Atypical pneumonia (Review)

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Abstract. Atypical pneumonia encompasses diverse pathogens, such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* species, which differ from typical bacterial pneumonia in their extrapulmonary manifestations. Clinical differentiation relies on systemic involvement rather than on standalone symptoms. Despite challenges in distinct diagnosis, syndromic approaches and weighted point systems aid in accurate presumptive diagnoses. Antibiotic treatment, often non-β-lactams due to the unique cell structures of atypical pathogens, targets intracellular processes. Macrolides, tetracyclines, quinolones and ketolides are effective due to their intracellular penetration, crucial for combating these intracellular pathogens. The prevalence of atypical pneumonia varies globally, with Europe, Asia/Africa and Latin America reporting detection rates between 20-28%. *Streptococcus pneumoniae* remains a primary cause of pneumonia; however, atypical pathogens contribute significantly to this disease, being more prevalent in outpatient settings and among young adults. *Legionella* stands out in severe hospitalized cases and is associated with higher mortality rates. Diagnosis proves challenging due to overlapping symptoms with other respiratory infections. Differentiation among pathogens, such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* relies on subtle clinical variations and imaging findings. Diagnostic methods include serological studies, cultures and polymerase chain reaction, each with limitations in sensitivity or specificity. Prognosis varies widely. Atypical pneumonia can progress to severe forms with fatal outcomes, causing multi-organ damage. Complications extend beyond the respiratory system, affecting the cardiovascular system, exacerbating conditions such as chronic obstructive pulmonary disease and asthma, and potentially linking to conditions such as lung cancer. Increasing antibiotic resistance poses a significant challenge, influencing treatment outcomes and prolonging illness duration.

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Contents

1. Introduction

The term 'atypical pneumonia' was originally used to describe community-acquired pneumonias (CAPs) due to viruses that differed from bacterial CAPs as regards the clinical and radiologic features. Over time, this term has evolved to denote lower respiratory infections caused by specific respiratory microorganisms, including *Legionella* species, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Chlamydia psittaci* (psittacosis), *Coxiella burnetii* (Q fever) or *Francisella tularensis* (tularemia) (1-3).

CAPs differ from typical bacterial CAPs via several key mechanisms. Typical CAPs are most commonly caused by pathogens, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, which primarily present with more acute symptoms, such as a high fever, productive cough and localized chest pain. These infections are typically associated with radiographical findings of lobar consolidation and respond well to β-lactam antibiotics, which target the bacterial cell wall. By contrast, atypical CAPs are caused by pathogens such as *Legionella* species, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*, which often present with a more insidious onset, milder respiratory symptoms, and prominent extrapulmonary manifestations, such as headache, myalgia and gastrointestinal symptoms. Atypical pathogens generally lack cell walls or reside intracellularly,

rendering them resistant to β-lactam antibiotics. As a result, treatment typically requires antibiotics that can penetrate cells, such as macrolides, tetracyclines or fluoroquinolones. Moreover, while typical CAPs usually exhibit well-defined lobar consolidation upon imaging, atypical CAPs often exhibit diffuse interstitial patterns or patchy infiltrates, reflecting their distinct pathophysiology and clinical course (1-3).

Atypical CAPs account for ~15% of all CAP cases. Although community outbreaks linked to atypical pneumonia pathogens exist, the majority of cases of atypical CAP are sporadic. These atypical microorganisms can occasionally result in outbreaks of pneumonia acquired in nursing homes or are acquired in medical facilities. Identifying atypical pneumonia as the cause of nosocomial infections is infrequent.

Among adults with less severe or ambulatory CAP, atypical microorganisms are more widespread compared to typical bacterial pathogens. *Legionella* notably contributes to severe CAP cases in hospitalized patients (4,5).

Atypical pneumonias can be clinically categorized into zoonotic transmission-based and non-zoonotic forms. Zoonotic atypical pneumonias encompass Q fever, psittacosis and tularemia, while non-zoonotic types involve CAPs caused by *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella*. Both zoonotic and non-zoonotic atypical pneumonias fundamentally differ from bacterial CAPs. Yet, the key distinguishing factor between atypical and typical CAP pathogens lies in the presence or absence of extrapulmonary indications. All atypical pulmonary pathogens, irrespective of their zoonotic or non-zoonotic nature, induce systemic infectious diseases primarily affecting the lungs (pneumonia). By contrast, pneumonias caused by *Moraxella catarrhalis*, *Streptococcus pneumoniae* or *Haemophilus influenzae* typically manifest with clinical findings and results from laboratory testing confined to the respiratory system. Once this differentiation is established in CAP cases with extrapulmonary signs, clinicians can identify the characteristic organ involvement pattern, facilitating focused diagnostic considerations (6,7).

Every atypical pulmonary pathogen displays a preference for particular extrapulmonary organ systems. What sets apart atypical pneumonias is individual clinical or laboratory findings, but also the distinct pattern of organ engagement. For instance, extrapulmonary organ involvement caused by *Legionella* markedly differs from that caused by *Chlamydia pneumoniae* or *Mycoplasma pneumoniae*, forming the basis for an initial clinical assessment. Identifying these unique extrapulmonary patterns linked to each atypical pathogen generally enables an accurate preliminary clinical diagnosis. However, this preliminary diagnosis is not definitive and should prompt targeted diagnostic tests to confirm or exclude specific pathogens (8).

The majority of research has not effectively distinguished typical from atypical pneumonias due to its focus on comparing the individual clinical and laboratory aspects of both pathogen types (9-12). These studies have found minimal discernible differences in standalone findings (9-12). Few studies have utilized a syndromic diagnosis (9-12), while only one study (10) employed a weighted syndromic point system. This system distinguishes atypical pneumonias by using a scoring system based on the presence of specific clinical features, such as symptoms and laboratory results, which are weighted according to their association with atypical pathogens. The weighted system helps clinicians to prioritize testing and treatment for atypical pathogens when the clinical presentation aligns more closely with the characteristics typical of atypical pneumonias, such as the longer duration of symptoms before seeking care, the presence of certain epidemiological factors, and the absence of findings more common in typical bacterial pneumonias. Using this weighted approach, considering the relative clinical specificity of characteristic clinical findings, clinicians can effectively differentiate between typical and atypical pneumonias, even presumptively diagnosing Legionnaire's disease accurately (9-12). The significance of atypical pneumonias lies not merely in their clinical occurrence, but also in other clinical and public health considerations, demanding distinct therapeutic approaches compared to typical CAPs (13).

Atypical pathogens such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are prevalent among young adults with CAP in outpatient settings, surpassing typical CAP-causing pathogens in this context. They, along with *Legionella*, significantly contribute to severe CAP cases. Unlike typical bacteria susceptible to β-lactam antimicrobial treatment due to their vulnerable cell walls, the majority of atypical pathogens lack these walls. Some are intracellular, such as *Legionella*, while others, such as *Mycoplasma pneumoniae*, use paracellular pathways for entry (14). Antimicrobials that disrupt intracellular protein synthesis effectively combat these atypical pathogens. Macrolides and tetracyclines impede bacterial protein synthesis inside cells. Quinolones and recently developed ketolides exhibit high efficacy against atypical pathogens, particularly *Legionella*. Given the intracellular nature of some atypical pathogens such as *Legionella*, effective antibiotic penetration into alveolar macrophages (AMs) is crucial. Macrolides, tetracyclines, quinolones and ketolides exhibit a tendency to accumulate in AMs (15-18).

Atypical CAP pathogens are more commonly encountered in outpatient cases and play a particularly crucial role in the severity of CAP among hospitalized patients. Additionally, public health concerns contribute to the significance of certain atypical CAP pathogens. *Chlamydia pneumoniae* infection is potentially involved in coronary artery disease and neurological diseases, such as multiple sclerosis. Moreover, infections from *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* could complicate asthma. Both pathogens are notable causes of nonexudative pharyngitis (19-25). Zoonotic atypical pneumonias have historically been pivotal in areas endemic to these diseases. Psittacosis continues to be a key factor in causing CAP among individuals who have contact with psittacine birds. Q fever sporadically occurs among those in proximity to parturient cats or in sheep-raising regions. Endocarditis poses an infrequent yet critical issue in endemic Q fever zones. Tularemia, with its various clinical presentations, may coincide with pneumonia. In endemic regions, tularemia remains a pertinent and potentially serious infectious disease (26-29). Atypical pathogens bear greater importance due to diagnostic challenges, susceptibility to non-β-lactam antibiotics, and the severity of associated complications.

2. Prevalence of atypical pneumonia

According to a previous study, the detectable rates of atypical pathogens differ across regions, with the rates being as follows:

North America at 22%, Europe at 28%, Latin America at 21% and Asia/Africa at 20% (30). Various countries and regions exhibit distinct rates of atypical pathogen detection.

The methods used to detect atypical pathogens, such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella* species, can vary widely between regions. Some regions may rely more heavily on serological testing, which detects antibodies produced in response to infection, while others may use more advanced molecular techniques, such as polymerase chain reaction (PCR) or multiplex PCR, which directly identify the genetic material of the pathogens. PCR is generally more sensitive and specific but is also more costly and requires sophisticated laboratory equipment that may not be available in all regions.

In addition, the criteria used to diagnose atypical pneumonia can differ between regions due to variations in clinical guidelines, healthcare practices and the experience of healthcare providers. Some regions may adopt broader or more inclusive criteria that capture a wider range of cases, while others may use more stringent criteria, potentially leading to differences in detection rates. For example, the inclusion of certain clinical symptoms, the timing of sample collection, and the use of confirmatory tests such as paired serology can influence the reported prevalence of atypical pathogens (31).

The prevalence of atypical pathogens can be influenced by local epidemiological factors, including climate, population density and the prevalence of comorbid conditions. For instance, *Legionella* infections are more common in areas with certain environmental conditions, such as the presence of contaminated water sources. Additionally, variations in public health measures, vaccination rates and the presence of endemic diseases can affect the distribution and detection of atypical pathogens. Furthermore, regions with more advanced healthcare systems and better access to diagnostic tools are likely to have higher detection rates of atypical pathogens as they can employ more sensitive and specific diagnostic tests. By contrast, regions with limited healthcare infrastructure may have lower detection rates due to reliance on less sensitive methods or the unavailability of certain diagnostic technologies. Furthermore, differences in the methods through which health data are collected, reported and interpreted can also contribute to regional variations in detection rates. Some regions may have more robust surveillance systems and mandatory reporting of atypical pneumonia cases, leading to higher reported detection rates, while others might underreport cases due to lack of surveillance infrastructure or different public health priorities (31).

Europe. Previously, a survey on CAP outbreaks encompassing 3,523 patients (15% outpatients, 85% inpatients) between November, 1996 and July, 2008 revealed 1,463 patients with identifiable causes. *Streptococcus pneumoniae* emerged as the primary cause in Europe, accounting for 42% of the detectable rate, while atypical pathogens and mixed infections also played significant roles at 18 and 14%, respectively (32). In Spain, Capelastegui *et al* (33) noted a 50% detectable rate in their prospective study, where atypical pathogens were more prevalent among outpatients (67%) than inpatients (30.6%). In addition, two studies in The Netherlands highlighted *Streptococcus pneumoniae* as the primary cause of CAP, with varying detectable rates for atypical pathogens (9 and 20%) (34,35).

Israel. Conversely, a study in northern Israel showcased a 52.4% detectable rate for atypical pathogens (*Chlamydia pneumoniae,* 20.6%, *Mycoplasma pneumoniae*, 18.3%, *Legionella pneumophila* 7.1%, and others) (36).

China. An extensive epidemiological survey conducted in China revealed results that differed from those in European countries (37). In that study, atypical pathogens were the primary cause of CAP. *Mycoplasma pneumoniae* was the most common pathogen, with a prevalence of 20.7%, followed by *Streptococcus pneumoniae* at 10.3% (37). Co-infections, particularly with bacteria and atypical pathogens, were prominent in community respiratory infections (37). In two national CAP surveys in performed China (38), *Mycoplasma pneumoniae* surpassed *Streptococcus pneumoniae* as the most common cause among adults, with rates of 38.9 and 32.6%, respectively. Chen *et al* (39) reported *Mycoplasma pneumoniae* as the predominant pathogen, with a positive percentage of 40.78%, exhibiting a significant association with seasons, particularly prevalent in late summer and autumn.

Chile. In Chile, among 356 patients, *Streptococcus pneumoniae* and viruses were predominant, with atypical pathogens contributing to 22% of the infections (40). In a clinical study conducted in Santiago, Chile, focusing on 104 patients with severe CAP between 2005 and 2006, the top seven identified etiological agents were observed. *Streptococcus pneumoniae* accounted for 26%, while *Legionella pneumophila* followed closely at 8.6%. Other pathogens included *Mycoplasma pneumoniae* (6%), *Chlamydia pneumoniae* (4%), Gram-negative bacillus (3%), influenza A virus (3%) and *Staphylococcus aureus* (3%). Notably, *Legionella pneumophila* ranks as the second etiological agent in severe CAP cases, following *Streptococcus pneumoniae*. The global mortality at 28 days in severe CAP was 25%, with *Legionella pneumophila* exhibiting a mortality rate of 33.3% (three out of nine cases); however, this difference was not significant when compared to non-*Legionella* severe CAP mortality (33 vs. 24.5%) (41).

USA and other regions. The incidence of *Legionella pneumophila* in CAP is relatively high worldwide, particularly in the USA (14%) (42) and Spain (12.5%) (43). Even in Asia, the incidence stands relatively high at 6.6% (43).

According to a previous study, the general occurrence of atypical pathogens such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* among individuals experiencing severe pneumonia stood at 8.1%, varying widely from 0 to 48.1%. Notably, the prevalence in adults was slightly lower than that described in children. Notably, the combined group that did not differentiate between adults and children exhibited a prevalence of 12.1%, significantly influencing the overall prevalence rates (44).

3. Diagnostic approach

Clinical presentation. A schematic illustration of the key symptoms and clinical presentations of pathogens is presented

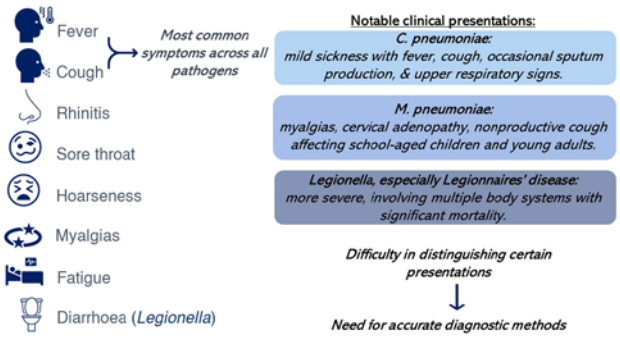

Figure 1. Schematic illustration providing a summary of the common symptoms and important clinical presentations of pathogens.

in Fig. 1. Pneumonia caused by *Chlamydia pneumoniae* manifests as a mild illness, primarily characterized by fever and cough, often followed by upper respiratory signs, such as rhinitis and a sore throat. In the study in 2013 by Conklin *et al* (45), the duration of cough ranged from 1 to 64 days, averaging ~21 days. While a non-productive cough is typically associated with this condition, ~70% of patients exhibited sputum production during *Chlamydia pneumoniae* outbreaks in 2006 and 2013 (45). There are difficulties in distinguishing this presentation from *Mycoplasma pneumoniae* or pneumonia caused by respiratory viruses. Despite earlier notions suggesting that hoarseness and laryngitis were more prevalent in *Chlamydia pneumoniae* infection than in *Mycoplasma pneumoniae* infection, previous comparisons of clinical characteristics have indicated the opposite (46,47).

It has been reported that rhinitis, cough and hoarseness were notably more prevalent in *Mycoplasma pneumoniae* infection compared with *Chlamydia pneumoniae* infection (47). The same researchers observed that C-reactive protein (CRP) and aspartate aminotransferase levels were substantially higher in *Chlamydia pneumoniae* infection than in *Mycoplasma pneumoniae* infection. However, other clinical symptoms and laboratory findings between the two pathogens did not exhibit significant differences (47) according to an earlier study, patients with pneumonia caused by both *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* have notably lower CRP and white blood cell values than in those with pneumonia caused by *Streptococcus pneumonia* (46).

No specific symptom, laboratory marker, or combination of findings reliably distinguishes C. pneumoniae-induced pneumonia from that caused by other respiratory pathogens. Additionally, concurrent infection with other pathogens alongside *Chlamydia pneumoniae* can affect the clinical presentation (45).

Pneumonia stemming from *Mycoplasma pneumoniae* often presents a challenging clinical scenario due to its mild and ambiguous symptoms, such as myalgias, cervical adenopathy, nonproductive cough and fatigue, rendering differentiation from other viral upper respiratory infections and atypical bacterial infections difficult (32,48,49).

Mycoplasma pneumoniae commonly affects children attending school and young adults, often causing outbreaks during the autumn season (32,48-50). These outbreaks typically affect individuals in close contact with infected patients within households or confined spaces (51). Apart from its unconventional symptoms, the manifestations of *Mycoplasma pneumoniae* can differ markedly, spanning from mild upper respiratory symptoms to pneumonia and various manifestations unrelated to the lungs. These include cardiovascular, dermatological and central nervous system symptoms, even without the presence of pneumonia (52).

Legionella infections manifest primarily in two forms: i) Legionnaires' disease, a severe pneumonia resulting from *Legionella* infection. It often involves multiple body systems, notably the lungs and gastrointestinal tract, with associated significant mortality rates (53). ii) Pontiac fever is a mild, self-limiting flu-like illness. Pontiac fever is characterized by mild fever, chills, myalgia, and headaches lasting 2-5 days, typically resolving without substantial mortality (54).

While *Legionella* primarily affects individuals aged ≥50 years, instances have been documented in infants and neonates (55). Distinguishing Legionnaires' disease from pneumonia caused by other pathogens can be challenging due to similar clinical symptoms; however, the presence of diarrhea and heightened creatinine kinase levels may signal a *Legionella* infection (10). *Legionella*-induced pneumonia often occurs in clusters, but not through person-to-person transmission, typically stemming from exposure to the same infection source. Contaminated water or soil largely account for Legionella infections. Risk factors include rainfall, high humidity, and working in gardens with compost (56-58). Although the majority of cases of Legionnaires' disease are associated with *Legionella pneumophila*, several other bacterial species have been identified as causative agents of *Legionella* lung infections (58,59).

Zoonotic atypical CAPs stemming from Q fever, psittacosis or tularaemia typically manifest following exposure to their respective carriers. Notably, psittacosis stands as an outlier, potentially transmissible through contact with healthy or ailing psittacine birds. By contrast, incidences of tularemia and Q fever CAP are not arbitrary; establishing a recent epidemiological background is imperative before suspecting these diagnoses. Should a patient displaying atypical pneumonia lack a recent contact history associated with psittacosis, Q fever, or tularaemia, the likelihood of a zoonotic atypical CAP is exceedingly low (19-22). Thus, it can reasonably be inferred that the patient is experiencing a non-zoonotic atypical pneumonia linked to *Legionella*, *Mycoplasma pneumoniae*, or *Chlamydia pneumonia* (59).

Collectively, pneumonia caused by *Chlamydia pneumoniae, Mycoplasma pneumoniae* and *Legionella* species presents with distinct clinical features. *Chlamydia pneumoniae* typically leads to a milder, more insidious onset of symptoms, including a prolonged cough, low-grade fever, and common respiratory symptoms, such as a sore throat and hoarseness. *Mycoplasma pneumoniae* often affects younger populations, with a gradual onset characterized by a dry cough, fever and extrapulmonary manifestations, such as skin rashes and neurological symptoms. By contrast, *Legionella* infections, particularly *Legionella pneumophila*, cause a more severe form of pneumonia known as Legionnaires' disease. This presents with high fever, chills, myalgia and prominent gastrointestinal symptoms, such as diarrhea, often accompanied by neurological signs, such as confusion. *Legionella pneumophila* progresses rapidly and can lead to severe,

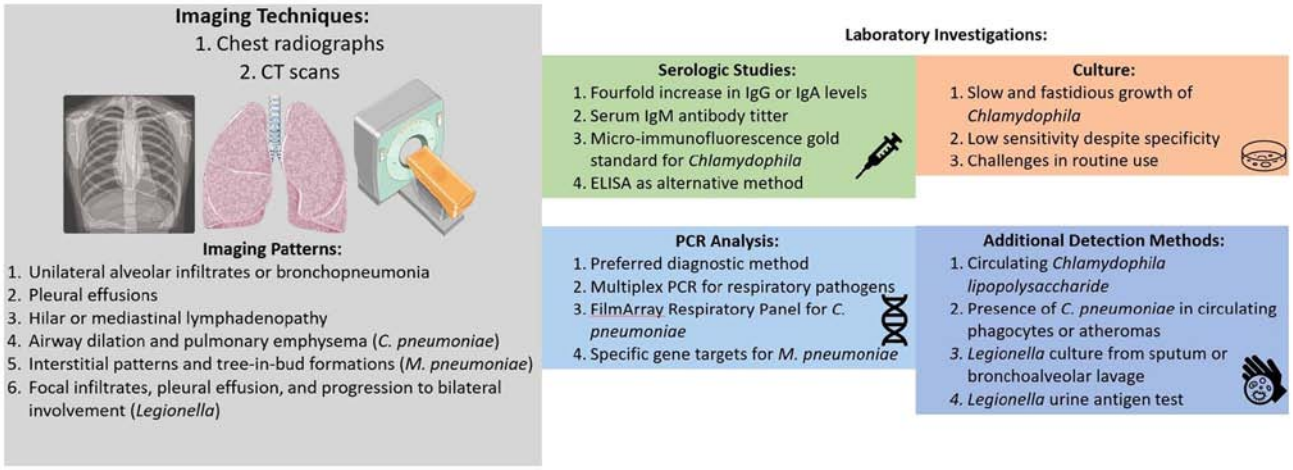

Figure 2. Imaging techniques and characteristics and comparison of laboratory investigations. Parts of this image derived from the free medical site http://smart.servier.com/(accessed on 15 December 2023) by Servier, licenced under a Creative Commons Attribution 3.0 Unported Licence.

potentially life-threatening outcomes, particularly in older adults and individuals with underlying health conditions (60).

Imaging. An illustration of the imaging techniques and characteristics, and comparison of laboratory investigations for the detection of infection is presented in Fig. 2. As regards *Chlamydia pneumoniae*, initially, chest radiographs typically reveal a unilateral pattern of alveolar infiltrates or consolidation, often limited to a single lobe. The lower lobe involvement is more frequent than detecting lesions in the middle or upper lobe (60-63). Instances of interstitial pneumonia manifest relatively infrequently. Approximately a quarter of patients may exhibit small to moderate pleural effusions, while findings, such as hilar or mediastinal lymphadenopathy are less commonly observed in chest radiographs. Variations in findings may hinge on the timing of imaging during the illness, the diagnostic method used, and the exclusion of concomitant respiratory pathogens. In a previous study involving 55 patients classified with primary infection, initial chest radiographs depicted predominantly unilateral findings, while subsequent radiographs taken around 3.8 days later revealed predominantly bilateral findings (61).

In a previous retrospective analysis of thin-section CT scans from 24 patients with serologically diagnosed with CAP caused by *Chlamydia pneumoniae*, Nambu *et al* (64) observed a marked increase in airway dilation compared to *Streptococcus pneumoniae* or *Mycoplasma pneumoniae*-related pneumonia cases, along with a higher incidence of pulmonary emphysema compared to *Mycoplasma pneumoniae* cases, but not *Streptococcus pneumoniae* cases. Their study suggested that the elevated airway dilation and pulmonary emphysema may stem from pre-existing obstructive lung disease rather than the infection itself (64). Despite significant findings in pulmonary emphysema and airway dilation, neither these nor other CT scan observations were able to reliably distinguish *Chlamydia pneumoniae*-related pneumonia from that caused by other pathogens (64). Overall, CT scan or radiograph results in C. pneumoniae cases exhibit broad variability and lack specificity for identifying the pathogen as the cause of pneumonia (61-64).

The imaging characteristics of *Mycoplasma pneumoniae* infections mirror their elusive nature. Chest radiographs commonly reveal diffuse interstitial patterns, occasionally disproportionate to the physical symptoms of patients. On chest CT scans, the interstitial alterations apparent in the radiographs manifest as tree-in-bud formations (65). In a 2016 prospective study by Gong *et al* (65) involving 1,280 pediatric cases of pneumonia caused by *Mycoplasma pneumoniae* between 2010 and 2014, a substantial proportion of patients exhibited extensive patchy infiltrates, both unilateral and bilateral, suggesting that the diagnosis of pneumonia could not be solely determined based on imaging characteristics.

Legionellosis chest radiographs have been described in multiple reports (66,67). While some attempts have been made to outline specific patterns indicative of *Legionella*, the radiographic findings in *Legionella* infection demonstrate significant variability, predominantly influenced by the timing of the radiograph in the course of the illness. Certain temporal features, however, can augment the probability of diagnosing *Legionella* pneumonitis. Initially, poorly defined focal infiltrates are common, with around 10% concurrent with pleural effusion. These infiltrates tend to progress to adjacent lobes, eventually becoming bilateral, with pleural effusions occurring in about 35% of cases. This progression often persists despite appropriate antimicrobial treatment and even in the presence of clinical improvement. Immunocompromised individuals exhibit a similar pattern, often displaying a high incidence of cavitation and hilar adenopathy. A lengthy resolution phase, lasting up to 6 months, frequently occurs, occasionally resulting in residual densities. Attempts to associate radiographic characteristics with disease severity and mortality have had limited success (68).

Collectively, imaging studies reveal distinct patterns for each type of pneumonia. *Chlamydia pneumoniae* typically presents on a chest X-ray with diffuse interstitial infiltrates, often patchy or involving the lower lobes, with occasional segmental consolidation. *Mycoplasma pneumoniae* is usually associated with reticulonodular patterns or patchy consolidations on an X-ray, predominantly in the lower lobes, and occasionally, hilar lymphadenopathy. CT scans may reveal

bronchial wall thickening and centrilobular nodules. By contrast, pneumonia caused by *Legionella* is characterized by rapidly progressing lobar consolidation, often with bilateral involvement on chest X-ray. CT imaging may reveal dense consolidations, nodular opacities, ground-glass changes and sometimes small pleural effusions, reflecting the more aggressive and widespread nature of this infection (69).

Laboratory investigations. Established methods to detect *Chlamydia pneumoniae* infection involve serological studies and the culture or PCR analysis of respiratory tract samples. An organized discussion of the different testing methods is provided below:

Serological tests. Traditionally, the diagnosis of *Chlamydia pneumoniae* infection has hinged on serology, necessitating a 4-fold increase in IgG or IgA levels between acute and convalescent serum samples. Serological approaches are generally intricate as patients must return after 4 to 6 weeks from the initial presentation to confirm the diagnosis retrospectively. Moreover, this retrospective nature renders serological outcomes minimally impactful on treatment decisions. Different serological criteria used for diagnosis upon initial presentation, such as a serum IgM antibody titer of 1:16 or higher, strongly depend on when the sample was collected. This is due to the potential absence of a titer rise early in acute infection or reinfection. Depending entirely on initial serologic samples for diagnosis, without confirming retrospectively using convalescent serum samples, poses the risk of overlooking 25 to 33% of infections. The initial serological testing could require several days to produce results, further limiting their utility in making initial management decisions. Possible cross-reactivity between *Chlamydia pneumoniae* antigens and antigens from other *Chlamydia* species limits the specificity of serological techniques. Microimmunofluorescence is considered the gold standard for serological diagnosis (70,71).

ELISA, an alternative method, may be less intricate and more objectively interpretable than microimmunofluorescence (69). However, complement fixation is not recommended for diagnosis due to its limited sensitivity and specificity (70,72).

PCR technology. Considering the constraints of serology and culture, the PCR analysis of respiratory samples has become the preferred diagnostic method. Multiplex PCR can assess multiple potential respiratory pathogens without a significant decrease in sensitivity compared to singleplex PCR testing (73). In 2012, the FDA sanctioned the FilmArray Respiratory Panel, employing multiplex PCR to identify *Chlamydia pneumoniae* and other microorganisms from nasopharyngeal swabs (74). PCR, however, faces specificity limitations due to asymptomatic carriage and persistent identification of *Chlamydia pneumoniae* on respiratory swabs even after clinical symptom resolution, possibly extending for several weeks to months following antibiotic therapy (75,76). This persistence complicates definitively attributing positive PCR results to persistent infection, reinfection, or ongoing asymptomatic carriage, potentially involving other pathogens (76). Moreover, *Chlamydia pneumoniae* detection in respiratory samples does not exclude coinfection with other pathogens, affecting clinical presentation as observed in multiple studies (72,76). Other detection methods include identifying *Chlamydia* lipopolysaccharide in circulation or the presence of *Chlamydia pneumoniae* in circulating phagocytes or atheromas. However, these approaches are technically complex and presently restricted to research settings (70).

Traditionally, the diagnosis of *Mycoplasma pneumoniae* relied on cultures and serology, with culture isolation once deemed the gold standard. However, due to the slow and inconsistent growth of *Mycoplasma pneumoniae*, routine culturing is no longer common and offers limited clinical utility (48,50). Other diagnostic avenues include serologic studies using ELISA to quantify bacterial antibody expression, microparticle agglutination and complement fixation assays. Definitive diagnosis in serologic studies required paired sera demonstrating a significant 4-fold increase in IgG or subsequent seroconversion 3-4 weeks later (77-80). Yet, due to delayed antibody production and seroconversion, these tests hold limited utility for the diagnosis of acute *Mycoplasma pneumoniae* infections in clinical settings and are more retrospective for epidemiological studies (50,77-79).

As culture and serology have shortcomings in the diagnosis of *Mycoplasma pneumoniae*, diagnostic methods are shifting toward faster molecular techniques, such as nucleic acid amplification. Molecular diagnostics enable the timely detection of *Mycoplasma pneumoniae* infections and are increasingly pivotal in clinical diagnosis. An array of laboratory techniques, such as nucleic acid amplification, multilocus variable number tandem-repeat analysis, and multilocus sequence typing, are becoming prominent (50). These tests deliver rapid, highly specific, and sensitive results (50,77). Several tests employ real-time PCR to target specific gene regions of *Mycoplasma pneumoniae*, including those encoding the P1 gene, 16S ribosomal RNA, the ATPase operon, and the community-acquired respiratory distress syndrome toxin (50,77-80). This technology has led to multiplex PCR development, allowing for the detection of various atypical pathogens, including *Chlamydia pneumoniae*, *Chlamydia psittaci*, *Legionella* species and other respiratory viruses (50,72). Nonetheless, debate persists over which sample types provide the best sensitivity and specificity for these assays. Studies have suggested that sputum samples yield more positive results compared to nasopharyngeal aspirates, nasopharyngeal swabs, or oropharyngeal swabs (79,81).

Since numerous aspects of *Legionella* closely resemble both typical and atypical pneumonias, relying on clinical symptoms or radiological evidence offers limited diagnostic value. The CDC indeed relies on several methods to confirm *Legionella* infections. These include culturing *Legionella* bacteria from respiratory samples, such as sputum or bronchoalveolar lavage, detecting the *Legionella* antigen in urine, or observing a significant increase (≥4-fold) in *Legionella*-specific antibodies in the blood serum of patients when comparing acute and convalescent samples (82). PCR-based diagnostic tests, although demonstrating specificity and sensitivity in ongoing assessments, are pending approval by the FDA. Other methods, such as direct immunostaining, are being utilized to identify the bacterium, but often necessitate invasive procedures to procure tissue for testing (83).

Culture methods. Culture, although considered specific due to a low asymptomatic carriage rate, has limited sensitivity

due to the slow and fastidious growth of *Chlamydia* species, often requiring weeks (68,84,85). Previous studies indicate a minimal frequency of growth in culture, even when infection is identified through serology or PCR (68). Some researchers in 2010 (84) discouraged routine culture use due to the inability to detect any positive results among 6,981 respiratory specimens, despite *Chlamydia* species accounting for 5 to 22% of CAP and other respiratory infections.

Due to the challenging nature of isolating *Chlamydia psittaci*, its diagnosis relies entirely on serological methods. In individuals lacking immunity or prior exposure, heightened tube agglutination tests for *Chlamydia psittaci* serve as a definitive diagnostic tool. Similarly, the diagnosis of tularemia and Q fever relies on serology due to the highly infectious, perilous and elusive nature of these organisms. In individuals lacking immunity or previous exposure, acute increases in *Francisella tularensis* IgM/IgG levels serve as diagnostic indicators. As regards Q fever or tularemia, apart from initially elevated acute titers, the diagnosis of these zoonotic CAPs is contingent upon a 4-fold increase in titers between acute and convalescent samples taken 4-8 weeks apart (83).

Collectively, the diagnosis of atypical pneumonia can be achieved through several methods, each with distinct advantages and limitations. Serologic testing, while widely available and cost-effective, often suffers from delayed diagnosis due to the need for paired sera to detect rising antibody titers, and it may produce false positives due to cross-reactivity with other pathogens (6,71). Culture methods offer high specificity and allow for direct pathogen identification and susceptibility testing; however, they are time-consuming, have a low sensitivity and require specialized media, rendering them less practical for routine diagnostics (72,83). PCR assays provide a highly sensitive and specific method for early pathogen detection, delivering rapid results that can significantly impact patient management. However, PCR is more costly, requires specialized equipment and may detect non-viable organisms, complicating the interpretation of positive results (60,75). Combining these methods can enhance diagnostic accuracy, particularly in complex cases of atypical pneumonia.

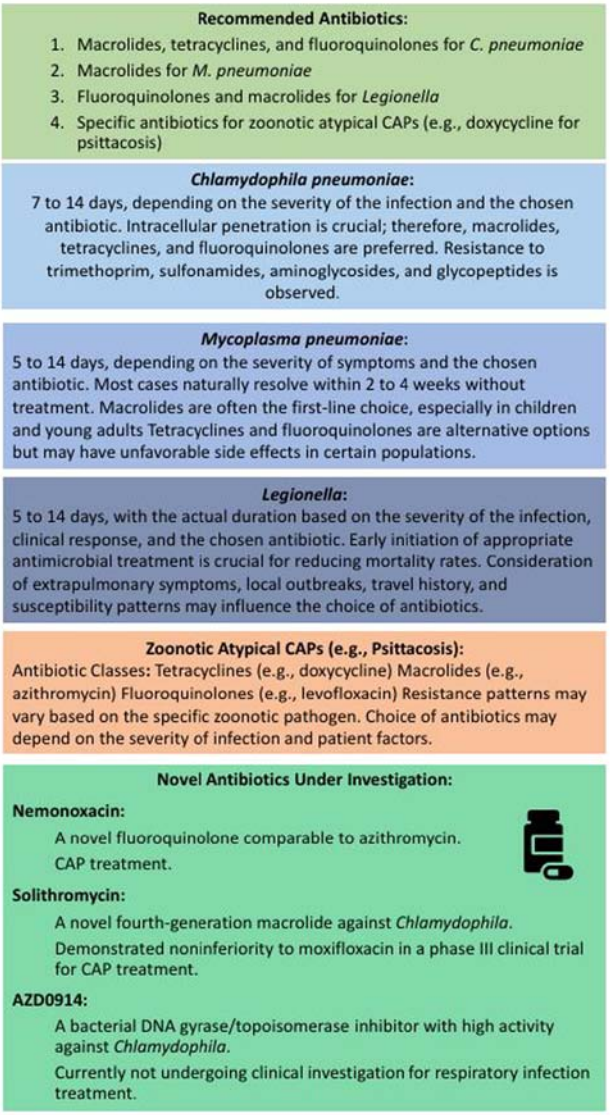

Figure 3. Schematic illustration providing a summary of recommended antibiotics, special considerations for each pathogen and novel treatments under investigation.

4. Treatment

The antibiotic treatment recommendations (Fig. 3) for *Chlamydia pneumoniae* face limitations due to the absence of standardized diagnostic criteria and reliance on serology alone in most past studies. The 2007 guidelines from the Infectious Diseases Society of America (IDSA) acknowledge a lack of robust evidence supporting specific antibiotic therapies for this pathogen (85). Consequently, treatment suggestions are still largely based on expert opinions. In cases where symptoms reappear after a standard antibiotic course, experts recommend prolonged treatment upon identification of *Chlamydia* species (70).

Effective antibiotic therapy against *Chlamydia pneumoniae* necessitates intracellular penetration due to its nature as an obligate intracellular microorganism. Antibiotic classes, such as macrolides, tetracyclines and fluoroquinolones, which disrupt DNA and protein synthesis, display *in vitro* activity against this pathogen, thus becoming the recommended drugs for clinical treatment (86).

Macrolide and tetracycline antibiotics are effective against atypical pathogens, such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* species, primarily due to their ability to penetrate and act within host cells, targeting intracellular processes. These atypical pathogens are often intracellular or lack the typical cell wall structure, which renders them inherently resistant to β-lactam antibiotics such as penicillin (4).

Among fluoroquinolones, ciprofloxacin exhibits a higher minimum inhibitory concentration compared to others in this class, potentially reducing its efficacy. Notably, *Chlamydia pneumoniae* exhibits resistance to trimethoprim, sulfonamides, aminoglycosides and glycopeptides. While penicillin and amoxicillin display *in vitro* activity against *Chlamydia* species, they are not recommended as routine therapies for *Chlamydia pneumoniae*. Resistance to the recommended treatments is infrequent and does not appear to contribute to treatment ineffectiveness or the persistence of *Chlamydia pneumoniae* identified in respiratory samples following the

completion of therapy. This is evidenced by isolates obtained from patients following appropriate therapy, displaying *in vitro* sensitivity (86).

Three new antimicrobial agents, solithromycin nemonoxacin and AZD0914, have exhibited *in vitro* activity against *Chlamydia* species but are currently undergoing trial phases and await FDA approval for treatment (87-89). Nemonoxacin, a new fluoroquinolone, demonstrates *in vitro* effectiveness similar to that of azithromycin, doxycycline and levofloxacin (88). Clinical trials involving 256 and 192 patients with mild to moderately severe CAP have demonstrated the effectiveness of nemonoxacin in treating all identified patients with *Chlamydia pneumoniae*, albeit a total of only 9 patients between both trials (90-91).

Solithromycin a novel fourth-generation macrolide, has been shown to exhibit *in vitro* activity against *Chlamydia* species and has demonstrated non-inferiority to moxifloxacin in a phase III clinical trial for CAP treatment; however, that study did not specifically identify patients with *Chlamydia* infection (92). AZD0914 exhibits potent activity against *Chlamydia* species and various other respiratory pathogens *in vitro* as a bacterial DNA gyrase/topoisomerase inhibitor. Nevertheless, it is not currently undergoing clinical investigation for respiratory infection treatment (88).

Infection caused by *Mycoplasma pneumoniae* often goes undetected, as patients tend to forgo seeking treatment due to the gradual onset of symptoms (32,48,49). The bacterium has an extended incubation period of ~3 weeks, and symptomatic shedding can persist for up to 4 months; however, the majority of cases naturally resolve within 2 to 4 weeks without treatment (32,48,77).

When patients seek clinical care, their treatment is commonly directed by the IDSA guidelines for CAP, considering the symptoms of the patient and imaging outcomes (93). *Mycoplasma pneumoniae*, being a small bacterium lacking a cell wall, inherently resists β-lactam antimicrobials. Despite this, it is usually treated in empirical CAP treatment with macrolide, often in the absence of a confirmed laboratory diagnosis. This antimicrobial treatment has the potential to reduce the duration of the illness, requiring a course of antibiotics ranging from 5 days to 2 weeks, depending on the selected antibiotic for individuals affected by the infection (94,95). Due to its prevalence among children and young adults, macrolides have become the preferred treatment choice. Tetracyclines and fluoroquinolones, while effective, are associated with unfavorable side-effects that are more problematic in younger patients, such as dentition discoloration with tetracyclines and tendinitis with fluoroquinolones (95).

Managing extrapulmonary symptoms or complex cases of *Mycoplasma pneumoniae* infection beyond antibiotic treatment remains uncertain in terms of specific treatment protocols. For patients with *Mycoplasma pneumoniae*-associated extrapulmonary conditions, understanding the inflammatory nature of the bacteria is crucial (96). Through pathways linked to Toll-like receptor 2, the bacteria can prompt pro-inflammatory cytokine production and inflammasome activity. This could clarify why symptoms are more common among young adults, as they typically have a stronger immune response compared to infants or elderly patients who may not generate the same level of response (97). In patients with central nervous system complications or severe pneumonia caused by *Mycoplasma pneumoniae*, there have been reports suggesting the potential benefits of steroids and immunoglobulin therapy, although these findings have not been validated in clinical trials (56,98). Additionally, for severe pneumonia leading to acute respiratory distress syndrome, reports indicate potential benefits from extracorporeal membrane oxygenation and the use of steroids (56,79,81).

The primary treatment for pneumonia due to *Legionella* involves antibiotics. Failure to administer appropriate antimicrobial treatment at an early stage is linked to high mortality rates (99,100). Selecting the right antibiotic is not solely based on its *in vitro* ability to kill or inhibit bacteria, but also on its capacity to penetrate host tissue cell membranes, where *Legionella* resides. Among the most commonly used and highly effective antibiotics for treating Legionnaires' disease are fluoroquinolones and macrolides. Including these agents in the initial treatment plan is advisable when *Legionella* infection is suspected due to local outbreaks, travel history or extrapulmonary symptoms (86).

Early reports from the initial outbreak of Legionnaires' disease found that tetracycline and erythromycin were more effective than other antibiotics, such as β-lactams, while the use of steroids was linked to unfavorable outcomes (53). Erythromycin, a historically preferred antibiotic, has exhibited high effectiveness against Legionnaires' disease, but may cause notable side-effects, particularly when administered intravenously (100-103). Azithromycin, another macrolide, has demonstrated high efficacy with fewer side-effects in treating Legionella infection, often used when erythromycin does not yield results (104,105).

Clarithromycin, rifampin, ciprofloxacin and doxycycline are other effective antibiotics against *Legionella*, either used individually or in combination with erythromycin (98). Research findings suggest that fluoroquinolones demonstrate effectiveness comparable to, or even greater than, erythromycin in treating Legionnaires' disease. Levofloxacin has exhibited a high efficacy, with shorter periods of hospitalization and early clinical responses, becoming a favored antibiotic for this condition (40,106-108).

While the majority of antibiotic therapies span 5 to 10 days and effectively treat *Legionella* infection, immunocompromised patients may require longer durations, up to 3 weeks. Administration routes vary based on infection severity, with parenteral therapy preferred for severe cases, transitioning to oral treatment once a positive response is observed (101).

Antibiotic resistance in *Legionella* species is rarely reported in clinical settings, although *in vitro* resistance has been observed. Previous reports have highlighted instances of fluoroquinolone resistance in patients undergoing treatment, emphasizing the need for close monitoring during ongoing antibiotic therapy (109,110). Table I summarizes the effective therapies for atypical pneumonia microorganisms.

Increased antibiotic resistance in the treatment of atypical pneumonia, caused by pathogens such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella* species, can significantly affect treatment outcomes and disease progression. When atypical pneumonia pathogens, particularly *Mycoplasma pneumoniae*, develop resistance to commonly

Table I. Most effective therapies for atypical pneumonia.

Microorganism	Effective therapies
Chlamydia pneumoniae	Macrolides, tetracyclines, fluoroquinolones
Mycoplasma pneumoniae	Macrolides, tetracyclines, fluoroquinolones
Legionella species	Fluoroquinolones, macrolides
Chlamydia psittaci (psittacosis)	Tetracyclines (e.g., doxycycline), macrolides (e.g., azithromycin), fluoroquinolones
Coxiella burnetii (Q fever)	Tetracyclines (e.g., doxycycline), fluoroquinolones
Francisella tularensis (tularemia)	Aminoglycosides (e.g., streptomycin, gentamicin), tetracyclines (e.g., doxycycline), fluoroquinolones

used antibiotics, such as macrolides (e.g., azithromycin, clarithromycin), patients may experience delayed a clinical improvement. For instance, macrolide-resistant *Mycoplasma pneumoniae* has been increasingly reported, particularly in Asia. In cases where macrolide resistance is present, the initial antibiotic therapy may fail, leading to prolonged symptoms, such as persistent cough, fever and malaise, and necessitating the use of alternative antibiotics such as fluoroquinolones or tetracyclines, which may have a broader side-effect profile. Antibiotic resistance can lead to more severe disease progression due to ineffective initial treatment. For example, in *Legionella* infections, delayed or inappropriate antibiotic therapy due to resistance can result in a higher risk of complications, such as acute respiratory distress syndrome (ARDS), multi-organ failure, or even death, particularly in vulnerable populations, such as the elderly or immunocompromised patients. The timely administration of effective antibiotics is critical in treating Legionnaires' disease, and resistance can undermine this, leading to more aggressive disease progression.

Resistance to first-line antibiotics often requires switching to second- or third-line treatments, which may be less effective, more toxic, or more expensive. For instance, patients with macrolide-resistant *Chlamydia pneumoniae* may require alternative treatments, such as doxycycline or fluoroquinolones, which could extend the duration of therapy and hospitalization. This not only increases healthcare costs, but also places patients at higher risk of hospital-acquired infections and other complications associated with prolonged hospital stays. In some cases, antibiotic resistance can lead to the failure to completely eradicate the infection, resulting in chronic or recurrent pneumonia. This is particularly concerning in *Chlamydia pneumoniae* infections, where resistance can lead to a chronic, low-grade infection that persists despite treatment, potentially contributing to the chronic inflammatory state and associated complications, such as chronic bronchitis or worsening of chronic obstructive pulmonary disease (COPD).

When antibiotic-resistant atypical pneumonia is not adequately treated, there is a higher risk of ongoing transmission, particularly in community or healthcare settings. For example, patients with macrolide-resistant *Mycoplasma pneumoniae* may remain infectious for a longer period of time, leading to outbreaks in settings, such as schools, military barracks, or long-term care facilities, where close contact facilitates the spread of infection (111-113).

5. Prognosis

Pneumonia caused by atypical pathogens typically presents as mild or moderate, although its progression to severe pneumonia often results in a fatal outcome (6). A previous retrospective study revealed that among patients with pneumonia infected with *Chlamydia pneumoniae*, ARDS developed in 6 out of 11 cases (114). The mortality rate was notably high, reaching 83% among those with APACHE II scores ≥12 and 100% among those with CURB-65 scores ≥2 (114). Detecting multi-lobar involvement at an earlier stage is crucial. In Europe, a previous study involving patients with pneumonia averaging 66 years of age highlighted a worse prognosis among elderly patients with *Legionella pneumophila* infection (115). That study reported an overall mortality rate as high as 23%, with a majority of fatalities attributed to UK community-acquired *Legionella pneumophila* infections (115). Complications arising from atypical pathogen infections extend beyond the respiratory system, leading to a poorer prognosis. These complications include damage to various organs such as the heart, liver, kidneys, blood system and mucous membranes. Atypical pathogen infections can exacerbate conditions, such as COPD, induce bronchial asthma, progress to ARDS and potentially increase the risk of lung cancer. In cases of the acute exacerbation of COPD, atypical pathogens, predominantly *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, account for 5-10% of cases, with as many as 14% associated with *Mycoplasma pneumoniae* and 5.0-8.9% with *Chlamydia pneumoniae* infections (116). Interaction between *Chlamydia pneumoniae* infection and allergic inflammation may exacerbate the symptoms of asthma (117,118). *Legionella pneumophila* pneumonia tends to progress to ARDS more frequently compared to other pathogens (41). While the association between *Chlamydia pneumoniae* infection and lung cancer remains debatable, studies suggest a potential link (119-122). Complications in the cardiovascular system induced by atypical pathogen infections include coronary artery disease, myocardial infarction, unstable angina, atherosclerosis and cerebral infarction. Studies have shown a higher incidence of *Chlamydia pneumoniae* infections among patients with coronary artery disease (CAD), with implications for myocardial infarction and the occurrence of more extensive vessel lesions. Antibiotic treatment, particularly with azithromycin, has exhibited positive correlations with the secondary prevention of CAD. Additionally, *Chlamydia pneumoniae* infection

has been significantly associated with an increased risk of cerebral infarction (123-125). Extrapulmonary complications, such as hepatic function insufficiency and septic shock, also arise. Severe-atypical CAP has been shown to present significantly in Vietnamese children, with various factors such as age, co-infection with bacteria and viruses, and respiratory/cardiac system malformations significantly associated with its severity (126). Increasing antibiotic resistance poses a critical factor affecting prognosis. The widespread use of antibiotics has prompted atypical pathogens to alter their form, structure and metabolism, complicating antibiotic treatment. Reports from Japan, Germany, France and China have highlighted increasing macrolide resistance rates in *Mycoplasma pneumoniae* strains, necessitating longer antibiotic therapy durations and delayed fever resolution in macrolide-resistant cases. Alternative therapies with moxifloxacin or levofloxacin have been employed for macrolide-resistant strains (95,127-129). Patients infected with macrolide-resistant *Mycoplasma pneumoniae* have experienced more persistent symptoms, leading to therapeutic changes from macrolides to tetracycline or fluoroquinolone for a more rapid clinical improvement. Macrolide-resistant groups have exhibited a higher incidence of extrapulmonary complications, such as liver function abnormalities, myocarditis, rash and encephalitis, along with more severe radiological findings compared to macrolide-sensitive groups. The interplay between drug resistance and complications contributes to severe clinical symptoms, prolonged illnesses and a worse prognosis (130,131). The treatment of pneumonia caused by *Chlamydia psittaci* typically involves antibiotics. Tetracyclines, such as doxycycline or tetracycline itself, are often considered the first-line treatment for psittacosis. Macrolides, such as azithromycin, and fluoroquinolones can also be effective alternatives for treating this type of pneumonia. The duration of antibiotic treatment and specific medication choice may vary based on the severity of the infection, the overall health of the patient and any existing medical conditions (132,133).

In the case that a patient does not respond to treatment for atypical pneumonia, it is important to consider alternative diagnoses, including lung adenocarcinoma, particularly in the case that symptoms persist or worsen. The key difference is that while atypical pneumonia is an infectious disease that typically responds to antibiotics or antiviral treatments, lung adenocarcinoma is a type of cancer that may present with similar respiratory symptoms, such as cough and chest discomfort, but will not improve with antimicrobial therapy. Instead, lung adenocarcinoma often requires further analyses through imaging studies, such as a CT scan, and possibly a biopsy to confirm the diagnosis and guide appropriate oncological treatment. Therefore, in the case that there is no clinical improvement with standard pneumonia treatments, lung adenocarcinoma should be considered as a potential underlying cause, prompting further diagnostic evaluation (134).

6. Conclusions and future perspectives

In conclusion, atypical pneumonia, caused by diverse pathogens, such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* species, presents diagnostic challenges due to its varied symptoms and systemic impact. Despite this complexity, antibiotics targeting intracellular processes have proven effective, though antibiotic resistance poses a growing concern. While *Streptococcus pneumoniae* remains a primary cause, atypical pathogens significantly contribute to cases, particularly among young adults and in outpatient settings. Diagnosis methods, while valuable, have limitations in accuracy. The prognosis of atypical pneumonia varies widely, potentially leading to severe complications beyond the respiratory system and impacting overall health. Managing this condition demands a nuanced approach considering the diverse pathogens involved and their varied clinical impacts.

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DAS and VEG conceptualized the study. IGL, KT, PS, NT, VEG and DAS made a substantial contribution to the interpretation and analysis of the data from the literature to be included in the review, and wrote and prepared the draft of the manuscript. DAS and VEG analyzed the data from the literature to be included in the review and provided critical revisions. All authors contributed to manuscript revision, and all authors have read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, AI tool Chat GPT was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tool as necessary, taking full responsibility for the ultimate content of the present manuscript.

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