123 - 229 Agents Used to Treat Parasitic Infections

229 Agents Used to Treat Parasitic Infections

TABLE 228-1 Parasitic Infections, by Organ System and Signs/Symptomsa ORGAN SYSTEM, MAJOR SIGN(S)/SYMPTOM(S) PARASITE(S) GEOGRAPHIC DISTRIBUTION COMMENTS Muscular System Myalgias, myositis Trichinella Worldwide Palpebral swelling; high-level eosinophilia Bloodstream Fever without localizing symptoms Plasmodium Tropics and subtropics Consider in any patient from a malarious area. Babesia New England, United States Geographically limited; worse with splenectomy T. brucei rhodesiense, T. brucei gambiense Sub-Saharan Africa Limited to tsetse fly range; painful chancre; adenopathy and cyclical fevers; early (rhodesiense) or late (gambiense) central nervous system involvement Filariae Asia, India Periodic fever with eosinophilia, adenolymphangitis, chronic lymphangitis L. donovani complex Tropics and subtropics Hepatosplenomegaly, fever, wasting; AIDS-defining infection aSee also text and Tables S12-1, S12-2, and S12-3 for vectors and routes of transmission. ■ ■FURTHER READING Blackburn D et al: Outbreak of locally acquired mosquito-transmitted malaria—Florida and Texas, May–July 2023. MMWR 72:973, 2023. Conrad MD et al: Evolution of partial resistance to artemisinins in malaria parasites in Uganda. N Engl J Med 389:722, 2023. Diaz AV et al: Reaching the World Health Organization elimination targets for schistosomiasis: The importance of a One Health perspective. Philos Trans R Soc Lond B Biol Sci 378:20220274, 2023. Loukas A et al: The yin and yang of human soil-transmitted helminths. PART 5 Infectious Diseases Int J Parasitol 51:1243, 2021. Rubin EJ: Making the worm turn. N Engl J Med 388:1908, 2023. Thomas A. Moore

Agents Used to Treat Parasitic Infections Parasitic infections continue to afflict more than half of the world’s population and impose a substantial health burden, particularly in underdeveloped nations, where they are most prevalent. The reach of some parasitic diseases, including malaria, has expanded over the past few decades due to factors such as deforestation, population shifts, global warming, and other climatic events. Although there have been significant advances in vaccine development and vector control, chemotherapy remains the single most effective means of controlling parasitic infections. Efforts to combat the spread of some diseases are hindered by the development and spread of drug resistance, the limited introduction of new antiparasitic agents, the proliferation of counterfeit medications, profiteering, and, most recently, the widespread and unsupported use of antiparasitic agents to treat COVID-19, all of which have dramatically increased the cost of these once-affordable agents. However, there are good reasons to be optimistic.

Ambitious global initiatives aimed at controlling or eliminating threats such as AIDS, tuberculosis, and malaria continue to demonstrate success. The ongoing efforts of multinational partnerships to address the substantial burden imposed by neglected tropical diseases have generated new effective antiparasitic agents. In addition, agents approved for other uses are being re-evaluated for antiparasitic efficacy, and some have been subsequently repurposed. This chapter deals exclusively with the agents used to treat infections due to parasites. Specific treatment recommendations for the

(Continued) parasitic diseases of humans are listed in subsequent chapters. Many of the agents discussed herein are approved by the U.S. Food and Drug Administration (FDA) but are considered investigational for the treatment of certain infections. Drugs marked in the text with an asterisk (*) are available through the Centers for Disease Control and Prevention (CDC) Drug Service (telephone: 404-639-3670; email: drugservice@ cdc.gov). Drugs marked with a dagger (†) are available only through their manufacturers; contact information for these manufacturers may be available from the CDC. Table 229-1 presents a brief overview of each agent (including some drugs that are covered in other chapters), along with major toxicities, spectrum of activity, and safety for use during pregnancy and lactation. Albendazole Like all benzimidazoles, albendazole acts by selectively binding to free β-tubulin in nematodes, inhibiting the polymerization of tubulin and the microtubule-dependent uptake of glucose. Irreversible damage occurs in gastrointestinal (GI) cells of the nematodes, resulting in starvation, death, and expulsion by the host. This fundamental disruption of cellular metabolism offers treatment for a wide range of parasitic diseases. Albendazole is poorly absorbed from the GI tract, a feature that is advantageous for the treatment of intestinal helminths but not for that of tissue helminth infections (e.g., hydatid disease and neurocysticercosis), which requires a sufficient amount of active drug to reach the site of infection. Administration with a high-fat meal (~40 g) increases the drug’s absorption by up to fivefold. The metabolite albendazole sulfoxide is responsible for the drug’s therapeutic effect outside the gut lumen. Albendazole sulfoxide crosses the blood-brain barrier, reaching a level significantly higher than that achieved in plasma. The high concentrations of albendazole sulfoxide attained in cerebrospinal fluid (CSF) may explain the efficacy of albendazole in the treatment of neurocysticercosis. Albendazole is extensively metabolized in the liver, but there are few data regarding the drug’s use in patients with hepatic disease. Singledose albendazole therapy in humans is largely without side effects (overall frequency, ≤1%). More prolonged courses (e.g., as administered for cystic and alveolar echinococcal disease) have been associated with liver function abnormalities and bone marrow toxicity. Thus, when prolonged use is anticipated, the drug should be administered in treatment cycles of 28 days interrupted by 14-day intervals off therapy. Prolonged therapy with full-dose albendazole (800 mg/d) should be approached cautiously in patients also receiving drugs with known effects on the cytochrome P450 system. Amodiaquine Amodiaquine has been widely used in the treatment of malaria for >60 years. Like chloroquine (the other major 4-aminoquinoline), amodiaquine is now of limited use because of the spread of resistance. Amodiaquine interferes with hemozoin formation through complexation with heme. It is rapidly absorbed and acts as a prodrug after oral administration; the principal plasma metabolite, monodesethylamodiaquine, is the predominant antimalarial agent. Amodiaquine

TABLE 229-1 Overview of Agents Used for the Treatment of Parasitic Infections DRUGS BY CLASS PARASITIC INFECTION(S) ADVERSE EFFECTS 4-Aminoquinolines Amodiaquine Malariab Agranulocytosis, hepatotoxicity No information Not assigned Yesc Chloroquine Malariab Occasional:

pruritus, nausea, vomiting, headache, hair depigmentation, exfoliative dermatitis, reversible corneal opacity Rare: irreversible retinal injury, nail discoloration, blood dyscrasias Piperaquine Malariab Occasional: GI disturbances None reported Not assigned Yes 8-Aminoquinolines Primaquine Malariab Frequent: hemolysis in patients with G6PD deficiency Occasional: methemoglobinemia, GI disturbances Rare: CNS symptoms Tafenoquine Malariab Frequent: hemolysis in patients with G6PD deficiency, mild GI upset Occasional: methemoglobinemia, headache Aminoalcohols Halofantrine Malariab Frequent: abdominal pain, diarrhea Occasional: ECG disturbances (dose-related prolongation of QTc and PR interval), nausea, pruritus; contraindicated in persons who have cardiac disease or who have taken mefloquine in the preceding 3 weeks Lumefantrine Malariab Occasional: nausea, vomiting, diarrhea, abdominal pain, anorexia, headache, dizziness Aminoglycosides Paromomycin Amebiasis,b infection with Dientamoeba fragilis, giardiasis, cryptosporidiosis, leishmaniasis Frequent: GI disturbances (oral dosing only) Occasional: nephrotoxicity, ototoxicity, vestibular toxicity (parenteral dosing only) Amphotericin B Amphotericin B Leishmaniasis,e amebic meningoencephalitis Frequent: fever, chills, hypokalemia, hypomagnesemia, nephrotoxicity Occasional: vomiting, dyspnea, hypotension deoxycholate Amphotec (InterMune) Amphotericin B lipid complex, ABLC (Abelcet) Amphotericin B, liposomal (AmBisome) Antimonials Meglumine Leishmaniasis Frequent: arthralgias/myalgias, pancreatitis, ECG changes (QT prolongation, T-wave flattening or inversion) antimoniateh Artemisinin and derivatives Malariag Occasional: neurotoxicity (ataxia, convulsions), nausea, vomiting, anorexia, contact dermatitis Arteether No information Not assigned Yesc Artemether Artemether levels decreased by darunavir, etravirine, and nevirapine Artesunateh Mefloquine: levels decreased and clearance accelerated by artesunate Dihydroartemisinin Mefloquine: increased absorption Not assigned Yesc

MAJOR DRUG–DRUG INTERACTIONS PREGNANCY CLASSa BREAST MILK Antacids and kaolin: reduced absorption of chloroquine Ampicillin: bioavailability reduced by chloroquine Cimetidine: increased serum levels of chloroquine Cyclosporine: serum levels increased by chloroquine Not assignedd Yesc Quinacrine: potentiated toxicity of primaquine Contraindicated Yes No information Not assigned Yes Concomitant use of agents that prolong QTc interval contraindicated C No information CHAPTER 229 Plasma levels increased by darunavir and nevirapine, decreased by etravirine Not assigned No information Agents Used to Treat Parasitic Infections No major interactions Oral: B Parenteral: not assignedd No information Antineoplastic agents: renal toxicity, bronchospasm, hypotension Glucocorticoids, ACTH, digitalis: hypokalemia Zidovudine: increased myelo- and nephrotoxicity B No information Antiarrhythmics and tricyclic antidepressants: increased risk of cardiotoxicity Not assigned No information C Yesc C Yesc (Continued)

TABLE 229-1 Overview of Agents Used for the Treatment of Parasitic Infections DRUGS BY CLASS PARASITIC INFECTION(S) ADVERSE EFFECTS Atovaquone Malaria,b babesiosis Frequent: nausea, vomiting Occasional: abdominal pain, headache Azoles Fluconazole Itraconazole Ketoconazole Leishmaniasis Serious: hepatotoxicity Rare: exfoliative skin disorders, anaphylaxis Benzimidazoles

 Albendazole Ascariasis, capillariasis, clonorchiasis, cutaneous larva migrans, cysticercosis,b echinococcosis,b enterobiasis, eosinophilic enterocolitis, gnathostomiasis, hookworm, lymphatic filariasis, microsporidiosis, strongyloidiasis, trichinellosis, trichostrongyliasis, trichuriasis, visceral larva migrans Occasional: nausea, vomiting, abdominal pain, headache, reversible alopecia, elevated aminotransferases Rare: leukopenia, rash Mebendazole Ascariasis,b capillariasis, eosinophilic enterocolitis, enterobiasis,b hookworm,b trichinellosis, trichostrongyliasis,

trichuriasis,b visceral larva migrans Occasional: diarrhea, abdominal pain, elevated aminotransferases Rare: agranulocytosis, thrombocytopenia, alopecia Thiabendazole Strongyloidiasis,b cutaneous larva migrans,b visceral larva migransb Frequent: anorexia, nausea, vomiting, diarrhea, headache, dizziness, asparagus-like urine odor Occasional: drowsiness, giddiness, crystalluria, elevated aminotransferases, psychosis Rare: hepatitis, seizures, angioneurotic edema, StevensJohnson syndrome, tinnitus Triclabendazole Fascioliasis, paragonimiasis Occasional: abdominal cramps, diarrhea, biliary colic, transient headache Benznidazole Chagas disease Frequent: rash, pruritus, nausea, leukopenia, paresthesias Clindamycin Babesiosis, malaria, toxoplasmosis Occasional: pseudomembranous colitis, abdominal pain, diarrhea, nausea/vomiting Rare: pruritus, skin rashes Diloxanide furoate Amebiasis Frequent: flatulence Occasional: nausea, vomiting, diarrhea Rare: pruritus

(Continued) MAJOR DRUG–DRUG INTERACTIONS PREGNANCY CLASSa BREAST MILK Plasma levels decreased by rifampin, tetracycline, atazanavir, efavirenz, lopinavir/ritonavir; bioavailability decreased by metoclopramide C No information Warfarin, oral hypoglycemics, phenytoin, cyclosporine, theophylline, digoxin, dofetilide, quinidine, carbamazepine, rifabutin, busulfan, docetaxel, vinca alkaloids, pimozide, alprazolam, diazepam, midazolam, triazolam, verapamil, atorvastatin, cerivastatin, lovastatin, simvastatin, tacrolimus, sirolimus, indinavir, ritonavir, saquinavir, alfentanil, buspirone, methylprednisolone, trimetrexate: plasma levels increased by azoles Carbamazepine, phenobarbital, phenytoin, isoniazid, rifabutin, rifampin, antacids, H2-receptor antagonists, proton pump inhibitors, nevirapine: decreased plasma levels of azoles Clarithromycin, erythromycin, indinavir, ritonavir: increased plasma levels of azoles C Yes Dexamethasone, praziquantel: plasma level of albendazole sulfoxide increased by ~50% C Yesc Cimetidine: inhibited mebendazole metabolism C No information Theophylline: serum levels increased by thiabendazole C No information No information Not assigned Yes No major interactions Not assigned No information No major interactions B Yesc None reported Contraindicated No information (Continued)

TABLE 229-1 Overview of Agents Used for the Treatment of Parasitic Infections DRUGS BY CLASS PARASITIC INFECTION(S) ADVERSE EFFECTS Eflornithinef (difluoromethylornithine, DFMO) Trypanosomiasis Frequent: pancytopenia Occasional: diarrhea, seizures Rare: transient hearing loss Emetine and dehydroemetine Amebiasis, fascioliasis Severe: cardiotoxicity Frequent: pain at injection site Occasional: dizziness, headache, GI symptoms Folate antagonists Dihydrofolate reductase inhibitors Pyrimethamine Malaria,b isosporiasis, toxoplasmosisb Occasional: folate deficiency Rare: rash, seizures, severe skin reactions (toxic epidermal necrolysis, erythema multiforme, StevensJohnson syndrome) Proguanil and Malaria Occasional: urticaria Rare: hematuria, GI disturbances chlorproguanil Trimethoprim Cyclosporiasis, isosporiasis Hyperkalemia, GI upset, mild stomatitis Dihydropteroate Malaria,b toxoplasmosisb Frequent: GI disturbances, allergic skin reactions, crystalluria Rare: severe skin reactions (toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome), agranulocytosis, aplastic anemia, hypersensitivity of the respiratory tract, hepatitis, interstitial nephritis, hypoglycemia, aseptic meningitis synthetase inhibitors: sulfonamides Sulfadiazine Sulfamethoxazole Sulfadoxine Dihydropteroate synthetase inhibitors: sulfones Dapsone Leishmaniasis, malaria, toxoplasmosis Frequent: rash, anorexia Occasional: hemolysis, methemoglobinemia, neuropathy, allergic dermatitis, anorexia, nausea, vomiting, tachycardia, headache, insomnia, psychosis, hepatitis Rare: agranulocytosis Fumagillin Microsporidiosis Rare: neutropenia, thrombocytopenia

None reported No information No information Furazolidone Giardiasis Frequent: nausea/vomiting, brown urine Occasional: rectal itching, headache Rare: hemolytic anemia, disulfiramlike reactions, MAO inhibitor interactions Iodoquinol Amebiasis,b balantidiasis, D. fragilis infection Occasional: headache, rash, pruritus, thyrotoxicosis, nausea, vomiting, abdominal pain, diarrhea Rare: optic neuritis, peripheral neuropathy, seizures, encephalopathy Lactones Ivermectin Ascariasis, cutaneous larva migrans, gnathostomiasis, loiasis, lymphatic filariasis, onchocerciasis,b scabies, strongyloidiasis,b trichuriasis Occasional: fever, pruritus, headache, myalgias Rare: hypotension Moxidectin Onchocerciasis Occasional: fever, pruritus, headache, myalgias Rare: orthostatic hypotension, elevated transaminases

(Continued) MAJOR DRUG–DRUG INTERACTIONS PREGNANCY CLASSa BREAST MILK No major interactions Contraindicated No information None reported X No information Sulfonamides, proguanil, zidovudine: increased risk of bone marrow suppression when used concomitantly C Yes Atazanavir, efavirenz, lopinavir/ ritonavir: plasma levels of proguanil decreased C Yes Methotrexate: reduced clearance Warfarin: effect prolonged Phenytoin: hepatic metabolism increased C Yes Thiazide diuretics: increased risk of thrombocytopenia in elderly patients Warfarin: effect prolonged by sulfonamides Methotrexate: levels increased by sulfonamides Phenytoin: metabolism impaired by sulfonamides Sulfonylureas: effect prolonged by sulfonamides B Yes CHAPTER 229 Agents Used to Treat Parasitic Infections Rifampin: lowered plasma levels of dapsone C Yes Risk of hypertensive crisis when administered for >5 days with MAO inhibitors C No information No major interactions C No information No major interactions C Yesc No major interactions C Yesc (Continued)

TABLE 229-1 Overview of Agents Used for the Treatment of Parasitic Infections DRUGS BY CLASS PARASITIC INFECTION(S) ADVERSE EFFECTS Macrolides Azithromycin Babesiosis Occasional: nausea, vomiting, diarrhea, abdominal pain Rare: angioedema, cholestatic jaundice Spiramycinh Toxoplasmosis Occasional: GI disturbances, transient skin eruptions Rare: thrombocytopenia, QT prolongation in an infant, cholestatic hepatitis Mefloquine Malariab Frequent: lightheadedness, nausea, headache Occasional: confusion; nightmares; insomnia; visual disturbance; transient and clinically silent ECG abnormalities, including sinus bradycardia, sinus arrhythmia, first-degree AV block, prolongation of QTc interval, and abnormal T waves Rare: psychosis, convulsions, hypotension Melarsoprolf Trypanosomiasis Frequent: myocardial injury, encephalopathy, peripheral neuropathy, hypertension Occasional: G6PD-induced hemolysis, erythema nodosum leprosum Rare: hypotension PART 5 Infectious Diseases Metrifonate Schistosomiasis Frequent: abdominal pain, nausea, vomiting, diarrhea, headache, vertigo, bronchospasm Rare: cholinergic symptoms Miltefosine Leishmaniasis,b primary amebic meningoencephalitis Frequent: mild and transient (1–2 days) GI disturbances within first 2 weeks of therapy (resolve after treatment completion); motion sickness Occasional: reversible elevations of creatinine and aminotransferases Niclosamide Intestinal cestode infectionsb Occasional: nausea, vomiting, dizziness, pruritus Nifurtimox Chagas disease Frequent: nausea, vomiting, abdominal pain, insomnia, paresthesias, weakness, tremors Rare: seizures (all reversible and dose-related) Nitazoxanide Cryptosporidiosis,b giardiasisb Occasional: abdominal pain, diarrhea Rare: vomiting, headache Nitroimidazoles Metronidazole Amebiasis,b balantidiasis, dracunculiasis, giardiasis b, trichomoniasis,b D. fragilis infection Frequent: nausea, headache, anorexia, metallic aftertaste Occasional: vomiting, insomnia, vertigo, paresthesias, disulfiram-like effects Rare: seizures, peripheral neuropathy Tinidazole Amebiasis,b giardiasis, trichomoniasis Occasional: nausea, vomiting, metallic taste

(Continued) MAJOR DRUG–DRUG INTERACTIONS PREGNANCY CLASSa BREAST MILK Cyclosporine and digoxin: levels increased by azithromycin Nelfinavir: increased levels of azithromycin B Yes No major interactions Not assignedd Yesc Administration of halofantrine <3 weeks after mefloquine use may produce fatal QTc prolongation. Mefloquine may lower plasma levels of anticonvulsants. Levels are decreased and clearance is accelerated by artesunate. Mefloquine decreases plasma levels of ritonavir and possibly other protease inhibitors. C Yes No major interactions Not assigned No information No major interactions B No No major interactions Not assigned No information No major interactions B No information No major interactions Not assigned No information Increases plasma levels of highly protein-bound drugs (e.g., phenytoin, warfarin) B No information Warfarin: effect enhanced by metronidazole Disulfiram: psychotic reaction Phenobarbital, phenytoin: accelerate elimination of metronidazole Lithium: serum levels elevated by metronidazole Cimetidine: prolonged half-life of metronidazole Oral solutions of antiretrovirals containing alcohol: disulfiram effect due to alcohol B Yes See metronidazole C Yes (Continued)

TABLE 229-1 Overview of Agents Used for the Treatment of Parasitic Infections DRUGS BY CLASS PARASITIC INFECTION(S) ADVERSE EFFECTS Oxamniquine Schistosomiasis Occasional: dizziness, drowsiness, headache, orange urine, elevated aminotransferases Rare: seizures Pentamidine isethionate Leishmaniasis, trypanosomiasis Frequent: hypotension, hypoglycemia, pancreatitis, sterile abscesses at IM injection sites, GI disturbances, reversible renal failure Occasional: hepatotoxicity, cardiotoxicity, delirium Rare: anaphylaxis Piperazine and derivatives Piperazine Ascariasis, enterobiasis Occasional: nausea, vomiting, diarrhea, abdominal pain, headache Rare: neurotoxicity, seizures Diethylcarbamazinef Lymphatic filariasis, loiasis, tropical pulmonary eosinophilia Frequent: dose-related nausea, vomiting Rare: fever, chills, arthralgias, headache Praziquantel Clonorchiasis,b cysticercosis, diphyllobothriasis, hymenolepiasis, taeniasis, opisthorchiasis, intestinal trematodes, paragonimiasis, schistosomiasisb Frequent: abdominal pain, diarrhea, dizziness, headache, malaise Occasional: fever, nausea Rare: pruritus, singultus Pyrantel pamoate Ascariasis, eosinophilic enterocolitis, enterobiasis,b hookworm, trichostrongyliasis Occasional: GI disturbances, headache, dizziness, elevated aminotransferases Pyronaridine Malaria Occasional: headache, nausea None reported to date B Yes Quinacrineh Giardiasisb Frequent: headache, nausea, vomiting, bitter taste Occasional: yellow-orange discoloration of skin, sclerae, urine; begins after 1 week of treatment and lasts up to 4 months after drug discontinuation Rare: psychosis, exfoliative dermatitis, retinopathy, G6PD-induced hemolysis, exacerbation of psoriasis, disulfiramlike effects Quinine and quinidine Malaria, babesiosis Frequent: cinchonism (tinnitus, hightone deafness, headache, dysphoria, nausea, vomiting, abdominal pain, visual disturbances, postural hypotension), hyperinsulinemia resulting in life-threatening hypoglycemia Occasional: deafness, hemolytic anemia, arrhythmias, hypotension due to rapid IV infusion Quinolones Ciprofloxacin Cyclosporiasis, isosporiasis Occasional: nausea, diarrhea, vomiting, abdominal pain/discomfort, headache, restlessness, rash Rare: myalgias/arthralgias, tendon rupture, CNS symptoms (nervousness, agitation, insomnia, anxiety, nightmares, or paranoia); convulsions

(Continued) MAJOR DRUG–DRUG INTERACTIONS PREGNANCY CLASSa BREAST MILK No major interactions C No information No major interactions C No information None reported C No information None reported Not assignedd No information No major interactions B Yes CHAPTER 229 No major interactions C No information Primaquine: toxicity potentiated by quinacrine C No information Agents Used to Treat Parasitic Infections Carbonic anhydrase inhibitors, thiazide diuretics: reduced renal elimination of quinidine Amiodarone, cimetidine: increased quinidine levels

Nifedipine: decreased quinidine levels; quinidine slows metabolism of nifedipine Phenobarbital, phenytoin, rifampin: accelerated hepatic elimination of quinidine Verapamil: reduced hepatic clearance of quinidine Diltiazem: decreased clearance of quinidine X Yesc Probenecid: increased serum levels of ciprofloxacin Theophylline, warfarin: serum levels increased by ciprofloxacin C Yes (Continued)

TABLE 229-1 Overview of Agents Used for the Treatment of Parasitic Infections DRUGS BY CLASS PARASITIC INFECTION(S) ADVERSE EFFECTS Suraminf Trypanosomiasis Frequent: immediate: fever, urticaria, nausea, vomiting, hypotension; delayed (up to 24 h): exfoliative dermatitis, stomatitis, paresthesias, photophobia, renal dysfunction Occasional: nephrotoxicity, adrenal toxicity, optic atrophy, anaphylaxis Tetracyclines Balantidiasis, D. fragilis infection, malaria; lymphatic filariasis (doxycycline) Frequent: GI disturbances Occasional: photosensitivity dermatitis Rare: exfoliative dermatitis, esophagitis, hepatotoxicity aBased on U.S. Food and Drug Administration (FDA) pregnancy categories of A–D, X. bApproved by the FDA for this indication. cNot believed to be harmful. dUse in pregnancy is recommended by international organizations outside the United States. eOnly AmBisome has been approved by the FDA for this indication. fAvailable through the CDC. gOnly artemether (in combination with lumefantrine) and artesunate have been approved by the FDA for this indication. hAvailable through the manufacturer. Abbreviations: ACTH, adrenocorticotropic hormone; AV, atrioventricular; CNS, central nervous system; ECG, electrocardiogram; G6PD, glucose 6-phosphate dehydrogenase; GI, gastrointestinal; MAO, monoamine oxidase. and its metabolites are all excreted in urine, but there are no recommen dations concerning dosage adjustment in patients with impaired renal function. Agranulocytosis and hepatotoxicity can develop with repeated use; therefore, this drug should not be used for prophylaxis. Indeed, because of its adverse effects and widespread resistance, amodiaquine is no longer in use in Europe or the United States, and it was dropped from malaria control programs as a single agent by the WHO in 1990; however, it remains effective in some areas when combined with other antimalarial drugs (e.g., artesunate, sulfadoxine-pyrimethamine). PART 5 Infectious Diseases Amphotericin B See Table 229-1 and Chap. 217. Antimonials† Despite associated adverse reactions and the need for prolonged parenteral treatment, the pentavalent antimonial com pounds (designated Sbv) have remained the first-line therapy for all forms of leishmaniasis throughout the world, primarily because they are affordable and effective and have survived the test of time. Pentavalent antimonials are active only after bioreduction to the tri valent Sb(III) form, which inhibits trypanothione reductase, a critical enzyme involved in the oxidative stress management of Leishmania species. The fact that Leishmania species use trypanothione rather than glutathione (which is used by mammalian cells) may explain the parasite-specific activity of antimonials. The drugs are taken up by the reticuloendothelial system, and their activity against Leishmania species may be enhanced by this localization. Resistance is a major problem in some areas. Although low-level unresponsiveness to Sbv was identified in India in the 1970s, incre mental increases in both the recommended daily dosage (to 20 mg/kg) and the duration of treatment (to 28 days) satisfactorily compensated for the growing resistance until around 1990. Since then, the capacity of Sbv to induce long-term cure in patients with kala-azar who live in eastern India has steadily eroded. Co-infection with HIV impairs the treatment response. Pentavalent antimonials are available in aqueous solution and are administered parenterally. Antimony appears to have two elimination phases. When the drug is administered IV, the mean half-life of the first phase is <2 h; the mean half-life of the terminal elimination phase is nearly 36 h. This slower phase may be due to conversion of pentavalent antimony to a trivalent form that is

the likely cause of the side effects often seen with prolonged therapy. In 2020, the global manufacturer of sodium stibogluconate notified the CDC that the product would be discontinued due to the inability to source the necessary raw materials. As a result, CDC ended its dis tribution program following expiration of the last lot in use. However, meglumine antimoniate is available from the manufacturer through the FDA (301-796-1400). Artemisinin Derivatives* Artesunate, artemether, artemotil, and the parent compound artemisinin are sesquiterpene lactones derived from the wormwood plant Artemisia annua. These agents are at least

(Continued) MAJOR DRUG–DRUG INTERACTIONS PREGNANCY CLASSa BREAST MILK No major interactions Not assigned No information Warfarin: effect prolonged by tetracyclines D Yes 10-fold more potent in vivo than other antimalarial drugs and presently show no cross-resistance with known antimalarial drugs; thus, they have become first-line agents for the treatment of severe falciparum malaria. The artemisinin compounds are rapidly effective against the asexual blood forms of Plasmodium species but are not active against intrahepatic forms. With the exception of artesunate, artemisinin and its derivatives are highly lipid soluble and readily cross both host and parasite cell membranes. One factor that explains the drugs' highly selective toxicity against malaria is that parasitized erythrocytes con centrate artemisinin and its derivatives to concentrations 100-fold higher than those in uninfected erythrocytes. The antimalarial effect of these agents results primarily from the active metabolite dihydroar temisinin; in the presence of heme or molecular iron, the endoperoxide moiety of dihydroartemisinin decomposes, generating free radicals and other metabolites that damage parasite proteins. The compounds are available for oral, rectal, IV, or IM administration, depending on the derivative. Following FDA approval in May 2020, artesunate became commercially available in the United States. Artemisinin and its derivatives are cleared rapidly from the cir culation. Their short half-lives limit their value for prophylaxis and monotherapy. Side effects appear to be minor, although sinus bra dycardia and transient first-degree heart block have been reported. Although seen in animal models, embryotoxicity and neurotoxicity have not been identified in humans despite active investigation. These agents should be used only in combination with another, longer-acting agent (e.g., artesunate-mefloquine, dihydroartemisinin-piperaquine). A combined formulation of artemether and lumefantrine is widely available for the treatment of acute uncomplicated falciparum malaria acquired in areas where Plasmodium falciparum is resistant to chloroquine and antifolates. Atovaquone Atovaquone is a hydroxynaphthoquinone that exerts broad-spectrum antiprotozoal activity via selective inhibition of para site mitochondrial electron transport. This agent exhibits potent activity against toxoplasmosis and babesiosis when used with pyri methamine and azithromycin, respectively. Atovaquone possesses a novel mode of action against Plasmodium species, inhibiting the elec tron transport system at the level of the cytochrome bc1 complex. The drug is active against both the erythrocytic and the exoerythrocytic stages of Plasmodium species; however, because it does not eradicate hypnozoites from the liver, patients with P. vivax or P. ovale infections must be given radical prophylaxis. Malarone is a fixed-dose combination of atovaquone and progua nil used for malaria prophylaxis as well as for the treatment of acute, uncomplicated P. falciparum malaria. Malarone has been shown to be effective in regions with multidrug-resistant P. falciparum. Resistance to atovaquone develops rapidly via mutations in the parasite's mito chondrial cytochrome b complex. However, the mutations result in sterility of female parasites; thus, atovaquone-resistant parasites cannot

be transmitted to another person. This situation may explain why clini cal resistance has yet to be reported. The bioavailability of atovaquone varies considerably. Absorption after a single oral dose is slow, increases two- to threefold with a fatty meal, and is dose-limited above 750 mg. The elimination half-life is increased in patients with moderate hepatic impairment. Because of the potential for drug accumulation, the use of atovaquone is generally contraindicated in persons with a creatinine clearance rate <30 mL/min. No dosage adjustments are needed in patients with mild to moderate renal impairment. Azithromycin See Table 229-1 and Chap. 149. Azoles See Table 229-1 and Chap. 217. Benznidazole Introduced in 1971, this oral nitroimidazole deriva tive is used to treat Chagas disease, with cure rates of 80–90% recorded in acute infections. Benznidazole is believed to exert its trypanocidal effects by generating oxygen radicals to which the parasites are more sensitive than mammalian cells because of a relative deficiency in antioxidant enzymes. Benznidazole also appears to alter the balance between pro- and anti-inflammatory mediators by downregulating the synthesis of nitrite, interleukin (IL) 6, and IL-10 in macrophages. Benznidazole is highly lipophilic and readily absorbed. The drug is extensively metabolized; only 5% of the dose is excreted unchanged in the urine. Benznidazole is well tolerated; adverse effects are rare and usually manifest as GI upset or pruritic rash. Following FDA approval in 2018, this drug is now commercially available in the United States. Chloroquine This 4-aminoquinoline has marked, rapid schizon ticidal and gametocidal activity against blood forms of P. ovale and

P. malariae and against susceptible strains of P. vivax and P. falciparum. It is not active against intrahepatic forms (P. vivax and P. ovale). Para sitized erythrocytes accumulate chloroquine in significantly greater concentrations than do normal erythrocytes. Chloroquine, a weak base, concentrates in the food vacuoles of intraerythrocytic parasites because of a relative pH gradient between the extracellular space and the acidic food vacuole. Once it enters the acidic food vacuole, chlo roquine is rapidly converted to a membrane-impermeable protonated form and is trapped. Continued accumulation of chloroquine in the parasite’s acidic food vacuoles results in drug levels that are 600-fold higher at this site than in plasma. The high accumulation of chloro quine results in an increase in pH within the food vacuole to a level above that required for the acid proteases’ optimal activity, inhibiting parasite heme polymerase; as a result, the parasite is effectively killed with its own metabolic waste. Compared with susceptible strains, chloroquine-resistant plasmodia transport chloroquine out of intra parasitic compartments more rapidly and maintain lower chloroquine concentrations in their acid vesicles. Hydroxychloroquine, a congener of chloroquine, is equivalent to chloroquine in its antimalarial efficacy but is preferred to chloroquine for the treatment of autoimmune disor ders because it produces less ocular toxicity when used in high doses. Chloroquine is well absorbed. However, because it exhibits exten sive tissue binding, a loading dose is required to yield effective plasma concentrations. A therapeutic drug level in plasma is reached 2–3 h after oral administration (the preferred route). Chloroquine can be administered IV, but excessively rapid parenteral administration can result in seizures and death from cardiovascular collapse. The mean half-life of chloroquine is 4 days, but the rate of excretion decreases as plasma levels decline, making once-weekly administration possible for prophylaxis in areas with sensitive strains. About one-half of the par ent drug is excreted in urine, but the dose should not be reduced for persons with acute malaria and renal insufficiency. Ciprofloxacin See Table 229-1 and Chap. 149. Clindamycin See Table 229-1 and Chap. 149. Dapsone See Table 229-1 and Chap. 188. Dehydroemetine Emetine is an alkaloid derived from ipecac; dehy droemetine is synthetically derived from emetine and is considered less

toxic. Both agents are active against Entamoeba histolytica and appear to work by blocking peptide elongation and thus inhibiting protein synthesis. Emetine is rapidly absorbed after parenteral administration, rapidly distributed throughout the body, and slowly excreted in the urine in unchanged form. Both agents are contraindicated in patients with renal disease.

Diethylcarbamazine* A derivative of the antihelminthic agent piperazine with a long history of successful use, diethylcarbamazine (DEC) remains the treatment of choice for lymphatic filariasis and loiasis and has also been used for visceral larva migrans. Although piperazine itself has no antifilarial activity, the piperazine ring of DEC is essential for the drug's activity. DEC's mechanism of action remains to be fully defined. Proposed mechanisms include immobilization due to inhibition of parasite cholinergic muscle receptors, disrup tion of microtubule formation, and alteration of helminthic surface membranes resulting in enhanced killing by the host's immune system. DEC enhances adherence properties of eosinophils. The develop ment of resistance under drug pressure (i.e., a progressive decrease in efficacy when the drug is used widely in human populations) has not been observed, although DEC has variable effects when administered to persons with filariasis. Monthly administration provides effective prophylaxis against both bancroftian filariasis and loiasis. DEC is well absorbed after oral administration, with peak plasma concentrations reached within 1–2 h. No parenteral form is available. The drug is eliminated largely by renal excretion, with <5% found in feces. If more than one dose is to be administered to an individual with renal dysfunction, the dose should be reduced commensurate with the reduction in creatinine clearance rate. Alkalinization of the urine prevents renal excretion and increases the half-life of DEC. Use in patients with onchocerciasis can precipitate a Mazzotti reaction, with pruritus, fever, and arthralgias. Like other piperazines, DEC is active against Ascaris species. Patients co-infected with this nematode may expel live worms after treatment. CHAPTER 229 Agents Used to Treat Parasitic Infections Diloxanide Furoate Diloxanide furoate, a substituted acetanilide, is a luminally active agent used to eradicate the cysts of E. histolytica. After ingestion, diloxanide furoate is hydrolyzed by enzymes in the lumen or mucosa of the intestine, releasing furoic acid and the ester diloxanide; the latter acts directly as an amebicide. Diloxanide furoate is given alone to asymptomatic cyst passers. For patients with active amebic infections, diloxanide is generally admin istered in combination with a 5-nitroimidazole such as metronidazole or tinidazole. Diloxanide furoate is rapidly absorbed after oral admin istration. When coadministered with a 5-nitroimidazole, diloxanide levels peak within 1 h and disappear within 6 h. About 90% of an oral dose is excreted in the urine within 48 h, chiefly as the glucuronide metabolite. Diloxanide furoate is contraindicated in pregnant and breast-feeding women and in children <2 years of age. Eflornithine* Eflornithine (difluoromethylornithine, or DFMO) is a fluorinated analogue of the amino acid ornithine. Although originally designed as an antineoplastic agent, eflornithine has proven effective against some trypanosomatids. Eflornithine has specific activity against all stages of infection with Trypanosoma brucei gambiense; however, it is inactive against T. b. rhodesiense. The drug acts as an irreversible suicide inhibitor of orni thine decarboxylase, the first enzyme in the biosynthesis of the poly amines putrescine and spermidine. Polyamines are essential for the synthesis of trypanothione, an enzyme required for the maintenance of intracellular thiols in the correct redox state and for the removal of reactive oxygen metabolites. However, polyamines are also essential for cell division in eukaryotes, and ornithine decarboxylase is similar in trypanosomes and mammals. The selective antiparasitic activity of eflornithine is partly explained by the structure of the trypanosomal enzyme, which lacks a 36-amino-acid C-terminal sequence found on mammalian ornithine decarboxylase. This difference results in a lower turnover of ornithine decarboxylase and a more rapid decrease of poly

amines in trypanosomes than in the mammalian host. The diminished effectiveness of eflornithine against T. b. rhodesiense appears to be due

to the parasite’s ability to replace the inhibited enzyme more rapidly than T. b. gambiense.

Eflornithine is less toxic but more costly than conventional therapy. It can be administered IV or PO. The dose should be reduced in renal failure. Eflornithine readily crosses the blood-brain barrier; CSF levels are highest in persons with the most severe central nervous system (CNS) involvement. Flubendazole This agent, a methylcarbamate benzimidazole, is highly active against a broad spectrum of gut nematodes and filaria. Its antihelminthic effect is similar to other benzimidazoles; however, it is also an effective inducer of reactive oxygen species and disrupts glucose transport and metabolism. It has limited solubility in water, so bioavailability is very low, but absorption increases if taken after meals, and is further enhanced when reconstituted as a cyclodextrin-based formulation. It is approved for human use in Europe but not in the Unites States. Fosmidomycin Originally developed in the 1970s as an antibiotic, this Streptomyces-derived agent is an aminopropylphosphonic acid that exhibits antimalarial activity through inhibition of 1-deoxy-Dxylulose 5-phosphate reductoisomerase, an essential enzyme on the non-mevalonate pathway of isoprenoid biosynthesis, a pathway that is common in most eukaryotes but absent in humans. For >15 years, fosmidomycin has been evaluated alone and in combination with other antimalarials, and it has demonstrated both safety and efficacy. However, the drug is highly charged—resulting in a short plasma halflife (3.5 h)—causing high rates of recrudescent malaria, particularly in children. It is not currently available, but clinical studies are ongoing. Fumagillin† Originally discovered as an antiangiogenic compound derived from the fungus Aspergillus fumigatus, fumagillin is a waterinsoluble antibiotic that is active against microsporidia and is used topically to treat ocular infections due to Encephalitozoon species. When given systemically, fumagillin was effective but caused thrombocytope nia in all recipients in the second week of treatment; this side effect was readily reversed when administration of the drug was stopped. Fuma gillin acts by binding to methionine aminopeptidase 2, thus inhibiting microsporidial replication by irreversibly blocking the active site. PART 5 Infectious Diseases Furazolidone This nitrofuran derivative is an effective alternative agent for the treatment of giardiasis and also exhibits activity against Isospora belli. Because it is the only agent active against Giardia that is available in liquid form, it is most often used to treat young chil dren. Furazolidone undergoes reductive activation in Giardia lamblia

trophozoites—an event that, unlike the reductive activation of met ronidazole, involves an NADH oxidase. The killing effect correlates with the toxicity of reduced products, which damage important cellular components, including DNA. Although furazolidone had been thought to be largely unabsorbed when administered orally, the occurrence of systemic adverse reactions indicates that this is not the case. More than 65% of the drug dose can be recovered from the urine as colored metab olites. Omeprazole reduces the oral bioavailability of furazolidone. Furazolidone is a monoamine oxidase (MAO) inhibitor; thus, caution should be used in its concomitant administration with other drugs (especially indirectly acting sympathomimetic amines) and in the consumption of food and drink containing tyramine during treat ment. However, hypertensive crises have not been reported in patients receiving furazolidone, and it has been suggested that—because furazolidone inhibits MAOs gradually over several days—the risks are small if treatment is limited to a 5-day course. Because hemolytic anemia can occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and glutathione instability, furazolidone treatment is contraindicated in mothers

who are breast-feeding and in neonates. Halofantrine This 9-phenanthrenemethanol is one of three classes of arylaminoalcohols first identified as potential antimalarial agents by the World War II Malaria Chemotherapy Program. Its activity is believed to be similar to that of chloroquine, although it is an oral alternative for the treatment of malaria due to chloroquine-resistant P. falciparum.

Halofantrine is thought to share one or more mechanisms with the 4-aminoquinolines, forming a complex with ferriprotoporphyrin IX and interfering with the degradation of hemoglobin. It has been shown to bind to plasmepsin, a hemoglobin-degrading enzyme unique to plasmodia. Halofantrine exhibits erratic bioavailability, but its absorption is significantly enhanced when it is taken with a fatty meal. The elimi nation half-life of halofantrine is 1–2 days; it is excreted mainly in feces. Halofantrine is metabolized into N-debutyl-halofantrine by the cytochrome P450 enzyme CYP3A4. Grapefruit juice should be avoided during treatment because it increases both halofantrine's bioavailability and halofantrine-induced QT interval prolongation by inhibiting CYP3A4 at the enterocyte level. Halofantrine should not be given simultaneously with or <3 weeks after mefloquine because of the potential occurrence of a fatal prolongation of the QTc interval on electrocardiography. Iodoquinol Iodoquinol (diiodohydroxyquin), a hydroxyquinoline, is an effective luminal agent for the treatment of amebiasis, balantidia sis, and infection with Dientamoeba fragilis. Its mechanism of action is unknown. It is poorly absorbed. Because the drug contains 64% organi cally bound iodine, it should be used with caution in patients with thy roid disease. Iodine dermatitis occurs occasionally during iodoquinol treatment. Protein-bound serum iodine levels may be increased dur ing treatment and can interfere with certain tests of thyroid function. These effects may persist for as long as 6 months after discontinuation of therapy. Iodoquinol is contraindicated in patients with liver disease. Most serious are the reactions related to prolonged high-dose therapy (optic neuritis, peripheral neuropathy), which should not occur if the recommended dosage regimens are followed. Ivermectin Ivermectin (22,23-dihydroavermectin) is a derivative of the macrocyclic lactone avermectin produced by the soil-dwelling actinomycete Streptomyces avermitilis. Ivermectin is active at low doses against a wide range of helminths and ectoparasites. It is the drug of choice for the treatment of onchocerciasis, strongyloidiasis, cutaneous larva migrans, and scabies. Ivermectin is highly active against micro filariae of the lymphatic filariases but has no macrofilaricidal activity. When ivermectin is used in combination with other agents such as DEC or albendazole for treatment of lymphatic filariasis, synergistic activity is seen. Although active against the intestinal helminths Ascaris lumbricoides and Enterobius vermicularis, ivermectin is only variably effective in trichuriasis and is ineffective against hookworms. Wide spread use of ivermectin for treatment of intestinal nematode infec tions in sheep and goats has led to the emergence of drug resistance in veterinary practice; this development may portend problems in human medical use. Data suggest that ivermectin acts by opening the neuromuscular membrane-associated, glutamate-dependent chloride channels. The influx of chloride ions results in hyperpolarization and muscle paralysis— particularly of the nematode pharynx, with consequent blockage of the oral ingestion of nutrients. As these chloride channels are present only in invertebrates, paralysis is seen only in the parasite. Ivermectin is available for administration to humans only as an oral formulation. The drug is highly protein bound; it is almost completely excreted in feces. Both food and beer increase the bioavailability of ivermectin significantly. Ivermectin is distributed widely throughout the body; animal studies indicate that it accumulates at the highest concentration in adipose tissue and liver, with little accumulation in the brain. Few data exist to guide therapy in hosts with conditions that may

influence drug pharmacokinetics. Ivermectin is generally administered as a single dose of 150–200 µg/kg. In the absence of parasitic infection, the adverse effects of ivermectin in therapeutic doses are minimal. Adverse effects in patients with filarial infections include fever, myalgia, malaise, lightheadedness, and (occasionally) postural hypotension. The severity of such side effects is related to the intensity of parasite infection, with more symp toms in individuals with a heavy parasite burden. In onchocerciasis, skin edema, pruritus, and mild eye irritation may also occur. The adverse effects are generally self-limiting and only occasionally require

symptom-based treatment with antipyretics or antihistamines. More severe complications of ivermectin therapy for onchocerciasis include encephalopathy in patients heavily infected with Loa loa. Lumefantrine Lumefantrine (benflumetol), a fluorene arylamino alcohol derivative synthesized in the 1970s by the Chinese Academy of Military Medical Sciences (Beijing), has marked blood schizonticidal activity against a wide range of plasmodia. This agent conforms struc turally and in mode of action to other arylaminoalcohols (quinine, mefloquine, and halofantrine). Lumefantrine exerts its antimalarial effect as a consequence of its interaction with heme, a degradation product of hemoglobin metabolism. Although its antimalarial activity is slower than that of the artemisinin-based drugs, the recrudescence rate with the recommended lumefantrine regimen is lower. The phar macokinetic properties of lumefantrine are reminiscent of those of halofantrine, with variable oral bioavailability, considerable augmenta tion of oral bioavailability by concomitant fat intake, and a terminal elimination half-life of ~4–5 days in patients with malaria. Artemether and lumefantrine have synergistic activity, and the combined formulation of artemether and lumefantrine is effective for the treatment of falciparum malaria in areas where P. falciparum is resistant to chloroquine and antifolates. Mebendazole This benzimidazole is a broad-spectrum antipara sitic agent widely used to treat intestinal helminthiases. Its mechanism of action is similar to that of albendazole; however, it is a more potent inhibitor of parasite malic dehydrogenase and exhibits a more spe cific and selective effect against intestinal nematodes than the other benzimidazoles. Mebendazole is available only in oral form but is poorly absorbed from the GI tract; only 5–10% of a standard dose is measurable in plasma. The proportion absorbed from the GI tract is extensively metabolized in the liver. Metabolites appear in the urine and bile; impaired liver or biliary function results in higher plasma mebendazole levels in treated patients. No dose reduction is warranted in patients with renal function impair ment. Because mebendazole is poorly absorbed, its incidence of side effects is low. Transient abdominal pain and diarrhea sometimes occur, usually in persons with massive parasite burdens. Mefloquine Mefloquine is used for prophylaxis of chloroquineresistant malaria; high doses can be used for treatment. Despite the development of drug-resistant strains of P. falciparum in parts of Africa and Southeast Asia, mefloquine remains an effective drug throughout most of the world. Cross-resistance of mefloquine with halofantrine and with quinine has been documented in limited areas. Like quinine and chloroquine, this quinoline is active only against the asexual eryth rocytic stages of malarial parasites. Unlike quinine, however, meflo quine has a relatively poor affinity for DNA and, as a result, does not inhibit the synthesis of parasitic nucleic acids and proteins. Although both mefloquine and chloroquine inhibit hemozoin formation and heme degradation, mefloquine differs in that it forms a complex with heme that may be toxic to the parasite. Mefloquine HCl is poorly water soluble and intensely irritating when given parenterally; thus, it is available only in tablet form. Its absorption is adversely affected by vomiting and diarrhea but is sig nificantly enhanced when the drug is administered with or after food. About 98% of the drug binds to protein. Mefloquine is excreted mainly in the bile and feces; therefore, no dose adjustment is needed in per sons with renal insufficiency. The drug and its main

metabolite are not appreciably removed by hemodialysis. No dosage adjustments are indi cated for the achievement of plasma concentrations in dialysis patients. Pharmacokinetic differences have been detected among various ethnic populations; however, these distinctions are of minor importance com pared with host immune status and parasite susceptibility. In patients with impaired liver function, the elimination of mefloquine may be prolonged, leading to higher plasma levels. Mefloquine should be used with caution by individuals participating in activities requiring alertness and fine-motor coordination because dizziness, vertigo, or tinnitus can develop and persist. If the drug is to be administered for a prolonged period, periodic evaluations are

recommended, including liver function tests and ophthalmic examina tions. Sleep abnormalities (insomnia, abnormal dreams) have occa sionally been reported. Psychosis and seizures occur rarely; mefloquine should not be prescribed to patients with neuropsychiatric conditions. The development of acute anxiety, depression, restlessness, or confu sion may be considered prodromal to a more serious event, and the drug should be discontinued.

Concomitant use of quinine, quinidine, or drugs producing β-adrenergic blockade may cause significant electrocardiographic abnormalities or cardiac arrest. Halofantrine must not be given simul taneously with or <3 weeks after mefloquine because a potentially fatal prolongation of the QTc interval on electrocardiography may occur. No data exist on mefloquine use after halofantrine use. Administration of mefloquine with quinine or chloroquine may increase the risk of convulsions. Mefloquine may lower plasma levels of anticonvulsants. Caution should be exercised with concomitant antiretroviral therapy, because mefloquine has been shown to exert variable effects on rito navir pharmacokinetics that are not explained by hepatic CYP3A4 activity or ritonavir protein binding. Vaccinations with attenuated live bacteria should be completed at least 3 days before the first dose of mefloquine. Women of childbearing age who are traveling to areas where malaria is endemic should be warned against becoming pregnant and encouraged to practice contraception during malaria prophylaxis with mefloquine and for up to 3 months thereafter. However, in the case of unplanned pregnancy, use of mefloquine is not considered an indica tion for pregnancy termination. Analysis of prospectively monitored cases demonstrates a prevalence of birth defects and fetal loss compa rable to background rates. Melarsoprol* Melarsoprol has been used since 1949 for the treat ment of human African trypanosomiasis. This trivalent arsenical compound is indicated for the treatment of African trypanosomiasis with neurologic involvement and for the treatment of early disease that is resistant to suramin or pentamidine. Melarsoprol, like other drugs containing heavy metals, interacts with thiol groups of several different proteins; however, its antiparasitic effects appear to be more specific. Trypanothione reductase is a key enzyme involved in the oxidative stress management of both Trypanosoma and Leishmania species, help ing to maintain an intracellular reducing environment by reduction of disulfide trypanothione to its dithiol derivative dihydrotrypano thione. Melarsoprol sequesters dihydrotrypanothione, depriving the parasite of its main sulfhydryl antioxidant, and inhibits trypanothione reductase, depriving the parasite of the essential enzyme system that is responsible for keeping trypanothione reduced. These effects are synergistic. The selectivity of arsenical action against trypanosomes is due at least in part to the greater melarsoprol affinity of reduced trypanothione than of other monothiols (e.g., cysteine) on which the mammalian host depends for maintenance of high thiol levels. Melar soprol enters the parasite via an adenosine transporter; drug-resistant strains lack this transport system. CHAPTER 229 Agents Used to Treat Parasitic Infections Melarsoprol is always administered IV. A small but therapeuti cally significant amount of

the drug enters the CSF. The compound is excreted rapidly, with ~80% of the arsenic found in feces. Melarsoprol is highly toxic. The most serious adverse reaction is reactive encephalopathy, which affects 6% of treated individuals and usually develops within 4 days of the start of therapy, with an average case–fatality rate of 50%. Glucocorticoids are administered with melar soprol to prevent this development. Because melarsoprol is intensely irritating, care must be taken to avoid infiltration of the drug. Metrifonate Metrifonate has selective activity against Schistosoma haematobium. This organophosphorous compound is a prodrug that is converted nonenzymatically to dichlorvos (2,2-dichlorovinyl dimeth ylphosphate, DDVP), a highly active chemical that irreversibly inhibits the acetylcholinesterase enzyme. Schistosomal cholinesterase is more susceptible to dichlorvos than is the corresponding human enzyme. The exact mechanism of action of metrifonate is uncertain, but the drug is believed to inhibit tegumental acetylcholine receptors that mediate glucose transport.

Metrifonate is administered in a series of three doses at 2-week intervals. After a single oral dose, metrifonate produces a 95% decrease in plasma cholinesterase activity within 6 h, with a fairly rapid return to normal. However, 2.5 months are required for erythrocyte cholinester ase levels to return to normal. Treated persons should not be exposed to neuromuscular blocking agents or organophosphate insecticides for at least 48 h after treatment.

Metronidazole and Other Nitroimidazoles See Table 229-1 and Chap. 149. Miltefosine In the early 1990s, miltefosine (hexadecylphosphocho line), originally developed as an antineoplastic agent, was discovered to have significant antiproliferative activity against Leishmania species, T. cruzi, and T. brucei parasites in vitro and in experimental animal models. Miltefosine is the first oral drug that has proved to be highly effective and comparable to amphotericin B against visceral leishmani asis in India, where antimonial-resistant cases are prevalent. Miltefo sine is also effective in previously untreated visceral infections. Cure rates in cutaneous leishmaniasis are comparable to those obtained with antimony. Miltefosine is also effective against the free-living ameba Naegleria fowleri. The activity of miltefosine is attributed to interaction with cell signal transduction pathways and inhibition of phospholipid and sterol bio synthesis. Resistance to miltefosine has not been observed clinically. The drug is readily absorbed from the GI tract, is widely distributed, and accumulates in several tissues. The efficacy of a 28-day treatment course in Indian visceral leishmaniasis is equivalent to that of ampho tericin B therapy; however, it appears that a shortened course of 21 days may be equally efficacious. PART 5 Infectious Diseases General recommendations for the use of miltefosine are limited by the exclusion of specific groups from the published clinical trials: per sons <12 or >65 years of age, persons with the most advanced disease, breast-feeding women, HIV-infected patients, and individuals with significant renal or hepatic insufficiency. Moxidectin Like ivermectin, moxidectin is a macrocyclic lactone that is an effective antihelminthic. In 2018, the FDA approved its use for the treatment of onchocerciasis. The primary mode of action of moxidectin is believed to be like that of ivermectin; however, there are likely different binding sites, as suggested by the identification of ivermectin-resistant helminths that are susceptible to moxidectin. The drug is well tolerated, with most adverse effects attributed to death of microfilariae. Some adverse effects occurred more commonly com pared with ivermectin, including orthostatic hypotension (5 vs 2%) and elevated transaminases (1 vs 0.6%). In clinical trials, no clinically significant differences in the pharmacokinetics were observed with age, gender, weight, or renal impairment. The effect of hepatic dysfunction is unknown. Niclosamide† Niclosamide is active against a wide variety of adult tapeworms but not against tissue cestodes.

The drug uncouples oxida tive phosphorylation in parasite mitochondria, thereby blocking the uptake of glucose by the intestinal tapeworm and resulting in the para site's death. Niclosamide rapidly causes spastic paralysis of intestinal cestodes in vitro. Its use is limited by its side effects, the necessarily long duration of therapy, the recommended use of purgatives, and— most important—limited availability (i.e., on a named-patient basis from the manufacturer). Niclosamide is poorly absorbed. Tablets are given on an empty stomach in the morning after a liquid meal the night before, and this dose is followed by another 1 h later. For treatment of hymenolepiasis, the drug is administered for 7 days. A second course is often pre scribed. The scolex and proximal segments of the tapeworms are killed on contact with niclosamide and may be digested in the gut. However, disintegration of the adult tapeworm results in the release of viable ova, which theoretically can result in autoinfection. Although fears of the development of cysticercosis in patients with Taenia solium infections have proved unfounded, it is still recommended that a brisk purgative be given 2 h after the first dose.

Nifurtimox This nitrofuran compound is an inexpensive and effective oral agent for the treatment of acute Chagas disease. Try panosomes lack catalase and have very low levels of peroxidase; as a result, they are very vulnerable to by-products of oxygen reduc tion. When nifurtimox is reduced in the trypanosome, a nitro anion radical is formed and undergoes autooxidation, resulting in the generation of the superoxide anion O2 –, hydrogen peroxide (H2O2), hydroperoxyl radical (HO2), and other highly reactive and cytotoxic molecules. Despite the abundance of catalases, peroxidases, and superoxide dismutases that neutralize these destructive radicals in mammalian cells, nifurtimox has a poor therapeutic index. Prolonged use is required, but the course may have to be interrupted because of drug toxicity, which develops in 40–70% of recipients. Nifurtimox is well absorbed and undergoes rapid and extensive biotransformation; <0.5% of the original drug is excreted in urine. In 2020, the FDA approved this agent for the treatment of Chagas disease in children; it is now commercially available. Nitazoxanide Nitazoxanide is a 5-nitrothiazole compound used for the treatment of cryptosporidiosis and giardiasis; it is active against other intestinal protozoa as well. The drug is approved for use in children 1–11 years of age. The antiprotozoal activity of nitazoxanide is believed to be due to interference with the pyruvate-ferredoxin oxidoreductase (PFOR) enzyme–dependent electron transfer reaction that is essential to anaerobic energy metabolism. Studies have shown that the PFOR enzyme from G. lamblia directly reduces nitazoxanide by transfer of electrons in the absence of ferredoxin. The DNA-derived PFOR protein sequence of Cryptosporidium parvum appears to be similar to that of G. lamblia. Interference with the PFOR enzyme–dependent electron transfer reaction may not be the only pathway by which nitazoxanide exerts antiprotozoal activity. After oral administration, nitazoxanide is rapidly hydrolyzed to an active metabolite, tizoxanide (desacetyl-nitazoxanide). Tizoxanide then undergoes conjugation, primarily by glucuronidation. It is rec ommended that nitazoxanide be taken with food; however, no studies have been conducted to determine whether the pharmacokinetics of tizoxanide and tizoxanide glucuronide differ in fasted versus fed sub jects. Tizoxanide is excreted in urine, bile, and feces, and tizoxanide glucuronide is excreted in urine and bile. The pharmacokinetics of nitazoxanide in patients with impaired hepatic and/or renal function have not been studied. Tizoxanide is highly bound to plasma protein (>99.9%). Therefore, caution should be used when administering this agent concurrently with other highly plasma protein–bound drugs that have narrow therapeutic indices, as competition for binding sites may occur. Oxamniquine This tetrahydroquinoline derivative is an effective alternative agent for the treatment of S. mansoni, although susceptibil ity to this drug exhibits regional variation. Oxamniquine exhibits

anti cholinergic properties, but its primary mode of action seems to rely on ATP-dependent enzymatic drug activation generating an intermediate that alkylates essential macromolecules, including DNA. In treated adult schistosomes, oxamniquine produces marked tegumental altera tions like those seen with praziquantel but that develop less rapidly, becoming evident 4–8 days after treatment. Oxamniquine is administered orally as a single dose and is well absorbed. Food retards absorption and reduces bioavailability. About 70% of an administered dose is excreted in urine as a mixture of pharmacologically inactive metabolites. Patients should be warned that their urine might have an intense orange-red color. Side effects are uncommon and usually mild, although hallucinations and seizures have been reported. Paromomycin (Aminosidine) First isolated in 1956, this amino glycoside is an effective oral agent for the treatment of infections due to intestinal protozoa. Parenteral paromomycin appears to be effective against visceral leishmaniasis in India. Paromomycin inhibits protozoan protein synthesis by binding to the 30S ribosomal RNA in the aminoacyl-tRNA site, causing misreading

of mRNA codons. Paromomycin is less active against G. lamblia than standard agents; however, like other aminoglycosides, paromomycin is poorly absorbed from the intestinal lumen, and the high levels of drug in the gut compensate for this relatively weak activity. If absorbed or administered systemically, paromomycin can cause ototoxicity and nephrotoxicity. However, systemic absorption is very limited, and tox icity should not be a concern in persons with normal kidneys. Topical formulations are not generally available. Pentamidine Isethionate This diamidine is an effective alterna tive agent for some forms of leishmaniasis and trypanosomiasis. It is available for parenteral and aerosolized administration. Although its mechanism of action remains undefined, it is known to exert a wide range of effects, including interaction with trypanosomal kinetoplast DNA; interference with polyamine synthesis by a decrease in the activ ity of ornithine decarboxylase; and inhibition of RNA polymerase, topoisomerase, ribosomal function, and the synthesis of nucleic acids and proteins. Pentamidine isethionate is well absorbed, highly tissue bound, and excreted slowly over several weeks, with an elimination half-life of 12 days. No steady-state plasma concentration is attained in persons given daily injections; the result is extensive accumulation of pentami dine in tissues, primarily the liver, kidney, adrenal gland, and spleen. Pentamidine does not penetrate well into the CNS. Pulmonary con centrations of pentamidine are increased when the drug is delivered in aerosolized form, but not when it is delivered systemically. Rapid (<1-h) infusion of intravenous pentamidine often results in hypotension. Because electrolyte disturbances and mild to moderate nephrotoxicity occur commonly, pentamidine should be used with caution with other nephrotoxic agents. Pancreatitis and QT prolonga tion may also occur; cumulative damage to pancreatic islet cells may result in drug-induced diabetes mellitus. Similarly, hypoglycemia can develop, although much less commonly when pentamidine is given by the inhaled route. Piperaquine This bisquinoline was synthesized in the 1960s and used widely for malaria control in China until resistance emerged. The development of artemisinin-based combination therapy led to its evaluation as a partner drug, and it is now combined with dihydroarte misinin. Piperaquine is highly lipophilic and has a prolonged half-life (~20 days), thus providing a period of posttreatment prophylaxis. The drug’s mechanisms of action and resistance have not been well studied but are presumed to be similar to the other 4-aminoquinolines. Piperazine The antihelminthic activity of piperazine is confined to ascariasis and enterobiasis. Piperazine acts as an agonist at extra synaptic γ-aminobutyric acid (GABA) receptors, causing an influx of chloride ions in the nematode somatic musculature. Although the ini tial result is hyperpolarization of the muscle fibers, the ultimate effect is flaccid paralysis, leading to the

expulsion of live worms. Patients should be warned, as this occurrence can be unsettling. Praziquantel This heterocyclic pyrazinoisoquinoline derivative is highly active against a broad spectrum of trematodes and cestodes. It is the mainstay of treatment for schistosomiasis and is a critical part of community-based control programs. All of the effects of praziquantel can be attributed either directly or indirectly to an alteration of intracellular calcium concentrations. Although the exact mechanism of action remains unclear, the major mechanism is disruption of the parasite tegument, causing tetanic contractures with loss of adherence to host tissues and, ultimately, disintegration or expulsion. Praziquantel induces changes in the anti genicity of the parasite by causing the exposure of concealed antigens. Praziquantel also produces alterations in schistosomal glucose metabo lism, including decreases in glucose uptake, lactate release, glycogen content, and ATP levels. Praziquantel exerts its parasitic effects directly and does not need to be metabolized to be effective. It is well absorbed but undergoes exten sive first-pass hepatic clearance. Levels of the drug are increased when it is taken with food, particularly carbohydrates, or with cimetidine.

Serum levels are reduced by glucocorticoids, chloroquine, carbam azepine, and phenytoin. Praziquantel is completely metabolized in humans, with 80% of the dose recovered as metabolites in urine within 4 days. It is not known to what extent praziquantel crosses the placenta, but retrospective studies suggest that it is safe in pregnancy.

Patients with schistosomiasis who have heavy parasite burdens may develop abdominal discomfort, nausea, headache, dizziness, and drows iness. Symptoms begin 30 min after ingestion, may require spasmolytics for relief, and usually disappear spontaneously after a few hours. Primaquine Phosphate Primaquine, an 8-aminoquinoline, has a broad spectrum of activity against all stages of plasmodial development in humans but has been used most effectively for eradication of the hepatic stage of these parasites. Primaquine must be metabolized by the host to be effective. It is, in fact, rapidly metabolized; only a small fraction of the dose of the parent drug is excreted unchanged. Although the parasiticidal activity of the three oxidative metabolites remains unclear, they are believed to affect both pyrimidine synthesis and the mitochondrial electron transport chain. The metabolites appear to have significantly less antimalarial activity than primaquine; however, their hemolytic activity is greater than that of the parent drug. Primaquine causes marked hypotension after parenteral admin istration and therefore is given only by the oral route. It is rapidly and almost completely absorbed from the GI tract. Patients should be tested for G6PD deficiency before they receive primaquine. The drug may induce the oxidation of hemoglobin into methemoglobin, regardless of the G6PD status of the patient. Primaquine is otherwise well tolerated. CHAPTER 229 Proguanil (Chloroguanide) Proguanil inhibits plasmodial dihy drofolate reductase and is used with atovaquone for oral treatment of uncomplicated malaria or with chloroquine for malaria prophylaxis in parts of Africa without widespread chloroquine-resistant P. falciparum. Proguanil exerts its effect primarily by means of the metabolite cycloguanil, whose inhibition of dihydrofolate reductase in the para site disrupts deoxythymidylate synthesis, thus interfering with a key pathway involved in the biosynthesis of pyrimidines required for nucleic acid replication. There are no clinical data indicating that folate supplementation diminishes drug efficacy; women of childbearing age for whom atovaquone/proguanil is prescribed should continue taking folate supplements to prevent neural tube birth defects. Agents Used to Treat Parasitic Infections Proguanil is extensively absorbed regardless of food intake. The drug is 75% protein bound. The main routes of elimination are hepatic biotransformation and renal excretion; 40–60%

of the proguanil dose is excreted by the kidneys. Drug levels are increased and elimination is impaired in patients with hepatic insufficiency. Pyrantel Pamoate Pyrantel is a tetrahydropyrimidine formulated as pamoate. This safe, well-tolerated, inexpensive drug is used to treat a variety of intestinal nematode infections but is ineffective in trichu riasis. Pyrantel pamoate is usually effective in a single dose. Its target is the nicotinic acetylcholine receptor on the surface of nematode somatic muscle. Pyrantel depolarizes the neuromuscular junction of the nematode, resulting in its irreversible paralysis and allowing the natural expulsion of the worm. Pyrantel pamoate is poorly absorbed from the intestine; >85% of the dose is passed unaltered in feces. The absorbed portion is metabolized and excreted in urine. Piperazine is antagonistic to pyrantel pamoate and should not be used concomitantly. Pyrantel pamoate has minimal toxicity at the oral doses used to treat intestinal helminthic infection. It is not recommended for pregnant women or for children <12 months old. Pyrimethamine When combined with short-acting sulfon amides, this diaminopyrimidine is effective in malaria, toxoplas mosis, and isosporiasis. Unlike mammalian cells, the parasites that cause these infections cannot use preformed pyrimidines obtained through salvage pathways but rather rely completely on de novo pyrimidine synthesis, for which folate derivatives are essential cofac tors. The efficacy of pyrimethamine is increasingly limited by the

development of resistant strains of P. falciparum and P. vivax. Single amino acid substitutions to parasite dihydrofolate reductase confer resistance to pyrimethamine by decreasing the enzyme’s binding affinity for the drug.

Pyrimethamine is well absorbed; the drug is 87% bound to human plasma proteins. In healthy volunteers, drug concentrations remain at therapeutic levels for up to 2 weeks; drug levels are lower in patients with malaria. At the usual dosage, pyrimethamine alone causes little toxicity except for occasional skin rashes and, more rarely, blood dyscrasias. Bone marrow suppression sometimes occurs at the higher doses used for toxoplasmosis; at these doses, the drug should be administered with folinic acid. Pyronaridine This potent antimalarial is a benzonaphthyridine derivative first synthesized by Chinese researchers in 1970. Like chloroquine, pyronaridine targets hematin formation, inhibiting the production of β-hematin by forming complexes with it, with conse quent enhancement of hematin-induced hemolysis. However, this drug is more potent than chloroquine: for complete lysis, pyronaridine is required at only 1/100th of the concentration needed with chloroquine. It also inhibits glutathione-dependent heme degradation. Despite its similar mode of action, pyronaridine remains effective against chloroquine-resistant strains. When combined with artesunate, it is effective for the treatment of acute, uncomplicated infection caused by P. falciparum or P. vivax in areas of low transmission with evidence of artemisinin resistance. Pyronaridine is readily absorbed, widely distributed throughout the body, metabolized by the liver, and excreted in urine and stool. Its use is contraindicated in patients with severe liver or kidney impairment. Pyronaridine inhibits both CYP2D6 and P-glycoprotein in vitro, and these effects may have clinical relevance for patients taking medica tions for cardiac disease (e.g., metoprolol and digoxin). PART 5 Infectious Diseases Quinacrine† Despite being one of the first antimalarials, the anti protozoal mechanism of quinacrine has not been fully elucidated. It is generally considered to intercalate into DNA and thereby inhibit repli cation and transcription. The drug also inhibits adenosine uptake, ATP incorporation into RNA, and NADH oxidase—the same enzyme that activates furazolidone. The differing relative quinacrine uptake rate between human cells and G. lamblia may explain the selective toxicity of the drug. Resistance correlates with decreased drug uptake. Quinacrine is rapidly absorbed from the intestinal tract and is widely

distributed in body tissues. Alcohol is best avoided because of a disulfiram-like effect. Although its production was discontinued in 1992, quinacrine can be obtained commercially from compounding pharmacies. Quinine and Quinidine When combined with another agent, the cinchona alkaloid quinine is effective for the oral treatment of both uncomplicated, chloroquine-resistant malaria and babesiosis. Quinine acts rapidly against the asexual blood stages of all forms of the human malaria parasites. For severe malaria, only quinidine (the dextroisomer of quinine) is available in the United States. Quinine concentrates in the acidic food vacuoles of Plasmodium species. The drug inhibits the nonenzymatic polymerization of the highly reactive, toxic heme mol ecule into the nontoxic polymer pigment hemozoin. Quinine is readily absorbed when given orally. In patients with malaria, the elimination half-life of quinine increases according to the severity of the infection. However, toxicity is avoided by an increase in the concentration of plasma glycoproteins. The cinchona alkaloids are extensively metabolized, particularly by CYP3A4; only 20% of the dose is excreted unchanged in urine. The drug's metabolites are also excreted in urine and may be responsible for toxicity in patients with renal failure. Renal excretion of quinine is decreased when cimetidine is taken and increased when the urine is acidic. The drug readily crosses the placenta. Quinidine is both more potent as an antimalarial and more toxic than quinine. Its use requires cardiac monitoring. Dose reduction is necessary in persons with severe renal impairment.

Spiramycin† This macrolide is used to treat acute toxoplasmosis in pregnancy and congenital toxoplasmosis. While the mechanism of action is similar to that of other macrolides, the efficacy of spiramycin in toxoplasmosis appears to stem from its rapid and extensive intracel lular penetration, which results in macrophage drug concentrations 10–20 times greater than serum concentrations. Spiramycin is rapidly and widely distributed throughout the body and reaches concentrations in the placenta up to five times those in serum. This agent is excreted mainly in bile. Indeed, in humans, the urinary excretion of active compounds represents only 20% of the administered dose. Serious reactions to spiramycin are rare. Of the available macrolides, spiramycin appears to have the lowest risk of drug interactions. Compli cations of treatment are rare but, in neonates, can include life-threaten ing ventricular arrhythmias that disappear with drug discontinuation. Spiramycin is not formally approved for use in the United States, but it is accessible through a compassionate use program for toxoplasmosis in pregnancy through the FDA (301-796-1400). Sulfonamides See Table 229-1 and Chap. 149. Suramin* This derivative of urea is the drug of choice for the early stage of African trypanosomiasis. The drug is polyanionic and acts by forming stable complexes with proteins, thus inhibiting multiple enzymes essential to parasite energy metabolism. Suramin appears to inhibit all trypanosome glycolytic enzymes more effectively than it inhibits the corresponding host enzymes. Suramin is parenterally administered. It binds to plasma proteins and persists at low levels for several weeks after infusion. Its metabo lism is negligible. This drug does not penetrate the CNS. Tafenoquine Tafenoquine is an 8-aminoquinoline with causal prophylactic activity. Its prolonged half-life (2–3 weeks) allows longer dosing intervals when the drug is used for prophylaxis. Tafenoquine has been well tolerated in clinical trials. When tafenoquine is taken with food, its absorption is increased by 50% and the most commonly reported adverse event—mild GI upset—is diminished. Like prima quine, tafenoquine is a potent oxidizing agent, causing hemolysis in patients with G6PD deficiency as well as methemoglobinemia. It has been commercially available since FDA approval in 2018. Tetracyclines See Table 229-1 and Chap. 149. Thiabendazole Discovered in 1961, thiabendazole remains one of the most potent of the numerous benzimidazole derivatives. However, its use has declined significantly because of a higher frequency of adverse effects than is seen with other, equally effective agents. Thiabendazole is active against most intestinal nematodes that infect humans.

Although the exact mechanism of its antihelminthic activity has not been fully elucidated, it is likely to be similar to that of other benzimidazole drugs: namely, inhibition of polymerization of parasite β-tubulin. The drug also inhibits the helminth-specific enzyme fumarate reductase. In animals, thiabendazole has antiinflammatory, antipyretic, and analgesic effects, which may explain its usefulness in dracunculiasis and trichinellosis. Thiabendazole also suppresses egg and/or larval production by some nematodes and may inhibit the subsequent development of eggs or larvae passed in feces. Despite the emergence and global spread of thiabendazole-resistant trichostrongyliasis among sheep, there have been no reports of drug resistance in humans. Thiabendazole is available in tablet form and as an oral suspension. The drug is rapidly absorbed from the GI tract but can also be absorbed through the skin. Thiabendazole should be taken after meals. This agent is extensively metabolized in the liver before ultimately being excreted; most of the dose is excreted within the first 24 h. The usual dose of thiabendazole is determined by the patient’s weight, but some treatment regimens are parasite specific. No adjustments are recom mended in patients with renal or hepatic failure; only cautious use is advised. Coadministration of thiabendazole to patients taking theophylline can result in an increase in theophylline levels by >50%. Therefore,

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