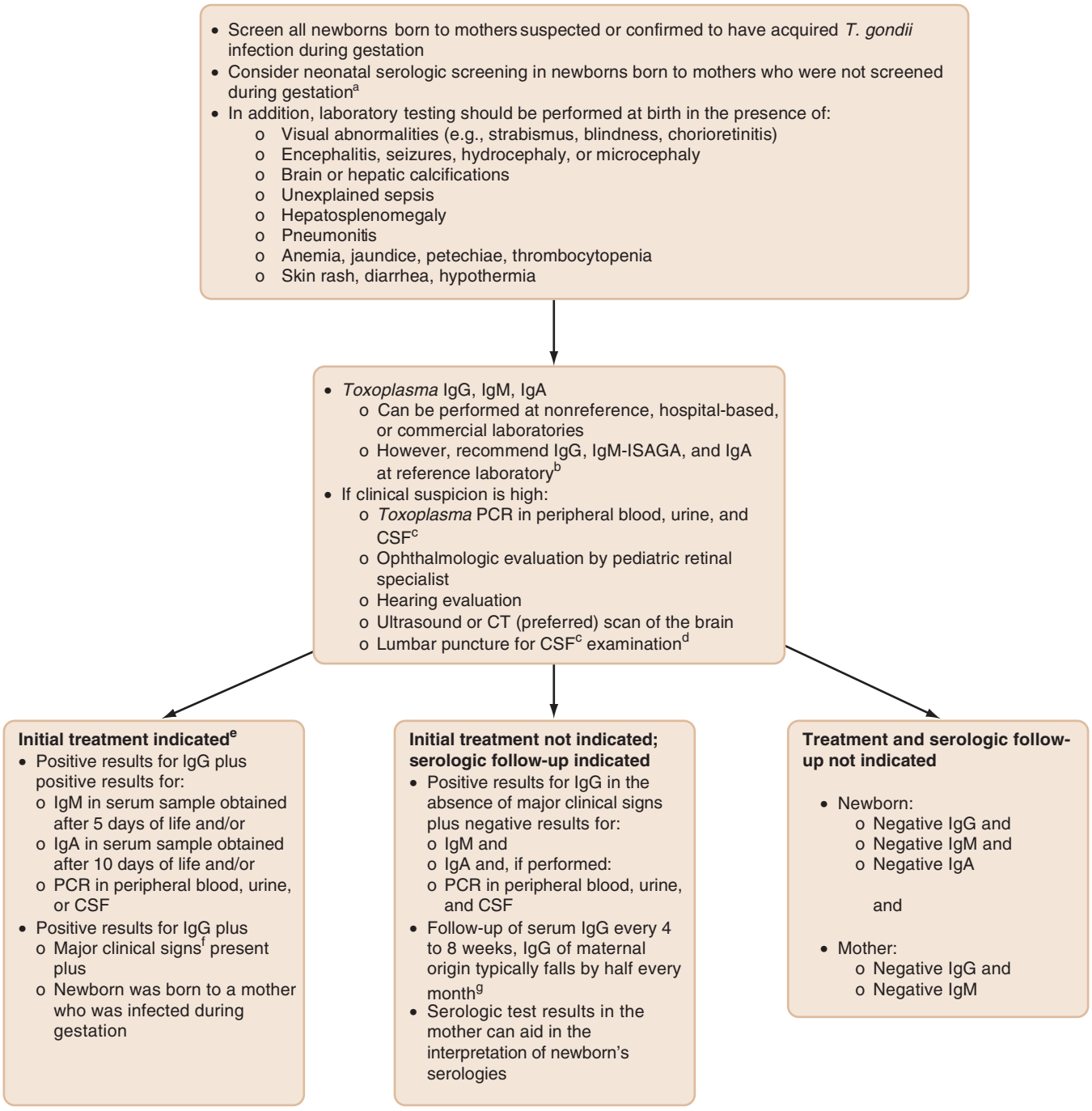

FIG. 278.9 Diagnostic approach and management algorithm of the newborn whose mother has been suspected or confirmed to have acquired toxoplasmosis during gestation. *CSF,* Cerebrospinal fluid; *CT,* computed tomography; *IgG, IgM,* and *IgA,* immunoglobulins G, M, and A, respectively; *ISAGA,* immunosorbent agglutination assay; *PCR,* polymerase chain reaction. [a]Consider consultation with a physician expert in management of toxoplasmosis during pregnancy (e.g., in the United States, Palo Alto Medical Foundation–*Toxoplasma* Serology Laboratory [PAMF-TSL], www.pamf.org/serology/; 650-853-4828; e-mail, toxolab@pamf.org or US [Chicago] National Collaborative Treatment Trial Study, 773-834-4152). [b]Consider sending serum sample to a reference laboratory (e.g., PAMF-TSL). [c]Testing CSF assumes that lumbar puncture is clinically indicated, deemed safe, and feasible. [d]In an attempt to confirm the diagnosis of congenital toxoplasmosis, CSF should be sent for cell count and differential (congenital toxoplasmosis is one of the few causes of eosinophilic meningitis), protein (congenital toxoplasmosis is one of the few causes of extreme elevation of CSF protein), glucose, and *T. gondii* PCR. [e]The recommended regimen is pyrimethamine plus sulfadiazine plus folinic acid (see text). [f]Major clinical signs are referred here: chorioretinitis, brain calcifications, and hydrocephalus. [g]Maternally transferred IgG antibodies usually decline and disappear within 6 to 12 months of life.

obtained from peripheral blood (and not from the umbilical cords) are preferred. In a retrospective study of 164 untreated infants age 0 to 180 days, in the United States, *T. gondii*–specific IgM, IgA, and IgE antibodies were demonstrable in 86.6%, 77.4%, and 40.2% of the infants, respectively.[338] Testing for IgM and IgA antibodies increased the sensitivity of making the diagnosis of congenital toxoplasmosis to 93%, compared with testing for IgM or IgA alone. The sensitivity of the IgM and IgA has been reported to be somewhat lower in cohorts of treated (prenatal treatment) infants: 64% to 70% for IgM, 53% to 65% for IgA, and 66% to 81% for both.[458]

If IgG antibodies are detected but serologic tests for IgM and IgA antibodies are negative and *T. gondii* is not isolated, follow-up serologic

testing in suspect cases is indicated to attempt to establish the diagnosis. Maternally transferred antibodies usually decline and disappear within 6 to 9 months.

Studies using the Western blot technique have shown that maternal and infant sera may recognize different *T. gondii* antigens when the infant is congenitally infected.[459,460] Combining Western blot with conventional serologic analysis (i.e., IgG, IgM, and IgA tests) has been reported to be more sensitive for the diagnosis of congenital toxoplasmosis at birth and within the first 3 months of life than either test alone.[460–462] Recently, three IgM-bands at 75, 90, and 100 kilodaltons (also known as the "IgM triplet") have been reported to increase the sensitivity of the diagnosis of congenital toxoplasmosis to 95.8% when combined with prenatal and serologic neonatal tests.[463]

Additional diagnostic methods that have been used successfully to diagnose the infection in infants are direct demonstration of the organism by isolation in mice or cell culture (e.g., placental tissue, body fluid) and PCR in body fluids (e.g., CSF, blood, and urine).[407,464–468] In a study of 161 consecutive infants, CSF PCR was positive in 27 of the 58 (46.5%) congenitally infected infants and was negative in each of the 103 infants without congenital toxoplasmosis.[468] Evaluation of infants with suspected congenital toxoplasmosis should always include ophthalmologic examination, radiologic studies (particularly to detect the presence of cerebral calcifications; if feasible, CT is preferred over ultrasound), and examination of CSF. A more detailed discussion of diagnostic procedures in congenitally infected infants is available from Peyron and colleagues.[9]

In the absence of a systematic screening program for pregnant women, a secondary prevention program that consists of serologic testing of all newborns for IgM antibodies against *T. gondii* has been implemented in Massachusetts.[469,470] Using routine screening of all newborns, congenital infection was confirmed in approximately 1 in 12,000 infants. Greater than 90% of these were identified only through neonatal screening and not through initial clinical examination.

In infants with congenital toxoplasmosis or congenital infection, a rebound in IgG and IgM antibody titers is frequently observed after discontinuation of therapy. In our experience such a serologic rebound has not been shown to be clinically significant.[9]

THERAPY

Currently recommended drugs against *T. gondii* act primarily against the tachyzoite form and thus do not eradicate the encysted form (bradyzoite). Pyrimethamine is considered to be the most effective anti-*Toxoplasma* agent, and it should, if possible, always be included in a combination drug regimen used against the parasite. Pyrimethamine is a folic acid antagonist. The most common side effect is dose-related suppression of the bone marrow, which may be decreased by concomitant administration of folinic acid (calcium leucovorin). It is not well established how often a blood count should be obtained; a reasonable strategy would be to check a peripheral blood cell and platelet count twice weekly until hematologic parameters have stabilized in a nontoxic range, and then every 2 to 4 weeks. Folinic acid should be administered concomitantly to avoid bone marrow suppression. The parenteral form of folinic acid is well absorbed orally, and 10 to 20 mg/day of folinic acid (up to 50 mg/day is used in AIDS patients) may be given orally (e.g., with orange juice at the same time as the pyrimethamine). Whereas folinic acid does not inhibit the action of pyrimethamine on tachyzoites, folic acid does and should not be used in patients being treated with pyrimethamine. Less serious side effects of pyrimethamine include GI distress, rash, headaches, and a bad taste in the mouth.

Unless there are circumstances that preclude the use of more than one drug, there is no role for monotherapy in the treatment of toxoplasmosis. A second drug, such as sulfadiazine or clindamycin, should be added. Sulfadiazine acts synergistically with pyrimethamine; most other sulfonamides have inferior activity. The patient must maintain a good urine output to prevent crystalluria and oliguria. The most common side effects associated with sulfadiazine are skin rashes, which may be life threatening,[471] and crystal-induced nephrotoxicity.[472] Worsening encephalopathy, hallucinations, or a new onset of psychiatric symptoms in patients with AIDS may be sulfadiazine induced and must be considered in the patient who is nonresponsive to otherwise appropriate anti-*Toxoplasma* treatment.[473] A drug rash with sulfonamide therapy does not necessarily preclude its use because successful desensitization protocols have been reported.[474,475] Clindamycin appears to act by targeting translation in the apicoplast of *T. gondii*.[40] Adverse reactions to clindamycin include rash, nausea, vomiting, and diarrhea, which may be associated with *Clostridioides difficile* (formerly *Clostridium difficile*) infection. Myopathy with electromyographic abnormalities and elevated serum creatine phosphokinase levels have been described.[476]

Although clinical experience with TMP-SMX is more limited, this drug combination, which targets folate metabolism in a manner similar to pyrimethamine plus sulfadiazine, has documented activity and can be used in patients requiring parenteral therapy or those in whom cost of pyrimethamine becomes prohibitive.[477] Atovaquone combined with pyrimethamine or sulfadiazine, or in unusual circumstances as a single agent, is another less-well-studied alternative for patients who can be treated with oral therapy. The role of other drugs, including azithromycin, clarithromycin, and dapsone, is less clear; they should only be used as alternatives when the regimens described earlier cannot be used and should be used in combination with pyrimethamine whenever possible.

Spiramycin has been used in pregnant women to reduce transplacental transmission to the fetus; it has not been shown to be effective for acute therapy, maintenance therapy, or primary prophylaxis of TE in AIDS patients. There is no evidence that spiramycin is teratogenic.

Although drugs used to treat toxoplasmosis in the setting of different clinical entities are basically the same, careful attention should be given to the dose and dosing regimen. Recommended doses in immunocompromised patients are usually higher than those in immunocompetent patients. For instance, the recommended dose of pyrimethamine for patients with TE is 50 to 75 mg/day after a loading dose of 200 mg, whereas the dose to treat fetal infection during pregnancy is 25 to 50 mg/day after a loading dose of 100 mg/day for 2 days in the mother.

Therapy Regimens in Specific Clinical Entities

Toxoplasmosis in the Immunocompetent Patient

Treatment of immunocompetent adults with the lymphadenopathic form is rarely indicated; this form is usually self-limited. One small randomized trial demonstrated efficacy of a 1-month course of TMP-SMX in reducing lymphadenopathy (65% response vs. 22% for placebo).[478] If visceral disease is clinically overt or symptoms are severe or persistent, treatment may be indicated for 2 to 4 weeks, followed by reassessment of the patient's condition (Table 278.2). Infections acquired by laboratory accident or transfusion of blood products are potentially more severe, and patients who have been infected in these ways probably should be treated (see Table 278.2).

Toxoplasmosis in the Immunodeficient Patient

Because experience with treatment of toxoplasmosis in immunodeficient patients has been most extensively studied in patients with AIDS, this section focuses primarily on this group of patients. However, information on treatment in AIDS patients likely can, in large part and in the absence of data, be extrapolated directly to other immunodeficient patients (see Table 278.2).

If left untreated, toxoplasmosis in immunodeficient patients is often lethal. Treatment is recommended for 4 to 6 weeks after the resolution of all signs and symptoms (often for 6 months or longer). At one medical center, 80% of non-AIDS immunodeficient patients with toxoplasmosis improved with specific therapy.[479] This rate of improvement is similar to that observed in appropriately treated AIDS patients with TE.[435,480] Chronic (latent) asymptomatic infection in immunodeficient patients is not treated.

The exact dosing schedule for the treatment of toxoplasmosis in non-AIDS immunocompromised patients has not been defined. However, useful information in this regard has resulted from studies performed in AIDS patients with toxoplasmosis.

Therapy for toxoplasmosis in AIDS patients includes acute (primary or induction) treatment, chronic maintenance treatment (secondary

TABLE 278.2 Treatment Regimens for Toxoplasmosis in Immunocompetent and Immunocompromised Patients

	IMMUNOCOMPETENT PATIENTS[b]	IMMUNOCOMPROMISED PATIENTS, INCLUDING THOSE WITH AIDS, TRANSPLANTS, CANCER, OR TAKING IMMUNOSUPPRESSOR DRUGS[c]
Preferred Regimen		
Pyrimethamine (PO)	50 mg q12h for 2 days, followed by 25–50 mg daily	200-mg loading dose, followed by 50 (<60 kg) –75 mg/day (≥60 kg)
plus		
Folinic acid[d] (PO)	10–20 mg daily (during and 1 wk after therapy with pyrimethamine)	10–20 mg daily (up to 50 mg/day) (during and 1 wk after therapy with pyrimethamine)
plus		
Sulfadiazine (PO)	1 g q6h	1000 (<60 kg)–1500 mg (≥60 kg) q6h
Preferred Alternative Regimens		
Pyrimethamine–folinic acid	Same doses as above	Same doses as above
plus		
Clindamycin (PO or IV)	300 mg q6h	600 mg q6h (up to 1200 mg q6h)
or		
Atovaquone (PO)	1500 mg PO twice daily	1500 mg PO twice daily
Trimethoprim-sulfamethoxazole (PO or IV)	10 mg/kg/day (trimethoprim component) divided in two to three doses	10 mg/kg/day (trimethoprim component) divided in two to three doses (doses as high as 15–20 mg/kg/day have been used)
Alternative Regimens With Limited Supportive Data[e]		
Pyrimethamine–folinic acid	Same doses as above	Same doses as above
plus		
Clarithromycin (PO)	500 mg q12h	500 mg q12h
or		
Dapsone (PO)	100 mg/day	100 mg/day
or		
Azithromycin (PO)	900–1200 mg/day	900–1200 mg/day
Sulfadiazine (PO)	Same doses as above	Same doses as above
plus		
Atovaquone (PO)	Same doses as above	Same doses as above

[a]Assistance is available for the diagnosis and management of toxoplasmosis at the Palo Alto Medical Foundation–*Toxoplasma* Serology Laboratory; Palo Alto, CA; www.pamf.org/serology/; 650-853-4828; toxolab@pamf.org.
[b]Indicated in patients with (1) ocular disease associated with primary infection or reactivation of latent infection; (2) severe disease, including myocarditis, myositis, hepatitis, pneumonia, brain, or skin lesions and lymphadenopathy; (3) persisting symptoms; and (4) laboratory accidents.
[c]After the successful use of a combination regimen during the acute/primary therapy phase, same agents at half doses are usually used for maintenance or secondary prophylaxis; for pyrimethamine, use 25 mg (<60 kg) to 50 mg/day (>60 kg); for clindamycin, use 600 mg PO every 8 hours.
[d]Folinic acid (leucovorin); should always be given with pyrimethamine to minimize toxicity; folic acid must not be used as a substitute for folinic acid.
[e]These agents have been used in clinical studies with small numbers of patients and have response rates lower than the standard regimens (see text for references). They should be used only in patients who are intolerant of the standard regimens.
AIDS, Acquired immunodeficiency syndrome; *IV,* intravenously; *PO,* orally.

prophylaxis), and primary prophylaxis. There are no convincing data from prospective, carefully designed trials to allow the recommendation of monotherapy for induction, maintenance, or primary prophylaxis. Because relapse occurs in up to 80% of cases[471] after the discontinuation of primary therapy, maintenance therapy is recommended for all patients until the CD4 count rises above 200 cells/mm^3 for at least 6 months in response to ART (plasma HIV viral load will often be below detection limits during this period).

Acute therapy should be for at least 3 weeks,[100] and up to 6 weeks or more may be required for more severely ill patients who have not achieved a complete response. Pyrimethamine combined with sulfadiazine and folinic acid is the therapy of choice for AIDS patients with toxoplasmosis and is the standard to which experimental regimens should be compared. This regimen is associated with clinical response in 68% to 95% of patients with TE.[480,481] Unfortunately, up to 40% of patients develop side effects from one or more of the drugs, often requiring discontinuation of one or both agents.[232,426] Pyrimethamine-clindamycin and folinic acid appear comparable in efficacy to pyrimethamine-sulfadiazine,[480,482] but this combination also has substantial toxicity. TMP-SMX[483–485] (at 10 mg/kg/day of the TMP component, divided in two doses) has shown efficacy similar to the pyrimethamine-sulfadiazine regimen (with a more rapid radiologic response in the TMP-SMX group) in a randomized pilot trial in 77 patients with AIDS[477]; this provides an alternative regimen for situations in which parenteral therapy is required or when pyrimethamine is unavailable or unafordable. An international, noncomparative study of atovaquone[486,487] (administered orally as a suspension), combined with either pyrimethamine or sulfadiazine as treatment for acute disease, demonstrated 6-week response rates of 75% (21/28 patients) for atovaquone-pyrimethamine and 82% (9/11) for atovaquone-sulfadiazine.[488] Serum levels of atovaquone may predict response but are not commercially available.[487] Doses of atovaquone lower than currently recommended for treatment (750 mg twice daily vs. 1500 mg twice daily) can often achieve therapeutic levels if not coadministered with efavirenz, which can reduce atovaquone levels by approximately 45%.[489] TMP-SMX and atovaquone both are active against *Pneumocystis,* and thus anti-*Pneumocystis* prophylaxis does not need to be administered when these drugs are used. Because clindamycin-pyrimethamine has no demonstrated anti-*Pneumocystis*

activity, additional prophylaxis (e.g., aerosolized pentamidine) needs to be coadministered if patients are at risk for developing *Pneumocystis* pneumonia.

In a 13-patient pilot study of TE using the combination of pyrimethamine, 75 mg/day, and clarithromycin, 1 g every 12 hours, 62% of patients had a complete and 23% a partial clinical response; 15% of patients died by week 3 of therapy,[490] and adverse events resulted in discontinuation of therapy in 27%. No long-term follow-up data are available, and no additional studies with this drug combination have been published. Doses of clarithromycin higher than 500 mg twice daily have been associated with increased mortality in HIV-infected patients receiving therapy for *Mycobacterium avium* infection and should not be used.[491,492]

Dapsone in combination with pyrimethamine has been reported anecdotally to be effective for the treatment of TE when used in an oral dose of 100 mg/day with 25 mg/day of oral pyrimethamine.[493] Doxycycline has had success in the treatment of TE in a few patients when used at 300 mg/day IV in three divided doses.[494] A dosage of 100 mg twice a day was given to six patients intolerant to pyrimethamine-sulfadiazine, but five had associated neurologic and radiologic recurrences while receiving the drug.[495] Further studies are needed to compare the relative efficacy and toxicity of these alternative regimens. Although azithromycin plus pyrimethamine is effective for the treatment of some cases of TE in AIDS patients, its use should be limited, based on results of a recent study demonstrating an inferior response rate, especially during maintenance therapy.[496,497] Alternative regimens used for acute therapy and their dosage schedules are listed in Table 278.2.

Corticosteroids are often given to patients with TE for the reduction of cerebral edema and raised intracranial pressure. The clinical response and survival in patients with TE who received corticosteroids in addition to antimicrobial therapy have been reported to be no different from that of those who received antimicrobial agents alone.[435] The use of these agents may complicate the interpretation of empirical therapy of TE because partial clinical and radiologic improvement may be seen solely resulting from a reduction in cerebral edema and inflammation or a response of CNS lymphoma; moreover, they may further compromise the immune systems of these already very immunodeficient patients. Their use thus should be limited to situations where clinically significant edema or a mass effect is present.

Seizures occur in up to 35% of patients with TE.[426] One retrospective study demonstrated a poorer outcome in those patients who received anticonvulsant therapy, compared with those who did not.[471] Whether this result represents a true drug effect or a selection bias, given that those receiving anticonvulsant therapy are likely to be more severely ill, is unclear. Anticonvulsant agents may be responsible for numerous side effects and drug interactions; for instance, potentially serious interactions can occur between agents such as carbamazepine, phenobarbital, or phenytoin and other drugs used to treat HIV infection, such as protease inhibitors. Anticonvulsant therapy is probably best administered only when seizures have occurred.[471]

The time to clinical response in AIDS patients with TE who were receiving appropriate anti-*Toxoplasma* therapy has been evaluated in a study that included an objective, graded neurologic examination.[435] Of those with a response, 91% improved with respect to at least half of their baseline abnormalities by day 14.[435] AIDS patients with presumed TE had some degree of improvement within 7 to 10 days of the initiation of appropriate anti-*Toxoplasma* therapy. By contrast, a significant number of patients with an alternative diagnosis, including lymphoma, exhibited signs of clinical deterioration as early as 3 to 5 days after the initiation of the empirical regimen for presumed TE.[435] Headaches and seizures were insensitive indicators for a response to therapy. In some cases toxoplasmosis has progressed to death despite the use of appropriate drug regimens.[480,482]

After successful primary therapy, drug dosages are generally decreased for maintenance therapy. No single maintenance regimen that is efficacious with an acceptable adverse reaction profile has yet been identified. Relapse of TE occurs in approximately 20% to 30% of patients who are receiving maintenance therapy, in part because of nonadherence to and patient intolerance of the prescribed regimen.[232] Pyrimethamine, 25 mg/day, plus sulfadiazine, 500 mg four times daily, has been associated with the lowest relapse rate[480] and is recommended unless there are contraindications or cost considerations preventing its use. When daily therapy with pyrimethamine-sulfadiazine was compared with a twice-weekly regimen for the prevention of recurrence of TE, the latter was found to be less effective.[498,499] Although a subsequent trial by the same group found that three-times weekly therapy was equivalent to daily therapy, the relapse rates for both groups (≈14.5/100 patient-years) was higher than was seen with daily therapy (4.4/100 patient-years) in the earlier study.[499,500] Patients receiving the pyrimethamine-sulfadiazine combination do not require another regimen for PCP prophylaxis. Whereas 25% of patients receiving pyrimethamine-clindamycin subsequently developed PCP,[501] no patient receiving pyrimethamine-sulfadiazine developed PCP.[499,501] One 17-patient study demonstrated that TMP-SMX could be safely substituted for pyrimethamine-sulfadiazine after a median of 24-months' maintenance therapy in patients also receiving ART; the major benefit was in decreasing pill burden.[502]

Because of drug toxicity, many patients are unable to continue taking the pyrimethamine-sulfadiazine combination for maintenance therapy. A higher relapse rate has been reported with the use of pyrimethamine-clindamycin compared with pyrimethamine-sulfadiazine for chronic maintenance of TE; hence it is recommended that the clindamycin dose be 1800 mg/day if tolerated.[480,503,504] Encouraging results have been reported with other drug combinations. These include Fansidar (pyrimethamine-sulfadoxine), which has been used in a dose of one tablet twice weekly,[505] and pyrimethamine-dapsone administered on an intermittent schedule (two to three times a week).[506–508] The long half-life of these agents allowed the longer dosing interval, but Fansidar (currently not available in the United States) may have an increased risk of severe cutaneous reactions, and the longer half-life results in slower drug clearance after discontinuation of therapy.[509] When pyrimethamine was used alone as maintenance therapy at 50 mg/day[510,511] and 100 mg/day,[510] the relapse rates were 10% to 28% and 5%, respectively. Atovaquone alone or in combination regimens also appears to have activity based on uncontrolled trials; combination therapy (with sulfadiazine or pyrimethamine) should be used whenever possible.[486–488,512]

The optimal time to initiate ART in HIV-infected patients with TE has not been well defined. In one randomized trial of 282 patients with opportunistic infections other than tuberculosis (only 5% with TE), which compared early (median, 12 days after initiation of opportunistic infection therapy) to deferred (median, 45 days) initiation of ART, the secondary end point of AIDS progression or death occurred significantly less frequently in the early initiation group.[513] Thus, in the absence of contraindications, ART can reasonably be started 2 to 3 weeks after diagnosis of TE.

Primary prophylaxis against *T. gondii* in patients with AIDS has been shown to be effective in preventing acute TE.[514–517] In addition, the use of combination ART in HIV-infected patients has had a profound effect in decreasing the incidence of TE in these patients.[101,103] Primary prophylaxis is recommended for patients who have detectable *Toxoplasma* IgG antibodies and whose lowest $CD4^+$ count has been less than 100/mm^3 (many experts use <200/mm^3 as the cutoff rather than 100/mm^3), regardless of the HIV RNA viral load.[504] TMP-SMX (1 double-strength or single-strength tablet/day), dapsone (50 mg/day) plus pyrimethamine (50 mg/wk), and Fansidar (twice weekly; not available in the United States) have been reported to be effective in preventing the first episode of TE.[504,514,517,518] Atovaquone (1500 mg daily) alone or combined with pyrimethamine (25 mg daily) can also be used, although failures in HSCT patients have been reported.[519]

Studies have demonstrated that it is safe to discontinue primary anti-*Toxoplasma* prophylaxis or chronic maintenance therapy when the recovery of a $CD4^+$ count greater than 200 cells/mm^3 is achieved and sustained in patients on ART.[300–302,520,521] It is important to recognize that in most of these studies, the median $CD4^+$ count was greater than 300 cells/mm^3 at enrollment, and viral loads were below detection limits or reasonably controlled in most patients. More recent data from a European collaboration after multiple cohorts demonstrated a low risk of developing TE in seropositive patients with $CD4^+$ counts of 100 to 200 cells/mm^3 and HIV plasma viral loads below detection limits even if they are not receiving primary prophylaxis; similar benefit was not, however, seen in patients receiving chronic maintenance therapy for

prior TE.[522] Current recommendations are to discontinue prophylaxis in patients receiving cART when the CD4 count has risen above 200 cells/mm^3 for at least 3 months (primary prophylaxis) or 6 months (chronic maintenance), and to consider discontinuing primary prophylaxis in patients with CD4 counts of 100 to 200 cells/mm^3 if HIV plasma viral loads are below detection limits for 3 to 6 months.[504]

At present, TMP-SMX is used by most transplant teams as prophylaxis against *Pneumocystis* pneumonia. Its use has also been shown to protect against toxoplasmosis. However, TMP-SMX is not protective in every case, and some patients are not able to tolerate the drug combination. In addition, in some patients sulfonamides may be contraindicated. Thus use of TMP-SMX alone may be sufficient for prevention of toxoplasmosis in patients who are seronegative for *T. gondii* antibodies and who receive heart transplants from seropositive donors (i.e., D^+/R^- patients).[523] The optimal schedule for administration of TMP-SMX in heart transplant patients has not been defined. Physicians must decide whether a schedule of daily administration or administration three times each week is to be used. We routinely recommend daily use of single-strength TMP-SMX whenever feasible.[15]

Roxithromycin, administered at 900 mg once a week and may be given in three divided doses,[524] has been reported in a small randomized trial to be effective for primary prophylaxis; roxithromycin is unavailable in the United States. Based on a number of clinical trials, pyrimethamine alone cannot be recommended for primary prophylaxis.[98,525,526] Clarithromycin[527] and spiramycin[528] have been ineffective for primary prophylaxis when they were used alone. In a randomized, placebo-controlled, primary prophylaxis trial, clindamycin (600 mg/day) was associated with an unacceptably high rate of associated GI disease, in particular diarrhea.[529]

Data on the outcome of treatment of AIDS patients with toxoplasmosis outside the CNS are limited; available information on the therapy of ocular[291,530,531] and pulmonary involvement[285,532] indicates that these forms of toxoplasmosis are also responsive to treatment. Therapy was successful in 50% to 77% of patients with pulmonary toxoplasmosis.[285,532]

Ocular Toxoplasmosis

A recent report from the American Academy of Ophthalmology highlighted the limited data that are available from randomized controlled trials with well-defined end points demonstrating the benefits of therapy.[533] Treatment is most likely indicated in the following settings: any decrease in visual acuity, macular or peripapillary lesions, lesions greater than one optic disk diameter, lesions associated with a moderate-to-severe vitreous inflammatory reaction, the presence of multiple active lesions, the persistence of active disease for more than 1 month, and any ocular lesions associated with recently acquired infection. Because the disease can be self-limited in immunocompetent patients, many clinicians may not treat small, peripheral retinal lesions that are not immediately vision threatening.[14,316,534–536]

The reported benefits of medical therapy are related primarily to the clinical presentation.[316,534] Because there is so much variation in the clinical manifestations of the retinal disease, and because the disease may be self-limited even without treatment, the response to therapy is difficult to interpret. The combination of pyrimethamine (100-mg loading dose given over 24 hours for 2 days, followed by 25–50 mg daily) and sulfadiazine (1 g given four times daily for 4–6 weeks), depending on the clinical response, which is considered "classic" therapy for ocular toxoplasmosis, is the most common drug combination used (see Table 278.2).[534] TMP-SMX showed responses similar to pyrimethamine-sulfadiazine in a recent randomized, single-blind trial, although the latter regimen was used at lower-than-standard doses.[537] Two recent, open, randomized trials found no differences in response rates to intravitreal clindamycin plus dexamethasone compared with an oral regimen combining pyrimethamine, sulfadiazine, leucovorin, and prednisone/prednisolone.[538,539]

Clindamycin (300 mg orally every 6 hours for a minimum of 3 weeks) has also been used with favorable clinical results.[534] Intravitreal clindamycin combined with dexamethasone has been shown to have similar benefits to the oral combination regimen of pyrimethamine and sulfadiazine.[464] Intravitreal TMP-SMX combined with dexamethasone has shown benefit in small uncontrolled studies.[540,541] Other drugs that may have activity but have been inadequately studied include atovaquone and pyrimethamine plus azithromycin.[542,543] A small randomized trial comparing oral azithromycin to TMP-SMX found no difference in clinical responses.[544]

Systemic corticosteroids are indicated when lesions involve the macula, optic nerve head, or papillomacular bundle, although no randomized trials have demonstrated their benefit compared with antimicrobial therapy alone.[545] Corticosteroid therapy alone may be associated with progressive disease.[546] Photocoagulation has been used both for the treatment of active lesions and for prophylaxis against the spread of lesions because new lesions appear contiguous to old lesions.[534] In some patients vitrectomy and lens removal may be necessary.

Given the high relapse rate seen in some patients with ocular toxoplasmosis, prevention of recurrences would be highly desirable. A randomized, open-label trial of 124 patients in Brazil found that TMP-SMX (1 double-strength tablet every 3 days) was effective in decreasing the frequency of recurrences from 24% to 7% in a population at high risk for recurrences.[214] Although a 10-year follow-up report suggested that efficacy was lost once drug was stopped,[547] a subsequent randomized, placebo-controlled Brazilian trial confirmed the efficacy of prophylactic TMP-SMX (1 double-strength tablet every 2 days) and suggested sustained benefit for 2 years after discontinuing therapy.[548] Such a regimen should be used in patients with frequent or severe recurrences.[549]

For the approach to ocular toxoplasmosis during pregnancy see "Acute Acquired *Toxoplasma* Infection in Pregnant Women."

Acute Acquired *Toxoplasma* Infection in Pregnant Women

Treatment of the acutely infected pregnant woman does not completely eliminate but does decrease the incidence and severity of fetal infection. Because there is usually a delay between the acquisition of acute maternal infection, infection of the placenta, and subsequent infection of the fetus, identification of acute maternal infection necessitates immediate institution of treatment of the mother. Most experience of maternal treatment to prevent transmission to the fetus has been with spiramycin (3 g/day, obtainable in the United States from the FDA, 301-796-1400; after hours, 301-796-8210) (Table 278.3). Spiramycin has been accepted by most investigators as being effective in reducing the frequency of maternal transmission of *T. gondii* to the fetus by approximately 60%.[331,382] Spiramycin is indicated for patients confirmed or suspected to have been infected before 14 weeks of gestation. It appears that its maximal efficacy is best achieved when given within 8 weeks of seroconversion.[334] Spiramycin should be continued until delivery, even if results of the amniotic fluid PCR are negative and ultrasound examinations are normal. A retrospective study suggested that the combination of spiramycin and TMP-SMX (after the 14th week) is more effective than spiramycin alone in reducing transmission during the second trimester.[550] If spiramycin cannot be used or is not available, it may be replaced by sulfadiazine (with appropriate precautions at term) or clindamycin alone. However, there are no data on the efficacy of sulfonamides, including sulfadiazine, or clindamycin when these drugs are used for this purpose.

Because spiramycin does not reliably cross the placenta,[551] if fetal infection is documented or highly suspected or maternal infection is confirmed or highly suspected of having been acquired at 14 weeks of gestation or later, the recommended therapeutic regimen is the combination of sulfadiazine (initial dose 75 mg/kg, followed by 50 mg/kg every 12 hours; maximum, 4 g/day), pyrimethamine (50 mg every 12 hours for 2 days, followed by 50 mg daily), and folinic acid (10–20 mg daily, during, and 1 week after completion of pyrimethamine therapy) (see Table 278.3).[334a,334b] Such treatment might be an alternative to the termination of pregnancy when abortion is not allowed by law or for women who desire to continue their pregnancy. Pyrimethamine should not be used in the first 14 weeks of pregnancy because of a concern for teratogenicity. In this circumstance, if indicated, sulfadiazine plus clindamycin can be considered, although there are no data on its efficacy in this situation.[9] In addition, pyrimethamine-sulfadiazine is also recommended for pregnant women in whom a recently acquired acute infection is highly suspected or confirmed during the late second or third trimesters; this is due to the high rates of vertical transmission observed in those

TABLE 278.3 Treatment Regimens for Toxoplasmosis During Pregnancy and for Congenital Disease

INDICATION	DRUG REGIMEN
Pregnant Women	
Pregnant women suspected or confirmed of having acquired infection before 14 weeks of gestation. Not recommended during pregnancy if the fetus has documented or suspected infection (see below)	**Spiramycin (oral)**[b]**:** 1 g (3 million units) q8h (for a total of 3 g or 9 million units/day) Spiramycin should be continued until delivery, even if fetal infection is not detected (e.g., negative amniotic fluid PCR test and negative follow-up ultrasound)
Pregnant women at ≥14 weeks of gestation and (1) in whom it is suspected or confirmed that acute infection was acquired at or after 14 weeks of gestation or (2) who have a positive amniotic fluid PCR test or an abnormal ultrasound suggestive of congenital toxoplasmosis	**Pyrimethamine:** 50 mg q12h for 2 days, followed by 50 mg daily *plus* **Sulfadiazine:** 75 mg/kg (first dose), followed by 50 mg/kg q12h (max., 4 g/day) *plus* **Folinic acid**[b]**:** 10–20 mg daily during and for 1 wk after pyrimethamine therapy Pyrimethamine is teratogenic and should not be used during pregnancy before week 18 (in some centers in Europe, it is used as early as week 14). Sulfadiazine should not be used alone; consider clindamycin plus sulfadiazine
Infants	
Congenital infection; treatment regimen is usually recommended for 1 yr	**Pyrimethamine:** 1 mg/kg q12h for 2 days, followed by 1 mg/kg/day for 2 or 6 mo, followed by 1 mg/kg/day every Monday, Wednesday, and Friday *plus* **Sulfadiazine:** 50 mg/kg q12h *plus* **Folinic acid**[c]**:** 10 mg three times weekly **Prednisone (if CSF protein ≥1 g/dL or severe chorioretinitis):** 0.5 mg/kg q12h (until CSF protein <1 g/dL or resolution of severe chorioretinitis)
Older Children	
Active disease; treatment is usually continued for 1–2 wk beyond resolution of clinical manifestations	**Pyrimethamine:** 1 mg/kg q12h (max., 50 mg) for 2 days, followed by 1 mg/kg/day (max., 25 mg) *plus* **Sulfadiazine:** 75 mg/kg (first dose), followed by 50 mg/kg q12h (max., 4 g/day) *plus* **Folinic acid**[a]**:** 10–20 mg three times weekly **Prednisone (severe chorioretinitis):** 1 mg/kg/day in two divided doses; max., 40 mg/day, rapid taper

[a]Assistance is available for the diagnosis and management of toxoplasmosis at the Palo Alto Medical Foundation–*Toxoplasma* Serology Laboratory; Palo Alto, CA; www.pamf.org/serology/; 650-853-4828; toxolab@pamf.org; or US (Chicago) National Collaborative Treatment Trial Study; 773-834-4152.
[b]Spiramycin is not teratogenic, and it is available in the United States through the investigational new drug process at the US Food and Drug Administration (301-796-1600). Prior consultation with medical consultants is required.
[c]Folinic acid (leucovorin) should always be given with pyrimethamine to minimize toxicity; folic acid must not be used as a substitute for folinic acid.
CSF, Cerebrospinal fluid; *max.,* maximum; *PCR,* polymerase chain reaction.

stages of gestation and should be recommended even though fetal infection may not yet have been confirmed.

A group of European investigators reported between 1999 and 2007 that, in their studies, a significant effect of prenatal treatment on the risk of vertical transmission and clinical signs of congenital toxoplasmosis was not detected.[552–555] These results are not surprising because the studies included very few untreated women in their analysis, most untreated women were infected during the third trimester, and severe cases were excluded.[556,557] More recently, several studies from Europe have consistently reported evidence for an association between early treatment and reduced risk in the incidence and severity of congenital toxoplasmosis.[334,336,337,558,559] Given that recent studies have consistently reported a clinically significant benefit[556] and that a significant benefit was never ruled out in previous studies, most authorities continue to recommend spiramycin or pyrimethamine-sulfadiazine for women with suspected or confirmed acute *T. gondii* infection acquired during gestation.

Pregnant women with toxoplasmic chorioretinitis as a result of reactivation of chronic disease do not have a higher risk to transmit the parasite to their offspring than do pregnant women who have been infected before pregnancy and do not have ocular disease.[560] Their eye disease should be treated according to the indications discussed in the section "Ocular Toxoplasmosis." Pregnant women with toxoplasmic chorioretinitis thought to be a manifestation of recently acquired infection should be treated because of both the eye disease and the risk of transmission of the infection to their fetus.

Congenital Infection

Detailed information on and recommendations for the postnatal treatment of congenital toxoplasmosis are reviewed elsewhere,[9,561] but we favor continuous sulfadiazine (50 mg/kg every 12 hours), pyrimethamine (loading dose, 1 mg/kg every 12 hours for 2 days; then beginning on day 3, 1 mg/kg per day for 2 or 6 months; then this dose every Monday, Wednesday, and Friday), and folinic acid (10 mg three times weekly during and for 1 week after pyrimethamine therapy) for a minimum of 12 months (see Table 278.3).[557,562] Serial follow-up to gauge the response of the infant to therapy should include neuroradiology, ophthalmologic examinations, and CSF analysis if indicated.[9] Fansidar (unavailable in the United States) has also been used and reported to be well tolerated,[563,564] although safety concerns and availability of alternative regimens preclude recommending its use.

Studies have shown that outcomes are substantially better for most, but not all, infants treated from the neonatal period for 12 months with pyrimethamine-sulfadiazine and leucovorin, compared with historical control subjects receiving no or short-course therapy.[562,565–567] Improvement in intellectual function, regression of retinal lesions, reduction in anticonvulsant drug requirements, and prevention of auditory sequelae appear to be the major benefits of such treatment, which was combined with CSF shunting if required.[562] Signs of active infection resolved within weeks of initiation of treatment. In a significant number of treated children, cerebral calcifications diminished in size or resolved.[567] They also reported that new central chorioretinal lesions were uncommon (14%) in children with congenital toxoplasmosis who have been treated during their first year of life, compared with historical reports of much higher rates (≥82%) for untreated children or those treated for only 1 month near birth.[349]

PREVENTION AND PROPHYLAXIS

General Methods

Prevention is most important in seronegative pregnant women and immunodeficient patients. It is most readily accomplished through education of these patients by their personal physicians (Table 278.4). The goal is to avoid the ingestion of and contact with tissue cysts or sporulated oocysts. Tissue cysts in meat are made noninfectious by heating the meat to 67C°/153°F (i.e., should be cooked to "well done" with no pink meat visible in the center) or by freezing it to –20°C/–4°F (which is not attainable in most home freezers) for at least 48 hours. Meat that is smoked, cured in brine, or dried may still be infectious. Oysters, clams, or mussels should not be eaten raw. Hands should be washed thoroughly after handling raw meat or vegetables, eggs should not be eaten raw, and unpasteurized milk (particularly milk from goats) should be avoided. Vectors such as flies and cockroaches should be controlled. Areas contaminated with cat feces should be avoided altogether. Disposable gloves should be worn while disposing of cat litter material, working in the garden, or cleaning a child's sandbox. Oocysts are killed if the cat litter pan is soaked in nearly boiling water for 5 minutes. If the litter pan is cleaned every day, oocysts will not have a chance to sporulate. Serologic testing of cats is unwarranted because testing does not demonstrate whether the infected cat is excreting oocysts. Untreated water has been shown to be an effective vehicle for the transmission of the parasite, and drinking water sources potentially contaminated with oocytes should be avoided.

Serologic Screening and Prophylaxis Acute *Toxoplasma gondii* Infection and Toxoplasmosis in the Immunodeficient Patient

Transmission of *T. gondii* and death caused by the infection have resulted from the transfusion of leukocyte-rich blood products and by organ transplantation in immunodeficient patients. Transmission of infection by these routes may occur frequently enough to warrant screening for antibody to *T. gondii* in leukocyte-rich blood product donors and possibly to exclude seropositive people as organ donors to seronegative potential recipients whenever feasible.

Primary prophylaxis can prevent toxoplasmosis in patients dually infected with HIV and *T. gondii* (see "Toxoplasmosis in the Immunodeficient Patient" under "Therapy"). Prophylactic treatment (pyrimethamine, 25 mg orally every day for 6 weeks after transplantation) has been used with apparent success in seronegative recipients of hearts transplanted from seropositive donors.[568] However, TMP-SMX used for PCP prophylaxis in solid-organ transplant patients is also effective as primary prophylaxis against *T. gondii* and can be used without addition of pyrimethamine. Primary prophylaxis in BMT and HSCT patients is particularly challenging because TMP-SMX cannot safely be used early (i.e., before engraftment), whereas in patients with all other transplant organs, it can be used immediately after transplantation. Atovaquone is an alternative, but its efficacy has not been evaluated in controlled trials, and breakthroughs have been reported.[569] A preemptive approach using *Toxoplasma* PCR in whole blood, similar to the strategy for preventing CMV disease using serum PCR, should be entertained for immunocompromised patients in whom prophylaxis is not feasible during periods of high risk for development of toxoplasmosis.[281]

TABLE 278.4 Measures to Prevent Primary *Toxoplasma gondii* Infection

- Avoid contact with materials potentially contaminated with cat feces, especially handling of cat litter and gardening. Gloves are advised when these activities are necessary. Because oocysts require 1 to 2 days to mature, dispose of all cat feces daily.
- Disinfect cat litter box with near-boiling water for 5 minutes before handling.
- Avoid mucous membrane contact when handling raw meat.
- Wash hands thoroughly after contact with raw meat.
- Kitchen surfaces and utensils that have come in contact with raw meat should be washed.
- Freeze meat to –20°C (–4°F) for at least 48 hours.
- Cook meat to 67°C (153°F) or "well done" (meat should not be "pink" in the center).
- Avoid ingestion of dried, smoked, or cured meat because they may be infectious.
- Wash fruits and vegetables before consumption.
- Refrain from skinning animals.
- Avoid drinking untreated water potentially contaminated with oocysts.
- Avoid drinking unpasteurized goat's milk.
- Avoid eating raw oysters, clams, and mussels.

Congenital *Toxoplasma gondii* Infection and Toxoplasmosis

Congenital toxoplasmosis is a preventable disease. It is therefore the responsibility of physicians who care for pregnant women to educate them on how they can prevent themselves from becoming infected and thereby not place their fetus at risk. A lack of adoption of a systematic serologic screening program in the United States leaves education as the principal means of preventing this tragic disease. If physicians choose to screen their patients serologically, the appropriate tests must be used, the laboratory performing the tests must be competent, and the test results must be interpreted correctly. Nonreference laboratories can effectively accomplish the initial screening testing by simultaneously performing IgG and IgM antibody tests. Women with positive results in the initial IgG antibody test should have a test for IgM antibody performed on the same serum. Only IgM-positive test results need to be sent to a reference laboratory for confirmatory testing (e.g., PAMF-TSL).[359,379,381] Clinical decisions should not be made based on positive IgM test results alone. In patients with IgG antibodies at any titer, a negative IgM antibody test result in the first trimester, and no clinical signs of acute toxoplasmosis, no further testing would be necessary because the probability of acute acquired infection in these women is extremely low. Given the same circumstances in the second trimester of pregnancy, a negative IgM test result rules out, for practical purposes, recent acquisition of acute infection. A negative IgM test in the third trimester may occur in a patient who acquired the infection earlier in gestation.

In some countries (e.g., France, Austria, Italy, Slovenia, Lithuania, and Uruguay), initially seronegative pregnant women are retested at various intervals during gestation to detect seroconversion and institute treatment.[570] Monthly screening of seronegative pregnant women was recently reported to significantly decrease the risk of vertical transmission and of clinical signs at 3 years of age.[558] The appropriate use of prenatal diagnosis, followed by the optimal use of spiramycin and/or pyrimethamine-sulfadiazine–folinic acid, can markedly reduce the incidence of clinically significant congenital toxoplasmosis.[a] Its absence is often associated with poor outcomes.[338] Results of a study in France[333] on the incidence of *T. gondii* infection in fetuses of women whose date of acquiring the infection during the gestation was known and who were treated with spiramycin are shown in Table 278.5.

[a]References 333, 336, 337, 558, 571, 572.

TABLE 278.5 Rates of Congenital Transmission in 270 Women and the Sensitivity and Negative Predictive Value of Amniotic Fluid PCR for Prenatal Diagnosis of Congenital Toxoplasmosis, According to Gestational Age at Which Maternal Infection Was Acquired

GESTATIONAL AGE AT MATERNAL INFECTION[a] (wk)	NO. OF INFECTED FETUSES[b]/TOTAL (%)	AMNIOTIC FLUID PCR	
		Sensitivity (CI) (%)	NPV (CI) (%)
±6	0/14 (0)	N/A	100 (78–100)
7–11	7/50 (14)	29 (8–65)	90 (81–98)
12–16	7/61 (11.5)	57 (21–94)	95 (86–98)
17–21	14/66 (21.2)	93 (68–99)	98 (90–99.7)
22–26	16/36 (44.4)	63 (39–86)	77 (61–93)
27–31	19/30 (63.3)	68 (48–89)	65 (42–87)
≥32	12/13 (92.3)	50 (22–78)	14 (3–52)
TOTAL	75/270 (28)	N/A	N/A

[a]Maternal infection was diagnosed by seroconversion in the 270 women; 261 (97%) were given treatment with spiramycin.
[b]Congenital infection was diagnosed by the persistence of *Toxoplasma* immunoglobulin antibodies after 1 year of life.
CI, Confidence interval; *N/A,* not applicable; *NPV,* negative predictive value; *PCR,* polymerase chain reaction.
Note: The positive predictive value was 100%, regardless of gestational age.
Modified from Montoya JG, Remington JS. Management of Toxoplasma gondii *infection during pregnancy.* Clin Infect Dis. *2008;47:554–566.*

In pregnant women infected with both HIV and *T. gondii*, we recommend that primary prophylaxis against *T. gondii* be introduced when their CD4 T-cell count falls below 200/mm^3. If the patient is receiving TMP-SMX, additional prophylaxis is probably not necessary. Otherwise, spiramycin can be used at a dose of 3 g/day.

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279 Giardia lamblia

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SHORT VIEW SUMMARY

Definition

- Giardiasis, caused by the protozoan *Giardia lamblia*, is a common cause of sporadic, endemic, and epidemic diarrhea throughout the world.
- Infected persons can have acute diarrhea with malaise, cramping and bloating, chronic diarrhea with malabsorption, or asymptomatic infection. Asymptomatic infection is most common in children, particularly in low-income settings, and may contribute to poor nutrition.

Epidemiology

- *Giardia* is one of the most widely distributed enteric parasites.
- In the United States there are approximately 17,000 documented infections annually, with estimated infections of more than 1.2 million; it is most frequently reported in children aged 1 to 9 years and adults aged 40 to 54 years.
- In low-income countries, *Giardia* infects nearly all children by the age of 10 years.
- Transmission of this fecal-oral parasite is most common through person-to-person transmission and through untreated or inadequately treated surface water, and occasionally via contaminated food.
- Although specific human genotypes (assemblages A and B) are found in some animals, epidemics of giardiasis caused by animals have not been reliably observed. Animals typically harbor other assemblages.

Diagnosis

- A clinical syndrome of diarrhea and or other gastrointestinal symptoms lasting 7 to 10 days, and often associated with weight loss without fever, is helpful in distinguishing giardiasis from other enteric infections.
- Useful epidemiologic risk factors are a history of travel, drinking untreated surface water, having young children in daycare, or engaging in sexual practices with the potential for fecal-oral transmission.
- Stool examination for ova and parasites is the traditional method of diagnosis.
- Antigen detection is widely available and is more sensitive and specific than stool examination for ova and parasites. Polymerase chain reaction assays are becoming more widely used and can identify the assemblage.

Therapy

- Tinidazole is the drug of choice, taken in a single dose (see Table 279.3).
- Alternatives are metronidazole, nitazoxanide, and albendazole.
- Potential adverse events associated with treatment should be discussed with the patient.
- Treatment during pregnancy requires special considerations (see "Therapy").
- Post-*Giardia* irritable bowel syndrome, lactose intolerance, or another organism or cause should be considered if treatment appears to fail. If parasites are present, then re-treatment with a drug of a different class is usually successful.

Prevention

- Prevention of giardiasis requires the proper handling and treatment of drinking and recreational water supplies, good personal hygiene, and protection of food supplies from contamination.
- Bringing water to a boil, filtration, and careful halogenation can be effective measures to treat small volumes of water.

DESCRIPTION OF THE PATHOGEN

Giardia was probably described in the late 1600s, when van Leeuwenhoek likely discovered it in his own stool. It was in the early 1900s that the parasite received the genus name *Giardia*. The designated species name for the human parasite has been *lamblia*; *intestinalis* and *duodenalis* are also used. The genus *Giardia* is in the category of intestinal flagellates in the division Protozoa. The life cycle of *G. lamblia* has two stages: the motile dividing trophozoite present in the intestine of the host, and the environmentally resistant infectious cyst excreted in the feces. The trophozoite is 9 to 21 µm long and 5 to 15 µm wide (Fig. 279.1A). It has a convex dorsal surface and a flat ventral surface containing a disk with contractile proteins used for attachment (sucking or adhesive disk). There are four pairs of posteriorly directed flagella that are involved in locomotion and perhaps attachment.[1–3] The protozoan has two anteriorly placed diploid nuclei, each with a prominent central karyosome and a complete copy of the genome.[4] In stained preparations, the nuclei create the characteristic facelike image. Each of the two *Giardia* nuclei maintains a high degree of homozygosity, most likely through fusion and exchange of DNA during encystation.[5,6] Median bodies—tight collections of microtubules—are visualized transversely in a clawlike manner in *G. lamblia* and have been used to identify morphologically distinct types of *Giardia*. Of the *Giardia* spp., only *G. lamblia* has been successfully cultured in vitro.[7] Growth[8] is enhanced by the presence of biliary lipids and a high concentration of cysteine, consistent with the predilection of *Giardia* for colonizing the upper small bowel. The trophozoite divides by longitudinal binary fission and has a doubling time in culture of 6 to 12 hours. It is an aerotolerant anaerobe that scavenges oxygen to enhance survival.[9] *Giardia* uses glucose as the major source of carbohydrate energy, metabolizing it to the end products of acetate, ethanol, alanine, and carbon dioxide; adenosine triphosphate (ATP) is generated during this process.[8] Metabolism of arginine via the arginine dihydrolase pathway is another mechanism for ATP generation.

The differentiation of *Giardia* into species traditionally depended on morphology and the host of origin, with a number of species described: *G. lamblia* in humans, *Giardia muris* in mice, *Giardia agilis* in amphibians, *Giardia psittaci* in parakeets, and *Giardia microti* in voles and muskrats (Table 279.1) However, molecular studies later revealed morphologically identical *Giardia* that were found in both humans and animals. The earliest molecular typing of these *Giardia* isolates divided them into at least three groups,[10] which were subsequently renamed and expanded into eight genotypes or referred to as assemblages A to H based on sequence differences in housekeeping genes[11,12] (see Table 279.1).[12,13,14] Assemblages A (often subtype AII) and B are associated with most but not all[15] human infections and a number of nonhuman mammalian hosts.[11,13,14] Their biology, biochemistry, and molecular mechanisms differ and fit criteria to be separate species.[16,17] Occasional infections with non-A, non-B assemblages, including assemblage E, have been reported in humans.[15] Improved sequencing methods using a broader sampling of isolates will better define genetic diversity and range of *Giardia* genotypes.[12,15,18]

[a]All material in this chapter is in the public domain, with the exception of any borrowed figures or tables.

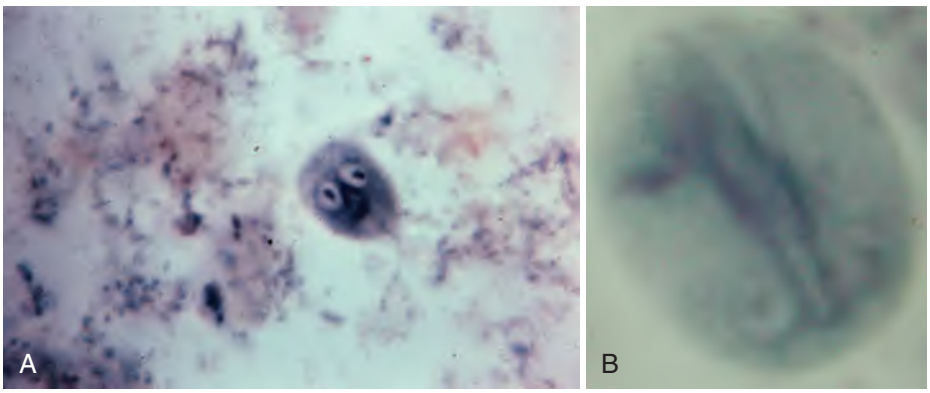

FIG. 279.1 *Giardia lamblia* trophozoite (A) and cyst (B) are demonstrated in a trichrome stain of fecal material. Note the prominent nuclei in the trophozoite. In the cyst, centrally located axonemes, a clawlike median body, and two nuclei can be seen.

TABLE 279.1 Typing of *Giardia* Species

NAME	GENOTYPE	HOST RANGE
Giardia agilis		Amphibians
Giardia ardeae		Birds
Giardia microti		Muskrats and voles
Giardia muris		Rodents
Giardia psittaci		Birds
Giardia lamblia	Assemblage A	Humans, primates, dogs, cats, cattle, sheep, deer, rodents
	Assemblage B	Humans, primates, dogs, cattle, horses, beaver
	Assemblage C	Dogs
	Assemblage D	Dogs
	Assemblage E	Cattle, goats, sheep, pig
	Assemblage F	Cats
	Assemblage G Assemblage H	Rodents Marine vertebrates

Modified from Feng Y, Xiao L. Zoonotic potential and molecular epidemiology of Giardia species and giardiasis. Clin Microbiol Rev. *2011;24:110–140.*

Different *G. lamblia* genotypes have unique capacities to establish infection and to cause disease in animal models and experimental human infections, but whether specific genotypes differ in virulence in human natural infections[8,12,19–22] is unclear.

Some Unique Biologic Aspects

The genome of the prototypic assemblage A isolate, WB (http://giardiadb.org),[23] is approximately 11.7 Mb, distributed over five chromosomes. Analysis of its small subunit ribosomal RNA[8,24] sequence and genes of certain pathways[25] indicate that it is one of the earliest-branching eukaryotes.[23] The genome is compact and simplified, including DNA synthesis, transcription, RNA processing, and cell-cycle machinery. The parasite contains only a few introns, extremely short promoters, sometimes 60 bp or less, overlapping transcriptional controlling elements, and mitosomes, remnants of earlier mitochondria.[26,27] Pathways to synthesize phospholipids, fatty acids, cholesterol, and purine and pyrimidine nucleosides are reduced or lacking, so these essential metabolic building blocks are largely scavenged from the small intestine milieu. There are only enzymes sufficient for remodeling but not synthesis of lipid membrane components.[8,23] Except for alanine, amino acids are taken up from the environment.

Because *Giardia* is an early-branching, highly adapted organism and an important disease-causing parasite, many aspects of its unique biology have been extensively studied and reviewed elsewhere.[8] However, a few important examples of its particularities include surface antigenic variation, a unique vesicular transport system devoid of a Golgi apparatus, and the processes of encystation and excystation.

Giardia is the only known intestinal dwelling organism to undergo frequent surface antigenic variation.[28,29] A single variant-specific surface protein (VSP) is expressed on the surface of *Giardia* and, after several generations, is replaced by another VSP.[29–32] VSPs are a family of about 250 cysteine-rich proteins with similar motifs and general structure and a conserved transmembrane carboxyl-terminal sequence.[30,33] Although all VSPs are transcribed, only one is expressed. The others VSPs are possibly eliminated by interference RNA mechanisms.[32,34] Antigenic variation occurs during infection of humans and animals, in vitro in culture, and during encystation.[8,30] Although it is important in evading the host immune response, certain VSPs are favored or disallowed even in the absence of an adaptive immune response.[35] Specific VSPs seem to have unique physical-chemical characteristics that allow them to be biologically selected and expressed or disfavored and not expressed, depending on the intestinal environment and host.[35]

G. lamblia trophozoites encyst to form fibrillary, oval, thin-walled cysts 8 to 12 µm long and 7 to 10 µm wide (see Fig. 279.1B). *Giardia* encystation is a model system for vesicular transport and developmental biology because *Giardia* lacks a typical Golgi apparatus that is an essential component of vesicular transport in most higher organisms.[5,36–38] Encystation induced in vitro[39] is a complex process involving many of *Giardia's* basic processes[5,40,41,42] The early phase is characterized by the formation of highly characteristic encystment vesicles (ESVs), in which cyst wall proteins (CWPs) 1 through 3 and other molecules are processed.[36,43,44] The late phase of encystation consists of transport of the CWPs to the cell surface, their assembly with *N*-acetylgalactosamine (GalNAc) into the cyst wall, and then nuclear division and DNA replication without cell division so that cysts are generated with a ploidy of 16N.[5,38,39,41,45] At ultrastructural analysis, the cyst wall contains CWPs and GalNAc polymer in insoluble fibrils.[46]

Excystation is a highly coordinated process that is initiated when cysts are exposed to environmental stimuli, such as gastric acid and pancreatic enzymes.[5,47] The process is complex and well described morphologically but not well understood on a molecular level.[48–50] An excyzoite containing four nuclei (4N each) is released; this divides twice without further DNA replication, resulting in four daughter trophozoites.[5,51]

EPIDEMIOLOGY

Giardia is widely distributed. In the United States, *G. lamblia* has been demonstrated in 4% to 7% of submitted stool specimens, making it the most commonly identified intestinal parasite. US. epidemiologic surveys of giardiasis from 2011 to 2012 found that 15,223 to 16,868 cases were reported annually, with the case rates in different states varying from 1.7 to 29.2 cases per 100,000 persons and an overall mean of 5.8.[52] Because of substantial underreporting, a current estimate is that more than 1.2 million cases may occur annually, accounting for an estimated

$34 million dollars in annual hospitalization costs.[53,54] Only 1.3% of cases were associated with a detected outbreak.[52] *Giardia* was most frequently reported in children 1 to 9 years old and to a lesser extent in adults 40 to 54 years old, and during the early summer through early fall months[52]; these findings are similar to those in Canada and other high-income countries.[55] In the United States, coenteric infections with *Giardia* are uncommon (2.2%).[56]

In low-income regions of the world, *Giardia* is one of the first enteric pathogens to infect infants.[57–60,61] In these settings, incidence ranges from 37.7% to 96.4% in the first 2 years of life, and 40% of these children have persistent (>8 weeks) infection. Peak prevalence rates of 15% to 30% occur in children younger than 10 years.[62,63,64,65,66] Nearly all children in these settings become infected, and *Giardia* is frequently detected together with other viral, bacterial, and parasitic pathogens.[60,67]

Natural acquisition of the parasite occurs through fecal-oral ingestion of *Giardia* cysts through contaminated water, food, or person-to-person transmission. *Giardia* cysts survive well in the environment, particularly in cold water. *Giardia* was the most frequent cause of outbreaks of diarrhea resulting from drinking water in the United States from 1971 to 2006[68]; however, the risk from drinking water dropped substantially in the 1980s and continues to steadily decline[69] as improved measures for water treatment have been implemented. Recreational water,[70] primarily in treated swimming venues and lakes, is also a risk for *Giardia*. Surface water can become contaminated by human or animal sources[69,71] so backpackers who do not adequately treat water can become infected. Most waterborne outbreaks can be traced to untreated or improperly treated water or faulty purification systems.[68,72,73] Food handler contamination at restaurants due to poor hand hygiene, particularly with produce, has been linked to the majority of foodborne outbreaks.[69,74,75]

Person-to-person transmission occurs in groups with close contact and an increase in fecal contamination, especially between young children and their parents and siblings, in men who have sex with men, and between young children in daycare centers. Historically, the prevalence of *Giardia* in children in daycare has been as high as 20% to 50%,[76] which seems to have decreased in the United States lately. Many young children are asymptomatic, but they can spread the infection within their homes and contribute to secondary spread within their communities.[77,78]

Giardia was the pathogen identified most frequently in returning travelers and immigrants seeking medical care and diagnosed with infectious gastrointestinal disease—diagnosed at a rate of 31 per 1000 ill returned adult travelers.[79] Travel to the Indian subcontinent was the highest-risk destination.

Many mammalian hosts such as gerbils, mice, beavers, sheep, cattle, dogs, and cats (see Table 279.1)[11,12,14,80,81] have harbored or been experimentally infected with *Giardia* morphologically similar to, and in some instances identical to, the genotypes infecting humans. Genetic subtyping indicates the low zoonotic potential for most animal isolates.[12,18] The strongest epidemiologic link for animal isolates associated with outbreaks of human infection were Canadian waterborne outbreaks of giardiasis linked to beavers.[82,83]

PATHOGENESIS AND IMMUNE RESPONSE

Giardia was once thought to be a harmless commensal, but its association with symptomatic diarrhea, malabsorption in children, disease after waterborne outbreaks, travel, and experimental human infections[19] has clearly established its pathogenicity. Pathophysiologic mechanisms need to explain the variety of symptoms and clinical outcomes that occur in exposed and infected populations, the high level of asymptomatic infections in endemic regions compared with common symptomatic epidemic disease in primarily nonendemic intermittently exposed populations, and the variety of infection rates and symptoms in singular populations. Although there is a large body of experimental data, as a group the studies are particularly difficult to interpret because of the variability of the models and methods employed. Most nonhuman experimental infections have used a variety of rodent and small mammal models with either *G. muris* in mice or rats or different human *Giardia* isolates in mice, gerbils, or rats. Frequently, the isolates used were not well characterized. Many of the findings, particularly those from studies of immunity, are based on murine host responses and extrapolated to human infections. The emerging picture reveals a complex interaction between a genetically diverse, adaptable group of closely related, morphologically similar organisms and their hosts.

Infection occurs after oral ingestion of as few as 10 to 25 cysts.[84] The ability to establish infection and to cause diarrhea varies among isolates, assemblages, and possibly VSP expression patterns.[8,19–21,35,85] After excystation, trophozoites adhere to the brush border of the epithelium via their ventral disk[1] and multiply in the upper small bowel. Adherence can be modified or prevented by means of a number of mechanisms.[86] The parasite may avoid being expelled by mechanical means.[87] Small bowel biopsies in most cases show little inflammation. However, some may demonstrate villous shortening and atrophy[23,88]; and the degree of histologic abnormality correlates with severity of clinical manifestations.[89–91] Among the postulated mechanisms of trophozoite pathogenesis in the small intestine—mucosal invasion, elaboration of an enterotoxin, and disruption of the intestinal epithelial brush border and function—there is little reproducible evidence that mucosal invasion or production of an enterotoxin occurs. *G. lamblia* does disrupt brush border functional enzymes, including disaccharidases in vitro in human small intestinal epithelial cell monolayers.[92] Trophozoites also disrupt tight junctions, increase permeability, and induce apoptosis.[93–96,97] Many of these effects are caspase-3 dependent.[93,94] Epithelial barrier dysfunction and apoptosis have also been seen in duodenal biopsy specimens from persons with giardiasis and some murine models of persistent infection.[98,99]

The effects of *Giardia* on epithelial cells in vitro appear nutrient dependent. High glucose concentrations can counteract caspase-3–dependent epithelial cell apoptosis through upregulation of the sodium-dependent glucose cotransporter in response to *Giardia* proteases.[100] *Giardia*-mediated arginine consumption reduces epithelial cell proliferation.[101] Arginine consumption may favor parasite colonization by suppressing arginine-dependent nitric oxide synthetase in the host, thus limiting the protective effect of nitric oxide[102,103] These interactions may partially explain dietary influences on epithelial cell responses and *G. lamblia* persistence in mice.[99,104]

Host immunity plays a role in clearance of the parasite,[51] protection against reinfection, and pathogenesis.[51] In part, the findings are dependent on the model system that is used. Immune responses in humans, especially during acute illness, are not well studied, and much of the information is extrapolated from mouse and gerbil models of infection with *G. muris* or *G. lamblia.* There are differences in the immune responses of mice to infection with a rodent *G. muris* compared with infections with *G. lamblia* isolated from humans.[99] Immune responses and course of infection also differ among *G. lamblia* isolates of different assemblages.[105,106] Time-dependent clearance of *G. lamblia* in murine models coincides with upregulation of intestinal genes related to α-defensin function, mast cell proteases, and antibody production.[107] Early mechanisms of control of *G. lamblia*–infected mice include interleukin-6 (IL-6).[108,109] This effect may be mediated via IL-6–producing mast cells and subsequent increased intestinal motility.[110–112] In addition, dendritic cells producing IL-6 can reverse the inability of IL-6–deficient mice to clear *G. lamblia.*[113] Innate immune-mediated signaling through TLR2 may counteract parasite clearance and in turn promote infection.[114] T-cell responses control infection, whereas B-cell responses appear to be more important at later time points.[115]

Several observations indicate that partial protective immunity can develop to *Giardia* infection. Protective immunity to reinfection develops in most rodent and gerbil infection models; partial immunity also develops in some situations in humans.[19,35,105] Lower rates of symptomatic disease were found in long-term residents of endemic areas of North America than in visitors or short-term residents.[116,117] In contrast, reinfection is common, particularly in children, in endemic settings.[59,60,64,118] Previously infected volunteers can be reinfected with the identical isolate after treatment but at a lower intensity and without symptoms.[19] Possible reasons for the ability to become reinfected are exposure to a different genotype, expression of a different VSP by an individual isolate, age and nutritional status of the host, and inability to develop intestinal immunity after a single infection.

Both B-cell and T-cell immunity appear to play essential roles in protective immunity,[110] but which arm of the immune system is dominant

depends on the infection model studied. A systemic antibody response occurs in individuals with *Giardia*. Although serum immunoglobulin M (IgM) and IgG antibodies develop and with complement can be lethal to *Giardia* trophozoites,[29] it is likely that gastrointestinal IgA antibodies secreted into the lumen where trophozoites are located play a more important role.[119–121] Failure to develop IgA against specific *Giardia* antigens has been suggested to correlate with chronic giardiasis in humans.[122] Evidence supporting a role for humoral antibodies. specifically IgA responses, in the control of *Giardia* infection initially has come from the increase in chronic giardiasis in patients with common variable immunodeficiency (CVID).[123] Because these patients may also have cellular immune defects, this association neither supports nor refutes humoral mechanisms. Patients living with acquired immunodeficiency syndrome (AIDS) do not have an increased susceptibility to *Giardia,* although they uncommonly develop severe disease that is difficult to treat.[124,125] More recent studies have demonstrated that natural exposure in immunocompetent adults leads to development of $CD4^+$ memory T-cell responses.[126,127] These cells produce greater IL-17A after stimulation with *Giardia* antigens in exposed compared with unexposed individuals.[126]

In mice, immunization with the full repertoire of VSPs expressed by a single isolate can lead to protection against homologous *Giardia* challenge.[128] This effect coincides with the development of broad anti-VSP antibodies, but the mechanisms are likely multifactorial. Either complete absence of IgA or defective transcellular transport due to deletion of the polymeric immunoglobulin receptor (pIgR) is associated with inability to resolve infection in humans.[110,119,121,129] The mechanism by which IgA prevents or helps to clear infection is probably by binding to trophozoites and preventing a critical adherence step. However, there is no evidence that IgA can kill trophozoites, and studies comparing IgA-expressing or total B-cell–deficient mice have demonstrated that B-cell–mediated clearance of *Giardia* is not limited to IgA production.[121]

More recently, IL17A has been identified as a key regulator of host defense responses against *Giardia* in animal models. Consequences of impaired IL-17A signaling through the cognate IL17RA receptor include defective transcellular IgA transport through pIgR together with reductions in several antimicrobial peptides.[130,131] Similar to humans, IL17A-producing $CD4^+$ T cells increase in mice following *Giardia* challenge. However, $CD4^+$ T-cell–depleted mice are unable to clear parasites despite robust IL17A upregulation, likely from innate sources.[130]

The role for T-cell responses in parasite control and pathogenesis is substantial. Athymic, T-cell–deficient mice are unable to clear infection with *G. muris* or *G. lamblia* until the mice are reconstituted with lymphoid cells, particularly the $CD4^+$ helper T lymphocyte.[115,132,133] After reconstitution, animals develop an abnormal intestinal histologic appearance that parallels the changes seen in some humans with giardiasis: flattening of villi, crypt hypertrophy, and a mononuclear cell infiltration of the submucosa.[89,134] Similarly, $CD4^+$ T-cell neutralization prolongs infection but also attenuates brush border defects in *Giardia*-infected mice.[106]

The complex host immune responses to *Giardia,* and immunomodulatory properties of the parasite itself, influence mucosal responses and disease manifestations of other pathogens in vitro and in animal models. The cathepsin B–like cysteine protease produced by some *Giardia* strains is capable of cleaving mucosal-derived IL-8, limiting neutrophil chemotaxis, and attenuating proinflammatory intestinal responses to other stimuli.[104,135,136] In a murine malnutrition model, sequential coinfection with *Giardia* and then enteroaggregative *Escherichia coli* enhanced weight loss and partially altered the mucosal responses observed during enteroaggregative *E. coli* infection alone.[137]

There is increasing recognition that resident microbiota influence both *Giardia* susceptibility and pathogenesis. Singer and Nash made the first sentinel observation that murine microbiota are capable of protecting against infection even in severely immunocompromised mice.[138] In addition, some *Lactobacillus* strains limit growth of *Giardia* through bile-salt hydrolases.[139] Microbiota, however, also contribute to *Giardia* pathogenesis. Jejunal aspirate cultures from patients with symptomatic giardiasis are more pathogenic to germ-free mice than axenic trophozoites (assemblage A).[140] These manifestations may be the result of direct microbial interactions. *Giardia* alters the intestinal bacterial composition throughout the gut of mice[141] and perturbs gut microbial amino acid metabolism in vivo.[137] Culturing otherwise commensal bacteria in the presence of *Giardia* or its products functionally promotes their pathogenic potential.[142,143] In some models, increases in mucosal-associated bacteria and myeloid inflammation persist beyond parasite clearance.[97,144] In contrast, antibiotics that reduce intestinal bacteria result in diminished $CD8^+$ T-cell activity and disaccharidase deficiency and prevent host growth impairment after *Giardia* challenge, even during malnutrition.[137,145] Whether and to what extent these clearly relevant interactions between *Giardia* and other microbes influence outcomes in humans, including post-*Giardia* infection sequelae, require further investigation.

CLINICAL MANIFESTATIONS

The clinical manifestations of giardiasis are broad and range from asymptomatic cyst passage to acute diarrhea and dehydration necessitating hospitalization. Infections may be short or prolonged, resulting in spruelike symptoms of chronic diarrhea with malabsorption. The proportion of individuals manifesting symptoms in a population appears to be influenced by *Giardia* prevalence and possibly age at first exposure, with significant variability in nonendemic versus endemic populations, the host nutritional and immune status and genetic makeup, coinfection with other enteric organisms, and the assemblage or strain of the prevalent *Giardia*. The natural history of *Giardia* infections in nonendemic populations is uncertain because most patients have not been rigorously followed without treatment and because of the demonstrated variability of different *Giardia* genotypes to cause disease. Patients with or without symptoms may self-cure or become chronically infected, sometimes lasting years.[146]

After the ingestion of *G. lamblia* cysts, there is an incubation period of 1 to 2 weeks before the onset of symptoms. The prepatent and incubation periods after instillation of 50,000 axenically grown trophozoites into the small intestine can be as short as 5 and 6 days, respectively.[19] Symptoms may occur before detection of cysts.[19] Symptomatic giardiasis is characterized by the acute onset of diarrhea, abdominal cramps, bloating, and flatulence (Table 279.2). The patient usually has malaise, nausea, and anorexia and may report sulfuric belching. Foul-smelling flatus and stools are common complaints, as is weight loss. Vomiting and upper gastrointestinal symptoms occur less frequently but may sometimes be a dominant symptom, leading to a delay in diagnosis. Fever and tenesmus are atypical and should raise suspicions for an alternative diagnosis. Initially, stools may be profuse and watery; the median number of stools per day has been as high as nine.[147] In short-term travelers, giardiasis is an infrequent cause of diarrhea compared with bacterial causes; it is more common in long-term travelers. Gross blood, pus, mucus, and

TABLE 279.2 Symptoms of Giardiasis

	PERCENTAGE	RANGE
Diarrhea	89	64–100
Malaise	84	72–97
Flatulence	74	35–97
Foul-smelling, greasy stools	72	57–79
Abdominal cramps	70	44–85
Bloating	69	42–97
Nausea	68	59–79
Anorexia	64	41–82
Weight loss	64	56–73
Vomiting	27	17–36
Fever	13	0–21
Urticaria	9	4–14
Constipation	9	0–17

Data from Hill DR. Giardiasis. Issues in diagnosis and management. Infect Dis Clin North Am. *1993;7:503–525.*

microscopic polymorphonuclear white blood cells (WBCs) are absent, and, if present, suggest another or concomitant diagnosis.

One of the most important distinguishing features of giardiasis is the prolonged duration of diarrhea, which is commonly intermittent with waxing and waning symptoms and usually is accompanied by weight loss. At the time of presentation, most patients have been symptomatic for more than 1 week to 10 days.[147] Weight loss of about 10 pounds occurs in more than 50% of patients with prolonged symptoms.[148] Unusual reported associations include urticaria, other skin rashes, reactive arthritis,[149] eye complaints, biliary tract disease, and gastric infection.[147] These are uncommon, and it is unclear whether a casual relationship exists. Gastric infection occurs in the presence of achlorhydria and has been seen in conjunction with *Helicobacter pylori* in both adult and child populations.[150,151]

Although most persons with giardiasis have a relatively benign course, some can have an acute severe illness necessitating hospitalization. Children and pregnant women were particularly affected in the United States,[152] but not in a similar study of those hospitalized in Scotland.[153]

Patients who develop chronic diarrhea may report weight loss, profound malaise, lassitude, occasional headache, and diffuse abdominal and epigastric discomfort, often exacerbated by eating. Stools, passed frequently in small volume, commonly because of malabsorption, may be greasy and foul smelling or frothy and yellowish. Waxing and waning symptoms over months is characteristic. Infected children can present with spruelike disease and failure to thrive.[91,154] Consequently, malabsorption of vitamins A and B_{12}, protein, D-xylose, and iron develops.[155,156] Lactase is the most common disaccharidase deficiency, occurring in 20% to 40% of cases,[157] with post-*Giardia* lactose intolerance sometimes persisting for several weeks after treatment. This is often confused with relapse or reinfection. Some individuals may be intolerant to specific fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.[158]

Post-*Giardia* irritable bowel syndrome (IBS) is increasingly recognized in nonendemic settings. Both IBS-like symptoms and chronic fatigue have reportedly lasted for years after primary infection in a previously unexposed nonendemic population in Norway.[159] These *Giardia*-exposed patients with persisting symptoms have developed elevated serum sCD40L, a finding that warrants confirmation in other populations.[160] Within a US insurance database, a single episode of giardiasis increased the likelihood of a new IBS diagnosis within the next year (hazard ratio [HR], 4.8; 95% confidence interval [CI], 3.6–6.4) that was only slightly attenuated after adjustment for anxiety, depression, and health care utilization (HR, 3.9; 95% CI. 2.9–5.4).[161]

Giardia is a nearly universal infection in children residing in low-income regions of the world. Despite the high prevalence of *Giardia* infection in these children, the vast majority of infections are asymptomatic; the variability in manifestations has been perplexing.[162] Although many *Giardia* infections in this setting do not result in acute diarrhea, there is evidence that the parasite is associated with persistent diarrhea and nutritional abnormalities. In a review and meta-analysis of studies describing *Giardia* in children younger than 5 years, *Giardia* was not seen to cause acute diarrhea (odds ratio [OR], 0.60; 95% CI, 0.38–0.94; $P < .03$) but was associated with diarrhea lasting at least 14 days (persistent diarrhea; OR, 3.2; 95% CI, 1.50–6.76; $P < .001$).[163] In several subsequent case-controls studies of pathogen-attributable causes of pediatric diarrhea in these settings, *Giardia* was detected more often in controls than cases of moderate-to-severe acute diarrhea,[164,165] a finding that has not been universally observed[60] and merits more analysis. Unlike viruses, *Cryptosporidium,* and other gastrointestinal pathogens associated with acute diarrhea,[166] there is no clear relationship between quantitative *Giardia* burden or stool inflammatory markers and symptomatic infection in these children.[60,167]

Persistent *Giardia* infection, either with or without diarrhea, could be part of the larger condition of childhood environmental enteric dysfunction in low-income regions. Studies over the last 20 years have documented stunting in Brazilian and Ecuadorian children infected with *Giardia*,[59,168] poor intestinal permeability in Nepali children,[169] low weight-for-age and height-for-age in Brazilian children with persistent symptomatic giardiasis,[63,170,171] underweight status in Rwandan children,[172] significant wasting in Malaysian and Indian children,[62,173,174] and decreased cognitive function in Peruvian children with multiple episodes of giardiasis.[58] In a prospective study of 629 children in Bangladesh where 74% of children had had a *Giardia* exposure by 2 years of life, *Giardia* in the first 6 months of life, regardless of symptoms, was associated with decreased length-for-age scores.[61] In a larger multicenter study including >2000 children, early *Giardia* exposures and persistent infections were also associated with impaired growth attainment by 2 years of life.[60] The findings of these studies suggest that treatment of infection might help to reverse some of the deleterious effects.[59,175–177] However, persistent infections and reinfections occur so rapidly that repeated therapy is currently impractical and not indicated.[60,64,178,179–180]

In contrast, longitudinal studies in Bangladeshi children[181,182] and Peruvian children[64] did not demonstrate effects on well-being or nutrition, and in a setting where children were well-nourished, asymptomatic infection did not have apparent deleterious effects.[183,184] Furthermore, many children and adults will be simultaneously infected with other bacterial, viral, and parasitic infections, and there is the potential for adverse synergy.[185,186]

DIAGNOSIS

The diagnosis of giardiasis should be considered in all patients with prolonged diarrhea, particularly if it is associated with malabsorption or weight loss, a history of recent travel to an endemic area, ingestion or exposure to untreated water sources, the presence of small children in the home who attend daycare centers, or sexual risk factors. In the usual patient with uncomplicated giardiasis, the WBC count is normal without eosinophilia, and gastrointestinal imaging is nondiagnostic. The diagnosis depends on detection of the parasite or its specific antigen or DNA in the feces.

Microscopic detection of cysts or trophozoites in feces for ova and parasites (O&P) is the traditional way to diagnose most gastrointestinal parasites. The O&P test is time-consuming and costly; the sensitivity is dependent on the number of organisms, the skill of the microscopist, the amount of feces examined, and the time taken to examine the stool. A 90% chance or greater of detecting a true *Giardia* infection requires three stool examinations over multiple days.[148,187,188] Tests requiring little training with high sensitivity and specificity and ease of performance such as assays to detect the *Giardia* soluble specific cyst wall antigen(s) of *Giardia* or cyst detection with immunofluorescence are widely available,[189,190] reproducible, and rapidly performed.[191] Polymerase chain reaction (PCR)–based diagnostic testing,[12,192,193,194,195] with *Giardia* usually included as one target in a larger array of gastrointestinal pathogens, has become commercially available in the United States. Comparisons between the *Giardia* antigen tests and PCR testing indicate that PCR testing is at least as sensitive and in some formats twice as sensitive[166] as antigen detection tests.

The detection of *Giardia* antigen in stools has proved to be extremely useful in diagnosing clinically significant infections. These assays are most helpful when giardiasis is the leading consideration. They are often less expensive than an O&P examination and are 85% to 98% sensitive and 90% to 100% specific.[189,190,196–200] Various methods to detect *Giardia* trophozoites in the small intestine were previously used to establish or confirm the diagnosis. Because of the availability of highly sensitive noninvasive tests, small intestinal sampling is rarely required.

Testing for systemic anti-*Giardia* antibody is neither generally available nor useful in the individual case because of persistence of antibodies from prior infections. Detection of IgG antibodies has been useful in seroepidemiologic studies.[201–204]

THERAPY

Susceptibility testing of *Giardia* is not performed because of the difficulty in establishing cultures from clinical specimens and the lack of standardization of sensitivity testing.[205] Drug resistance can be induced in vitro[206]; however, the significance of this is unclear because some isolates that appear clinically resistant are susceptible in vitro, and vice versa. Most information on drug efficacy, therefore, is provided by clinical trials and cumulative experience.[205,207,208,209] The drug of choice for the therapy of giardiasis in the United States is tinidazole (Tindamax; Mission Pharmacal, San Antonio, TX) (Table 279.3). Like metronidazole, it is a member of the nitroimidazole family. It has high efficacy (approximately

TABLE 279.3 Treatment of Giardiasis

DRUG (FDA PREGNANCY CATEGORY)[a]	DOSAGE	
	ADULT	PEDIATRIC
Tinidazole (C)	2 g, single dose	50 mg/kg, single dose (maximum, 2 g)
Metronidazole[b] (B)	250 mg tid × 5–7 days	5 mg/kg tid × 7 days
Nitazoxanide (B)	500 mg bid × 3 days	Age 12–47 mo: 100 mg bid × 3 days Age 4–11 yr: 200 mg bid × 3 days
Albendazole[b] (C)	400 mg qd × 5 days	15 mg/kg/day × 5–7 days (maximum, 400 mg)
Paromomycin[b] (NC)	500 mg tid × 5–10 days	30 mg/kg/day in 3 doses × 5–10 days
Quinacrine[c] (C)	100 mg tid × 5–7 days	2 mg/kg tid × 7 days
Furazolidone[c] (C)	100 mg qid × 7–10 days	1.25–2 mg/kg qid × 10 days

[a]FDA pregnancy categories: B, Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. C, Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
[b]Not an FDA-approved indication. Maximum of 8.8 mg/kg/day and not recommended for <1 month of age.
[c]No longer produced in the United States; may be obtained from some compounding pharmacies.
FDA, US Food and Drug Administration; *NC,* not categorized.

90%) and a favorable side effect profile, and because of a longer half-life than metronidazole, it can be given once daily.[205] Tinidazole is effective as a single dose for both children and adults and was approved in 2004.[210] Although the US Food and Drug Administration (FDA) has never approved metronidazole for giardiasis, there are over 50 years of experience in using it.

Metronidazole is given in divided doses for 5 to 7 days, with an efficacy of 80% to 95%. Adverse effects for tinidazole and metronidazole are similar: a metallic taste; nausea; dizziness; headache; and, rarely, reversible neutropenia, peripheral neuropathy, or seizures. When taken with alcohol, they can produce a disulfiram-like effect. High-dose, short-course regimens of metronidazole have lower efficacy rates and are sometimes poorly tolerated. There have been concerns about potential mutagenicity of metronidazole; however, this has not been documented in humans.[211] There have been reports of increasing nitroimidazole treatment failures.[207]

The mechanism of action of metronidazole and presumably tinidazole is reductive activation of the nitro group by acceptance of electrons from parasite ferredoxins, although other pathways to activate the nitro group may be involved.[212–214] Nitazoxanide (Alinia; Romark Laboratories, Tampa, FL) was approved in 2003 for use in pediatric giardiasis and cryptosporidiosis and, more recently, for giardiasis treatment in adults.[215] There is limited clinical experience with this drug compared with the nitroimidazoles; efficacy is in the range of 65% to 85% with a 3-day treatment course.[216,217] Its mechanism of action is inhibition of pyruvate-ferredoxin oxidoreductases; however, there does not appear to be cross-resistance with metronidazole-resistant parasites.[218] Its main side effect is gastrointestinal upset.

Meta-analyses of a limited number of trials of albendazole (400 mg for 5 days), a benzimidazole, compared with standard regimens of metronidazole have shown comparable results.[208,219] Albendazole is attractive because it is usually better tolerated than the nitroimidazoles, has efficacy against many intestinal helminths, and is used in low-income regions to decrease intestinal parasitism. However, more clinical experience will be needed to determine its place in therapy.

Quinacrine and furazolidone are no longer manufactured in the United States. Quinacrine has an efficacy of more than 90%, and can be obtained through compounding pharmacies; it is given in divided doses for 5 to 7 days (see Table 279.3). The most common side effects are bitter taste, nausea, vomiting, and abdominal cramping. Yellow discoloration of the skin, urine, and sclerae can occasionally occur. Exfoliative dermatitis is rare. Psychosis occurs uncommonly, and we avoid its use in patients with a significant psychiatric history. Furazolidone has a success rate of about 80% to 85% but may cause gastrointestinal side effects and brown urine and may cause mild hemolysis in glucose-6-phosphate dehydrogenase–deficient individuals.

For patients in whom one drug course fails or who infrequently relapse, a switch to a drug from a different class is generally effective.[205,220] For the unusual patient who is not cured with single-drug therapies, combination treatment, often with metronidazole and quinacrine, can be effective.[125,221,222] A randomized trial comparing metronidazole alone versus metronidazole plus the probiotic *Saccharomyces boulardii* demonstrated higher cure rates in the combination group.[223] When refractory infection is suspected, it is important to establish true persistence by obtaining a repeat stool examination to distinguish it from post-*Giardia* IBS or lactose intolerance. For pregnant women with giardiasis, there is no consistently recommended therapy because of the theoretical adverse effects of anti-*Giardia* drugs on the fetus.[205] When disease is mild and hydration and nutrition can be maintained, therapy can be delayed until after delivery, or at least until after the first trimester. If treatment is necessary, paromomycin, an oral nonabsorbable aminoglycoside,[224] can be tried. In limited clinical experience, this approach has an efficacy rate of 60% to 70%.[224] Paromomycin is given in divided doses for 5 to 10 days (see Table 279.3). Metronidazole has been used extensively in pregnancy for the treatment of trichomoniasis. The teratogenic effect appears to be minimal and, if present, is greatest during the first trimester, when both metronidazole and tinidazole should not be used.[205,225] If therapy cannot be avoided, then metronidazole, tinidazole, and nitazoxanide can probably be used safely in the last two trimesters of pregnancy. Table 279.3 lists the FDA pregnancy categories for each of the agents.

There is no established role for nonpharmaceutical therapies. A number of studies have found various effects on *Giardia* infections, disease, or interactions with other gut pathogens as a result of micronutrient administration[167,226–228] The interpretation and generality of the effects are unclear and require confirmation. However, the findings of these studies suggest a complex interaction of micronutrients with the pathogenicity of enteric organisms.

A defined management approach to chronic post-*Giardia* infection chronic sequelae in nonendemic populations has yet to be established.[229]

PREVENTION

The prevention of giardiasis requires proper handling and treatment of water used for communities and good personal hygiene. Although halogenation (e.g., chlorine and iodine) alone is sufficient to kill *G. lamblia* cysts, important variables, such as water temperature, clarity, pH, and contact time, alter the efficacy of chlorine, and higher chlorine levels (4–6 mg/L) may be required.[72,230] Thus, in addition to chlorination, public water supplies intended for drinking should also be subjected to coagulation-flocculation, sedimentation, and filtration.[69]

Travelers to low-income regions of the world or to wilderness areas should consider all water potentially contaminated because of the wide array of animal and human reservoirs of giardiasis. Bringing water to a boil is sufficient to kill all protozoal cysts; at high altitudes, boiling for a minute is reasonable. If boiling is impossible, halogenation is generally effective for *Giardia,* but *Cryptosporidium* is resistant.[72,230] There are many chlorine-based (e.g., chlorine bleach: 5% to 6%, 2 to 4 drops/L) or iodine-based (e.g., tincture of iodine: 2%, 5 drops/L) preparations in liquid or tablet form.[230] Contact time should be increased for water that is cold, and the concentration of halogen should be increased for turbid water. Personal water filters with pores of an "absolute" micron size of 0.2 to 1.0 µm can be used.[230] Filtered water should also be halogenated to kill enteric viruses if they are considered a risk. Uncooked foods that may have been washed or prepared in contaminated water should be avoided.

Giardiasis outbreaks in daycare centers can be difficult to resolve. Some recommend that only symptomatic children be treated; however, infected children transmit *Giardia* to parents and family members, with further potential spread to the community. Therefore, each situation requires an individual decision. If strict hand washing and treatment of