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CHAPTER 134

Approach to the Patient in the Tropics with Pulmonary Disease

Gregory J. Martin

Pulmonary disease is one of the leading causes of morbidity and mortality throughout the world, and respiratory tract infections are the most frequent infections of humans. Four of the 10 leading causes of global death reported to the World Health Organization (WHO) are attributable to some form of acute or chronic pulmonary disease (***Table 134.1***). Lower respiratory infection (mainly pneumonia) is the leading cause of death in the developing, often tropical, nations.[1]

The viral, bacterial, fungal, and protozoal etiologies of worldwide lung infections are protean. Tropical pulmonary disease includes most temperate climate etiologies as well as a greater incidence and prevalence of tuberculosis (TB), human immunodeficiency virus (HIV)-related disease, and helminthic infections. In addition, a few etiologies are unique to the tropics. Diverse factors such as poverty, crowding, malnutrition, and proximity to animals have additional impacts and are responsible for diseases that are infrequently encountered outside the tropics.

As developing nations make economic transitions, smoking, air pollution, and unregulated occupational and environmental exposures have become significant risk factors for chronic obstructive pulmonary disease (COPD), respiratory tract malignancies, and pneumoconioses. This effect has been most dramatic in large nations with rapid economic changes such as India and China where rates of COPD and respiratory malignancies now exceed those in developed nations.[2,3]

As travel increases, agents responsible for localized outbreaks of disease in remote, undeveloped areas have been more frequently imported to the industrialized world. Vigilance for respiratory illness in the tropics is now recognized as crucial in identifying diseases and trends that will impact health in temperate nations. Most notably in 2003, the ability of a zoonotic coronavirus to infect humans led to the severe acute respiratory syndrome (SARS). SARS rapidly became a public health emergency not only in much of Asia but also in Canada and, to a lesser extent, the United States and Europe, with deaths in 774 of 8098 cases in 29 nations.[4]

Novel influenza viruses have commonly been first discovered in tropical Asian populations where animals, especially chickens, ducks, and pigs, are often kept in close proximity to humans. As outbreaks of avian and swine influenza occur in these areas, sporadic cases of these same strains occur in humans, creating the potential for human–zoonotic recombinations and returning travelers presenting with these "exotic" strains.[5] Novel influenza viruses may be encountered in countries with advanced diagnostics and then later determined to have been circulating in a less well-developed setting for some time, as was demonstrated with the swine–avian–human recombinant H1N1 pandemic strain in 2009.

This chapter aims to facilitate developing a differential diagnosis for patients presenting with pulmonary complaints who are in, or had exposure in, the tropics. Infectious etiologies are more fully considered in pathogen-specific chapters. Emphasis is on those entities found exclusively or more commonly in the tropics or, like respiratory infections in children, those that have a major impact on public health. Common respiratory infections in industrialized, temperate settings are also frequent in the tropics, whereas some pulmonary infections, especially those associated with parasites, are rarely encountered in the temperate setting. Parasitic etiologies associated with respiratory disease from the tropics and their geographic distributions must be considered (***Table 134.2***).[6]

Clinicians evaluate patients' illnesses in geographic areas differently depending on the local disease prevalence and on the resources available. In developing a differential diagnosis for respiratory complaints, it is helpful to consider patients' epidemiologic groups that have considerable differences in their exposures and risk factors:

1. Lifelong residents of the tropics (and those who have recently emigrated from the tropics) who may have established, long-standing infections or infectious sequelae.
2. Travelers from temperate areas who have returned from the tropics after short (less than 3 months) visits; this would include immigrants who return to their tropical home to visit friends and family (generally the highest-risk travelers).
3. Expatriates from temperate areas who are currently living in the tropics or have recently returned from years in the tropics.

The etiologies and diagnostic approaches to each of these groups may be quite different as the intensity of their exposures, potential contact with infected individuals, and access to medical care (and advanced diagnostics) may vary significantly.[7]

ACUTE RESPIRATORY TRACT INFECTIONS, INCLUDING PNEUMONIA

Acute respiratory tract infections (ARIs) include a spectrum of illnesses from colds and influenza to pharyngitis and pneumonia. Upper respiratory illnesses (URIs) are the most common infections in humans in both temperate and tropical climates and are primarily viral in etiology. The frequency of URIs among children is much greater than in adults.[8] Although the frequency of URIs in the tropics appears to be no higher than in temperate climates, children in the tropics often suffer multiple comorbid conditions including chronic malnutrition. Undernourished children experience respiratory infections, coupled with bouts of diarrhea, intestinal helminths, epidemic measles, and more. These comorbidities allow what would be a mild respiratory illness in a healthy child to cause significant morbidity or mortality.[9] The role of viral URIs, particularly influenza and respiratory syncytial virus, in predisposing individuals to subsequent bacterial pneumonia, predominantly with *Streptococcus pneumoniae* and *Haemophilus influenzae,* has emphasized the importance of controlling epidemic influenza in developing nations where vaccines have been historically underutilized.[10]

Acute lower respiratory infections cause most of the respiratory disease-associated deaths worldwide and pneumonia kills significantly more children than any other illness (***Fig. 134.1***).[11] Pneumonia is the primary focus in the WHO's effort to decrease childhood mortality by two-thirds between 1990 and 2015. Although all age groups have some

Table 134.1 Ten Leading Causes of Death Worldwide, 2004

Rank	Cause of Death	% of Total Deaths
1	Coronary heart disease	12.2
2	Cerebrovascular disease	9.7
3	**Lower respiratory infections**[a,b]	**7.1**
4	**Chronic obstructive pulmonary disease**[b]	**5.1**
5	Diarrheal disease	3.7
6	Human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS)	3.5
7	**Tuberculosis**[b]	**2.5**
8	**Cancers of the trachea, bronchus, lung**[b]	**2.3**
9	Road traffic accidents	2.2
10	Prematurity and low birth weight	2.0

[a]*Lower respiratory infections are the leading cause of death in lower-income (mainly tropical) nations, causing 11.2% of deaths.*
[b]*Attributable to some form of acute or chronic pulmonary disease.*
(Reproduced from WHO. The top 10 causes of death. WHO Fact Sheet No. 310. Geneva: WHO, 2008.)

Box 134.1 Etiologies of Childhood Pneumonia in the Tropics

Bacterial Etiologies

Streptococcus pneumoniae (30–50%)
Haemophilus influenzae b (10–30%)

Other Frequent Bacterial Etiologies

Staphylococcus aureus
Salmonella spp. (nontyphoidal)
Nontypable *Haemophilus influenzae*
Mycobacterium tuberculosis (causing acute pneumonia)
Klebsiella pneumoniae
Bordetella pertussis
Group B *Streptococcus*

Viral Etiologies

Respiratory syncytial virus (15–40%)
Influenza A and B
Parainfluenza
Rubeola (measles)
Human metapneumovirus
Adenovirus

Other Agents (Sporadic or Outbreaks)

Mycoplasma pneumoniae
Chlamydia spp.
Pseudomonas spp.
Escherichia coli
Pneumocystis jirovecii (HIV-associated)
Histoplasma spp.
Toxoplasma gondii
Hantaviruses
Hemorrhagic fever viruses

(Extracted from: Rudan I, Boschi-Pinto C, Biloglav Z, et al. Epidemiology and etiology of childhood pneumonia. Bull WHO. 2008;86:408.)
HIV, human immunodeficiency virus.

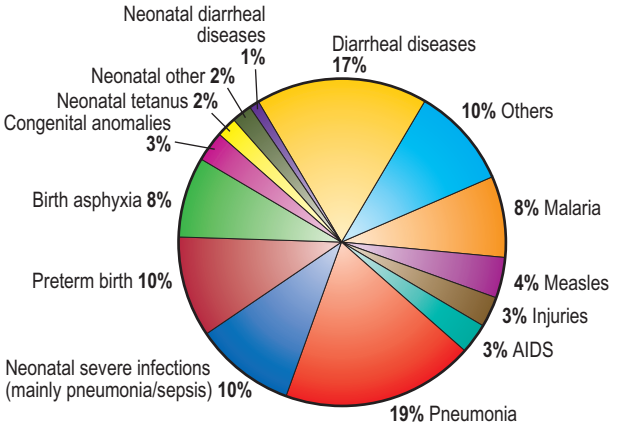

Figure 134.1 Global deaths in children under 5 in 2004. Pneumonia is the leading killer of children worldwide. AIDS, acquired immunodeficiency syndrome.

deaths associated with pneumonia, the greatest burden is borne by elderly adults and children (***Fig. 134.2***),[12] especially those younger than 5 years old. One in five deaths worldwide in children under 5 years old is due to pneumonia. These 2 million annual deaths exceed those from acquired immunodeficiency syndrome (AIDS), malaria, and measles combined.[11]

WHO data reveal a marked difference in the proportion of deaths in children less than 5 years old caused by pneumonia and neonatal sepsis (usually pneumonia-associated) in industrialized nations (5%) versus those in tropical sub-Saharan Africa (28%) and South Asia (34%) (***Fig. 134.3***).[13] The role of coinfection with HIV and/or malnutrition in ARI-associated deaths cannot be overemphasized. WHO data from Botswana, currently the nation with the highest prevalence of HIV infection, revealed that approximately 60% of childhood deaths are due to HIV/AIDS, often associated with respiratory coinfections.[14]

S. pneumoniae and *H. influenzae* remain the most important bacterial causes of pneumonia in young children (***Box 134.1***),[15] accounting for 40–80% of the deaths from pneumonia and neonatal sepsis. The use of *H. influenzae* b (Hib) and, more recently, pneumococcal conjugate vaccines, has dramatically decreased the frequency of these infections in developed countries but, due to their cost, they remain underutilized in the developing nations.[10]

The role of pneumonia associated with *Staphylococcus aureus* and nontyphoidal *Salmonella* remains controversial. In one large, prospective, multicentered study in the tropics, *Staphylococcus aureus* was found in 42% of those children with positive cultures and exceeded even *S. pneumoniae*.[14] Another study in Malawi found nontyphoidal *Salmonella* in the blood of children with radiologic evidence of pneumonia.[16] Nontypable *H. influenzae* and *Mycobacterium tuberculosis* have also been found in lung aspirates in children with acute pneumonia in some studies.[17]

Common causes of atypical pneumonia, such as *Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella* spp., are probably as common in the tropics as they are in temperate areas but have been inadequately studied. There have been numerous reports of outbreaks of legionellosis associated with travel, especially among the elderly. Nearly half of the cases of *Legionella* pneumonia in the United Kingdom are travel-associated.[17]

Fungal etiologies should also be considered if another diagnosis is not readily evident. Although *Histoplasma* sp. infections are not uncommon in many temperate areas, they are also found in much of the tropics and often overlap in distribution with endemic fungal infections such as *Paracoccidioides brasiliensis* in South America and *Penicillium marneffei* in Southeast Asia. Although paracoccidioidomycosis may occur in immunocompetent and HIV-infected individuals, penicilliosis occurs almost exclusively in HIV-infected individuals where, along with cryptococcosis, it is a common opportunistic pathogen. Although each of these mycoses starts with pulmonary disease the progression to a systemic illness with skin, central nervous system (CNS), and other visceral involvement is much more common in the immunocompromised. These infections, common in their endemic zones, should be especially considered in the setting of an "atypical" pneumonia in an immunocompromised host.

Measles, one of the most important viral respiratory diseases, is associated with significant morbidity and mortality in much of the developing world. Since measles vaccination was introduced in 1963, there has been a marked decrease in cases, and the WHO has a goal of worldwide eradication by 2015.[18] Despite a 74% drop in measles deaths globally from 2000 to 2007, there were more than 20 million cases and 197000 deaths in 2007, 95% in children less than 5 years old.[19] Due to recent trends among some groups to avoid childhood immunizations, measles should be considered in the differential diagnosis for fever associated with rash in a returning traveler, especially a child. Death from measles is usually associated with either primary viral pneumonia or secondary bacterial infection with *S. pneumoniae, H. influenzae, S. aureus,* or in some cases secondary viral

Table 134.2 Parasites Associated with Respiratory Illness

Parasite	Distribution
Nematodes	
Roundworms	
Ascaris spp.	Worldwide
Toxocara canis and *T. cati*	Worldwide
Hookworm	
Necator americanus	Southeast Asia, West and Central Africa
Ancyclostoma duodenale	South Europe, North Africa, India, China, Japan
A. caninum	South United States, Mexico, Africa, Asia, South America
Necator brasiliense	South America, Caribbean
Strongyloides stercoralis	Worldwide
Trichinella spiralis	Worldwide
Filaria	
Loa loa	West and Central Africa
Wuchereria bancrofti	Pacific, Asia, Africa, China, Americas
Brugia malayi	Southeast Asia
Dirofilaria immitis	Southeast Asia, America, South Africa, Australia
Other nematodes	
Gnathostoma spinigerum	India, Philippines, Thailand
Strongyloides stercoralis	Worldwide
Trichinella spiralis	Worldwide
Trematodes	
Schistosomes	
Schistosoma mansoni	Africa, South Arabia, South America, Caribbean
S. haematobium	Africa, Middle East
S. japonicum	Far East
S. intercalatum	West and Central Africa
Lung flukes	
Paragonimus westermanii	Far East, China, Japan, Philippines
P. africanus	Africa
P. caliensis	South and Central America
Cestodes	
Hydatid disease	
Echinococcus granulosus	Australia, Africa, South America (endemic)
E. multilocularis	Worldwide
Pentastomes	
Linguatula serrata	Worldwide
Armillifer sp.	Worldwide
Protozoa	
Entamoeba histolytica	Worldwide
Plasmodium falciparum	Africa, South and Central America, Asia
Toxoplasma gondii	Worldwide
Leishmania donovani	Africa, Middle East, South America, Asia
Other	
Pneumocystis jirovecii	Worldwide

(Modified from Savani DM, Sharma OP. Eosinophilic lung disease in the tropics. Clin Chest Med. 2002;23:377.)

infection with herpes simplex or adenovirus. Studies have demonstrated a marked reduction in measles-associated morbidity and mortality after initiation of childhood vitamin A supplementation. This is especially evident in refugee settings where malnutrition with a superimposed measles outbreak may be the leading cause of death.[20]

Particular settings in the tropics may suggest the role of certain bacterial organisms. Examples include staphylococcal pneumonia complicating measles and varicella, pertussis in areas with inadequate childhood immunization, and *Klebsiella* pneumonia in lower socioeconomic rural settings with alcoholism and malnutrition.

Chronic cavitary upper-lobe infiltrates in a patient from Southeast Asia may be misidentified as TB but actually represent melioidosis, an acute or chronic infection with *Burkholderia pseudomallei*, a Gram-negative soil saprophyte endemic to Southeast Asia and part of Australia (see Chapter 33). Melioidosis accounts for 20% of all community-acquired bacteremia in northeast Thailand and is associated with death in 40% of treated patients.[21] It was also the most common cause of fatal, community-acquired pneumonia at a regional referral hospital in the Northern Territory of Australia. In a series of 252 cases of melioidosis in Australia, half presented with pneumonia and one-quarter were bacteremic, 15%

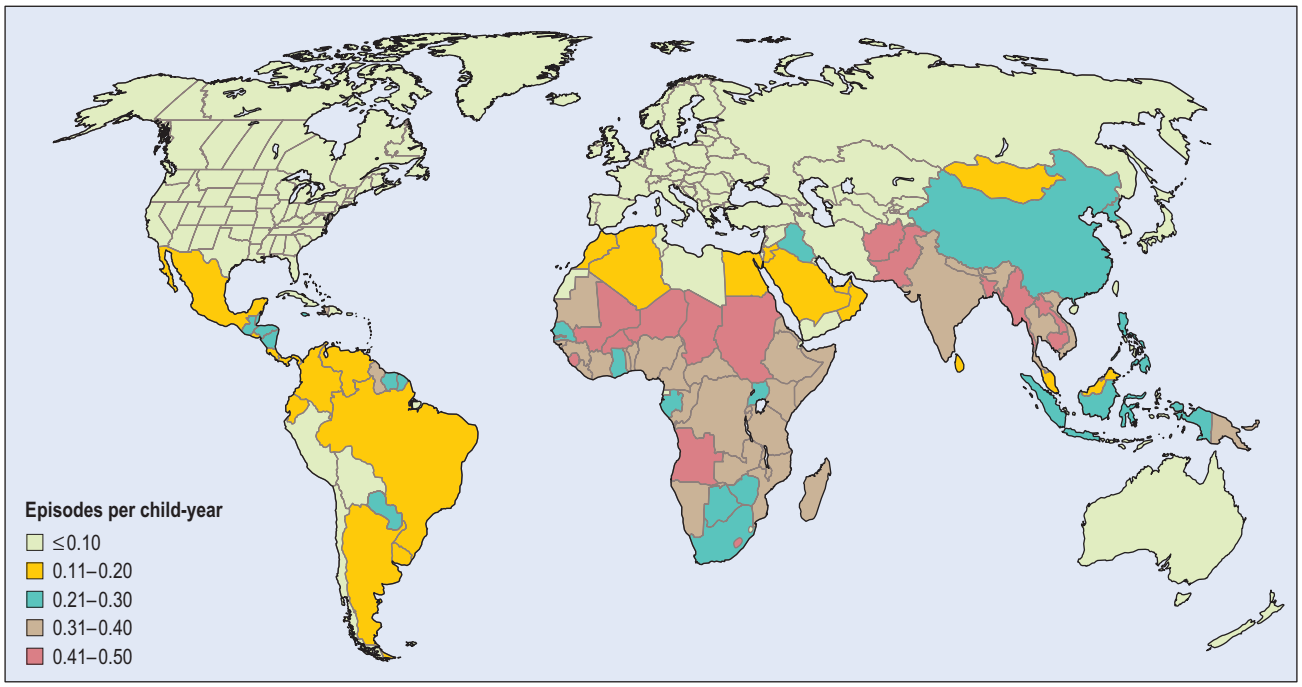

Figure 134.2 Incidence of childhood clinical pneumonia at the country level. (Modified from Rudan I, Boschi-Pinto C, Bilogav Z, et al. Epidemiology and etiology of childhood pneumonia. Bull WHO. 2008;86:408.)

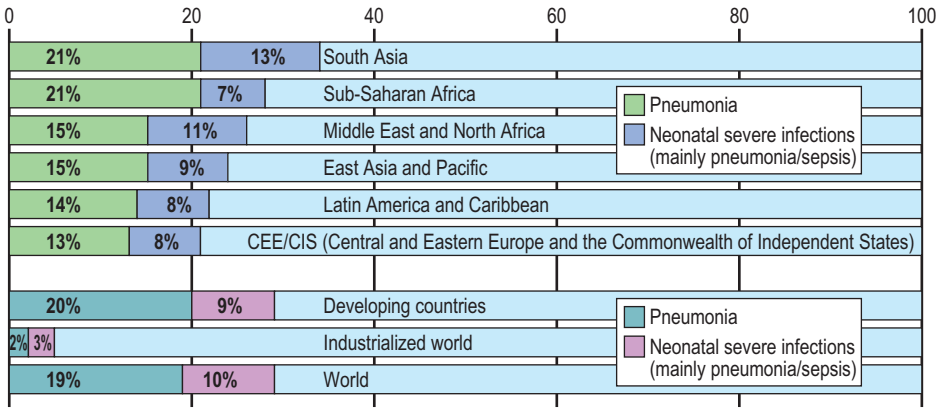

Figure 134.3 Percentage of deaths in children under 5 years old due to pneumonia. (Reproduced from UNICEF/WHO. Pneumonia: The Forgotten Killer of Children. Geneva: WHO, 2006.)

presented with pneumonia and septic shock, and 84% of the septic individuals died.[22] Melioidosis is well documented to occur months to years after exposure and should remain in the differential diagnosis for those with appropriate exposure who present with chronic, subacute, or acute pulmonary disease that may appear to be TB.[23]

Occupational exposures may suggest an etiology for unusual bacterial pneumonias such as anthrax, Q fever, tularemia, and leptospirosis. Outbreaks associated with hantaviruses, pneumonic plague, influenza, and SARS coronavirus are each potential etiologies for pneumonia that may be very regionally specific. Infections with *Paragonimus*, *Echinococcus*, and *Entamoeba histolytica* do not cause typical air space disease but may present like pneumonia and should be considered in the differential diagnosis. Since these rarer etiologies may be encountered sporadically nearly worldwide, it is helpful to query online resources at the time of evaluating a patient. The WHO's Global Outbreak and Alert Response Network (www.who.int/csr/outbreaknetwork/en/) or the US Centers for Disease Control and Prevention's travel notices (www.cdc.gov/travel) have current information on disease outbreaks globally that are helpful when evaluating a returning traveler with pulmonary disease.

There are a number of considerations in treating patients with lower respiratory infections. Bacterial antimicrobial resistance has become an increasing problem worldwide, including in the tropics; however, a lack of antibiotic availability in underserved areas has led to lower prevalence of resistant organisms. Conversely, poorly controlled access to antibiotics and inappropriate use have led to much higher levels of resistance in other areas. One study in Uganda identified 95% of *S. pneumoniae* as penicillin-resistant and 75% of *H. influenzae* as β-lactamase-producing.[24] Despite this resistance, there was a good clinical response to ampicillin, even among HIV-infected individuals.

Availability of antibiotics in developing nations is variable. Many nations have access to less expensive penicillin, ampicillin, chloramphenicol, erythromycin, tetracycline, and aminoglycosides; but more expensive third-generation cephalosporins, fluoroquinolones, and newer macrolides, commonly used in developed nations, are often unavailable. Empiric therapy for adults and children with pneumonia in the tropics has become increasingly difficult with the growing prevalence of HIV infection in many regions. WHO-recommended regimens have, in some studies, been found to be inadequate and recommendations for modifications are imminent.[14]

Availability of oxygen and vaccines may have the greatest impact on respiratory infections in the tropics. Studies have demonstrated a reduction in pneumonia deaths by over one-third with the addition of pulse oximetry and oxygen in hospitals.[24] Additional use of pneumococcal, Hib, measles, pertussis, and influenza vaccines in poorer nations will likely have a significant effect on morbidity and mortality from respiratory infections in the tropics.[25]

CHRONIC COUGH

Cough, a common symptom of URIs, is also frequently associated with pneumonia, COPD, bronchiectasis, sinusitis, and asthma. URIs are among the most common illnesses of travelers but most cough persisting for less than 2 months is associated with relatively benign viral or bacterial etiologies. However, cough may be associated with recent infection with *Ascaris*, hookworm, *Strongyloides,* or schistosomes. Cough persisting for more than 2 months is considered chronic, and a far wider differential diagnosis (***Box 134.2***) should be considered, especially with tropical exposure.[26,27]

In developing a differential diagnosis for chronic cough, indepth inquiry into the patient's travel background and exposure history must be obtained. A knowledge of which infectious agents are endemic to the area is crucial. A short-term traveler to an urban area of the tropics may have only a remote opportunity to have encountered helminths or TB, whereas those with long-term travel to remote areas, and extensive exposure to the local population, have probably had ample opportunity to be exposed to a wide range of endemic infections. Similar exposure considerations should be applied to those who live in the tropics: an urban office worker is much less likely to have had the constant animal, insect, and freshwater contact of a rice farmer in rural areas. Conversely, individuals living in some rural tropical areas may all have some degree of chronic cough due to smoke exposure from indoor fires for cooking and heating.

Box 134.2 Considerations in the Differential Diagnosis of Cough of Greater than 2 Months' Duration, Etiologies Worldwide, and Those More Common in the Tropics

Worldwide

Infection-associated

- Postinfectious inflammation
- Tuberculosis
- Endemic mycoses
- Eosinophilic bronchitis
- HIV-associated opportunistic infections
- Recurrent aspiration

Environment-associated

- Allergic and nonallergic rhinitis
- Reactive airways disease (asthma)
- Pneumoconiosis

Other

- Cigarette smoking
- Chronic obstructive pulmonary disease
- Bronchiectasis
- Congestive heart failure
- Pulmonary neoplasm
- Gastroesophageal reflux
- Sarcoidosis
- Interstitial lung disease
- Angiotensin-converting enzyme inhibitor-associated

Tropics

Infection-associated

- Tuberculosis
- Loeffler's syndrome (helminthic pulmonary transmigration)
- Schistosomiasis (acute or late-stage disease)
- Tropical pulmonary eosinophilia (filarial infection with hypersensitivity)
- Paragonimiasis
- Penicilliosis
- Paracoccidioidomycosis
- Melioidosis
- Chagas disease-associated congestive heart failure

Environment-associated

- Indoor air pollution (heating, cooking)

HIV, human immunodeficiency virus.

TB should nearly always be considered in the differential of chronic cough if there is associated fever, weight loss, and pulmonary infiltrates, particularly in infants and young children. Schistosomiasis and intestinal helminths should be considered in "eco-tourists," campers, and those who report freshwater exposure as well as denizens of the rural tropics. Endemic mycoses, melioidosis, and environmental toxins are potential etiologies that should be entertained in the context of the appropriate geographic region and exposure history. Chest radiographs and serology, as well as sputa and stool microscopy, will usually confirm these diagnoses (if they have been considered).

A complete blood count (CBC) with differential should always be obtained, as cough associated with a helminth infection may have a normal total leukocyte count but a significantly elevated eosinophil count that would guide the diagnostic evaluation (see Chapter 131). Chest radiographs (CXR) are indicated in evaluation of chronic cough as characteristic radiologic findings are seen with many diagnoses. Abnormal CXRs in resource-rich nations are often further evaluated by computed tomography (CT) scan. Although readily available in most developed nations, CT scanners are not available in many tropical countries.[28] Similarly, availability of bronchoscopic evaluation is variable outside developed nations but should be considered if the etiology of cough cannot be determined with less invasive testing. Sputum examination is generally available in most areas and is most important to rule out TB. In contrast to some other diagnostic modalities, microscopists in the developing world are often quite experienced and skilled in reading stains for acid-fast bacteria, protozoa, and helminths. In industrialized nations, routine sputa, and even bronchoscopic samples, are often not examined for fungi, mycobacteria, or parasites. These etiologies, more common in the tropics, should nearly always be considered in the diagnostic evaluation and may require special consideration with technicians and pathologists in the laboratory to ensure specimens are handled appropriately and that the best diagnostic modalities are utilized.

HEMOPTYSIS

Regardless of tropical or temperate exposure, the development of significant hemoptysis nearly always warrants diagnostic evaluation. While trivial hemoptysis with scant streaks of blood is not uncommon with bronchitis, the differential diagnosis should remain broad, especially in those with tropical exposure. While studies of the etiology of hemoptysis vary significantly depending on geographic location (and decade of publication), hemoptysis often indicates an underlying serious disease.

Although bronchiectasis and neoplasia are the most common causes of hemoptysis in developed nations, TB may exceed these noninfectious etiologies in developing nations. Understanding the prevalence of TB in the area of exposure is crucial in developing a differential diagnosis. In a 1997 Israeli study of 208 patients presenting with hemoptysis, only 3 (1.4%) were associated with TB.[29] Similarly, in a 1952 study from Boston, only 2 (1.9%) of 105 cases of hemoptysis were attributed to TB.[30] Conversely, in a 2002 study from Turkey of 108 cases of hemoptysis, 18 (17.4%) were associated with TB[31] and in a 2001 study of 52 patients with hemoptysis from Kuwait, 17 (32.7%) of the cases were attributed to either "old" or active pulmonary TB.[32] A similar study performed in an area with much higher TB rates, such as Afghanistan or sub-Saharan Africa, might find TB in an even greater percentage of patients with hemoptysis.

The role of other infectious etiologies such as *S. pneumoniae, Haemophilus*, melioidosis, endemic mycoses, ameba, and helminthic agents (ascaris, hookworm, *Strongyloides, Echinococcus,* and *Paragonimus)* should all be considered in the differential diagnosis based on the location of the exposure (***Box 134.3***). Hemoptysis evaluation should start with CXR but may require CT or bronchoscopy with biopsies to make a definitive diagnosis. Advising the microbiology and pathology laboratories of the potential for fungal, mycobacterial, and parasitic disease will ensure that appropriate stains and cultures are performed.

Box 134.3 Considerations in the Differential Diagnosis of Hemoptysis, Etiologies Worldwide, and Those More Common in the Tropics

Worldwide	Tropics
Bronchiectasis	Tuberculosis
Bronchogenic neoplasm	Endemic mycoses
Bronchitis	Paragonimiasis
Congestive heart failure	Pulmonary echinococcal cyst
Tuberculosis	Amebic lung abscess
Endemic mycoses	Leptospirosis
Vasculitides (e.g., Wegener's)	Melioidosis
Blood dyscrasias	

EOSINOPHILIA ASSOCIATED WITH PULMONARY COMPLAINTS

Patients presenting for medical attention in (or after visiting) the tropics not uncommonly (up to 5%) are found to have eosinophilia.[33] Although generally not considered to be clinically significant until reaching an absolute eosinophil count of greater than 1500, a relative increase in eosinophils on a CBC will often lead to pulmonary or infectious diseases consultation. The differential diagnosis and evaluation of eosinophilia are considered in Chapter 131.

Evaluation of patients with eosinophilia can be very difficult, especially in the absence of significant symptoms to help guide the assessment. A thorough account of both domestic and tropical travel must be included in the history as well as a detailed inquiry into use of prescription drugs, over-the-counter drugs, and supplements as the etiology may be a hypersensitivity reaction rather than an infection. There are many nonparasitic and noninfectious etiologies that should be considered in the evaluation (see Chapter 131).[34] Stool, sputa, and serologic assays are frequently negative during the larval stages in the pulmonary vasculature.

The intestinal helminths most commonly associated with transmigration of larvae through the lung leading to eosinophilia, frequently referred to as Loeffler's syndrome, are *Ascaris, Strongyloides,* and the hookworms *Necator* and *Ancyclostoma*.[35] Larvae penetrate into the alveolar spaces, are coughed into the mouth and then swallowed, thereby completing their journey to the intestinal tract where the adult stages live. *Ascaris* is most likely to be associated with development of significant pulmonary symptoms; hookworm and *Strongyloides* usually cause minimal inflammation during pulmonary transmigration. Loeffler's syndrome occurs 10–12 days after ingestion of *Ascaris* eggs (or 5–10 days after penetration of hookworm larva) and, if there are symptoms, is characterized by 5–10 days of nonproductive cough, burning substernal chest pain, and frequently, wheezing and rales. CXR reveals ill-defined, patchy, homogeneous consolidation or, occasionally a fine miliary pattern. Infiltrates may be unilateral or bilateral, have indefinite borders, and range from a few millimeters to 2–3 cm.[33,36]

Migration of *Toxocara canis* or *T. cati* larvae in pulmonary tissues as a manifestation of visceral larva migrans (see Chapter 109) is associated with high levels of eosinophilia, and may be associated with fever, hepatosplenomegaly, and transient reticulonodular infiltrates.[34,37]

Schistosomes may be associated with eosinophilia and chest symptoms (see Chapter 122). Acute schistosomiasis (3–8 weeks after schistosome penetration) may be associated with headache, malaise, dyspnea, wheezing, and nonproductive cough, especially while recumbent in bed. Pulmonary symptoms may coincide with the fever (Katayama syndrome) associated with acute infection, but more commonly present a few weeks after resolution of fever and are associated with marked (30–50%) eosinophilia, mild to moderate leukocytosis, and liver enzyme abnormalities.[38] Pulmonary symptoms are likely an immune manifestation in the lung while the organism has become established elsewhere.[39]

Chronic pulmonary disease is a complication of established schistosomal infections as ectopic migration of schistosome eggs occurs. This becomes more common in late disease as portal hypertension leads to portacaval shunts and deposition of eggs embolized in the pulmonary vasculature. The granulomatous response to eggs in the pulmonary vessels leads to pulmonary hypertension and eventually cor pulmonale. Finally, some helminths (mainly *Paragonimus* and *Echinococcus*) establish their adult stage in the lung and may be associated with years of waxing-and-waning eosinophilia and leading to misdiagnosis as TB or fungal infection[37,40] (see Chapters 120 and 123).

Table 134.3 Considerations in the Differential Diagnosis of Pleural Effusions, Etiologies Worldwide, and Those More Common in the Tropics

Worldwide	Frequency of Diagnosis	Tropics
Heart failure	Common	Tuberculosis
Parapneumonic malignancy	Less frequent	Paragonimiasis
Pulmonary embolus		Cryptococcosis
Cirrhosis		Histoplasmosis
Tuberculosis		Amebiasis
Endemic mycoses		Toxocariasis
Nephrotic syndrome		Echinococcosis
Idiopathic		Sparganosis
Hypothyroidism		Gnathostomiasis
Drug hypersensitivity		
Asbestosis		
Collagen vascular disease		
Pancreatitis		

PLEURAL EFFUSION

The etiologies of pleural effusion are extensive (***Table 134.3***). Common noninfectious etiologies such as malignancies, heart or liver failure, collagen vascular diseases, and others predominate in temperate areas. The differential diagnosis of pleural effusion after tropical exposure is skewed due to the high prevalence of TB and HIV-associated disease and the increased incidence of helminthic and fungal infections. In one study from Zimbabwe of 100 consecutive patients with pleural effusion of unknown etiology, pleural biopsy led to a TB diagnosis in 58.[41] Temperate areas with a high TB incidence may also have TB as a common cause of pleural effusion. A study of 642 pleural effusions in Spain (in an area with TB incidence of 95 per 100 000) found TB responsible for 25%, neoplasia for 23%, and congestive heart failure for 18%.[42,43] In areas with low TB prevalence, pleural effusions are rarely associated with TB and are much more commonly a sign of malignancy.

Evaluation of pleural effusion should involve consideration of the clinical setting. Bilateral pleural effusion in a patient with underlying heart disease returning from the tropics is still likely a pleural transudate related to heart failure. Presence of fever, pleuritic chest pain, and leukocytosis are obvious indicators of potential infectious etiologies and are indications for thoracentesis. In addition to cell count, differential, pH, chemistries, Gram stain, and bacterial culture that are routinely obtained, consideration of mycobacterial or fungal disease should prompt appropriate stains and cultures.[44] If CXR or the clinical scenario is consistent with TB, then a large volume of pleural fluid (at least 10 mL) should be centrifuged and the pellet examined with acid-fast (and fungal) stains and culture to increase the diagnostic yield. Adenosine deaminase levels in the pleural fluid, pleural biopsy, and tuberculin skin testing may also be considered as potentially helpful in determining the diagnosis.

An effusion with eosinophilic pleocytosis at pleurocentesis appropriately prompts consideration of helminthic etiologies (***Table 134.4***).[45–47] Although estimates are that 5–16% of pleural effusions are eosinophilic (greater than 10% of nucleated cells are eosinophils), only a minority of eosinophilic effusions are due to infectious etiologies, and even fewer are due to helminths. In most studies, blood or air in the pleural space is most commonly associated with eosinophilic pleural effusion, but malignancy, infection, pulmonary embolus, drug-induced, and asbestos-associated all

Table 134.4 Etiology and Clinical Features of Eosinophilic Pleural Effusions

Etiology	Clinical Features
Chest trauma or thoracic medical procedure	Presence of air or blood in the pleural cavity Pleural fluid is bloody or straw-colored
Malignancy, either primary pulmonary or pleural or metastatic	Increased eosinophils, even in nonbloody effusions
Parapneumonic effusions	Eosinophils appear a month or more after resolution of infiltrate Gram stain and culture are negative for bacteria
Tuberculosis (TB), either pleural or associated with pulmonary infiltrates or nodule(s)	Although eosinophils are rarely associated with TB, the frequency of pleural effusion due to TB is common in the tropics
Endemic fungi such as coccidioidiomycosis, histoplasmosis, cryptococcisis, penicilliosis	If living in or traveling from an endemic area
Parasitic infections: Paragonimiasis, ascariasis, strongyloidiasis, echinococcosis, filariasis, loiasis, toxocariasis, dracunculiasis, amebiasis, cutaneous myiasis	Travel to or living in endemic areas: Pleural fluid exam may reveal ova, larva, or other parasitic forms Paragonimiasis is the most common parasitic etiology (associated with pleural pH <7.1 and glucose <60 mg/dL)
Medication-associated: Nitrofurantoin, isotretinoin, fluoxetine, warfarin, dantrolene, gliclazide, mesalamine, bromocriptine	Usually weeks to months after drug administration but may be as short as hours or as long as years
Pulmonary embolism	18% of pleural effusions are eosinophilic Pleuritic chest pain and dyspnea greater than would be expected with size of effusion
Asbestosis or other pneumoconioses	History of occupational exposure, Pleural effusion is usually the sole radiographic abnormality Up to 50% of asbestos-associated effusions are eosinophilic
Idiopathic	Most commonly in middle-aged males with small to moderate, unilateral effusion. May be long-standing but associated with a good prognosis Should prompt consideration of undiagnosed parasitic infections

(Modified from Kalomenidis I, Light RW. How to approach a patient with an eosinophilic pleural effusion. J Respir Dis. 2003;24:247.)

occur.[45,46] In a 2009 retrospective study of 2205 patients, 135 with eosinophilic effusions, one-third had malignancy, although the higher the percentage of eosinophils in the effusion, the less likely to be associated with malignancy.[47] Patients in or from the tropics presenting with eosinophilic pleural effusion (who do not have an identified etiology) should also have a sputum examination and culture for fungi and mycobacteria. Sputum and stool should be examined for ova and parasites. Bronchoscopy and/or lung biopsy are considerations if less invasive diagnostic evaluation is unrevealing. If biopsies are performed, it is important to consider evaluating tissue for fungi, mycobacteria, and parasitic etiologies in the microbiology and pathology labs.

Of all the parasitic etiologies, *Paragonimus* infections (see Chapter 123) are the most likely to be associated with a significant eosinophilic pleural effusion. Asian studies have found that approximately 50% of cases of paragonimiasis are associated with pleural effusions.[48,49] Findings of pleural pH less than 7.1 and pleural fluid glucose less than 60 mg/dL are characteristic.[46] Sputa exam with *Paragonimus* ova can confirm the diagnosis.

Despite aggressive evaluation, as many as one-quarter of eosinophilic pleural effusions remain undiagnosed, but the prognosis, even if the effusion has been prolonged, has been shown to be better than for those with a noneosinophilic effusion.[46,47]

TUBERCULOSIS

The importance of including TB (see Chapter 35) in the differential diagnosis of nearly all pulmonary complaints from the tropics cannot be overemphasized. Although prevalence and mortality associated with TB are dropping globally, the increase in global population yields increased total cases. Over 85% of the 9.27 million new TB cases in the world in 2007 were from Africa and Asia and 15% of these individuals were HIV-positive.[50] In children, 90% of TB cases and 95% of TB deaths occur in developing nations. Many of these same nations are also burdened with the highest HIV infection rates. As the two infections act synergistically to cause progression of the other, the effects have been devastating, especially in sub-Saharan Africa (see Chapters 81 and 139).

The incidence of multidrug resistance has been a further complication of TB in the tropics.[51] Inadequate treatment and follow-up have led to gradually increasing levels of drug resistance, thus requiring not only sensitivity testing but also more expensive, and potentially more toxic, therapy.

Numerous studies have documented the frequency of TB in those who have immigrated from the tropics. Concerns about travelers visiting areas of high TB endemicity and potential exposures during air travel are frequently raised.[52] Although the increased emphasis on case-finding has yielded a recent rise in the number of air travel-associated cases, the risk of acquiring TB infection among short-term travelers and on flights is quite low.[53] Despite commonly held misconceptions about aircraft air systems, rapid filtering of air leaving the cabin near the floor and released overhead removes most infectious particles. Transmission of TB on aircraft, although extensively reported by the media, has rarely been documented.[54]

In contrast to short-term travelers, those remaining in areas with a high TB prevalence have infection rates approaching that of local populations. This was seen most dramatically in long-term Dutch travelers to Africa, Asia, and Latin America, where their risk of infection increased from approximately 10 to 2000 infections per 100 000 person-years. Health care workers with direct patient contact had more than threefold greater risk of TB than other travelers.[55] Obviously, in considering TB it is critical to know the TB prevalence in the source nation as well as contacts with TB, the living situation, and the activity of the individual evaluated.

Numerous studies have documented that immigrants to developed nations have a much higher incidence of TB disease than natives of developed nations. In 2007, 58% of incident cases of TB in the United States occurred in the foreign-born, and disease incidence is 10 times greater in foreign- than US-born individuals.[56] Approximately 25% of immigrant TB cases diagnosed in the United States present within the first year of immigration. The incidence of active TB among political asylum seekers in

London was 241 per 100 000, 20 times greater than the overall incidence in England.[57] Clearly individuals from developing nations who present with pulmonary complaints, especially chronic cough associated with hemoptysis, weight loss, and night sweats, should have TB considered as one of the most likely etiologies and have CXR, possibly a tuberculin skin test or interferon-γ releasing assay (for those with a history of prior Bacille Calmette–Guérin immunization), and sputa examination as part of the evaluation.

PLASMODIUM-ASSOCIATED PULMONARY FINDINGS

Plasmodium falciparum and, to a lesser extent, *P. vivax* have been associated with significant pulmonary involvement in a minority of infected patients (see Chapter 96). There is no evidence that malarial infections are associated with a true pneumonitis, but pulmonary edema can develop during the treatment of falciparum malaria, especially more severe cases. Malaria-associated pulmonary edema is noncardiogenic (high cardiac index and low systemic vascular resistance) and is considered by most authorities to be consistent with the acute respiratory distress syndrome (ARDS) and related to the malaria-associated increase in pulmonary permeability.[58] Pulmonary edema occurs in less than 1% of all cases of falciparum malaria.[59] More recently, three of five marines who returned to the United States from Liberia in 2003 with greater than 10% falciparum parasitemia developed ventilatory failure and an ARDS-like presentation 48–72 hours after initiation of antimalarial treatment and clearance of parasitemia (unpublished personal data). Malaria-associated pulmonary disease should be considered in the differential diagnosis of those returning from a malarious region with unexplained pulmonary edema.

HIV-ASSOCIATED PULMONARY DISEASE

Like TB, the prevalence of HIV in many tropical areas, especially sub-Saharan Africa, makes it an important consideration in the differential diagnosis of pulmonary disease (see Chapters 81 and 139). TB coinfection is clearly the greatest threat to HIV-infected individuals in the tropics. In 2007, the WHO reported that HIV-infected individuals in sub-Saharan nations with high HIV rates are 20 times more likely to develop TB than those who are HIV-uninfected, yielding rates of TB/HIV coinfection greater than 250 per 100 000.[50] In a study of African children dying from respiratory illness in Zambia, *Pneumocystis jirovecii* (formerly *P. carinii*) pneumonia was exceeded only by acute pyogenic pneumonia as the cause of death in HIV-infected children who were under a year old. Cytomegalovirus, TB, and interstitial lung disease were all common findings.[60]

Etiologies of HIV-associated infectious pulmonary diseases in the tropics include all those seen in temperate areas and an extensive variety of pathogens (see Chapter 139). A few notable geographic considerations are the prevalence of *Penicillium marneffei* and melioidosis in Southeast Asia and Australia, paracoccidioidomycosis in South America, and blastomycosis in areas of Africa, South America, and Asia. These diseases are often erroneously attributed to TB, even in the areas where they are most common. With the frequency of multiple simultaneous pulmonary infections in HIV infection, even for those diagnosed with TB the possibility of additional diagnoses should be considered.

NONINFECTIOUS ETIOLOGIES OF TROPICAL RESPIRATORY DISEASE

Tobacco Use in Developing Nations

Estimates are that a half billion of the world's current population will be killed by tobacco and, by 2030, 8 million people will die annually from tobacco-related diseases, with 80% of these deaths in the developing world. Tobacco currently is a risk factor for six of the eight leading causes of death and its impact has been increasing annually. Aggressive marketing has led to male smoking prevalence that exceeds 50% in much of Asia and Latin America.[61] This consequence of "development" is the most preventable etiology of pulmonary disease.

Rheumatic Heart Disease Presenting with Pulmonary Symptoms

Currently 12 million people worldwide are affected by rheumatic fever (RF) or rheumatic heart disease (RHD). These sequelae of β-hemolytic streptococcal infection continue to be common problems in the tropics. Two-thirds of those afflicted are between 5 and 15 years of age. RHD incidence rates in most developed nations are <1 per 100 000; in Sudan it is 100 per 100 000 and in China 150 per 100 000. Prevalence rates as high as 77.8 per 1000 (in Samoa) have been described and are many-fold higher than in the developed world. The WHO estimates that up to 1% of all schoolchildren in Africa, Asia, Latin America and the eastern Mediterranean may have signs of RHD.[62] Pulmonary complaints and fever in the tropics may represent acute rheumatic carditis or bacterial endocarditis complicating prior rheumatic heart damage. Fever, cough, hemoptysis, and dyspnea may lead to misdiagnosis of a primary pulmonary infection. Pulmonary hypertension or congestive heart failure with pulmonary edema due to RHD is not uncommon in impoverished countries, where secondary prophylaxis to prevent recurrent RHD episodes is difficult to administer and valve replacements are unavailable. Consideration of RF is almost forgotten in much of the industrialized world but should be considered in adults who grew up in the tropics and in children who have recently arrived or visited areas of the tropics with significant rates of RF/RHD.

Pulmonary Diseases Caused by Occupational and Environmental Exposures

Discussion of pulmonary disease in the tropics cannot ignore the role of environmental exposures in acute and chronic lung disease. Poorly regulated working conditions in agriculture and mining have resulted in substantial burdens of occupationally related and environmental lung disease in many regions. Although good prevalence data are lacking, it is likely there are millions of cases of silicosis worldwide and possibly comparable numbers of other lung disorders due to cotton dust (byssinosis), extrinsic allergic alveolitis caused by microbial contamination of agricultural products such as sugar cane, and airway injury from indiscriminant use and poor control of indoor and outdoor air pollutants.[63,64]

There is a dramatic increase in both TB risk and virulence in populations with silicosis, and in those with exposure to silica without overt silicosis. In areas where large portions of men have been recruited into mining, as in southern Africa, this risk factor is very broadly disseminated and may account in part for very high rates of TB in these regions. In a study of 304 men from Botswana who had been employed in South African mines for a mean of 15 years, 30% had pneumoconiosis and 6.8% had progressive massive fibrosis; additionally 26% had a history of, or current, TB.[65]

While adult males are the primary victims of occupational exposures, children and women face increased risk from indoor, nonoccupational exposures due to the use of dung and other biomass fuels for cooking and heating. When combusted, these materials emit everything from silica and other minerals to hazardous air pollutants such as oxides of sulfur and nitrogen, resulting in various clinical syndromes, including silicosis ("hut lung" in this setting), chronic bronchitis, asthma, and increased risk of respiratory tract infection.[66,67] The most severely affected regions are those with colder climates, such as the South American Andes, mountainous regions of central Asia, and the high plains of Africa.

Ambient air pollution due to rapid urbanization has resulted in levels of ozone, oxides of nitrogen, and other irritants (photo-oxidant pollution) that are much higher than even in the worst cities in Europe and North

America. Data from Latin America, India, and China suggest that very high rates of respiratory infection and asthma may be resulting.[67]

SUMMARY

Developing a differential diagnosis for a patient presenting with pulmonary complaints after exposure in the tropics requires clinicians to consider a broad range of infectious and noninfectious etiologies. Determining a diagnosis compels a careful review of a patient's travel and exposure history, as well as the ascertainment of the geographic ranges of various infectious agents. Recognition that many common etiologies of respiratory illness in temperate areas are also common in developing tropical areas will assist in guiding the diagnostic evaluation.

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