Review

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Atypical pathogen infection in community-acquired pneumonia

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Summary **Community-acquired pneumonia (CAP) is a world wide cause of morbidity and mortality. The etiology of CAP is different between countries and changes over time. With the increasing incidence, atypical pathogens are attracting more and more attention all over the world. In many countries, atypical pathogens are one of the main pathogens of CAP, and even could be the most prevalent etiology in China. Atypical pathogen infections can cause multi-system complications, which leads to a worse prognosis. Although still controversial, empirical antibiotic coverage of atypical pathogens in CAP may improve outcomes, shorten length of hospitalization, reduce mortality and lower total hospitalization costs. The macrolide resistance rate of atypical pathogens, especially *Mycoplasma Pneumoniae* (*M. Pneumoniae*) is high, so fluoroquinolones or tetracyclines should be considered as alternative therapy.**

Keywords: Atypical pathogen, community-acquired pneumonia (CAP), macrolide-resistant, empirical atypical coverage

1. Introduction

Community-acquired pneumonia (CAP) is one of the common diseases that pose a threat to human health. A few CAP inpatients develop severe community-acquired pneumonia (SCAP) and require intensive care unit (ICU) treatment. Due to frequent complications and a long hospitalization period, mortality among these patients is high (*1-3*). More than 2 million children under age 5 are killed by pneumonia every year world wide, more than AIDS, malaria, and measles combined (*4*). According to statistics based on a survey conducted by 122 research centers from 35 countries with 4300 patients, the incidence of pneumonia caused by atypical pathogens is high, with a detectable rate over 20% (*5*). In recent years, faced with aging society, increasing damaging factors to the immune system, changing nature of pathogens and rising antibiotic resistance, the treatment of CAP now encounters many new problems. Some scholars believe that atypical respiratory pathogens like the *Mycoplasma Pneumoniae* (*M. Pneumoniae)* and *Chlamydophila pneumoniae* (*C. Pneumoniae*) will replace *Streptococcus pneumoniae* as the most common pathogens for CAP (*6*).

Despite the absence of the earliest documentation of atypical pneumonia, the disease gradually became known in the 1920s and 1930s *via* various reports and papers at the time (*7-9*). The term atypical pneumonia can be interpreted in a sense that the pneumonia is caused by atypical pathogens or the patients present atypical clinical symptoms. Using a broader definition, atypical pathogens include all pathogens other than typical bacteria, *e.g.*, *Mycoplasma*, *Chlamydophila*, *Legionella*, *Rickett's organism*, *Coxiella*, *Bacillus tularense*, *Leptospira*, fungi, and various viruses (*10*). In a narrower sense, atypical pathogens causing pneumonia mainly include *M. Pneumoniae*, *C. Pneumoniae*, and *Legionella Pneumophila* (*L. Pneumophila*). Sometimes, *Rickettsia* and *Chlamydia psittaci* are also considered as atypical pathogens.

2. Clinical diagnosis of CAP

CAP due to *M. Pneumoniae* and *C. Pneumoniae* are usually seen in younger patients without comorbidity and has a mild clinical course. (*11,12*), while most pneumonia patients due to *L. Pneumophila* need to be treated in the ICU (*13,14*). The clinical symptoms of atypical pathogen CAP can be misleading, for the

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patients might have atypical symptoms like muscle pain, weakness, dry cough and so on (*15*).

CAP caused by *M. Pneumoniae* and *C. Pneumoniae* have similar clinical symptoms: generally no distinctive characteristics of normal bacteria infection; highly concentrated in the family; coughing lasting for over 5 days without sputum and no acute deterioration; normal or slight elevation of WBC; and procalcitonin level, ≤ 0.1 μg per liter. *L. Pneumophila* pneumonia has similar clinical symptoms compared to common bacterial pneumonia: super acute cause accompanied with septic shock, and lack of upper respiratory symptoms. It can also present acute deterioration of initial upper respiratory illnesses, which reminds clinicians of co-infection of virus and bacteria; white-cell count, > 15,000 or ≤ 6,000 cells per cubic millimeter; dense segmental or lobar consolidation, and procalcitonin level, ≥ 0.25 μg per liter (*16*).

L. Pneumophila pneumonia usually presents extrapulmonary symptoms: neurological symptoms like headache, drowsiness, disordered consciousness; cardiovascular abnormalities like relative infrequent pulse; gastrointestinal symptoms like nausea, vomiting, abdominal pain and liver dysfunction in the early phase like transient slightly increased aminotransferase; kidney damage like microscopic hematuria, moderate increase in creatinine; damage in the lung can be rales, pleural effussion, but the chest X-rays lack specificity.

Instead of consolidation in the lung, CAP caused by *M. Pneumoniae* can be mainly small airway infection, causing pulmonary interstitial change, which is hardly detectable in X-rays and presents as "tree-in-bud" in chest CT (*17*). In the high resolution chest CT, we may see lobule centricity nodules, bronchial wall thickening, lobular or period of distribution of ground glass and consolidation shadows, inclined to one side or both sides patchy distribution, also can be diffuse distribution. Chest CT of *C. Pneumoniae* pneumonia mainly presents as consolidation shadow, ground glass shadow, and patchy fuzzy shadow, which is consistent with the scope of bronchitis. It can also present centrilobular nodules, and "tree-in-bud" mixed with ground glass shadow and consolidation shadow, but rarely as the main observation.

Several diagnostic methods detect atypical pathogens, including: isolation, complement fixation, serologic testing, and molecular-based detection assays (*18,19*). Each of these methods has limitations. Isolation is considered to be the "gold standard", but it is tedious and time consuming, requires expertise, and yields inconsistent results. Antigen detection and serological tests are the most commonly applied technologies but have inadequate sensitivity and specificity. The sensitivity is only 31.8% with single IgM antibody testing to diagnose *M. Pneumoniae* pneumonia. When diagnosing *C. Pneumoniae* pneumonia, the sensitivity of adult IgA or IgG antibody tests is 78%, with specificity of 21-91% (*20*). Because of the delay in antibody generation, serological testing is not qualified for early diagnosis of the disease but is of great significance for epidemiology studies. Urinary antigen detection is recommended for the early diagnosis of *L. Pneumophila* pneumonia, but with the limitation of only detecting serotype 1. The molecular detection technology on the other hand could offer high sensitivity and specificity with fast speeds and high volumes, making it a promising alternative. Morozumi, *et al*. (*21*), using real-time PCR assays, determined 429 clinical specimens, and the sensitivities and specificities of *M. Pneumoniae* wee 100% and 95.4% respectively, compared with the results of conventional culture tests. The whole process from DNA extraction to analysis was finished in less than 2 hours, the limit of detection was 5 copies for *M. Pneumoniae*, 3 copies for *C. Pneumoniae*, and 2 copies for *L. Pneumophila*. So this can give great help to clinicians for rapid identification of the loads of atypical pathogens. In terms of *C. Pneumoniae*, standard procedures for testing, specimens and treatment are still missing and the impact on testing results is yet to be seen. Meanwhile, the PCR approach is overly complicated and very demanding for personnel and equipment, and therefore is not generally applied in labs.

3. Prevalence of atypical pneumonia

In Table 1, according to CAPO that is based on 4,337 patients: the atypical pathogen detectable rates in North America, Europe, Latin America and Asia/Africa are 22%, 28%, 21% and 20% respectively (*22*). However, different countries and regions have different atypical detectable rates. A CAP epidemic survey (*23*) that enrolled 3,523 CAP patients (15% outpatients and 85% inpatients) from November 1996 to July 2008 shows that 1,463 patients are etiology positive. The survey indicates that *Streptococcus pneumoniae* is the main cause of CAP in Europe with 42% of the detectable rate. Atypical pathogens and mixed infections are also significant causes with detectable rates standing at 18% and 14% respectively. Also in Spain, Alberto Capelastegui and his colleagues discovered a 50% detectable rate in a prospective study (*24*). Atypical pathogens were significantly more frequent among outpatients (67%), than among inpatients(30.6%). A study in Chile that included 356 patients showed that *Streptococcus pneumoniae* and viruses are the most common pathogens, with atypical pathogens accounting for 22% of the infections (*25*). Two studies in Netherlands found that *Streptococcus pneumoniae* was the main cause of CAP, with 25% and 22% of detectable rates. But there were inconsistent detectable rates between the two studies in terms of atypical pathogens (9% and 20%) (*26,27*). Whereas a study in the north of Israel shows the detectable rate of

Table 1. Studies of the prevalence of atypical pneumonia in different countries and regions

Authors	Country	Population	Main findings
Arnold FW, *et al*. (*22*)	21 countries (region: North America, Europe, Latin America, Asia/Africa.)	4,337 patients, from 21 countries, Sep. 1996 – Apr. 2004.	The incidence of CAP due to atypical pathogens was 22, 28, 21, and 20% in North America, Europe, Latin America, Asia/Africa, respectively.
Cillóniz C, *et al*. (*23*)	Spain	3,523 patients attending the Hospital Clinic, Nov. 1996 – Jul. 2008.	The most frequent aetiology among outpatients was the atypical pathogen group (36%), and in patients treated on the ward atypical pathogen took up 16%.
Capelastegui A, *et al*. (*24*)	Spain	700 patients recruited from Galdakao Hospital, Apr. 2006 – Jun. 2007	Atypical pathogens were significantly more frequent among outpatients (67%), while 30.6% among inpatients.
Luchsinger V, *et al*. (*25*)	Chile	356 patients in two hospitals, Feb. 2005 – Dec. 2007.	Streptococcus pneumoniae and RSV were the most common aetiology, while The incidence of CAP due to atypical pathogens was about 22%.
Spoorenberg S. *et al*. (*26*)	The Netherlands	505 patients admitted to the St. Antonius Hospital or the Gelderse Vallei Hospital, 2004 – 2010.	The incidence of CAP due to atypical pathogens was about 9% among inpatients.
Gageldonk-Lafeber ABV, *et al*. (*27*)	The Netherlands	339 patients from the Jeroen Bosch Hospital (JBH), Nov. 2007 – Jan. 2010.	Infection with atypical acteria was detected in 69 (20%) of the patients.
Fahmi S, *et al*. (*28*)	Israel	126 patients and 24 controls, conducted at HaEmek Medical Center, Afula, Nov. 2006 – Aug. 2007.	Atypical bacteria was found in 66 (52.4%), and co-infection was very frequent.
Liu YN, *et al*. (*29*)	China	665 adult patients at 12centers in 7 Chinese cities, Dec. 2003 – Nov.2004.	*M. Pneumoniae* was the most prevalent aetiology (126/610, 20.7%). Atypical pathogens were identified in 62/195 (31.8%) patients carrying bacterial pathogens.
Tao LL, *et al*. (*30*)	China	593 patients at 36 centers in 22 cities of 16 provinces, Jun. 2004 – Aug. 2005.	*M. Pneumoniae* was the most prevalent aetiology (38.9%) , and the incidence of CAP due to C. Pneumoniae and L. Pneumophila was 11.4% and 4.0%, respectively.
Chen K, *et al*. (*31*)	China	1,204 children patients, from Zhongda Hospital, Nanjing, Aug. 2011 – Aug. 2013.	*M. Pneumoniae* was the most predominant pathogen(40.78%), and the incidence of CAP due to *C. Pneumoniae* and *L. Pneumophila* was 0.91% and 0.33%, respectively.
Diego V, *et al*. (*32*)	Spain	3,934 non-immunosuppressed hospitalized patients of CAP admitted toHospital Universitari de Bellvitge, Feb. 1995 – Dec. 20 10.	214 (5.4%) had *L. Pneumophila* pneumonia.
Francisco A, *et al*. (*33*)	Spain	104 adult patients with severe CAP in four hospitals, Jan. 2005 – Jun. 2006.	An etiologic agent was identified in 62 patients (59.6%), with the second frequent being L. Pneumophila (8.6%), followed by *M. Pneumoniae* (6%), *C. Pneumoniae* (4%).

atypical pathogens is 52.4% (*C. Pneumoniae* 20.6%, *M. Pneumoniae* 18.3%, L pneumoniae 7.1% and others) (*28*). A large epidemiological survey from China in 2006 showed different results compared to that of the European countries, with atypical pathogens being the leading cause of CAP in China. *M. Pneumoniae* was the most prevalent etiology (20.7%), followed by *Streptococcus pneumoniae* (10.3%) (*29*). Co-infections took a great part of community respiratory infections, most of which was co-infection with bacteria and atypical pathogens. In another 2 national CAP surveys in China (*30*), *M. pneumoniae* infection had become the most common cause of CAP among adults, with rates of 20.7% and 38.9% respectively, far exceeding the rates of *Streptococcus pneumoniae* (10.3% and 14.8%). Keping Chen, *et al*. (*31*) reported that the most predominant pathogen was *M. Pneumoniae*, with a positive percentage of 40.78% and *M. Pneumoniae* was significantly associated with seasons, and was most common in the late summer and autumn.

L. Pneumophila is a relatively frequent causative pathogen among hospitalized patients with CAP and is associated with high mortality. A 15-year study (*32*) showed that among 3,934 non-immunosuppressed hospitalized patients with CAP, 214 (5.4%) had *L. Pneumophila* pneumonia, and 38 (17.8%) patients required ICU admission, and the inhospital case-fatality rate was 6.1% (13 of 214patients). In a clinical study from Santiago, Chile, a total of 104 patients with severe CAP were observed from 2005 to 2006. All the patients required ICU admission, of whom an etiologic agent was identified in 62 patients (59.6%), top 7 were as follows: *Streptococcus pneumoniae* (26%), *L. Pneumophila* (8.6%), *M. Pneumoniae* (6%), *C. Pneumoniae* (4%), Gram-negative bacillus (3%), influenza A virus (3%), and *Staphylococcus aureus* (3%). *L. Pneumophila* is the second etiologic agent in SCAP, after *Streptococcus pneumoniae*. Global mortality at 28 days in severe CAP was 25% and that of *L. Pneumophila* was 33.3% (three of nine cases), but the difference was not significant with non-Legionella severe CAP mortality (33% *vs* 24.5%) (*33*). There is a relatively high incidence of *L. Pneumophila* in global CAP, particularly in the United States (14%) (*12*) and Spain (12.5%) (*34*). Even in Asia, the incidence is as high as 6.6% (*32*).

4. The prognosis of patients with pneumonia due to atypical pathogen infection

As said before, pneumonia due to atypical pathogen infection is often mild or moderate, but when it turns into severe pneumonia, the outcome is usually fatal. A retrospective study showed that, acute respiratory distress syndrome (ARDS) developed in 6 of 11 pneumonia patients due to *C. Pneumoniae* infection, the mortality in the group of APACHE II ≥ 12 was 83%, and 100% in the group of CURB-65 ≥ 2 (*35*). Multi-lobar involvement, should be identified earlier. A study (*36*), conducted in Europe with a group of average age 66-year-old patients with pneumonia, showed that elderly patients with *L. Pneumophila* infection had a worse prognosis. The study reported that the general mortality was as high as 23%. Of those who died, five (83%) had UK community-acquired *L. Pneumophila*.

4.1. *Atypical pathogen infection can cause extrapulmonary complications, which leads to a worse prognosis*

Atypical pathogen infection can cause extrapulmonary complications, such as damage to heart, liver, kidney, blood system and mucous membrane. Sometimes, the infection appears to cause more severe disease with multisystem dysfunction. In the respiratory system, the complications can be exacerbation of chronic obstructive pulmonary disease (COPD), inducing bronchial asthma, developing to ARDS, increasing the risk of lung cancer etc. In the main causes of acute exacerbation of COPD (AECOPD), atypical pathogens account for 5-10%, mainly *M. Pneumoniae* and *C. Pneumoniae*, followed by *L. Pneumophila*. As many as 14% of patients with AECOPD are associated with *M. Pneumoniae* infection, and 5.0-8.9% with *C. Pneumoniae* infection (*37*). Infection with *C. Pneumoniae* may interact with allergic inflammation to increase asthma symptoms (*38,39*). *L. Pneumophila* pneumonia is more likely to develop to ARDS, compared to other pathogens (*33*). Although still controversial, *C. Pneumoniae* infection may be associated with lung cancer, and *C. Pneumoniae* infection may be a potential risk factor for lung cancer (*40-43*). Complications in the cardiovascular system can be as follows: inducing coronary artery disease, myocardial infarction, unstable angina, atherosclerosis and cerebral infarction. A study from China found that compared with healthy persons, the *C. Pneumoniae* infections in CAD patients were detected more, with a positive rate of 81.3% (104/128) to 46.3% (37/80), and the incidence rate of myocardial infarction or more than double vessel lesions was significantly higher in the *C. Pneumoniae* infection group (*44*). Another study showed that there was a positive correlation between azithromycin treatment and secondary prevention of CAD (*45*). A meta-analysis (*46*) indicated that *C. Pneumoniae* infection was significantly associated with an increased risk of cerebral infarction. There are other extrapulmonary complications, such as hepatic function insufficiency, and septic shock. Huong Ple T *et al*. (*47*) found that severe-atypical CAP presented at a significant rate in Vietnamese children (45.12%). The factors significantly associated with severe-atypical CAP were age, co-infection with typical bacteria, co-infection with respiratory viruses, respiratory/cardiac system malformation and neonatal pneumonia.

4.2. *Increasing resistance is an important factor for prognosis*

The wide application of antibiotics promoted atypical pathogens to change in form, structure, and metabolism, which increases the difficulty of antibiotic treatment. In Japan, the macrolide resistance rate of *M. Pneumoniae* increased every year among children, and the resistance rate was as high as 30.6% (37/121) in 2006 (*48*). Also the macrolide resistance rates were 3.0% in Germany (*49*), 9.8%in France (*50*). A report from China in 2010 indicated that the resistance rate of 67 *M. Pneumoniae* isolates from 356 ambulatory adult and adolescent patients with respiratory tract infection was 69% (46 of 67) (*51*). All 46 macrolide-resistant strains harbored point mutations in the 23S ribosomal RNA gene. In addition, it was also found that mutations in L4 and L22 were not responsible for macrolide resistance. Patients infected with macrolide-

resistant *M. Pneumoniae* required a significantly longer duration of antibiotic therapy and had a longer time of resolution of fever. Moxifloxacin or levofloxacin was the most common alternative therapy. 2013, Principi, *et al*. (*52*) reported that, in comparison with patients with susceptible strains treated with macrolide, most subjects with macrolide-resistant *M. Pneumoniae* have more persistent signs and symptoms that, in some cases, have led the attending physician to replace the macrolide with tetracycline or fluoroquinolone in order to obtain a more rapid clinical result. Another study showed that, the incidence of extrapulmonary complications in the macrolide-resistant (MR) group was significantly higher than that in the macrolide-sensitive (MS) group, such as liver function abnormalities, myocarditis, rash, encephalitis and so on. Moreover, the radiological findings were more serious in the MR group than in the MS group (*53*).

Thus, the interaction of drug resistance and complications, led to serious clinical symptoms, long durations, and worse prognosis.

5. Antibiotic treatment for atypical pneumonia

For the empirical treatment of CAP, it's recommended to consider the coverage of atypical pathogen with different guidelines (*54-57*). But, there are controversial results for atypical pathogen coverage treatment. A meta-analysis indicated that empirical antibiotic coverage of atypical pathogens in hospitalized patients with community-acquired pneumonia showed no benefit of survival or clinical efficacy in this synthesis of randomized trials (*58*). In contrast, a population-based, multicenter, retrospective cohort study in China got opposite results (*59*). The study was conducted from June 2010 to May 2011, and 827 CAP patients were enrolled. It indicated that the all-causes mortality was much lower in the atypical pathogen coverage (APC) group than in the non-APC group (0.9% *vs*. 4.9%, respectively). And clinical improvement at 72 h (87.7% *vs*. 85.0%) and the clinical cure rate (91.1% *vs*. 88.3%) were more favorable in the APC group, but with no significant difference. Moreover, the APC group had a shorter mean length of stay (10.2 days *vs*. 11.6 days). In addition, the mean total hospitalization costs for the APC group were markedly lower (US$ 1,172.7 *vs*. US$ 1,510.7).

In China, there is a significantly higher macrolide resistant rate for *M. Pneumoniae*, 71.4% for erythromycin and 60.4% for azithromycin, respectively, and no fluoroquinolone-resistant or tetracycline-resistant strains were observed (*60*). Compared with macrolide, patients of *L. Pneumophila* pneumoinia treated with fluoroquinolone tend to have shorter durations of fever, shorter hospitalization time, fewer complications and so on. In the CAP guidelines of many countries, fluoroquinolone is the priority selection for atypical pathogens. The infection group of Chinese Thoracic Society recommended that (*15*), based on current studies, if the patients get no better with macrolide treatment for 72 hours, clinicians should consider the possibility of macrolide-resistant *M. Pneumoniae*, and change to fluoroquinolones or tetracyclines. Moxifloxacin or levofloxacin was the most common alternative therapy.

6. Conclusion

Though the etiology of CAP is different between countries and changes over time, atypical pathogens were playing an important role in CAP all over the world. In China, atypical pathogens, such as *M. Pneumoniae*, *C. Pneumoniae*, *L. Pneumophila*, are part of the main causes, and *M. Pneumoniae* was the most prevalent pathogen. Atypical pathogen infections often cause mild or moderate pneumonia, but *L. Pneumophila* or co-infection with bacteria can lead to severe pneumonia and high mortality. Though still controversial, considering highly prevalent atypical pathogens, especially *M. Pneumoniae*, empirical antibiotic coverage of atypical pathogens is recommended, and it can improve the outcomes, shorten the length of hospitalization, reduce the mortality and lower total hospitalization costs. Macrolide resistance rate was high, but no quinolone-resistant *M. Pneumoniae* strain was found. So, if the patients get no better with macrolide treatment for 72 hours, fluoroquinolones or tetracyclines should be considered for alternative therapy. In China, it would be moxifloxacin or levofloxacin.

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