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Editorial

Challenges from atypical pathogens in diagnosis and treatment of community-acquired pneumonia

In 1920s when antibiotics were initially used, a new type of pneumonia was discovered in Europe. It is manifested with mild onset symptoms, without sputa, progressively developing into different degrees of pneumonia involving organs out of the lung and without responses to antibiotics, which is different from the typical pneumococcal pneumonia characterized by acute onset, fever and vomica.[1] In 1938, Reimann firstly used the "atypical pneumonia" to define this kind of infection in respiratory tract.[2] In 1970s, atypical pneumonia was introduced to medical literatures, indicating the pneumonia caused by *Mycoplasmas*, chlamydia, Legionellae, psittacosis and Rickett's organisms.[3] Currently, pathogens of atypical pneumonia are still not clearly defined,[4] generally referring to *Mycoplasmas*, chlamydia and Legionellae. Some researchers also included other nonpneumococcal pathogens such as viruses and Rickett's organisms which may also cause pneumonia. *Mycoplasmas*, chlamydia and Legionellae are considered as the important pathogens of community-acquired pneumonia (CAP) all over the world.[5,6] A study from 2001 to 2006 showed that the infections of these three pathogens accounted for 22%, 28%, 21% and 20% in patients with CAP in North America (USA and Canada), Europe, Latin America as well as Asia and Africa, respectively. Meanwhile, viral infection is also a great threat to the health of human beings. This editorial is focusing on the challenges from *Mycoplasmas*, chlamydia, Legionellae and viruses in diagnosis and/or treatment of CAP.

Drug resistance of *Mycoplasma pneumoniae* to macrolide antibiotics has attracted extensive attention of researchers. In 2001, mycoplasma with resistance to macrolide antibiotics were firstly found in children with CAP in Japan, and then it was also reported by researchers from other countries.[7] In recent years, the resistance rate of *M. pneumoniae* to macrolide antibiotics was dramatically increased in Asia, and the rate was even over 90% in some regions.[8] From the year 2008 to 2012, the resistance rates of *M. pneumoniae* to macrolide antibiotics were 68.9%, 90.0%, 98.4%, 95.4%, and 97.0% in CAP patients in Beijing, China, respectively;[8] the rates were 33.3%, 33.3%, 50.0%, and 60.0% in child CAP patients in Japan from the year 2008 to 2011, respectively, and 14.3%, 16.7%, 28.5%, and 37.5% in adult patients, respectively.[9] However, in regions out of Asia, the resistance rate was relatively low. For example, the rates were 0%, 2%, 8%, and 22% in The Netherlands, Denmark, France, and USA, and Israel, respectively.[10-14] Despite the resistance, infections of *Mycoplasmas* can also be cured in patients with the general condition by increasing the courses of treatments. As for severe cases caused by resistant mycoplasma, the efficacy of macrolide antibiotics is poor, and the disease deteriorates rapidly. Therefore, the treatment regimen should be modified right away, otherwise, prognosis will be impacted. Up to now, resistances of mycoplasma to quinolones have not been discovered.[15]

Till today, studies on chlamydia are limited. Serologic evidence shows that 50% of youths and 75% of the elderly had a history of chlamydia infection, with the initial infection at the school age and the secondary infection mostly at the adult age. Chlamydia infection accounts for 3-10% of CAP in adults.[16,17] A large-scale study showed that 7% of CAP had been caused by chlamydia infection all over the world: 8% for North America, 7% for Europe, 6% for Latin America and 5% for Asia and Africa.[6] A study from China also showed that chlamydia infection accounted for some proportions of CAP pathogens.[18] Due to the limited attention to chlamydia infection in the past, there are no rapid, standardized, and accurate methods for its diagnosis currently. Therefore, we should strengthen the monitoring, improve its diagnostic methods and achieve early diagnosis and treatment.[19]

At present, diagnosis and treatment of Legionella infection are great challenges. Studies out of China reported that 90% of Legionnaires' diseases were caused by *Legionella pneumophila*, and its serogroup 1 (LP1) accounted for 84%.[20] In Europe and America, urinary antigen assay is the first-line method to detect *Legionellae*, and 70-80% cases were diagnosed by this assay.[21,22] It is simple and easy and can be used in early diagnosis of Legionella infection. But it can only be used in detecting the LP1-type Legionellae, because it is only sensitive to the mAb3 site positive of the LP1-type Legionellae with a sensitive rate as high as 80-90%. However, the sensitive rate of urinary antigen assay is <50% for Legionellae serotype LP1 with non-mAb3 positive and other Legionella species.[23,24] Therefore, missed diagnosis frequently occurs. In China, serologic antibody detection is used to determine Legionella infection in most hospitals. However, the antibodies of Legionellae appear 2-3 weeks after the onset of the disease,[25] and 20-30% of patients do not

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produce antibodies;[26] therefore, serologic method is limited to be used in early diagnosis and missed diagnosis easily happen if only one serum sample is detected; yet it is still superior in patients without sputa or with negative urinary antigens. Culture method is the gold standard to diagnose infection of Legionellae. In addition to LP1-type Legionellae, other kinds of Legionellae can also be detected. But special culture medium is required for this method, and it is difficult to be cultured. It also takes a long period of time. Polymerase chain reaction (PCR) is rapid and specific in detecting Legionella infection, but it is a complicated procedure with a long period of time. Special facility is also needed for the procedure which is now carried out only in professional researching laboratories. PCR is promising technique which can be carried out in the clinic. A variety of methods should be developed so as to detect Legionella infection more effectively.

Legionella pneumonia often develops into severe pneumonia, and about 50%[27] of the patients have to be admitted in intensive care unit with mortality rates of 12.8-33%.[28,29] Therefore, infection of *Legionellae* cannot be ignored in patients with severe CAP and treatments should cover *Legionellae* before pathogenic diagnosis is made in severe CAP patients. In some severe cases, the disease course still cannot be reversed although treatments with full coverage are performed, which may be associated with superinfection induced by *Legionellae*. A study has ever shown that non *Legionella* bacteria were isolated from the pulmonary and hepatic tissues of mice with acute stage *Legionella* pneumonia, suggesting the occurrence of superinfection.[30] Hence, we should pay attention to the possible occurrence of superinfection. Besides, inhalation of high-concentration oxygen aggravates acute injury during *Legionella* pneumonia,[31] and early extra-corporeal membrane oxygenation, continuous renal replacement therapy may benefit the prognosis of severe cases.

Great challenges exist in the diagnosis of virus-associated CAP. Due to the poor specificity of viral antibody detection and difficulties in implementation of PCR assay, it is difficult to diagnose the sporadic viral infection. Influenza virus infection often involves many regions with severe cases difficult to be treated; therefore much attention should be paid. At the end of the year 2002, an acute respiratory infectious disease caused by the severe acute respiratory syndrome (SARS) coronavirus broke out, that is, the outbreak of SARS. It started from Guangzhou, China and then spread to Vietnam, Singapore, Canada, etc. Finally, the disease covered the Five Continents involving >30 countries. There were 8096 patients infected, of whom 774 died, and the mortality rate was 9.5%.[32] In March 2009, influenza A H1N1 (H1N1pdm09) broke out in Mexico, and then it spread rapidly to the U.S., later involving Canada, Spain, United Kingdom, New Zealand, Israel, and Germany. Till August 2010, almost every country had patients with confirmed H1N1 infection.[33] It was estimated that about 123,000-203,000 died of H1N1pdm09 infection in 2009 all over the world, and moreover, the mortality rate of patients <65 years old was very high.[34] In March 2013, Chinese researchers reported a new fatal influenza virus H7N9.[35-38] Till February 2014, there were 354 cases infected with H7N9 in China and 112 cases died at least, with a mortality rate as high as 32%.[39-41] Nowadays, the number of H7N9 infected cases is still increasing.

Studies showed that early use (within 48 h from the onset) of antiinfluenza virus drugs such as neuraminidase inhibitors (Oseltamivir, etc.,) may improve the symptoms of patients and reduce the rates of severity. Therefore, in a pandemic period of influenza, diagnosis of influenza cannot be excluded, although rapid diagnosis showed a negative result in patients with flu symptoms. Antiinfluenza treatment should be performed immediately according to the clinical diagnosis. However, H1N1 and H7N9 virus resistant to Oseltamivir have been reported[42,43] and we must attach great importance to this situation.

In conclusion, atypical pathogens play important roles in CAP, and unsolved challenges still exist in diagnosis and treatment of atypical pneumonia. Especially, pandemic outbreak caused by influenza viruses threatens greatly the health of human beings. It will benefit prognosis of patients to improve diagnostic methods and perform early individualized treatments.

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