Pneumonia in the tropics

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ABSTRACT

Pneumonia in the tropics poses a heavy disease burden. The complex interplay of climate change, human migration influences and socio-economic factors lead to changing patterns of respiratory infections in tropical climate but also increasingly in temperate countries. Tropical and poorer countries, especially South East Asia, also bear the brunt of the global tuberculosis (TB) pandemic, accounting for almost one-third of the burden. But, as human migration patterns evolve, we expect to see more TB cases in higher income as well as temperate countries, and rise in infections like scrub typhus from ecotourism activities. Fuelled by the ease of air travel, novel zoonotic infections originating from the tropics have led to global respiratory pandemics. As such, clinicians worldwide should be aware of these new conditions as well as classical tropical bacterial pneumonias such as melioidosis. Rarer entities such as co-infections of leptospirosis and chikungunya or dengue will need careful consideration as well. In this review, we highlight aetiologies of pneumonia seen more commonly in the tropics compared with temperate regions, their disease burden, variable clinical presentations as well as impact on healthcare delivery.

Key words: epidemiology, infection, pneumonia, tropical, tropics.

INTRODUCTION

Pneumonia continues to be an important cause of death and accounts for 16% of all deaths in children under the age of 5.¹ The disease burden, especially in children, is heaviest in South Asia and sub-Saharan Africa.² These regions have tropical climates, which are characterized by a hot climate present all year round, whilst large volumes of rainfall each year result in the spread of zoonotic diseases. Besides environmental influences, socio-economic factors also impact heavily on the epidemiology of tropical diseases. The tropics, which is the geographical region of the Earth centred on the equator and limited by the Tropic of Cancer on the north and the Tropic of Capricorn on the south, is also home to some of the poorest nations. Together with the movement of people triggered by globalization, mass migrations and climate change,² these dynamics have a profound effect upon the patterns of respiratory tract infections in the tropics.

CLIMATE CHANGE AND NATURAL DISASTERS

Climate change

Global temperatures have risen through the past decades due to greenhouse gas emissions, and we have also seen a rise in a number of extreme meteorological events such as tropical super Typhoon Haiyan in 2013.³ Warmer temperatures and altered rainfall patterns are anticipated to promote outbreaks of infectious diseases due to more hospitable environments for pathogens and lack of ready access to health care.⁴ Prevalence and mortality from pneumonia in children are the highest during rainy months in tropical and subtropical regions of Asia and Africa, which again highlights the pattern of pneumonia against climate.⁵ Global warming and climate change also result in an increase in average as well as nadir temperatures, even in temperate regions.⁶ Hence, areas that were previously free from tropical diseases may now encounter such entities. This is shown by an emergence of tropical diseases in temperate regions, such as an outbreak of leptospirosis in 1998 in Springfield, Illinois in the United States,⁷
Natural disasters and pneumonia

Natural disasters have been linked to disease outbreaks including pneumonia, due to an increased risk of water-, air- and vector-borne diseases. In the post-disaster period, Phase 1 is the impact phase (0–4 days) where victims are rescued and immediate treatment is provided for disaster-related injuries. Phase 2 which is the post-impact phase (4 days to 4 weeks post-disaster) is the period when the first surge of infectious diseases may surface, and Phase 3 the recovery phase (after 4 weeks) when symptoms of diseases with longer incubation periods may declare. Examples of such diseases are influenza and leptospirosis. A tertiary hospital reported an increase in patient admissions for pneumonia and tuberculosis (TB) in the aftermath of Typhoon Haiyan especially in the impact and post-impact phases, and the entity ‘tsunami lung’ has been described in victims who have pneumonia following a near-drowning episode after surviving a tsunami event. Victims described by Inoue et al. were rescued immediately after the tsunami and were in respiratory distress. The term tsunami lung describes both pneumonia from various organisms (such as Stenotrophomonas maltophilia, Burkholderia cepacia and Pseudomonas aeruginosa), as well as severe systemic after-effects such as disseminated aspergillosis.

VIRAL PNEUMONIAS

There are no clear differences in viral aetiologies of pneumonia when comparing tropical with temperate climates. Different authors have found varying impacts of precipitation on viral pneumonias. Respiratory syncytial virus (RSV) is a common causative pathogen in respiratory tract infections and was the most commonly isolated virus in children with respiratory tract infections in a Malaysian study, accounting for 70.6% of patients. In adults, most manifestations are in the upper respiratory tract, although about 10% will develop pneumonia. The virus is detected using polymerase chain reaction methods, immunofluorescent or immunoassay antigen detection, cultures or serology analysis. Treatment is mainly supportive. Aerosolized ribavirin can be used as a specific antiviral therapy for RSV, but this is less well studied in adults compared with infants.

Influenza A

Influenza, which remains a global health burden, displays seasonality. A recent study of viral infectious patterns according to time of the year in a Singaporean medical intensive care unit by Siow et al. showed peaking of influenza cases around the start and middle of the year. In this study, the most common viral isolate was the Influenza A H1N1/2009 virus, followed by human rhinovirus. The seasonal distribution of Influenza A in this study echoes the results of Tang et al. who found the incidence of Influenza A in Singapore to peak during January and June to July period, as well as Chew et al. who noted two peaks during the November to January and June to July period. In Singapore, months with heaviest rainfall are clustered around year-end (October to December), and drier months are clustered around mid-year, in June and July. Pharmacological treatments include antivirals such as oseltamivir and zanamivir to help shorten the duration of illness if administered within 48 h of onset of illness.

The seasonality of influenza therefore cannot be fully explained by rainfall alone. Multiple contributory reasons have been hypothesized, including host behaviour such as spending more time indoors during adverse weather conditions, and altered host defences, but uncertainties remain. We must consider the complex relationship of climate and human behaviour when determining patterns, not just for influenza, but for other respiratory viruses as well.

H5N1 avian influenza

The H5N1 strain of avian influenza was the causative agent of an influenza pandemic in Asia in 1997. Prevalent in poultry and wild birds, animal-to-human transmission occurs to cause a spectrum of pneumonia/pneumonitis, culminating in acute respiratory distress syndrome (ARDS). As of 20 April 2017, the World Health Organization (WHO) recorded a total of 858 confirmed human cases of H5N1 with 453 deaths with a 53% mortality rate. As recently as October 2016, WHO was notified of the Influenza A (H7N9) virus outbreak in China. Since then, it has been noted to have an increased number of cases in December and January. The major risk factor of infection was live poultry exposure. As live poultry markets are commonplace in China, and with Chinese New Year festivities the consumption of poultry in the populace will increase, there will be a higher risk of continued exposure leading to sporadic infections or small clusters of human cases.

Hantavirus

Hantavirus is associated with the Hantavirus pulmonary syndrome (HPS). Its manifestation is as a rapidly progressing non-cardiogenic pulmonary oedema and can mimic that of a severe pneumonia clinically and radiologically. HPS was first discovered in 1993 in the Southwestern United States, and since then has been described in Latin America as well. Risk factors are exposure to rural activities and rodents, and treatment is largely supportive. Other viruses associated with pneumonias are the corona viruses, such as the Middle Eastern respiratory syndrome corona virus (MERS-CoV) and severe acute respiratory syndrome corona virus (SARS-CoV). These entities are beyond the scope of discussion of this paper, but suffice to say their impact on global health has been daunting given 690 confirmed deaths out of 1936 confirmed MERS-CoV infections and more than 8000 cases of SARS-CoV, of which a large proportion
were concentrated within Asia (in particular, China, Hong Kong and Taiwan).34

BACTERIAL PNEUMONIA

There are differences between causative organisms encountered in the tropics compared with temperate climates. Due to both environmental and socioeconomic factors, diseases such as melioidosis, leptospirosis and TB are more widespread in the tropics—these will be discussed later. Observation of the aetiologies of community-acquired pneumonia (CAP) in an Asian outpatient setting showed that the most common isolates were Chlamydia pneumoniae, followed by Mycoplasma pneumoniae and Streptococcus pneumoniae.35

That same systematic review by Peto et al.35 identified S. pneumoniae as the most common pathogen in hospitalized patients with CAP. Although there was great variation in terms of proportion between countries in this study, frequency was similar to the trends observed in European studies quoted in the review and also comparable to findings by Siow et al.16 Interestingly, the most common Gram-negative bacillus isolated in the studies was Klebsiella, with higher proportions being reported in India and Southeast Asia. The authors found that Asian patients with CAP requiring hospitalization yielded a larger proportion of Gram-negative bacilli (9.0% vs 2.7%) and Staphylococcus aureus (4.0% vs 1.4%) isolates compared with referenced European studies.36 However, there was no comparison made between the Asian countries, as certain countries such as Korea and Japan experience a temperate climate compared with the tropical climates of Thailand and Malaysia.35

Siow et al. found the top two causative pathogens to be S. pneumoniae and Klebsiella pneumoniae in a recent study looking at bacterial isolates from severe CAP patients in a Singaporean medical intensive care unit.16 Streptococcus pneumoniae was the main Gram-positive bacterium isolate, and S. aureus was the next common Gram-positive organism. Otherwise, Gram-negative organisms such as K. pneumoniae, Escherichia coli and P. aeruginosa represented the majority of cases detected. Similarly, Lin et al.37 described K. pneumoniae not only as a prevailing cause of CAP with bacteraemia in a Taiwanese tertiary hospital, but also showed that it was associated with a more fulminating clinical course and worse prognosis when compared with patients with S. pneumoniae CAP with bacteraemia. In a series of severe CAP cases in Singapore, patients who had Gram-negative organisms isolated tended to have a worse outcome including a higher mortality, especially for patients with Pseudomonas and Burkholderia pseudomallei infections.38 This has changed the way local clinicians initiate their empiric treatment for patients admitted for severe CAP, with antibiotics deliberately chosen to cover Gram-negative organisms, melioidosis as well as Gram-positive pathogens. A systematic review by Goyet et al.39 looking at resistance patterns of CAP pathogens in Cambodia and neighbouring countries showed that up to 14% of S. pneumoniae and 26.5% of K. pneumoniae were resistant to amoxicillin-clavulanic acid. Streptococcus pneumoniae also displayed a high resistance to trimethoprim/sulfamethoxazole (average of 78.2%) and wide range of resistance patterns to cephalosporins: between 5.7% and 33.3% to ceftriaxone, and up to 47.4% to cefuroxime. There was also a mean high-level resistance rate to penicillin G of 25.2%. Burkholderia pseudomallei did not show resistance to first-line treatments cefazidime, carbapenems and trimethoprim/sulfamethoxazole. As a result of this study, the authors have advocated the preservation of fluoroquinolones as they are not warranted as first-line therapy, and they are also used to treat TB, which importantly is endemic in this region.39 This highlights the importance of continued surveillance of regional resistance patterns and revision of therapeutic guidelines.

MELIOIDOSIS

Melioidosis was first described by Krishnaswami and Whitmore in 1911, when they noticed a ‘glanders-like’ disease afflicting opiate addicts in Rangoon.40 Today, melioidosis still poses a threat to public health due to mortality rates up to 40%41 if early treatment is not instituted. In an endemic country like Thailand, it can account for up to 32% of the pathogens identified in adult patients with pneumonia.42 Currie and Kaestli41 estimated global mortality from melioidosis in 2015 to be 89 000, comparable with deaths from measles, and higher than those from dengue and leptospiral disease.

The causative pathogen, B. pseudomallei, is a Gram-negative rod that is found in soil and fresh water. It occurs mainly in Northern Australia, Southeast Asia, China and South Asia with increased incidences during rainy seasons. This is in contrast to temperate countries where melioidosis is extremely rare and almost always encountered in migrants or travellers.43

Presentation of melioidosis can be either acute or subacute. Acute illnesses usually present with pneumonia which can be associated with ARDS and shock. Subacute presentations may take a more insidious course, mimicking TB. There is also a propensity for the pathogen to spread haematogenously, and patients may present with extrapulmonary manifestations such as solid organ and skin abscesses, and even septic arthritis and encephalomyelitis. Diagnosis of melioidosis is confirmed on positive cultures. With potential mortality rates approaching 40%,41 a clinician’s suspicion must be high when faced with a patient with severe CAP coupled with an appropriate travel history. In the local context, because of being in an endemic region, intensive care units including those in Singapore have adopted empirical antibiotic treatment to include specific coverage for melioidosis (ceftriaxone and meropenem would be appropriate) for patients admitted with severe CAP.36,44 Indeed, in a prospective study over 20 years in Darwin, mortality rates have improved over time (22% described by the authors) with better recognition of the disease as well as early treatment with appropriate antibiotics.45
LEPTOSPIROSIS

Leptospirosis is a zoonotic disease prevalent in the tropics, with a much higher incidence than in temperate regions. Within the Asia Pacific region, high-incidence countries include Thailand, Bangladesh and Cambodia. There are also certain regions such as Korea and China where leptospirosis incidences, although low, are increasing.\(^{46}\) Leptospira are aerobic spirochetes. Both feral and domesticated animals can host the disease—commonly, dogs, cattle, rodents, swine, but interestingly, and rarely in cats. Human infection typically occurs after contact with contaminated urine, animal tissue, water or soil.

In the tropics, it especially affects low-income regions with poor sanitation, low education and poor housing, where outbreaks are common and morbidity is high. Even in higher income regions, heavy rainfall leading to flooding increase the risk of both humans and livestock exposure to contaminated water. For example, there was an outbreak in Anuradhapura, Sri Lanka. Anuradhapura is a region with abundant paddy fields for rice farming and was not previously known as an endemic area, so the diagnosis and outbreak of leptospirosis which followed flooding was initially challenged by local clinician.\(^{47}\) Recreational events such as caving, canoeing and freshwater swimming could expose humans to contaminated sources. An example highlighting the impact of these activities would be the 1998 leptospirosis outbreak in Springfield, Illinois, involving triathletes who were exposed to lake water.\(^7\)

Clinical features are variable. It can take a subclinical, self-limited course, or can progress to severe and potentially life-threatening illness complicated by jaundice, renal failure and ARDS, with reported mortality rates up to 30%.\(^{48}\) Typical presenting complaints include fever, myalgia, headaches and conjunctival insufflation. Cough, nausea, vomiting and diarrhoea are common. Dall’Antonia et al. described cough and haemoptysis in patients with serologically proven leptospirosis.\(^{49}\) Severe forms of the disease with multisystem dysfunction and ARDS-like syndromes may be fatal.\(^{50}\) Chest roentgenogram findings are non-specific; they commonly show non-segmental patchy or even nodular infiltrates with poorly defined margins usually in the lower lobes, which can be unilateral or bilateral.\(^{51}\) Interestingly, leptospirosis and chikungunya co-infection can potentially lead to a delayed diagnosis and subsequent deleterious outcomes. Nhan et al.\(^{52}\) described a fatal case of leptospirosis and chikungunya co-infection in a French-Polynesian outbreak during the rainy season, where diagnosis was delayed due to overlapping symptoms. Co-infections with dengue have also been described by Pan et al.,\(^{53}\) where three cases of co-infection were detected during a dengue outbreak. Again, diagnosis was challenging because of non-specific symptoms such as fever, chills and myalgia. Adding on to the diagnostic challenge, Sathiyakumar et al. described a case of haemorrhagic pneumonitis secondary to leptospirosis,\(^{54}\) which showcases the spectrum of clinical presentation.

The diagnosis of leptospirosis is both clinical and microbiological, but the gold standard is the microscopic agglutination test (MAT). Cumberland et al. found the MAT to have a sensitivity of between 30% and 76% (depending on when samples were taken in the disease’s time course), and 97% specificity.\(^{55}\) Leptospira can be grown in vitro from blood, cerebrospinal fluid and urine from infected hosts. However, the laboratory needs to be notified if Leptospira needs to be isolated as it requires specialized culture media, and time to positive cultures can take between 1 week and 3 months. Should the clinician strongly suspect leptospirosis clinically, empiric antibiotics such as doxycycline or ceftriaxone should be started.

SCRUB TYPHUS

The strain of rickettsial illness encountered in the tropics is scrub typhus—a mite-borne disease caused by Orientia tsutsugamushi, a Gram-negative coccobacillus. It is predominantly found in the Asia Pacific rim, with larval mites (’Chiggers’, from the genus Leptotrombidium) that live on vegetation and rodents. Wu et al. have described a rise in the incidence of scrub typhus in Mainland China between 2006 and 2014 with a 12.8 times increase.\(^{56}\) On top of seasonal peaks, the authors postulated that the increase of popularity in ecotourism have exposed more people to vector habitats.\(^{57}\)

Clinical manifestations typically include myalgia, high fevers, headaches, as well as a rash and eschar at the chigger bite. Scrub typhus is usually self-limiting over 2–3 weeks but is sometimes associated with severe illness and multiorgan failure leading to death, although this is rare.\(^{57–59}\) Pneumonia can occur in the late phase of the disease\(^{57,58,60}\) as well as in an ARDS-like picture.\(^{58}\) Pulmonary involvement is well described. Chest roentgenograms may be abnormal in 59–72% of patients, and may show bilateral diffuse reticulonodular opacities, septal lines and hilar lymphadenopathy. Consolidation is not common, and would tend to appear in the lower zones. Pleural effusions can be found in up to 42.6% of patients.\(^{59,61}\)

The diagnosis is confirmed on serological testing or eschar biopsy, but there should be a suspicion of scrub typhus infection if there is an appropriate exposure history. Patients who have been started on appropriate antibiotics (such as doxycycline, chloramphenicol and azithromycin) usually have defervescence of the fever within 48 h.

TUBERCULOSIS

Countries in the tropics bear the brunt of TB.\(^{62}\) and South East Asia holds approximately one-third of the global burden of TB.\(^{63}\) Peto et al. found more than 10% of cases of CAP in Asia were attributable to Mycobacterium tuberculosis.\(^{35}\) However, with the rise in tourism and immigration, TB is now seen in higher income countries, with a substantial proportion of cases diagnosed in immigrants in the United States and England.\(^{64,65}\) People at risk include those with poor nutrition, immunocompromised and those living in poorly ventilated and overcrowded environments.
Spirometry tends to demonstrate a restrictive pattern with airways obstruction, and airway obstruction is usually reversed by bronchodilators. Treatment with diethylcarbamazine is associated with rapid improvement in signs and symptoms, as well as a gradual trend towards normal in spirometric values, although permanent impairment in lung function can occur.74

**Paragonimiasis**

The causative pathogen, *Paragonimus westermani*, is endemic in much of Asia and South America. A food-borne trematode, infection is caused by ingestion of raw improperly cooked freshwater crabs. Patients may be asymptomatic although can also experience a chronic cough, chest pain and haemoptysis which can be recurrent. Radiological findings include pleural effusions, pneumothorax, ring shadows and consolidation on chest roentgenograms.7576 Computer tomography scanning can reveal cysts within the consolidated lung.76 Paragonimiasis is treated with triclabendazole or praziquantel.

**Strongyloides stercoralis**

Strongyloides infection is common in the tropics, sub tropics and warmer temperate climates. Nematode larvae spread haematogenously as well as via the lymphatics to the heart and lungs.

Patients can present with Loeffler’s syndrome and peripheral eosinophilia during larval migration through the lungs. Respiratory signs and symptoms include cough, bronchospasm and in some cases haemoptysis. Chest roentgenography can be normal. During larval migration, miliary nodules or ill-defined patchy consolidation may be present. In an overwhelming infection especially in the immunocompromised host, a marked bilateral alveolar pattern similar to that of pulmonary oedema can be seen, and clinically the patient would be in ARDS.757678 Diagnosis of strongyloides can be strengthened with examination of several stool samples on several days. Larvae may also be demonstrated on duodenal aspirates, sputum and bronchoalveolar lavage fluid.77 Ivermectin and albendazole can be used for effective treatment.7778 Additionally, clinicians need to be aware of gut translocation of enteric organisms especially in immunocompromised hosts, leading to further complications of sepsis.78

**Malaria**

Malaria is caused by the intraerythrocytic protozoa *Plasmodium*. It is transmitted to humans by the bite of the female *Anopheles* mosquito, and *falciparum malaria* is the most severe of all malarial infections. The symptoms leading to a suspicion of malarial infection are fever which can be cyclical, breathing difficulties and anaemia. Once the disease is suspected, light microscopy is the standard tool used to detect parasites on blood smears. Rapid diagnostic tests utilize antigen detection technology as an alternative when reliable light microscopy is unavailable, and the WHO is recommending its use as a field alternative when rapid
diagnosis is paramount. There is a wide range of pulmonary manifestations, from a non-productive cough to ARDS, occurring in up to 25% of adults with severe falciparum malaria infection although any strain of Plasmodium can lead to ARDS. The development of ARDS portends an extremely grave prognosis. Gachot et al. described a 33% mortality rate in patients with malaria and acute lung injury despite admission to an intensive care unit. Chest roentgenogram findings are non-specific and can range from confluent nodules to basal and/or bilateral pulmonary infiltrates, mimicking pulmonary oedema, although this is usually non-cardiogenic. Resistance to antimalarial drugs especially chloroquine and sulfadoxine-pyrimethamine has become widespread. WHO now recommends artemisinin-based combination therapy (ACT) as the first-line treatment in uncomplicated falciparum malaria. For uncomplicated, non-falciparum malaria in regions with low chloroquine resistance, chloroquine can be used.

OTHER PATHOGENS

We have summarized the common pathogens causing pneumonia in tropical regions in Table 1. Other differentials of pneumonia in the tropics would be TPE, pulmonary plague, histoplasmosis, cryptococcosis, thoracic actinomycosis, nocardiosis and pulmonary anthrax. However, these are beyond the scope of this review, and we would urge clinicians to practice careful history taking including a travel and exposure history, and conscientious examination to lead them towards the correct diagnosis.

CONCLUSIONS

The burdens of pneumonia in tropical and subtropical regions remain high, especially when coupled with global warming and climate change. With the advances in air travel, immigration patterns and international tourism would mean tropical diseases including pneumonias would be encountered in the temperate countries as well. It is important for clinicians to recognize these relations and conditions so that correct treatment can be instituted early, as some of the tropical diseases such as leptospirosis, melioidosis and malaria with ARDS herald a poor prognosis if treatment is delayed. Clinicians will need to be cognizant of co-infections with overlapping symptoms such as chikungunya or dengue co-infection with leptospirosis, as late diagnosis would potentially lead to deadly consequences.

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