

Helminths and the Respiratory System

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Introduction

The term “parasitism” denotes a relationship between 2 living organisms that has harmful consequences for 1 of the 2 (the host) and is beneficial to the other (the parasite). Although, in theory, the term “parasite” covers all organisms capable of causing damage to others, in medicine it has traditionally been used exclusively to refer to the protozoa, helminths, and arthropods that live temporarily or permanently in humans.¹ While a parasitic infection may give rise to clinical manifestations (parasitic diseases), it can also be asymptomatic.¹ With certain exceptions (chiefly severe amebiasis and malaria²), most of the parasites that affect the lungs are helminths, that is, invertebrate organisms resembling worms (vermes).

In this article we will review the whole range of respiratory diseases caused by these parasites in humans, providing an update on several topics dealt with in ARCHIVOS DE BRONCONEUMOLOGÍA by Cremades³ in 1998. We will begin with a brief overview of the main genera and species involved, followed by a description of the point in the life cycle of each parasite when contact with the respiratory apparatus takes place. The second part of the article is a review of the principal epidemiological characteristics, with particular emphasis on the geographical distribution of these diseases. This is followed by a description of the mechanisms of lung injury (the parasite’s aggression and the host’s defense) and of the clinical signs and symptoms produced. The final 2 sections cover diagnostic techniques and possible treatments.

Causal Agents

The chief human helminth infections are caused by various species of cestodes, trematodes, and nematodes. The forms of cestodiasis that affect the lungs are caused exclusively by larvae and never by adult worms (for example, *Taenia saginata*, *Taenia solium*, *Diphyllobothrium latum*, *Hymenolepis* species, and *Dipylidium caninum*). The main form of cestodiasis that affects the lung is hydatidosis or echinococcosis (caused by *Echinococcus granulosus*),⁴ while the lungs are only rarely affected by cysticerci (a larval form of *T solium*)⁵⁻⁷ or other species of *Echinococcus* (*Echinococcus multilocularis*, *Echinococcus vogeli*, and *Echinococcus oligarthrus*).⁴ The 2 genera of trematodes that can damage the lungs are *Schistosoma* and *Paragonimus*. While various species of the former can cause schistosomiasis, the disease is most often caused by *Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*.⁸ Schistosomiasis can affect the lung in 2 ways: Katayama syndrome during the acute phase, and embolization of eggs to the pulmonary arterioles during the chronic phase.⁸ Paragonimiasis is caused by infection with various species of *Paragonimus*, primarily *Paragonimus westermani*.^{9,10} Finally, the following types of nematodiasis can affect the lung: a) disease caused by certain intestinal helminths that inhabit the lung at some point in their life cycle, such as *Ascaris* species, hookworms (*Ancylostoma duodenale* and *Necator americanus*), and *Strongyloides* species^{11,12}; b) some forms of lymphatic filariasis (caused by *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*)¹³ and dirofilariasis (caused by *Dirofilaria immitis*)¹⁴; and c) tissue invading nematodiasis, such as toxocarosis (caused by *Toxocara canis* and *Toxocara cati*)¹⁵ and trichinosis (caused by various species of *Trichinella*).¹⁶

Fundamental Biological Characteristics

These helminths enter the host organism by 3 different routes (Figure). *E granulosus*, *P westermani*,

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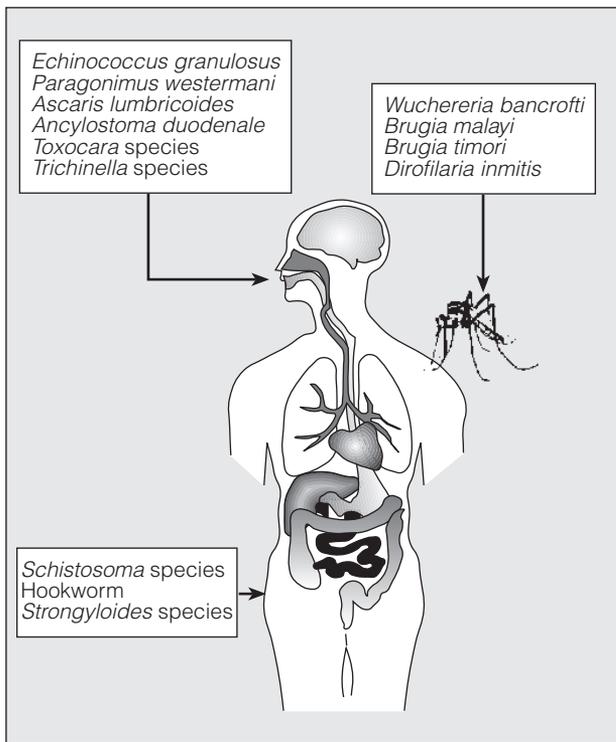


Figure. Helminth entry routes.

Ascaris lumbricoides, *A. duodenale*, and helminths of the *Toxocara* and *Trichinella* species enter when the host organism ingests food or water containing infective forms of the parasite. *Schistosoma* species, *Strongyloides stercoralis*, and hookworm penetrate the body through the skin. The filariae are transmitted by various arthropod vectors.

E. granulosus has an indirect life cycle. The canids and some felids are the hosts of the adult forms of this cestode, and the larvae (metacestodes) are found in a number of intermediate hosts, mainly ungulates and rodents.^{4,17} Humans become accidental intermediate hosts when they ingest helminth eggs, either directly from the definitive host or in water or vegetables contaminated with the excretions of the definitive hosts. Once ingested, eggs hatch in the small intestine and release oncospheres that burrow into the intestinal wall. These oncospheres travel through the bloodstream to the liver, where most of them remain. Some, however, travel through the venous system to the lung and may even pass through the pulmonary filter and reach other organs by way of the systemic circulation. Occasionally, cases have been reported in which oncospheres reached the lung from the intestinal tract through the lymph system (bypassing the pulmonary filter) or from the bronchial tree.¹⁷ When they reach the target organs, the oncospheres that have not been destroyed by the immune system form hydatid cysts that gradually grow in size as protoscolices and brood capsules are formed in their interior.¹⁷

The different species of *Schistosoma* have an indirect cycle involving several species of freshwater snail (of the

genera *Biomphalaria*, *Bulinus*, and *Oncomelania*), which function as specific intermediate hosts. Several phases of the schistosome's life cycle take place inside these hosts before cercariae are released into water.⁸ The cercariae are able to penetrate intact skin, and once inside the host's body they shed their tails to become schistosomula. These larvae migrate through the venous bloodstream to the pulmonary circulatory system and cross through it. Initially they invade the left chambers of the heart and later the mesenteric (*S. mansoni*) or vesical (*S. haematobium*) veins, where sexual differentiation takes place. The males and females are coupled in pairs, and eggs are released after fertilization has taken place. These eggs travel in both anterograde and retrograde directions, giving rise to the lesions characteristic of this disease (granulomas). In the course of this "chronic" phase, the lung is damaged when branches of the pulmonary arteries become embolized by eggs.

The cycle of the trematodes of the genus *Paragonimus*, which is also indirect but more complex than that of the schistosomes, involves 2 types of intermediate hosts: water snails (such as *Aroapyrgus* species, in which a cycle similar to that of the schistosomes takes place); and crustaceans (in which the cercariae become metacercariae).⁹ Humans become infected when they eat raw or undercooked crustaceans (especially crabs) that contain metacercariae. These metacercariae excyst in the intestinal tract. The larvae then migrate through the intestinal wall into the peritoneal cavity and subsequently cross the diaphragm into the pleural space. The immature worms then burrow into the pulmonary tissue, where they mature, giving rise to cysts containing bloody purulent fluid enclosed in a fibrous capsule. When the eggs are finally released they are expelled through the airway.⁹

The intestinal helminths mentioned above (*Ascaris* species, *A. duodenale*, *N. americanus*, and *Strongyloides* species) affect the lung when they migrate through the bronchial tree. Infection with *Ascaris* species,¹⁸ and sometimes with *A. duodenale*, is caused by the consumption of food infected with embryonated eggs of one of these nematodes. The eggs hatch in the intestinal tract, releasing larvae that penetrate the intestinal wall and are then carried by the venous bloodstream to the liver (where they cause no damage) and from there continue on through the right heart chambers to the pulmonary capillary bed. Eventually they cross the alveolocapillary membrane and migrate up the airway through the bronchioles, the bronchi, and the trachea until they reach the pharynx. At this point they are swallowed and return to the small intestine, the final home of the mature worm. Hookworm infection¹⁹ and *S. stercoralis* infection²⁰ usually follow a different cycle. The filariform larvae (third stage) enter the organism through the skin as a result of contact between bare feet and the ground. They migrate via the venous bloodstream to the branches of the pulmonary artery, and then follow a life cycle similar to that of the other intestinal helminths. One important difference between *S. stercoralis* and the other helminths is that it can reinfect the host from the intestine.

TABLE 1
Causative Agents and the Basic Characteristics of the Life Cycle of Helminths That Affect the Respiratory System

Genus	Species	Type of Cycle	Definitive Host(s)	Intermediate Host(s)	Method of Contagion
<i>Echinococcus</i>	<i>E granulosus</i>	Indirect	Canids	Ungulates, humans	Ingestion of eggs. Contact with dogs Consumption of water or food
<i>Schistosoma</i>	<i>S mansoni</i> <i>S haematobium</i> <i>S japonicum</i> * <i>S intercalatum</i> <i>S mekongi</i>	Indirect	Humans	Fresh water snails	Transdermal penetration by cercariae
<i>Paragonimus</i>	<i>P westermani</i>	Indirect	Humans, other mammals	Fresh water snails (1st). Crustaceans (2nd)	Consumption of raw or undercooked crustaceans
<i>Ascaris</i>	<i>A lumbricoides</i>	Direct	Humans		Ingestion of eggs in water or food
<i>Ancylostoma</i>	<i>A duodenale</i>	Direct	Humans		Transdermal penetration by larvae Ingestion of eggs in water or food
<i>Necator</i>	<i>N americanus</i>	Direct	Humans		Transdermal penetration by larvae
<i>Strongyloides</i>	<i>S stercoralis</i> <i>S fuellerborni</i>	Direct	Humans		Transdermal penetration by larvae Autoinfection
<i>Wuchereria</i> <i>Brugia</i>	<i>W bancrofti</i> <i>B malayi</i> <i>B timori</i>	Indirect	Humans	Hematophage Diptera (<i>Culex</i> species, <i>Aedes</i> species, <i>Anopheles</i> species)	Introduction of larvae by insect bite
<i>Dirofilaria</i>	<i>D immitis</i>		Canids		
<i>Toxocara</i>	<i>T canis</i> <i>T cati</i>	Direct	Dogs Cats		Ingestion of eggs present in the soil
<i>Trichinella</i>	<i>T spiralis</i> <i>T nativa</i> <i>T britovi</i> <i>T murrelli</i> <i>T nelsoni</i> <i>T pseudospiralis</i> <i>T papuae</i>	Autoheteroxenous	Mammals, humans		Ingestion of raw or undercooked meat from infested animals

*Also includes wild animals.

The filariases are the most common type of blood nematodiasis. Pulmonary involvement follows 2 different patterns: on the one hand, lymphatic filariasis—caused by *W bancrofti* and *Brugia* species and transmitted by various hematophage insects in the Diptera order—causes pulmonary lesions through the release of microfilariae that become trapped in the pulmonary vascular bed¹³; on the other hand, in patients with *D immitis* infection, lung injury is caused by embolization of larvae to the pulmonary vasculature.^{14,21}

Toxocariasis occurs when the host ingests embryonated eggs present in soil contaminated with stools from infected dogs and cats. Logically, this disease is more prevalent in young infants. The eggs hatch in the small intestine, releasing second-stage larvae that penetrate the intestinal wall, enter the bloodstream, and travel to various structures, such as the liver, the lungs, the central nervous system, and the ocular globe.²²

Infection with different species of *Trichinella* is caused by the consumption of raw or undercooked meat from infected pigs or boar.¹⁶ Excystation takes place in the intestinal tract. This is followed by sexual development, the fertilization of the females, and the release of first-stage larvae. These larvae enter lymphatic tissue and vessels and migrate to striated skeletal muscle, including the diaphragm and other respiratory muscles. The larvae then burrow into these muscles, where they grow and encyst.

Table 1 summarizes the main differences between the various helminths that affect the respiratory system.

Epidemiology

The distribution of *E granulosus* infection is cosmopolitan, and prevalence varies considerably from country to country and even within each country.^{23,24} The most important hyperendemic areas are the Mediterranean

TABLE 2
Epidemiology of Helminths That Affect the Respiratory System

Genus	Species	Indigenous Cases	World Distribution	No. of People Affected Worldwide
<i>Echinococcus</i>	<i>E granulosus</i>	Yes	Cosmopolitan	Varies greatly, depending on the affected zone
<i>Schistosoma</i>	<i>S mansoni</i> <i>S haematobium</i> <i>S japonicum</i> <i>S intercalatum</i> <i>S mekongi</i>	No	Africa, South America, the Caribbean, the Middle East Continental and insular Africa, Saudi Arabia, Iran China, the Philippines, Indonesia Central Africa Laos, Cambodia	200 million
<i>Paragonimus</i>	<i>P westermani</i> <i>P kellicoti</i> <i>P africanus</i> <i>P uterobilateralis</i> <i>P miyazakii</i>	No	Asia, Africa, South America United States of America Africa Africa Japan	22 million
<i>Ascaris</i>	<i>A lumbricoides</i>	Doubtful	Cosmopolitan	4500 million
<i>Ancylostoma</i>	<i>A duodenale</i>	No	Cosmopolitan	
<i>Necator</i>	<i>N americanus</i>	No	Cosmopolitan	
<i>Strongyloides</i>	<i>S stercoralis</i> <i>S fuellerborni fuellerboni</i> <i>S fuellerborni kelley</i>	Yes No No	Cosmopolitan Africa Papua-New Guinea	
<i>Wuchereria</i>	<i>W bancrofti</i>	No	Africa, India, Southeast Asia, South America	100 million
<i>Brugia</i>	<i>B malayi</i> <i>B timori</i>		South and Southeast Asia	
<i>Dirofilaria</i>	<i>D immitis</i>	Yes	Cosmopolitan	No data available
<i>Toxocara</i>	<i>T canis</i> <i>T cati</i>	Yes	Cosmopolitan	No data available
<i>Trichinella</i>	<i>T spiralis</i> <i>T nativa</i> <i>T britovi</i> <i>T murrelli</i> <i>T nelsoni</i> <i>T pseudospiralis</i> <i>T papuae</i>	Yes	Variable depending on the species	11 million

basin (Morocco, Tunisia, Libya, Israel, the Lebanon, southern Italy, Sardinia, and Spain), the countries of the former Soviet Union, East Africa (Somalia, Ethiopia, and Kenya), South America (Peru, Chile, Argentina, and Uruguay), parts of China, Malaysia, Sri Lanka, and India. Prevalence varies widely, ranging from 0.7 to 0.9 per 100 000 population in Israel to 1 per 1000 population in the Turkana Lake area of Kenya. Global mortality is estimated to be 0.2 per 100 000 population.⁴

In Spain, hydatidosis has been and still is an endemic disease in many areas (especially in Castile-León, Aragon, Navarra, La Rioja, Madrid, and Castile-La Mancha), with prevalence reaching considerable rates until a few years ago.²⁵ More recently, however, a decrease has been observed in the number of indigenous cases (Table 2), even as the number of imported cases is rising.²⁶

Human schistosomiasis is endemic in 76 countries worldwide and constitutes one of the most serious public health problems facing tropical and subtropical countries. It is estimated that some 200 million people are affected, and that the disease causes between 300 000 and 500 000

deaths annually.²⁷ The infection, which is caused by various species of *Schistosoma*, is more prevalent among the young and has a greater impact on their health. As the person grows older, the parasite load decreases and the individual's resistance to reinfection increases.²⁷ The distribution of schistosomiasis by species varies depending on the control strategies being used in the area and the appearance of new foci of infection.²⁸ In general, *S mansoni* infection occurs in many African countries, South America (Brazil, Surinam, and Venezuela), numerous Caribbean islands (including Puerto Rico, Saint Lucia, Guadalupe, Martinique, the Dominican Republic, Antigua, and Montserrat), and in some areas of the Middle East. Areas where infection with *S haematobium* is endemic include a large part of continental Africa, Madagascar and the Mauritius Islands, Saudi Arabia, and the Khuzestan province in Iran. The distribution of *S japonicum* infection is more restricted. It is found in various parts of China (the regions along the Yangtze river, the lake areas of the central region, and the mountainous areas of the

Szechuan and Yunnan provinces), the Philippines, and Indonesia (the central area of Sulawesi). The distribution of the other 2 forms of *Schistosoma* infection is very limited; *Schistosoma intercalatum* is found in Central Africa (principally Gabon, Cameroon, and Zaire, with more isolated foci in Nigeria, the Central African Republic, Chad, and Burkina Faso), and *Schistosoma mekongi* is found in Laos and Cambodia. Schistosomiasis is not an indigenous disease in Spain owing, among other factors, to the absence of the appropriate intermediate hosts.²⁹ However, a growing number of imported cases are being reported, affecting both immigrants and travelers. Although the number of cases reported to the Spanish Microbiologic Information System is low (2 or 3 per year), a review of cases published and reported at conferences indicates that the incidence of this disease in Spain greatly exceeds this.³⁰⁻³²

Infection by trematodes of the genus *Paragonimus* affects some 22 million people worldwide, and is endemic in various parts of Asian, African, and American countries.³³ The Asian countries most affected are Korea, Japan, Taiwan, central China, and the Philippines. However, the disease has also been reported in Vietnam, Sri Lanka, Indonesia, Malaysia, Laos, and Thailand. In Africa, it is found in the central and western part of the continent, mainly Cameroon, Nigeria, Guinea, Gambia, and Liberia. Cases have been reported in many South American countries, especially in Ecuador, Peru, Colombia, Venezuela, and parts of Brazil. The most predominant trematode species worldwide is *P. westermani*, although other species are found depending on the geographical zone (*Paragonimus kellicotti* in the United States of America,³⁴ *Paragonimus africanus* and *Paragonimus uterobilateralis* in Africa,³⁵ and *Paragonimus miyazakii* in Japan).³⁶ Because of the characteristics of this parasite's life cycle, most fluke infections are caused by the consumption of raw or undercooked crustaceans, although they can also result from the consumption of meat from paratenic hosts (pigs, bears, and rats). An interesting development is the possibility of cases of infection occurring in Western countries caused by the consumption of crustaceans pickled in wine or vinegar exported from endemic areas. No indigenous cases of paragonimiasis have been reported in Spain, and imported cases are rare.³⁷

Diseases caused by geohelminths are the most common parasitic disorders in the world; it is estimated that approximately 4500 million people are affected.³⁸ The 3 types of geohelminths that can affect the respiratory structures are *A. lumbricoides*, hookworm, and *Strongyloides* species. While infection with *A. lumbricoides* is cosmopolitan, prevalence is higher in developing countries located in tropical and subtropical areas.²⁴ In any case, the prevalence of this infection varies greatly depending on age (predominant in children) and the different regions of the countries. In Spain, very few cases (between 10 and 20 annually) were reported to the Microbiologic Information System until 1999, but the number of reported cases rose considerably in subsequent years,

probably as a result of immigration.⁴⁰ No conclusive data are available on the current presence of indigenous cases in Spain, but in any case they would be rare.^{41,42} Hookworm infections caused by *A. duodenale* and *N. americanus* are the most prevalent helminthic diseases worldwide.¹⁹ Distribution is cosmopolitan, with the highest rates occurring in Asia (particularly China) and sub-Saharan Africa. The distribution of *N. americanus* is more cosmopolitan, while that of *A. duodenale* is restricted to more specific areas. Unlike ascariasis, hookworm infection predominantly affects adults. Practically the only cases reported in Spain have been imported.^{39,43} Infection with nematodes of the genus *Strongyloides* is prevalent in large areas of the tropical regions of Asia, Africa, and America, with rates decreasing as the distance from the tropics increases. The 2 main species that infest humans are *S. stercoralis* and *S. fuelleborni*. It is estimated that between 80 and 100 million people living in the temperate zones of the planet are infected with *S. stercoralis*,⁴⁴ while infection with *S. fuelleborni* is found only in Papua New Guinea and parts of Africa.⁴⁵ In Spain, cases are commonly reported of indigenous strongyloidiasis (especially in the Autonomous Community of Valencia),^{20,46-48} and of imported forms.^{39,49}

There are 2 types of filarial infection that can damage the respiratory system, lymphatic filariasis and dirofilariasis. Lymphatic filariasis is caused by 3 species (*W. bancrofti*, *B. timori*, and *B. malayi*), and each one has a different geographical distribution. *W. bancrofti* infection has been reported in approximately 80 countries. Approximately one third of the cases reported have been in Africa, another third in India, and the balance in South Asia, the Pacific rim, and parts of Central and South America. The countries with the highest prevalence rates are India, Nigeria, Bangladesh, Indonesia, the Democratic Republic of the Congo, the Philippines, and Madagascar.⁵⁰ Infection with *Brugia* species is limited to South and Southeast Asia, in particular China, India, Indonesia, Malaysia, Timor, Sri Lanka, Thailand, and Vietnam. Worldwide, lymphatic filariasis affects some 120 million people.³⁸ In Spain, all reported cases of lymphatic filariasis have been imported.⁵¹ Infection with *D. immitis* is cosmopolitan. This parasite affects mainly dogs and cats in areas with a warm and temperate climate, although it is spreading progressively to other regions of the planet. This infection usually affects canids, particularly dogs, and it is only rarely diagnosed in humans.¹⁴ The intermediate hosts are approximately 70 species of mosquito belonging to various genera (*Culex*, *Aedes*, *Anopheles*, and *Mansonia*). In Spain, pulmonary dirofilariasis has been described as an indigenous disease in the province of Salamanca,^{52,53} although the high seroprevalence in dogs in other parts of the country, such as the Canary Islands,⁵⁴ suggests that this entity may be underdiagnosed.

Trichinosis is a disease of worldwide distribution, and it is currently estimated that over 11 million people are infected.⁵⁵ Trichinosis usually appears in the form of outbreaks owing to the characteristics of the life cycle

TABLE 3
Main Clinical Syndromes Associated With the Forms of Helminthiasis That Affect the Respiratory System

Clinical/Biological Pattern	Subtypes	Clinical Syndromes	Causative Agents
Pulmonary mass or nodule			<i>Echinococcus granulosus</i> . <i>Dirofilaria immitis</i>
Lung infiltrations	Without nonpulmonary involvement	Löffler syndrome	<i>Ascaris</i> species. <i>Ancylostoma duodenale</i> . <i>Necator americanus</i>
		Tropical pulmonary eosinophilia	<i>Wuchereria bancrofti</i> . <i>Brugia malayi</i> . <i>Brugia timori</i>
	With nonpulmonary involvement	Katayama syndrome	<i>Schistosoma</i> species
		Visceral larva migrans	<i>Toxocara</i> species
		Hyperinfection syndrome	<i>Strongyloides</i> species
Miliary pattern/pulmonary hypertension			<i>Schistosoma</i> species
Pleural effusion			<i>Paragonimus</i> species
Muscular involvement			<i>Trichinella</i> species

of the causative agent. These outbreaks occur in very diverse areas of the world including Eastern Europe (Russia, Romania, Poland, Bulgaria, former Yugoslavia, and the Baltic republics), the rural areas of Asia (especially China), and some South American countries (Argentina, Uruguay, Chile, and Mexico). The different species of *Trichinella* occupy different ecological niches. The most cosmopolitan species are *T spiralis* and *T pseudospiralis*, while the distribution of the other species is more restricted (for example, *T nativa*—which can survive freezing temperatures—is found in subarctic areas, whereas *T nelsoni*—which is capable of surviving high temperatures—is found in tropical regions).⁵⁶ In Spain, trichinosis is mainly an indigenous disease, and outbreaks have been reported in various regions.⁵⁷

It is difficult to establish the prevalence of toxocarasis in any region or country for the following reasons: *a*) the clinical picture is not pathognomonic, *b*) no direct parasitological diagnosis exists, and *c*) serologic techniques have a high cross-reactivity rate. Consequently, the data on diagnosis of clinical cases of toxocarasis (visceral larva migrans) in Spain are anecdotal with respect to both indigenous and imported cases. However, the high seroprevalence in humans in various regions of Spain (32.8% in children in Galicia,⁵⁸ 3.4% in the general population in the Canary Islands,⁵⁹ 14.1% in people with eosinophilia in Barcelona,⁶⁰ 8.5% in children living in the urban areas of Salamanca,⁶¹ and 1% in children in Madrid⁶²) suggests the existence of asymptomatic forms or underdiagnosis of clinical forms.

Disease Mechanisms and Clinical Manifestations

The helminths described above cause clinical signs and symptoms affecting the respiratory system by way of 2 main mechanisms: *a*) mechanical lesions caused by the presence of the parasite or by obstruction of vascular or bronchial structures; and *b*) immunological

response to the parasite or one of its component parts. The clinical signs and symptoms are sometimes scant, in which case abnormalities in the results of basic exploratory tests (for example, a chest radiograph and/or a complete blood count) are what reveal the presence of the helminthiasis.

Table 3 lists the main clinical and biological patterns of pulmonary involvement and the helminths that cause them.

Pulmonary Mass or Nodule

The 2 types of helminthiasis that give rise to this pattern are hydatid disease (1 or more pulmonary masses) and dirofilariasis (pulmonary nodules).

Hydatid disease is the most common form of pulmonary helminthiasis. The clinical and biological manifestations of this disease vary according to the number and state of the cysts present. The incubation period between contagion and the appearance of signs and symptoms varies widely, ranging from months to, more frequently, years. Although cases have been reported in patients of all ages from 1 to 75 years, the most common age range in the Mediterranean area is between 20 and 40 years. The prevalence is similar in males and females.^{4,17,63} In general, pulmonary hydatidosis is more common in children than the pure hepatic form of the disease is, an observation that has been attributed to the greater relative compressibility of the lung parenchyma.⁶⁴ Associated liver damage is less common than would appear logical from the pathogenic standpoint (20%-40%) and may depend on the strain of *E granulosus* responsible for the infection.⁶⁵ Overall, it is estimated that 70% to 80% of cases have solitary cysts and that multiple cysts are present in 20% to 30% of cases.^{64,66} Cysts are usually located in the lower lobes, especially in the lower region, and are evenly distributed in both lungs; size ranges from 1 to 20 centimeters.^{64,66} Clinical signs and symptoms depend on whether the cyst is intact or has ruptured and on the complications that

have been caused by the rupture.⁶⁷ Therefore, patients with uncomplicated pulmonary hydatid disease are usually asymptomatic; the most typical sign of a ruptured cyst is expectoration of hydatid material, while in complicated forms of the disease (with, for example, secondary bacterial infection or rupture into the pleural cavity) the patient presents multiple signs and symptoms.⁶⁷ In large case series, the features most commonly reported were cough (62%), chest pain (56%), expectoration (42%), and fever (32%).¹⁷ Up to 10% of cases may develop systemic anaphylaxis during rupture.¹⁷ Depending on the state of the cyst, imaging studies contribute a rich semiology, which has been reviewed in depth by Pedrosa et al⁶⁴ and Ramos et al.⁶⁷

Pulmonary dirofilariasis in humans is usually detected by way of radiographic abnormalities in asymptomatic patients or by the presence of nonspecific respiratory symptoms.¹³ The most common clinical sign is the presence of pulmonary nodules (persistent or transient) or granulomas.^{13,52,53}

Pulmonary Infiltrates

Pulmonary helminth infection is also detected when the patient develops respiratory symptoms (cough, expectoration, dyspnea, and occasionally hemoptysis or chest pain) in association with alveolar infiltrates on plain chest radiography. Concurrent nonpulmonary involvement can help to guide the diagnosis.

Without nonpulmonary involvement. The 2 typical clinical pictures are Löffler syndrome and tropical pulmonary eosinophilia. Löffler syndrome is one of the most confusing denominations in medicine. In addition to the linguistic problems it poses,⁶⁸ the term is used in 2 different ways in the medical literature. It is used to refer to both transient eosinophilic pulmonary infiltrates⁶⁹ and to endocarditis/myocarditis in a patient with eosinophilia.⁷⁰ In the first case, the original description of Löffler syndrome referred to the transit of a helminth (probably *Ascaris* species) through the lung,⁷¹ but the term was later applied to cases of pulmonary involvement and eosinophilia associated with parasitosis without transbronchial transit⁷² and even to transient pulmonary infiltrates caused by drug reactions.⁷³ In the strictest sense, the syndrome is characterized by the appearance of pulmonary infiltrates and peripheral blood eosinophilia secondary to transbronchial migration of *Ascaris* species.⁷⁴ Although classic texts often assert that hookworm, and even *Strongyloides* species, can be associated with Löffler syndrome, well documented cases are rare.

Tropical pulmonary eosinophilia, however, is a well defined syndrome.⁷⁵ Its pathogenesis is a hypersensitivity reaction to antigens of lymphatic filariae (*Wuchereria* species and *Brugia* species). Clinically, this syndrome is found mainly among males whose average age falls somewhere between 20 and 30 years, and important racial differences exist—the highest prevalence is found

in India. The clinical picture is usually characterized by severe asthma that does not respond well to conventional treatment. No abnormalities are found in the chest radiograph of 20% of patients; in the other 80%, the most common finding is reticulonodular infiltrates located mainly in the intermediate and lower lung fields.

With nonpulmonary involvement. When there is nonpulmonary involvement, the main candidate diagnoses are Katayama syndrome, toxocariasis (visceral larva migrans), and *Strongyloides* hyperinfection syndrome.

Since Katayama syndrome is characteristic of acute schistosomiasis it is found more often in travelers than in immigrants.^{8,76} When taking a clinical history it is standard practice to check whether the patient has been in contact with potentially infected fresh water 15 days to 3 months before the appearance of signs and symptoms. In the complete form of the syndrome, patients present with fever, headache, generalized muscular pain, pain in the right hypochondrium, and nonspecific respiratory symptoms (cough, dyspnea). Respiratory symptoms are more common in *S mansoni* infection than in disease caused by *S haematobium*. Physical examination often reveals painful hepatomegaly and occasionally splenomegaly. The most common abnormal findings are eosinophilia (almost always present) and abnormalities in the chest radiograph, primarily micronodular infiltrates, alveolar consolidation, and bronchial wall thickening.⁷⁷ This clinical picture is produced by a hypersensitivity reaction to the helminth. Since this reaction occurs during a stage in the parasite's life cycle before oviposition, direct parasitological studies (examination of stools and urine for eggs) are negative at this time.

Visceral toxocariasis (visceral larva migrans) is a childhood disease found primarily in children who eat dirt and/or bite their nails.^{15,78} The typical clinical signs are hepatic (painful hepatomegaly) and pulmonary (bronchospasm). Other manifestations that may occur include cutaneous symptoms (pruritus and urticaria), articular lesions (arthritis), myocarditis, glomerulonephritis, and neurological abnormalities (for example, epileptic seizures). The presence of elevated transaminase and immunoglobulin levels and eosinophilia is a very typical finding in basic blood analysis.

Strongyloides species infection in immunocompetent patients does not usually give rise to respiratory symptoms, although the presence of asthma has been attributed to this helminth in some cases. However, the situation is different in the case of disseminated strongyloidiasis, a condition usually caused by hyperinfection.⁷⁹ Although cases of disseminated strongyloidiasis in immunocompetent individuals have been reported, this entity is usually associated with 2 risk factors: corticosteroid use and human T-cell lymphotropic virus type 1 infection.^{79,80} In these circumstances, the rhabditiform larvae molt and become filariform larvae, which then enter the bloodstream. The

TABLE 4
Direct Diagnosis of the Helminthic Diseases That Affect the Respiratory System

Genus	Species	Direct Diagnosis
<i>Echinococcus</i>	<i>E granulosus</i>	Visual identification of parasites in expectorated material*
<i>Schistosoma</i>		Visual identification of eggs in feces and urine
<i>Paragonimus</i>		Visual identification of eggs in sputum or feces
<i>Ascaris</i>	<i>A lumbricoides</i>	Visual identification of eggs in feces
<i>Ancylostoma</i>	<i>A duodenale</i>	Visual identification of eggs in feces
<i>Necator</i>	<i>N americanus</i>	Visual identification of eggs in feces
<i>Strongyloides</i>		Visual identification of larvae in feces, sputum or bronchoalveolar lavage (direct examination, Baermann technique, Harada-Mori technique, and culture in agar)
<i>Wuchereria</i>	<i>W bancrofti</i>	Detection of microfilariae in blood (Knott)
<i>Brugia</i>	<i>B malayi</i> <i>B timori</i>	Immunochromatographic test (<i>Wuchereria</i> species)
<i>Dirofilaria</i>	<i>D immitis</i>	None available
<i>Toxocara</i>		None available
<i>Trichinella</i>		Muscle biopsy

*Rare in practice (only undertaken when cystic material is expectorated)

pulmonary signs and symptoms are very varied and correspond to 2 lesional patterns found in isolation or in association: *a*) bacterial infection (caused by bacteria transported from the intestinal tract); and *b*) diffuse alveolar hemorrhage.⁷⁹⁻⁸³ The clinical picture varies considerably, ranging from presentations with very few symptoms to more severe disease characterized by dyspnea, variable cough, hemoptysis, and precordial pressure. Digestive symptoms are also very common (abdominal pain, nausea, vomiting, diarrhea, and constipation). Chest radiography often reveals bilateral or focal interstitial pulmonary infiltrates. Unlike the other entities discussed, disseminated strongyloidiasis is not associated with eosinophilia, and this makes it more difficult for the clinician to reach a tentative diagnosis. Filariform or rhabditiform larvae and even parasite eggs can be detected in sputum and other respiratory samples.

Miliary Pattern and Pulmonary Hypertension

Chronic schistosomiasis is characterized by a miliary pattern found in association with pulmonary hypertension (and even findings indicative of cor pulmonale).^{77,84} This form of the disease corresponds to a granulomatous inflammatory response secondary to schistosome egg embolization; the hypertension is secondary to the granulomatous lesions. The clinical signs and symptoms—which are caused by the pulmonary hypertension—include dyspnea and dull chest pain, and in some cases findings indicative of right heart failure. The most characteristic finding on

TABLE 5
Treatment of the Helminthic Diseases that Affect the Respiratory System

Genus	Species	Treatment	References
<i>Echinococcus</i>	<i>E granulosus</i>	Surgery and/or antiparasitic drugs (albendazole ± praziquantel)	4, 66, 67, 94, 95, 96
<i>Schistosoma</i>		Katayama fever: praziquantel, 20 mg/kg every 12 h for 3 consecutive days + corticosteroids	27, 97
		Chronic forms Praziquantel, 20 mg/kg every 12 hours (1 day) Symptomatic treatment	84
<i>Paragonimus</i>		Praziquantel, 75 mg/kg/day for 3 consecutive days Pleural drainage	85
<i>Ascaris</i>	<i>A lumbricoides</i>	Albendazole, 400 mg as a single dose	12
<i>Ancylostoma</i>	<i>A duodenale</i>		
<i>Necator</i>	<i>N americanus</i>		
<i>Strongyloides</i>		Ivermectin	11
<i>Wuchereria</i>	<i>W bancrofti</i>	Tropical pulmonary eosinophilia Classic treatment: diethylcarbamazine, 6 mg/kg/day for 21 days Alternative options: ivermectin + corticosteroids	75
<i>Brugia</i>	<i>B malayi</i> <i>B timori</i>		
<i>Dirofilaria</i>	<i>D immitis</i>	Unnecessary	52, 53
<i>Toxocara</i>		Albendazole, 400 mg/12 h for 5 consecutive days	15
<i>Trichinella</i>		Albendazole, 400 mg/day for 3 days followed by albendazole, 400 mg/12 h for 15 days + corticosteroids	98

chest radiography is a miliary pattern (similar to that of tuberculosis) and the typical images associated with pulmonary hypertension.

Pleural Effusion

While pleural effusion may appear in several of the forms of helminthiasis mentioned above, this respiratory manifestation is particularly relevant in the case of paragonimiasis.⁸⁵ It is found in between 40% and 70% of patients and is associated with damage to the underlying lung parenchyma in the form of cystic lesions or nodules. While approximately 20% of patients in whom respiratory disease is detected by imaging studies are asymptomatic, the others present some symptom, such as cough or chest pain. An association with peripheral eosinophilia is very often found, particularly in cases with pleural involvement.

Muscular Involvement

Infection with different species of *Trichinella* primarily affects striated muscle tissue (skeletal or cardiac).⁸⁶ Consequently, pulmonary involvement in trichinosis is a result of involvement of the respiratory musculature and in particular of the diaphragm, the muscle most often affected.⁸⁷ More rarely, pulmonary symptoms may be due to the development of myocarditis and heart failure.⁸⁷

Diagnosis

Diagnosis of pulmonary helminthiasis depends initially on clinical suspicion based on the patterns discussed above. Except in the cases of pulmonary dirofilariasis and *Strongyloides* hyperinfection syndrome, peripheral blood eosinophilia is a common finding that can alert the clinician to suspect a possible diagnosis of helminthic disease. Once a tentative diagnosis has been reached, direct methods (detection of the parasite itself, or of specific proteins or genetic material) and indirect techniques (serology) are used to facilitate the final diagnosis.⁸⁸⁻⁹³ Table 4 summarizes the principal direct diagnostic techniques. Although commercial diagnostic procedures are available, we feel it is pertinent to indicate that these techniques can yield false results (both positive and negative), and that such failure gives rise to significant error in clinical practice (T. Gárate, personal communication).

Treatment

The treatment of helminthiasis affecting the respiratory system is principally pharmacological, with surgery being reserved for patients with hydatidosis.^{4,11,12,15,27,52,53,66,67,84,85,94-98} The drugs most commonly used are albendazole, ivermectin, praziquantel, and diethylcarbamazine—the last 3 of which are only available from suppliers outside Spain.

The treatment of pulmonary hydatidosis is based on surgery and/or pharmacotherapy (albendazole and/or praziquantel).^{4,66} The PAIR strategy (involving puncture, aspiration, injection, and re-aspiration) used in other areas of the body is not useful in this site. Surgery is the first-line treatment in the presence of large cysts, superficially located cysts, vital organ involvement, local complications, or a mass effect of cysts. For a comprehensive review of specific surgical techniques see Ramos et al.⁶⁷ Irrespective of the technique used, 2 considerations are important: *a*) if feasible, preoperative treatment (with albendazole alone or in combination with praziquantel) for 1 month will reduce the viability of the parasite;^{94,95} and *b*) it is essential to avoid the dissemination of protoscolices during the intervention. However, the utility of the intraoperative use of protoscolicidal agents (ethanol, hypertonic saline solution, and cetrimide) has not been clearly established. In addition to its preoperative utility, treatment with antiparasitic drugs is an appropriate option in cases that do not fulfill the above-mentioned indications for surgery. The most effective agent is albendazole used alone or in combination with praziquantel, the effect of which is indirect as it serves to increase the concentrations of albendazole. While 3- and 6-month cycles of albendazole were prescribed traditionally, with 15-day intervals between cycles, recent studies indicate that continuous treatment is more effective.⁹⁵

Table 5 shows the most useful therapeutic regimes for the other parasites discussed.

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