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Antiparasitic Therapy in Children

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Although parasitic infections are ubiquitous on a worldwide basis, with an estimated 1 billion persons infected with intestinal helminthes alone, physicians in the United States and other developed countries are often unfamiliar with the management of these diseases. Children are traveling internationally in larger numbers than ever before, however, and emigration from developing countries to the United States and other Western countries is increasing, so clinicians in these countries are confronted more frequently with parasitic diseases from the tropics. Treatment of parasitic infections presents many challenges for the clinician. One challenge is the markedly different therapy needed for some parasites that are genetically and morphologically similar. The coccidian protozoan, *Cyclospora cayetanensis* responds well to treatment with trimethoprim-sulfamethoxazole (TMP-SMX), whereas the morphologically similar protozoan, *Cryptosporidium parvum,* is resistant to most commonly used antimicrobial agents. Morphologically similar *Entamoeba* species also can complicate decisions regarding treatment. *Entamoeba histolytica* often causes invasive disease requiring treatment, but *Entamoeba dispar* is a benign commensal that can be ignored. Another challenge is the need to treat some parasites, such as the trypanosomes, with prolonged courses of highly toxic drugs. Optimal treatment of other parasitic organisms, such as malaria, requires an understanding of their complex life cycles. Finally, treatment of some parasitic infections requires special precautions because of the potential for serious adverse clinical reactions. If cysticerci in the brain are treated with antiparasitic agents, without concurrent steroid therapy, the resulting inflammatory response can precipitate seizures. The therapy of

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parasitic diseases requires careful attention to diagnostic studies and pathogen-specific therapy.

Parasites are defined as eukaryotic single-celled or multicellular microorganisms that differ from fungi in cell membrane structure. Parasites often are classified into two groups, single-celled parasites or protozoa and multicellular parasites or helminthes, including parasitic "worms." Parasites are often host specific, and many parasites found in humans are nonpathogenic.

This article is organized into three main sections, based on parasite structure and disease epidemiology: (1) protozoan infections found primarily in developing countries, (2) protozoan infections distributed globally and infections in immunocompromised hosts, and (3) helminth infections. Drugs used in the treatment of more than one type of parasite are presented once in detail, with reference to the detailed description in subsequent sections.

Treatment of protozoan infections found primarily in developing countries

Table 1 provides a quick reference to drugs of choice and dosages.

Malaria

Malaria is one of the most prevalent parasitic infections worldwide, and it is among the greatest health and development challenges facing developing countries today [1]. Nearly 2 billion people, a third of the world's population, live in malaria-endemic areas [2]. Each year, approximately 100 million people are infected with malaria, and mortality estimates range from 500,000 to 3 million people annually [2–4]. Ninety percent of deaths occur in Africa, where severe malaria and malaria-related mortality disproportionately affect children, pregnant women, and immunocompromised persons. Travelers without prior immunity visiting endemic areas also are at increased risk [5].

There are four *Plasmodium* species that cause human disease. Most cases of severe disease and death are caused by *P. falciparum,* whereas *P. vivax, P. ovale,* and *P. malariae* cause less severe disease [6]. Drug resistance is one of the major obstacles to effective disease control. It is estimated that in some areas, resistance to chloroquine exceeds 25%, and that other first-line drugs are losing their efficacy quickly [7]. It is estimated that chloroquine resistance results in a fourfold to eightfold increase in mortality rate [8].

Strategies for effective treatment depend on the species of malaria, drug resistance patterns where infection was acquired, and severity of disease [6,9]. Physicians should consult the Centers for Disease Control and Prevention website (www.cdc.gov) or a travel medicine service to identify areas where chloroquine is the recommended therapy. In the following sections, discussion is limited to treatment of disease only. Malaria prophylaxis is beyond the scope of this article.

Plasmodium falciparum

A 3-day course of chloroquine is the recommended first-line treatment of uncomplicated *P. falciparum,* in areas where sensitivity to chloroquine predominates [6,9]. Chloroquine is relatively inexpensive and well tolerated. Side effects include pruritus, dizziness, headache, diplopia, nausea, and malaise. Chloroquine-induced pruritus is accentuated in patients with concomitant filarial infection. These side effects are typically minor and transient. Serious side effects, such as hypotension and ECG abnormalities, can occur at high concentrations [6,7,9]. Chloroquine is the safest of the antimalarial drugs for use during pregnancy [3].

One of the most confusing aspects of choloquine therapy is the frequent reporting of dosages in terms of chloroquine "base" and chloroquine "salt." Calculation of chloroquine doses in terms of milligrams of base is relevant only when there are different salt preparations, as in some countries where there are sulfate, phosphate, and hydrochloride salts available. When several chloroquine salts are available, milligram dosages of these preparations providing equivalent amounts of chloroquine base vary with the molecular weight of the compound. Chloroquine phosphate (eg, Aralen) is the most common chloroquine salt preparation in pharmacies worldwide, and unless preparations other than choroquine phosphate are available, dosage calculations should be made based on chloroquine phosphate salt. Dosages of chloroquine base should be multiplied by 1.6 to determine the corresponding dose of chloroquine phosphate salt.

Quinine sulfate given three times daily and atovaquone-proguanil given once daily are the drugs of choice in areas with chloroquine resistance. Quinine sulfate can be used alone in a 7-day course or combined with doxycycline or clindamycin for a 3-day course. Alternatively, pyrimethamine-sulfadoxine can be given in one dose at the end of quinine treatment. Quinine combined with clindamycin is the recommended first-line treatment regimen for pregnant women with chloroquine-resistant malaria. Quinine sulfate is a relatively safe drug, although it may produce a syndrome known as *cinchonism* (name derived from the cinchona tree, from which quinine is extracted). Cinchonism is a symptom complex including tinnitus, high-tone hearing impairment, nausea, and vomiting. These side effects often interfere with completion of therapy. In large doses, side effects of quinine include hypotension, arrhythmias, visual impairment, and seizures [3,7]. Hyperinsulinemic hypoglycemia is an important complication of quinine therapy in pregnant women, who should have careful blood glucose monitoring during treatment.

Atovaquone-proguanil (Malarone) is an alternative to quinine sulfate. It is given once daily for 3 days. Absorption from the gastrointestinal tract increases when taken with food. Atovaquone-proguanil is generally well tolerated. The most common side effects include rash, fever, gastrointestinal upset, and CNS disturbances. This drug is contraindicated during pregnancy (category C) [7].

Alternative drugs for uncomplicated *P. falciparum* include mefloquine alone or in combination with one of the arteminisins—artesunate or artemether. Mefloquine is often used as a third-line drug because of its rare but significant

Table 1
Treatment of protozoan infections found primarily in developing countries

Parasite	Drug	Pediatric dosage	Adult dosage
Malaria			
P. falciparum (uncomplicated)			
Chloroquine-sensitive			
Drug of choice	Chloroquine phosphate (chloroquine salt, containing 60% chloroquine base by weight)*	16 mg/kg salt (10 mg/kg base), then 8.3 mg/kg salt (5 mg/kg base) at 6, 24, and 48 h	1 g salt (600 mg base), then 500 mg salt (300 mg base) at 6, 24, and 48 h
Chloroquine-resistant			
Drug of choice	Quinine sulfate *plus one of*	10 mg/kg three times daily × 3–7 d	650 mg three times daily × 3–7 d
	doxycycline *or*	2 mg/kg twice daily × 7 d	100 mg twice daily × 7 d
	clindamycin *or*	5 mg/kg three times daily × 7 d	300 mg four times daily × 7 d
	pyrimethamine-sulfadoxine	<5 kg: ¼ tab once 5–10 kg: ½ tab once 11–20 kg: 1 tab once 21–30 kg: 1½ tab once 31–40 kg: 2 tabs once >40 kg: 3 tabs once on the last day of quinine	3 tabs once on the last day of quinine
Alternatives	Atovaquone-proguanil	5–8 kg: 2 peds tabs once daily × 3 d 9–10 kg: 3 peds tabs once daily × 3 d 11–20 kg: 1 adult tabs once daily × 3 d 21–30 kg: 2 adult tabs once daily × 3 d 31–40 kg: 3 adult tabs once daily × 3 d >40 kg: 4 adult tabs once daily × 3 d	4 adult tabs daily × 3 d
	Mefloquine	15 mg/kg once, then 10 mg/kg after 12 h	750 mg once, then 500 mg after 12 h

	Artesunate	4 mg/kg/d × 3 d	4 mg/kg/d × 3 d
	plus mefloquine	15 mg/kg once, then 10 mg/kg after 12 h	750 mg once, then 500 mg after 12 h
P. falciparum (severe disease)			
Drugs of choice	Quinine sulfate	20 mg/kg load over 4 h, then 10 mg/kg over 2–4 h q8 h	20 mg/kg load over 4 h, then 10 mg/kg over 2–4 hrs q8 h
	Quinidine	10 mg/kg load over 1–2 h, then 0.02 mg/kg/min continuous infusion	10 mg/kg load over 1–2 h, then 0.02 mg/kg/min continuous infusion
Alternative	Artemether	3.2 mg/kg IM, then 1.6 mg/kg daily × 7 d	3.2 mg/kg IM, then 1.6 mg/kg daily × 7 d
P. vivax/P. ovale			
Drug of choice	Chloroquine phosphate (chloroquine salt, containing 60% chloroquine base by weight)*	16 mg/kg salt (10 mg/kg base), then 8.3 mg/kg salt (5 mg/kg base) at 6, 24, and 48 h	1 g salt (600 mg base), then 500 mg salt (300 mg base) at 6, 24, and 48 h
	plus primaquine	0.5 mg/kg × 14 d	30 mg once daily × 14 d
P. malariae			
Drug of choice	Chloroquine phosphate (chloroquine salt, containing 60% chloroquine base by weight)*	16 mg/kg salt (10 mg/kg base), then 8.3 mg/kg salt (5 mg/kg base) at 6, 24, and 48 h	1 g salt (600 mg base), then 500 mg salt (300 mg base) at 6, 24, and 48 h
Trypanosomiasis			
T.cruzi (Chagas disease)			
Drugs of choice	Benznidazole	<12 y: 10 mg/kg/day in twice daily × 30–90 d	5–7 mg/kg/d divided twice daily × 30–90 d
	Nifurtimox	1–10 y: 15–20 mg/kg/d 4 times daily × 90 d 11–16 y: 12.5–15 mg/kg/day 4 times daily × 90 d	8–10 mg/kg/d 4 times daily × 90 d
T.brucei gambiense (sleeping sickness)			
Hemolymphatic stage			
Drugs of choice	Pentamidine isethionate	4 mg/kg/day IM × 10 d	4 mg/kg/day × 10 d
	Suramin sodium	5 mg/kg (test dose) IV, then after 48 h 20 mg/kg/day on day 1, 3, 7, 14, and 21	100–200 mg (test dose) IV, then 1 g IV on day 1, 3, 7, 14, and 21

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Table 1 (*continued*)

Parasite	Drug	Pediatric dosage	Adult dosage
Trypanosomiasis			
T.brucei gambiense (sleeping sickness)			
CNS involvement			
Drugs of choice	Melarsoprol	2.2 mg/kg daily × 10 d	2.2 mg/kg daily × 10 d
	Eflornithine	400 mg/kg 4 times daily × 14 d	400 mg/kg 4 times daily × 14 d
T.brucei rhodesiense			
Hemolymphatic stage			
Drug of choice	Suramin sodium	5 mg/kg (test dose) IV, then after 48 h 20 mg/kg/day IV on day 1, 3, 7, 14, and 21	100–200 mg (test dose) IV, then 1 g IV on day 1, 3, 7, 14, and 21
CNS involvement			
Drug of choice	Melarsoprol	2–3.6 mg/kg/d × 3 d, then after 7 d 3.6 mg/kg/d × 3 d, then repeat after 7 d	2–3.6 mg/kg/d × 3 d, then after 7 d 3.6 mg/kg/d × 3 d, then repeat after 7 d
Leishmaniasis			
Visceral			
Drugs of choice	Sodium stibogluconate	20 mg Sb[†] /kg/d IV/IM × 28 d	20 mg Sb[†] /kg/d IV/IM × 28 d
	Meglumine antimonate	20 mg Sb[†] /kg/d IV/IM × 28 d	20 mg Sb[†] /kg/d IV/IM × 28 d
	Amphotericin B	0.5–1 mg/kg IV daily or every other day for 8 wk	0.5–1 mg/kg IV daily or every other day for 8 wk
	Liposomal amphotericin B	3 mg/kg/d IV for 1–5 d, then 3 mg/kg/d on day 14 and 21	3 mg/kg/d IV for 1–5 d, then 3/mg/kg/d on day 14 and 21
Alternate	Pentamidine	4 mg/kg IV/IM daily or every other day for 15–30 doses	4 mg/kg IV/IM daily or every other day for 15–30 doses

Cutaneous			
Drugs of choice	Sodium stibogluconate	20 mg Sb[†] /kg/d IV/IM × 20 d	20 mg Sb[†] /kg/d IV/IM × 20 d
	Meglumine antimonate	20 mg Sb[†] /kg/d IV/IM × 20 d	20 mg Sb[†] /kg/d IV/IM × 20 d
Alternative	Pentamidine	2–3 mg/kg IV/IM daily or every other day for 4–7 doses	2–3 mg/kg IV/IM daily or every other day for 4–7 doses
	Paromomycin	2x/d topically × 10–20 d	2x/d topically × 10–20 d
Mucosal			
Drugs of choice	Sodium stibogluconate	20 mg Sb[†] /kg/d IV/IM × 28 d	20 mg Sb[†] /kg/d IV/IM × 28 d
	Meglumine antimonate	20 mg Sb[†] /kg/d IV/IM × 28 d	20 mg Sb[†] /kg/d IV/IM × 28 d
	Amphotericin B	0.5–1 mg/kg IV daily or every other day for 8 wk	0.5–1 mg/kg IV daily or every other day for 8 wk
Amebiasis			
Entomoeba histolytica			
Drugs of choice	Metronidazole	30–50 mg/kg/d 3 times daily × 7–10 d	500–750 mg 3 times daily × 7–10 d
Noninvasive disease	Iodoquinol	30–40 mg/kg/d 3 times daily × 20 d	650 mg 3 times daily × 20 d
	Paromomycin	25–35 mg/kg/d 3 times daily × 7 d	25–35 mg/kg/d 3 times daily × 7 d
	Diloxanide furoate	20 mg/kg/d 3 times daily × 10 d	500 mg 3 times daily × 10 d

* Chloroquine salt (chloroquine phosphate) is the preparation available in pharmacies, and dosage calculations should be made based on chloroquine salt rather than chloroquine base, even though the latter is often used for describing dosages.

[†] Sb, antimony. Dosing of pentavalent antimonials should be done in consultation with infectious disease experts.

side effects, including life-threatening skin reactions, aplastic anemia, psychosis, seizures, and encephalopathy [7]. Although children are more likely than adults to vomit immediately after taking mefloquine, in general they tolerate the drug better than adults. Self-limited neuropsychiatric reactions, such as convulsions and psychosis, occur in about 1 in every 15,000 individuals receiving mefloquine for malaria prophylaxis, but the rate of these reactions in patients receiving antimalarial treatment dosages is about 10 times higher. Mefloquine should not be used in conjunction with quinine or quinidine because it can potentiate their cardiac toxicities, especially arrhythmias [9]. Mefloquine can be used during pregnancy, but should be used with caution in the first trimester (category C) [3]. Side effects for the arteminisins include mild gastrointestinal upset and rash. Serious CNS side effects, although rare, have been reported [7].

For the treatment of severe *P. falciparum,* intravenous quinine and quinidine are the drugs of choice. Both should begin with a loading dose to achieve therapeutic concentrations quickly. Both agents should be diluted in a crystalloid solution such as 5% dextrose. If intravenous administration is not possible, quinine can be given intramuscularly. When the patient can swallow, he or she should be switched to oral tablets to complete a 7-day course of therapy [7,9].

Another alternative drug for severe *P. falciparum* is intramuscular artemether. A loading dose should be given followed by daily injections for 7 days. If tolerated, oral therapy can instituted after 3 days of parenteral treatment and continued to complete a 7-day course [7,9].

Plasmodium vivax *and* Plasmodium ovale

Neither *P. vivax* nor *P. ovale* typically causes severe disease. The drug of choice for both is chloroquine for 3 days, followed by primaquine once daily for 14 days [6,9]. Primaquine is used to eradicate the dormant parasites within the liver (hypnozoites), which could cause relapse. Although typically well tolerated, primaquine is associated with severe hemolysis in patients with glucose-6 phosphate dehydrogenase (G6PD) deficiency. Screening for this deficiency, before using primaquine therapy, is recommended.

Plasmodium malariae

P. malariae is treated with a 3-day course of chloroquine alone. Chloroquine resistance has been reported in Indonesia [6].

Kinetoplastids (trypanosomiasis and leishmaniasis)

American Trypanosomiasis

American trypanosomiasis, also known as Chagas' disease, is caused by the flagellated protozoan *Trypanosoma cruzi.* Transmission is from the bite of a triatomine bug, which contaminates abraded skin or mucous membranes with feces containing trypomastigotes. Chagas' disease is the most important parasitic disease of Latin America, infecting roughly 10 million people [10,11]. The clinical course is characterized by an acute phase, which is often asymptomatic, and

a chronic phase. Children are more likely than adults to exhibit symptoms. Typically a chagoma, or red nodule, develops at the site of inoculation. Often inoculation occurs at the eyelid, causing unilateral periorbital edema. This is known as Romaña's sign, when accompanied by conjunctivitis and preauricular lymphadenitis. Infection is followed by fever, malaise, and lymphadenopathy, and complications include myocarditis, hepatosplenomegaly, and meningoencephalitis [10,12]. Manifestations of chronic Chagas' disease, including cardiac aneurysms, megaesophagus, and megacolon, are found almost exclusively in adults with long-standing infections. These late manifestations do not respond to antiparasitic therapy.

Treatment for acute Chagas' disease consists of benznidazole twice daily for 30 to 90 days or nifurtimox four times daily for 90 days. Benznidazole has greater trypanocidal activity than nifurtimox and has been associated with greater improvement in ECG abnormalities. Side effects of both drugs are common. For benznidazole, allergic dermopathy occurs in approximately 50% of patients. Peripheral neuropathy and granulocytopenia also are frequent. Side effects tend to disappear with interruptions in treatment. Patients receiving nifurtimox often experience nausea, vomiting, and weakness. Therapy also can lead to toxic hepatitis and CNS symptoms, such as seizures [13,14].

African Trypanosomiasis

African trypanosomiasis, also known as sleeping sickness, is caused by two morphologically identical protozoa—*Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*. Both protozoa are transmitted by the bites of tsetse flies. *T. brucei gambiense* typically causes a mild chronic illness occurring months to years after inoculation. Early manifestations of infection include intermittent fever, malaise, and lymphadenopathy, particularly in the posterior cervical chain. Signs and symptoms of meningoencephalitis, including behavior changes, somnolence, severe headaches, and coma, and death may follow. *T. brucei rhodesiense* typically causes an acute, severe, often fatal, generalized illness within weeks of inoculation; CNS symptoms are uncommon [15].

Treatment for sleeping sickness is highly toxic, and parasitic resistance is common [12,15,16]. Four drugs are available to treat sleeping sickness, and selection is based in part on CNS involvement. Suramin sodium can be used for infection with either *T. brucei gambiense* or *T. brucei rhodesiense,* but because it does not cross the blood-brain barrier, it is useful only during the hemolymphatic stages of infection. It is given intravenously in a test dose of 5 mg/kg, followed 48 hours later by 20 mg/kg on days 1, 3, 7, 14, and 21 [12,17]. Severe side effects, including anaphylaxis, neurotoxicity, and nephrotoxicity, have been reported.

Pentamidine isethionate, given in daily intramuscular injections for 10 days, is the recommended treatment for the hemolymphatic stage of *T. brucei gambiense*. This treatment is typically well tolerated, but hypotension and hypoglycemia may occur [15].

Melarsoprol is a highly toxic drug that is indicated for infections involving the CNS. It contains arsenic and can only be given intravenously. For *T. brucei gambiense,* the treatment course consists of daily intravenous injections for 10 days. The treatment course for *T. brucei rhodesiense* consists of a daily infusion on 3 consecutive days, repeated three times, each separated by 1 week [15]. Approximately 5% to 10% of patients develop an encephalopathic syndrome requiring the coadministration of steroids [15,18]. Other side effects reported include abdominal pain, vomiting, fever, and joint pain [19].

Eflornithine is the recommended drug of choice for patients who fail therapy with melarsoprol. Eflornithine treatment requires four infusions daily for 14 days followed by oral administration for 2 to 4 weeks [15,20]. Therapy is typically well tolerated, but side effects include seizures, abdominal complaints, granulocytopenia, and alopecia. Adverse reactions tend to be associated with length of treatment and are reversible when treatment is completed [15,20].

Leishmaniasis

Leishmaniasis is caused by a variety of different species of *Leishmania* parasites, which are transmitted by the bite of an infected sandfly. Infection is characterized by three major clinical syndromes: cutaneous, mucocutaneous, and visceral leishmaniasis [21,22]. Cutaneous disease is divided further into Old World and New World disease by their differing causal species of parasite and geographic distribution; however, the clinical manifestations are similar. Both diseases consist of ulcerative lesions that present on exposed areas of the face and extremities. Infection is often self-limited, and specific therapy is not required [12,21]. Mucocutaneous disease is caused most often by infection from *L. braziliensis*, presenting several months to years after an initial cutaneous lesion. Inflammation of mucosal tissue is followed by potentially disfiguring ulceration and death if disease results in compromise of the respiratory system [21]. Visceral disease results when parasites spread from skin macrophages to local lymph nodes and concentrate in the liver, spleen, and bone marrow. Illness is characterized by fever, weight loss, marked hepatosplenomegaly, and anemia, and death usually occurs within several years as a result of secondary bacterial infections or progressive emaciation [23].

Antimonial drugs, such as sodium stibogluconate and meglumine antimonite, are the mainstays of treatment for leishmaniasis, but the incidence of side effects is high. Dosing is based on antimony concentration in each drug, and treatment should be done in consultation with infectious disease experts. Currently, only sodium stibogluconate is available in the United States from the Centers for Disease Control and Prevention [24]. Treatment often requires a prolonged hospital stay with daily intramuscular or intravenous infusions for 20 to 28 days depending on location and species of leishmania [22]. Retreatment is commonly necessary. Side effects include abdominal pain, nausea, and arthralgias [12]. Prolonged treatment courses can lead to ECG abnormalities, including fatal arrhythmias. HIV-infected persons are prone to clinical pancreatitis [21,23,25,26]. Use of antimonials is becoming compromised because of parasitic resistance.

Reports from India show resistant disease in 65% of infections [27,28]. These drugs are greater than 90% effective in children with Mediterranean visceral leishmaniasis [25,26].

Amphotericin B is the drug of choice for treatment failures with antimonial drugs and is now first-line therapy in areas with high rates of drug resistance, such as India. Cure rates reach 97%, but cost is often a limiting factor. Side effects are common and include hypokalemia; anemia; renal impairment; and infusion-related side effects, such as fever, chills, bone pain, and thrombophlebitis. This regimen is given intravenously daily or every other day for 8 weeks. Liposomal preparations of amphotericin B have been shown to be highly effective and have better tolerance [21,23,25,29].

Pentamidine is an alternative second-line treatment. It is given intravenously or intramuscularly daily or every other day for 4 to 7 doses in cutaneous disease and for 15 to 30 doses in visceral disease. The use of pentamidine is limited because of side effects and the development of resistance [21,23].

Allopurinol in combination with antimonials has shown some usefulness when traditional therapy has failed. It is not recommended currently, however, because of lack of adequate clinical trials [23,30]. Topical paromomycin has shown benefit in cutaneous disease, but should be used only in geographic areas where mucocutaneous disease is rare [17].

Entamoeba histolytica

Entamoeba are pseudo–pod-forming, nonflagellated protozoa that can cause gastrointestinal disease, including amebic dysentery. Most are commensal organisms that do not cause disease in humans. *E. histolytica*, the organism that causes amebic colitis and liver abscess [31], is transmitted by the fecal-oral route. *E. histolytica* is most prevalent in tropical and developing countries, and in the United States it is most frequently found in travelers to endemic areas and recent immigrants [32]. The clinical spectrum of illness in patients with amebic colitis ranges from 1 to 3 weeks of mild diarrhea to grossly bloody dysentery with abdominal pain and tenesmus [31,33]. Often, amebic colitis is mistaken for inflammatory bowel disease [12]. The most common form of extraintestinal disease resulting from *E. histolytica* infection is liver abscess.

Four drugs are useful for the therapy of amebiasis. The recommended management strategy is to treat the invasive disease first, followed by the eradication of intestinal carriage of the organism with agents active in the intestinal lumen [31]. Oral metronidazole, three times daily for 7 to 10 days, is the mainstay for treatment of invasive disease. It is fairly well tolerated with common side effects, including nausea, vomiting, diarrhea, and metallic taste. Less frequently, patients experience neurotoxic effects, such as seizures, confusion, and irritability. Patients receiving metronidazole should avoid alcohol because of its disulfiram-like intolerance [31,32]. Other nitroimidazoles, such as tinidazole and ornidazole, seem to be as effective as metronidazole, but are unavailable in the United States [31,34].

After completion of treatment for invasive disease, a luminal drug is recommended for clearance of intestinal organisms. Three drugs are currently recommended: iodoquinol, paromomycin, and diloxanide furoate [31,32,35,36]. Iodoquinol is given orally three times daily for 20 days. Side effects include nausea, vomiting, diarrhea, and abdominal pain; iodoquinol is contraindicated in patients with allergy to iodine [32]. Paromomycin is given orally three times daily for 7 days. Side effects include diarrhea and gastrointestinal upset. Diloxanide furoate is given three times daily for 10 days. Side effects include gastrointestinal symptoms, such as nausea, vomiting, and flatulence [31,32].

Drainage or surgical removal of amebic liver abscess generally is not recommended. Drainage may be indicated, however, when abscesses are sufficiently large and rupture is of concern; in left lobe abscesses, which hold a higher risk for mortality; and in persons who fail to respond to medical therapy within 5 to 7 days [32].

Treatment of protozoan infections distributed globally and infections in immunocompromised hosts

Table 2 provides a quick reference to drugs of choice and dosages.

*Lumenal Flagellates (*Giardia *and* Trichomonas)

Giardiasis

Giardia lamblia, also known as *Giardia intestinalis* or *Giardia duodenalis*, is a flagellated protozoan that infects the gastrointestinal tract. It is the most frequent parasitic cause of enteritis in the United States and has a worldwide distribution. In industrialized countries, *Giardia* has a prevalence of 2% to 5%, and in developing countries prevalence is 20% to 30%. High-risk groups include children, previously uninfected adults and travelers, and immunocompromised persons. Rates of infection are highest in areas of poor sanitation and where water is unfiltered [37–39]. Clinical presentations of *Giardia* have a bimodal distribution with peaks at 0 to 5 years and 30 to 40 years [39].

Several drugs are effective in the treatment of giardiasis. The drug of choice is oral metronidazole. It usually is given three times daily for 5 to 7 days [40]. It has a cure rate of 80% to 95% [37,40,41]. An oral formulation of metronidazole is not marketed; however, a suspension can be prepared by thoroughly crushing the tablet and suspending it in cherry syrup [40]. Nitazoxanide, which is available as a tablet and an oral suspension, is approved by the Food and Drug Administration for treatment of *Giardia*. Dosing is usually twice daily for 3 days. Nitazoxanide is as effective as metronidazole for the treatment of *Giardia* and the treatment of metronidazole-resistant *Giardia* [17,42,43]. Nitazoxanide is well tolerated [44,45]. Alternative treatments include furazolidone, tinidazole, albendazole, and paromomycin [37,38]. Furazolidone is given four times daily for 7 to 10 days and is available in an oral solution, an advantage for pediatric patients. Side

effects include nausea, vomiting, and diarrhea. Cure rates are lower (about 70%) than rates for other options. This drug should be avoided in patients with G6PD deficiency because of hemolysis. Children younger than 1 month old also can experience hemolytic anemia owing to glutathione instability [40]. Single-dose tinidazole, a nitroimidazole, is another effective agent [37,40]. Albendazole has been shown to be safe and effective in treatment of helminth infections (see section on helminthes) and equally as effective as metronidazole in treating giardiasis in children [46]. This broad activity makes it ideal for treating patients with mixed infections [40]. Paromomycin, a poorly absorbed aminoglycoside, is recommended for the treatment of pregnant women. It is given three times daily for 7 days and has an efficacy of 50% to 70%. If systemically absorbed, it may cause ototoxicity and nephrotoxicity, and it should be used with caution in patients with renal impairment [37,40].

Trichomonas

Trichomonas vaginalis is a sexually transmitted flagellated protozoan that causes 3 to 4 million infections annually in the United States [47]. It is the most common nonviral sexually transmitted disease worldwide [48]. Most men who are infected are asymptomatic or have mild urethral discharge. Women often experience symptoms characterized by a malodorous yellow-green vaginal discharge with vulvar irritation [49]. The health consequences of these infections are substantial and include complications of pregnancy, association with cervical cancer, and predisposition to HIV infection [48]. Metronidazole is the drug of choice, resulting in a cure rate of approximately 95%. Sexual partners should be treated concurrently, even if asymptomatic. In older adolescents and adults, treatment can be given as a single large dose or alternatively in a twice-daily regimen for 7 days [48]. Children should receive three-times-daily dosing for 7 days [17]. Symptomatic pregnant women should be treated with the single-dose regimen [49].

Apicomplexa Infections (Coccidians [including Cryptosporidium*],* Babesia, and Toxoplasma*)*

Cryptosporidiosis

C. parvum is a coccidian parasite that infects the epithelial cells of the gastrointestinal and respiratory tracts of vertebrates [48,50]. Transmission is through ingestion of fecally contaminated food and water and direct person-to-person or animal-to-person spread [50]. This disease has been associated with diarrheal illness worldwide with severity of symptoms dependent on the host characteristics. High-risk populations include children in tropical developing areas and immunocompromised individuals [48,50]. Outbreaks secondary to food-borne transmission occur in more affluent countries. Cryptosporidiosis is characterized by profuse watery diarrhea, fever, anorexia, abdominal cramps, and vomiting. Infection is typically self-limited in immunocompetent hosts; diarrhea lasts approximately 10 to 14 days without therapy. Immunocompromised hosts often

Table 2
Treatment of protozoan infections distributed globally and infections in immunocompromised hosts

Parasite	Drug	Pediatric dosage	Adult dosage
Lumenal flagellates			
Giardia duodenalis			
Drugs of choice	Metronidazole	15 mg/kg/d 3 times daily × 5–7 d	250 mg 3 times daily × 5–7 d
	Nitazoxanide	1–3 y: 100 mg twice daily × 3 d 4–11 y: 200 mg twice daily × 3 d	500 mg twice daily × 3 d
Alternatives:	Furazolidone	6 mg/kg/d 4 times daily × 7–10 d	100 mg 4 times daily × 7–10 d
	Tinidazole	50 mg/kg × 1 dose	2 g × 1 dose
	Albendazole	15 mg/kg once daily × 5 d	400 mg once daily × 5 d
	Paromomycin	25–35 mg/kg/d 3 times daily × 7 d	25–35 mg/kg/d 3 times daily × 7 d
Trichomonas vaginalis			
Drug of choice	Metronidazole	15 mg/kg/d 3 times daily × 7 d	500 mg twice daily × 7 d; or 2 g × 1 dose
Apicomplexa infections			
Cryptosporidium parvum			
Drug of choice	Nitazoxanide	1–3 ys: 100 mg twice daily × 3 d 4–11 ys: 200 mg twice daily × 3 d	500 mg twice daily × 3 d
Alternative	Paromomycin		
Isospora belli			
Drug of choice	Trimethoprim-sulfmethoxazole	TMP 5 mg/kg, SMX 25 mg/kg twice daily × 10 d	TMP 160 mg, SMX 800 mg twice daily × 10 d
Prophylaxis in AIDS		TMP 5 mg/kg, SMX 25 mg/kg daily 3 times per wk	TMP 160 mg, SMX 800 mg daily 3 times per wk
Cyclospora cayetanensis			
Drug of choice	Trimethoprim-sulfmethoxazole	TMP 5 mg/kg, SMX 25 mg/kg twice daily × 10 d	TMP 160 mg, SMX 800 mg twice daily × 10 d
Prophylaxis in AIDS		TMP 5 mg/kg, SMX 25 mg/kg daily 3 times per wk	TMP 160 mg, SMX 800 mg daily 3 times per wk

Babesia microti			
Drug of choice	Quinine *plus* clindamycin	25 mg/kg/d 3 times daily × 7–10 d plus 20–40 mg/kg/d 3 times daily × 7–10 d	650 mg 3 times daily × 7–10 d plus 1.2 g IV 2 times daily or 600 mg 3 times daily × 7–10 d
	Atovaquone *plus* azithromycin	20 mg/kg twice daily × 7–10 d *plus* 12 mg/kg once daily × 7–10 d	750 mg twice daily × 7–10 d *plus* 600 mg once daily × 7–10 d
Toxoplasma gondii			
Pregnant female			
Drug of choice	Spiramycin		1 g three times daily until term or fetal infection
Alternative after first trimester if in utero transmission	Pyrimethamine *plus* sulfadiazine		50 mg twice daily × 2 d, then 50 mg once daily *plus* 50 mg/kg twice daily until term
Congenital infection			
Drugs of choice	Pyrimethamine *plus* sulfadiazine	2 mg/kg × 2 d; then 1 mg/kg × 6 mo, then once every M, W, F × 1 y *plus* 50 mg/kg twice daily × 1 y	
Immunocompromised host			
Drugs of choice	Pyrimethamine *plus* sulfadiazine	2 mg/kg × 3 d; then 1 mg/kg *plus* 50 mg/kg twice daily × 4 wk	25–100 mg/d plus 1–1.5 g 4 times daily × 4 wk
Alternative	Trimethoprim-sulfamethoxazole	TMP 5 mg/kg, SMX 25 mg/kg twice daily × 4 wk	TMP 160 mg, SMX 800 mg twice daily × 4 wk
AIDS-related pathogens			
Pneumocyctis jiroveci (formerly *P. carinii*)			
Drugs of choice	Trimethoprim-sulfamethoxazole	TMP 15 mg/kg/d, SMX 75 mg/kg/d IV/PO 4 times daily × 21 d	TMP 15 mg/kg/d, SMX 75 mg/kg/d IV/PO 4 times daily × 21 d
	Pentamidine	3–4 mg/kg/d IV once daily × 21 d	3–4 mg/kg/d IV once daily × 21 d
Prophylaxis			
Drug of choice	Trimethoprim-sulfamethoxazole	TMP 15 mg/m^2, SMX 750 mg/m^2 twice daily on 3 consecutive days per wk	1 tab (single or double strength) daily on 3 consecutive days per week
Alternatives	Dapsone	2 mg/kg/d or 4 mg/kg each week	50 mg twice daily or 100 mg once daily
	Pentamidine	>5 y: 300 mg IV/inhaled monthly	300 mg IV/inhaled monthly

(continued on next page)

Table 2 (*continued*)

Parasite	Drug	Pediatric dosage	Adult dosage
AIDS-related pathogens			
Prophylaxis			
Alternatives	Atovaquone	1–3 mo: 30 mg/kg once daily 4–24 mo: 45 mg/kg once daily >24 mo: 30 mg/kg once daily	1500 mg once daily
Microsporidiosis			
Drugs of choice	Albendazole		400 mg twice daily × 21 d
	Fumagillin		60 mg once daily × 14 d
Free-living ameba			
Naegleria fowleri			
Drug of choice	Amphotericin B	1.5 mg/kg twice daily × 3 d, then 1/mg/kg once daily × 6 d	1.5 mg/kg twice daily × 3 d, then 1/mg/kg once daily × 6 d
Acanthamoeba			
Drug of choice	See text		

have a prolonged course with chronic diarrhea and wasting and involvement of the biliary and pancreatic ducts [50].

Because cryptosporidiosis is self-limiting in most cases, treatment consists of maintaining adequate hydration and supportive care. In severe cases and in immunocompromised patients, however, several treatment options could be considered. Nitazoxanide is the drug of choice. It is available as a tablet and oral suspension and should be given twice daily for 3 days. In a study in Zambia, malnourished children treated with nitazoxanide showed clinical and microbiologic improvements and improved survival [51]. Paromomycin, a nonabsorbed aminoglycoside, has been shown to decrease stool excretion of oocytes in several trials. There are conflicting results with regards to its efficacy in treatment of cryptosporidiosis in patients with AIDS, however [52,53]. When used as a single therapy, treatment regimens have included two to four doses daily from 14 to 28 days. Paromomycin also has been used in combination with azithromycin for 4 weeks, followed by paromomycin alone for another 8 weeks with some improvement in clinical symptoms and decrease in oocyte passage [54].

Isospora *and* Cyclospora

Isospora belli and *C. cayetanensis* are coccidian protozoa that can infect the small intestines and cause human disease. Both cause diarrheal diseases similar to cryptosporidiosis. *Cyclospora* has a worldwide distribution and is endemic in Nepal, Peru, and Haiti. Both infections are a common source of travel-related diarrhea, and both are spread by the fecal-oral routes through food and water [37]. In immunocompetent hosts, both produce self-limiting infections, but in immunocompromised hosts chronic diarrhea and anorexia can cause serious sequelae. The treatment for both infections is TMP-SMX twice daily for 7 to 10 days. In patients with AIDS, treatment should be the continuation of TMP-SMX three times per week as prophylaxis [37,55]. Formulations of TMP-SMX include tablet and oral suspension. Serious reactions include Stevens-Johnson syndrome, aplastic anemia, anaphylactoid and allergic reactions, hepatotoxicity, and nephrotoxicity. Daily pyrimethamine, with or without folinic acid, is an effective alternative for patients who cannot tolerate TMP-SMX [56].

Babesia

Babesia are tick-borne protozoa classified in the Apicomplexa phylum. Human disease is found almost exclusively in the United States and Europe. The most common species in northeastern United States is *B. microti,* transmitted mainly by *Ixodes scapularis* ticks, which are also the main vectors for Lyme disease [57,58]. *Babesia* manifestations range from asymptomatic disease to mild flulike symptoms to more severe symptoms mimicking malaria to death. The most common symptoms include fever, malaise, night sweats, and headache.

The drugs of choice are either oral quinine three times daily plus intravenous/oral clindamycin three times daily for 7 to 10 days or oral atovaquone twice daily

plus oral azithromycin once daily for 7 to 10 days [57]. In a study comparing the two treatment regimens in adults, both were similar with regards to clearing symptoms and parasitemia. Clindamycin and quinine were associated with a higher rate of adverse events, however [59].

Toxoplasma

Toxoplasma gondii is an obligate intracellular protozoan with a worldwide distribution. Cats are the definitive host, but *T. gondii* can infect most species of warm-blooded animals. Transmission can occur in-utero, by ingestion of food and water contaminated by cat feces, or by ingestion of undercooked meats infected with *T. gondii* oocysts [48,60]. In most healthy, immunocompetent individuals, infection with *T. gondii* is asymptomatic and resolves spontaneously without treatment. Treatment is indicated, however, for three populations of special concern: pregnant mothers, neonates, and immunocompromised persons.

Infection acquired early in the pregnancy can result in severe congenital toxoplasmosis, in utero fetal demise, or spontaneous abortion. Maternal infections contracted late in pregnancy are associated with a high frequency of vertical transmission, but most resulting congenital infections are asymptomatic. Treatment of pregnant women is aimed at decreasing vertical transmission and the frequency and severity of adverse outcomes for the fetus [60]. The drug of choice for acute toxoplasmosis in a pregnant woman is spiramycin three times a day. If, after the first trimester, there is no evidence of transmission to the fetus, spiramycin can be continued for the length of the pregnancy. If the fetus shows evidence of infection, pyrimethamine and sulfadiazine should be initiated. Pyrimethamine cannot be used in the first trimester because of its teratogenic effects [48,60,61].

Neonates with congenital toxoplasmosis usually are asymptomatic at birth. When present, clinical manifestations may include microcephaly, hydrocephalus, seizures, blindness, petechiae, and anemia. Infected infants should be treated with pyrimethamine once daily for 6 months, then three times weekly to complete 1 year, plus sulfadiazine twice daily for 1 year. While taking pyrimethamine, patients should receive leucovorin three times daily to prevent bone marrow suppression [60,62].

CNS disease is a common complication of toxoplasmosis in HIV-infected adults and children. Focal neurologic deficits include seizures, hemiparesis, cranial nerve palsies, and ataxia. Treatment consists of pyrimethamine plus sulfadiazine plus leucovorin acutely and for a minimum of 4 weeks after symptoms have resolved [60,63]. Clindamycin may be substituted for sulfadiazine if the patient is intolerant of sulfa drugs. TMP-SMX seems to have equal efficacy to pyrimethamine plus sulfadiazine in patients with AIDS and represents an alternative therapy [64]. When the acute therapy is complete, secondary prophylaxis, usually at half the treating dose, should be continued until the patient is no longer severely immunocompromised [60].

*AIDS-related pathogens (*Pneumocystis *and* Microsporidia*)*

Pneumocystis

Pneumocystis jiroveci, formerly known as *Pneumocystis carinii,* is the most common opportunistic infection in children with advanced HIV infection. It is classified as a fungus based on DNA sequence analysis, but retains several morphologic and biologic similarities to protozoa [63]. *P. jiroveci* is ubiquitous in mammals, and most humans have acquired antibody by 4 years of age. Most cases in industrialized countries occur in persons lacking cell-mediated immunity, especially HIV-infected persons. *Pneumocystis* is an extracellular parasite that infects the lungs, resulting in the classic tetrad of symptoms: tachypnea, dyspnea, cough, and fever. Rapidly progressing hypoxemia and subsequent respiratory failure follow [63,65].

The treatment of choice of *Pneumocystis* in HIV-infected children is intravenous TMP-SMX, steroids, and respiratory support. TMP-SMX is given in higher than normal dosages, divided into four daily doses for 21 days. Treatment can be switched to oral formulations when the patient's clinical status has improved [66]. Rates of adverse reactions to TMP-SMX are generally higher for HIV-infected children compared with normal children. Pentamidine, in a single daily intravenous dose for 21 days, is an alternative for patients who are intolerant of TMP-SMX. Pentamidine is similar in efficacy to TMP-SMX. Adverse effects of pentamidine include pancreatitis, hypoglycemia or hyperglycemia, hypotension, fever, rash, and neutropenia [67]. Atovaquone has been approved for the oral treatment of mild-to-moderate *Pneumocystis* in adult patients who are intolerant to TMP-SMX. Experience with this agent in children is limited. Common side effects include rash, fever, nausea, diarrhea, hyperglycemia, and elevated amylase levels [68]. Several other regimens (clindamycin plus primaquine, dapsone plus trimethoprim, and trimetrexate plus leucovorin) have been approved for use in adults, but have not been evaluated in children [69–71].

Guidelines for *Pneumocystis* prophylaxis in HIV-positive and HIV-exposed children were revised in 1995 and are shown in Box 1 [72]. TMP-SMX is the

Box 1. Guidelines for *Pneumocystis* prophylaxis in HIV-positive and HIV-exposed children

1. All HIV-infected and indeterminate children from 4 weeks to 12 months of life (prophylaxis can be stopped if HIV infection has been excluded after 4 months of age)
2. HIV-infected children aged:
   1–5 years: $CD4^+$ count <500/μL, CD4 percentage <15%
   6–12 years: $CD4^+$ count <200/μL, CD4 percentage <15%
3. All HIV-infected children treated for *P. jiroveci* pneumonia

prophylactic medication of choice, given once daily on 3 consecutive days per week. For persons intolerant of TMP-SMX, alternatives include daily oral dapsone, monthly aerosolized or intravenous pentamidine, or daily atovaquone. Dapsone has been associated with hemolytic anemia and is contraindicated in persons with G6PD deficiency [66].

Microsporida

Microsporida are obligate, intracellular protozoa that are ubiquitous in nature and infect numerous animals, including humans. Transmission occurs when spores are ingested, then organisms disseminate into host tissue, such as liver and kidneys, with excretion back into the environment through feces [73]. Before the HIV epidemic, there were few reported human cases of infection. More recently, the incidence of infection has increased dramatically, with most cases reported in immunocompetent persons [74,75]. Clinical features of disease caused by *Microsporida* include diarrhea, corneal infections, cholecystitis, hepatitis, nephritis, and peritonitis [73,75–77]. The drugs of choice for treatment of *Microsporida* are albendazole twice daily for 21 days and fumagillin once daily for 14 days. Albendazole has been shown to improve symptoms of diarrhea, but not to eradicate the organism. Albendazole usually is effective against *Encephalitozoon intestinalis,* but infections with *E. bienuesi* are more difficult to treat [78]. Fumagillin was effective at alleviating symptoms and eliminating the organism from stools in a study conducted in 10 patients with AIDS and 2 organ transplant recipients. Severe neutropenia and thrombocytopenia occurred in several patients [79].

*Free-Living Amebae (*Naegleria, Acanthamoeba*)*

Naegleria *and* Acanthamoeba

Naegleria fowleri and *Acanthamoeba* species are ‘‘free-living’’ amebic organisms because they do not need a secondary host to complete their life cycle. These organisms have a worldwide distribution and are found in soil, freshwater ponds, streams, rivers, and pools. Infection can result in primary amebic meningoencephalitis, an extremely rare and almost uniformly fatal infection [80]. *N. fowleri* causes an acute amebic meningoencephalitis, which initially is indistinguishable from primary bacterial meningitis, whereas *Acanthamoeba* causes a more indolent and subacute granulomatous amebic encephalitis [81].

The drug of choice for treatment of *N. fowleri* is amphotericin B. There have been reports of successful combinations of treatments with amphotericin B, rifampin, and chloramphenicol; amphotericin B and rifampin; amphotericin B, rifampin, and ketoconazole; and combinations of intravenous and intrathecal amphotericin B [82–84]. Outcome of treatment of *Acanthamoeba* infection usually is poor, although several cases have been treated successfully with the combination use of TMP-SMX, rifampin, and ketaconazole [85,86]. Other reports describe use of fluconazole, sulfadiazine, and pyrimethamine in combination with surgical resection of the CNS lesion [87].

Treatment of helminthic infections

Table 3 provides a quick reference to drugs of choice and dosages.

*Intestinal nematodes (*Ascaris, Trichuris, Enterobius, *and Hookworms) and Strongyloides species*

Helminth infections affect more than one quarter of the world's population, making them a major health priority. Campaigns for deworming, launched by the World Health Organization, are targeting high-risk groups, such as school-age children, preschool children, and women of childbearing age in the developing world. In the United States, high-risk groups include international travelers, refugees, recent immigrants, and international adoptees [88–90].

Five antihelminthic drugs are considered the drugs of choice against intestinal nematodes. The benzamidazoles, such as albendazole (single dose) and mebendazole (twice a day for 3 days), are effective first-line treatments against *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), *Ancylostoma duodenale,* and *Necator americanus* (hookworms). Albendazole administered twice a day for 2 days is the drug of choice against *Strongyloides stercoralis*. Albendazole and mebendazole are available as chewable tablets, and both are available as oral solutions [90,91]. Mebendazole is poorly absorbed by the gastrointestinal tract and exerts its action directly on the worms themselves. For extraluminal infections, appropriate tissue levels can be attained if the drug is taken with fatty foods. Side effects for both drugs are typically mild and transient. In a few cases, gastrointestinal symptoms (epigastric pain, nausea, diarrhea, and vomiting), CNS symptoms (dizziness, headache), migration of worms through the mouth, and rare allergic conditions have been reported [90]. Because of their teratogenic potential in animals, benzamidazoles are not recommended for children younger than 2 years of age. Side effects in infants 12 months old are similar to those of older children [92,93].

Pyrantel pamoate, available as an oral solution given as a single dose, is the drug of choice for *Enterobius vermicularis* (pinworm). Single-dose albendazole and mebendazole are effective alternatives. Regardless of the drug used, a second dose is required after 2 weeks. Pyrantel pamoate, as a single dose, is an effective alternative for *A. lumbricoides,* and once-daily dosing for 3 days is an alternative for *A. duodenale* and *N. americanus* [90]. Pyrantel pamoate should be used with caution in patients with hepatic dysfunction. No data exist for use in children younger than 2 years of age, but no age-related problems have been reported [94].

Cutaneous larva migrans, or creeping eruption, usually is caused by the larvae of *Ancylostoma brasiliense* and *Uncinaria stenocephala* (dog and cat hookworms). This infection can be treated topically with thiabendazole cream, two to three times daily for 5 to 10 days. In most cases, pruritus and larval migration resolve within 48 hours. Alternative treatments include albendazole (daily for 3 days) or ivermectin (daily for 1–2 days). Other topical treatments, such as

Table 3
Treatment of helminthic infections

Parasite	Drug	Pediatric dosage	Adult dosage
Intestinal nematode			
Roundworm *Ascaris lumbricoides*			
Drugs of choice	Albendazole	400 mg × 1 dose	400 mg × 1 dose
	Mebendazole	100 mg twice daily × 3 d	100 mg twice daily × 3 d
	Pyrantel pamoate	11 mg/kg once; repeat in 2 wk	11 mg/kg once; repeat in 2 wk
	Ivermectin	150–200 μg/kg × 1 dose	150–200 μg/kg × 1 dose
Whipworm: *Trichuris trichiura*			
Drugs of choice	Albendazole	400 mg × 1 dose	400 mg × 1 dose
	Mebendazole	100 mg twice daily × 3 d	100 mg twice daily × 3 d
	Ivermectin	150–200 μg/kg × 1 dose	150–200 μg/kg × 1 dose
Hookworm: *Ancylostoma duodenale* and *Necator americanus*			
Drugs of choice	Albendazole	400 mg × 1 dose	400 mg × 1 dose
	Mebendazole	100 mg twice daily × 3 d	100 mg twice daily × 3 d
	Pyrantel pamoate	11 mg/kg once daily × 3 d	11 mg/kg once daily × 3 d
Pinworm: *Enterobius vermicularis*			
Drugs of choice	Pyrantel pamoate	11 mg/kg once; repeat in 2 wk	11 mg/kg once; repeat in 2 wk
Alternatives	Albendazole	400 mg once; repeat in 2 wk	400 mg once; repeat in 2 wk
	Mebendazole	100 mg once; repeat in 2 wk	100 mg once; repeat in 2 wk
	Ivermectin	150–200 μg/kg × 1 dose	150–200 μg/kg × 1 dose
Strongyloides stercoralis			
Drugs of choice	Albendazole	400 mg twice daily × 2 d	400 mg twice daily × 2 d
Alternatives	Ivermectin	200 μg/kg once daily × 2 d	200 μg/kg once daily × 2 d
	Thiabendazole	50 mg/kg twice daily × 2 d	50 mg/kg twice daily × 2 d
Cutaneous larva migrans: *Ancylostoma brasiliense* and *Uncinaria stenocephala*			
Drugs of choice	Thiabendazole	Topically 2–3 times daily for 5–10 d	Topically 2–3 times daily for 5–10 d
	Albendazole	400 mg once daily × 3 d	400 mg once daily × 3 d
	Ivermectin	200 μg/kg once daily × 1–2 d	200 μg/kg once daily × 1–2 d

Blood and tissue nematodes			
Filariasis: *Onchocerca volvulus*			
Drug of choice	Ivermectin	150 μg/kg once monthly × 6–12 mo	150 μg/kg once monthly × 6–12 mo
Lymphatic filariasis: *Wuchereria bancrofti, Brugia malayi, Brugia timori*			
Drug of choice	Diethylcarbamazine	6 mg/kg × 1 dose	6 mg/kg × 1 dose
Visceral larva migrans: *Toxocara cari*			
Drug of choice	Albendazole	400 mg twice daily × 5 d	400 mg twice daily × 5 d
	Mebendazole	100–200 mg twice daily × 5 d	100–200 mg twice daily × 5 d
Cestodes			
Tapeworms			
Taeniasis: *T.saginata/T. solium*			
Drugs of choice	Niclosamide	50 mg/kg × 1 dose	2 g × 1 dose
	Praziquantel	5–10 mg/kg × 1 dose	5–10 mg/kg × 1 dose
Cysticercosis: *T.solium*			
Drug of choice	Albendazole	15 mg/kg twice daily × 15–30 d	400 mg twice daily × 15–30 d
Alternative	Praziquantel	50–100 mg/kg 3 times daily × 30 d	50–100 mg/kg 3 times daily × 30 d
Hydatid disease: *Echinococcus granulosus* and *E. multilocularis*			
Drugs of choice	Albendazole	15 mg/kg once daily for 1–6 mo	400 mg twice daily × 1–6 mo
Diphyllobothrium latum, Dipylidium caninum			
Drug of choice	Praziquantel	5–10 mg/kg × 1 dose	5–10 mg/kg × 1 dose
Hymenolepsis nana			
Drug of choice	Praziquantel	25 mg/kg × 1 dose	25 mg/kg × 1 dose
Trematodes			
Schistosomiasis			
Drug of choice	Praziquantel	40–60 mg/kg 2–3 times daily × 1 dose	40–60 mg/kg 2–3 times daily × 1 dose
Liver flukes: *Clonorchis sinesis*, *Opisthorchis viverrini*, and *Opisthorchis felineus*			
Drug of choice	Praziquantel	75 mg/kg 3 times daily × 1 dose	75 mg/kg 3 times daily × 1 dose
Alternative: (*C. sinesis*)	Albendazole	10 mg/kg once daily × 7 d	10 mg/kg once daily × 7 d
Lung fluke: *Paragonimus westermani*			
Drug of choice	Praziquantel	75 mg/kg 3 times daily × 2 d	75 mg/kg 3 times daily × 2 d

freezing the leading edge of the cutaneous trail, have been tried in the past, but are no longer recommended because of blistering and ulceration [91,103].

Ivermectin (single dose for 1–2 days) and thiabendazole (twice daily for 2 days) are acceptable alternatives to albendazole for the treatment of *S. stercoralis* [90, 95,96]. Ivermectin, as a single dose for the treatment of ascariasis, trichuriasis, and enterobiasis, is equal in efficacy to other agents, but it has limited activity against hookworms [94]. Studies suggest that giving a single combination dose of ivermectin plus albendazole produces superior cure rates and egg reduction for trichuriasis than with either drug used alone [97]. Neither ivermectin nor thiabendazole has been studied extensively in children, and safety profiles have not been established for children weighing less than 15 kg. Neither drug is recommended during pregnancy, but if treatment of heavy worm burden during pregnancy is required, ivermectin should be used because of its low risk of adverse events [90]. Thiabendazole is available in chewable tablets and oral solution. It is well absorbed and associated with side effects such as dizziness, nausea, diarrhea, and anorexia [96,98].

Blood and tissue nematodes (filarial parasites, Toxocara, *and visceral larva migrans)*

As with the intestinal nematodes, tissue and blood nematodes are a serious global public health problem. Currently, several World Health Organization–sponsored campaigns are geared toward the eradication of some severe nematode infections. These campaigns are based on antivector measures to decrease environmental exposure and are supplemented with mass treatment campaigns when appropriate.

Ivermectin, as a single dose repeated monthly for 6 to 12 months, is currently recommended for international campaigns against *Onchocerca volvulus* (the agent causing river blindness). It is microfilaricidal and results in approximately 95% reduction in dermal microfilariae after one dose. This drug has been shown to reduce or limit dramatically the transmission of filarial disease when used in community-based disease control programs. On an individual basis, this drug is not completely curative, however, because of its lack of effect on the adult parasite. Side effects of ivermectin are infrequent and often due to the inflammatory responses to the dead microfilariae. The frequency of common symptoms accompanying treatment, including rash, pruritus, and myalgias, is less with each subsequent treatment as the number of microfilariae decreases [99,100].

Lymphatic filariasis is caused by three different filariae species (*Wuchereria bancrofti, Brugia malayi*, and *Brugia timori*) and accounts for approximately 120 million infections per year globally [101]. Most cases of lymphatic filariasis are asymptomatic. Children frequently present with lymphadenopathy secondary to worm infestation of the lymph nodes, most commonly in the legs, arms, and scrotum. Tropical pulmonary eosinophilia, thought to result from immune responses to filarial antigens, rarely occurs in children [102]. Single-dose ivermectin given annually is an effective supplement to community-based control

programs, but treatment is not curative [100]. The drug of choice for treatment of lymphatic filariasis is single-dose diethylcarbamazine, which is available in tablet form. A 21-day course of diethylcarbamazine may be required for patients with tropical pulmonary eosinophilia. Although diethylcarbamazine is effective at clearing infection; there is little evidence to suggest that it reverses lymphatic damage or pulmonary fibrosis. Side effects of diethylcarbamazine include pruritus, maculopapular rash, fever, edema, and headache. Data in children are limited, but no other adverse events have been reported [94]. Diethylcarbamazine is effective in vitro against *Onchocerca volvulus*, but it cannot be used clinically because of the intense inflammatory response it causes with rapid killing of microfilariae.

Visceral larva migrans and ocular larva migrans usually are caused by infection most commonly resulting from *Toxocara cani*. Often the disease course for *Toxocara* is subclinical and self-limited, and treatment is controversial. For symptomatic disease, either albendazole or mebendazole twice daily for 5 days is recommended. For patients with ocular or neurologic manifestations, combination therapy with albendazole and corticosteroids is recommended [103,104].

Cestodes (tapeworms [including taeniasis and cysticercosis] and hydatid disease)

Cestodes, or tapeworms, are segmented worms that have two life cycle stages, the adult stage and larval stage, both of which cause disease in humans. Ingestion of undercooked meats containing larvae of *Taenia solium* (pork) or *Taenia saginata* (beef) results in taeniasis when the larvae mature into adult tapeworms. Taeniasis is characterized by mild symptoms of abdominal pain, bloating, nausea, and diarrhea [105]. Niclosamide and praziquantel are the drugs of choice for therapy. Niclosamide, as a single dose, is preferred because it is not absorbed from the intestinal tract, but it is currently not available in the United States. Praziquantel, as a single dose, is available in a scored tablet form [105,106]. Side effects of praziquantel include malaise, abdominal discomfort, headache, dizziness, and rarely urticaria. Safety profiles have not been established in children younger than 4 years old [94].

Cysticercosis and neurocysticercosis are caused by the larval stage of *T. solium,* but not *T. saginata*. In adults, the disease is characterized by symptoms related to increased intracranial pressure and immune-mediated inflammation. The disease differs in children, with generalized seizures a common initial sign, secondary to the cystic mass lesion itself or granuloma formation after cyst destruction [105,107]. Albendazole is the drug of choice for therapy; it is effective and relatively inexpensive. It is administered twice daily for 15 to 30 days and can be repeated as necessary. Praziquantel given three times daily for 15 to 30 days is an alternative. Although effective anticysticercal treatment is available, the decision to treat is controversial because symptoms related to neurocysticercosis are thought to result from the inflammatory response accompanying the death of the organism [105,107]. Studies confirm that neurologic

symptoms increase early in the course of treatment. Persons who are not treated, however, have a higher frequency and persistence of neurologic symptoms. These neurologic symptoms can be ameliorated by the concomitant use of dexamethasone and anticonvulsants [108].

Hydatid disease is caused by the larval forms of the dog tapeworms, *Echinococcus granulosus* and *Echinococcus multilocularis* [90,109]. In adults, dissemination of cysts to multiple different tissue sites, especially the liver and lungs, can follow ingestion. Echinococcus is the most common cause of liver cysts worldwide. Symptoms may be mild for many years or result in serious complications, including death. Dissemination to the brain and eyes in more common in childhood. The mainstay of treatment, when possible, is surgical removal of any cysts. In some cases, such as uncomplicated liver cysts, percutaneous aspiration and injection of a protoscolicidal agent is effective. In other cases, either in conjunction with surgery or when surgery is contraindicated, chemotherapy with oral benzimadoles is warranted. Albendazole and mebendazole have been shown to be beneficial, but albendazole is preferred because of poor tissue penetration of mebendazole. Treatment may need to continue for 6 months [17,110]. *Diphyllobothrium* species (fish tapeworm), *Dipylidium caninum* (dog and cat tapeworm), *Hymenolepsis nana* (dwarf tapeworm), and *Hymenolepsis diminuta* (rodent tapeworm) are other tapeworms that cause human disease, which can be treated with single-dose praziquantel [111].

Trematodes (schistosomes, lung and liver flukes)

Schistosomiasis, also known as *bilharziasis,* is caused by the parasitic blood flukes called *schistosomes*. The World Health Organization estimates that approximately 200 million people are infested worldwide, ranking it second to malaria in terms of global public health importance [112,113]. Numerous schistosome species can affect many different animals, with almost all human cases resulting from *S. mansoni, S. haematobium, S. japonicum, S. mekongi,* and *S. intercalatum*. These different species have differing global distributions and differing predilections for sites of residence within the host [112]. These parasites have a complex life cycle that involves snails as the intermediate host. Prevention efforts are geared toward mass chemotherapy, improved sanitation, and snail control through environmental engineering or molluscacides [114,115].

The drug of choice for treatment of all schistosome species is praziquantel, given in either two or three doses for 1 day [112,116]. Praziquantel is one of the safest antihelminthic medications with minimal side effects. It has not been tested in pregnant and lactating women, however, and is classified as Pregnancy category B. Currently, countries such as Ghana, China, Egypt, and the Philippines have adopted the routine treatment of pregnant women with praziquantel because of a presumed disproportionate risk from infection compared with treatment [116].

Clonorchis sinesis, Opisthorchis viverrini, and *Opisthorchis felineus* constitute a group of trematodes termed *liver flukes,* which reside in the human biliary

tract. Infections are caused by ingestion of uncooked fish that have been infested with larval cysts. Praziquantel, given in three doses for 1 day, is the drug of choice for the three trematodes. Albendazole, given daily for 7 days, is an alternative for *C. sinesis* [17].

Paragonimus westermani, the lung fluke, is a trematode commonly causing human disease in eastern Asia. After ingestion of uncooked crabs or crayfish, the larvae penetrate through the diaphragm into the pleural space and migrate through lung tissue into the bronchi. Approximately 1% of infections result in cerebral disease, which is more common among children [117]. Praziquantel, given three times daily for 2 days, is the drug of choice. For patients developing cerebral disease, corticosteroids given concurrently with praziquantel can reduce symptoms of inflammation caused by dying flukes [17].

Summary

Parasitic infections in children present many challenges for the pediatrician. These complex diseases are often difficult to diagnose and require pathogen-specific treatment with drugs that are unfamiliar to many clinicians. International travel and immunodeficiency states, such as AIDS, have been factors in the increasing prevalence and clinical importance of these infections in children. As in bacterial and viral infections, the emergence of drug resistance is a continuing potential threat. From endemic malaria in persons in sub-Saharan Africa to giardiasis in children US daycare centers to *Pneumocystis* infections in AIDS patients, it is likely that parasitic infections will remain a persistent challenge for public health and infectious disease specialists for many years to come.

References

[1] Sachs J. Helping the world's poorest. Economist 1999;14:17–20.
[2] Guerin PJ, Olliaro P, Nosten F, et al. Malaria: current status of control, diagnosis, treatment, and a proposed agenda for research and development. Lancet Infect Dis 2002;2:564–73.
[3] Alecrim WD, Espinosa FEM, Alecrim MGC. Emerging and re-emerging diseases in Latin America: *Plasmodium falciparum* infection in the pregnant patient. Infect Dis Clin North Am 2000;14:83–95.
[4] Shann F. The management of severe malaria. Pediatr Crit Care Med 2003;4:489–90.
[5] World Health Organization. World malaria situation in 1994. Parts I–III. Wkly Epidemiol Rec 1997;72:269–90.
[6] Suh KN, Kain KC, Keystone JS. Malaria. Can Med Assoc J 2004;170:1693–702.
[7] Winstanley P. Modern chemotherapeutic options for malaria. Lancet Infect Dis 2001;1:242–50.
[8] Trape JF, Pison G, Preziosi MP, et al. Impact of chloroquine resistance on malaria mortality. C R Acad Sci III 1998;321:689–97.
[9] John CC. Drug treatment of malaria in children. Pediatr Infect Dis J 2003;22:649–50.
[10] Miles MA. The discovery of Chagas disease: progress and prejudice. Infect Dis Clin North Am 2004;18:247–60.
[11] Prata A. Clinical and epidemiological aspects of Chagas disease. Lancet Infect Dis 2001;1:92–100.

[12] American Academy of Pediatrics. Summaries of infectious diseases. In: Pickering LK, editor. Red book: 2003 report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village (IL): American Academy of Pediatrics; 2003.
[13] Estani SS, 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;59:526–9.
[14] Viotti R, Vigliano C, Armenti H, Segura E. Treatment of chronic Chagas' disease with benznidazole: clinical and serological evolution with long-term follow-up. Am Heart J 1994;127: 151–62.
[15] Legros D, Ollivier G, Gastellu-Etchegorry M, et al. Treatment of human African trypanosomiasis—present situation and needs for research and development. Lancet Infect Dis 2002;2:437–40.
[16] Burchman RJ, Ogbunude PO, Enanza B, Barrett MP. Chemotherapy of African trypanosomiasis. Curr Pharm Des 2002;8:256–67.
[17] Drugs for parasitic infections. Med Lett Drugs Ther. Available at: www.medletter.com/. Accessed November 4, 2004.
[18] Pepin J, Milord F, Khonde AN, et al. Risk factors for encephalopathy and mortality during melarsoprol treatment of *trypanosoma brucei gambiense* sleeping sickness. Trans R Soc Trop Med Hyg 1995;89:92–7.
[19] Ortega-Barria E. Trypanosoma species (trypanosomiasis). In: Long SS, Pickering LK, Prober CG, editors. Principles and practice of pediatric infectious diseases. 2nd ed. New York: Churchill Livingstone; 2003. p. 1324–30.
[20] Burri C. Eflornithine for the treatment of human African trypanosomiasis. Parasitol Res 2003; 90:S49–52.
[21] Markle WH, Makhoul K. Cutaneous leishmaniasis: recognition and treatment. Clin Infect Dis 1997;25:677–84.
[22] Zuckerman A, Lainson R. *Leishmania*. In: Kreier JP, editor. Parasitic protozoa, vol 1. New York: Academic Press; 1977. p. 77–87.
[23] Guerin PJ, Olliero P, Sundar S, et al. Visceral leishmaniasis: current status of control, diagnosis and treatment, and a proposed research and development agenda. J Infect Dis 1999;180:564–7.
[24] Kafetzis DA, Maltezou HC. Visceral leishmaniasis in paediatrics. Curr Opin Infect Dis 2002; 15:289–94.
[25] Kafetzis DA. An overview of paediatric leishmaniasis. J Postgrad Med 2003;49:31–8.
[26] Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. Am J Trop Med Hyg 1992; 46:296–306.
[27] Sundar S, Pai K, Kumar R, et al. Resistance to treatment in Kala-azar: speciation of isolates from northeast India. Am J Trop Med Hyg 2001;65:193–6.
[28] Lira R, Sundar S, Makharia A, et al. Evidence that the high incidence of treatment failures in Indian Kala-azar is due to the emergence of antimony-resistant strains of leishmania donovani. J Infect Dis 1999;180:564–7.
[29] Meyerhoff A. US Food and Drug Administration approval of Ambisome (liposomal amphoteracin B) for treatment of visceral leishmaniasis. Clin Infect Dis 1999;28:42–8.
[30] Di Martino L, Mantovani MP, Gradoni L. Low dosage combination of meglumine antimoniate plus allopurinol as first choice treatment of infantile visceral leishmaniasis in Italy. Trans Soc Trop Med Hyg 1990;84:534–5.
[31] Li E, Stanley SL. Protozoa: amebiasis. Gastroenterol Clin North Am 1996;25:471–92.
[32] Hughes MA, Petri WA. Amebic liver abscess. Infect Dis Clin North Am 2000;14:565–82.
[33] Adams EB, MacLeod IN. Invasive amebiasis: amebic dysentery and its complications. Medicine 1977;56:315–24.
[34] Bassily S, Farid Z, El-Masry A, Mikhail EM. Treatment of intestinal *E. histolytica* and *G. lamblia* with metronidazole, tinidazole, and ornidazole: a comparative study. J Trop Med Hyg 1987;90:9–12.

[35] McAuley JB, Juranek DD. Paromomycin in the treatment of mild-to-moderate intestinal amebiasis. Clin Infect Dis 1992;15:551–2.
[36] McAuley JB, Herwaldt BL, Stokes SL, et al. Diloxinide furoate for treating asymptomatic *Entamoeba histolytica* cyst passers: 14 years' experience in the United States. Clin Infect Dis 1992;15:464–8.
[37] Katz DE, Taylor DN. Parasitic infections of the gastrointestinal tract. Gastroenterol Clin North Am 2001;30:797–815.
[38] Lebwohl B, Deckelbaum RJ, Green PH. Giardiasis. Gastrointest Endosc 2003;57:906–13.
[39] Procop GW. Gastrointestinal infections. Infect Dis Clin North Am 2001;15:1073–108.
[40] Gardner TB, Hill DR. Treatment of giardiasis. Clin Microbiol Rev 2001;14:114–28.
[41] Hill DR, Nash TE. Intestinal flagellate and ciliate infections. In: Guerrant RL, Walker DH, Weller PF, editors. Tropical infectious diseases. Philadelphia: Churchill Livingstone; 1999. p. 703–12.
[42] Ortiz JJ, Ayoub A, Gargala G, Chegne NL, Favennec L. Randomized clinical study of nitazoxanide compared to metronidazole in the treatment of symptomatic giardiasis in children from northern Peru. Aliment Pharmacol Ther 2001;15:1409–15.
[43] Abboud B, Lemee V, Gargala G, et al. Successful treatment of metronidazole and albendazole resistant giardiasis with nitazoxanide in a patient with acquired immunodeficiency syndrome. Clin Infect Dis 2001;32:1792–4.
[44] Diaz E, Mondragon J, Ramirez E, Bernal R. Epidemiology and control of intestinal parasites with nitazoxanide in children in Mexico. Am Trop Med Hyg 2003;68:384–5.
[45] White Jr AC. Nitazoxanide: an important advance in anti-parasitic therapy. Am Trop Med Hyg 2003;68:382–3.
[46] Hall A, Nahar Q. Albendazole as a treatment for infections with *Giardia duodenalis* in children in Bangladesh. Trans R Soc Trop Med Hyg 1993;87:84–6.
[47] Lossick J. Epidemiology of urogenital trichomoniasis. In: Honinberg BM, editor. Trichomonads parasitic in humans. New York: Springer-Verlag; 1989. p. 311–23.
[48] Christie JD, Garcia LS. Emerging parasitic infections. Clin Lab Med 2004;24:737–72.
[49] Centers for Disease Control and Prevention. Sexually transmitted disease treatment guidelines. MMWR Morb Mortal Wkly Rep 2002;51(RR06):1–80.
[50] Kosek M, Alcantara C, Lima A, Guerrant RL. Cryptosporidiosis: a review. Lancet Infect Dis 2001;1:262–9.
[51] Amadi B, Mwiya M, Musuku J, et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomized controlled trial. Lancet 2002;360: 1375–80.
[52] White Jr AC, Chappell CL, Hayat CS, Kimball KT, Flanigan TP, Goodgame RW. Paromomycin for cryptosporidiosis in AIDS: a prospective, double-blind, placebo-controlled trial. J Infect Dis 1994;170:419–24.
[53] Hewitt RG, Yainnoutsos CT, Higgs ES, Carey JT, Geiseler PJ, Soave R. Paromomycin: no more effective than placebo for treatment of cryptosporidiosis in patients with advanced human immunodeficiency virus infection. Clin Infect Dis 2000;31:1084–92.
[54] Smith NH, Cron S, Valdez LM, Chappell CL, White Jr AC. Combination drug therapy for cryptosporidiosis in AIDS. J Infect Dis 1998;178:900–3.
[55] Pape JW, Verdier RI, Boncy M, Boncy J, Johnson Jr WD. Cyclospora infection in adults infected with HIV: clinical manifestations, treatment and prophylaxis. Ann Intern Med 1994; 121:654–7.
[56] Weiss LM, Perlman DC, Sherman J, Tanowitz H, Wittner M. *Isospora belli* infection: treatment with pryimethamine. Ann Intern Med 1988;109:474–5.
[57] Krause PJ. Babesiosis. Med Clin North Am 2002;86:361–73.
[58] Speilman A. Human babesiosis on Nantucket Island: transmission by nymphal *Ixodes* ticks. Am J Trop Med Hyg 1976;25:784–7.
[59] Krause PJ, Lepore T, Sikand VJ, et al. Atovaquone and azithromycin for the treatment of human babesiosis. N Engl J Med 2000;343:1454–8.

[60] Montoya JG, Liesenfeld O. Toxoplasmosis. Lancet 2004;363:1965–76.
[61] Bale JF. Congenital infections. Neurol Clin North Am 2002;20:1039–60.
[62] Sanchez PJ. Perinatal infections. Clin Perinatol 2002;29:799–826.
[63] Abrams EJ. Opportunistic infections and other clinical manifestations of HIV disease in children. Pediatr Clin North Am 2000;47:79–108.
[64] Torre D, Casari S, Speranza F, et al. Randomized trial of trimethoprim-sulfamethoxazole vs. pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Italian Collaborative Study Group. Antimicrob Agents Chemother 1998;42:1346–9.
[65] Bye MR, Bernstein LJ, Glaser J, Kleid D. *Pneumocystis carinii* pneumonia in young children with AIDS. Pediatr Pulmonol 1990;9:251–3.
[66] Hughes WT. *Pneumocystis carinii* pneumonia: new approaches to diagnosis, treatment and prevention. Pediatr Infect Dis J 1991;10:391–9.
[67] Rieder MJ, King SM, Read S. Adverse reaction to trimethoprim-sulfamethoxazole among children with human immunodeficiency virus infection. Pediatr Infect Dis J 1997;16:1028.
[68] Dohn MN, Weinberg WG, Torres RA, et al. Oral atovaquone compared with intravenous pentamidine for *Pneumocystis carinii* pneumonia in patients with AIDS. Atovaquone study group. Ann Intern Med 1994;121:174–80.
[69] Toma E, Thorne A, Singer J, et al. Clindamycin with primiquine vs. trimethoprim-sulfamethoxazole therapy for mild and moderately severe *Pneumocystis carinii* pneumonia in patients with AIDS: a multicenter, double-blind, randomized trial. Clin Infect Dis 1998;27:524–30.
[70] Black JR, Feinberg J, Murphy RL, et al. Clindamycin and primiquin therapy for mild-to-moderate episodes of *Pneumocystis carinii* pneumonia in patients with AIDS. AIDS Clinical Trials Group 044. Clin Infect Dis 1994;18:905–13.
[71] Sattler FR, Frame P, Davis R, et al. Trimetrexate with leucovorin versus trimethoprim-sulfamethoxazole for moderate to severe episodes of *Pneumocystis carinii* pneumonia in patients with AIDS: a prospective, controlled multicenter investigation of the AIDS Clinical Trials Group Protocol 029/031. J Infect Dis 1994;170:165–72.
[72] Centers for Disease Control and Prevention. 1995 Revised guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for children infected with or perinatally exposed to human immunodeficiency virus. MMWR Morb Mortal Wkly Rep 1995;44(RR-4):1–11.
[73] Bryan RT, Cali A, Owen RL, Spencer HC. Microsporidia: opportunistic pathogens in patients with AIDS. Prog Clin Parasitol 1991;2:1–26.
[74] Weber R, Bryan RT. Microsporidial infections in immunodeficient and immunocompetent patients. Clin Infect Dis 1994;19:517–21.
[75] Weber R, Bryan RT, Schwartz DA, Owen RL. Human microsporidial infections. Clin Microbiol Rev 1994;7:426–61.
[76] Wittner M, Tanowitz HB, Weiss LM. Parasitic infections in AIDS patients: cryptosporidiosis, isosporiasis, microsporidiosis, cyclosporiasis. Infect Dis Clin North Am 1993;7:569–86.
[77] Orenstein JM, Dieterich DT, Kotler DP. Systemic dissemination by a newly recognized intestinal microsporidia species in AIDS. AIDS 1992;6:1143–50.
[78] Weber R, Sauer B, Spycher MA, et al. Detection of *Septata intestinalis* in stool specimens and coprodiagnostic monitoring of successful treatment with albendazole. Clin Infect Dis 1994;19:342–5.
[79] Molina JM, Tourneur M, Sarfati C, et al. Fumagillin treatment of intestinal microsporidiosis. N Engl J Med 2002;346:1963–9.
[80] Jain R, Prabhakar S, Modi M, Bhatia R, Sehgal R. Naegleria meningitis: a rare survival. Neurol India 2002;50:470–2.
[81] Galarza M, Cuccia V, Sosa FP, Monges JA. Pediatric granulomatous cerebral amebiasis: a delayed diagnosis. Pediatr Neurol 2002;26:153–6.
[82] Wang A, Kay R, Poon WS. Successful treatment of amoebic meningoencephalitis in a Chinese living in Hong Kong. Clin Neurol Neurosurg 1993;95:249–52.
[83] Poungvarin N, Jariya P. The fifth non-lethal case of primary amebic meningoencephalitis. J Med Assoc Thai 1991;74:112.

[84] Brown RL. Successful treatment of primary amebic meningoencephalitis. Arch Intern Med 1991;151:1201–2.
[85] Singhal T, Bajpai A, Kalra V, et al. Successful treatment of *Acantamoeba* meningitis with combination oral antimicrobials. Pediatr Infect Dis J 2001;20:623–7.
[86] Sison JP, Kemper CA, Loveless M, McShane D, Visvesvara GS, Deresinski SC. Disseminated *Acanthamoeba* infection in patients with AIDS: case reports and reviews. Clin Infect Dis 1995; 20:1207–16.
[87] Seijo Martinez M, Gonzalez-Mediero G, Santiago P, et al. Granulomatous amebic encephalitis in a patient with AIDS: isolation of *Acanthamoeba* sp. group II from brain tissue and successful treatment with sulfadiazine and fluconazole. J Clin Microbiol 2000;38:3892–5.
[88] Muennig P, Pallin D, Sell R, Chan MS. The cost effectiveness of strategies for the treatment of intestinal parasites in immigrants. N Engl J Med 1999;340:773–9.
[89] Crawford FG, Vermund SH. Parasitic infections in day care centers. Pediatr Infect Dis J 1987;6:744–9.
[90] Urbani C, Albonico M. Antihelminthic drug safety and drug administration in the control of soil-transmitted helminthiasis in community campaigns. Acta Trop 2003;86:215–21.
[91] American Academy of Pediatrics. Drugs for parasitic infections. In: Pickering LK, editor. Red book: 2003 report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village (IL): American Academy of Pediatrics; 2003. p. 744–70.
[92] Montresor A, Stoltzfus RJ, Albonico M, et al. Is the exclusion of children under 24 months from antihelmintic treatment justifiable? Trans R Soc Trop Med Hyg 2002;96:197–9.
[93] Montresor A, Awasthi A, Crompton DWT. Use of benzimidoles in children younger than 24 months for the treatment of soil-transmitted helminthiasis. Acta Trop 2003;86:223–32.
[94] Wilson CM, Freedman DO. Antiparasitic agents. In: Long SS, Pickering LK, Prober CG, editors. Principles and practice of pediatric infectious diseases. 2nd ed. New York: Churchill Livingstone; 2003. p. 1547–58.
[95] Naquira C, Jimenez G, Guerra JG, et al. Ivermectin for human strongyloidiasis and other intestinal helminths. Am J Trop Med Hyg 1989;40:304–9.
[96] Schaffel R, Nucci M, Portugal R, et al. Thiabendazole for the treatment of strongyloides in patients with hematologic malignancies. Clin Infect Dis 2000;31:821–2.
[97] Belizario VY, Amarillo ME, de Leon WU, de los Reyes AE, Bugayong MG, Macatangay BJC. A comparison of the efficacy of single doses of albendazole, ivermectin, and diethylcarbamazine alone or in combinations against *Ascaris* and *Trichuris* spp. Bull World Health Organ 2003;81:35–42.
[98] Grove DI. Treatment of strongyloidiasis with thiabendazole: an analysis of toxicity and effectiveness. Trans R Soc Trop Med Hyg 1982;76:114–8.
[99] Elgart GW, Meinking TL. Ivermectin. Dermatol Clin 2003;21:277–82.
[100] Richard-Lenoble D, Chandenier J, Gaxotte P. Ivermectin and filariasis. Fundam Clin Pharm 2003;17:199–203.
[101] Michael E, Bundy DA, Grenfell BT. Re-assessing the global prevalence and distribution of lymphatic filariasis. Parasitology 1996;112:409–28.
[102] Boggild AK, Keystone JS, Kain KC. Tropical pulmonary eosinophilia: a case series in a setting of nonendemicity. Clin Infect Dis 2004;39:1123–8.
[103] Caumes E. Treatment of cutaneous larva migrans and toxocara infection. Fundam Clin Pharm 2003;17:213–6.
[104] Dinning WJ, Gillespie SH, Cooling RI, Maizels RM. Toxocariasis: a practical approach to management of ocular disease. Eye 1988;2:580–2.
[105] Garcia HH, Gonzalez AE, Evans CA, Gilman RH. Taenia solium cysticercosis. Lancet 2003; 362:547–56.
[106] Flisser A, Sarti E, Sarti R, Schantz PM, Valencia S. Effect of praziquantel on protozoan parasites. Lancet 1995;345:316–7.
[107] Maguire JH. Tapeworms and seizures-treatment and prevention. N Engl J Med 2004;350:215–7.
[108] 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;350:249–58.

[109] Thompson RCA. Biology and systematics of Echinococcus. In: Thompson RCA, Lambery AJ, editors. Echinococcus and hydatid disease. London: CAB International; 1995. p. 1–37.
[110] Yorganci K, Sayek I. Surgical treatment of hydatid cysts of the liver in the era of percutaneous treatment. Am J Surg 2002;184:63–9.
[111] Richards Jr FO. *Diphyllobothrium, Dipylidium, and Hymenolepsis* species. In: Long SS, Pickering LK, Prober CG, editors. Principles and practice of pediatric infectious diseases. 2nd ed. New York: Churchill Livingstone; 2003. p. 1351–4.
[112] Elliott DE. Schistosomiasis. Gastroenterol Clin North Am 1996;25:599–625.
[113] Sturruck R. The parasites and their life cycles. In: Jordan P, Webbe G, Sturruck R, editors. Human schistosomiasis. Wallingford, UK: CAB International; 1993. p. 1–31.
[114] Parraga IM, Assis AM, Prado MS, et al. Gender differences in growth of school-aged children with schistosomiasis and geohelminth infection. Am J Trop Med Hyg 1996;55:150–6.
[115] Capron A. Schistosomiasis: forty years' war on the worm. Parasitol Today 1998;14:379–84.
[116] Olds GR. Administration of praziquantal to pregnant and lactating women. Acta Trop 2003;86: 185–95.
[117] Harinasuta T, Pungpak S, Keystone J. Trematode infections—opisthorchiasis, clonorchiasis, fascioliasis, and paragonimiasis. Infect Dis Clin North Am 1993;7:699–716.