Pneumonia in the tropics: Report from the Task Force on tropical diseases by the World Federation of Societies of Intensive and Critical Care Medicine

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ABSTRACT

The aetiology of community acquired pneumonia varies according to the region in which it is acquired. This review discusses those causes of CAP that occur in the tropics and might not be readily recognizable when transplanted to other sites. Various forms of pneumonia including the viral causes such as influenza (seasonal and avian varieties), the coronaviruses and the Hantavirus as well as bacterial causes, specifically the pneumonic form of *Yersinia pestis* and melioidosis are discussed.

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1. Introduction

In general, community acquired pneumonia (CAP) is caused by pathogens that are common to all geographical areas; *S. pneumoniae*, viruses, chlamydia, mycoplasma, legionella and less commonly *S. aureus* and *K. pneumoniae*. However some organisms are endemic to specific regions and early recognition and awareness of these is critical to the diagnosis and to a favourable outcome. This is no less the case in residents of or travellers to tropical regions. This review discusses those that are most prevalent and which can cause potentially lethal infections.

2. Viral infections

In adults, respiratory viruses account for 10% to 40% of CAP and the most common of these are influenza, parainfluenza, adenovirus and respiratory syncytial viruses (RSV) [1,2]. Influenza viruses which are classified by their core proteins (i.e. A, B or C) and belong to the family orthomyxoviridae, cause predominantly respiratory disease in humans. Influenza type A and B account for >50% of viral pneumonia in adults whereas influenza C infections generally cause mild respiratory disease and are not thought to cause epidemics [3]. The close contact between humans and animals in tropical areas may enhance the genetic reassortment of influenza viruses which when disseminated into the human population may result in pandemics [4]. Other important respiratory viruses in the tropics that can cause severe pneumonia are Influenza A H1N1, avian influenza viruses (H5N1, H7N9), Severe Acute Respiratory Syndrome associated Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [5,6]. Standard, droplet and contact precautions are recommended for these selected acute respiratory infections and whenever possible patients should be placed in airborne infection isolation rooms.

3. Influenza viruses

Influenza viruses have been associated with annual epidemics and intermittent pandemics throughout the world. Despite the absence of a winter season in the tropics, consistent seasons of infection have nevertheless been observed. The composition of the antigenic surface glycoproteins of the influenza virus, hemagglutinin (H) and neuraminidase (N) are used for subtyping, resulting in names like H3N2 and H1N1. Antigenic drift represents the minor changes of H and N side chains and is responsible for seasonal epidemics. Influenza pandemics occur less frequently and these result from major changes in antigenic structure in the envelope glycoproteins (antigenic shift) resulting from reassortment of various viruses such as swine, equine and human varieties. Contemporary geographic distributions show that East, South and Southeast Asia influence unduly the evolution of seasonal influenza A (H3N2), exporting most of the evolutionarily strains that ultimately spread globally. The obvious role of Asia in H3N2's evolution has been ascribed to the seasonal nature of influenza in temperate climates [7].

Seasonal influenza is an acute respiratory illness caused by influenza A or B viruses. Given that these infections including the pandemic variety H1N1 now occur in all parts of the world they will not be discussed in any detail in this treatise.

3.1. Avian influenza viruses

Avian influenza viruses (e.g. H5N1 and H7N9) have emerged relatively recently and cause disease in humans and currently remain a potential threat, particularly in the Southeast Asia [5,8].

3.1.1. Avian influenza H5N1

The first association of avian influenza H5N1 with clinical respiratory disease was in 1997 in Hong Kong, as a human infection transmitted from birds. Later H5N1 re-emerged in humans in 2003 as a highly pathogenic virus resulting from antigenic drift to which a larger number of species were vulnerable and conferring resistance to adamantine antivirals [9]. As yet, human to human transmission is rare and the vast majority of cases are related to contact with birds. Travellers who have a history of recent exposure to birds in affected areas and who present with otherwise unexplained ARDS should be screened. H5N1 has been reported from 16 countries and is currently most prevalent in Egypt [9]. As of August 2017, from 859 laboratory confirmed cases of influenza A H5N1, 453 (53%) patients have died [10].

3.1.1.1. Clinical. Following exposure, the incubation period is seven days or less. Clinical characteristics include fever, respiratory illness, pneumonia, diarrhoea and encephalopathy. Laboratory abnormalities may include leukopenia, lymphopenia, thrombocytopenia and elevated serum aminotransferases. Complications include multi-organ failure, pulmonary haemorrhage, pneumothorax and pancytopenia. Radiographic findings include diffuse or patchy infiltrates and segmental or lobar consolidation. Progression to respiratory failure is associated with diffuse bilateral ground-glass infiltrates.

3.1.1.2. Diagnosis. A comprehensive travel and epidemiological history is critical in suspected cases. Patients who meet clinical and epidemiological criteria should be tested for H5N1 avian influenza infection. Diagnosis can be established by rRT-PCR or viral culture of respiratory specimens. Serological testing is not helpful in the acute setting but useful for retrospective diagnosis [11].

3.1.2. Avian influenza H7N9

3.1.2.1. Introduction. Another avian influenza virus, H7N9, derived from reassortment of at least four avian influenza viruses, has caused severe pneumonia in some patients. It emerged in 2013 and originated from Eastern China [12]. Additional cases have been detected in mainland China, Hong Kong, Macao, Taiwan and Malaysia. Similar to H5N1 this virus occurs primarily in bird handlers or following recent exposure to live poultry or potentially contaminated environments. To date, there is no evidence of sustained human-to-human transmission. The incubation period has been estimated to be from 3 to 7 days, but can be as long as 10 days.

3.1.2.2. Clinical. Presenting signs and symptoms may include fever, cough, dyspnoea, headache, myalgia and malaise. Patients present with LRTI which may progress rapidly to pneumonia and potentially acute respiratory failure, ARDS, septic shock, multi-organ failure, rhabdomyolysis and encephalopathy. Severe illness and fatal outcome have been frequently observed in pregnant women, older persons and

those with chronic illnesses [13,14]. As of mid-August 2017, a total of 1557 laboratory-confirmed cases have been reported to WHO including 605 (39%) deaths [10].

3.1.2.3. Diagnosis. Real-time reverse-transcriptase polymerase reaction (rRT-PCR) for avian influenza A H7N9 is the preferred diagnostic test, since rapid antigen tests may be insensitive for novel or avian influenza strains. Nasopharyngeal swabs or aspirates should be obtained for testing [11].

3.2. Treatment of seasonal, avian and pandemic influenza A viruses

Vaccination is the best method of protection during a pandemic however if not available or if a patient contracts influenza then antiviral therapy is indicated in certain circumstances. Currently two classes of antiviral drugs are available for the treatment and prevention of influenza: the neuraminidase inhibitors (oseltamivir, zanamivir and peramivir) and the adamantines (amantadine and rimantadine) [15]. The adamantines block M2 protein channels and inhibit the uncoating of the influenza virus after it enters the host cells. They are only active against influenza A not B viruses and due to a marked increase in resistant isolates, many countries do not recommend that they be used except in combination with neuraminidase inhibitors in selected case. Therefore, adamantines are not recommended for treatment of novel influenza A virus infections [16].

Neuraminidase inhibitors are recommended to treat patients hospitalised with seasonal influenza, inclusive of H1N1, and avian influenza (H5N1 and H7N9) infections. In adults, the dose of oseltamivir is 75 mg orally twice daily; inhalational zanamivir is 10 mg (two inhalations) twice daily; and peramivir is 600 mg IV once daily. In patients with severe influenza, there are insufficient data to recommend the use of inhaled zanamivir or IV peramivir as empirical therapy. As such empirical treatment with oseltamivir should be started as soon as possible for all hospitalised cases associated with severe disease, and for confirmed and probable outpatient cases. Early therapy (especially within 48 h of illness onset) can shorten the duration of the symptoms in high-risk patients and reduce secondary complications associated with influenza. The recommended duration of antiviral therapy is five days for uncomplicated disease. In severely ill hospitalised or immunocompromised patients, longer courses of treatment (e.g. 10 days) should be considered. In these circumstances, a higher dose of oseltamivir has been recommended by some experts (150 mg twice daily) in adults with normal renal function. However, oral oseltamivir has been reported to be adequately absorbed in critically ill patients and higher dosing may not provide additional clinical benefit. In obese patients, studies have demonstrated adequate exposure to oseltamivir carboxylate (active metabolite of oseltamivir) with the 75 mg twice daily dosing regimen. Limited data suggest that oseltamivir administered by oro/naso-gastric tube is well absorbed in critically ill patients, including in those on continuous renal replacement therapy and ECMO [16].

For patients who cannot absorb or tolerate oral oseltamivir, the use of IV peramivir or investigational IV zanamivir should be considered. It is possible that novel influenza A viruses may become resistant to oseltamivir and peramivir during treatment but remain susceptible to zanamivir. In resistant infection, zanamivir is the preferred agent and can be delivered by inhalation or by the intravenous route. Corticosteroid treatment is controversial with some reports showing benefit and others harm. In all cases of severe influenza whatever the type bacterial coinfection is possible and as such, appropriate antimicrobial treatment directed toward those organisms causing bacterial acute community acquired pneumonia, and mechanical ventilation as required can reduce the mortality rate. Extracorporeal membrane oxygenation (ECMO) has been utilised

in some patients with ARDS and one study showed a possible mortality benefit in patients who were referred to a specialised ECMO centre [17].

Ongoing monitoring for antiviral resistance among avian influenza A viruses is crucial. Some evidence of antiviral resistance has been reported in highly pathogenic avian influenza (HPAI) "Asian H5N1 viruses" and "Asian H7N9 viruses". Future treatment strategies may make use of new generation broadly reactive monoclonal antibodies. In addition, a viral RNA polymerase inhibitor, favipiravir is registered for the treatment of pandemic influenza in Japan [3].

4. Coronaviruses

Potentially life-threatening coronavirus infections are caused by the Severe Acute Respiratory Syndrome associated Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [6].

4.1. Severe Acute Respiratory Syndrome (SARS-CoV)

Cases of SARS were first noted in Guangdong Province, China in November 2002. The illness spread to 30 countries in North America, South America, Europe and Asia before the outbreak was contained. SARS-CoV is a novel coronavirus that jumped the species barrier from civet to man. Based upon clusters of cases in Hong Kong and Canada, SARS-CoV is transmitted by means of close person-to-person contact via droplets or fomites. It has been suggested that airborne and faecal-oral transmissions is also possible [18].

The incubation period is two to seven days and approximately 95% will develop symptoms by 10 days. This is followed by an influenza like (ILI) prodrome (stage 1) of high fever (>38 °C), malaise, headache, myalgia and chills without upper respiratory tract symptoms. About 10% to 20% of patients have diarrhoea. The prodrome may last for three to seven days after which involvement of the LRT (stage 2) occurs and this begins with a non-productive cough and dyspnoea. This may progress to acute hypoxaemia with radiologic progression to pneumonia. About 20% of patients progress to stage 3 and develop features of ARDS that may require mechanical ventilation. The chest radiograph shows diffuse interstitial infiltrates characteristics of ARDS. Risk factors for poor outcomes include older age, underlying comorbidities such as diabetes, atypical symptoms and elevated lactate dehydrogenase on admission [18,19].

4.1.1. Diagnosis
The diagnosis is based on clinical, epidemiological and laboratory criteria and case definitions have been developed by the Centers for Disease Control and Prevention. The reverse transcriptase polymerase chain reaction (RT-PCR) and serum antibodies as measured by enzyme-linked immunosorbent assay (ELISA) testing, are two reliable tests for diagnosis. However serologic testing during the acute illness has limited value since antibodies typically develop several weeks into the illness.

4.1.2. Treatment
There is no specific treatment recommended except for supportive care. The benefit or otherwise of antiviral drugs or glucocorticoids has not been established for treatment of SARS [20].

4.2. Middle East Respiratory Syndrome Coronavirus (MERS-COV)

4.2.1. Introduction
MERS is a newly recognized highly lethal respiratory illness caused by MERS-CoV. MERS-CoV is a zoonotic virus and studies have shown that humans are infected through contact with infected dromedary camels or infected people. The disease was first reported in Saudi Arabia in June 2012 [21]. So far, all cases have been linked through travel to, or

residence in, countries in and near the Arabian Peninsula. Outside the Arabian Peninsula, the largest known outbreak of MERS occurred in the Republic of Korea in 2015 which was also linked to a traveller returning from the Arabian Peninsula. A total of 186 confirmed patients with MERS-CoV infection across 16 hospitals were identified. Eighty-two (44.1%) of the cases were patients exposed in hospitals, 61 (32.8%) were caregivers, and 25 (13.4%) were hospital staff [22]. A total of 83.2% of the cases were linked to five super- spreaders, all of whom presented with pneumonia and were in contact with hundreds of people.

Since 2012, although 27 countries have reported cases of MERS-CoV, 80% have been reported by Saudi Arabia. MERS-CoV can infect anyone and patients have ranged in age from <1 to 99 years old.

4.2.2. Clinical

The incubation period for MERS is usually about 5 to 6 days, but can range from 2 to 14 days. Most patients present with a severe acute respiratory illness manifested by shortness of breath but preceded by fever, cough, myalgia and arthralgia. Rapid progression to pneumonia may occur within the first week, often requiring mechanical ventilation and other organ support such as renal dialysis [23]. Patients in the Korean outbreak had fever and chills as the most common symptoms but gastrointestinal symptoms including diarrhoea and nausea/vomiting have also been reported. As of August 2017, 35% of laboratory-confirmed MERS-CoV cases reported to WHO have died. Studies have shown that older age and pre-existing comorbidities are important risk factors for death [23,24]. Those with mild symptoms (such as cold-like symptoms) or no symptoms at all usually recover.

4.2.3. Diagnosis

Case definitions have been developed by WHO, the Centers for Disease Control and Prevention (USA) and the Ministry of Health of Saudi Arabia. Confirmation of the diagnosis is by rRT-PCR performed on respiratory secretions.

4.2.4. Treatment

Currently, there is no vaccine to prevent MERS-CoV infection and no proven antiviral therapy. Management includes preventive daily hygiene measures and travel precautions. Thereafter symptomatic and supportive therapy is required [25].

5. Hantavirus

5.1. Hantavirus pulmonary syndrome

The Hantavirus is a member of the Bunyaviridae family and the genus includes >50 different viruses that manifest with a wide spectrum of clinical illnesses [26]. The pathogenesis of Hantavirus is related to the targeting of vascular endothelial cells, alveolar macrophages and follicular dendritic cells, as well as the renal tubular epithelium [27]. The induction of vascular or capillary leak is a key component of the pathogenicity [28].

Transmission to humans is via contact with, or inhalation of aerosolised urine, saliva or faeces of the rodent host (family Muridae). As it is predominately a rural disease, risk factors include farming, land development and camping, however due to the method of inoculation, it is usually acquired indoors [27]. Person to person transmission has been documented previously in some subtypes so respiratory precautions are recommended for health care workers.

It is estimated that over 30,000 cases of Hantavirus occur globally each year, with the majority in Asia [29]. It causes two major clinical syndromes namely Hantavirus pulmonary syndrome (HPS) and haemorrhagic fever with renal syndrome (HFRS) with the former occurring predominantly in the Americas [26]. Reports have indicated that there is an increasing incidence of HPS in South America [30].

The case definition of the HPS as per the Centers for Disease Control and Prevention (CDC) is: 'a febrile illness with bilateral diffuse interstitial edema that may resemble the acute respiratory distress syndrome, with respiratory compromise requiring supplemental oxygen developing within 72 hours of hospitalisation, in a previously healthy person' [31].

The incubation period is two to three weeks followed by a number of phases that include [29]; a prodrome with nonspecific viral symptoms however also with thrombocytopenia, lasting for 1 to 5 days; and the pulmonary phase in which symptoms of respiratory failure predominate progressing extremely rapidly (over 8 to 24 h), to shock, coagulopathy, pulmonary oedema, bronchorrhea, arrhythmia and death. Lastly in the recovery phase patients often have a period of significant diuresis as endothelial function recovers and fluid redistribution occurs, with urine outputs of 300 to 500 ml per hour for 24 h [27]; Thereafter there is a convalescent phase which can be prolonged over weeks to months [28].

Hantavirus is diagnosed by serology, with Hantavirus IgM positive by the time symptoms are present. If an appropriate history of exposure is obtained, the presence of thrombocytopenia, hemoconcentration, >10% immunoblasts and a lack of toxic granulation has a high sensitivity and specificity for Hantavirus [28]. Chest radiograph abnormalities consistent with interstitial oedema are usually present on admission which worsen as respiratory function declines [27]. Advanced respiratory and haemodynamic monitoring and support, may be necessary, inclusive of mechanical ventilation and extracorporeal membrane oxygenation (ECMO) which is often a challenge in LICs [28]. It is recommended that intravenous fluids are minimised with the early institution of vasopressor and inotropic support as aggressive fluid resuscitation has been shown to increase the risk of respiratory failure [28]. Unfortunately, no specific antiviral therapy has been demonstrated to be effective.

6. Melioidosis

Burkholderia pseudomallei is a gram negative pathogen endemic to South East Asia, northern Australia, India, south China and Taiwan and cases have been documented in Brazil and elsewhere in South America, Papua New Guinea, Fiji, and New Caledonia [32]. Despite being the most common cause of fatal community acquired bacteremic pneumonia in North east Thailand and Darwin, it is seldom recognized when imported to areas where it is not endemic [33].

The prevalence varies in affected regions and may be related to climatic conditions, being particularly influenced by rainfall, having reached record rates (50.2 cases per 100,000 people) after heavier than usual precipitation in 2009–2010 in Northern Australia [33].

Global mortality estimates are extremely high, similar to deaths from measles and much higher than leptospirosis and dengue, infections that receive considerably more attention. In fact the mortality may be even higher, as diagnosis is low in endemic areas primarily due to the low resource settings in which it occurs, as laboratory facilities are generally poor to non-existent [34].

Infection occurs from inoculation from contaminated soil or water, through abrasions, ingestion or inhalation with subsequent haematogenous spread. Those with chronic diseases such as diabetes, renal failure and cystic fibrosis or those on immunosuppressive agents appear to be more susceptible [35,36].

6.1. Clinical

Most of the infections in endemic areas are asymptomatic with a significant number having antibodies but no history of disease [37]. However at least 50% of cases present with pneumonia of varying severity ranging from a nodular infiltrate with septic shock which has a mortality of up to 90%, to a lobar consolidation presenting with less florid features. The former often has little in the way of respiratory symptoms, presenting with fever, hypotension and organ dysfunction [35]. The more indolent form may mimic tuberculosis radiologically, most

commonly involving the upper lobes, however it may also occur in the lower lobes in which case pleural effusions and empyema may occur [32,37]. Pulmonary and diffuse metastatic abscesses (involving spleen, kidney, prostate and liver), osteomyelitis, and arthritis may also occur [35].

6.2. Diagnosis

The diagnosis is dependent on obtaining a positive culture. Melioidosis must be considered in the differential of all febrile patients that have visited endemic regions, as antibiotics used routinely for community acquired pneumonia are not effective, and inappropriate therapy in severe disease increases mortality. Although *B. pseudomallei* grows readily, laboratories may misidentify the organism as a pseudomonas which may lead to confusion and potentially incorrect therapy prior to the availability of the antibiogram. Certain specific culture media may enhance growth however these are not always available outside of endemic areas [38].

Serological tests are available and a positive indirect hemagglutination test (IHA) or enzyme-linked immunosorbent assay (ELISA) in a traveller may raise the suspicion of melioidosis but definitive diagnosis is based on culture positivity [33,39].

6.3. Treatment

Treatment for severe disease is administered as an initial intensive intravenous phase with combinations of ceftazidime or meropenem/imipenem with cotrimoxazole for at least 10 days as recommended in Thailand or 14 days as recommended in Australia. Thereafter an oral eradication phase consisting of cotrimoxazole or amoxicillin/clavulanate is administered for 12–20 weeks (Thailand) or 3 months (Australia) [40].

7. *Yersinia pestis*

Yersinia pestis is a gram negative coccobacillus and is notorious historically as the cause of 'the black plague'. *Y. pestis* is likely to have caused three major pandemics which led to significant loss of life. In the first in the 6th century AD it is thought that in some regions, between 50 and 60% of the population may have perished [41]. According to the WHO, currently there are high rates of plague in the Democratic Republic of Congo, Madagascar and Peru.

The disease has three clinical syndromes: bubonic, pneumonic or septicaemic [41]. Pneumonic plague leads to purulent, exudative bronchopneumonia that is usually fatal if untreated [42].

The Yersinioses are zoonotic infections in which humans are accidental hosts via contact with an infected animal, usually with the flea as the vector. The infection can be acquired via a bite from a flea, scratches or bites from infected animals or rodents or inhalation of infected respiratory secretions. The infecting organisms are carried via lymphatics to the local lymph node which and this is followed by a severe inflammatory reaction [43].

There were 3248 cases of plague reported to the WHO between 2010 and 2015 with 584 deaths with 95% of cases from Africa. Areas affected by plague include North America, the former Soviet Union, Africa, Asia and South America [44].

The majority of cases are of the bubonic form (80 to 95%) which manifests with fever, chills, malaise, dizziness and associated lymphadenitis causing intense pain and swelling in a lymph node region. If untreated, dissemination occurs to the lungs or meninges in 50% of cases causing pneumonia or meningitis. Septicaemic plague can occur without the bubonic illness in 10 to 20% of cases and is a severe illness that can lead to profound multi-organ failure [43].

Pneumonic plague can either be primary or secondary. The former develops from aerosol exposure to *Y. pestis*, with symptoms developing 1 to 6 days after inoculation [45]. This can be caused by person to person spread via exposure to respiratory droplets and is the cause of outbreaks in extended families. Secondary pneumonic plague is due to dissemination of *Y. pestis* into the lungs during either the bubonic or septicaemic phases and occurs in approximately 10% of patients [41]. Recent data suggested that pneumonic forms are increasing in incidence accounting for 23% of global plague cases [44].

A high index of suspicion is important in order to make the diagnosis, which is then confirmed by serology or culture or by more recently developed rapid diagnostic tests [46,47]. A high percentage of blood cultures are positive in septicaemic plague and gram stain and culture of sputum or lymph node aspirate is the usual means of diagnosis demonstrating small gram negative coccobacilli [48].

The mortality rate of plague if untreated is between 50 and 90% with pneumonic plague having a mortality of 100% if untreated and 50% if treated. Previously streptomycin was the preferred antibiotic however in most cases gentamicin is now preferred. Alternative agents include doxycycline and tetracycline. Fluoroquinolones are the preferred agents for post-exposure prophylaxis [45].

8. Conclusion

CAP is usually managed according to national guidelines that are directed toward those organisms seen most frequently in each region. The conditions described above may not be seen frequently if at all in other parts of the world and as such may not be treated appropriately and may also result in considerable spread. All intensivists should be aware of these conditions and make sure that a good travel history is obtained in each and every case.

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