

## Antiparasitic Therapy

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After completing this article, you should be able to: (1) recognize clinical presentations of the major protozoan and helminth infections in humans, (2) prescribe appropriate treatment for protozoan and helminth infections, and (3) recognize the adverse effects of antiparasitic therapies.

**Parasitic diseases affect more than 2 billion people globally and cause substantial morbidity and mortality, particularly among the world's poorest people. This overview focuses on the treatment of the major protozoan and helminth infections in humans. Recent developments in antiparasitic therapy include the expansion of artemisinin-based therapies for malaria, new drugs for soil-transmitted helminths and intestinal protozoa, expansion of the indications for antiparasitic drug treatment in patients with Chagas disease, and the use of combination therapy for leishmaniasis and human African trypanosomiasis.**

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AL = artemether-lumefantrine; CBC = complete blood cell count; CL = cutaneous leishmaniasis; CNS = central nervous system; DEC = diethyl-carbamazine; G6PD = glucose-6-phosphate dehydrogenase; HAT = human African trypanosomiasis; HIV = human immunodeficiency virus; LF = lymphatic filariasis; ML = mucocutaneous leishmaniasis; NCC = neurocysticercosis; STH = soil-transmitted helminth; TMP-SMX = trimethoprim-sulfamethoxazole; VL = visceral leishmaniasis; VLM = visceral larva migrans

Parasitic diseases cause substantial morbidity and mortality worldwide, taking the heaviest toll among the world's poorest people. This article reviews the treatment of the major protozoan and helminth infections in humans.

### PROTOZOA AND THE DISEASES THEY CAUSE

Protozoa are single-celled eukaryotes that cause a diverse array of human diseases. They are generally categorized as systemic or intestinal and usually do not cause eosinophilia.

#### SYSTEMIC PROTOZOA

**Malaria.** Human malaria is caused by the mosquito-borne parasites *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*, which parasitize red blood cells and cause hemolytic anemia. Malaria kills nearly 1 million people and causes almost 300 million symptomatic illnesses annually. It is found in sub-Saharan Africa, Asia, Oceania, and Latin America. Uncomplicated malaria can manifest as fever, anemia, thrombocytopenia, myalgias, cough, and diarrhea. Severe malaria is defined in part by

respiratory distress, renal failure, altered mental status or seizures, intolerance of oral medications, metabolic acidosis or hypoglycemia, and parasitemia greater than 5%. The mortality rate of severe malaria is high.

#### Treatment of Uncomplicated *P falciparum* Malaria.

The preferred treatment for uncomplicated *P falciparum* malaria acquired in areas with chloroquine resistance is atovaquone-proguanil, artemether-lumefantrine (AL), or oral quinine plus doxycycline.<sup>1</sup>

Atovaquone-proguanil is a well-tolerated, oral fixed-dose combination. Atovaquone inhibits parasite mitochondrial electron transport. Proguanil inhibits the dihydrofolate reductase step in purine synthesis and lowers the concentration of atovaquone necessary to kill *Plasmodium* species. Adverse effects include nausea, vomiting, abdominal pain, and hepatitis.

Artemether-lumefantrine is an oral fixed-dose combination recently approved in the United States. Artemether is a semisynthetic derivative of artemisinin, a sesquiterpene lactone. Lumefantrine, a fluorene derivative, may interfere with heme metabolism. Artemether-lumefantrine is rapidly effective against all erythrocytic stages of malaria. Adverse effects include nausea, vomiting, dizziness, headache, and possibly QT prolongation.<sup>2</sup> It should be taken with fatty foods to increase absorption.

Oral quinine plus doxycycline (or plus tetracycline or clindamycin) is effective for uncomplicated malaria. Quinine is an aryl-amino alcohol, which may cause toxic heme accumulation in the parasite. It can cause cinchonism (nausea,

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sea, vomiting, tinnitus, high-frequency hearing loss, and dizziness). Both tetracyclines and clindamycin inhibit expression of the *Plasmodium* apicoplast genome. Adverse effects include nausea, vomiting, abdominal pain, candidiasis, and photosensitivity for doxycycline and nausea, vomiting, abdominal pain, and diarrhea for clindamycin.

Mefloquine, an aryl-amino quinoline, has the same mechanism of action as quinine. Due to resistance, it is not recommended for patients infected in much of Southeast Asia. It can cause neuropsychiatric disturbances and QT prolongation at treatment doses and is a second-line agent.

Chloroquine is recommended for uncomplicated *P falciparum* malaria acquired in areas without chloroquine resistance. It is a 4-aminoquinoline and may act by disrupting heme metabolism. Adverse effects include nausea, vomiting, diarrhea, headache, and blurred vision. Pruritis also occurs, mostly in African patients. Hydroxychloroquine is an acceptable alternative.<sup>1</sup>

**Treatment of Severe Malaria.** Severe malaria (usually caused by *P falciparum*) should be treated with parenteral medications, such as intravenous artesunate, quinine, or quinidine. Artesunate is preferred because it works faster, is more effective, and is better tolerated than quinine.<sup>3,4</sup> In the United States, artesunate is available from the Centers for Disease Control and Prevention for severe malaria in patients who meet certain criteria.<sup>5</sup> Artesunate is combined with atovaquone-proguanil, doxycycline, clindamycin, or mefloquine to prevent recurrent parasitemia.<sup>3</sup> Artesunate is well tolerated, with adverse effects similar to artemether. At high doses, it may cause neutropenia.<sup>6</sup>

Quinidine gluconate, which has the same mechanism of action as quinine, is available for severe malaria in the United States. Patients should be monitored with telemetry and have blood glucose and drug levels followed up closely. Adverse effects include infusion-related hypotension, QT prolongation, torsades de pointes, and hypoglycemia. Although less cardiotoxic than quinidine, parenteral quinine is not available in the United States. It can cause infusion-related hypotension, hypoglycemia, and cinchonism. Both quinine and quinidine should be combined with doxycycline, tetracycline, or clindamycin, and patients can transition to oral therapy after improvement.

**Treatment of Uncomplicated Non-falciparum Malaria.** Chloroquine plus primaquine is effective for uncomplicated *P vivax* and *P ovale* malaria in most of the world. Patients infected in areas with chloroquine-resistant *P vivax* and *P ovale* (particularly Papua New Guinea and Indonesia) should be treated with atovaquone-proguanil, mefloquine, or quinine plus doxycycline. Patients infected with *P vivax* or *P ovale* should receive primaquine (an 8-aminoquinolone) for 14 days to prevent relapse. Because primaquine can cause hemolytic anemia in glucose-6-phosphate dehydro-

genase (G6PD)-deficient patients, G6PD levels should be measured before use. Other adverse effects include nausea and vomiting. *P malariae* or *P knowlesi* infections can usually be treated with chloroquine.<sup>1,7</sup>

**Resistance.** Chloroquine resistance is widespread. Due to resistance, mefloquine is not recommended for malaria acquired in much of Southeast Asia. Parts of South America and equatorial Africa also have high mefloquine treatment failure rates.<sup>8</sup> Atovaquone-proguanil-resistant *P falciparum* is rare. The World Health Organization recommends that artemisinins be used exclusively in combination regimens, but strains of *P falciparum* with decreased sensitivity to artemisinins have emerged along the border between Cambodia and Thailand, in part because of long-standing monotherapy practices.<sup>9</sup> Of 22 African countries, 2 (Ghana and Burkina Faso) had failures in more than 10% of *P falciparum* cases treated with AL in one study.<sup>8</sup> Treatment failure rates with AL of more than 20% have occurred only in Cambodia.<sup>8</sup> Chloroquine-resistant *P vivax* occurs primarily in Southeast Asia and Oceania, but cases have been reported in South America, Ethiopia, and the Solomon Islands. *P vivax* treatment failure rates of more than 10% with AL have occurred in Papua New Guinea.<sup>8</sup> The Worldwide Antimalarial Resistance Network has developed an online database of malaria resistance.<sup>10</sup>

Treatment regimens for all types of malaria are summarized in Table 1.

**New Developments.** Arterolane, a synthetic trioxolane derived from artemisinins, is undergoing phase 3 clinical trials in combination with piperazine for *P falciparum* malaria.<sup>11</sup> In 2 recent clinical trials, both once-daily pyronaridine-artesunate and azithromycin plus artesunate were noninferior to AL for *P falciparum* malaria.<sup>12,13</sup>

**African Trypanosomiasis.** Human African trypanosomiasis (HAT, or sleeping sickness) is caused by 2 subspecies of *Trypanosoma brucei* that are endemic only to Africa and transmitted by tsetse flies. In the United States, only 1 or 2 cases occur annually (among returning travelers). *T brucei rhodesiense* causes a rapidly progressive disease in Eastern and Southern Africa, whereas *T brucei gambiense* causes a more indolent disease in West and Central Africa. Initially, patients develop fever, lymphadenopathy, hepatosplenomegaly, and rash. Later, a chronic meningoencephalitis occurs with headaches, listlessness, disordered sleep, and neuromuscular dysfunction. Drugs for HAT are toxic; however, left untreated, the disease is fatal.

***T b gambiense.*** Pentamidine and suramin are available for early-stage *T b gambiense* disease. Neither drug crosses the blood-brain barrier, and for late-stage (central nervous system [CNS]) disease, eflornithine and melarsoprol are used (Table 1).

TABLE 1. Treatment Regimens for Protozoal Infections in Adults<sup>a</sup>

	Medication	Dose	Adverse effects	Additional information
	First-line treatment			
	Second-line treatment			
<b>Systemic protozoa</b>				
Malaria—uncomplicated				
<i>Plasmodium falciparum</i> or species unknown				
Chloroquine-resistant area (everywhere except Central America west of Panama Canal, Haiti, Dominican Republic, and parts of the Middle East)	Atovaquone-proguanil	250 mg/100 mg, 4 adult tablets orally every day for 3 d	Nausea, vomiting, hepatitis	Should be taken with food
	<i>OR</i> Artemether-lumefantrine	20 mg/120 mg, 4 tablets oral starting dose, followed by 4 tablets orally 8 h later, followed by 4 tablets orally twice a day for 2 d	Headache, dizziness, vomiting	Should be taken with fatty foods
	<i>OR</i> Quinine <sup>b</sup>	625 mg salt orally 3 times a day for 7 d for patients infected in Southeast Asia or for 3 d in other patients	Cinchonism, <sup>c</sup> hypoglycemia	
	<i>plus</i> Doxycycline <i>or</i> Tetracycline	100 mg orally twice a day 250 mg orally 4 times a day	Nausea, vomiting, abdominal pain, candidiasis, photosensitivity	
	<i>or</i> Clindamycin	6-7 mg/kg orally 3 times a day for 7 d	Nausea, vomiting, diarrhea, abdominal pain	
	Mefloquine <sup>b</sup>	750 mg salt oral loading dose followed by 500 mg salt orally 6-12 h after initial dose	Nausea, vomiting, vivid dreams, dysphoria, mood changes, QT prolongation	
Chloroquine-sensitive area (Central America west of Panama Canal, Haiti, Dominican Republic, and parts of the Middle East)	Chloroquine <sup>b</sup>	1000 mg salt oral loading dose followed by 500 mg salt orally at 6 h, 24 h, and 48 h	Nausea, vomiting, headache, dizziness, pruritis (usually in African patients), photosensitivity	
	Hydroxychloroquine <sup>b</sup>	800 mg salt oral loading dose followed by 400 mg salt orally at 6 h, 24 h, and 48 h	Retinal toxicity unlikely with short-term use	
Malaria—severe Usually <i>P falciparum</i>	Artesunate per CDC protocol	2.4 mg/kg IV at 0 h, 12 h, 24 h, and 48 h, then once per day if IV still necessary		Can be requested from CDC Malaria Hotline <sup>d</sup>
	<i>plus</i> Atovaquone-proguanil, doxycycline, clindamycin, or mefloquine			
	Quinidine <sup>b</sup>	Loading dose of 10 mg/kg salt IV over 1-2 h followed by 0.02 mg/kg/min salt continuous infusion for 24 h	Infusion-related hypotension, QT and QRS prolongation, arrhythmias, hypoglycemia	Continuous ECG and close BP and blood glucose monitoring mandatory
	Once improved, switch to oral quinine	625 mg salt orally 3 times a day		
	<i>plus</i> Doxycycline <i>or</i> Tetracycline <i>or</i> Clindamycin	100 mg IV/orally twice daily for 7 d 250 mg orally 4 times daily for 7 d 10 mg/kg IV loading dose then 5 mg/kg IV every 8 h (or oral dose as above) for 7 d Total duration of quinidine/quinine therapy is 7 d for patients infected in Southeast Asia, 3 d for elsewhere		

(continued on next page)

TABLE 1. **Continued**<sup>a</sup>

	Medication	Dose	Adverse effects	Additional information
	First-line treatment			
	Second-line treatment			
<b>Systemic protozoa (continued)</b>				
Malaria—uncomplicated <i>Plasmodium vivax</i> or <i>Plasmodium ovale</i> All regions except Papua New Guinea and Indonesia (or other areas with documented chloroquine resistance)	Chloroquine Followed by primaquine <sup>b</sup>	See <i>P falciparum</i> 52.6 mg salt orally every day for 14 d	Nausea and vomiting, hemolytic anemia with G6PD deficiency	
	Hydroxychloroquine Followed by primaquine	See <i>P falciparum</i>		
Malaria—uncomplicated <i>P vivax</i> or <i>P ovale</i> Chloroquine-resistant areas (Papua New Guinea and Indonesia)	Quinine plus Doxycycline, tetracycline, or clindamycin Followed by primaquine or Atovaquone-proguanil Followed by primaquine	See <i>P falciparum</i>  See <i>P falciparum</i>		
	Mefloquine Followed by primaquine	See <i>P falciparum</i>		
Malaria—uncomplicated <i>Plasmodium malariae</i> or <i>Plasmodium knowlesi</i>	Chloroquine or Hydroxychloroquine	See <i>P falciparum</i>		
African trypanosomiasis Early (hemolymphatic stage) <i>Trypanosoma brucei</i> <i>gambiense</i>	Pentamidine	4 mg/kg/d IM for 7-10 d	Hypotension (with IV infusion), hypo- glycemia, hepatitis, pancreatitis, leuko- penia, sterile abscesses, nephrotoxicity	
	Suramin	100-200 mg IV (test dose) followed by 1 g IV on days 1, 3, 7, 14, and 21	Nephrotoxicity, rash (including exfoliative dermatitis), fatal hyper- sensitivity reaction (1 in 20,000 doses), peripheral neuropathy, myelosuppression	Available from CDC Drug Service <sup>e</sup>
<i>Trypanosoma brucei</i> <i>rhodesiense</i>	Suramin	Dosed as above		
Late (CNS stage) <i>T b gambiense</i>	Eflornithine	100 mg/kg IV every 6 h for 14 d	Fever, seizures, myelo- suppression, peripheral neuropathy, diarrhea, hypertension, rash	Given as prolonged infusion. Contact CDC Drug Service regarding avail- ability <sup>e</sup>
	or Eflornithine plus Nifurtimox	200 mg/kg IV every 12 h for 7 d  5 mg/kg orally 3 times a day for 10 d	Nausea, vomiting, anorexia, abdominal pain, insomnia, peripheral neuropathy, hepatitis. Avoid alcohol	Available from CDC Drug Service <sup>e</sup>
	Melarsoprol	2.2 mg/kg/d IV for 10 d	Vomiting, nephrotoxicity, hepatitis, myocardial damage, peripheral neuropathy, fever, thrombocytopenia, reac- tive encephalopathy (often fatal). Encephalopathy risk reduced by coadmin- istration of corticoste- roids. Contraindicated with G6PD deficiency	Available from CDC Drug Service <sup>e</sup>

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TABLE 1. Continued<sup>a</sup>

	Medication	Dose	Adverse effects	Additional information
	First-line treatment			
	.....			
	Second-line treatment			
<b>Systemic protozoa (continued)</b>				
<i>T b rhodesiense</i>	Melarsoprol	2.0-3.6 mg/kg/d IV for 3 d. Repeat course after 7 d and then again 7 d after the completion of the 2nd course		Available from CDC Drug Service <sup>c</sup>
American trypanosomiasis (Chagas disease)	Benznidazole	2.5-3.5 mg/kg orally twice a day for 60 d	Nausea, vomiting, anorexia, insomnia, peripheral neuropathy, dermatitis, myelosuppression. Disulfiram-like reaction with alcohol	Contact CDC Drug Service <sup>c</sup> regarding availability Should be taken with food
	Nifurtimox	2-3 mg/kg orally every 6-8 h for 90 d		Should be taken after meals Available from CDC Drug Service <sup>c</sup>
Leishmaniasis				
Visceral	Liposomal amphotericin	Immunocompetent adults: 3 mg/kg IV once a day on days 1-5, 14, and 21 Immunocompromised adults: 4 mg/kg IV once a day on days 1-5, 10, 17, 24, 31, and 38	Nephrotoxicity, electrolyte wasting, hypertension, infusion reaction, chills/rigors	Multiple regimens used, including shorter-course amphotericin-based regimens and combination regimens
	Sodium stibogluconate or Miltefosine	20 mg/kg IV or IM once a day for 28 d 2.5 mg/kg/d (maximum 150 mg/d) orally for 28 d	Nausea, vomiting, severe vertigo, headache, diarrhea	Not commercially available in the US; contact Caligor Rx, Inc, for availability <sup>f</sup>
	or Paromomycin	15 mg/kg/d IM for 21 d	Nephrotoxicity, ototoxicity, hepatitis	
Cutaneous	Sodium stibogluconate	20 mg/kg/d IV or IM for 20 d	Pentavalent antimonials: nausea, vomiting, abdominal pain, pancreatitis, hepatitis, myalgias, myelosuppression, ECG abnormalities	Available from CDC Drug Service <sup>c</sup> Decision whether to use systemic therapy for cutaneous leishmaniasis is complex. When used, most appropriate drug depends in part on infecting species and region acquired
	Miltefosine	2.5 mg/kg/d (maximum 150 mg/d) orally for 28 d		
	or Fluconazole	200 mg orally once a day for 6 wk	Headache, anorexia, hepatitis, alopecia	
	or Liposomal amphotericin	3 mg/kg IV once a day on days 1-5, 14, and 21		Optimal dosing regimen not defined
	or Pentamidine	2-3 mg/kg IV or IM once a day or every other day for 4-7 d		

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TABLE 1. **Continued**<sup>a</sup>

	Medication	Dose	Adverse effects	Additional information
	First-line treatment			
	Second-line treatment			
<b>Systemic protozoa (continued)</b>				
Mucocutaneous	Sodium stibogluconate	20 mg/kg/d IV or IM for 28 d		
	Liposomal amphotericin or Amphotericin deoxycholate or Miltefosine	3 mg/kg IV once a day 0.5-1.0 mg/kg IV once a day for 1 mo 2.5 mg/kg (maximum 150 mg/d) orally once a day for 28 d		Multiple regimens used
Babesiosis	Atovaquone	750 mg orally twice a day	Rash, abdominal pain, diarrhea, nausea, vomiting, headache, insomnia, methemoglobinemia, hepatotoxicity	Higher doses, longer duration of therapy for immunosuppressed patients (see text)
	<i>plus</i> Azithromycin	500 mg orally for 1 d then 250 mg orally once a day for 7-10 d	Nausea, vomiting, abdominal pain, diarrhea, headache, hepatotoxicity	
	Quinine <i>plus</i> Clindamycin	650 mg orally 3 times a day 300-600 mg IV every 6 h or 600 mg orally 3 times a day for 7-10 d		
Toxoplasmosis	Pyrimethamine	200 mg orally once followed by 50 mg (if <60 kg) or 75 mg (if >60 kg) orally once a day	Myelosuppression, abdominal pain, rash, headaches, dysgeusia	No treatment for acute illness in nonpregnant/immunocompetent patients
	<i>plus</i> Sulfadiazine	1 g/kg (if <60 kg) or 1.5 g/kg (if >60 kg) orally 4 times a day	Myelosuppression, rash, crystal-induced nephropathy	Duration of therapy based on clinical situation
	<i>plus</i> Folinic acid	10-25 mg orally once a day		
	TMP-SMX	5/25 mg/kg orally or IV every 12 h Higher doses have been used in some cases	Rash, urticaria, nausea, vomiting, myelosuppression. Rarely: Stevens-Johnson syndrome, renal insufficiency, hyperkalemia, hepatitis	Consider concomitant systemic corticosteroids for chorioretinitis
	For patients with sulfa allergy: Pyrimethamine <i>plus</i> Folinic acid <i>plus either</i> Clindamycin <i>or</i> Atovaquone	Doses as above 600 mg IV every 6 h or 450 mg orally 4 times a day 750 mg orally every 6 h		
Acquired during pregnancy	Consider spiramycin <i>or</i> Pyrimethamine/sulfadiazine depending on clinical situation and gestational age (see text) Suggest expert consultation (see box to right)		Spiramycin: nausea, abdominal pain, diarrhea	Commercially unavailable in the US but can be obtained from PAMF-TSL <sup>g</sup>
Congenital	Consider prolonged pyrimethamine/sulfadiazine Suggest expert consultation (see box to right)			University of Chicago Congenital Toxoplasmosis Study Group may be able to provide clinical guidance <sup>h</sup>

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TABLE 1. Continued<sup>a</sup>

	Medication	Dose	Adverse effects	Additional information
	First-line treatment			
	Second-line treatment			
<b>Intestinal/genitourinary protozoa</b>				
Giardiasis	Tinidazole or Metronidazole	2 g orally once 250 mg orally 3 times a day for 5-7 d	Anorexia, metallic taste, alcohol-induced disulfiram-like reaction, headache, peripheral neuropathy, seizures, neutropenia	
	Nitazoxanide	500 mg orally twice a day for 3 d	Nausea, vomiting, abdominal pain, diarrhea	
<b>Amebiasis (<i>Entamoeba histolytica</i>)</b>				
Asymptomatic carrier	Luminal agent: Paromomycin	8-12 mg/kg orally 3 times a day for 7 d	Nausea, vomiting, abdominal pain	
	or Iodoquinol	650 mg orally 3 times a day for 20 d	Nausea, vomiting, diarrhea, pruritis, headache	
	Diloxanide	500 mg orally 3 times a day for 10 d		Commercially unavailable in the US but may be available through Abbott India Ltd <sup>†</sup>
Amebic colitis	Metronidazole or Tinidazole Followed by luminal agent (see above)	500-750 mg orally 3 times a day for 10 d 2 g orally once a day for 3 d		
Amebic liver abscess or other disseminated disease	Metronidazole or Tinidazole Followed by luminal agent (see above)	750 mg orally or IV 3 times daily 2 g orally once a day		Length of metroni- dazole or tinida- zole component of therapy often based on clinical response
<b>Cryptosporidiosis</b>				
Non-AIDS-associated AIDS-associated	Nitazoxanide HAART Consider nitazoxanide	500 mg orally twice a day for 3 d		
<b>Cyclosporiasis</b>				
Non-AIDS-associated AIDS-associated	TMP-SMX TMP-SMX	1 DS tablet orally twice a day for 7-10 d 1 DS tablet orally 4 times a day for 10 d followed by twice a day for 3 wk		
	Ciprofloxacin	500 mg orally twice a day for 7 d followed by 1 tablet orally 3 times a week for 2 wk	Nausea, vomiting, abdominal pain. Rarely: tendinopathy, neuro- psychiatric effects	
<b>Isosporiasis</b>				
Non-AIDS-associated AIDS-associated	TMP-SMX TMP-SMX	1 DS tablet orally twice a day for 10 d 1 DS tablet orally 4 times a day for 10 d followed by twice a day for 3 wk		
	Ciprofloxacin	500 mg orally twice a day for 7 d		
Dientamoebiasis	Iodoquinol	650 mg orally 3 times a day for 20 d		
<i>Blastocystis hominis</i>	Nitazoxanide	500 mg orally twice a day for 3 d		Treatment contro- versial

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TTABLE 1. **Continued**<sup>a</sup>

	Medication	Dose	Adverse effects	Additional information
First-line treatment				
.....				
Second-line treatment				
<b>Intestinal/genitourinary protozoa (continued)</b>				
Trichomoniasis	Tinidazole	2 g orally once		Sexual partners should be treated
	Metronidazole	2 g orally once or 500 mg orally twice a day for 7 d		
<b>Free-living amebae</b>				
<i>Naegleria fowleri</i>	Therapy should include amphotericin B Consider intrathecal amphotericin Combination systemic therapy is essential: consider addition of azoles, rifampin, or other anti-microbial agents (see text)			
<i>Acanthamoeba</i> species GAE and disseminated disease	Combination therapy is essential and should include pentamidine, azoles, sulfonamides, and possibly flucytosine (see text)			
<i>Acanthamoeba</i> keratitis	Topical chlorhexidine	0.02%		May be available via compounding pharmacies <sup>j</sup>
	Polyhexamethylene biguanide	0.02%		
<i>Balamuthia mandrillaris</i>	Combination therapy is essential and should likely include flucytosine, pentamidine, fluconazole, sulfadiazine, macrolides (see text)			

<sup>a</sup> BP = blood pressure; CDC = Centers for Disease Control and Prevention; CNS = central nervous system; DS = double-strength; ECG = electrocardiography; GAE = granulomatous amebic encephalitis; G6PD = glucose-6-phosphate dehydrogenase; HAART = highly active antiretroviral therapy; IM = intramuscular; IV = intravenous; TMP-SMX = trimethoprim-sulfamethoxazole; PAMF-TSL = Palo Alto Medical Foundation Toxoplasma Serology Laboratory; US = United States.

<sup>b</sup> Dosing conversion for base formulation dose based on salt formulation dose: oral quinine 625 mg salt = 542 mg base; IV quinidine 10 mg/kg salt = 6.25 mg/kg base and 0.02 mg/kg/min salt = 0.0125 mg/kg/min base; oral mefloquine 750 mg salt = 684 mg base, and 500 mg salt = 456 mg base; oral chloroquine 1000 mg salt = 600 base, and 500 mg salt = 300 mg base; oral hydroxychloroquine 800 mg salt = 620 mg base and 400 mg salt = 310 mg base; oral primaquine 52.6 mg salt = 30 mg base.

<sup>c</sup> Symptoms of cinchonism include nausea, vomiting, dizziness, tinnitus, and high-frequency hearing loss.

<sup>d</sup> CDC Malaria Hotline (770-488-7788 M-F 9:00 AM to 5:00 PM EST or 770-488-7100 other hours).

<sup>e</sup> CDC Drug Service (404-639-3670).

<sup>f</sup> Caligor Rx, Inc, New York, NY (212-369-6000 or for emergencies 917-692-0195).

<sup>g</sup> PAMF-TSL (650-853-4828).

<sup>h</sup> University of Chicago Congenital Toxoplasmosis Study Group (773-834-4152).

<sup>i</sup> Diloxanide may be available from Abbott India Ltd, Mumbai, India (+91 22 67978888).

<sup>j</sup> A compounding pharmacy that specializes in ophthalmic drugs is Leiter's Park Avenue Pharmacy in San Jose, CA (800-292-6773).

Pentamidine, an aromatic diamidine, is preferred for early-stage disease. Pentamidine reduces the mitochondrial membrane potential and binds to nucleic acids. It is given intramuscularly and can cause hypotension, hypoglycemia, leukopenia, nephrotoxicity, hepatitis, and pancreatitis.

Suramin, a sulfonated naphthylamine, inhibits multiple trypanosome metabolic enzymes. It is a second-line treatment for early-stage disease because of toxicity, including

exfoliative dermatitis, peripheral neuropathy, nephrotoxicity, myelosuppression, and a potentially fatal hypersensitivity reaction. Suramin is active against *Onchocerca volvulus*, and reactions (from dying parasites) can occur in coinfecting patients.<sup>14</sup>

Eflornithine, which inhibits ornithine decarboxylase, is the preferred drug for late-stage *T b gambiense* disease. It is less toxic than melarsoprol but not reliably effective



against *T b rhodesiense*. Adverse reactions include fever, myelosuppression, hypertension, rash, peripheral neuropathy, and diarrhea.

Melarsoprol, an organic arsenical agent, remains the most widely used drug against late-stage HAT despite being the most toxic. Its mechanism of action is unknown. The most feared adverse effect is reactive encephalopathy, which occurs in 5% to 10% of patients and is fatal in half of cases.<sup>14</sup> Coadministration of corticosteroids lowers the risk of encephalopathy.<sup>15</sup> Other adverse effects include vomiting, abdominal pain, thrombophlebitis, peripheral neuropathy, fever, and thrombocytopenia.

Nifurtimox-eflornithine combination therapy was more effective than eflornithine monotherapy for late-stage *T b gambiense* and enabled shorter treatment courses in 2 clinical trials.<sup>16</sup> Another trial found that melarsoprol-nifurtimox combination therapy was more effective than melarsoprol alone.<sup>17</sup> However, a subsequent study found that patients with late-stage *T b gambiense* disease who were treated with melarsoprol-nifurtimox had higher death rates than those treated with other combination regimens.<sup>18</sup>

***T b rhodesiense*.** There is little new clinical evidence regarding the treatment of *T b rhodesiense*. Suramin is used for early-stage disease, and melarsoprol is used for late-stage disease (Table 1).<sup>14</sup>

**Resistance.** Up to 30% of patients infected with *T b gambiense* do not respond to melarsoprol,<sup>19</sup> and 6% to 8% may receive no benefit from eflornithine in some regions.<sup>20</sup> Suramin and melarsoprol resistance have occurred in clinical isolates of *T b rhodesiense* from Tanzania.<sup>21</sup>

**Drugs in Development.** Clinical trials with fexinidazole, an oral 5-nitroimidazole active against *T b gambiense* and *T b rhodesiense*, are under way.<sup>22</sup>

**American Trypanosomiasis.** American trypanosomiasis (Chagas disease) is caused by *Trypanosoma cruzi*, which is endemic only to Latin America and is usually transmitted by blood-feeding triatomine insects. Acute infection is often asymptomatic, but patients may have unilateral palpebral edema or an erythematous, indurated skin lesion with regional lymphadenopathy. Fever, diffuse lymphadenopathy, hepatosplenomegaly, and (less commonly) meningoencephalitis and myocarditis may occur. Acute disease is generally self-limited. Most patients are subsequently asymptomatic (a state termed *indeterminate Chagas*). Years to decades later, 20% to 40% of cases progress to chronic Chagas disease, which affects the heart (eg, cardiomyopathy, chronic heart failure, and arrhythmias) and the gastrointestinal tract (eg, achalasia, megaesophagus, constipation, obstruction, and megacolon).

The nitroheterocyclic compounds nifurtimox and benznidazole are used to treat Chagas disease (Table 1). Ben-

znidazole is better tolerated and generally considered the drug of choice.<sup>23</sup> Contraindications to treatment include pregnancy and renal and hepatic insufficiency.

Nifurtimox is a 5-nitrofur derivative; its mechanism of action is not well understood. Adverse effects include anorexia, abdominal pain, vomiting, insomnia, paresthesias, peripheral neuropathy, and hepatitis. Discontinuation due to intolerance is common.<sup>24</sup> During therapy, clinicians should screen for peripheral neuropathy, monitor liver and renal function, and obtain a complete blood cell count (CBC).

Benznidazole is a nitroimidazole derivative that may increase phagocytosis. Adverse effects include vomiting, anorexia, dermatitis, and myelosuppression. Dose-dependent peripheral neuropathy, severe rash, fever, or lymphadenopathy should prompt discontinuation. Clinicians should check for rash and monitor CBCs as well as liver and renal function test results during treatment.

Although clinical evidence supporting treatment for Chagas disease is limited, most authorities recommend treatment for acute and congenital infections, infections in children, and reactivated infections in immunocompromised patients.<sup>23</sup> The role of therapy in indeterminate and chronic Chagas disease in adults is more controversial, but evidence is emerging that select patients in these groups may benefit.<sup>25</sup> Recent studies suggest that benznidazole for indeterminate or early chronic Chagas disease may improve parasite clearance rates<sup>26,27</sup> and prevent progression to cardiomyopathy.<sup>28</sup> A multicenter, placebo-controlled trial involving benznidazole for the treatment of chronic Chagas disease is under way.<sup>29</sup>

**Resistance and Drugs in Development.** Although strains of *T cruzi* resistant to both nifurtimox and benznidazole can be generated in vitro, documentation of clinical resistance is scarce. Several new triazoles, squalene synthase inhibitors, and cysteine protease inhibitors have shown efficacy in animal models.<sup>25</sup> A phase 2 clinical trial of posaconazole vs benznidazole for chronic Chagas disease is under way.<sup>30</sup>

**Leishmaniasis.** *Leishmania* species are transmitted primarily by sandflies and cause 3 clinical syndromes: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucocutaneous leishmaniasis (ML).

**Visceral Leishmaniasis.** Visceral leishmaniasis is caused predominantly by *Leishmania donovani* on the Indian subcontinent and East Africa and by *Leishmania infantum/chagasi* elsewhere. Infection with these species results in subclinical infection in most patients and kala-azar (fever, weight loss, hepatosplenomegaly, hyperglobulinemia, neutropenia, and death) in a minority. Ninety percent of VL cases occur in India, Bangladesh, Nepal, Sudan, and

Brazil. The drug of choice for VL in the United States is liposomal amphotericin (Table 1). Multiple dosing schedules and other treatment regimens are used globally.

Liposomal amphotericin, a polyene, forms pores in cell membranes. In India, single-dose liposomal amphotericin was as effective as 29 days of amphotericin B deoxycholate in a recent trial.<sup>31</sup> Amphotericin causes nephrotoxicity, electrolyte loss, fever, and rigors; however, these occur less frequently with liposomal formulations.

Miltefosine, a synthetic phospholipid analogue and the only orally available drug for VL, causes apoptosis-like cell death. Cure rates appear similar to those obtained with amphotericin in India.<sup>32</sup> Adverse effects include nausea, vomiting, vertigo, diarrhea, hepatitis, renal insufficiency, and teratogenicity. There is concern that monotherapy may lead to drug resistance.<sup>33</sup>

Pentavalent antimonial agents, such as sodium stibogluconate, were previously the therapeutic choice for VL. Currently, resistance limits their use, especially in South Asia.<sup>34</sup> Antimonial agents inhibit several parasitic enzymes, but they are poorly tolerated. Adverse effects include anorexia, vomiting, pancreatitis, hepatitis, myalgias, cytopenias, QT prolongation, and arrhythmias. Renal and liver function tests, CBCs, amylase/lipase measurements, and electrocardiography should be monitored during treatment. Response rates are variable and relapses common.

Paromomycin, an aminoglycoside that inhibits metabolism and mitochondrial respiration, is an alternative for VL. Paromomycin was noninferior to amphotericin in India in a recent study.<sup>35</sup> Adverse effects include ototoxicity, nephrotoxicity, and hepatotoxicity.

Combination therapy for VL may shorten treatment duration, decrease toxicity, and prevent resistance.<sup>36</sup> In Sudan, paromomycin plus antimony was more effective than antimony alone.<sup>37</sup> Single-dose liposomal amphotericin plus short-course miltefosine was effective and well tolerated in India, as was single-dose liposomal amphotericin plus short-course paromomycin and short-course miltefosine plus paromomycin.<sup>38</sup>

**Cutaneous Leishmaniasis.** Cutaneous leishmaniasis usually presents as nodular skin lesions that slowly enlarge and ulcerate. Ninety percent of CL cases occur in Afghanistan, Pakistan, Syria, Saudi Arabia, Algeria, Iran, Brazil, and Peru. Because the lesions of CL usually heal spontaneously, the decision to treat depends on lesion location and size, the region of acquisition and infecting species, the risk of progression to ML (limited to some New World CL infecting species), and patient preference.

New World CL is commonly caused by *Leishmania braziliensis*, *Leishmania mexicana*, and *Leishmania panamensis*. When the decision is made to treat, antimonial agents are usually used (Table 1). Combination therapy with al-

lopurinol or pentoxifylline plus antimonial agents may be more effective than antimonial agents alone.<sup>39</sup> A 4-week course of miltefosine was as effective as antimonial agents in Colombia but less effective than antimonial agents in Guatemala.<sup>40</sup> Pentamidine has been used for CL caused by *Leishmania guyanensis* in French Guyana, Surinam, and Brazil but is toxic and less effective.<sup>41</sup>

Old World CL is caused mainly by *Leishmania major*, *Leishmania tropica*, or *Leishmania aethiopica*. When systemic treatment is deemed necessary, antimonial agents are usually used (Table 1). Fluconazole cured 79% of CL patients in Saudi Arabia with *L major* at 3 months; however, a subsequent observational study showed no benefit from fluconazole.<sup>42,43</sup> Miltefosine has been used successfully to treat Old World CL.<sup>44</sup> Topical therapy, such as 15% paromomycin-12% methylbenzethonium ointment and intralesional antimonial agents, may be an alternative treatment option for Old World CL. Imiquimod, a topical immunomodulator, improved cure rates in Peru when given with parenteral antimonial agents<sup>45</sup>; however, no benefit was seen in a similar trial in Iran.<sup>46</sup>

Amphotericin (particularly liposomal formulations) has been used successfully in a growing number of CL patients infected in both the Old and New World. Infections caused by at least 5 different *Leishmania* species have been successfully treated with liposomal amphotericin; however, experience remains limited, and the optimal dosing regimen has not yet been determined.<sup>47</sup>

**Mucocutaneous Leishmaniasis.** Patients with CL caused by certain New World *Leishmania* species (eg, *L braziliensis*) can develop ML (ulcerative lesions in the nose, mouth, and pharynx). Mucocutaneous leishmaniasis is usually treated with a 28-day course of antimonial therapy, but response rates are variable and relapses common (Table 1).<sup>33</sup> Cure rates with antimonial agents plus pentoxifylline were higher than with antimonial agents alone in Brazil.<sup>48</sup> Amphotericin and pentamidine have also been used. Oral miltefosine cured 83% of patients with mild ML and 58% with more extensive ML in Bolivia.<sup>49</sup>

**Resistance.** Resistance to pentavalent antimonial agents occurs in 40% to 60% of patients with VL in Bihar, India.<sup>34</sup> Resistance has also been reported from Sudan.<sup>50</sup>

**Drugs in Development.** Sitamaquine (an oral 8-aminoquinoline) cured 50% to 90% of patients with VL in phase 2 trials. Adverse effects included nephrotoxicity and methemoglobinemia (with G6PD deficiency).<sup>51</sup> Trials with azithromycin, amphotericin, miltefosine, and low-dose antimonial agents for CL are ongoing.

**Babesiosis.** *Babesia microti* is the most common cause of babesiosis. This predominantly tick-borne zoonosis is endemic to southern New England, New York, the north

central American Midwest, and Europe. *Babesia* species parasitize red blood cells. Infections are commonly asymptomatic but can be associated with a mild to moderate febrile illness or fulminant hemolytic anemia (usually in patients with immunosuppression or splenectomy). Treating asymptomatic, immunocompetent patients is generally unnecessary unless parasitemia persists for 3 months or more.<sup>52</sup> For mild to moderate illness, atovaquone plus azithromycin is as effective (and better tolerated) than the previous standard, oral quinine plus clindamycin (Table 1).<sup>53</sup> Severe disease can be treated with a 7- to 10-day course of oral quinine plus intravenous clindamycin.<sup>52</sup> Relapse is common in immunocompromised patients, and some authors recommend 6 or more weeks of therapy (including 2 weeks after blood smears are negative).<sup>54</sup> Exchange transfusion is indicated for severe babesiosis (parasitemia of 10% or more; significant hemolysis; or renal, hepatic, or pulmonary compromise). Coinfection with Lyme disease or anaplasmosis should be considered in patients with babesiosis because the same tick transmits all 3 pathogens.

Atovaquone monotherapy can induce resistance in animal models, and resistance emerged during atovaquone and azithromycin treatment in 3 immunocompromised patients.<sup>55</sup>

**Toxoplasmosis.** Toxoplasmosis is most commonly acquired by consuming undercooked meat or other food or water containing *Toxoplasma gondii* cysts. After acute infection, *T. gondii* remains latent and persists for life. Although acute infection is usually asymptomatic, 10% to 20% of patients develop lymphadenopathy or a self-limited mononucleosis-like syndrome. *T. gondii* can also cause chorioretinitis. Immunocompromised patients can develop toxoplasmic encephalitis (usually reactivation of latent disease) and, less commonly, disseminated disease. Toxoplasmosis acquired during pregnancy can cause spontaneous abortion, hydrocephalus, intracranial calcifications, mental retardation, and seizures in the baby. Nonpregnant, immunocompetent patients with acute toxoplasmosis generally do not require antimicrobial therapy. For eye disease, treatment usually includes anti-*Toxoplasma* agents plus systemic corticosteroids. Immunocompromised patients with toxoplasmosis should be treated with 2 antimicrobial agents.

Pyrimethamine (the most effective anti-*Toxoplasma* agent available) plus sulfadiazine (with folinic acid) is preferred (Table 1). Pyrimethamine inhibits dihydrofolate reductase, depleting folate and impairing nucleic acid synthesis. Adverse effects include dose-dependent myelosuppression (which can be ameliorated with concurrent folinic acid), abdominal pain, rash, and headaches. Pyrimethamine is combined with sulfadiazine, another

folate antagonist. In addition to rash and myelosuppression, sulfadiazine can cause crystal-induced nephropathy. Trimethoprim-sulfamethoxazole (TMP-SMX) has similar efficacy to pyrimethamine-sulfadiazine for toxoplasmic encephalitis and chorioretinitis; however, unlike pyrimethamine-sulfadiazine, it is also available intravenously.<sup>56,57</sup> Pyrimethamine plus clindamycin is also effective. If none of these drugs can be used, clarithromycin, azithromycin, atovaquone, and dapsone are alternatives.

**Toxoplasmosis During Pregnancy.** In the United States, spiramycin is generally recommended for toxoplasmosis acquired during pregnancy to reduce the risk of congenital toxoplasmosis (Table 1),<sup>58</sup> although its efficacy is controversial.<sup>59</sup> Spiramycin, a macrolide that inhibits protein synthesis, is well tolerated. Its main adverse effects are abdominal pain and diarrhea. When maternal infection occurs at 18 weeks of gestation or later, or fetal transmission is confirmed, pyrimethamine-sulfadiazine plus folinic acid is usually recommended. Congenitally infected infants are generally treated for 12 months with pyrimethamine-sulfadiazine plus folinic acid (Table 1).

**New Developments.** A clinical trial comparing spiramycin with pyrimethamine-sulfadiazine for the prevention of congenital toxoplasmosis in the babies of women infected at 14 weeks of gestation or later is under way.

#### INTESTINAL AND GENITOURINARY PROTOZOA

**Giardiasis.** *Giardia lamblia* (also called *Giardia duodenalis* and *Giardia intestinalis*) infects the small intestine. It is found worldwide and is a common cause of travelers' diarrhea and childhood diarrhea in areas with poor sanitation. Water-borne transmission is most common, followed by person-to-person and food-borne spread. Some infections are asymptomatic, but most cause diarrhea (often lasting several weeks). Abdominal cramps, bloating, flatulence, weight loss, lactose intolerance, and malabsorption with oily, foul-smelling stools can occur.

Giardiasis can be treated with a single dose of tinidazole (Table 1), which cures more than 90% of cases.<sup>60</sup> This 5-nitroimidazole is converted into toxic radicals that damage DNA. Adverse effects include dysgeusia, nausea, abdominal discomfort, and alcohol-induced disulfiram-like reactions. Rarely, peripheral neuropathy, seizures, and neutropenia occur. Metronidazole, widely used to treat giardiasis in the United States, has a similar mechanism of action and similar adverse effects; a 5- to 7-day course has slightly lower efficacy.<sup>60</sup> Nitazoxanide, an oral nitrothiazolyl-salicylamide, appears to inhibit pyruvate:ferredoxin oxidoreductase. A 3-day course cures 80% to 85% of patients.<sup>60,61</sup> It is generally well tolerated but can cause nausea and vomiting. A recent meta-analysis found that albenda-

zole had comparable efficacy and was better tolerated than metronidazole.<sup>62</sup>

**Amebiasis.** *Entamoeba histolytica*, a protozoan transmitted by the fecal-oral route, is most common in tropical regions. Most infected persons remain asymptomatic, but 10% annually develop invasive disease that presents as nonbloody diarrhea or amebic dysentery. Most adults have gradually worsening diarrhea and abdominal pain; rare complications include liver abscess, toxic megacolon, and ameboma. Asymptomatic persons infected with *E histolytica* are treated to prevent transmission and invasive disease (Table 1). For asymptomatic infections, a “luminal agent” (that is active against cysts), such as paromomycin or iodoquinol, is sufficient. Iodoquinol is an 8-hydroxyquinoline; both it and paromomycin are poorly absorbed and can cause nausea and abdominal cramps. Optic and peripheral neuropathy can occur with prolonged use. Diloxanide is an alternative luminal agent. Symptomatic infections should be treated with a tissue amebicide (eg, metronidazole or tinidazole) plus a luminal agent. Tinidazole may be better tolerated and more effective than metronidazole.<sup>63</sup> Cure rates of greater than 90% have been seen with nitazoxanide,<sup>64</sup> but comparative data with nitroimidazoles are limited.

**Cryptosporidiosis.** *Cryptosporidium parvum* and *Cryptosporidium hominis*, the most common causes of cryptosporidiosis, are found worldwide. They cause diarrhea, which is usually self-limited in immunocompetent hosts. In immunocompromised hosts (particularly patients with AIDS), diarrhea may be severe and persistent. Nitazoxanide accelerates symptom resolution in human immunodeficiency virus (HIV)–negative patients, but results have been mixed in HIV-infected patients, with efficacy greatest in those with CD<sub>4</sub> cell counts higher than 50/μL (Table 1).<sup>65</sup> In patients with AIDS, initiation of antiretroviral agents, particularly protease inhibitors, improves symptoms.<sup>65</sup> Paromomycin, nitazoxanide, macrolides, and rifamycins appear to be ineffective in HIV-infected patients.<sup>66</sup> Several thiazolidines have in vitro activity against *C parvum*.<sup>67</sup>

**Cyclosporiasis.** *Cyclospora cayetanensis* is found worldwide, with highest prevalence in Haiti, Guatemala, Peru, and Nepal. It causes watery diarrhea with abdominal cramps, fatigue, and anorexia. Diarrhea can persist for months, particularly in HIV-infected patients. Cyclosporiasis is treated with TMP-SMX (Table 1). Ciprofloxacin is a less effective alternative; limited data suggest nitazoxanide may also be effective.<sup>68,69</sup>

**Isosporiasis.** Found most commonly in tropical and subtropical regions, isosporiasis is caused by *Isospora belli*.

Symptoms are similar to those of cyclosporiasis. Diarrhea is often self-limited in immunocompetent hosts but may be prolonged in those who are immunocompromised. Treatment is with TMP-SMX, and, as with cyclosporiasis, higher doses are used in patients with AIDS (Table 1). Ciprofloxacin, pyrimethamine (with folinic acid),<sup>70</sup> and nitazoxanide<sup>71</sup> are alternatives.

**Dientamoeba fragilis.** *D fragilis* is a trichomonad that may cause diarrhea and may be associated with irritable bowel syndrome. Iodoquinol is the preferred treatment; metronidazole, paromomycin, and tetracyclines have also been used successfully (Table 1).<sup>72</sup>

**Blastocystis hominis.** *B hominis* is a protozoan that has also been linked to irritable bowel syndrome. Whether it truly causes disease is controversial, but some evidence supports a trial of antiparasitic therapy in infected patients with abdominal pain or diarrhea and no alternative explanation for their symptoms.<sup>73</sup> Therapeutic options include nitazoxanide, metronidazole, and iodoquinol (Table 1).

**Trichomonas vaginalis.** Trichomoniasis is a common sexually transmitted infection caused by *T vaginalis*. In women, *T vaginalis* can cause vaginal discharge and pruritis, but 50% of infections may be asymptomatic. In men, infections are usually asymptomatic but can cause urethritis. Treatment with a single dose of tinidazole cures 86% to 100% of patients; metronidazole is an alternative (Table 1).<sup>74</sup> Sexual partners should also be treated.

In one study, 10% of *Trichomonas* isolates were resistant to metronidazole and less than 1% were resistant to tinidazole.<sup>75</sup> Patients who do not respond to single-dose metronidazole should be treated with 500 mg of metronidazole twice daily for 7 days. If no improvement is seen, 2 g of metronidazole or tinidazole daily for 5 days is recommended.<sup>74</sup> Other successful regimens have included high-dose tinidazole plus doxycycline or ampicillin with clotrimazole pessaries<sup>76</sup> and intravaginal paromomycin.<sup>77</sup>

### Free-Living Amebae

**Naegleria fowleri.** *N fowleri* is a thermophilic protist found worldwide in soil and fresh water. It causes primary amebic meningoencephalitis, which is almost universally fatal within days of infection via the nasopharynx from warm fresh water. Symptoms may begin with altered taste or smell, followed by fever, vomiting, and rapid progression to confusion, coma, and death. Most survivors have received amphotericin, and drugs used successfully in combination with amphotericin include miconazole, fluconazole, ornidazole, rifampin, sulfisoxazole, and chloramphenicol.<sup>78,79</sup> Miltefos-

ine, voriconazole, and chlorpromazine have been effective in experimental settings.

Treatment should include intravenous amphotericin and consideration of intrathecal amphotericin in confirmed or highly suspect cases (Table 1). Combination antimicrobial therapy seems warranted; the addition of azoles, rifampin, or other antimicrobial agents should be considered.

***Acanthamoeba Species.*** *Acanthamoeba* species are found worldwide in soil, dust, and fresh water. They cause granulomatous amebic encephalitis and disseminated disease, which usually occur in immunocompromised persons, and amebic keratitis, which occurs in immunocompetent hosts with contact lens use or ocular trauma. Granulomatous amebic encephalitis presents insidiously, with altered mental status, focal neurologic deficits, fever, headache, seizures, and CNS mass lesions, and is usually fatal. The drugs used most frequently in successfully treated cases are pentamidine, azoles, sulfonamides, and possibly flucytosine (Table 1). Almost all patients who survived received combination chemotherapy.<sup>78,80,81</sup> Amebic keratitis is a vision-threatening infection that causes corneal ulceration and blindness if not treated promptly. Topical chlorhexidine or polyhexamethylene biguanide appear to be the most effective medical treatments.

***Balamuthia mandrillaris.*** Found worldwide in soil, *B mandrillaris* causes a subacute or chronic meningoencephalitis in immunocompromised and immunocompetent hosts. Patients may present with skin lesions, fever, headache, vomiting, seizures, CNS mass lesions, and focal neurologic deficits. Clusters of disease have recently been reported in patients with previously unexplained encephalitis and in transplant recipients.<sup>82,83</sup> Only 8 cases of successfully treated infections with *Balamuthia* species have been reported; all received a prolonged course of combination chemotherapy. Successful treatment regimens have included flucytosine, pentamidine, fluconazole, sulfadiazine, and a macrolide; albendazole and itraconazole; and albendazole, fluconazole, and miltefosine (Table 1).<sup>84,85</sup>

## HELMINTHS AND THE DISEASES THEY CAUSE

Helminths are multicellular worms that do not reproduce in humans (with the exceptions of *Strongyloides* and *Capillaria*). They often provoke an eosinophilic response in their human hosts, particularly when they invade tissue. Helminths are broadly categorized as cestodes, trematodes, or nematodes.

### CESTODES (TAPEWORMS)

Cestodes cause disease as segmented, ribbon-like adult tapeworms in the gastrointestinal lumen or as juvenile tis-

sue cysts. The preferred treatment is praziquantel for most intestinal cestodes and benzimidazoles for tissue/larval cestodes.

***Taenia saginata.*** Also known as beef tapeworm, *T saginata* is the most common *Taenia* species that infects humans. It is found worldwide, with highest prevalence in Latin America, Africa, the Middle East, and Central Asia. Humans become infected after consuming undercooked/raw infested beef. Most infections are asymptomatic, but some patients have abdominal cramps or malaise. Treatment is with praziquantel; niclosamide and nitazoxanide are alternatives (Table 2).<sup>86</sup> Praziquantel is very effective for taeniasis. It is an oral pyrazinoisoquinolone derivative that damages the tegument and causes paralysis. Adverse effects include dizziness, headache, abdominal pain, vomiting, diarrhea, and hepatitis. Niclosamide works by uncoupling oxidative phosphorylation. Adverse effects include nausea and abdominal pain.

***Taenia solium.*** Also known as pork tapeworm, *T solium* is endemic to Latin America, sub-Saharan Africa, and Asia, where free-range pigs are raised. Taeniasis, intestinal infection with the adult tapeworm, results from eating undercooked pork containing cysticerci (larval cysts). Cysticercosis (tissue infection with *T solium* larval cysts) results from ingestion of *T solium* eggs, which are spread from a person with intestinal taeniasis or via fecal-oral autoinfection. Cysticercosis involving subcutaneous tissue or skeletal muscle is usually asymptomatic. With neurocysticercosis (NCC), cysts in the CNS can cause seizures, hydrocephalus, or chronic meningitis.

Although *T solium* intestinal infection is usually asymptomatic, patients are treated to prevent cysticercosis. Praziquantel is first-line treatment, and niclosamide is an alternative (Table 2). The decision to treat NCC with antiparasitic agents is complex; the location, number, and type of cysts and clinical manifestations should be considered. Corticosteroids are given concurrently to decrease the inflammatory response and risk of seizures as the parasite degenerates. In general, patients with intraparenchymal cysts should be treated with albendazole plus corticosteroids. Patients with only intraparenchymal calcifications generally do not require antiparasitic therapy. Patients with subarachnoid cysts should generally receive prolonged courses of albendazole plus corticosteroids. Surgical removal is indicated for intraventricular, intraocular, and spinal cysts. Intraocular cysts should be excluded before initiating antiparasitic therapy for cysticercosis. If present, intraocular cysts should be surgically removed before administration of antiparasitic treatment to avoid irreversible eye damage due to the resulting inflammatory response.

TABLE 2. Treatment Regimens for Helminth Infections in Adults<sup>a</sup>

	Medication	Dose	Adverse effects	Additional information
First-line treatment				
Second-line treatment				
<b>Cestodes</b>				
Intestinal tapeworm infection <i>Taenia saginata</i> <i>Taenia solium</i> <i>Diphyllobothrium latum</i>	Praziquantel	5-10 mg/kg orally once	Dizziness, headache, abdominal pain, nausea, hepatitis	
	Niclosamide	2 g orally once	Nausea, vomiting, diarrhea, headache	Not commercially available in the US but may be obtained from Expert Compounding Pharmacy <sup>b</sup> . Tablets should be chewed before swallowing.
	or Nitazoxanide	500 mg orally twice a day for 3 d	Nausea, vomiting, abdominal pain, diarrhea	
<i>Hymenolepis nana</i>	Praziquantel	25 mg/kg orally once		
	Niclosamide	2 g orally once, followed by 1.5 g orally once a day for 6 d		
	or Nitazoxanide	500 mg orally once a day or twice a day for 3 d		
Cysticercosis (see above for intestinal <i>T solium</i> infection)	Albendazole	400 mg orally twice a day for 2-4 wk with corticosteroids given before, during, and after treatment to decrease seizure risk	Abdominal pain, nausea, vomiting, myelosuppression, alopecia, hepatitis. Can precipitate seizures in patients with neurocysticercosis	Should be taken with food. Decision regarding whether to treat is complex (see text). Ocular cysticercosis should be excluded before initiating systemic therapy.
	Praziquantel	33 mg/kg orally 3 times a day for 1 d followed by 15 mg/kg orally 3 times a day for 2-4 wk with corticosteroids given before, during, and after treatment to decrease seizure risk	Can precipitate seizures in patients with neurocysticercosis	
Echinococcosis <i>Echinococcus granulosus</i>	Albendazole	400 mg orally twice a day for 1-6 mo; consider PAIR		Treatment decision is complex; management strategies depend in part on cyst stage (see text)
		Consider albendazole; definitive therapy is surgical		
<b>Trematodes</b>				
Schistosomiasis <i>Schistosoma mansoni</i> , <i>Schistosoma haematobium</i> , or <i>Schistosoma intercalatum</i>	Praziquantel	20 mg/kg orally twice a day for 1 d		
	<i>Schistosoma japonicum</i> or <i>Schistosoma mekongi</i>	Praziquantel	20 mg/kg orally 3 times a day for 1 d	

(continued on next page)

TABLE 2. Continued<sup>a</sup>

	Medication	Dose	Adverse effects	Additional information
	First-line treatment			
	Second-line treatment			
<b>Trematodes (continued)</b>				
Fascioliasis	Triclabendazole	10 mg/kg orally once or twice	Abdominal pain	Contact CDC Drug Service regarding availability <sup>c</sup>
	Bithionol	30-50 mg/kg orally every other day for 20-30 d	Nausea, vomiting, abdominal pain, pruritis, urticaria	Unavailable in US
	or Nitazoxanide	500 mg orally twice a day for 7 d		
Clonorchiasis/opisthorchiasis	Praziquantel	25 mg/kg orally 3 times a day for 2 d		
	Albendazole	10 mg/kg/d orally for 7 d		
Paragonimiasis	Praziquantel	25 mg/kg orally 3 times a day for 2 d		
	Triclabendazole	10 mg/kg orally twice		Contact CDC Drug Service regarding availability <sup>c</sup>
	or Bithionol	30-50 mg/kg orally every other day for 20-30 d		Unavailable in US
Intestinal flukes	Praziquantel	25 mg/kg orally 3 times a day for 1 d		
<b>Nematodes</b>				
Intestinal nematodes				
Ascariasis	Albendazole or Mebendazole	400 mg orally once 500 mg orally once or 100 mg orally twice a day for 3 d		
	Ivermectin	150-200 µg/kg orally once	Nausea, diarrhea, hepatitis, or dizziness	Can be obtained from Expert Compounding Pharmacy <sup>b</sup>
	or Pyrantel pamoate	11 mg/kg (maximum 1 g) orally for 3 d	Abdominal pain, nausea, vomiting, diarrhea	
Trichuriasis (whipworm)	Albendazole or Mebendazole	400 mg orally once a day for 3-7 d 100 mg orally twice a day for 3-7 d		
	Ivermectin	200 µg/kg orally once a day for 3 d		
Hookworm ( <i>Necator americanus</i> , <i>Ancylostoma duodenale</i> )	Albendazole or Mebendazole	400 mg orally once 100 mg orally twice a day for 3 d		
	Pyrantel pamoate	11 mg/kg (maximum 1 g) orally once a day for 3 d		
Enterobiasis (pinworm)	Albendazole or Mebendazole	400 mg orally once 100 mg orally once		Treatment course should be repeated 2 wk later
	Ivermectin	200 µg/kg orally once		
Strongyloidiasis				
Chronic intestinal infection	Ivermectin	200 µg/kg orally once a day for 2 d		
	Albendazole or Thiabendazole	400 mg orally twice a day for 10-14 d 25 mg/kg orally twice a day for 3-7 d	Similar to albendazole	
Disseminated/hyperinfection	Ivermectin	200 µg/kg orally once a day until 7-14 d after clearance of parasite		
	Possible role for subcutaneous (veterinary) formulations of ivermectin or combination ivermectin/albendazole regimens			

(continued on next page)

TABLE 2. **Continued**<sup>a</sup>

	Medication	Dose	Adverse effects	Additional information
First-line treatment				
Second-line treatment				
<b>Extra-intestinal nematodes</b>				
Trichinellosis	Albendazole or Mebendazole	400 mg orally twice a day for 8-14 d 200-400 mg orally 3 times a day for 3 d, followed by 400-500 mg orally 3 times a day for 10 d		Consider concomitant corticosteroids
Toxocariasis				
Visceral larva migrans	Albendazole or Mebendazole	400 mg orally twice a day for 5 d 100-200 mg orally twice a day for 5 d		Consider concomitant corticosteroids
Ocular larva migrans	Albendazole	400-800 mg orally twice a day for 28 d		
<b>Filarial infections</b>				
Lymphatic filariasis	DEC	2 mg/kg orally 3 times a day for 1 d or 12 d	Nausea, fever, asthma- like symptoms, and arthralgias	
	Ivermectin <i>With or without</i> albendazole	150-400 µg/kg orally once 400 mg orally once		
	Possible role for doxycycline	200 mg/d for 4-8 wk		
Tropical pulmonary eosinophilia	DEC	2 mg/kg orally 3 times a day for 2-3 wk		
Onchocerciasis	Ivermectin	150 µg/kg orally once, repeated every 6-12 mo until asymptomatic		DEC contraindicated
	Possible role for doxycycline	200 mg/d for 4-8 wk		
Loiasis	DEC	2-3 mg/kg orally 3 times a day for 2-3 wk		Available from CDC Drug Service <sup>c</sup> Antiparasitic therapy associated with encephalopathy in patients with high-grade parasi- temia; consider pretreatment apheresis
	Albendazole	200 mg orally twice a day for 3 wk		
<b>Other tissue nematodes</b>				
Cutaneous larva migrans	Albendazole	400 mg orally once a day for 3 d		
	Ivermectin	200 µg/kg orally once a day for 1-2 d		
<i>Angiostrongylus cantonensis</i> (eosinophilic meningitis)	Albendazole	400 mg orally twice a day for 2-3 wk (plus corticosteroids)		
Baylisascariasis	Albendazole	400 mg orally twice a day for 1-2 wk (plus corticosteroids)		
Gnathostomiasis	Albendazole	400 mg orally twice a day for 21 d		
	Ivermectin	200 µg/kg orally once a day for 2 d		
Capillariasis	Mebendazole	200 mg orally twice a day for 20 d		
	Albendazole	400 mg orally twice a day for 10 d		

<sup>a</sup> CDC = Centers for Disease Control and Prevention; DEC = diethylcarbamazine; PAIR = percutaneous puncture, aspiration, injection, reaspiration.

<sup>b</sup> Expert Compounding Pharmacy, Lake Balboa, CA (800-247-9767).

<sup>c</sup> Contact CDC Drug Service (404-639-3670).



Albendazole is a broad-spectrum benzimidazole that inhibits microtubule formation. It can cause nausea, abdominal pain, rash, alopecia, leukopenia, and hepatitis. Emerging evidence suggests that antiparasitic therapy decreases seizures in patients with live intraparenchymal cysts.<sup>87</sup> Praziquantel is a second-line agent for NCC. Disadvantages of praziquantel include lower efficacy, lower drug levels when coadministered with corticosteroids, and more drug-drug interactions.

**Dwarf Tapeworm.** The dwarf tapeworm *Hymenolepis nana* is found worldwide, with highest prevalence in Asia, southern/eastern Europe, Latin America, and Africa. Transmission is usually fecal-oral. Infections are usually asymptomatic, but some patients have abdominal discomfort and diarrhea. Treatment is with praziquantel at higher doses and longer courses than for taeniasis (Table 2). Niclosamide and nitazoxanide are alternatives.<sup>71,88</sup>

***Diphyllobothrium latum.*** Infection with *D latum* results from eating raw or undercooked fish. Outbreaks have occurred in South America, Japan, Siberia, Europe, and North America. Infection is usually asymptomatic, but some patients have weakness, dizziness, salt craving, diarrhea, and passage of proglottids in their stool. The parasite interferes with vitamin B<sub>12</sub> absorption and can cause megaloblastic anemia. Treatment is with praziquantel or, alternatively, niclosamide (Table 2).

**Drugs in Development.** Tribendimidine is a diamidine derivative of amidantel, an older acetylcholine receptor agonist used to treat hookworm. Treatment with tribendimidine has yielded cure rates similar to albendazole for intestinal taeniasis.<sup>89</sup>

**Echinococcosis.** *Echinococcus granulosus* and *Echinococcus multilocularis* cause cystic and alveolar echinococcosis, respectively. *E granulosus* infection results from ingesting food or water contaminated with *Echinococcus* eggs or from contact with infected dogs. The disease affects pastoral communities, particularly in South America, the Mediterranean littoral, Eastern Europe, the Middle East, East Africa, Central Asia, China, and Russia. After infection, the parasites encyst, usually in the liver, or less commonly in the lungs. Initially, cysts are asymptomatic, but over the course of months to years they enlarge and cause symptoms. Cyst rupture can cause anaphylaxis. With *E multilocularis* infection (which is less common than *E granulosus*), cysts usually form in the liver. They are aggressive, eventually invading contiguous structures with tumor-like progression and can metastasize, usually to the lungs and brain.

Management strategies depend on the cyst stage and include percutaneous puncture, aspiration, injection, and

reaspiration (PAIR); surgery; antiparasitic chemotherapy; and expectant management.<sup>90</sup> Select patients may be treated with albendazole alone (Table 2). A prolonged course is recommended to prevent recurrence after surgery or percutaneous treatment. There may be some benefit to combination praziquantel plus albendazole before and after surgical interventions.<sup>91</sup>

#### TREMATODES (FLATWORMS)

With the exception of fascioliasis, the preferred treatment for trematodes (flukes) is praziquantel.

**Schistosomiasis.** More than 200 million people globally are infected by *Schistosoma* species. The 3 species of primary medical importance are *Schistosoma mansoni* (found primarily in Africa, the Arabian Peninsula, and South America), *Schistosoma japonicum* (China, the Philippines, Southeast Asia, and Indonesia), and *Schistosoma haematobium* (Africa and the Arabian peninsula).

Infection occurs after skin contact with infested fresh water; 1 to 2 days later, patients may develop a papular, pruritic rash. About 1 to 2 months later, a minority develop Katayama fever, with myalgias, cough, eosinophilia, abdominal pain, fever, and hepatosplenomegaly. *S mansoni* and *S japonicum* can cause chronic hepatic/intestinal disease (abdominal pain, hepatic fibrosis, and portal or pulmonary hypertension). *S haematobium* can cause genitourinary disease (hematuria, genital lesions, urinary strictures/obstruction, and bladder cancer). In endemic areas, schistosomiasis contributes to anemia and growth retardation in children.

The treatment of choice for schistosomiasis is praziquantel (Table 2).<sup>92</sup> Higher doses are recommended for *S japonicum* (and *Schistosoma mekongi*) infections compared with the other *Schistosoma* species. Praziquantel has little activity against eggs or immature worms (schistosomulae) and cannot abort early infection. Patients treated early in their infection must be retreated with praziquantel after the adult worms have matured (usually in 6 to 12 weeks). Although artesunate has activity against schistosomulae, it is not usually used for schistosomiasis, in part because of concern about causing artemisinin-resistant malaria.<sup>93</sup> For Katayama fever, corticosteroids are often coadministered with praziquantel.<sup>94</sup> *S mansoni* resistance to praziquantel has been observed.<sup>95</sup> *S mansoni* can also be treated with oxamniquine, and *S haematobium* with metrifonate (Table 2); however, these drugs are not currently available in the United States.<sup>96</sup>

**Fascioliasis.** Fascioliasis, caused mainly by *Fasciola hepatica*, is endemic to more than 60 countries and is most highly prevalent in sheep-raising areas of Peru, Bolivia, France, Portugal, Egypt, and Iran. Infection results from

eating freshwater plants infested with metacercariae. About 6 to 12 weeks after infection, larvae enter the liver. This acute (migratory) stage of infection can last 2 to 4 months and presents with marked eosinophilia, abdominal pain, fever, and weight loss. Computed tomography reveals multiple migratory, branching hepatic abscesses. *F hepatica* later moves to the bile ducts, where it produces eggs after 3 to 4 months. Some patients develop intermittent biliary obstruction, but many are asymptomatic during the chronic (biliary) stage of infection. Unlike other trematodes, *F hepatica* responds poorly to praziquantel, and triclabendazole (a benzimidazole that inhibits microtubule formation) is the treatment of choice (Table 2). Efficacy is 80% to 90%, but resistance has been reported.<sup>97</sup> Triclabendazole is well tolerated aside from abdominal pain. Bithionol is an alternative but requires longer courses and causes more adverse effects. Cure rates are 60% with a 7-day course of nitazoxanide and 70% with a 10-day course of artesunate.<sup>98</sup>

**Clonorchiasis and Opisthorchiasis.** The Opisthorchiidae family of liver flukes contains 3 major species: *Clonorchis sinensis*, *Opisthorchis viverrini*, and *Opisthorchis felineus*. Infection results from eating undercooked freshwater fish infested with metacercariae. *C sinensis* is endemic primarily to East Asia, *O viverrini* to Southeast Asia, and *O felineus* to Russia and other former Soviet republics. Adult worms deposit eggs in the biliary system; symptoms are uncommon, but patients may have fever, abdominal pain, hepatomegaly, and eosinophilia. Complications include ascending cholangitis, pancreatitis, and biliary pigment stones. Infection may increase the risk of cholangiocarcinoma. The treatment of choice is praziquantel (Table 2)<sup>99</sup>; albendazole is an alternative.<sup>100</sup> Tribendimidine preliminarily appears to be as efficacious as praziquantel.<sup>101</sup>

**Paragonimiasis.** Paragonimiasis is caused by *Paragonimus* species lung flukes, of which *Paragonimus westermani* is the best described. It is most common in East and Southeast Asia. Infection results from eating undercooked crabs or crayfish infested with metacercariae. Adult worms lay eggs in the lung, and acute infection can cause diarrhea, abdominal pain, fever, chest pain, eosinophilia, and cough. Subsequently, patients may develop eosinophilic pleural effusions or bronchiectatic and cavitary lung disease with cough and hemoptysis, often mimicking tuberculosis. Less commonly, lesions develop in the CNS, skin, or other sites. Treatment with praziquantel results in rapid clinical improvement and has high cure rates (Table 2).<sup>102</sup> Triclabendazole is also effective.<sup>103</sup> Bithionol is an alternative but requires longer courses and is more toxic.<sup>104</sup>

**Intestinal Flukes.** More than 60 flukes infect the human intestinal tract. The best known are *Fasciolopsis buski*, *Heterophyes heterophyes*, *Metagonimus yokogawai*, and *Echinostoma* species. Most cases occur in Asia, but there are foci in Africa and the Middle East. All intestinal flukes are food-borne, and most result in asymptomatic infection. Praziquantel is the preferred treatment; however, triclabendazole is also effective (Table 2).<sup>105</sup>

#### NEMATODES (ROUNDWORMS)

Nematodes are a diverse group of parasites that are among the most prevalent of human infections. They are categorized as intestinal or extraintestinal. Except for *Strongyloides* and filarial infections, benzimidazoles are the treatments of choice.

#### Intestinal Nematodes

**Soil-Transmitted Helminths.** The most common intestinal nematodes are *Ascaris lumbricoides*, *Trichuris trichiura* (whipworm), and the human hookworms *Ancylostoma duodenale* and *Necator americanus*. These organisms are also termed *soil-transmitted helminths* (STHs) because their eggs or larvae must develop in soil before becoming infectious. More than 1 billion people are infected with *Ascaris*, and nearly as many with whipworm or hookworm, most commonly in tropical areas with poor sanitation. Humans acquire *Ascaris* and *Trichuris* primarily through the fecal-oral route and hookworm primarily by walking barefoot on infested soil. Although pulmonary symptoms can occur early after infection with *Ascaris* or hookworm, adult worms in the bowel lumen generally cause no symptoms or only mild abdominal pain, nausea, or diarrhea. *Ascaris* can rarely cause intestinal or biliary obstruction, appendicitis, and intestinal perforation. Whipworm can cause rectal prolapse, and hookworm causes chronic anemia. Chronic infection with the STHs can impair growth and cognitive development in children and adversely affect pregnancies.

Short-course albendazole (or mebendazole) cures 88% to 95% of infections with *Ascaris* (Table 2).<sup>106</sup> For *Trichuris*, short-course cure rates are low, and patients should receive 3 to 7 days of therapy.<sup>107</sup> Preliminary data suggest mebendazole may be superior to albendazole for whipworm and that combination therapy with ivermectin may be superior to benzimidazole monotherapy.<sup>107</sup> For hookworm, albendazole is preferred over mebendazole.<sup>106</sup> Soil-transmitted helminths may be developing resistance to benzimidazoles.<sup>108</sup>

None of the available alternative therapies is superior to albendazole or mebendazole for all 4 STH species. The acetylcholine receptor agonist pyrantel pamoate is an alternative for *Ascaris* and hookworm, and ivermectin is an

alternative for *Ascaris* and whipworm. Newer treatments include nitazoxanide for *Ascaris* and whipworm and tribendimidine for *Ascaris* and hookworm.<sup>109,110</sup>

***Enterobius vermicularis.*** *E. vermicularis* (pinworm) causes enterobiasis, which occurs worldwide and does not disproportionately affect residents of tropical countries. The worms live in the proximal colon and migrate to the perianal region to lay eggs that become infectious after 6 hours. Transmission is mainly person-to-person, often via fecal-oral contamination of hands or fomites. Institutional or familial spread is common. Although most infections are asymptomatic, perianal pruritis can be severe. Single-dose albendazole or mebendazole is highly effective (Table 2).<sup>111</sup> Alternatives include ivermectin or pyrantel pamoate. Household and other close contacts should be treated, and treatment should be repeated after 2 weeks because of frequent reinfection and autoinfection.<sup>112</sup>

***Strongyloides stercoralis.*** Strongyloidiasis is caused by *S. stercoralis*, an intestinal nematode usually acquired by walking barefoot on infested soil. *S. stercoralis* is found in the tropics, subtropics, and limited foci in the United States and Europe, where poor sanitation and a warm, moist climate coexist. Unlike nearly all other helminths, *Strongyloides* can complete its life cycle within humans, allowing for amplification of the parasite, person-to-person transmission, and lifelong persistence. Chronic infection is usually asymptomatic, although abdominal pain, nausea, eosinophilia, and diarrhea can occur. Acute infection causes eosinophilia and sometimes rash or cough. In immunosuppressed patients, hyperinfection (a dramatic increase in the worm burden) and dissemination can occur, causing abdominal pain, diarrhea, polymicrobial sepsis, bronchopneumonia, or meningitis. Hyperinfection risk is highest in patients receiving corticosteroids or cancer chemotherapeutics, and in those coinfecting with human T-cell lymphotropic virus.

Uncomplicated strongyloidiasis should be treated with oral ivermectin, which cures 70% to 85% of chronically infected patients (Table 2).<sup>113</sup> This monocyclic lactone binds chloride channels in helminth nerve and muscle cells, resulting in paralysis and death. Ivermectin is well tolerated, only rarely causing nausea, diarrhea, hepatitis, or dizziness when used for intestinal nematodes. Resistance is rare. Less effective alternatives include thiabendazole and albendazole.<sup>114</sup> Hyperinfection or disseminated strongyloidiasis should be treated with oral ivermectin, usually in prolonged courses.<sup>115</sup> Experimental use of veterinary parenteral ivermectin has been successful in treating disseminated strongyloidiasis.<sup>116,117</sup> Patients have also been successfully treated with ivermectin plus albendazole.<sup>118</sup> Screening should be considered in anyone (particularly patients with current or impending immunosuppression) with

any history of exposure to endemic areas, even if many years before. Due to the risk of hyperinfection, all patients infected with *Strongyloides* should be treated.

### Extraintestinal (Tissue) Nematodes

***Trichinellosis.*** Trichinellosis is caused by multiple species in the *Trichinella* genus, of which *Trichinella spiralis* is the best described. Infection results from eating undercooked meat containing *Trichinella* cysts (traditionally pork, but most US cases are now due to bear or other wild game meat). Symptoms include diarrhea, myositis, periorbital edema, conjunctivitis, fever, and eosinophilia. Rarely, patients can die of myocarditis or encephalitis. The benefit of antiparasitic therapy is uncertain, but most patients are treated with albendazole (or mebendazole) plus corticosteroids (Table 2).<sup>119</sup>

***Toxocariasis.*** Toxocariasis is usually caused by *Toxocara canis* or *Toxocara cati*. The eggs of *T. canis* or *T. cati*, which are the most common causes of toxocariasis, are passed in dog or cat (respectively) feces into the environment, where they become infectious after 3 to 4 weeks. Human infections, which result from ingesting eggs in contaminated soil, can be asymptomatic (covert toxocariasis) or present as a larva migrans syndrome. Visceral larva migrans (VLM) occurs most commonly in young children. It is usually asymptomatic but can cause cough, fever, and wheezing. Visceral larva migrans causes eosinophilia and often hepatomegaly; splenomegaly and lymphadenopathy are less common. It is usually self-limited, and treatment with antihelminthic agents is controversial. If antiparasitics are used, albendazole is the drug of choice (Table 2); alternatives include mebendazole, thiabendazole, ivermectin, or the piperazine diethylcarbamazine (DEC).<sup>120,121</sup> Corticosteroids are usually added in severe cases. Ocular larva migrans usually presents as a chorioretinal granuloma. Albendazole may be effective but in higher doses and longer courses than for VLM (Table 2).<sup>122</sup> Surgery is sometimes required.

***Filariasis.*** The filariae are vector-borne tissue nematodes generally found in residents of endemic areas, although travelers occasionally become infected.

**Lymphatic filariasis (LF)** is caused by the mosquito-borne helminths *Wuchereria bancrofti* and *Brugia* species. More than 120 million people have LF, mainly in Southern Asia, sub-Saharan Africa, Oceania, and parts of Latin America. Adult worms reside in lymphatics and release microfilariae, which circulate nocturnally in the blood. These parasites harbor rickettsia-like *Wolbachia* endosymbionts, which female worms require to reproduce. Most patients have asymptomatic eosinophilia, but fever, adenolymphan-

gitis, lymphedema, hydrocele, or elephantiasis can occur. Some patients develop tropical pulmonary eosinophilia, with nocturnal asthma, cough, fever, weight loss, and high-grade eosinophilia.

Parasitemic patients should receive DEC. A 1-day course appears to be as effective as the traditional 12-day regimen (Table 2).<sup>123</sup> Antiparasitic treatment in patients with lymphedema or elephantiasis who are not actively infected is controversial. Patients with tropical pulmonary eosinophilia should receive a 2- to 3-week course of DEC. Adverse effects include nausea, fever, asthma-like symptoms, and arthralgias. Therapy for all filarial infections may be associated with allergic-like reactions resulting from degenerating filariae and *Wolbachia*, for which antihistamines and corticosteroids may be useful. Diethylcarbamazine kills microfilariae but has only modest activity against adult worms. It should not be given to persons from areas coendemic for onchocerciasis or *Loa loa* unless these infections have been excluded. Alternatives for LF include ivermectin and albendazole. Prolonged courses of doxycycline (which kills and sterilizes adult worms as a result of anti-*Wolbachia* activity) may have a role.<sup>124</sup>

**Onchocerciasis**, also known as *river blindness*, is caused by *Onchocerca volvulus*. Transmitted by *Simulium* blackflies, onchocerciasis is found in equatorial Africa and limited foci in Latin America and the Arabian Peninsula. Infection can cause dermatitis, subcutaneous nodules, keratitis, chorioretinitis, and blindness. Ivermectin is the treatment of choice (Table 2), although it kills only microfilariae, not adult worms.<sup>125</sup> Ivermectin must be used with caution if coinfection with *L loa* is possible. The adverse effects of ivermectin include fever, rash, dizziness, pruritis, myalgias, arthralgias, and lymphadenopathy, mostly due to dying filariae and *Wolbachia*. Suramin is active against adult worms, but toxicity precludes use in most cases. Moxidectin, a drug in development that is closely related to ivermectin (but with higher potency), is also active against onchocerciasis.<sup>126</sup> Prolonged doxycycline therapy may have a role because of its anti-*Wolbachia* activity. Diethylcarbamazine should not be administered to persons infected with onchocerciasis because blindness can result from the subsequent ocular inflammatory response.

**Loiasis** is caused by *L loa*, a helminth that is transmitted by *Chrysops* flies and is endemic to Central and West Africa. Adult worms migrate in subcutaneous tissues, and microfilariae circulate diurnally in the blood. *L loa* does not harbor *Wolbachia*. Most infected persons have asymptomatic eosinophilia; some have urticaria, Calabar swellings (migratory, subcutaneous, angioedematous lesions), and visible "eye worms" migrating across the conjunctivae. Hematuria, proteinuria, and en-

cephalitis (usually precipitated by treatment) also occur. Diethylcarbamazine is effective against loiasis, although multiple courses may be necessary (Table 2).<sup>127</sup> Treatment can cause pruritis, arthralgias, Calabar swellings, fever, eye worms, diarrhea, and renal failure. Patients with detectable microfilaremia (particularly >2500 microfilariae/mL) are at risk of treatment-associated encephalopathy, which may be ameliorated by pretreatment apheresis. Ivermectin is active against *L loa*, but albendazole (which acts more slowly) is associated with a lower risk of encephalopathy than DEC or ivermectin.<sup>128</sup>

### Other Tissue Nematodes

**Cutaneous Larva Migrans.** Migration of dog and cat hookworms (eg, *Ancylostoma braziliense*) in the dermis can cause a serpiginous rash termed *cutaneous larva migrans*. The rash occurs after skin contact with infested soil and is usually seen on the lower extremities. Cutaneous larva migrans can be associated with eosinophilia or pulmonary infiltrates but is self-limited. Albendazole or ivermectin may hasten resolution (Table 2).<sup>129</sup>

**Angiostrongylus cantonensis.** Human infection with *A cantonensis* occur after ingesting snails, slugs, or leafy vegetables containing snails, slugs or slime trails with larvae. Endemic primarily to Asia and Oceania, infection can cause a prolonged (but usually self-limited) eosinophilic meningitis. Although antiparasitic therapy is controversial, albendazole plus corticosteroids is often used (Table 2).<sup>130</sup>

**Baylisascaris procyonis.** *B procyonis* (ie, raccoon roundworm) can rarely cause a form of VLM. Human infections result from contact with soil contaminated with raccoon feces. Severe meningoencephalitis can occur, usually in children. Treatment is not well defined, but albendazole plus corticosteroids has been used successfully (Table 2).<sup>131</sup>

**Gnathostoma spinigerum.** *G spinigerum*, which is acquired by eating undercooked freshwater fish, chicken, or pork, is the most common cause of gnathostomiasis. Although it is endemic primarily to Southeast Asia, infections also occur in Latin America and elsewhere. Symptoms include eosinophilia, migratory subcutaneous swellings, and (rarely) fulminant meningoencephalitis. Treatment is with albendazole or ivermectin (Table 2).<sup>132</sup>

**Capillaria philippinensis.** *C philippinensis* is the most common cause of capillariasis, which results from eating infected freshwater fish. Endemic primarily to Southeast Asia and the Middle East, the parasite inhabits the small bowel, causing diarrhea, malabsorption, and (uncommonly) fever and eosinophilia. As with *Strongyloides*, these helminths can multiply in humans, sometimes causing overwhelming infection. Mebendazole or albendazole can be life-saving (Table 2).<sup>133</sup>

## CONCLUSION

A wide array of parasites infect humans, causing some of the most prevalent infectious diseases globally. Recent advances in the treatment of malaria, leishmaniasis, and Chagas disease have brought needed improvements to the management of these diseases. Helminth infections are managed with a smaller pharmaceutical armamentarium than protozoal infections, but good treatment options are now available for many trematode, intestinal cestode, and intestinal nematode infections. Despite a relatively narrow therapeutic pipeline for new antiparasitic drugs, there have been significant improvements in the treatment of these widespread infections in the past 2 decades.

## REFERENCES

- Centers for Disease Control and Prevention (CDC). Guidelines for treatment of malaria in the United States. <http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf>. Accessed April 29, 2011.
- Maude RJ, Plewes K, Faiz MA, et al. Does artesunate prolong the electrocardiograph QT interval in patients with severe malaria? *Am J Trop Med Hyg*. 2009;80:126-132.
- Dondorp A, Nosten F, Stepniewska K, Day N, White N. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet*. 2005;366:717-725.
- Dondorp AM, Fanello CI, Hendriksen IC, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet*. 2010;376:1647-1657.
- Centers for Disease Control and Prevention (CDC). Notice to readers: new medication for severe malaria available under an investigational new drug protocol. *Morb Mortal Wkly Rep*. 2007;56(30):769-770. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5630a5.htm>. Accessed April 29, 2011.
- Bethell D, Se Y, Lon C, et al. Dose-dependent risk of neutropenia after 7-day courses of artesunate monotherapy in Cambodian patients with acute *Plasmodium falciparum* malaria. *Clin Infect Dis*. 2010;51:e105-e114.
- Daneshvar C, Davis TM, Cox-Singh J, et al. Clinical and parasitological response to oral chloroquine and primaquine in uncomplicated human *Plasmodium knowlesi* infections. *Malar J*. 2010;9:238.
- World Health Organization (WHO). *Global Report on Antimalarial Drug Efficacy and Drug Resistance: 2000-2010*. 2nd ed. Geneva, Switzerland: World Health Organization; 2010. [http://whqlibdoc.who.int/publications/2010/9789241500470\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241500470_eng.pdf). Accessed April 29, 2011.
- Dondorp AM, Nosten F, Yi P, et al. Artemisinin resistance in *Plasmodium falciparum* malaria. *N Engl J Med*. 2009;361:455-467.
- Worldwide Antimalarial Resistance Network (WWARN). Web site <http://www.wwarn.org/>. Accessed April 29, 2011.
- Valecha N, Looareesuwan S, Martensson A, et al. Arterolane, a new synthetic trioxolane for treatment of uncomplicated *Plasmodium falciparum* malaria: a phase II, multicenter, randomized, dose-finding clinical trial. *Clin Infect Dis*. 2010;51:684-691.
- Tshefu AK, Gaye O, Kayentao K, et al. Efficacy and safety of a fixed-dose oral combination of pyronaridine-artesunate compared with artemether-lumefantrine in children and adults with uncomplicated *Plasmodium falciparum* malaria: a randomised non-inferiority trial. *Lancet*. 2010;375:1457-1467.
- Thriemer K, Starzengruber P, Khan WA, et al. Azithromycin combination therapy for the treatment of uncomplicated falciparum malaria in Bangladesh: an open-label randomized, controlled clinical trial. *J Infect Dis*. 2010;202:392-398.
- Brun R, Blum J, Chappuis F, Burri C. Human African trypanosomiasis. *Lancet*. 2010;375:148-159.
- Pepin J, Milord F, Guern C, Mpia B, Ethier L, Mansinsa D. Trial of prednisolone for prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. *Lancet*. 1989;1:1246-1250.
- Priotto G, Kasparian S, Mutombo W, et al. Nifurtimox-eflornithine combination therapy for second-stage African *Trypanosoma brucei gambiense* trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. *Lancet*. 2009;374:56-64.
- Bisser S, N'Siesi FX, Lejon V, et al. Equivalence trial of melarsoprol and nifurtimox monotherapy and combination therapy for the treatment of second-stage *Trypanosoma brucei gambiense* sleeping sickness. *J Infect Dis*. 2007;195:322-329.
- Priotto G, Fogg C, Balasegaram M, et al. Three drug combinations for late-stage *Trypanosoma brucei gambiense* sleeping sickness: a randomized clinical trial in Uganda. *PLoS Clin Trials*. 2006;1:e39.
- Brun R, Schumacher R, Schmid C, Kunz C, Burri C. The phenomenon of treatment failures in Human African Trypanosomiasis. *Trop Med Int Health*. 2001;6:906-914.
- Priotto G, Pinoges L, Fursa IB, et al. Safety and effectiveness of first line eflornithine for *Trypanosoma brucei gambiense* sleeping sickness in Sudan: cohort study. *BMJ*. 2008;336:705-708.
- Kibona SN, Matemba L, Kaboya JS, Lubega GW. Drug-resistance of *Trypanosoma b. rhodesiense* isolates from Tanzania. *Trop Med Int Health*. 2006;11:144-155.
- Torreale E. Fexinidazole: a rediscovered nitroimidazole drug candidate moving into clinical development for HAT. Presented at 57th ASTMH Annual Meeting. New Orleans, LA: December 7-11, 2008.
- Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: a systematic review. *JAMA*. 2007;298:2171-2181.
- Lauria-Pires L, Braga MS, Vexenat AC, et al. Progressive chronic Chagas heart disease ten years after treatment with anti-*Trypanosoma cruzi* nitroderivatives. *Am J Trop Med Hyg*. 2000;63:111-118.
- Urbina JA. Specific chemotherapy of Chagas disease: relevance, current limitations and new approaches. *Acta Trop*. 2010;115:55-68.
- de Andrade AL, Zicker F, de Oliveira RM, et al. Randomised trial of efficacy of benznidazole in treatment of early *Trypanosoma cruzi* infection. *Lancet*. 1996;348:1407-1413.
- Sosa Estani S, Segura EL, Ruiz AM, Velazquez E, Porcel BM, Yampotis C. Efficacy of chemotherapy with benznidazole in children in the indeterminate phase of Chagas' disease. *Am J Trop Med Hyg*. 1998;59:526-529.
- Viotti R, Vigliano C, Lococo B, et al. Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment: a non-randomized trial. *Ann Intern Med*. 2006;144:724-734.
- Marin-Neto JA, Rassi A Jr, Avezum A Jr, et al. The BENEFIT trial: testing the hypothesis that trypanocidal therapy is beneficial for patients with chronic Chagas heart disease. *Mem Inst Oswaldo Cruz*. 2009;104(suppl 1):319-324.
- National Institutes of Health; National Library of Medicine; US Department of Health and Human Services. Clinical trial for the treatment of chronic Chagas disease with posaconazole and benznidazole (CHAGASAZOL). ClinicalTrials.gov Web site. <http://clinicaltrials.gov/ct2/show/NCT01162967>. Accessed April 29, 2011.
- Sundar S, Chakravarty J, Agarwal D, Rai M, Murray HW. Single-dose liposomal amphotericin B for visceral leishmaniasis in India. *N Engl J Med*. 2010;362:504-512.
- Sundar S, Jha TK, Thakur CP, et al. Oral miltefosine for Indian visceral leishmaniasis. *N Engl J Med*. 2002;347:1739-1746.
- Murray HW, Berman JD, Davies CR, Saravia NG. Advances in leishmaniasis. *Lancet*. 2005;366:1561-1577.
- Sundar S, More DK, Singh MK, et al. Failure of pentavalent antimony in visceral leishmaniasis in India: report from the center of the Indian epidemic. *Clin Infect Dis*. 2000;31:1104-1107.
- Sundar S, Jha TK, Thakur CP, Sinha PK, Bhattacharya SK. Injectable paromomycin for visceral leishmaniasis in India. *N Engl J Med*. 2007;356:2571-2581.
- van Griensven J, Balasegaram M, Meheus F, Alvar J, Lynen L, Boelaert M. Combination therapy for visceral leishmaniasis. *Lancet Infect Dis*. 2010;10:184-194.
- Melaku Y, Collin SM, Keus K, Gatluak F, Ritmeijer K, Davidson RN. Treatment of kala-azar in southern Sudan using a 17-day regimen of sodium stibogluconate combined with paromomycin: a retrospective comparison with 30-day sodium stibogluconate monotherapy. *Am J Trop Med Hyg*. 2007;77:89-94.
- Sundar S, Sinha PK, Rai M, et al. Comparison of short-course multi-drug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. *Lancet*. 2011;377:477-486.
- Gonzalez U, Pinart M, Rengifo-Pardo M, Macaya A, Alvar J, Tweed JA. Interventions for American cutaneous and mucocutaneous leishmaniasis. *Cochrane Database Syst Rev*. 2009;CD004834.
- Soto J, Berman J. Treatment of New World cutaneous leishmaniasis with miltefosine. *Trans R Soc Trop Med Hyg*. 2006;100(suppl 1):S34-S40.

41. van der Meide WF, Sabajo LO, Jensema AJ, et al. Evaluation of treatment with pentamidine for cutaneous leishmaniasis in Suriname. *Int J Dermatol.* 2009;48:52-58.
42. Alrajhi AA, Ibrahim EA, De Vol EB, Khairat M, Faris RM, Maguire JH. Fluconazole for the treatment of cutaneous leishmaniasis caused by *Leishmania major*. *N Engl J Med.* 2002;346:891-895.
43. Morizot G, Delgiudice P, Caumes E, et al. Healing of Old World cutaneous leishmaniasis in travelers treated with fluconazole: drug effect or spontaneous evolution? *Am J Trop Med Hyg.* 2007;76:48-52.
44. van Thiel PP, Leenstra T, Kager PA, et al. Miltefosine treatment of *Leishmania major* infection: an observational study involving Dutch military personnel returning from northern Afghanistan. *Clin Infect Dis.* 2010;50:80-83.
45. Miranda-Verastegui C, Tulliano G, Gyorkos TW, et al. First-line therapy for human cutaneous leishmaniasis in Peru using the TLR7 agonist imiquimod in combination with pentavalent antimony. *PLoS Negl Trop Dis.* 2009;3:e491.
46. Firooz A, Khamesipour A, Ghoorchi MH, et al. Imiquimod in combination with meglumine antimoniate for cutaneous leishmaniasis: a randomized assessor-blind controlled trial. *Arch Dermatol.* 2006;142:1575-1579.
47. Wortmann G, Zapor M, Ressler R, et al. Liposomal amphotericin B for treatment of cutaneous leishmaniasis. *Am J Trop Med Hyg.* 2010;83:1028-1033.
48. Machado PR, Lessa H, Lessa M, et al. Oral pentoxifylline combined with pentavalent antimony: a randomized trial for mucosal leishmaniasis. *Clin Infect Dis.* 2007;44:788-793.
49. Soto J, Toledo J, Valda L, et al. Treatment of Bolivian mucosal leishmaniasis with miltefosine. *Clin Infect Dis.* 2007;44:350-356.
50. Maltezou HC. Drug resistance in visceral leishmaniasis. *J Biomed Biotechnol.* 2010;2010:617521. <http://www.hindawi.com/journals/jbb/2010/617521/>. Accessed April 29, 2011.
51. Wasunna MK, Rashid JR, Mbui J, et al. A phase II dose-increasing study of sitamaquine for the treatment of visceral leishmaniasis in Kenya. *Am J Trop Med Hyg.* 2005;73:871-876.
52. Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2006;43:1089-1134.
53. Krause PJ, Lepore T, Sikand VK, et al. Atovaquone and azithromycin for the treatment of babesiosis. *N Engl J Med.* 2000;343:1454-1458.
54. Krause PJ, Gewurz BE, Hill D, et al. Persistent and relapsing babesiosis in immunocompromised patients. *Clin Infect Dis.* 2008;46:370-376.
55. Wormser GP, Prasad A, Neuhaus E, et al. Emergence of resistance to azithromycin-atovaquone in immunocompromised patients with *Babesia microti* infection. *Clin Infect Dis.* 2010;50:381-386.
56. Soheilian M, Sadoughi MM, Ghajarnia M, et al. Prospective randomized trial of trimethoprim/sulfamethoxazole versus pyrimethamine and sulfadiazine in the treatment of ocular toxoplasmosis. *Ophthalmology.* 2005;112:1876-1882.
57. Torre D, Casari S, Speranza F, et al; Italian Collaborative Study Group. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. *Antimicrob Agents Chemother.* 1998;42:1346-1349.
58. Montoya JG, Remington JS. Management of *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis.* 2008;47:554-566.
59. Thiebaut R, Leproust S, Chene G, Gilbert R. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. *Lancet.* 2007;369:115-122.
60. Busatti HG, Santos JF, Gomes MA. The old and new therapeutic approaches to the treatment of giardiasis: where are we? *Biologics.* 2009;3:273-287.
61. Rossignol JF. *Cryptosporidium* and *Giardia*: treatment options and prospects for new drugs. *Exp Parasitol.* 2010;124:45-53.
62. Solaymani-Mohammadi S, Genkinger JM, Loffredo CA, Singer SM. A meta-analysis of the effectiveness of albendazole compared with metronidazole as treatments for infections with *Giardia duodenalis*. *PLoS Negl Trop Dis.* 2010;4:e682.
63. Gonzales ML, Dans LF, Martinez EG. Antiamoebic drugs for treating amoebic colitis. *Cochrane Database Syst Rev.* 2009;CD006085.
64. Rossignol JF, Kabil SM, El-Gohary Y, Younis AM. Nitazoxanide in the treatment of amoebiasis. *Trans R Soc Trop Med Hyg.* 2007;101:1025-1031.
65. Cabada MM, White AC Jr. Treatment of cryptosporidiosis: do we know what we think we know? *Curr Opin Infect Dis.* 2010;23:494-499.
66. Abubakar I, Aliyu SH, Arumugam C, Hunter PR, Usman NK. Prevention and treatment of cryptosporidiosis in immunocompromised patients. *Cochrane Database Syst Rev.* 2007;CD004932.
67. Gargala G, Le Goff L, Ballet JJ, Favennec L, Stachulski AV, Rossignol JF. Evaluation of new thiazolide/thiadiazolide derivatives reveals nitro group-independent efficacy against in vitro development of *Cryptosporidium parvum*. *Antimicrob Agents Chemother.* 2010;54:1315-1318.
68. Verdier RI, Fitzgerald DW, Johnson WD Jr, Pape JW. Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of *Isospora belli* and *Cyclospora cayentanensis* infection in HIV-infected patients: a randomized, controlled trial. *Ann Intern Med.* 2000;132:885-888.
69. Zimmer SM, Schuetz AN, Franco-Paredes C. Efficacy of nitazoxanide for cyclosporiasis in patients with sulfa allergy. *Clin Infect Dis.* 2007;44:466-467.
70. Weiss LM, Perlman DC, Sherman J, Tanowitz H, Wittner M. *Isospora belli* infection: treatment with pyrimethamine. *Ann Intern Med.* 1988;109:474-475.
71. Romero Cabello R, Guerrero LR, Munoz Garcia MR, Geyne Cruz A. Nitazoxanide for the treatment of intestinal protozoan and helminthic infections in Mexico. *Trans R Soc Trop Med Hyg.* 1997;91:701-703.
72. Stark D, Barratt J, Roberts T, Marriott D, Harkness J, Ellis J. A review of the clinical presentation of dientamoebiasis. *Am J Trop Med Hyg.* 2010;82:614-619.
73. Rossignol JF, Kabil SM, Said M, Samir H, Younis AM. Effect of nitazoxanide in persistent diarrhea and enteritis associated with *Blastocystis hominis*. *Clin Gastroenterol Hepatol.* 2005;3:987-991.
74. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep.* 2010;59:1-110.
75. Schwelbe JR, Barrientes FJ. Prevalence of *Trichomonas vaginalis* isolates with resistance to metronidazole and tinidazole. *Antimicrob Agents Chemother.* 2006;50:4209-4210.
76. Mammen-Tobin A, Wilson JD. Management of metronidazole-resistant *Trichomonas vaginalis*—a new approach. *Int J STD AIDS.* 2005;16:488-490.
77. Tayal SC, Ochogwu SA, Bunce H. Paromomycin treatment of recalcitrant *Trichomonas vaginalis*. *Int J STD AIDS.* 2010;21:217-218.
78. Schuster FL, Visvesvara GS. Opportunistic amoebae: challenges in prophylaxis and treatment. *Drug Resist Updat.* 2004;7:41-51.
79. Vargas-Zepeda J, Gomez-Alcala AV, Vasquez-Morales JA, Licea-Amaya L, De Jonckheere JF, Lares-Villa F. Successful treatment of *Naegleria fowleri* meningoencephalitis by using intravenous amphotericin B, fluconazole and rifampicin. *Arch Med Res.* 2005;36:83-86.
80. Saxena A, Mittal S, Burman P, Garg P. *Acanthamoeba* meningitis with successful outcome. *Indian J Pediatr.* 2009;76:1063-1064.
81. Aichelburg AC, Walochnik J, Assadian O, et al. Successful treatment of disseminated *Acanthamoeba* sp. infection with miltefosine. *Emerg Infect Dis.* 2008;14:1743-1746.
82. Centers for Disease Control and Prevention (CDC). Notes from the field: transplant-transmitted *Balamuthia mandrillaris*—Arizona, 2010. *MMWR Morb Mortal Wkly Rep.* 2010;59:1182.
83. Schuster FL, Yagi S, Gavali S, et al. Under the radar: *Balamuthia* amoebic encephalitis. *Clin Infect Dis.* 2009;48:879-887.
84. Deetz TR, Sawyer MH, Billman G, Schuster FL, Visvesvara GS. Successful treatment of *Balamuthia* amoebic encephalitis: presentation of 2 cases. *Clin Infect Dis.* 2003;37:1304-1312.
85. Martinez DY, Seas C, Bravo F, et al. Successful treatment of *Balamuthia mandrillaris* amoebic infection with extensive neurological and cutaneous involvement. *Clin Infect Dis.* 2010;51:e7-e11.
86. Lateef M, Zargar SA, Khan AR, Nazir M, Shoukat A. Successful treatment of niclosamide- and praziquantel-resistant beef tapeworm infection with nitazoxanide. *Int J Infect Dis.* 2008;12:80-82.
87. Garcia HH, Pretell EJ, Gilman RH, et al. A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. *N Engl J Med.* 2004;350:249-258.
88. Chero JC, Saito M, Bustos JA, Blanco EM, Gonzalez G, Garcia HH. *Hymenolepis nana* infection: symptoms and response to nitazoxanide in field conditions. *Trans R Soc Trop Med Hyg.* 2007;101:203-205.
89. Xiao SH, Hui-Ming W, Tanner M, Utzinger J, Chong W. Tribendimidine: a promising, safe and broad-spectrum anthelmintic agent from China. *Acta Trop.* 2005;94:1-14.
90. Brunetti E, Kern P, Vuitton DA. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. *Acta Trop.* 2010;114:1-16.
91. Bygott JM, Chiodini PL. Praziquantel: neglected drug? ineffective treatment? or therapeutic choice in cystic hydatid disease? *Acta Trop.* 2009;111:95-101.
92. Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. *Lancet.* 2006;368:1106-1118.

93. Boulanger D, Dieng Y, Cisse B, et al. Antischistosomal efficacy of artesunate combination therapies administered as curative treatments for malaria attacks. *Trans R Soc Trop Med Hyg.* 2007;101:113-116.
94. Ross AG, Vickers D, Olds GR, Shah SM, McManus DP. Katayama syndrome. *Lancet Infect Dis.* 2007;7:218-224.
95. Ismail M, Botros S, Metwally A, et al. Resistance to praziquantel: direct evidence from *Schistosoma mansoni* isolated from Egyptian villagers. *Am J Trop Med Hyg.* 1999;60:932-935.
96. Ferrari ML, Coelho PM, Antunes CM, Tavares CA, da Cunha AS. Efficacy of oxamniquine and praziquantel in the treatment of *Schistosoma mansoni* infection: a controlled trial. *Bull World Health Organ.* 2003;81:190-196.
97. Moll L, Gaasenbeek CP, Vellema P, Borgsteede FH. Resistance of *Fasciola hepatica* against triclabendazole in cattle and sheep in The Netherlands. *Vet Parasitol.* 2000;91:153-158.
98. Favennec L, Jave Ortiz J, Gargala G, Lopez Chegne N, Ayoub A, Rossignol JF. Double-blind, randomized, placebo-controlled study of nitazoxanide in the treatment of fascioliasis in adults and children from northern Peru. *Aliment Pharmacol Ther.* 2003;17:265-270.
99. Bunnag D, Harinasuta T. Studies on the chemotherapy of human opisthorchiasis in Thailand: I. Clinical trial of praziquantel. *Southeast Asian J Trop Med Public Health.* 1980;11:528-531.
100. Liu YH, Wang XG, Gao P, Qian MX. Experimental and clinical trial of albendazole in the treatment of *Clonorchiasis sinensis*. *Chin Med J (Engl).* 1991;104:27-31.
101. Soukhathammavong P, Odermatt P, Sayasone S, et al. Efficacy and safety of mefloquine, artesunate, mefloquine-artesunate, tribendimidine, and praziquantel in patients with *Opisthorchis viverrini*: a randomised, exploratory, open-label, phase 2 trial. *Lancet Infect Dis.* 2011;11:110-118.
102. Udonsi JK. Clinical field trials of praziquantel in pulmonary paragonimiasis due to *Paragonimus uterobilateralis* in endemic populations of the Ikwun Basin, Nigeria. *Trop Med Parasitol.* 1989;40:65-68.
103. Calvopina M, Guderian RH, Paredes W, Chico M, Cooper PJ. Treatment of human pulmonary paragonimiasis with triclabendazole: clinical tolerance and drug efficacy. *Trans R Soc Trop Med Hyg.* 1998;92:566-569.
104. Kim JS. Treatment of *Paragonimus westermani* infections with bithionol. *Am J Trop Med Hyg.* 1970;19:940-942.
105. Bunnag D, Radomyos P, Harinasuta T. Field trial on the treatment of fasciolopsiasis with praziquantel. *Southeast Asian J Trop Med Public Health.* 1983;14:216-219.
106. Keiser J, Utzinger J. Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis. *JAMA.* 2008;299:1937-1948.
107. Knopp S, Mohammed KA, Speich B, et al. Albendazole and mebendazole administered alone or in combination with ivermectin against *Trichuris trichiura*: a randomized controlled trial. *Clin Infect Dis.* 2010;51:1420-1428.
108. Albonico M, Bickle Q, Ramsan M, Montresor A, Savioli L, Taylor M. Efficacy of mebendazole and levamisole alone or in combination against intestinal nematode infections after repeated targeted mebendazole treatment in Zanzibar. *Bull World Health Organ.* 2003;81:343-352.
109. Galvan-Ramirez ML, Rivera N, Loeza ME, et al. Nitazoxanide in the treatment of *Ascaris lumbricoides* in a rural zone of Colima, Mexico. *J Helminthol.* 2007;81:255-259.
110. Diaz E, Mondragon J, Ramirez E, Bernal R. Epidemiology and control of intestinal parasites with nitazoxanide in children in Mexico. *Am J Trop Med Hyg.* 2003;68:384-385.
111. Wen LY, Yan XL, Sun FH, Fang YY, Yang MJ, Lou LJ. A randomized, double-blind, multicenter clinical trial on the efficacy of ivermectin against intestinal nematode infections in China. *Acta Trop.* 2008;106:190-194.
112. Matsen JM, Turner JA. Reinfection in enterobiasis (pinworm infection). Simultaneous treatment of family members. *Am J Dis Child.* 1969;118:576-581.
113. Igual-Adell R, Oltra-Alcaraz C, Soler-Company E, Sanchez-Sanchez P, Matogo-Oyana J, Rodriguez-Calabuig D. Efficacy and safety of ivermectin and thiabendazole in the treatment of strongyloidiasis. *Expert Opin Pharmacother.* 2004;5:2615-2619.
114. Marti H, Haji HJ, Savioli L, et al. A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of *Strongyloides stercoralis* and other soil-transmitted helminth infections in children. *Am J Trop Med Hyg.* 1996;55:477-481.
115. Keiser PB, Nutman TB. *Strongyloides stercoralis* in the immunocompromised population. *Clin Microbiol Rev.* 2004;17:208-217.
116. Turner SA, Maclean JD, Fleckenstein L, Greenaway C. Parenteral administration of ivermectin in a patient with disseminated strongyloidiasis. *Am J Trop Med Hyg.* 2005;73:911-914.
117. Marty FM, Lowry CM, Rodriguez M, et al. Treatment of human disseminated strongyloidiasis with a parenteral veterinary formulation of ivermectin. *Clin Infect Dis.* 2005;41:e5-e8.
118. Pornsuriyasak P, Nitichareonpong K, Sakapibunn A. Disseminated strongyloidiasis successfully treated with extended duration ivermectin combined with albendazole: a case report of intractable strongyloidiasis. *Southeast Asian J Trop Med Public Health.* 2004;35:531-534.
119. Watt G, Saisorn S, Jongsakul K, Sakolvaree Y, Chaicumpa W. Blinded, placebo-controlled trial of antiparasitic drugs for trichinosis myositis. *J Infect Dis.* 2000;182:371-374.
120. Sturchler D, Schubarth P, Gualzata M, Gottstein B, Oetli A. Thiabendazole vs. albendazole in treatment of toxocarasis: a clinical trial. *Ann Trop Med Parasitol.* 1989;83:473-478.
121. Magnaval JF. Comparative efficacy of diethylcarbamazine and mebendazole for the treatment of human toxocarasis. *Parasitology.* 1995;110(pt 5):529-533.
122. Barisani-Asenbauer T, Maca SM, Hauff W, et al. Treatment of ocular toxocarasis with albendazole. *J Ocul Pharmacol Ther.* 2001;17:287-294.
123. Centers for Disease Control and Prevention (CDC). Parasites—lymphatic filariasis: guidance for evaluation and treatment. [http://www.cdc.gov/parasites/lymphaticfilariasis/health\\_professionals/dctx.html](http://www.cdc.gov/parasites/lymphaticfilariasis/health_professionals/dctx.html). Accessed April 29, 2011.
124. Hoerauf A. Filariasis: new drugs and new opportunities for lymphatic filariasis and onchocerciasis. *Curr Opin Infect Dis.* 2008;21:673-681.
125. Udall DN. Recent updates on onchocerciasis: diagnosis and treatment. *Clin Infect Dis.* 2007;44:53-60.
126. Taylor MJ, Hoerauf A, Bockarie M. Lymphatic filariasis and onchocerciasis. *Lancet.* 2010;376:1175-1185.
127. Padgett JJ, Jacobsen KH. Loiasis: African eye worm. *Trans R Soc Trop Med Hyg.* 2008;102:983-989.
128. Klion AD, Massougbdji A, Horton J, et al. Albendazole in human loiasis: results of a double-blind, placebo-controlled trial. *J Infect Dis.* 1993;168:202-206.
129. Albanese G, Venturi C, Galbiati G. Treatment of larva migrans cutanea (creeping eruption): a comparison between albendazole and traditional therapy. *Int J Dermatol.* 2001;40:67-71.
130. Chotmongkol V, Wongjitrat C, Sawadpanit K, Sawanyawisuth K. Treatment of eosinophilic meningitis with a combination of albendazole and corticosteroid. *Southeast Asian J Trop Med Public Health.* 2004;35:172-174.
131. Pai PJ, Blackburn BG, Kazacos KR, Warriar RP, Begue RE. Full recovery from *Baylisascaris procyonis* eosinophilic meningitis. *Emerg Infect Dis.* 2007;13:928-930.
132. Nontasut P, Bussaratid V, Chullawichit S, Charoensook N, Visetsuk K. Comparison of ivermectin and albendazole treatment for gnathostomiasis. *Southeast Asian J Trop Med Public Health.* 2000;31:374-377.
133. Cross JH. Intestinal capillariasis. *Clin Microbiol Rev.* 1992;5:120-129.

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