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Anthelmintic Drugs

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DRUG LIST

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Infection by *helminths* (worms) may be limited solely to the intestinal lumen or may involve a complex process with migration of the adult or immature worm through the body before localization in a particular tissue. Complicating our understanding of the host–parasite relationship and the role of chemotherapy in helminth-induced infections is the complex life cycle of many of these organisms. Whereas some helminths have a simple cycle of egg deposition and development of the egg to produce a mature worm, others must progress through one or more hosts and one or more morphological stages, each metabolically distinct from the other, before emerging as an adult. Furthermore, an infective form may be either an adult worm or an immature worm. Treatment may be further complicated by infection with more than one genus of helminth. Pathogenic helminths can be divided into the following major groups: *cestodes* (flatworms), *nematodes* (roundworms), *trematodes* (flukes) and less frequently, *Acanthocephala* (thorny-headed worms).

The complex life cycle and host–parasite relationship means that treatment is sometimes difficult and

may have to be protracted. Most available anthelmintic drugs exert their antiparasitic effects by interference with (1) energy metabolism, (2) neuromuscular coordination, (3) microtubular function, and (4) cellular permeability. The mode of action of most drugs used in the treatment of helminthic infections is summarized in Table 54.1. Some of the drugs used in the treatment of diseases caused by helminths also are used in the treatment of specific protozoal diseases.

TREATMENT FOR INFECTIONS CAUSED BY NEMATODES

Nematodes are long, cylindrical unsegmented worms that are tapered at both ends. Because of their shape, they are commonly referred to as roundworms. Some intestinal nematodes contain a mouth with three lips, and in some the mouth contains cutting plates. Infection occurs after ingestion of embryonated eggs or tissues of another host that contain larval forms of the nematodes.

TABLE 54.1 Mode of Action of Drugs Employed in Chemotherapy of Helminthic Diseases

Drug	Mode of Action	Specific Effect
Piperazine	Paralyzes helminth muscle	Blocks myoneural junction; causes chloride-dependent hyperpolarization, flaccid paralysis
Ivermectin	Paralyzes helminth muscle	Blocks transmission of nerve signals by interactions with glutamate-gated chloride channels
Pyrantel	Paralyzes helminth muscle	Depolarization and spastic paralysis
Niclosamide	Inhibits production of energy	Uncouples anaerobic oxidative phosphorylation in tapeworm mitochondria, causing decreased ATP synthesis
Mebendazole	Inhibits protein function	Binds to tubulin and inhibits polymerization
Diethylcarbamazine	Enhances phagocytosis and killing	Sensitizes microfilaria, entraps them in reticuloendothelial system
Praziquantel	Paralyzes helminth muscle	Increases membrane permeability, unmask surface proteins
Thiabendazole	Inhibits energy production, protein function	Inhibits fumarate reductase, ATP synthesis; binds to tubulin
Bithionol	Inhibits energy production	Uncouples oxidative phosphorylation
Suramin	Inhibits energy production	Inhibits muscle enzymes of glycolysis and oxygen consumption

Some of the nematodes (filarial worms and guinea worms) live in blood, lymphatics, and other tissues and are referred to as blood and tissue nematodes. Others are found primarily in the intestinal tract. One group, hookworms, undergoes a developmental cycle in soil. The larvae penetrate the skin of humans, enter the venules, and are carried to the lungs, where they enter the alveoli, sometimes causing pneumonitis. The larvae then migrate up the trachea and are swallowed. In the intestine, they attach to the mucosa, and using the cutting plates and a muscular esophagus, feed on host blood and tissue fluid. This may result in vague abdominal pains, diarrhea and, if many worms are present, anemia.

Strongyloides stercoralis infection is acquired, like hookworm, from filariform larvae in contaminated soil that penetrate the skin. This parasite maintains itself for many decades in the small intestine asymptotically. Persons treated with immunosuppressive drugs or who are debilitated by chronic illness may be at risk for widespread tissue invasion or hyperinfection syndrome. Prompt treatment may be life saving in disseminated disease.

Other intestinal nematodes are acquired by ingestion of eggs from soil. These groups lack cutting plates and may not cause anemia. Still other nematodes, such as pinworms, migrate from the anus to lay eggs, which are transmitted by fingers or through the air. The eggs are ingested and the adult worm develops in the intestinal tract. In some cases, the appendix may be invaded, resulting in symptoms of appendicitis. In most cases, the symptoms are perianal pruritus and a restlessness associated with the migration of the female worm through the anus to the perianal skin. Other nematodes, such as *Ascaris* spp., are ingested in egg form but have a migration similar to that of the hookworm.

The filarial worms differ from other nematodes in that they are threadlike and are found in blood and tissue. The infective larvae enter following the bite of an infected arthropod (fly or mosquito). They then enter the lymphatics and lymph nodes. Fever, lymphangitis, and lymphadenitis are associated with the early stage of the disease. Chronic infections may be characterized by elephantiasis as a result of lymphatic obstruction. Some species of filarial worms migrate in the subcutaneous tissues and produce nodules and blindness (onchocerciasis).

Piperazine

Piperazine (*Vermizine*) contains a heterocyclic ring that lacks a carboxyl group. It acts on the musculature of the helminths to cause reversible flaccid paralysis mediated by chloride-dependent hyperpolarization of the muscle membrane. This results in expulsion of the worm. Piperazine acts as an agonist at gated chloride channels on the parasite muscle.

Piperazine has been used with success to treat *A. lumbricoides* and *E. vermicularis* infections, although mebendazole is now the agent of choice. Piperazine is administered orally and is readily absorbed from the intestinal tract. Most of the drug is excreted in the urine within 24 hours.

Piperazine is an appropriate alternative to mebendazole for the treatment of ascariasis, especially in the presence of intestinal or biliary obstruction. Cure rates of more than 80% are obtained following a 2-day regimen.

Side effects occasionally include gastrointestinal distress, urticaria, and dizziness. Neurological symptoms of ataxia, hypotonia, visual disturbances, and exacerbation

tions of epilepsy can occur in patients with preexisting renal insufficiency. It should not be used in pregnant women because of the formation of a potentially carcinogenic and teratogenic nitrosamine metabolite. Concomitant use of piperazine and chlorpromazine or pyrantel should be avoided.

Diethylcarbamazine

Diethylcarbamazine citrate (*Hetrazan*) is active against several microfilaria and adult filarial worms. It interferes with the metabolism of arachidonic acid and blocks the production of prostaglandins, resulting in capillary vasoconstriction and impairment of the passage of the microfilaria. Diethylcarbamazine also increases the adherence of microfilariae to the vascular wall, platelets, and granulocytes.

Diethylcarbamazine is absorbed from the gastrointestinal tract, and peak blood levels are obtained in 4 hours; the drug disappears from the blood within 48 hours. The intact drug and its metabolites are excreted in the urine.

Diethylcarbamazine is the drug of choice for certain filarial infections, such as *Wuchereria bancrofti*, *Brugia malayi* and *Loa loa*. Since diethylcarbamazine is not universally active against filarial infections, a specific diagnosis based on blood smears, biopsy samples, and a geographic history is important. Dosage should be adjusted in patients with renal impairment.

Caution is necessary when using this agent, particularly when treating onchocerciasis. The sudden death of the microfilariae can produce mild to severe reactions within hours of drug administration. These are manifested by fever, lymphadenopathy, cutaneous swelling, leukocytosis, and intensification of any preexisting eosinophilia, edema, rashes, tachycardia, and headache. If microfilariae are present in the eye, further ocular damage may result. Other side effects are relatively mild and range from malaise, headache, and arthralgias to gastrointestinal symptoms.

Ivermectin

Ivermectin (*Mectizan*) acts on parasite-specific inhibitory glutamate-gated chloride channels that are phylogenetically related to vertebrate GABA-gated chloride channels. Ivermectin causes hyperpolarization of the parasite cell membrane and muscle paralysis. At higher doses it can potentiate GABA-gated chloride channels. It does not cross the blood-brain barrier and therefore has no paralytic action in mammals, since GABA-regulated transmission occurs only in the central nervous system (CNS). Ivermectin is administered by the oral and subcutaneous routes. It is rapidly absorbed. Most of the drug is excreted unaltered in the feces. The half-life is approximately 12 hours.

Ivermectin has broad-spectrum activity in that it can affect nematodes, insects, and acarine parasites. It is the drug of choice in onchocerciasis and is quite useful in the treatment of other forms of filariasis, strongyloidiasis, ascariasis, loiasis, and cutaneous larva migrans. It is also highly active against various mites. It is the drug of choice in treating humans infected with *Onchocerca volvulus*, acting as a microfilaricidal drug against the skin-dwelling larvae (microfilaria). Annual treatment can prevent blindness from ocular onchocerciasis. Ivermectin is clearly more effective than diethylcarbamazine in bancroftian filariasis, and it reduces microfilaremia to near zero levels. In brugian filariasis diethylcarbamazine-induced clearance may be superior. It also is used to treat cutaneous larva migrans and disseminated strongyloidiasis. Its safe use in pregnancy has not been fully established.

The side effects are minimal, with pruritus, fever, and tender lymph nodes occasionally seen. The side effects are considerably less than those associated with diethylcarbamazine administration.

Suramin

Suramin is widely used as a macrofilaricide in human onchocerciasis, and its action on microfilariae also is considerable. It also is useful in the treatment of the hemolymphatic stage of African trypanosomiasis. Early treatment of the infection with suramin clears trypanosomes from the blood and lymphatics within 30 minutes and keeps them clear for approximately 3 months. Suramin inhibits a number of filarial enzymes involved with carbohydrate metabolism as well as the production of adenosine triphosphate (ATP). It is 35 times more inhibitory to the dihydrofolate reductase of *O. volvulus* than to the same enzyme in human tissue. It is a potent inhibitor of reverse transcriptase, the DNA polymerase of retroviruses, and also has some effects on the infective and cytopathic effects of HIV. It is being evaluated as an anticancer drug, reducing pain and delaying progression in hormone-refractory prostate cancer. Its most significant toxicity has been the development of severe polyradiculoneuropathy.

Pyrantel Pamoate

Pyrantel pamoate (*Antiminth*) is a agonist at the nicotinic acetylcholine receptor, and its actions result in depolarization and spastic paralysis of the helminth muscle. Its selective toxicity occurs primarily because the neuromuscular junction of helminth muscle is more sensitive to the drug than is mammalian muscle. This drug is administered orally, and because very little is absorbed, high levels are achieved in the intestinal tract. Less than 15% of the drug and its metabolites are excreted in urine.

Pyrantel pamoate is active against several roundworms: *A. lumbricoides*, *Ancylostoma duodenale*, *Necator americanus*, and *E. vermicularis*. Pyrantel is an alternative drug of choice in treating infections with *A. lumbricoides*, *E. vermicularis* (pinworms), and hookworms (*N. americanus* and *A. duodenale*). It is not recommended for pregnant patients or for children under age 1 year.

Although most of the drug remains in the intestinal lumen, enough can be absorbed systemically to cause headache, dizziness, and drowsiness. No major adverse effects have been reported on renal, hepatic, or hematological systems.

BENZIMIDAZOLES

Several benzimidazoles are in use for the treatment of helminthic infections. Three of these, mebendazole, thiabendazole and albendazole, are described in this section. They have a broad range of activity against many nematode and cestode parasites, including cutaneous larva migrans, trichinosis, disseminated strongyloidiasis, and visceral larva migrans. A fourth, triclabendazole, is considered as the drug of choice for *Fasciola hepatica* therapy.

Thiabendazole

Thiabendazole (*Mintezol*) inhibits fumarate reductase and electron transport-associated phosphorylation in helminths. Interference with ATP generation decreases glucose uptake and affects the energy available for metabolism. Benzimidazole anthelmintics as a class (e.g., thiabendazole, mebendazole, and albendazole), bind selectively to β -tubulin of nematodes (roundworms), cestodes (tapeworms), and trematodes (flukes). This inhibits microtubule assembly, which is important in a number of helminth cellular processes, such as mitosis, transport, and motility.

Thiabendazole is administered orally and is rapidly absorbed from the intestinal tract, with peak plasma levels achieved in 1 to 2 hours. The drug is metabolized in the liver and excreted in urine within 24 to 48 hours as glucuronide and sulfate esters. Approximately 10% is found in feces.

Thiabendazole shows a broad spectrum of activity against the following nematodes: *A. lumbricoides*, *N. americanus*, *A. duodenale*, *E. vermicularis*, *S. stercoralis*, and *Trichuris trichiura* (whipworm). It has largely been replaced with safer drugs for all but *Strongyloides* spp. At present, thiabendazole is the drug of choice for the treatment of cutaneous larva migrans (creeping eruption), strongyloidiasis, trichostrongyliasis, and trichinosis.

Anorexia, nausea, vomiting, drowsiness, and vertigo occur in up to one-third of patients. Diarrhea, pruritus,

rash, hallucinations, crystalluria, and leukopenia are less common; shock, hyperglycemia, lymphadenopathy, and Stevens-Johnson syndrome are rare. Some patients report that their urine smells like asparagus, a reaction related to excretion of the metabolite asparagine.

Mebendazole

Unlike thiabendazole, mebendazole (*Vermox*) does not inhibit fumarate reductase. While mebendazole binds to both mammalian and nematode tubulin, it exhibits a differential affinity for the latter, possibly explaining the selective action of the drug. The selective binding to nematode tubulin may inhibit glucose absorption, leading to glycogen consumption and ATP depletion.

Mebendazole is given orally; it is poorly soluble, and very little is absorbed from the intestinal tract. About 5 to 10%, principally the decarboxylated derivatives, is recovered in the urine; most of the orally administered drug is found in the feces within 24 hours.

Mebendazole is used primarily for the treatment of *A. lumbricoides*, *T. trichiura*, *E. vermicularis*, and hookworm infections, in which it produces high cure rates. It is an alternative agent for the treatment of trichinosis and visceral larva migrans. Owing to its broad-spectrum anthelmintic effect, mixed infections (ascariasis, hookworm infestation, or enterobiasis in association with trichuriasis) frequently respond to therapy. High doses have been used to treat hydatid disease, but albendazole is now thought to be superior.

Abdominal discomfort and diarrhea may occur when the worm load is heavy. Its use is contraindicated during pregnancy.

Albendazole

Albendazole appears to cause cytoplasmic microtubular degeneration, which in turn impairs vital cellular processes and leads to parasite death. There is some evidence that the drug also inhibits helminth-specific ATP generation by fumarate reductase.

Albendazole is given orally and is poorly and variably absorbed (<5%) because of its poor water solubility. Oral bioavailability is increased as much as five times when the drug is given with a fatty meal instead of on an empty stomach. Concurrent treatment with corticosteroids increases plasma concentrations of albendazole. The drug is rapidly metabolized in the liver to an active sulfoxide metabolite. The half life of the metabolites is 8 to 12 hours.

Albendazole has a broad spectrum of activity against intestinal nematodes and cestodes, as well as the liver flukes *Opisthorchis sinensis*, *Opisthorchis viverrini*, and *Clonorchis sinensis*. It also has been used successfully against *Giardia lamblia*. Albendazole is an effective treatment of hydatid cyst disease (echinococcosis), especially

when accompanied with praziquantel. It also is effective in treating cerebral and spinal neurocysticercosis, particularly when given with dexamethasone. Albendazole is recommended for treatment of gnathostomiasis.

TREATMENT FOR INFECTIONS CAUSED BY CESTODES

Cestodes, or tapeworms, are flattened dorsoventrally and are segmented. The tapeworm has a head with round suckers or sucking grooves. Some tapeworms have a projection (*rostellum*) that bears hooks. This head, or *scolex* (also referred to as the hold-fast organ), is used by the worm to attach to tissues. Drugs that affect the scolex permit expulsion of the organisms from the intestine. Attached to the head is the neck region, which is the region of growth. The rest of the worm consists of a number of segments, called *proglottids*, each of which contains both male and female reproductive units. These segments, after filling with fertilized eggs, are released from the worm and discharged into the environment.

Cestodes that parasitize humans have complex life cycles, usually requiring development in a second or intermediate host. Following their ingestion, the infected larvae develop into adults in the small intestine. Although most patients remain symptom free, some have vague abdominal discomfort, hunger pangs, indigestion, and anorexia, and vitamin B deficiency may develop. In some cestode infections, eggs containing larvae are ingested; the larvae invade the intestinal wall, enter a blood vessel, and lodge in such tissues as muscle, liver, and eye. Symptoms are associated with the particular organ affected.

Niclosamide Mechanism of Action

For many years, niclosamide (*Niclocide*) was widely used to treat infestations of cestodes. Niclosamide is a chlorinated salicylamide that inhibits the production of energy derived from anaerobic metabolism. It may also have adenosine triphosphatase (ATPase) stimulating properties. Inhibition of anaerobic incorporation of inorganic phosphate into ATP is detrimental to the parasite. Niclosamide can uncouple oxidative phosphorylation in mammalian mitochondria, but this action requires dosages that are higher than those commonly used in treating worm infections.

The drug affects the scolex and proximal segments of the cestodes, resulting in detachment of the scolex from the intestinal wall and eventual evacuation of the cestodes from the intestine by the normal peristaltic action of the host's bowel. Because niclosamide is not absorbed from the intestinal tract, high concentrations can be achieved in the intestinal lumen. The drug is not oxicidal.

Clinical Use

Niclosamide has been used extensively in the treatment of tapeworm infections caused by *Taenia saginata*, *Taenia solium*, *Diphyllobothrium latum*, *Fasciolopsis buski*, and *Hymenolepis nana*. It is an effective alternative to praziquantel for treating infections caused by *T. saginata* (beef tapeworm), *T. solium* (pork tapeworm), and *D. latum* (fish tapeworm) and is active against most other tapeworm infections. It is absorbed by intestinal cestodes but not nematodes. A single dose is usually adequate to produce a cure rate of 95%. With *H. nana* (dwarf tapeworm), a longer treatment course (up to 7 days) is necessary. Niclosamide is administered orally after the patient has fasted overnight and may be followed in 2 hours by purging (magnesium sulfate 15–30 g) to encourage complete expulsion of the cestode, especially *T. solium*, although this is not always considered necessary. Cure is assessed by follow-up stool examination in 3 to 5 months. With the availability of other agents, niclosamide is no longer widely used. The most widely employed agents are praziquantel and the benzimidazoles.

Adverse Effects

No serious side effects are associated with niclosamide use, although some patients report abdominal discomfort and loose stools.

TREATMENT FOR INFECTIONS CAUSED BY TREMATODES

Trematodes (flukes) are nonsegmented flattened helminths that are often leaflike in shape. Most have two suckers, one found around the mouth (oral sucker) and the other on the ventral surface. Most are hermaphroditic. The eggs, which are passed out of the host in sputum, urine, or feces, undergo several stages of maturation in other hosts before the larvae enter humans. The larvae are acquired either through ingestion of food (aquatic vegetation, fish, crayfish) or by direct penetration of the skin. After ingestion, most trematodes mature in the intestinal tract (intestinal flukes); others migrate and mature in the liver and bile duct (liver flukes), whereas still others penetrate the intestinal wall and migrate through the abdominal cavity to the lung (lung flukes). Diarrhea, abdominal pain, and anorexia are common symptoms associated with trematode infestation. Liver flukes may cause bile duct blockage, liver enlargement, upper right quadrant pain, and diarrhea. Liver function tests are usually altered. Lung flukes produce pulmonary symptoms such as cough, hemoptysis, and chest pain.

The *schistosomes* (blood flukes) are a distinct group of trematodes. These helminths are cylindrical at the anterior end and flattened at the posterior end. The

sexes are separate. The larvae penetrate skin that is in contact with contaminated water and then migrate through the lymphatics and blood vessels to the liver. After maturing, schistosomes migrate into the mesenteric or vesicular vein, where the adults mate and release eggs. The eggs secrete enzymes that enable them to pass through the wall of the intestine (*Schistosoma mansoni* and *Schistosoma japonicum*) or bladder (*Schistosoma haematobium*). In addition, some eggs may be carried to the liver or the lung by the circulation. Penetration of the skin is associated with petechial hemorrhage, some edema, and pruritus that disappears after about 4 days. Approximately 3 weeks after trematode penetration, patients complain of malaise, fever, and vague intestinal symptoms. With the laying of eggs, acute symptoms of general malaise, fever, urticaria, abdominal pain, and liver tenderness are reported. Diarrhea or dysentery is associated with infestations by *S. mansoni* and *S. japonicum*, whereas hematuria and dysuria are commonly caused by *S. haematobium*. In the chronic form of the disease, fibrosis and hyperplasia can occur in the tissues the eggs inhabit.

Praziquantel

The neuromuscular effects of praziquantel (*Biltricide*) appear to increase parasite motility leading to spastic paralysis. The drug increases calcium permeability through parasite-specific ion channels, so that the tegmental and muscle cells of the parasite accumulate calcium. This action is followed by vacuolization and the exposure of hitherto masked tegmental antigens, lipid-anchored protein, and actin. Insertion of the drug into the fluke's lipid bilayer causes conformational changes, rendering the fluke susceptible to antibody- and complement-mediated assault.

Praziquantel is readily absorbed (80% in 24 hours) after oral administration, with serum concentrations being maximal in 1 to 3 hours; the drug has a half-life of 0.8 to 1.5 hours. Its bioavailability is reduced by phenytoin or carbamazepine and increased by cimetidine. Dexamethasone decreases plasma praziquantel levels by 50%. Praziquantel is excreted by the kidneys.

Praziquantel is an extremely active broad-spectrum anthelmintic that is well tolerated. It is the most effective of the drugs used in the treatment of schistosomiasis, possessing activity against male and female adults and immature stages. Unlike other agents, it is active against all three major species (*S. haematobium*, *S. mansoni*, and *S. japonicum*). In addition, it has activity against other flukes, such as *C. sinensis*, *Paragonimus westermani*, *O. viverrini*, and the tapeworms (*D. latum*, *H. nana*, *T. saginata*, and *T. solium*). It is not as effective against *F. hepatica*. It is used effectively in the treatment of clonorchiasis and paragonimiasis and is an effective alternative agent to niclosamide in the treatment of tapeworm infestations.

Adverse reactions tend to occur within a few hours of administration. They include gastrointestinal intolerance with nausea, vomiting, and abdominal discomfort. This may be due to the liberation of helminth proteins from dead worms rather than any direct effect of the drug.

Oxamniquine

Oxamniquine (*Vansil*) is a tetrahydroquinoline that stimulates parasite muscular activity at low concentrations but causes paralysis at higher concentrations. The drug may act by esterification and binding of DNA, leading to the death of the schistosome by interruption of its nucleic acid and protein synthesis. The fluke may esterify oxamniquine to produce a reactive metabolite that alkylates parasite DNA. Resistance results from absent or defective esterifying activity of the drug. Oxamniquine has a restricted range of efficacy, being active only against *S. mansoni* infections.

Oxamniquine is given orally and is readily absorbed from the intestinal tract. Peak concentrations in plasma are obtained in about 3 hours. The drug is excreted in urine mostly as a 6-carboxyl derivative.

Side effects include CNS toxicity with unsteadiness and occasionally seizures, especially in patients with a history of seizures. It is contraindicated in pregnancy.

Bithionol

Bithionol (*Actamer*) is a phenolic derivative whose mode of action is related to uncoupling of parasite-specific fumarate reductase-mediated oxidative phosphorylation. The drug is administered orally and is absorbed from the intestinal tract. Peak blood levels are achieved in 4 to 8 hours. Excretion is mainly by the kidneys.

Bithionol is used in treatment of *F. hepatica* infections and as an alternative to praziquantel in the treatment of infestation by *P. westermani*. It is highly active against the adult worm but exerts no action against the migratory stages. A second course of treatment is required for complete cure in 20 to 30% of patients.

Side effects are generally mild and transient; they include nausea, vomiting, diarrhea, headache, dizziness, urticaria, and other skin rashes in 50% of patients.

Metrifonate

Metrifonate is an organophosphorous compound that is effective only in the treatment of *S. haematobium*. The active metabolite, dichlorvos, inactivates acetylcholinesterase and potentiates inhibitory cholinergic effects. The schistosomes are swept away from the bladder to the lungs and are trapped. Therapeutic doses produce no untoward side effects except for mild cholinergic symptoms. It is contraindicated in pregnancy, previous insecticide exposure, or with depolarizing neuromuscular blockers. Metrifonate is not available in the United States.

Study QUESTIONS

- A migrant Mexican worker in Texas has had fever, myalgias, and headache for 10 days. Initially he thought he was recovering from stomach flu; his examination is significant for conjunctival hemorrhage, bilateral periorbital edema, and severe tenderness of neck muscles and jaws. A diagnosis of trichinosis is considered. Which of the following aspects of trichinosis are particularly important?

 - Eggs in the feces are almost always present.
 - A negative biopsy of muscle excludes the infection.
 - Suramin is used in its treatment with considerable success.
 - Mebendazole plus steroids for severe symptoms may be indicated.
 - Thiabendazole is not effective.
- While serving with Doctors Without Borders in Malaysia, you are seeing a patient who has intermittent cough, shortness of breath, and wheezing. Investigation reveals eosinophilia, absence of microfilaria in the blood, and a chest radiograph showing scattered reticulonodular infiltrates. Which of the following points is the most important if your diagnosis is tropical pulmonary eosinophilia (TPE)?

 - Symptoms get progressively worse and are not fluctuating.
 - Absence of microfilariae in blood makes the diagnosis unlikely.
 - Eosinophilia, although commonly seen, is not usually very high.
 - Ivermectin is the drug of choice.
 - Diethylcarbamazine is effective therapy.
- A 10-year-old girl in North Carolina has had abdominal pain and cramps for the past few days. Her examination produced normal findings except for nonspecific abdominal discomfort with a complete blood count showing anemia and 22% eosinophils (elevated). A stool specimen revealed the characteristic eggs of *A. lumbricoides*. The drug of choice in treating this is

 - Piperazine
 - Pyrantel pamoate
 - Mebendazole
 - Albendazole
 - Thiabendazole
- A 15-year-old Hispanic boy is brought in with seizures. No prior history of fever, chills, trauma, or headaches was reported on admission. Computed tomography reveals three ring-enhancing cystic lesions in the brain parenchyma, and a diagnosis of neurocysticercosis is made. Initial therapy in the management of this condition should include

 - Niclosamide
 - Praziquantel
 - Albendazole
 - Surgery
 - Thiabendazole
- A patient with a history of frequenting sushi bars on the West Coast is admitted with abdominal pain, weakness, irritability, and dizziness. His neurological examination produced normal findings even though he had some complaints of paraesthesias. Diphyllbothriasis is diagnosed after stool studies are done. Management of this tapeworm infection is with

 - Praziquantel or niclosamide
 - Ivermectin
 - Albendazole
 - Vitamin B₁₂
 - Piperazine

ANSWERS

- D.** Trichinosis should be suspected in a patient who has any of the cardinal features of periorbital edema, myositis, fever, and eosinophilia. Infection is acquired after consumption of inadequately cooked pork, bear, or walrus infected with viable larvae. Stool examination does not contain the eggs of the parasite but may contain larvae. Muscle biopsy from a tender, swollen muscle (preferably deltoid or gastrocnemius) may establish the diagnosis, but a negative biopsy does not exclude this infection, especially in light parasitemias. Suramin is not used in trichinosis. Although thiabendazole is effective, mebendazole is the drug of choice, and frequently steroids are also used for severe symptoms.
- E.** TPE is caused by microfilariae in the lungs and hyperimmune responsiveness to bancroftian or malayan filariasis. Paroxysmal respiratory symptoms may fluctuate in severity. Eosinophilia, almost always present, is usually very high, and the absence of microfilariae in the blood does not rule out TPE. A presumptive clinical diagnosis can be made by response to therapy without a lung biopsy. Diethylcarbamazine for 14 days is an effective therapy that can be repeated if symptoms persist. The role of ivermectin in TPE has not been established.
- D.** In the United States intestinal helminths produce mild disease with nonspecific findings. Piperazine or pyrantel pamoate may be used for the treatment of ascariasis. Mebendazole is an effective drug to be taken for 3 days. Thiabendazole is not used in this condition but is used commonly in strongyloidiasis. Albendazole at a single dose of 400 mg is the preferred mode of therapy. It is a

convenient agent for mass treatment programs that target school children in endemic areas.

4. **C.** Albendazole (approved by the U. S. Food and Drug Administration for this indication) has a 90% efficacy rate in neurocysticercosis. The initial therapy of parenchymal disease with seizures should focus on symptomatic treatment with anticonvulsants. However, while destroying the cyst, albendazole may result in a profound parenchymal brain reaction and in severe neurological defects or retinal damage (i.e., loss of vision and optic neuritis) in eye lesions. Corticosteroids should be given concomitantly in these situations. In ventricular disease with obstructive hydrocephalus, surgery with shunting can be helpful. Treatment with niclosamide or praziquantel should be considered later to eliminate the adult tapeworm in the gut and prevent further reinfection. Neither piperazine nor thiabendazole is effective in this indication.
5. **A.** *D. latum*, the fish tapeworm acquired from consumption of raw fish in endemic areas, is best treated with praziquantel or niclosamide. Ivermectin is effective for filarial infections, especially *O. volvulus*. Albendazole, although highly effective in some tapeworm infections, is not used in fish tapeworm infections. Vitamin B₁₂ deficiency is due to the parasite competing with the host for the vitamin, sometimes absorbing 80% of ingested amounts. Patients may develop megaloblastic anemia and mild to severe central nervous system manifestations (subacute combined degeneration of spinal cord). Mild B₁₂ deficiency should be treated

with vitamin injections in addition to specific drug therapy. Piperazine, a roundworm treatment, is not used for this indication.

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CASE Study An Extensive History: Always Useful

The patient is a 64-year-old male resident of a mental institution with a chief complaint of cough and rash. He was a Vietnam veteran with a history of non-Hodgkin's lymphoma treated with combination chemotherapy containing prednisone. Two months later he developed a progressive cough, dyspnea, midepigastic pain, diarrhea, and what he describes as an itchy rash on the lower abdominal wall. The patient's physical examination revealed a thin man in mild distress with a temperature of 100°F (37.8°C), blood pressure 124/70 mmHg, pulse 120, and respiratory rate 25 per minute. Rales were heard throughout his lung fields. His abdomen was soft and flat, with hypoactive bowel sounds. There was marked tenderness without rebound noted on palpation of the epigastric

area, with no masses. His skin examination revealed a migratory serpiginous urticarial rash distributed over the lower abdomen, lower trunk, and buttocks (larva currens). Examination of the peripheral blood showed a white count of 16,190/mm³ (normal, 4,000–12,000/mm³) and eosinophils 66% (markedly elevated). His chest radiograph showed diffuse pulmonary infiltrates. A transbronchial lung biopsy showed eosinophilic granulomatous inflammation of the bronchial epithelium. Bronchoalveolar lavage revealed *S. stercoralis* filariform larvae. Microscopic examination of the stool revealed rhabditiform larvae of *S. stercoralis*. Based on the knowledge of *S. stercoralis* hyperinfection syndrome, which agent or agents would be a logical choice for treatment of this life-threatening disease?

CASE Study An Extensive History: Always Useful

ANSWER: Until recently thiabendazole was the drug of choice to treat strongyloidiasis. Parasite eradication in uncomplicated infections is approximately 90% or higher. However, *S. stercoralis* is a significant health risk in many developing countries and even in parts of eastern Kentucky and rural Tennessee. It presents a serious potential for severe disease in the many military servicemen who were stationed in Southeast Asia during World War II and the Vietnam era. In fact, it was first described in 1876 as “diarrhea of China” in French colonial troops in Indochina by Louis Alexis Norman, physician first class in the French Navy. It is acquired by infective larvae that penetrate the skin and frequently maintain a low level of autoinfection asymptotically for many decades. Hyperinfection and widespread dissemination may occur following immunosuppression or chronic disease. Prompt

treatment can be lifesaving, as hyperinfection syndrome is associated with mortality rates up to 86%. Steroids may suppress the eosinophil response normally seen in this disease, so an appropriate history must be taken and characteristic intestinal and skin findings examined, and a high index of suspicion is needed to make a timely diagnosis of patients who spent time in endemic areas. In immunocompromised hosts, persistent infection and relapse may complicate therapy with thiabendazole (even when given over 7 to 10 days). Alternative therapy with ivermectin appears as effective (64–100% cure rates) as thiabendazole with fewer side effects. Other drug choices are albendazole (cure rates of 38–81%) and mebendazole, but these have not been approved by the FDA for this indication.