Classification of Parasitic Diseases

2

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Classification

Parasites are primarily divided into ectoparasites/arthropods, which live on the surface of other organisms, such as lice or ticks, and (endo)parasites, which live within organisms. Parasites occur in nature in two major forms, namely, protozoa, which are single-cell eukaryotic organisms, and helminths, which are multicellular organisms. Helminths are otherwise called worms. Protozoa can be further divided based on their mode of reproduction and their means of movement into amebae/Sarcodina, flagellates/Mastigophora, sporozoans/Apicomplexa, and ciliates/Ciliophora. The first two belong to the same phylum. Helminths can be divided into flatworms and nematodes/roundworms. Flatworms are further subdivided into tapeworms/cestodes and flukes/trematodes [1–3]. Ectoparasites/arthropods will not be covered in this chapter. Common terms in parasitology and their respective definitions are shown in Table 2.1.

Diagnosis of Parasitic Diseases

Parasites most often are large enough and have a typical morphology, so diagnosis of parasitic diseases relies primarily on microscopy. However, antigen, antibody tests, as well as molecular methods are also used for the identification of parasites and disease diagnosis [1, 3].

A. *Microscopy* continues to be the mainstay for the detection and identification of most parasitic diseases. Microscopic examination can be performed either directly from the collected specimen or after concentration, and the use of specific staining (i.e., Giemsa, hematoxylin, trichrome stain) enhances sensitivity.

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Table 2.1 Commonly used terms in parasitology and their respective explanations

Term	Definition
Trophozoite	Motile, reproducing form
Cyst	Nonmotile, nonreproducing, usually surrounded by a thick membrane
Promastigotes	Flagellated forms
Amastigotes	Non-flagellated forms
Larva(e)	Immature form(s) (helminths)
Definite host	Sexual phase occurs
Intermediate host	Asexual phase occurs
Reservoir	Population of organisms in which the pathogen (naturally) lives
Obligate parasite	Needs the host to complete its life cycle
Facultative parasite	It can survive both as free-living organism and within the host

Determination of the morphologic characteristics of protozoa and adult forms of helminths, as well as specific features of eggs or larvae, allows the identification of each parasite. Specimens should be examined promptly, i.e., stool within 1 hour from collection. Since cysts are passed intermittently in the stools, at least three separate specimens should be examined.

B. *Antigen detection* is possible for *Entamoeba histolytica*, *Giardia lamblia*, *Plasmodium* spp., *Cryptosporidium* spp., and *Trichomonas vaginalis* with good sensitivity.

C. *Nucleic acid-based tests* are routinely used for *Trichomonas vaginalis* and *Plasmodium* spp. These tests may also be useful for the detection of parasites like *Trypanosoma* spp., *Toxoplasma gondii*, or *Leishmania* spp., when only few organisms may be present in a biologic sample. For the detection of other parasites, nucleic acid-based tests are available in reference laboratories.

D. *Serology* may be useful for diagnosis in non-endemic regions, as a large percent of the population may have a positive serology in endemic countries.

E. *Culture* is rarely possible for parasites, and if so, it is available usually only at reference laboratories. One exception is *Trichomonas vaginalis*, which can be cultured in commercially available media.

Protozoa

Taxonomic classification of protozoa has changed with the application of phylogenetic analysis, and some organisms formerly categorized as protozoa have been found to be genetically closer to fungi, for example, *Pneumocystis jirovecii* and *Microsporidia* [4, 5]. A clinically relevant classification of protozoa entails the separation according to the affected organ system and/or their mode of transmission (Table 2.2).

Amebae typically use pseudopodia and/or protoplasmic flow to move. The main representative organisms are *Entamoeba*, *Acanthamoeba*, and *Naegleria*. Flagellates are characterized by possessing one or more flagella(s), which is a structure resembling a whip and helps the parasite move. They also sometimes contain an undulating membrane (i.e., trypanosomes). Medically important organisms in this group

Table 2.2 Major protozoa, which cause disease in humans according to the site of infection

Site of infection	Protozoa	Mode of transmission
Intestinal protozoa	*Entamoeba histolytica*	Fecal-oral/ingestion of cysts
	Giardia lamblia	Fecal-oral/ingestion of cysts
	Cryptosporidium spp. (*Cryptosporidium hominis*, *Cryptosporidium parvum*)	Fecal-oral/ingestion of oocysts
	Cystoisospora species (*Cystoisospora belli*)	Fecal-oral/ingestion of oocysts
	Cyclospora species (Cyclospora cayetanensis)	Fecal-oral/ingestion of oocysts
	Balantidium coli	Fecal-oral
Urogenital Protozoa	*Trichomonas vaginalis*	Sexual transmission
Blood and tissue Protozoa	*Plasmodium* species	Female *Anopheles* mosquito
	Babesia species (*Babesia microti*)	Ticks, blood transfusion
	Toxoplasma gondii	Ingestion of parasites from undercooked meat, ingestion of oocysts after contact with cat feces, blood transfusion, transplacental
	Trypanosoma species *T. cruzi.* *T. brucei gambiense.* T. brucei gambiense.	Reduviid (kissing) bug, blood transfusion, transplacental Tsetse fly Tsetse fly
	Leishmania species *L. donovani* (visceral leishmaniasis). *L. tropica*, *L. major* (Old World cutaneous leishmaniasis). *L. mexicana* complex (New World cutaneous leishmaniasis). *L. aethiopica*, *L. Mexicana pifano* (disseminated cutaneous leishmaniasis). *L. braziliensis* complex (mucocutaneous leishmaniasis).	Sandfly
	Acanthamoeba	Exposure to contaminated water usually after swimming in freshwater lakes, hot springs, rivers, and swimming pools and/or eye trauma
	Naegleria	Inhalation of contaminated water usually after swimming in freshwater lakes, hot springs, rivers, and swimming pools
	Sarcocystis spp.	Food-borne (meat)

are (A) flagellates which involve the intestinal and genitourinary system, like *Giardia* and *Trichomonas*, respectively, and (B) flagellates which circulate in the blood and can invade tissues, like *Trypanosoma* and *Leishmania* [2, 6].

Sporozoa have a complex life cycle involving intermediate hosts, which is characterized by sexual and asexual reproductive phases. These parasites are almost always intracellular. Major organisms in this group are *Plasmodium*, *Babesia*, *Cryptosporidium*, *Cyclospora*, and *Toxoplasma*. Ciliates possess two types of nuclei in each cell, and they have cilia, organized in rows or patches. The only medically important human parasite of this group is *Balantidium coli*, a very big cell which can be found in the intestinal tract of infected individuals, though actual disease in humans is rare [2, 6].

A separate group, formerly categorized as Sporozoa, are Microsporidia. However, recent genomic analysis has demonstrated that these organisms are more closely related to fungi [5]. These diverse spore-forming organisms possess a characteristic polar filament (or polar tube), and they can infect a large variety of hosts. The main species causing human disease are *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*, and they are opportunistic pathogens [2].

Amebae

Entamoeba

The life cycle of *Entamoeba histolytica* consists of two stages, the trophozoite and cyst stage. Cysts are acquired by ingestion of fecally contaminated food or water. Within the intestine, cysts differentiate to form trophozoites (ileum), which cause dysentery by invading the colonic mucosa (cecum and colon), and through which they can spread via the bloodstream to the liver, or less commonly to the lung and brain. Cysts and trophozoites are being passed with feces to the environment, where cysts can survive, whereas trophozoites are killed by exposure to air. Anal-oral transmission in men who have sex with men (MSM) has also been reported. Humans are the only host [4, 5].

Infection with *E. histolytica* is asymptomatic in 90% of cases. The clinical syndromes of amebiasis include acute intestinal amebiasis (amebic dysentery), chronic amebiasis, and liver abscess. Less commonly, a granulomatous lesion, called an ameboma, may be found in the cecum or retrosigmoid area and must be differentiated from colonic adenocarcinoma. Liver abscess can present with fever, right-upper-quadrant pain, weight loss, and hepatomegaly. Aspiration fluid from the abscess is thick, contains necrotic material, and has a characteristic brownish color, resembling anchovy paste [4, 5].

Diagnosis is made by microscopic examination of the stool for trophozoites or cysts. Stool is usually heme positive, and there is paucity of neutrophils. Trophozoites contain ingested red blood cells. Their nucleus has a characteristic appearance with small central nucleolus and fine chromatin granules at the border of the nuclear membrane. Cysts have small size and contain four nuclei, which is an important

diagnostic characteristic. Trophozoites are rare in liver abscess aspirates because they are usually present near the capsule. Cysts of *E. histolytica* and *E. dispar* are morphologically indistinguishable, but stool ELISA for Gal/GalNAc lectin can differentiate the two species, since it is only positive in *E. histolytica*. Antibodies against trophozoite antigens do not offer lifelong protection, and reinfection can occur. However, serologic tests can be used for the diagnosis of invasive amebic disease [1–4].

Free-living amebae* are *Acanthamoeba*, *Naegleria*, and *Balamuthia

The first two are found worldwide and have been isolated from fresh water lakes, taps, swimming pools, hot springs, as well as air conditioning and heating units. *Balamuthia* has been found in soil.

Naegleria causes meningoencephalitis following either aspiration of contaminated (with cysts or trophozoites) water or inhalation of contaminated dust. *Naegleria* invades the meninges via the nasal mucosa and cribriform plate. The presentation and findings resemble that of purulent bacterial meningitis, cranial nerve palsies are common, and progression can be rapid with an overall poor prognosis. Motile trophozoites in CSF wet mount confirm the diagnosis, while serology is not helpful [2, 4, 6].

Balamuthia mandrillaris also causes amebic meningoencephalitis with a usually subacute course but grave prognosis. Brain imaging yields hypodense space-occupying lesions, and CSF shows pleocytocis with a neutrophilic or monocytic predominance [2, 4, 6].

Acanthamoeba causes granulomatous amebic encephalitis and keratitis**.** Granulomatous amebic encephalitis occurs most commonly in immunosuppressed or debilitated patients and has a subacute course with headache, altered mental status, cranial nerve palsies, focal neurologic deficit, or ataxia. Diagnosis is made by detection of trophozoites or cysts in CSF or biopsy specimens, and prognosis is extremely poor. Keratitis by *Acanthamoeba* can occur via trauma and exposure to contaminated water or most commonly with the use of extended-wear contact lenses (while swimming or sub-optimally disinfected). *Acanthamoeba* cysts can be identified in corneal scrapings or biopsy specimens. Corneal invasion and abscess formation can lead to vision loss, and these infections are hard to treat [2, 4, 6].

Flagellates

Trypanosoma

The *Trypanosoma* subspecies which elicit disease in humans are (a) *Trypanosoma cruzi*, which is the cause of Chagas disease (American trypanosomiasis), (b) *Trypanosoma brucei gambiense*, and (c) *Trypanosoma brucei rhodesiese*. The last two are the etiologic agents of sleeping sickness (African trypanosomiasis).

T. cruzi is transmitted by the triatomine insects (*reduviid bugs*), which acquire the parasite after feeding from infected humans or animals. Parasites multiply in the insect's gut and are then released with bug feces onto the skin or mucosa of the host at the time of the insect bite. Transmission has also been reported with organ donation, blood transfusion, vertically from mother to child, as well as after laboratory accident exposure. Clinical disease can be divided into three entities, an acute self-limiting febrile illness, an indeterminate phase of asymptomatic Chagas disease (detectable antibodies and minimal, if any, parasitemia), and in few patients a clinical syndrome with gastrointestinal and cardiac involvement and serious prognosis. Megaesophagus can result in severe reflux and aspiration pneumonitis; megacolon presents with constipation and sometimes obstruction, volvulus, and sepsis; and cardiac disease includes rhythm disturbances, dilated cardiomyopathy, thromboembolism, and heart failure [7, 8]. Detection of parasites by microscopic examination of blood or of Giemsa-stained thin and thick blood smears as well as hemoculture or PCR can confirm the diagnosis of acute Chagas, whereas serology is the test of choice for the diagnosis of chronic Chagas disease [3, 7, 8].

T. brucei gambiense (West African) and the *T. brucei rhodesiense* (East African) are morphologically indistinguishable and are transmitted to humans via infected tsetse flies (*Glossina* genus). The parasites multiply in the insect's midgut and then migrate to the salivary gland from where they are released to inoculate the host's skin at the time of the blood meal. What is interesting about these trypanosomes is that they can evade immune response mechanisms for a long period by extensive antigenic variation of their surface glycoproteins [8, 9]. Human African trypanosomiasis or sleeping sickness initially presents as an acute febrile illness that can lead many years later to severe neurologic impairment and death, in untreated patients. Apart from having a different epidemiology, the clinical syndromes associated with the two subspecies are quite distinct. A painful chancre may appear at the inoculation site, and stage I disease is characterized by fever, lymphadenopathy, as well as generalized symptoms, hepatosplenomegaly, and tachycardia. Stage II disease involves the CNS and is more acute (<9 months) in East African trypanosomiasis, whereas in West African, it can occur after many months or years. Neurologic symptoms comprise of daytime somnolence, progressive indifference, loss of speech, extrapyramidal signs, ataxia, and progressive neurologic impairment. Diagnosis is made by detection of the parasites after microscopic examination of the blood, buffy coat, bone marrow, lymph node aspirate, chancre aspirate, or CSF. Serology has variable sensitivity and specificity [2, 8, 9].

Leishmania

Leishmania species are intracellular protozoa, transmitted by phlebotomine sandflies and cause different clinical syndromes according to the *Leishmania* species, the geographic location, and host response. *Leishmania* infect macrophages in the dermis, nasopharyngeal mucosa, and reticuloendothelial system resulting in

cutaneous, mucosal, and visceral leishmaniasis (kala-azar) respectively. Sandflies at the time of the blood meal regurgitate the promastigotes into the skin of the host, and these are phagocytosed by macrophages where they are transformed to amastigotes. When ingested by sandflies, amastigotes transform to promastigotes. The clinical course of the infection largely depends on the balance between T_H1 and T_H2 immune responses [2, 10, 11]. An extensive review of these syndromes is beyond the scope of this chapter. The major *Leishmania* species with their respective clinical syndromes are included in Table 2.2. Diagnosis relies on detection of the parasite by microscopic examination of bone marrow aspirates, dermal scrapings, impression smears of biopsy specimens, or other tissue specimens. Also, molecular methods have been developed for the detection and identification of *Leishmania* species [1, 3].

Giardia

Giardia lamblia causes giardiasis, which presents as diarrhea and is one of the most common parasitic diseases in developed and developing countries. Transmission occurs with ingestion of cysts (as low as ten) from fecally contaminated water or food. Trophozoites are released from cysts in the small intestine and attach to the epithelium, but they do not spread hematogenously. Cysts, which are excreted in stool, can survive in the environment, especially in cold fresh water, and they are killed by boiling or removed by water filtration. Most commonly, giardiasis causes epidemics in day-care centers, and episodic infections have been reported. Diarrhea is associated with abdominal pain, bloating, flatus, belching, and nausea and usually lasts more than 1 week, and chronic or intermittent symptoms are more frequently encountered than with other infectious causes [2, 12]. Diagnosis is made by detection of cysts or trophozoites in stool with microscopy or detection of parasite antigen in feces. Alternatively, parasites may be detected in duodenal fluid or biopsy of the small intestine. Giardia cysts contain four nuclei and are approximately 8–12 μm × 7–10 μm in size, whereas trophozoites are characteristically pear-shaped and flattened and contain two nuclei and four pairs of flagella [2, 3].

Trichomonas

Trichomonas vaginalis is transmitted with sexual contact and causes vaginitis in women and urethritis, epididymitis, or prostatitis in men. *T. vaginalis* is a motile, pear-shaped, 10 × 7 μm in size organism, with a central nucleus and four anterior flagella. It only exists as a trophozoite, which can be detected by microscopic examination of wet mount of vaginal fluid or prostatic secretions, albeit with moderate sensitivity. Alternatively, direct immunofluorescence staining, which has better sensitivity, can be used, or culture, which however is more time-consuming and usually not routinely available [12].

Sporozoa

Babesia

Babesiosis is a vector-borne disease transmitted by ticks, while the reservoir of Babesia species is wild and domestic animals. Most of the documented cases in the United States are due to *Babesia microti*, while in Europe the infection is rare, and the most commonly isolated *pathogen is Babesia divergens.* Transmission can occur also by blood transfusion in endemic areas. Infection in immunocompetent hosts is usually asymptomatic or self-limiting, but it can be life-threatening (hemolytic anemia, disseminated intravascular coagulation, multi-organ failure) in asplenic, immunocompromised, or elderly individuals. Diagnosis is made by the detection of ring forms or characteristic tetrads (resembling a Maltese cross) in thin blood smears. Other tests are the immunofluorescence antibody test (IgG) for *B. microti*, which however cannot differentiate past from active infection and PCR-based species-specific tests [2, 13].

Toxoplasma

Toxoplasma gondii is an intracellular parasite that infects mammals and birds. Its life cycle consists of two stages, the nonfeline and feline stage. During the nonfeline stage, cysts are ingested by the host, and after exposure to the acidic gastric secretions, sporozoites are released and infect the epithelial cells of the small intestine. There, they are transformed into tachyzoites which multiply within the cells, until these rupture, releasing more parasites which can reach other tissues via the bloodstream. Cyst forms containing bradyzoites (slowly replicating parasites) can persist in some organs like the brain and muscle. The feline stage takes place within the parasite's definite host, the cat. Ingestion of cysts is followed by the formation of gametes, whose fusion results in a zygote which is secreted in the feces in the form of unsporulated cyst (envelope only), which then transforms to sporulated oocyst or sporozoites after exposure to air. Transmission in humans is mainly through ingestion of oocysts from contaminated soil or bradyzoites (tissue cysts) from undercooked meat. Transmission also occurs transplacentally, and gestational age at the time of (primary) infection is critical in predicting the risk of transmission and the risk of congenital infection [2, 14].

In immunocompetent individuals, *T. gondii* most commonly causes an asymptomatic self-limiting disease. It can also manifest with lymphadenopathy, usually cervical, and generalized symptoms. Complications such as pneumonia, myocarditis, pericarditis, and meningoencephalitis or encephalopathy are rare. Immunocompromised individuals specifically patients with AIDS or lymphoproliferative disorders receiving chemotherapy can develop clinical toxoplasmosis, most commonly (more than 50%) with CNS involvement manifesting as meningoencephalitis or ring enhancing mass-like lesions. Ocular toxoplasmosis represents 35% of all chorioretinitis cases in the United States and Europe and is believed to result from congenital infection and to a much lesser extent from acquired infection [14, 15].

Diagnosis of toxoplasmosis can be made by detection of *T. gondii* tachyzoites in body fluids or lymph nodes. The isolation of cysts from tissues is not diagnostic of acute infection. However, more commonly, serology (IgG, IgM, IgA) is used for diagnosis, and molecular PCR-based techniques are also available for the detection of *T. gondii* in biologic samples. Imaging of the brain with CT, MRI, or CT/SPECT is necessary for the evaluation and diagnosis of CNS toxoplasmosis [3].

Cryptosporidium

The most common encountered *Cryptosporidium* species in human infections are *Cryptosporidium hominis* and *Cryptosporidium parvum*, which cause a self-limited diarrheal disease in immunocompetent individuals, while they can have a more severe and protracted course in immunocompromised patients, including those with AIDS. Transmission occurs via the fecal-oral route with the ingestion of oocysts, which release sporozoites that later form into merozoites, which infect epithelial cells. Infections can occur in travelers, day-care centers, and water recreational facilities [16–18]. Cysts are small (4–5 μm) and may not be easily detected in routine fecal preparations; therefore modified acid-fast stain or direct immunofluorescence stain and enzyme immunoassays may be needed for diagnosis [16].

Cystoisospora, Cyclospora

Isospora and *Cyclospora* also cause diarrheal disease after ingestion of oocysts. Similar to *Cryptosporidium*, patients with HIV/AIDS may have a more protracted course with weight loss, fatigue, and chronic diarrhea. Modified acid-fast stain may help in the diagnosis of *Isospora* large cycts (approximately 25 μm) and *Cyclospora* cycts (8–10 μm), although the latter stain variably but they can be seen under UV light microscopy.

Plasmodium

Plasmodium species are the etiologic agents of malaria, which is endemic in more than 100 countries worldwide. The five human *Plasmodium* species, namely, *Plasmodium falciparum*, *Plasmodium malaria*, *Plasmodium ovale*, *Plasmodium vivax*, and *Plasmodium knowlesi*, are transmitted by the bite of the female *Anopheles* spp. mosquito. At the time of the blood meal, infected mosquitos inoculate sporozoites, which travel via the bloodstream to the liver, where they replicate in hepatocytes (intrahepatic or proerythrocytic schizogony). Merozoites are released from the liver cells into the bloodstream and infect red blood cells (intraerythrocyte stage), where they transform into trophozoites and replicate every 48 to 72 hours. At the end of this stage, schizonts burst and release merozoites, which again infect other RBCs. After asexual reproduction, some of the parasites transform into distinct sexual forms, the gametes, which are ingested by mosquitoes upon their blood meal.

Female and male gametes form a zygote at the midgut of the insect, which matures into an ookinete and then an oocyst, which releases sporozoites who then migrate at the salivary gland. The periodic release of merozoites in the bloodstream causes periodic fever and chills, which is typical for malaria. Malaria presents with fever, chills or rigors, malaise, headache, muscle aches, arthralgias, abdominal pain, or discomfort, and patients have anemia and splenomegaly. Severe malaria, which is almost always caused by *P. falciparum*, may result in cerebral malaria, hypoglycemia, acidosis, renal failure, pulmonary edema, and liver dysfunction and can be complicated with septicemia [2, 19, 20]. An extensive review of these syndromes is beyond the scope of this chapter. Diagnosis is confirmed with microscopy of Giemsa-stained thin and thick peripheral blood smears, and Plasmodium species can be differentiated based on their morphology. Antigen-based diagnostic tests are also routinely used as well as molecular PCR-based methods [3].

Helminths

Helminths comprise of flatworms (Platyhelminthes) and roundworms (nematodes).

Flatworms (Platyhelminthes) are further divided into two classes: Cestoda (Digenea, tapeworms) and Trematoda (flukes) (Table 2.3).

Table 2.3 Major flatworm infections, which cause disease in humans, according to the site of infection

Site of infection	Flatworm	Mode of transmission
A. Cestodes (tapeworms).		
Intestinal tapeworms	*Taenia saginata* (beef tapeworm)	Ingestion of larvae in undercooked beef
	Taenia solium (pork tapeworm)	Ingestion of larvae in undercooked pork, ingestion of eggs (fecal-oral)
	Diphyllobothrium latum (fish tapeworm)	Ingestion of larvae in undercooked fish
	Hymenolepis nana (dwarf tapeworm)	Fecal-oral
Somatic/tissue tapeworms	*Echinococcus* spp. *Echinococccus granulosus* *Echinococcus multilocularis*	Ingestion of eggs
	Taenia solium (pork tapeworm)	Ingestion of larvae in undercooked pork, ingestion of eggs (fecal-oral)
B. Trematodes (flukes).		
Intestinal flukes	*Fasciolopsis buski*	Fecal-oral
	Heterophyes heterophyes	Fecal-oral
Liver flukes	*Fasciola hepatica*	Ingestion of cysts (watercress)
	Clonorchis sinensis	Ingestion of undercooked fish
Lung flukes	*Paragonimus* spp. (*Paragonimus westermani*)	Ingestion undercooked crayfish or crabs
Blood flukes	*Schistosoma* spp. *Schistosoma mansoni* *Schistosoma haematobium* *Schistosoma japonicum*	Skin penetration

Trematodes (Flukes)

Trematodes are parasitic species that affect a considerable number of people worldwide and cause significant morbidity and mortality. For clinical purposes, they can be divided into two large categories: intestinal and tissue flukes. Tissue flukes can be further divided into three categories: blood flukes, hepatic/biliary flukes, and lung flukes.

They have common morphological characteristics, including the shape of the body and the suckers.

Except schistosomes, all trematodes are hermaphroditic. Male and female schistosomes coexist in the same body. The life cycle of the trematodes includes an asexual part in the intermediate host, usually specific species of freshwater snails, and a sexual part in the definitive host, which is humans. The life cycle begins with the ingestion of the cercaria or through skin penetration (schistosomes). Cercaria are produced during the asexual stage in the snails. After ingestion, adult trematodes proceed to the sexual production of eggs which are excreted with feces, sputum, or urine, according to the type and the location of the fluke. Then the eggs infect the intermediate hosts, which are snails and some species of fish and crabs.

The most important pathogens of this category are *Schistosoma* species (blood flukes), *Clonorchis sinensis* (liver flukes), and *Paragonimus westermani* (lung flukes) [21].

Schistosoma Species (Blood Flukes)

Schistosomiasis is caused by five species of the genus *Schistosoma*. The most important ones are *S. mansoni* and *S. japonicum*, which affect the intestinal tract and the liver, and *S. haematobium,* which affects the urinary tract. As mentioned above, the free-swimming tailed cercariae of the parasite penetrate the skin in order to infect humans. As they enter the subcutaneous tissue, they leave their tail and transform into schistosomula. The schistosomulas migrate through the veins to the liver, where the parasite matures to the adult fluke which contains the male and the female attached to the same body. After the maturity (in about 6 weeks), the parasite migrates through the portal circulation to the vesical (*S. haematobium*) and the intestinal (mesenteric) veins. The adult flukes can reach up to 2 cm in length. Serologic. After mating, the parasites produce and deposit their eggs intravascularly. These penetrate the endothelium and reach the genitointestinal tissues, from where they are finally excreted into feces and urine [2, 22].

At the penetration site, a localized erythema or dermatitis can be observed. Acute infection (Katayama syndrome) is characterized by systematic symptoms like fever, headache, malaise, and cough. Diarrhea may be present, and hepatosplenomegaly, lymphadenopathy, and eosinophilia during the migration stage are common findings. In chronic schistosomiasis, patients can be asymptomatic. Cirrhosis may develop with portal hypertension, ascites, massive splenomegaly, esophageal varices, and hepatic failure. Urinary schistosomiasis is usually present with hematuria and dysuria. Chronic fibrotic changes can lead to hydroureter or hydronephrosis, chronic kidney disease, bacterial urinary tract infections, and bladder cancer. Diagnosis is established by the detection of the characteristic eggs in the stools or

urine or other infected tissues (rectum, bladder, and liver biopsy most commonly). Quantitative determination is important. More than 400 eggs per gram of feces or per 10 ml of urine suggests heavy infection with higher risk of complication. The *S. haematobium* egg is a large ovum with a terminal spine. *S. mansoni* eggs are large eggs with lateral spine. *S japonicum* eggs are smaller than *S. mansoni*'s eggs with a small spine. Serologic tests (ELISA) are available with high sensitivity and specificity but cannot distinguish the acute or chronic phase, so the diagnosis depends also on the clinical presentation and the history of exposure. Other diagnostic tests include the detection of circulating schistosome antigens in the blood and other body fluids (urine, CSF) [2, 22].

Liver/Biliary Flukes

Fasciolia hepatica

Fasciola hepatica and *Fasciola gigantica* are known as sheep liver flukes. Sheep and humans are infected by the ingestion of the parasite eggs usually through the consumption of aquatic plants such as watercress. After ingestion, metacercariae penetrate the intestinal wall and reach the liver and the biliary system, where the hermaphrodite flukes produce their eggs. Symptoms can occur during the acute phase of migration or the chronic infection. At the migration phase, fever, abdominal pain primarily at the right upper quadrant, hepatomegaly, eosinophilia, leukocytosis, and urticaria may occur. On the other hand, chronic infection is characterized by biliary obstruction, jaundice, cholangitis, and biliary cirrhosis. Diagnosis is made by the detection of the parasite ova in the stool examination. This may be difficult at the early stages of the disease in which high degree of suspicion is critical for the diagnosis. Imaging studies with CT scan may reveal hypodense migratory lesions. Serologic tests are useful with high sensitivity and specificity. Antigen detection methods are also used in veterinary medicine with high sensitivity and specificity, but more trials are needed in humans [3, 22, 23].

Clonorchis and *Opisthorchis* (Asian/Oriental Fluke)

Clonorchis sinensis, *Opisthorchis viverrini*, and *Opisthorchis felineus* are endemic in Asian countries. Humans are incidental hosts and are infected by eating raw or undercooked fish contaminated with the metacercariae of the parasite. The parasite excysts in the duodenum and migrates through the Vater's ampulla to the biliary tree. In the bile ducts, the parasite matures and can reach 1–2 cm in length. As it is a hermaphrodite parasite, it produces eggs, which are excreted with the bile to the feces and released in the environment, where they are ingested by freshwater snails (first intermediate host). The snails release the larvae that transform into cercariae which are eaten by the freshwater fish (second intermediate host). Infected individuals may be asymptomatic. Right upper quadrant pain may be present in the acute phase, especially during parasite migration, accompanied with fever, eosinophilia, and hepatomegaly. Cholangitis and biliary obstruction with jaundice also may occur. Chronic inflammation of the bile ducts causes hyperplasia and fibrosis, and the infection with *C. sinensis* has been related to cholangiocarcinoma. Diagnosis is

established with the detection of the characteristic eggs of the parasite in stool. In the acute phase, diagnosis may be difficult because eggs are detected in feces 3–4 weeks after infection. Serologic and molecular tests have been also been developed and are used to support the diagnosis [22, 24].

Lung Flukes

Paragonimiasis

The main representative in this category is *Paragonimus westermani*. The life cycle of *Paragonimus* includes two intermediate hosts as described in clonorchiasis. Humans are infected by the ingestion of raw or undercooked crayfish or crabs, which contain parasite metacercariae in their muscles and viscera. After ingestion, the eggs excyct in the duodenum and migrate through the peritoneum, the diaphragm, and the pleural cavity to the lungs. In the lungs, they mature in about 2 months, and they form cyst lesions. The eggs of the parasite pass to the environment by the sputum, or they are swallowed again and are excreted with the feces. The first intermediate hosts in the environment are snails, who release larvae, which are taken by crayfish and crabs. As seen in other migrating parasites, during the acute phase of migration, fever, urticaria, and eosinophilia may develop. When parasites encyst in the lungs, they can cause symptoms of pneumonia, productive cough, brownish sputum, bronchitis, bronchiectasis, chest pain, pleural effusion, lung abscess, and diarrhea. Extrapulmonary disease is rare but may occur, mainly in the CNS with symptoms of space-occupying lesion, such as headache, focal neurologic signs, and seizures. Diagnosis is made by the detection of the parasite's eggs in the sputum or stool. Serologic tests may be helpful especially in CNS infection or when stool examination is negative. Imaging studies may reveal lung infiltrates, bronchiectasis, abscess and nodular cavities with or without calcification, pleural effusion, and fibrosis [22, 25].

Intestinal Flukes (*Heterophyes heterophyes* and *Fasciolopsis buski*)

Humans are infected by eating raw plants (*F.buski*) and freshwater fish (*H. heterophyes*) which contain eggs of the parasite. After ingestion, the parasites mature in the small intestine and produce eggs that pass through the feces. Infection is usually asymptomatic. In heavy parasitosis, diarrhea and abdominal pain may occur. Eosinophilia may be seen in the blood count. Diagnosis is made by the detection of the parasite's ova in the stools [22].

Cestode Infections

Tapeworms (cestodes) consist of two parts: the scolex and the proglottids. The parasite uses the scolex (a rounded head) to attach to the small intestine mucosa. The mature proglottids produce the eggs (hermaphroditic) which are excreted in the feces in order to transmit to various hosts. The length of tapeworms varies, and it can reach several meters. It depends on the number of proglottids, which can count

more than 1000. The eggs are very similar morphologically among the different *Taenia* species. As a result, differences in the morphology of the scolex and the proglottids comprise the basis of the diagnosis and species identification.

Tapeworms are divided into two categories: intestinal tapeworms (non-invasive) and tissue (somatic, invasive) tapeworms. The four major tapeworms that cause non-invasive infections are *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tapeworm, the adult form), *Diphyllobothrium latum* (fish tapeworm) and *Hymenolepis nana* (dwarf tapeworm). *Taenia solium* can also cause invasive infection by the form of cysticercosis (larvae). Invasive tapeworm infection is caused by two major pathogens: *Taenia solium*, the cause of cysticercosis, and *Echinococcus* species, primary *Echinococcus granulosus* (hydatid disease) and secondary *Echinococcus multilocularis* [21].

Intestinal (Non-invasive) Cestodes

Taenia saginata (Beef Tapeworm)

T. saginata is transmitted to humans by ingesting raw or undercooked beef, which contains larvae of the parasite. Humans are the definitive host. The larvae attach to the small intestine and mature in the adult form that can reach 10 m in length, a process that can last for 2–3 months. Most of the patients are asymptomatic. Symptoms like abdominal pain or cramps, diarrhea, malaise, loss in appetite, and weight loss can occur. Usually patients notice the parasite in their feces, and as the proglottids are often motile, they can have perianal discomfort and pruritus. Diagnosis relies on the detection of the proglottids in the feces. The scolex has four suckers but no hooks that characterize *T. solium*. Also, *T. saginata* has 15–30 uterine branches in each gravid proglottid segment, in contrast to 7–12 in *T. solium*. Eggs are morphologically indistinguishable, and serologic tests are not helpful for the diagnosis [2, 26].

Taenia solium (Pork Tapeworm)

T. solium is transmitted to humans by eating raw or undercooked pork meat. The adult forms of the parasite cause taeniasis, and the clinical futures are similar to *T. saginata* infection. The larval forms can cause invasive infection, cysticercosis, which is discussed separately. The tapeworm can reach 3 m in length. Diagnosis is made similarly to *T. saginata*, and it depends on the detection of the parasite segments in the feces. The distinction between *T. solium* and *T. saginata* is made by the different characteristics of scolex and gravid proglottids as described above.

Diphyllobothrium latum (Fish Tapeworm)

Humans are infected by consuming raw or undercooked freshwater fish. Fish acquire the parasite by eating freshwater crustaceans containing embryos from the parasite eggs. The adult form is the longest tapeworm, and it can reach 20–25 meters in length .Maturation lasts from 3 to 5 weeks, and the parasite resides in the ileum. Clinically, most patients are asymptomatic, but non-specific gastrointestinal

symptoms may occur. Occasionally, intestinal obstruction may develop, and rarely cholangitis and cholesystitis may occur due to migration of the proglottids. The infection may also cause vitamin B12 deficiency by two mechanisms: (1) consumption of the vitamin from the parasite and (2) dissociation of the vitamin from the intrinsic factor, which results in vitamin malabsorption. Diagnosis relies on detection of characteristic eggs (oval shape, operculum) in the stool [2, 26].

Hymenolepis nana (Dwarf Tapeworm)

H. nana is the most common tapeworm infection. The parasite is transmitted between humans without requiring intermediate host. Infection follows the ingestion of food contaminated with human feces containing *H. nana* eggs. The egg is attached in the small intestine mucosa and matures to the adult form. The adult form can reach 2–5 cm length and is considered the smallest tapeworm that infects humans. It matures over 10–12 days. Then it releases fertilized eggs, which either can pass through the feces or can cause autoinfection by reattaching in the small intestinal wall. The clinical manifestations include non-specific gastrointestinal symptoms, although the infection is mostly asymptomatic, even with high numbers of parasites. Diagnosis is made with the detection of eggs in stool [26].

Tissue (Somatic, Invasive) Cestodes

Cysticercosis

Cysticercosis, as mentioned above, is caused by the larval forms of *T. solium*, the pork tapeworm. The infection occurs with the consumption of food or water contaminated with human feces, containing the eggs of the parasite. The consumption of raw or undercooked pork meet only causes taeniasis. Autoinfection may occur when a carrier host with tapeworm consumes contaminated food or water by his or her own feces containing the eggs of *T. solium*. The life cycle of the parasite begins when humans ingest raw or undercooked pork, which contains the larvae. The helminths mature in the small intestine producing many eggs daily by the gravid proglottids. Three to five proglottids are released daily in the feces, and each one produces up to 50,000 eggs, which can survive for several months in the environment. The intermediate host is the pig, which consumes food contaminated with human feces. Then the larvae mature in the intestine of the animal, penetrate the intestinal wall, intersperse to the tissues, and cause cysticerci. The parasite shows tropism for striated muscle tropism [26, 27].

Cysticerci can potentially affect any tissue and organ. Most commonly they infect the brain/CSF, the skeletal muscles, the skin and subcutaneous tissue, and the eye. Neurologic symptoms of hydrocephalus or increased intracranial pressure symptoms (confusion, headache, vomiting, blurred vision, dizziness, ataxia, hypertension, bradycardia, papilledema) and seizures are common. The presentation of these symptoms depends on the location and the expansion of the cysticerci. In the eye, the larvae can be visualized in the vitreous, and they can cause uveitis and retinitis. Subcutaneous nodules may develop that contain the parasites. In most of the

cases, the diagnosis is based on a combination of clinical manifestations, imaging, and serologic tests [27–29].

The absolute diagnostic criterion is the detection of the parasite in the tissues. This can be achieved in three ways: (a) histological detection of the parasite in biopsy material or surgically excised tissue, (b) visualization of the parasite by fundoscopy, and (c) neuroimaging with MRI or CT scan to detect the lesions containing the scolex. The lesions are cystic and may present with enhancement and nodular calcifications. They can reach 5–20 mm in diameter, and if they are located in the subarachnoid space or the ventricles, they can cause obstructive hydrocephalus. Another helpful examination is serological testing in the blood. Specific antibodies can be detected with ELISA. However some patients may not develop antibodies (single and calcificated lesions). Antigen detection methods have developed, but they are not widely available. Response to empiric therapy with albendazole or praziquantel is another useful criterion for the diagnosis. Diagnostic criteria of cysticercosis have been developed and can be found elsewhere [30, 31].

Echinococcus Species

The most important pathogen in this category is *Echinococcus granulosus* (dog tapeworm). Less common infections occur due to *Echinococcus multilocularis* (found in foxes). The definitive hosts are canines. Life cycle begins when eggs originating in the small intestine of dogs are excreted through feces in the environment. Ingestion of eggs by intermediate hosts, which include sheep, humans, cattle, goats, camels, and horses, is followed by the development of oncosphere embryos in the intestine and their migration primarily to the liver, but also the lungs, the brain, and the bones, where they develop into hydatid cysts. Skeletal muscles, kidneys, and spleen are alternative locations.

E. granulosus is a small tapeworm. The scolex is similar to *T. solium*, consisting of hooks and four suckers, with the difference that *E. granulosus* has only three proglottids, and it can reach 5 mm in length. In humans, the two most affected organs are the liver (65%) and the lungs (25%). Larvae develop into hydatid cysts. They are fluid-filled unilocular lesions with an external layer, a thick membrane of fibrous tissue, and an inner germinal layer. The inner layer contains scoleces, daughter cysts, and brood capsules which are germinating cystic structures that produce protoscolices (new larvae). *E. multilocularis* is generally a more aggressive pathogen, which causes multilocular cysts with local and distant spread [2, 26].

The cysts of *E. granulosus* develop slowly over the years. The signs and symptoms depend on the location and the size of the cyst. Infected individuals may commonly be asymptomatic until the cyst is enlarged and presents as a space-occupying lesion. Symptoms include abdominal pain and discomfort, mostly in the right upper quadrant, biliary obstruction and jaundice, cholangitis, cirrhosis, and portal hypertension. Pulmonary symptoms like chest pain, cough, bronchial obstruction, and dyspnea may occur with lung cysts. The cysts may be secondarily infected with bacteria and transform into abscesses. If the cyst is located in the brain, it can cause

headache and focal neurologic symptoms. Rupture of the cyst may cause dissemination of the parasites, which can form new cysts, severe allergic reaction, and anaphylactic shock. This may occur spontaneously or during the surgical removal of the cyst [26, 27, 32]. Hydatid cyst disease is extensively described in other chapters.

Imaging studies are essential for the diagnosis. Ultrasonography, MRI, and CT scan are the most common examinations performed for the evaluation of the cysts. Daughter cysts in a larger cyst are considered pathognomonic. Imaging usually reveals well-defined cysts with thick or thin walls. Mural calcification of the cyst may be seen which makes the cysts inactive. In the lungs, cysts present as solid masses with central necrosis and plaque-like calcifications. Serologic tests may be useful for the diagnosis, and they are up to 90% positive if liver cysts are present. Negative tests do not exclude the diagnosis. ELISA and immunoblotting techniques are used with sensitivity and specificity up to 80% [3, 26, 27, 33].

Nematodes (Roundworms)

Nematodes can be divided into intestinal nematodes, tissue nematodes, and nematodes whose larvae cause disease (larva migrans) (Table 2.4).

Table 2.4 Major roundworm infections, which cause disease in humans, according to the site of infection

Site of infection	Roundworm	Mode of transmission
Intestinal roundworms	*Ascaris lumbricoides* (roundworm of humans)	Fecal-oral
	Ancylostoma duodenale (Old World hookworm)	Skin penetration
	Necator americanus (New World hookworm)	Skin penetration
	Enterobius vermicularis (pinworm)	Fecal-oral
	Trichuris trichiura (whipworm)	Fecal-oral
	Strongyloides stercoralis	Skin penetration, autoinfection
	Anisakidae	Ingestion of uncooked saltwater fish
Tissue roundworms	*Trichinella spiralis*	Undercooked pork or wild game
	Wuchereria bancrofti	*Culex* mosquitoes
	Brugia malayi	*Mansonia*, *Anopheles* mosquitoes
	Loa loa	*Chrysops* (deerflies)
	Onchocerca volvulus	*Simulium* (blackflies)
	Dracunculus medinensis	Water
	Angiostrongylus cantonensis	Undercooked seafood, snails
Larva migrans syndromes	*Toxocara canis* and *Toxocara cati*	Oral/ingestion of eggs
	Ancylostoma braziliense	Skin penetration

Intestinal Nematodes

Infection with intestinal nematodes is very common worldwide, as more than one billion people are infected with one or more intestinal nematodes. However, these organisms are more common in resource-poor countries, where sanitation may be limited, and in immigrants and refugees from these countries. They have complex life cycles and vary in size from 1 mm to few centimeters. Intestinal roundworm infections may contribute to malnutrition. Clinical disease often requires prolonged stay in an endemic area, because in order to acquire a heavy burden of adult worms, one has to have repeated exposure to the infectious parasite forms [34]. Roundworm infections are commonly associated with parasitemia (Table 2.5).

Ascaris lumbricoides

Ascaris Lumbricoides reside in the small intestine and is the largest parasite in its group, reaching up to 40 cm in length. Transmission is via the fecal-oral route, when humans ingest eggs (residing in soil). Larvae hatch in the small intestine, invade through the mucosa, and migrate to the lungs (9–12 days after egg ingestion) where they ascend the bronchial tree, and then they are swallowed again reaching the small intestine and maturing into adult forms. Clinical manifestations include pulmonary and gastrointestinal symptoms. During lung migration, a nonproductive cough, chest discomfort, and fever may develop. Eosinophilia is common at early stages. Chest X-ray may show evidence of eosinophilic pneumonitis (Loffler's syndrome) with fleeting infiltrates. Symptoms from the intestinal tract, like abdominal pain or obstruction, usually occur with heavy parasite burden. Complications include intussusception, volvulus and perforation, cholecystitis, cholangitis, pancreatitis, or, rarely, liver abscess and should be included in the differential diagnosis of acute abdomen in endemic areas. Diagnosis is made by macroscopic detection of adult worms in feces or sputum and/or eggs in stool [2, 34, 35].

Table 2.5 Parasites most commonly associated with eosinophilia

Site of infection	Flatworm
Roundworms	*Ascaris lumbricoides*
	Ancylostoma spp.
	Trichinella spiralis
	Strongyloides stercoralis
	Wuchereria bancrofti, *Brugia* spp., *Lao loa*, *Onchocerca volvulus*
	Toxocara spp.
	Angiostrongylus cantonensis
	Gnathostoma spinigerum
Tapeworms/cestodes	*Echinococcus granulosus*
	Taenia solium
Flukes/Trematodes	*Schistosoma* spp.
	Clonorchis sinensis
	Fasciola hepatica
	Paragonimus spp.

Ancylostoma duodenale (Old World Hookworm), *Necator americanus* (New World Hookworm)

Ancylostoma duodenale (Old World hookworm) and *Necator americanus* (New World hookworm) cause hookworm disease when there is heavy parasite burden and/or prolonged duration of infection. Infection when combined with decreased iron uptake can result in iron deficiency anemia. However, most infections are asymptomatic. Adult worms attach to the small bowel mucosa (sucking blood) and produce eggs, which are excreted with feces. In the soil, larvae hatch and transform to the infective adult filariform worms. These penetrate the skin and reach the lung through the bloodstream, where they ascend the bronchial airways and are swallowed and descend to the small intestine. Symptoms are usually mild and include pruritic dermatitis, subcutaneous migration, pneumonitis, abdominal pain, and inflammatory diarrhea. Eosinophilia is usually present, and iron deficiency anemia as well as hypoproteinemia can develop, as mentioned above. Diagnosis is made by microscopic detection of hookworm eggs in stool samples [34, 35].

Enterobius vermicularis (Pinworm)

Infection with *Enterobius vermicularis* is very common in children worldwide. Transmission occurs with ingestion of parasite eggs, which then hatch in the small intestine and give rise to larvae that migrate to the colon after maturing into the adult forms. Male and female reproduce in the colon, and the female worm releases the eggs at the perianal skin area at night. After scratching the area, infectious embryonated eggs can cause re-infection through contamination of fingers and re-ingestion. Diagnosis is made using the clear cellulose acetate tape technique in order to recover eggs from the perianal area and examine them microscopically. Worms may also be seen in stool [2].

Trichuris trichiura (Whipworm)

Trichuris trichiura infection is more common in tropical areas and resource-poor countries. The life cycle is similar to that of *Enterobius vermicularis*. Most infections are asymptomatic; however it can cause diarrhea or rectal prolapse due to increased peristalsis in children with heavy parasite burden. The adult worm is whip-like, and eggs are barrel (or lemon)-shaped, and their detection confirms the diagnosis [2, 35].

Strongyloides stercoralis

Strongyloides stercoralis, as opposed to other helminths, has the ability to replicate within the human host; thus persistent infection can develop without repeated exposure to infective larvae from the environment. This is particularly important in immunocompromised patients who can present with disseminated disease due to these autoinfection cycles. Strongyloides is a facultative parasite and can survive in the soil as a free-living organism. Transmission occurs when filariform larvae from the soil penetrate the skin and reach the lungs via the bloodstream; there they ascend the airways, and they are swallowed and descend to the small intestine. The female worms reproduce in the intestinal mucosa by parthenogenesis, and eggs hatch

releasing larvae which migrate to the lumen and are excreted with feces. Rhabditiform larvae can also transform to infective forms that penetrate the mucosa or perianal skin and re-infect the host. Clinical symptoms are usually mild and include recurrent urticaria, a serpiginous eruption at the site of larva migration known as "larva currens," gastrointestinal symptoms, weight loss, colitis, and rarely bleeding or obstruction. Eosinophilia is present, and pulmonary symptoms are not frequent. Hyperinfection syndrome occurs more commonly in patients receiving glucocorticoids, and it can be life-threatening presenting as disseminated disease affecting many organs. Due to the disruption of enteric mucosal barrier, it is usually accompanied by Gram-negative bacteremia (also polymicrobial). Diagnosis is based on larvae detection in serial stool samples or if needed in duodenal aspirates or biopsy specimens. These are 250 μm in length and can be distinguished morphologically by hookworms due to their short buccal cavity. ELISA-based antibody tests are used for diagnosis, with good sensitivity for uncomplicated infections [35–38].

Tissue Roundworms

Trichinella spp.

Infection with *Trichinella* species (eight are recognized), most commonly *T. spiralis*, causes trichinellosis. Transmission occurs after ingestion of undercooked meat containing cysts, most usually pork but also other carnivores or wild game. Larvae excyst in the small intestine mucosa and mature into adult forms. Adult females produce eggs, and larvae are released via the bloodstream to different organs; however cysts develop in striated muscle cells, where they can remain viable for many years. When the parasite burden is high, diarrhea or other gastrointestinal symptoms can occur 1 week after infection. Low parasite burden infections are asymptomatic. During the second week, symptoms due to muscle invasion or larval migration may develop. The latter presents as hypersensitivity reaction with eosinophilia, rash, and fever, but also periorbital and facial edema as well as subconjuctival, retinal, and splinter hemorrhages are described. Complications include myocarditis, tachyarrhythmias, pneumonitis, and, less frequently, encephalitis. Muscle edema, myalgias, muscle weakness, and myositis symptoms reflect larval encystment, and affected areas are the extraocular muscles; muscles of the neck, face, and back; biceps; and diaphragm. Eosinophilia is very common and peaks between weeks 2 and 4 after infection; CPK is also elevated and clinical suspicion is important for diagnosis. Serologic tests can confirm the diagnosis; otherwise a muscle (1gr) biopsy may be needed for microscopic detection of cysts [2, 39, 40].

Wuchereria bancrofti, Brugia malayi, Loa loa, Onchocerca volvulus, Dracunculus medinensis

Filariasis affects more than 170 million people worldwide. Although eight filarial worms infect humans, five of them cause clinically important disease. These are *Wuchereria bancrofti*, *Brugia malayi*, *Loa loa*, *Onchocerca volvulus*, and *Dracunculus medinensis*. The filarial parasites are transmitted by mosquitos and

other arthropods. Their life cycle is complex and involves a larval stage within the insect and an adult worm phase, which is carried out in the lymphatics or subcutaneous tissues in humans. Adult worms produce microfilariae, which can either circulate in the bloodstream or penetrate the skin. Arthropods ingest microfilariae, which develop into infective larvae within the insect. Filariasis usually occurs after repeated exposure to the infectious forms of the parasite and typically manifests as chronic infection, especially in endemic areas. Nonetheless, the disease can have a more acute presentation in newly exposed individuals (non-natives) [34].

W. bancrofti and *B. malayi* cause lymphatic filariasis, which can lead to significant lymphatic obstruction due to inflammatory changes and eventually fibrosis of the lymphatics, triggered by the filarial adult worms. In extreme forms, lymphedema can evolve to elephantiasis of (usually lower) extremities. Diagnosis is based on detection of microfilariae in blood or other biologic specimens. Antigenic detection and PCR-based tests are also useful, if available [2, 3, 34].

Onchocerciasis is the cause of "river blindness," while *Loa loa* (African eye worm) causes loiasis and can manifest with episodic Calabar swellings (localized areas of angioedema) [2, 34].

Larva Migrans Syndromes

Toxocara canis (dog) and *Toxocara cati* (cat) cause visceral larva migrans. The definite host is the dog, and humans are accidental dead-end hosts. Diagnosis is made with the detection of larvae in tissue. The larvae can migrate in various organs, where they are encapsulated and die. However, granulomas can form around the dead larvae, and the mechanism is a delayed hypersensitivity response. Blindness is the most serious complication. Serologic tests can be useful, and eosinophilia and hypergammaglobulinemia are supportive of the diagnosis [2].

Ancylostoma braziliense (cat) and *Ancylostoma caninum* (dogs) cause cutaneous larva migrans. Larvae enter the human host via skin penetration, but they cannot complete their life cycle. As larvae migrate through the subcutaneous tissues, a creeping eruption occurs, which is intensely pruritic [2].

Angiostrongylus cantonensis, *Gnathostoma spinigerum*, and *Baylisascaris* can cause eosinophilic meningitis.

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