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# Atypical pneumonia – etiology, epidemiology, clinical presentations, diagnosis and treatment – a review of literature

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## Abstract

Community-acquired pneumonia is a prevalent infectious disease with significant global morbidity and mortality. Atypical pneumonia, is characterized by milder symptoms and different pathogens, including *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Legionella spp.* Unlike typical pneumonia caused by *Streptococcus*

*pneumoniae* and *Haemophilus influenzae*, atypical pneumonia presents with non-specific symptoms such as headache, fatigue, mild fever, and sore throat. Epidemiologically, atypical pneumonia constitutes over 15% of community-acquired pneumonia cases, with prevalence varying by region. It can be transmitted through aerosolized droplets, direct contact, or environmental exposure. Diagnostic challenges arise from inability of atypical pathogens to be detected via conventional Gram staining or culture techniques, it requires molecular assays like polymerase chain reaction and serological tests. Imaging, including X-ray, computed tomography, and ultrasonography, allow identifying characteristic lung abnormalities, yet their findings often overlap with other respiratory infections. Treatment strategies differ from those for typical pneumonia, as β-lactam antibiotics are ineffective against atypical pathogens due to lack of cell wall. Treatment recommendations include macrolides, tetracyclines, and fluoroquinolones. Complications of atypical pneumonia, though less frequent, can be severe, particularly in high-risk populations. Potential complications range from acute respiratory distress syndrome and cardiovascular conditions to neurological manifestations. Early diagnosis, coupled with targeted antibiotic therapy is essential to improve patients outcomes and reduce complications. This review provides a comprehensive overview of the etiology, clinical presentation, diagnostic challenges, treatment options, and potential complications of atypical pneumonia, emphasizing the need for continued research and improved diagnostic methodologies to enhance patient care.

**Keywords:**

Atypical pneumonia, pneumonia, walking pneumonia, community-acquired pneumonia, epidemiology of atypical pneumonia, symptoms of pneumonia, clinical presentation of atypical pneumonia, detecting atypical pneumonia, diagnosis of atypical pneumonia, antibiotic therapy in pneumonia, atypical pneumonia's treatment, complications of atypical pneumonia.

## 1. Introduction

Community-acquired pneumonia (CAP), i.e., acute infection of the lung parenchyma acquired outside the hospital, is a frequent disease and has a large impact on morbidity and mortality worldwide[1]. In addition to typical pneumonia, we also recognize atypical pneumonia - known also as walking pneumonia. It was initially described during the 20th century for a lung

infection with clinical and radiological characteristics differing from *S. pneumoniae* infection[2]. Walking pneumonia is a mild infection and caused by not typical bacteria - especially *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae* and *Legionella species*. The prevalence of atypical pneumonia varies globally, with Europe, Asia/Africa and Latin America reporting detection rates between 20-28%[3]. The infection can occur during the whole year yet most typically during autumn and winter. Typical pneumonia is most commonly caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*, leading to high fever, a productive cough, and localized chest pain. On the contrary, symptoms in the atypical are: sore throat, chest pain or discomfort, low-grade fever, malaise, cough, sneezing and headache. The treatment differs from that of typical pneumonia, because of the distinct cellular structure - typical bacterial pathogens classically respond to β-lactam antimicrobial therapy, because they have a cell wall amenable to β-lactam disruption, while most atypical pathogens do not have a bacterial cell wall, some are intracellular (e.g., *Legionella spp.)*, and some are paracellular (e.g., *M. pneumoniae*)[4].

## 2. Etiology and epidemiology

Atypical pneumonia accounts for more than 15% of all CAP cases, though its incidence can vary depending on the geographic location[4]. This condition is caused by pathogens that differ from the usual agents responsible for pneumonia. The most common causes include bacteria: *Mycoplasma pneumoniae, Chlamydophila pneumoniae*, and *L. pneumophila*. These pathogens are distinguished by their inability to be detected through standard Gram staining and culture techniques, which requires the use of alternative diagnostic methods. Other potential pathogens that can cause atypical pneumonia include *Chlamydia psittaci* (psittacosis), *Coxiella burnetii* (Q fever), *Francisella tularensis* (tularemia) and respiratory viruses like: respiratory syncytial virus (RSV), adenoviruses, influenza and parainfluenza viruses, SARS-CoV-1 and SARS-CoV-2.[4,5]. Atypical bacterial pneumonias are clinically categorized based on their mode of transmission into nonzoonotic and zoonotic types. The most common non-zoonotic bacteria responsible for atypical bacterial pneumonia are*:*

- *Mycoplasma pneumonia* is a common cause of CAP in children and young adults. Outbreaks are often seen in places where people live or interact in close proximity for long periods, including nursing homes, schools, and colleges.
- *Chlamydophila pneumoniae* is transmitted from person to person through aerosolized respiratory droplets, primarily affecting school-aged children and older adults.

Outbreaks are commonly seen in environments such as schools, military camps, prisons, and long-term care facilities.

- *Legionella spp.* is mainly found in aquatic environments, and outbreaks typically occur when contaminated water is aerosolized. Common sources include household showers, air conditioning units, hospital ventilators and nebulizers.

Zoonotic bacterial pneumonias are less frequent in the general population and are primarily associated with specific environmental exposures and contact with particular animal hosts. When addressing the prone individuals for viral infections, the groups most at risk include: the elderly, immunocompromised patients, young children, organ transplant recipients, pregnant women and healthcare workers[6].

## 3. Clinical presentation

Atypical pneumonia presents with a variety of symptoms that differ from those of typical pneumonia, making diagnosis more difficult. Common symptoms include: fever, a dry cough, headaches, fatigue and shortness of breath. In some cases, it may also cause extrapulmonary issues, such as skin rashes and neurological symptoms: encephalitis or Guillain-Barré syndrome[7,8]. A significant characteristic is the absence of a high fever and productive cough, as this type of pneumonia is usually associated with milder symptoms [9]. However, the clinical manifestation may vary depending on the specific pathogen responsible for the infection. Pneumonia caused by *Mycoplasma pneumoniae* usually begins gradually, with symptoms such as headache, fatigue, mild fever, and sore throat. Dry cough is common, and chest pain or shortness of breath may occur alongside it. Other signs of upper respiratory infection, like a runny nose, sinusitis, ear infections, and swollen lymph nodes may also be present along with this type of pneumonia. In more severe cases, difficulty breathing, low oxygen levels, blood pressure, and confusion can occur, though these are less common compared to pneumonia caused by other pathogens. *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* pneumonia share similar symptoms but differ in a few key ways. *Mycoplasma pneumoniae* causes more acute infection, while *Chlamydophila pneumoniae* is usually chronic. *Mycoplasma pneumoniae* often presents with otitis, bullous myringitis, and mild pharyngitis, which are less common in *Chlamydophila pneumoniae* cases. Laryngitis is more common in *Chlamydophila pneumoniae* pneumonia, so patients with hoarseness should be suspected of having it until proven otherwise. Both infections rarely involve cardiac or pulmonary issues, but gastrointestinal symptoms are more frequent in *Mycoplasma*

*pneumoniae*[10]. *Legionella pneumophila* often progresses rapidly and can become severe. The mortality rate for Legionella-related pneumonia is about 10%, but it can increase to 27% and more, if patients don't receive proper antibiotic treatment early on[4]. Although no clinical symptoms can definitively distinguish Legionella disease from other types of pneumonia, certain factors may increase suspicion. These include: gastrointestinal symptoms like nausea, vomiting, and diarrhea; hyponatremia; elevated liver enzymes; C-reactive protein levels above 100 mg/L; and a lack of response to standard pneumonia treatment[10]. Although atypical pneumonia is generally less severe than typical pneumonia, it can still result in significant complications, particularly in high-risk populations. A thorough understanding of its varied clinical presentations is essential for effective diagnosis and management.

## 4. Laboratory diagnostic:

### *Legionella pneumophila*

The diagnosis of legionellosis is based on the presence of clinical and/or radiological symptoms as well as laboratory tests. According to the 2024 report from the European Centre for Disease Prevention and Control (ECDC), most cases in Europe (90%) are diagnosed using a urinary antigen test that detects the lipopolysaccharide antigen specific to serogroup I of *L. pneumophila*[11,12]. The sensitivity of this test is estimated to be around 74-79% for all *Legionella* serogroups[13]. The persistence of microbial antigens can lead to false-positive results. Studies indicate that the antigen may remain detectable in urine for several months to even a year, particularly in immunosuppressed patients[14]. The cultivation of *Legionella spp.* on solid media is currently considered the gold standard for diagnosing legionellosis. Selective Buffered Charcoal Yeast Extract (BCYE) agar is used for this purpose, containing L-cysteine hydrochloride, α-ketoglutaric acid, iron pyrophosphate, yeast extract, and charcoal. On this medium, the microorganism grows as small (1-3 mm) colonies with a ground-glass appearance[12,15]. Studies have shown a higher percentage of positive cultures obtained from lower respiratory tract samples than from nasopharyngeal or throat swabs[16]. Additionally, the main advantage of solid media culture is the ability to isolate a strain for antimicrobial susceptibility testing and serotyping[17]. Legionellosis is commonly diagnosed using enzyme immunoassay (EIA) or immunofluorescence assay (IFA) tests that detect specific antibodies. However, these tests exhibit relatively low sensitivity and specificity. The use of molecular techniques, such as polymerase chain reaction (PCR), allows the detection of all serogroups of *Legionella pneumophila*. Additionally, this test is characterized by high sensitivity and specificity[12]. However, a disadvantage of this method is the limited availability of the necessary equipment in laboratories to perform PCR testing.

### *Mycoplasma pneumoniae*

One of the most commonly used tests for diagnosing *Mycoplasma pneumoniae* infections is serological testing, which enables the detection of cold agglutinins, a humoral response to infection by the microorganism[18]. Antibody titers persist in the body for up to six weeks[19].

However, a disadvantage of this method is its low specificity. Cold agglutinins can also appear in infections caused by Epstein-Barr virus, cytomegalovirus, and bacteria such as *Klebsiella pneumoniae*, as well as in cases of malignant lymphoid cell tumors or autoimmune diseases. Additionally, cold agglutinins are rarely detected in very young children[20]. The cultivation of *Mycoplasma pneumoniae* on solid media is highly demanding. Cultures can be obtained from throat swabs, bronchoalveolar lavage fluid, or sputum, but the microorganism's growth takes up to six weeks due to its slow division time of six hours. As a result, culture is considered an insensitive method and is not recommended for the diagnosis of *Mycoplasma pneumoniae*[12]. Molecular methods may serve as an alternative to the above techniques. Studies by Zhao et al. suggest that the use of the ddPCR technique could be effective in detecting the microorganism in tested samples[21]. However, other identification methods, such as qPCR, may exhibit low sensitivity and specificity, as demonstrated in studies by Chang et al. and Zhang et al.[22,23].

***Chlamydophila pneumoniae***

According to the 2024 guidelines from the Centers for Disease Control and Prevention (CDC), the best method for detecting *Chlamydophila pneumoniae* in a tested sample is nucleic acid amplification testing (NAAT), such as qPCR[24]. Studies by Boman et al. have shown that this method can be successfully used in routine diagnostics[25]. Serological diagnosis of chlamydial respiratory infections primarily relies on microimmunofluorescence, which helps detect IgM antibodies in serum. This method is recommended by the CDC[24]. However, difficulties in performing the test, low IgM antibody titers in adults, and high background noise due to the presence of IgG antibodies may contribute to false-negative results[12,24,26]. Other serological methods, such as complement fixation, enzyme immunoassay (EIA), or whole-cell fluorescence, are not recommended for diagnosing *Chlamydophila pneumoniae* due to their limited sensitivity and specificity. These limitations can result in the inability to distinguish between active and past infections[24]. Due to the numerous challenges associated with culturing the microorganism on solid media, this method is not recommended for the diagnosis of chlamydial respiratory tract infections.

## 5. Imaging

***Legionella pneumophila***

Tools like X-ray, computed tomography (CT) and ultrasonography are essential in diagnosis of *Legionella pneumophila*, although each has its own limitations. X-ray is an easily accessible and affordable imaging method however it lacks in resolution and accuracy[27]. Radiographic

features include middle and lower zone predominance, parenchyma opacities, pleural effusions and occasionally a bulging fissure sign[28,29]. In immunocompromised patients circumscribed peripheral densities and cavities are common findings. Nevertheless, approximately half of the *L. pneumophila* patients show non-specific radiographic image which comprises of only bilateral parenchyma opacities and pleural effusions, which can overlap with other types of pneumonia and cannot give a definitive diagnosis. Furthermore, the radiographic severity does not correlate with clinical outcome[27,30]. CT scans offer more accuracy in diagnosis of legionellosis as more than 80% of the patients show typical changes of ground glass opacities (GGO) compounded with clear border consolidation, which are concentrated mainly around the hilum[31]. In the immunocompromised group abscesses and cavities may appear[27]. Ultrasonography is a method of diagnosis in *L. pneumophila* which still needs further refinement and exploration. It has been shown that hypoechoic lesions with irregular boundaries, small consolidations, and multiple B-lines can be associated with *L. pneumophila*[32].

***Mycoplasma pneumoniae***

The findings on the X-ray image may not correlate with clinical symptoms which can be milder than radiographic findings. Typical image includes lower zone predominance- unilateral or bilateral, perihilar bronchopneumonia with reticulonodular opacity, bronchial cuffing and linear atelectasis. Interstitial disease may cause pseudo consolidations. Small effusions present in up to 20% of cases may indicate a more severe ruse of the disease. In CT scans the characteristic image comprises of peribronchial thickening, centrilobular nodular and tree in bud pattern, patchy distribution. Radiographic findings additionally include hazy, lobular and GGO, pseudoconsolidations and pleural effusions[33]. The clinical features observed in lung ultrasound for *Mycoplasma pneumonia* present as hypoechoic areas with intense signal reflections. Owing to the elevated gas content within the bronchi, a pronounced gas echo may emerge, often accompanied by the comet tail sign. In instances where inflammatory exudate is present in the bronchi, a low-frequency echo can be detected, known as "bronchial fluid"[34,35]

***Chlamydophila pneumoniae***

There is no radiographic finding specific only for *C. pneumoniae*, however the combination of certain clinical symptoms compounded with radiographic findings may suggest the diagnosis of *C. pneumoniae* before the cultures and serology results are available. Most chest radiographs reveal bilateral hyperinflation and widespread infiltrates, presenting a range of radiographic patterns such as interstitial, reticular nodular, atelectasis, coalescence, and bronchopneumonia. Pleural effusions and lobar consolidations are absent. The radiographic alterations frequently

indicate a more severe condition than what is noted clinically[36]. It has been found out that most of the feature of *C. pneumoniae* present in CT scans are non-specific and overlap with other types of pneumonia caused by *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*. The characteristics include consolidations, GGO, bronchovascular bundle thickening, nodules, pleural effusion, lymphadenopathy, reticular or linear opacity, airway dilatation, pulmonary emphysema, and bilateral lung involvement. Bronchovascular bundle thickening and airway dilatation were however significantly more frequent in patients with chlamydiosis than in those affected by pneumonia of different etiology examined in the study[37]. Features present in lung ultrasonography may aid the diagnostic process, however the abnormalities overlap with other kinds of pneumonia, especially atypical. Holistic approach is essential to produce a correct diagnosis. Thus, clinical manifestation and laboratory tests must be taken into account.

6. Treatment

## Legionella pneumophila

The antibiotics of choice for the treatment of *L. pneumophila* infections are fluoroquinolones, such as levofloxacin, ciprofloxacin, and ofloxacin. Second-line antibiotics include macrolides and doxycycline. However, studies suggest that combination therapy consisting of fluoroquinolones and macrolides may also be effective[38]. The use of β-lactam antibiotics is not recommended for the treatment of *Legionella pneumophila* infections due to the production of β-lactamases by most strains and the lack of antibiotic penetration into macrophages, where the microorganism resides and replicates[12]. To date, no other resistance mechanisms have been observed in *L. pneumophila*[39].

#### *Mycoplasma pneumoniae*

In the treatment of *M. pneumoniae* infections, antimicrobial agents act bacteriostatically. Macrolides and second-generation tetracyclines (doxycycline) are the first-line antibiotics for adults, with fluoroquinolones serving as an alternative treatment. For pediatric patients, antibiotic therapy should primarily rely on macrolides, as doxycycline may cause tooth discoloration in children, and fluoroquinolones can damage joint cartilage[40]. An increasing rate of macrolide resistance in *M. pneumoniae* has been observed. According to the latest 2024 CDC report, macrolide resistance prevalence is approximately 5% in Europe, around 10% in the United States, and significantly higher in Japan and China, where resistant strains account for 50–80% of cases[41].

Due to the absence of a cell wall, *M. pneumoniae* is inherently resistant to penicillin and cephalosporins.

*Chlamydophila pneumoniae*

According to CDC guidelines, the first-line antibiotics for the treatment of *Chlamydia spp.* infections include azithromycin, administered as a loading dose of 500 mg on the first day, followed by a maintenance dose of 250 mg for the next four days. Alternative treatment options include doxycycline, clarithromycin, and fluoroquinolones. To date, no cases of resistance to any of the administered antibiotics have been reported in *C. pneumoniae*[42,43].

## 7. Complications of atypical pneumonia

### *Legionella pneumophila*

*L. pneumophila* can lead to a variety of serious complications especially among the immunocompromised patients. Thus, early detection and treatment is vital.

- **Respiratory complications:** acute respiratory failure and acute lung injury have been observed in severe cases which often necessitate intensive care and mechanical ventilation[44,45].
- **Extrapulmonary manifestations:** complications including multi-organ failure, acute liver injury and sepsis have been observed[44]. Additionally, *L. pneumophila* can be a causing factor in rhabdomyolysis resulting in acute renal failure and cerebellar dysfunction. Neurological complications incorporate inflammatory polyneuropathy[46,47].
- **High mortality rates:** mortality rates in legionellosis can reach up to 40% and are significantly higher among immunocompromised individuals[45].

### *Mycoplasma pneumoniae*

While the majority of *M. pneumoniae* cases present as mild respiratory disease, early diagnosis and treatment are paramount in mitigating the risk of various, potentially life-threatening complications.

- **Pulmonary complications:** *M. pneumoniae* can lead to lung necrosis associated with prolonged fever and elevated serum markers like lactate dehydrogenase (LDH) and D-dimer. In severe cases *M. pneumoniae* can result in acute respiratory distress syndrome (ARDS), requiring hospitalisation in the intensive care unit[48,49].
- **Extrapulmonary complications:** involve myocarditis, thrombus formation, myocardial infarction, left ventricular disfunction[50,51], cerebral infarction[52] and autoimmune haemolytic anaemia [49].

***Chlamydophila pneumoniae***

Although the majority of patients experience mild course of the disease and present only transient symptoms it is important to note that complications of *C. pneumoniae* can be severe. Respiratory, cardiovascular, and neurological problems can result from *Chlamydophila pneumoniae* infection.

- **Respiratory complications:** *C. pneumoniae* can be a causing factor in respiratory difficulties including aggravation of pre-existing, chronic diseases, like asthma and chronic obstructive pulmonary disease (COPD)[53] .
- **Cardiovascular complications:** the correlation between chlamydiosis and myocardial infarction, unstable angina and atherosclerosis has been established[54].
- **Neurological complications:** *C. pneumoniae* sequelae encompass hemophagocytic lymphohistiocytosis and encephalitis, which can lead to flaccid paralysis[55] .

## 8. Conclusions

Atypical pneumonia, a form of community-acquired pneumonia, can be caused by bacteria different from typical pathogens, primarily *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Legionella spp*. The symptoms are generally milder and include sore throat, low-grade fever, cough, headache, and fatigue. In some cases, it may also cause extrapulmonary manifestations, such as skin rashes and neurological symptoms, including encephalitis or Guillain-Barré syndrome. Diagnostics include bacterial culture, PCR and serologic tests. Radiographic imaging typically reveals interstitial changes without the characteristic pulmonary infiltrates seen in typical pneumonia. Since atypical bacteria lack a cell wall, they are resistant to β-lactam antibiotics. Consequently, treatment consists of macrolides, tetracyclines, or fluoroquinolones. Complications may include severe lung damage, respiratory failure, rhabdomyolysis, and neurological issues such as flaccid paralysis or cerebral infarction. Cardiovascular complications, including myocardial infarction and left ventricular dysfunction, may also occur.

## 9. Disclosure:

### Author's contribution:

Conceptualization: MG; methodology: SZ; software: MW; check: AS; formal analysis: MG; investigation: MG and AS; resources: MW; data curation: SZ and AS; writing- rough preparation: MG; writing-review and editing: AS and MW, visualization: SZ; supervision: MG;

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