

Atypical Pneumonia: Diagnostic Challenges and Therapeutic Approaches

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ABSTRACT

Atypical pneumonia refers to a group of lower respiratory tract infections caused by specific respiratory pathogens that differ clinically and radiologically from typical bacterial community-acquired pneumonia (CAP). These infections involve both zoonotic and non-zoonotic transmission routes, with non-zoonotic cases being more common. A key distinguishing feature of atypical CAP is its frequent extrapulmonary involvement, which distinguishes it from the classic presentation of CAP. Therefore, recognition of clinical syndromes plays an important role in increasing clinical suspicion, guiding the initiation of empirical antibiotic therapy, and supporting targeted diagnostic evaluations. This review aims to consolidate current knowledge to improve the understanding and clinical recognition of atypical pneumonia. We performed a comprehensive literature search on PubMed, focusing on the clinical presentation, diagnostic approach, and management of atypical pneumonia. The causative pathogens are often associated with systemic effects and a wide range of extrapulmonary manifestations. Furthermore, some of these organisms pose challenges in laboratory identification due to their difficulty in cultivation and the risks associated with isolation. Consequently, syndromic diagnosis remains essential in initiating timely treatment and directing further diagnostic workup.

Keywords: Atypical pneumonia, *Mycoplasma pneumoniae*, Legionnaire's disease, Community-acquired pneumonia (CAP)

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Introduction

The term “atypical pneumonia” was historically used to describe viral community-acquired pneumonias (CAPs) that differed from typical bacterial CAPs in both clinical presentation and radiographic findings. Over recent decades, its usage has evolved to refer specifically to lower respiratory tract infections caused by distinct respiratory pathogens. These include three zoonotic agents—*Chlamydia psittaci*, *Francisella tularensis*, and *Coxiella burnetii*—and three non-zoonotic organisms: *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* spp. [1–3]. A key clinical distinction from typical CAP is the frequent presence of extrapulmonary

manifestations, a hallmark common to all forms of atypical CAP [1, 2]. This review highlights the clinical characteristics and management strategies associated with atypical pneumonia.

Materials and Methods

We conducted a literature search using the PubMed database to identify relevant studies. The following Medical Subject Headings (MeSH) terms were used in the search strategy: (“Atypical Pneumonia”[Mesh]) AND (“Clinical Features”[Mesh] AND “Diagnosis”[Mesh] AND “Approach”[Mesh] AND “Management”[Mesh]). Articles were included if they addressed at least one of the following aspects: clinical presentation, diagnostic methods, or therapeutic management of atypical pneumonia. Studies that did not meet these criteria were excluded.

Results and Discussion

Review

Atypical CAPs represent approximately 15% of all cases of community-acquired pneumonia. Although these infections can occur in outbreak settings, the majority present as sporadic cases in the general population. Outbreaks have occasionally been reported in institutional environments, such as nursing homes or hospitals, but these remain relatively rare. Atypical pathogens are more frequently implicated in milder forms of pneumonia, often referred to as “walking pneumonia,” compared to typical bacterial agents. In contrast, among hospitalized patients with severe CAP, *Legionella* species are a notable cause [2–4].

Etiology

Clinically, atypical pneumonia can be categorized based on transmission route into zoonotic and non-zoonotic infections. Zoonotic forms include psittacosis, Q fever, and tularemia, caused by *Chlamydia psittaci*, *Coxiella burnetii*, and *Francisella tularensis*, respectively. Non-zoonotic agents include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species. While both categories differ substantially from typical bacterial CAPs, the primary distinguishing feature is the presence or absence of extrapulmonary involvement. Atypical pneumonias are often systemic infections with pulmonary involvement, whereas typical CAPs, such as those caused by *Streptococcus pneumoniae*, tend to produce symptoms and laboratory findings localized to the lungs. Recognizing this distinction allows clinicians to better evaluate organ involvement patterns and narrow down the differential diagnosis [1–3, 5].

Pathogenesis and clinical presentation

Mycoplasma pneumoniae

Mycoplasma pneumoniae, classified as a bacterium, is notably the smallest known free-living organism [6]. It exists primarily in two subtypes—type 1 and type 2. Type 2 strains express the community-acquired respiratory distress syndrome (CARDS) toxin more frequently, a known virulence factor that induces vacuolization and may contribute to the degradation of respiratory epithelium [2, 7, 8]. Furthermore, this strain produces a robust biofilm, potentially shielding the organism from antibiotic penetration and host immune defenses [8].

M. pneumoniae is a common etiological agent of upper respiratory tract infections (URIs), acute bronchitis, and community-acquired pneumonia (CAP). Serological data indicate that approximately 1% of the U.S. population contracts *M. pneumoniae* annually [9]. Pediatric populations, particularly young children, are more frequently affected than adolescents or adults. Transmission primarily occurs via respiratory droplets, and the incubation period following exposure typically ranges from two to three weeks. During non-epidemic intervals, cases tend to rise in summer and peak in late autumn or early winter [10–12].

The clinical spectrum ranges from asymptomatic colonization and mild URIs to pneumonia and rare extrapulmonary complications [13]. Asymptomatic cases are widespread and may lead to prolonged carriage, often persisting for several weeks to months post-infection, with a median duration of approximately seven weeks [14].

The most frequent clinical manifestations include URIs and acute bronchitis. Symptoms of *M. pneumoniae*-related URIs mirror those caused by other pathogens and include cough, sore throat, rhinorrhea, coryza, and ear pain. The cough can be either productive or non-productive and may be accompanied by wheezing [15, 16]. In acute

bronchitis, a persistent or prolonged cough is the hallmark symptom. These respiratory infections are typically self-limiting, much like viral-induced URIs and bronchitis [17].

In the case of pneumonia, the condition is usually acquired in the community and exhibits a gradual onset. Initial symptoms may include headache, malaise, low-grade fever, and sore throat. Cough—either dry or wet—is common, and may be associated with pleuritic chest pain or dyspnea. Chest discomfort is often reported due to persistent coughing. Additional signs, such as rhinorrhea, sinusitis, otitis media, and cervical lymphadenopathy, may also be present. More severe symptoms like dyspnea, hypoxemia, hypotension, or altered mental status are less common than in pneumonias caused by typical bacterial pathogens [18, 19].

Extrapulmonary manifestations may occur in conjunction with, or independently of, respiratory symptoms. Although *M. pneumoniae* has been associated with a wide array of systemic conditions, only a subset has been confirmed as causative. These include hemolytic anemia, central nervous system (CNS) disorders, dermatological reactions, cardiac involvement, joint diseases, and gastrointestinal symptoms [18]. Hemolysis occurs in approximately 60% of cases, generally presenting as mild. The pathogenesis involves a change in the erythrocyte I antigen during infection, which stimulates the production of IgM autoantibodies, leading to immune-mediated hemolysis, commonly referred to as cold agglutinin disease [20]. Most cases are self-limited and do not require transfusion or immunosuppression, although severe, life-threatening anemia can occur, particularly in individuals with underlying hematological disorders such as sickle cell disease [21, 22].

CNS involvement is observed in about 0.1% of all infections but may affect up to 7% of hospitalized patients. It is more commonly reported in children than in adults. While a preceding respiratory illness is frequently noted, it is not universally present in CNS complications. Encephalitis is the most prevalent CNS presentation, followed by meningitis, peripheral neuropathy, Guillain-Barré syndrome (GBS), transverse myelitis, acute disseminated encephalomyelitis (ADEM), cranial nerve palsies, and cerebellar ataxia [23, 24].

Cutaneous and mucocutaneous manifestations are among the more frequent extrapulmonary symptoms. These include maculopapular or vesicular rashes, urticaria, erythema multiforme, Stevens-Johnson syndrome, and *M. pneumoniae*-induced rash and mucositis (MIRM). These skin findings often coincide with or follow respiratory symptoms, although this is not a strict requirement. Notably, while some skin lesions arise from direct bacterial infection, others are immune-mediated responses [25, 26].

Chlamydia pneumoniae

The pathogenic mechanism of *Chlamydia pneumoniae* is largely driven by its distinctive biphasic developmental cycle. In the extracellular environment, the organism exists as a small, metabolically inert elementary body with a rigid outer wall, enabling temporary survival outside the host. Upon entry into the respiratory tract, it binds to epithelial cells and penetrates them through receptor-mediated endocytosis. Once internalized, it remains within a phagosome, undergoing transformation and replication over 36 to 72 hours, producing numerous progeny that are eventually released to infect adjacent cells. During intracellular replication, chlamydial antigens are expressed on the host cell surface, eliciting an immune response. Notably, immunity against *Chlamydia* is short-lived, allowing for potential reinfection [27].

Clinically, the presentation of *C. pneumoniae*-associated CAP closely mirrors that of *M. pneumoniae*, though with some notable distinctions. While *M. pneumoniae* infections are typically acute, *C. pneumoniae* often presents as a chronic respiratory illness [1, 3]. Upper respiratory symptoms such as otitis, bullous myringitis, and mild, non-exudative pharyngitis are more frequently observed with *M. pneumoniae*, whereas these findings are uncommon in *C. pneumoniae*-associated CAP [28, 29]. Laryngitis, on the other hand, is a distinguishing feature of *C. pneumoniae*. Although not universal, it is commonly reported and serves as a key clinical clue; hence, a patient exhibiting hoarseness along with pneumonia should raise suspicion for *C. pneumoniae*. In contrast, elevated cold agglutinin titers in patients with CAP and upper respiratory involvement should suggest *M. pneumoniae* as the likely cause. Additionally, gastrointestinal symptoms are more often associated with *Mycoplasma pneumoniae*, while neither *Mycoplasma* nor *Chlamydia* infections characteristically involve direct cardiac or pulmonary structural pathology [29–32].

Legionella

Legionella species are responsible for a clinical spectrum termed legionellosis, which encompasses two main entities: Legionnaires' disease—a form of pneumonia—and the milder, non-pneumonic Pontiac fever [33]. The

pathogenesis of Legionnaires' disease centers on the inhalation of contaminated aerosols, leading to the deposition of *Legionella* in the lungs where it invades alveolar macrophages and proliferates intracellularly [34, 35].

Although no single clinical feature definitively distinguishes Legionnaires' disease from other pneumonias, several indicators may heighten diagnostic suspicion. These include gastrointestinal symptoms such as nausea, vomiting, and diarrhea; hyponatremia; elevated liver enzymes; high C-reactive protein levels (> 100 mg/L); and poor clinical response to standard pneumonia therapies. While some scoring tools have attempted to integrate these features to guide diagnosis, none have been sufficiently validated for reliable clinical use [36–39].

The most prevalent symptoms include fever, cough, and dyspnea. Onset typically occurs within 10 days following exposure to contaminated water or soil. A cough is often preceded by systemic symptoms such as fever and fatigue [36, 37]. Though uncommon, extrapulmonary manifestations can occur either in conjunction with pneumonia or independently, particularly in immunocompromised individuals [40]. These manifestations span a broad range and may include meningitis, cerebral abscesses, surgical wound infections, prosthetic joint infections, osteomyelitis, cellulitis, soft tissue abscesses, myocarditis, pericarditis, native and prosthetic valve endocarditis, peritonitis, and pyelonephritis [41–54]. Diagnosis of extrapulmonary *Legionella* infections typically requires direct identification of the organism at the site of infection via culture or polymerase chain reaction (PCR) testing [39].

Zoonotic infections

Psittacosis, caused by *Chlamydia psittaci*, typically presents in young to middle-aged adults with an abrupt onset of fever, intense headache, and a non-productive cough. However, asymptomatic presentations may also occur. Most patients have a recent history of bird exposure. The incubation period usually spans 5 to 14 days but can extend up to 39 days. Headaches are often accompanied by photophobia and can be severe. Although less frequent, symptoms such as pharyngitis, diarrhea, and altered mental status may also manifest. Diarrhea is reported in up to 25% of cases and is usually mild, though it can be more pronounced and occasionally dominate the clinical picture [55, 56].

While primarily a respiratory illness, psittacosis can involve multiple organ systems, leading to rare but potentially severe complications. Pulmonary complications may include respiratory failure. Renal manifestations can involve acute tubular necrosis, interstitial nephritis, or glomerulonephritis. Hepatic involvement may present as icteric hepatitis or hepatic granulomas. Hematologic abnormalities such as hemolytic anemia, thrombocytopenic purpura, pancytopenia, and thrombotic thrombocytopenic purpura have also been reported. Neurological complications may include encephalitis, meningitis, or increased intracranial pressure. Cutaneous signs, though uncommon, can include erythema nodosum, erythema multiforme, erythema marginatum, and panniculitis [57–61].

Tularemia, due to *Francisella tularensis*, arises from contact with infected animals or insect vectors. Its clinical spectrum ranges from asymptomatic infection to fulminant sepsis and death, with severity influenced by the strain's virulence, the route of exposure, and host immune status [62]. Nonspecific symptoms—such as fever, chills, anorexia, and malaise—generally appear 3 to 5 days post-exposure. These may resolve transiently and then recur. Other possible complaints include headache, chest discomfort, myalgia, gastrointestinal symptoms, and diarrhea, which may have abated by the time of clinical evaluation [63]. Clinical presentation varies by route of infection and typically aligns with one of six main forms: ulceroglandular, glandular, oculoglandular, pneumonic, pharyngeal (oropharyngeal), and typhoidal tularemia [62–65].

Q fever, attributable to *Coxiella burnetii*, is another zoonosis known to cause atypical pneumonia. The organism predominantly targets macrophages, which fail to eliminate it. After phagocytosis, *C. burnetii* survives and replicates in a large, acidic vacuole formed by lysosomal fusion. A sporulation-like mechanism allows the pathogen to resist environmental stress, enabling long-term persistence outside the host [66]. Infection generally occurs through inhalation of contaminated dust from infected animal excreta, milk, or birthing products. Notably, direct animal contact is not required for transmission [67].

The clinical expression of Q fever varies significantly. While some individuals remain asymptomatic or exhibit only mild symptoms, others develop substantial acute or chronic illness. Pneumonia caused by *C. burnetii* is usually mild, marked by high fever and dry cough, with minimal findings on chest auscultation. In more severe cases, acute respiratory distress may occur. Imaging findings are nonspecific and can resemble viral pneumonias; pleural effusions are uncommon. Beyond pulmonary symptoms, patients often report systemic complaints such

as severe headaches, muscle aches, and joint pain. Symptom duration typically ranges from one to three weeks [67–69].

Diagnostic approach

Culturing and isolating atypical pathogens is often difficult and potentially hazardous, making clinical syndromic diagnosis crucial. This strategy helps heighten diagnostic suspicion, guide empirical antibiotic therapy, and prompt the appropriate use of specific diagnostic tests for community-acquired pneumonia (CAP) caused by atypical organisms [2, 5].

Legionella can be rapidly detected using direct fluorescent antibody (DFA) staining of sputum, respiratory secretions, pleural fluid, or lung tissue. However, DFA positivity in sputum declines significantly once anti-*Legionella* therapy has begun. An indirect fluorescent antibody (IFA) test showing a single titer of 1:512 is also considered diagnostic. The *Legionella* urinary antigen test has improved disease recognition by offering a non-invasive diagnostic tool for *L. pneumophila*. While a positive result supports the diagnosis of Legionnaires' disease, a negative test does not exclude it [38]. A key advantage of this assay is its persistence—it may remain positive for weeks following the onset of urinary antigen excretion and even after clinical resolution. However, this test only detects *L. pneumophila*, the most common *Legionella* species. Since antigenuria emerges several days into the infection, early testing may yield false-negative results, similar to premature serological testing [33, 38, 49, 70].

M. pneumoniae and *C. pneumoniae* can be cultured from respiratory samples using specialized viral media, though this method is rarely employed in routine clinical practice. Instead, diagnosis typically relies on serological testing [71]. A positive IgM titer in the acute phase is diagnostic for either organism. A fourfold rise in IgG titers is indicative of prior exposure or infection but does not necessarily exclude an acute or concurrent infection [72]. Because *C. psittaci* is highly difficult to isolate, its diagnosis depends exclusively on serology. In patients without prior exposure or immunity, elevated titers in the tube agglutination (TA) test are confirmatory [73]. Tularemia and Q fever are similarly diagnosed via serologic methods due to the high infectivity and biosafety risks associated with culturing *F. tularensis* and *C. burnetii* [62, 68]. A rapid increase in IgM or IgG titers in immunologically naïve patients is definitive for tularemia [62]. For zoonotic CAPs like Q fever and psittacosis, diagnosis is typically based on a fourfold rise in antibody titers across paired acute and convalescent sera collected 4 to 8 weeks apart. An initially elevated titer alone, particularly in Q fever or tularemia, may suffice in previously unexposed individuals [2, 72]. In chronic Q fever, persistently high levels of *C. burnetii* IgG are characteristic, distinguishing it from acute disease [68].

Radiographically, atypical pneumonia lacks a consistent or pathognomonic chest X-ray pattern. *Tularemia* and *Legionella* may result in pleural effusions, while *M. pneumoniae* can occasionally cause minor effusions. Although *Legionella* does not produce a distinctive radiologic signature, it often presents with rapidly progressive and asymmetrical infiltrates [74].

Management

Because atypical bacteria do not respond to β -lactam antibiotics and standard susceptibility testing is often not feasible, empirical treatment primarily involves macrolides or newer fluoroquinolones. Current guidelines are largely informed by in vitro data, observational research, and expert consensus rather than robust clinical trials. Most community-acquired pneumonia protocols recommend initial therapy that includes agents active against atypical pathogens, commonly a respiratory fluoroquinolone combined with a macrolide and a β -lactam antibiotic [75]. In severe or refractory cases of legionellosis, combination therapy incorporating rifampicin alongside a fluoroquinolone has been trialed, though its effectiveness remains uncertain. The typical duration of treatment ranges from two to three weeks, although this recommendation is not strongly evidence-based [76, 77].

Once a microbiological diagnosis is confirmed, therapy can be tailored to the causative organism. For *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, doxycycline, macrolides, or newer fluoroquinolones such as levofloxacin are recommended [55]. In cases of *Legionella* infection, the preferred regimens include levofloxacin or a macrolide (azithromycin is favored) with or without rifampicin [55].

For zoonotic pathogens, tetracyclines constitute the cornerstone of treatment. Pneumonia caused by *Chlamydia psittaci* is typically managed with doxycycline due to its superior pharmacokinetic profile and lower incidence of gastrointestinal side effects. Alternative therapies for psittacosis include macrolides (erythromycin, azithromycin), chloramphenicol, rifampin, and fluoroquinolones [55, 78]. The preferred treatment for Q fever is also doxycycline;

alternatives for patients intolerant to tetracyclines include macrolides, trimethoprim-sulfamethoxazole, and fluoroquinolones [55, 79]. For tularemia, agents with proven clinical efficacy include streptomycin and gentamicin (especially), tetracyclines, fluoroquinolones, and chloramphenicol [55, 62].

Conclusion

Atypical pathogens causing pneumonia frequently result in systemic illness accompanied by a diverse array of extrapulmonary manifestations. Many of these organisms pose challenges in culture and carry biosafety risks, complicating laboratory diagnosis. Therefore, clinical syndromic recognition remains essential to raise diagnostic suspicion, initiate appropriate empirical antimicrobial therapy, and guide targeted diagnostic testing.

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