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REVIEW

Pleuropulmonary parasitic infections of present times-A brief review

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ABSTRACT

Pleuropulmonary infections are not uncommon in tropical and subtropical countries. Its distribution and prevalence in developed nations has been curtailed by various successfully implemented preventive health measures and geographic conditions. In few low and middle income nations, pulmonary parasitic infections still remain a problem, although not rampant. With increase in immunocompromised patients in these regions, there has been an upsurge in parasites isolated and reported in the recent past. *J Microbiol Infect Dis 2018; 8(4):165-180*

Keywords: *helminths, lungs, parasites, pneumonia, protozoans*

INTRODUCTION

Pulmonary infections are caused by bacteria, viruses, fungi and parasites [1]. Among these agents, parasites produce distinct lesions in the lungs due to their peculiar life cycles and pathogenicity in humans. The spectrum of parasites causing pleuropulmonary infections are divided into Protozoans and Helminths (Cestodes, Trematodes, Nematodes) [2]. Clinical diagnosis of these agents remains tricky as parasites often masquerade various other clinical conditions in their presentation. The commonest mimics of parasitic infections are tuberculosis and lung carcinoma [3,4].

To help clinicians and students understand the spectrum of all these parasitic lung infections, we discuss their epidemiology, clinical presentation, laboratory diagnosis, radiological diagnosis and management. This review intends to provide comprehensive knowledge about all parasites associated with pleuropulmonary infections, the early detection of which results in successful clinical outcomes.

I. Epidemiology of pleuropulmonary parasitic infections

Since parasites have a diverse mode of transmission, life cycle, host-parasite relationship, the distribution is varied. The epidemiological triad of agent, host, and environment for each parasite associated with lung infections are detailed hereunder.

Most of these parasites are prevalent in tropical and subtropical countries which corresponds to the distribution of vectors which help in completion of the parasite`s life cycle [6].

There has been a decline in parasitic infections due to health programs, improved socio-economic conditions. However, the latter part of the last century has seen resurgence in parasitic infections due to HIV, organ transplantations and increase in use of immunosuppressive agents [6]. Due to this reason, pulmonary physicians have developed a renewed interest in recent times in understanding pulmonary parasitic infections. This has also intrigued an interest among research fanatics to invent newer diagnostic tools in diagnosing these agents.

Definitions [7]:

Definitive host: Definitive hosts are the ones in which the parasite matures or passes its sexual stage. They are otherwise termed as primary hosts.

Intermediate host: Intermediate or secondary hosts are those in which the parasite passes its asexual state or is in a larval form.

Parasites which infect respiratory system of humans could be protozoans or helminths [8].

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The protozoan pulmonary infections are: Pulmonary malaria, pulmonary amoebiasis, pulmonary leishmaniasis, pulmonary trypanosomiasis, pulmonary toxoplasmosis, and pulmonary babesiosis [9]. Helminthic pulmonary infections are: Tropical pulmonary eosinophila caused by filarial parasites, pulmonary dirofilariasis, pulmonary strongyloidiasis, pulmonary ascariasis, pulmonary ancylostomiasis, pulmonary paragonimiasis, pulmonary schistosomiasis, pulmonary hydatid disease, pulmonary trichinellosis etc. [9]. The agents causing pleuropulmonary infections, host factors, prevalence (global and national), and mode of transmission are detailed hereunder in tables 1-5.

Table 1. List of parasitic agents causing pleuropulmonary infections [2,5].

PROTOZOANS	HELMINTHS
Amoeba : • *Entamoeba histolytica* **Hemoflagellates :** • *Leishmania donovani* • *Trypanosoma cruzi* **Sporozoa :** • *Plasmodium falciparum* • *Plasmodium knowlesi* • *Babesia microti* **Coccidian parasites :** • *Toxoplasma gondii* • *Cryptosporidium parvum* **Miscellaneous Protozoa :** *Balantidium coli*	**Cestodes :** • *Echinococcus granulosus* • *Echinococcus multilocularis* • *Echinococcus vogeli* **Trematodes :** • *Paragonimus westermani* • *Schistosoma haematobium* • *Schistosoma mansoni* **Intestinal nematodes :** • Hookworm (*Anycylostoma duodenale, Necator americanus*) • *Strongyloides stercoralis* • *Strongyloides fuelleborni* • *Ascaris lumbricoides* **Somatic nematodes :** • *Wuchereria bancrofti* • *Mansonella ozzardi* • *Trichinella spiralis* **Larva migrans :** • *Toxacara canis / Toxocara cati* • *Capillaria aerophila* • *Ascaris suum* • *Mammomonogamus laryngeus* • *Gnathostoma spinigerum*

Table 2. Host-parasite relationship of Protozoan parasites causing pulmonary infections [5].

Parasites (Agent)	Host	Route of transmission
Entamoeba histolytica	Man	Ingestion of food/water contaminated with cyst, sexual contact, vector
Leishmania donovani	Vertebrate host: Man, dog, rodents; Insect vector: Sandfly	Bite of infected sandfly, blood transfusion.
Trypanosoma cruzi	Humans; Vector : reduvid bugs, kissing bugs, triatomine bugs	Contamination of abrasions with reduvid bug`s feces, blood transfusion
Plasmodium falciparum *Plasmodium knowlesi*	Definitive host: Female Anopheles mosquito Accidental host: Man	Bite of female Anopheles mosquito, blood transfusion.
Babesia microti	Definitive host: Deer tick (*Ixodes scapularis*) Accidental host : Man	Bite of ticks, blood transfusion
Toxoplasma gondii	Definitive host : Cats, felines Intermediate host : Man, other mammals (sheep, goat, pig, cattle)	Ingestion of sporulated oocyst from soil, food, water, ingestion of tissue cyst, blood transfusion.
Cryptosporidium parvum	Man, other animals	Ingestion of contaminated food/water, autoinfection
Balantidium coli	Natural host: Pig Accidental host: Man	Ingestion of food/water contaminated with cysts

Table 3. Host-parasite relationship of helminths causing pulmonary infections [5].

Parasites	Host	Route of transmission
CESTODES		
Echinococcus granulosus	Definitive host: Dogs, other canine animals Intermediate host: Sheep Accidental intermediate host: Man	
Echinococcus multilocularis	Definitive host: Foxes, wolves, dogs, cats Intermediate host: Small wild rodents Accidental intermediate host: Man	Ingestion of food contaminated with eggs Mechanical vectors for eggs: flies
Echinococcus vogeli	Definitive host: Wild felids like wild cats, jaguars, brush dogs Intermediate host: Rodents	
TREMATODES		
Schistosoma haematobium *Schistosoma mansoni*	Definitive host: Man Intermediate host: Fresh water snails	Penetration of skin by infective cercariae present in contaminated water
Paragonimus westermani	Definitive host: Man, dogs, cats First intermediate host: Snails Second intermediate host: Crab	Eating uncooked, salted, pickled crab/cray fish containing metacercariae
NEMATODES		
Hookworm	Man	Penetration of skin by third stage (filariform) larva
Strongyloides stercoralis *Strongyloides fuelleborni*	Man	Penetration of skin by third stage (filariform) larva
Ascaris lumbricoides	Man	Ingestion of embryonated eggs from contaminated soil, water, food
Wuchereria bancrofti	Definitive host: Man Intermediate host: Mosquito (Culex, rarely Aedes or Anopheles)	Penetration of third stage filariform larvae deposited by mosquito bite
Mansonella ozzardi	Definitive host: Man Intermediate host: Culicoides	Penetration of third stage filariform larvae deposited by insect bite
Dirofilaria immitis	Human are unusual hosts, lower animals	Bite of mosquito containing L3 filariform larvae
Trichinella spiralis	Optimum host: Pig, Accidental host: Man	Ingestion of raw or uncooked pork or meat containing L1 larvae
LARVA MIGRANS		
Toxocara species	Felines are natural host, humans act as abnormal host	Ingestion of embryonated eggs in soil
Capillaria aerophila	Carnivores. Human infection is rare	Embryonated eggs
Ascaris suum	Pigs. Human infection is rare	Ingestion of egg with an L2 larva
Mammomonogamus laryngeus	Cattle. Human infection is rare	Ingestion of larva or egg containing larva
Gnathostoma spinigerum	Definitive host: Cats, dogs Accidental definitive host: Man Intermediate host: 1st - crustaceans, 2nd - fresh water fish	Ingestion of fish containing L3 larva (or rarely Cyclops containing L3 larva)

Table 4. Global and national distribution of protozoan parasites causing pulmonary infections [5,10-12].

Parasites	Global distribution	Prevalence in Indian states
Entamoeba histolytica	China, Central and South America, Indian subcontinents	Maharashtra, Tamil Nadu, Chandigarh
Leishmania donovani	Bangladesh, India, Sudan, Ethiopia, Brazil	Bihar, Jharkhand, West Bengal, Uttar Pradesh
Trypanosoma cruzi	Brazil, Argentina, Venezuela, United States, Canada, Japan, Australia	No published reports
Plasmodium falciparum	Sub-Saharan Africa, South East Asia, Mediterranean	Odisha, north-eastern states, Andhra Pradesh, Chhattisgarh, Gujarat, Jharkhand, Madhya Pradesh, Maharashtra, Rajasthan
Plasmodium knowlesi	Malaysian Borneo, Thailand, Philippines, Myanmar, Singapore, Vietnam, Indonesia	Andaman and Nicobar islands
Babesia microti	North Eastern United States, South Eastern Massachusetts, Europe	No published reports
Toxoplasma gondii	Low seroprevalence: North America, in South East Asia, Northern Europe, Sahelian countries of Africa Moderate prevalence: Central and Southern Europe High prevalence: Latin America and tropical African countries.	Sub-Himalayan parts of India, Delhi, Maharashtra, South India
Cryptosporidium parvom [13-15]	United Kingdom and New Zealand, Australia, China and Japan, middle east countries, Bangladesh, Nepal	North east states, Kolkata, Delhi, Varanasi, Manipal, Andhra Pradesh, Tamil Nadu
Balantidium coli	Indonesia, Pacific island of Truk	No published reports

II. Emergence and resurgence of pulmonary parasitic infections - current concepts

In spite of stringent policies to contain parasitic infections being rolled out by the World Health Organization, various factors which contribute to the emergence of parasitic infections have been described [47]. Two terms coined to elaborate the parasitic disease ecology are “spill-over” and “spill-back”. Spill over infection is one where the infection present in wild animal hosts gets transmitted to human beings and domestic animals. The reason behind a spill over is due to their intrusion into wild habitats [48]. Spill-back infections are those where wild animals (amplifiers) contract the parasitic infections from humans and domestic animals. These infections are further transmitted after amplification back to domestic animals and human beings residing at their periphery [47].

Among parasites causing pleuropulmonary infections, the following are examples where spill-over/spill-back has occurred: Leishmania, *Trypanosoma cruzi*, Toxoplasma, Sarcocystis, *Plasmodium knowlesi*, Echinococcus, Trichinella etc. [47]. So, one has to keep in mind these agents while making a differential diagnosis especially in geographic areas where a possible spill-over/spill-back may be anticipated.

III. Pathogenesis and immune response in pleuropulmonary parasitic infections [49].

The three key features of immune response against parasitic infections are: i) Nitric oxide mediated killing of eosinophils, ii) IgE antibodies against parasites, iii) Antibody dependent cell-mediated cytotoxicity (ADCC).

Nitric oxide and its derivatives within macrophages have much antimicrobial activity of against bacteria, fungi, protozoa and parasitic worms. Eosinophils are motile phagocytic cells that can migrate from the blood into the tissue spaces. Eosinophils are thought to play a role in the defense against parasitic organisms. The contents secreted by eosinophilic granules may damage the parasite membrane. Majority of humans mount significant IgE responses while encountering parasitic infections. After exposure to a parasite, serum IgE levels increase and sustained levels are observed until the parasite is successfully cleared from the body.

Table 5. Global and national distribution of helminthes causing pulmonary infections [5].

Parasites	Global distribution	Prevalence in India
Cestodes		
pEchinococcus granulosus	South America, Mediterranean countries, Eastern Europe, Northern Africa, Central Asia, India, Nepal	Uttar Pradesh, Tamil Nadu, Andhra Pradesh, Punjab, Pondicherry
Echinococcus multilocularis	Russia, Kazakhstan, China, South-Central Europe, North America	Maharashtra[16]
Echinococcus vogeli	Northern South America, Colombia, Panama, Venezuela	No reports
Trematodes		
Schistosoma haematobium	Caribbean islands, Madagascar, Arabian Peninsula	Maharashtra
Schistosoma mansoni	Caribbean islands, Madagascar, Arabian Peninsula, South America (Brazil and Argentina)	No cases reported so far
Paragonimus westermani	Korea, Japan, Taiwan, China, Philippines	North eastern states of India, mainly Manipur
Nematodes		
Hookworm	Southern Europe, Northern Africa, Northern Asia, Central and South America	Assam, West Bengal, Bihar, Odisha, Andhra Pradesh, Tamil Nadu, Kerala, Maharashtra
Strongyloides stercoralis	South East Asia, Sub-Saharan Africa, South America (Brazil)	Assam, Lucknow, Tamil Nadu, Andhra Pradesh, Mumbai, Pondicherry [17-24]
Strongyloides fuelleborni	Western Papua and New Guinea	No reports
Ascaris lumbricoides	Tropical countries, Bangladesh, China, United Kingdom, Denmark, India, Africa, Nepal[25]	Mumbai, Kashmir, Bihar, West Bengal, North east states, Assam [26,27,28]
Wuchereria bancrofti	Asia, Sub-Saharan Africa, South America, Pacific islands, Caribbean basin	Uttar Pradesh, Tamil Nadu, Andhra Pradesh, Kerala, Gujarat, Bihar, Jharkhand, North-eastern states, Punjab, Jammu and Kashmir
Mansonella ozzardi	Central and South America, Caribbean islands (Haiti, Trinidad), Bolivia, Brazil	No reports
Dirofilaria immitis	USA, Africa, South East Asia, Mediterranean countries	Assam, Kerala, Gujarat, Mumbai, Tamil Nadu [29-32]
Trichinella spiralis	South America, North America, Europe	Punjab, Uttarakhand
Toxocara species[33-37]	Bali, St. Lucia, Nepal, USA, Colombia	Uttar Pradesh, Kashmir, Chandigarh
Capillaria aerophila	Russia, Morocco, Iran, Taiwan, India	Andhra Pradesh, Vellore, Chandigarh [38-40]
Ascaris suum	Similar to *Ascaris lumbricoides*	Similar to *Ascaris lumbricoides*
Mammomonogamus laryngeus	Africa, Brazil, Southeast Asia	No reports
Gnathostoma spinigerum	Southeast Asia, Thailand, China, Japan	West Bengal, Madhya Pradesh, Maharashtra, Assam, Delhi [41-46]

Vasodilatation and increased vascular permeability are beneficial defense processes generated in response to parasitic infection. This results in an influx of plasma and inflammatory cells to encounter the parasite.

Protozoans are unicellular eukaryotic organisms. The type and effectiveness of immune response that develops to protozoan infection depends on the location of the parasite within the host. Many protozoans pass their life-cycle stages free within the bloodstream. During this stage, the type of immunity that plays a major role is humoral immune response. Whereas, many of these same protozoans are also capable of intracellular replication; during this stage, major role is taken over by cell mediated immune response in host defense [50].

Protozoans being unicellular parasites often grow within human cells; on the other hand, helminths are large multicellular organisms that reside/infest humans. They do not ordinarily multiply within humans and are not intracellular in nature. Although helminths are larger in size and are more accessible to the immune system than protozoans, most infected individuals carry few of these parasites. For this reason, the level of immunity generated to helminths is often very poor. Killing of helminths by eosinophils via antibody-dependent cellular cytotoxicity (ADCC) has also been postulated [51].

Fc receptors present on surface of eosinophils bind to IgE and IgG antibody-coated parasite. Once bound to the parasite, the eosinophil releases inflammatory mediators from their eosinophilic granules which further participates in antibody dependent cell-mediated cytotoxicity (ADCC), thereby damaging the parasite [49].

IV. Clinical features and role of imaging in pleuropulmonary parasitic infections

The clinical features produced by parasites infecting the lungs and pleura can be classified as follows [2]:

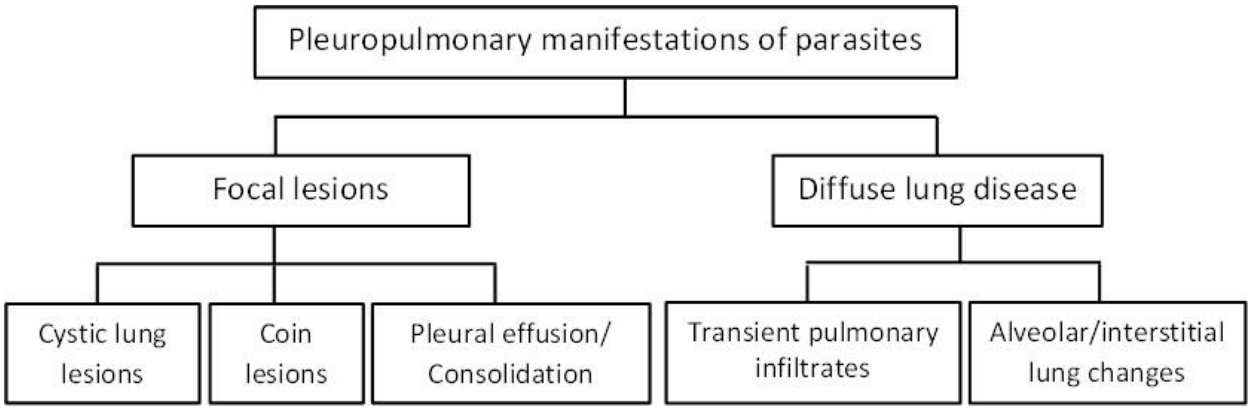

Figure 1. The main pleuropulmonary manifestations of parasites.

Focal lesions [2,9,52]:

Cystic lung lesions are produced by *Echinococcus granulosus, and Paragonimus westermanii.* Coin lesions are seen in *Dirofilaria immitis*.

Pleural effusion and/or consolidation is caused by *Entamoeba histolytica, Leishmania donovani, Cryptosporidium parvum, Paragonimus westermanii, Ascaris lumbricoides, Mansonella ozardi, and larva migrans*.

Diffuse lesions:

Transient pulmonary infiltrates are produced by *Ascaris lumbricoides*, Hookworm, *Toxocara species.*

Alveolar/interstitial lung changes are seen in *Leishmania donovani, Trypanosoma cruzi*, and *Plasmodium species, Babesia microti*, *Toxoplasma gondii, Schistosoma species, Strongyloides stercoralis, Wuchereria bancrofti, Echinococcus multilocularis, Ascaris lumbricoides,* and *larva migrans*.

V. Opportunistic pulmonary parasitic infections

The Centers for Disease Control and prevention defines opportunistic infections as “infections that are more severe and frequently occur because of immunosuppression in HIV-infected persons” [97]. However in early 1990s, individuals with opportunistic infections had an

improved quality of life and improved survival due to use of chemoprophylaxis for various infections [98].

ic involvement reported in HIV-infected patients is mainly due to Leismaniasis, strongyloidiasis and toxoplasmosis.

AIDS defining illness / AIDS defining clinical conditions are a list of diseases published in 1987 by the Centers for Disease Control and Prevention (CDC) that are associated with AIDS, and uniformly used as a guideline for AIDS diagnosis worldwide. It was first published with a list of 24 infections, to which infections were further added and updated in 1993 [99]. Toxoplasmosis due to its complexity in nature, is the only opportunistic parasitic infection included in AIDS-defining illnesses (ADI) ever since.[100] In the recent past, there is a consideration to include leishmaniasis in the CDC clinical category C for the definition of AIDS as an opportunistic pathogen [5].

On the other hand, the World Health Organization (WHO) has postulated four clinical stages of HIV/AIDS. The following parasitic infections are listed under clinical stage 4 suggestive of HIV wasting syndrome: Cryptosporidiosis and atypical disseminated leishmaniosis [101]. Therefore presence of these parasitic infections in an AIDS patient signifies the associated severity of HIV. The reason for this is that patients with clinical stage 4 HIV infection are recalcitrant to antiretroviral therapy.

Pulmonary manifestations of all the above mentioned parasites are more invasive and full blown due to progressive lack of cell mediated immunity [102]. Clinical features and radiological findings as similar as discussed above by take a turbulent course and much severe form.

VI. Laboratory diagnosis of pleuropulmonary parasitic infections [5,105,106]

Sample collection: Usual respiratory samples collected for testing parasites are sputum, tracheal aspirates, bronchoalveolar lavage, pleural fluid, lung tissue biopsy etc. Blood samples are used to examine parasites during primary parasitemia and disseminated infection. Eosinophilia is a common finding in all parasitic lung infections. In case of helminthic infestation, eosinophilia coincides with the larval migration.

The clinical spectrums of opportunistic infections are majorly limited to production of disseminated disease rather than focal lesions. System

Microscopy: Commonly used microscopic diagnosis include saline mount, iodine mount, permanent stains such as Iron-hematoxylin stain, trichrome stain, modified acid fast stain, Giemsa stain, Leishman`s stain, periodic acid Schiff stain, hematoxylin and eosin stain.

Saline mount is particularly helpful in visualizing motile trophozoites and larvae. Iodine mount delineates internal structures/nuclei of cysts and eggs. Concentration techniques done to increase the load of eggs/larvae in clinical specimens are salt flotation, sugar flotation, formol ether sedimentation methods.

Serological diagnosis plays a very minor role in diagnosis since it has less specificity and false positive results are not uncommon especially in high endemic areas. Microscopy and culture play a pivotal role and still remains the gold standard in many conditions. Molecular methods have a very high specificity, decreased turnaround time and have replaced conventional methods in many laboratories.

VII. Treatment and control of pleuropulmonary parasitic infections

Neglected tropical diseases are a group of 13 disabling conditions which were identified by the World Health Organization (WHO) in the year 2006. Ironically, 10 out of these 13 neglected tropical diseases are parasitic infections and 7 of them are associated with pulmonary involvement in immunocompetent as well as immunocompromised individuals. The pulmonary parasitic infections included as neglected tropical diseases are: Chagas disease, Leishmaniosis, Trypanosomiasis, Schistosomiasis, Filariasis, Ascariasis, Hookworm infection [107].

Identification of these infections is one major global level initiative as part of “Millenium development goals”. National programs in India are also noteworthy in containing parasitic infections, few of them being National malaria control program, National malaria eradication program, Roll back malaria, National vector borne disease control program etc. The most recent initiative taken by the Indian government in 2015 was “National Deworming Day” for soil

transmitted helminths which is being observed every year ever since on February 10th [108]. Due to all these initiatives, it is possible to contain preventable parasitic infections to a certain level.

Preventive chemotherapy in terms of mass drug administration has also been practiced in the world.

Examples of such are: 1. Salt containing diethylcarbamazine for Filariasis, 2. Praziquantel for Schistosomiasis, 3. Ivermectin for Onchocerciasis, 4. Adding albendazole to mass-drug administration regimens of diethylcarbamazine or ivermectin, 5. Albendazole and Mebendazole for soil transmitted helminths.

The above mentioned initiatives are supported by WHO in collaboration with pharmaceutical agencies who contribute to administration of drugs [107].

Targeted antiparasitic chemotherapeutic drugs with their mechanism of actions are detailed below in tables 11 and 12.

Table 6. Clinical and radiological features of pleuropulmonary protozoan infections.

Parasitic infections	Clinical features	Radiological features
Pulmonary amoebiasis	Pleuritis, fever, chest pain, cough with hemoptysis (expectoration of anchovy sauce pus), respiratory distress, shock	Pleural effusion, basal pulmonary involvement, elevation of hemodiaphragm, atelectasis, empyema, abscess
Pulmonary leishmaniasis	Pleural effusion, mediastinal adenopathy, pneumonitis. Consideration to include in CDC clinical category C (AIDS) [5]	Pneumonitis, pleural effusion
Pulmonary trypanosomiasis [53,54]	Aspiration pneumonitis	Pulmonary alveolar hemorrhage, alveolitis, pneumonitis, pulmonary emphysema
Pulmonary malaria [55-58]	Pulmonary edema, ARDS	Diffuse interstitial and pulmonary edema, pleural effusion, lobar consolidation, bilaterally pulmonary infiltrates, diffuse bilateral alveolar opacities, bilateral basal ground glass opacities
Pulmonary babesiosis [59]	Fever, diffuse-bilateral-interstitial pulmonary edema and respiratory distress syndrome	Noncardiogenic diffuse-bilateral-interstitial pulmonary edema and adult respiratory distress syndrome
Pulmonary toxoplasmosis [60]	Influenza like illness, fever, pneumonia	Interstitial pneumonia, diffuse alveolar damage, necrotizing pneumonia, obstructive or lobar pneumonia
Pulmonary cryptosporidiosis [61-63]	Chronic cough, fever, dyspnea, parasitic sinusitis	Lower zone consolidation, opacities
Balantidiosis [64,65]	Cough with expectoration, fever, hemoptysis, chest pain, respiratory failure	Upper lobe cavitary lesion, necrotizing lesion

Table 7. Clinical and radiological features of pleuropulmonary helminthic infections.

Parasites	Clinical features	Radiological findings
Echinococcus granulosus · *Cystic Echinococcosis* *Echinococcus multilocularis* Alveolar or pulmonary echinococcosis	Chest pain, cough, haemoptysis or pneumothorax, fever, wheeze, urticaria, anaphylaxis, empyema [66,67]	X ray and CT: Solitary or multiple round opacification mimicking lung tumors. Air-fluid level, water-lily sign, Cumbo's sign (onion peel sign), and crescent sign CT scan: Signet-ring sign, serpent sign, and

Echinococcus vogeli - Polycystic echinococcosis		inverse crescent sign [66,67]
Schistosomiasis	Fever, cough, dyspnoea, rash, pneumonitis, Loeffler-like syndrome, pulmonary hypertension [68]	X-Ray: Nodular ill-defined lesions or reticulonodular changes. CT: Nodular changes and ground glass opacification [69,70]
Paragonimiasis	Pleuritic chest pain, haemoptysis, chronic cough and fever. If pulmonary cysts erode into adjacent bronchi, patients may suffer life-threatening haemoptysis [71]	Patchy consolidation, pleural thickening, pleural effusion, nodular lesions, cystic lesions, cavities, ring shadows CT scan: Round low attenuation cystic lesions filled with fluid or gas may be seen within an area of consolidation [72,73]
Ancylostomiasis	Larval migration causes Loeffler's syndrome including dry cough, wheeze, dyspnea and fever. Bronchitis and bronchopneumonia [74]	Bronchitis, bronchopneumonia, transient pulmonary infiltrates, transient non-segmental areas of consolidation [75,76]
Strongyloides stercoralis	Cough, hemoptysis in hyperinfection syndrome: asthma, ARDS, intra-alveolar haemorrhage [77]	In hyperinfection syndrome: pulmonary infiltrates, military nodules, airspace opacities ARDS in severe disease, rarely granulomatous changes [78,79]
Strongyloides fuelleborni	Respiratory distress [80]	
Ascaris lumbricoides	Cough, wheeze, dyspnoea, chest pain, fever and haemoptysis, Loeffler`s syndrome, chronic eosinophilic pneumonia [81-84]	Transient nodular or diffuse pulmonary infiltrates, basal opacities, spontaneous pneumothorax [84,85]
Filariasis-Wuchereria bancrofti	Cough, dyspnoea, wheeze Fever, malaise, weight loss[86]	Bilateral reticulonodular shadowing, mediastinal lymphadenopathy [86]
Mansonella ozzardi [87]	Cough, pneumonia and plural effusion	Base reticular opacity
Dirofilaria immitis [75,88]	Chest pain, cough, haemoptysis, wheezing, fever, chills and malaise	Coin lesion - established lesions a central necrotic area is surrounded by a granulomatous reaction and fibrous wall. Dead worms may calcify.
Trichinella spiralis	Dyspnoea, cough and pulmonary Infiltrates [89]	Patchy infiltrates, exaggerated and fuzzy lung markings, hilar enlargement [90-91]
Toxocara species [75]	Cough, dyspnea, wheeze, asthma or bronchitis Hepatomegaly, splenomegaly, ocular lesions	Pulmonary infiltrates secondary bacterial pneumonia CT scan – Migratory nodular shadows with halos [92]
Larva migrans: *-Capillaria aerophila* *- Ascaris suum* *-Mammomonogamus laryngeus* *-Gnathostoma spinigerum*	Fever, cough, wheezing, respiratory distress, rhonchi [93-95]	Miliary infiltrates, atelectasis or areas of consolidation, granuloma, fibrosis, calcification [96]

Table 8. Association of CD4 count and pulmonary parasitic opportunistic infections [97].

CD4 count (cells/µl)	Opportunistic infections
<350	Malaria
<200	Amoebiasis, Strongyloidiasis, Schistosomiasis, Leishmaniasis, Chagas disease
<100	Cryptosporidiosis/Isosporiosis, Toxoplasmosis

Table 9. Laboratory diagnosis of pleuropulmonary parasitic infections (Protozoans) [5,105,106].

Condition	Microscopy	Culture	Serological diagnosis	Molecular diagnosis
Amoebiasis	Trophozoites in wet mount, permanent stains	Polyxenic and axenic culture	Isoenzyme analysis, ELISA for lectin Ag, Ab detection, IHA,	PCR targeting small subunit rRNA genes

			CIEP, IFA, CFT, SAT, CIA	
Leishmaniasis	LD bodies in Leishman, Giemsa or Wright stains	NNN medium, Schneider`s liquid medium	CFT, ELISA, IFA, DAT, ICT using rk39 antigen	PCR for Leishmania specific kinetoplast DNA
Trypanosomiasis	Wet mount and thin smear (Giemsa) for trypomastigotes	NNN medium, Yager`s liver infusion tryptose medium	ELISA, IFA, IHA, Western blot, CFT (Guerrerio Machado test), CLIA	PCR for *T.cruzi* specific kinetoplast or nuclear DNA
Malaria	Thick smear, thin smear - Leishman`s, Giemsa, Wright`s, JSB, QBC, fluorescence microscopy (Kawamoto`s technique)	RPMI1640, Delbecco`s modified Eagle medium, Medium 199	ELISA, IFA, IHA, ICT (HRP2, pLDH antigens)	PCR using BRK1 primer
Babesiosis	Thin smear (Giemsa stain) - Maltese cross forms	Animal inoculation in golden hamsters	IFA	PCR for 18S rRNA gene
Toxoplasmosis	Giemsa, PAS, silver stains, immunoperoxidase stain	Mice - intraperitoneal inoculation, tissue culture	DFA, ELISA, IFA, IHA, Sabin-Feldman dye test, IgG avidity, differential absorption test	PCR for Toxoplasma specific genes
Cryptosporidiosis	Wet mount, modified acid fast stain, rapid safranin methylene blue method, carbol fuschin negative staining method, UV epifluorescence	Cell culture (BHK, MDCK cell lines)[103]	ELISA for oocyst antigen, DFA, ICT	PCR for *C.parvum* specific genes
Balantidiosis	Wet mount for Trophozoites and cysts, trichrome stain, Mayer`s hematoxylin stain, iron hematoxylin stain	Boeck and Drdohlav egg serum medium, Balamuth`s media	-	PCR for small subunit rDNA or internal transcribed spacer regions of *B. coli*[104]

ELISA= Enzyme Linked Immunosorbent Assay
IHA= Indirect Haemagglutination
CIEP= Counter Immuno Electrophoresis
DAT= Direct agglutination test
ICT= Immunochromatography
SAT= Staphylococcal adherence test
CIA= Carbon immune assay
IFA= Indirect fluorescent antibody
NNN= Novy, McNeal, Nicolle
CLIA= Chemiluminescence immunoassay
DAF= direct antibody fluorescent test;
BHK= baby hamster kidney;
MDCK= Madin-Darby Canine Kidney;
QBC= Quantitative buffy coat;
PCR= Polymerase chain reaction;
HRP= Histidine rich protein;
pLDH= Plasmodium lactate dehydrogenase;
RPMI= Roswell Park Memorial Institute;
MRC 5= Medical Research Council cell strain 5.

Table 10. Laboratory diagnosis of pleuropulmonary parasitic infections (Helminths) [5,105,106].

Condition	Microscopy & culture	Serological diagnosis	Molecular diagnosis
Echinococcosis	Eggs: Saline and iodine mount, hydatid fluid: direct mount, acid fast stain, H&E stain, PAS	ELISA, immunoblot, CIEP, LAT, IFA, IHA, Ab detection using Em2 and EM-10 antigens	PCR, PCR-RFLP
Schistosomiasis	Wet mount for eggs	HAMA-FAST-ELISA, HAMA-EITB, IHA, IFA, detection of antigens by	PCR, RT-PCR

		ELISA (Circulating cathodic antigen – CCA, Circulating anodic antigen – CAA)	
Paragonimiasis	Wet mount – saline and iodine mount for eggs in sputum, H&E stain	CFT, ELISA (Ab detection against excretory-secretory antigen), Dot ELISA, IHA	PCR
Ancylostomiasis	Wet mount – saline and iodine mount Culture: Harada-Mori filter paper culture, Petri dish/ slant culture, charcoal culture, Baermann technique, agar plate culture	ELISA	Multiplex PCR
Strongyloidiasis	Wet mount – saline and iodine mount, entero test. Culture: Harada-Mori filter paper culture, Petri dish/ slant culture, charcoal culture, Baermann technique, agar plate culture	ELISA for Ab against crude larval antigens	Multiplex PCR
Ascariasis	Wet mount – saline and iodine mount for eggs, charcot leyden crystals in sputum	ELISA, IFA, IHA, micro precipitation test	Multiplex PCR
Filariasis	Thick and thin smear – Leishman`s stain, Giemsa, H&E, concentration techniques (Knott`s, membrane filtration), DEC provocation test, QBC	Antigen detection: using antibodies against Og4C3, AD12 antigens, ELISA Antibody detection: ELISA, ICT, IFA, IHA	DNA probe, PCR-RFLP based assay using ITS 1 – rRNA gene as primer
Trichinellosis	Muscle biopsy (H&E stain), Animal inoculation in rats	Bachman intradermal test, ELISA, CIEP	PCR
Larva migrans	H&E stain of tissue/muscle/skin biopsy Animal inoculation in rats	ELISA with TES-Ag (excretory-secretory antigens) of *T.canis*, CIEP	PCR

Table 11. Common antiprotozoan drugs, their clinical indications and mechanism of action [5].

Antiparasitic drugs	Mechanism of action
Amoebiasis (Extraintestinal)	
Metronidazole, tinidazole, ornidazole (nitroimidazole compound)	Bioactivated to form reduced cytotoxic products which damage DNA
Dehydroemetine	Inhibits protein synthesis
Chloroquine	Concentrating in parasite food vacuoles
Luminal agents (Paromomycin, Diloxanide furoate, Iodoquinol	Inhibits protein synthesis
Trypanosomiasis / Chagas disease	
Nifurtimox	Forms nitro-anion radical metabolite, which reacts with nucleic acids of parasite, causing a breakage in DNA
Benznidazole	Produces free radicals to which *T.cruzi* is sensitive
Malaria	
Chloroquine, Quinine, Mefloquine	Concentrates in parasite food vacuoles, preventing the polymerization of hemoglobin into the toxic product hemozoin
Artemisinin derivative (Artemisinin, artemether, arte-ether)	Generate highly active free radicals that damage parasite membrane
Primaquine	Generating reactive oxygen species
Sulfadoxine-pyrimethamine	Inhibits the production of enzymes involved in synthesis of folic acid within the parasites
Lumefantrine	Accumulation of heme and free radicals
Babesiosis: Clindamycin plus quinine, Atovaquone plus azithromycin	
Toxoplasmosis	
Cotrimoxazole (Trimethoprim-sulfamethoxazole	Inhibiting folate synthesis from PABA (para aminobenzoic acid), thus inhibiting purine metabolism
Spiramycin	Inhibition of protein synthesis in the cell during translocation
Cryptosporidiosis	
Nitazoxanide	Interferes with the PFOR enzyme dependent electron-transfer reaction, which is essential to anaerobic metabolism
***Balantidium coli*:** Tetracycline, Metronidazole	

Table 12. Common antihelminthic drugs, their clinical indications and mechanism of action[5]

Antiparasitic drugs	Mechanism of action
Cestodes	
Praziquantel	Increases permeability of the membranes of parasite cells toward calcium ions which causes contraction and paralysis of the parasite
Niclosamide	Uncouples oxidative phosphorylation
Albendazole	Causes loss of cytoplasmic micro tubules leading to impaired uptake of glucose by larval

	and adult stages of parasites and depleting glycogen stores
Trematodes	
Praziuantel	Discussed above
Tricalbendazole	Binds to beta-tubulin and prevent the polymerization of microtubules
Intestinal nematodes	
Mebendazole, Albendazole	Discussed above
Pyrantel pamoate	Acts as a depolarizing neuromuscular blocking agent, thereby causing sudden contraction, followed by spastic paralysis of helminths
Ivermectin	Kills by interfering with nervous system and muscle function, resulting in flaccid paralysis (more effective for disseminated strongyloidiasis)
Filarial nematodes	
Diethylcarbamazine (DEC)	An inhibitor of arachidonic acid metabolism in microfilaria making it susceptible to phagocytosis
Albendazole	Discussed above
Ivermectin	Discussed above (Alternative drug for Mansonella species)
Doxycycline	Targets the intracellular Wolbachia present inside the Microfilaria (Alternative drug for lymphatic filariasis)

Conclusion

Comprehensive knowledge and insight has been provided in this review on all possible parasites causing pleuropulmonary infections in all groups of patients. This will be a useful tool for pulmonary physicians and clinicians in suspecting, diagnosing, treating and preventing pleuropulmonary infections caused by parasites. Since the burden of parasites causing pulmonary infections is still high and sometimes fatal, it is necessary to have a comprehensive knowledge which would help in improving quality of patient care. Based on clinical presentations and in case of treatment failure for other infectious agents, empiric therapy can be tailored to include antiparasitic agents as well.

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