Atypical pneumonia (non-COVID-19)

Straight to the point of care
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## Disclaimer
Atypical pneumonia (non-COVID-19)

**Summary**

Community-acquired and often seen in young adults living in close proximity.

Diagnosis is mostly clinical. Molecular-based diagnosis of throat swabs or sputum can be performed. Serology can be used to confirm the diagnosis.

Treatment is often outpatient based with a macrolide antibiotic or doxycycline.

Extrapulmonary manifestations may occur, especially in *Mycoplasma pneumoniae* infections.

**Definition**

Atypical bacterial pneumonia is caused by atypical organisms that are not detectable on Gram stain and cannot be cultured using standard methods. The most common organisms are *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila*. Atypical bacterial pneumonia generally is characterized by a symptom complex that includes headache, low-grade fever, cough, and malaise. Constitutional symptoms often predominate over respiratory findings. Although in most cases presentation can be in the milder spectrum of community-acquired pneumonia, some cases, especially if caused by *L pneumophila*, may present as severe pneumonia, necessitating intensive care unit admission. Other possible pathogens include *Chlamydophila* species, *Legionella* species, *Coxiella burnetii* (Q fever), and respiratory viruses.
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Epidemiology

Atypical bacterial pathogens are a relatively common cause of lower respiratory diseases, including community-acquired pneumonia.[1] The incidence of atypical pathogens in community-acquired pneumonia is approximately 22% globally, but this varies with location.[2]

*Mycoplasma pneumoniae* causes up to 20% of cases of community-acquired pneumonia and has been implicated in some hospital-based epidemics. Infection is common in children and young adults, and is often seen in close community settings such as boarding schools, universities, and military bases.[3] It is the most commonly detected bacteria among children aged ≥5 years hospitalized with community-acquired pneumonia.[4] There is a relative increase in incidence during the late summer or fall. Epidemics occur at 3- to 6-year intervals.[1] Previous exposure is protective while smoking poses a risk for disease.[5] [6] [7] [8]

*Chlamydophila pneumoniae* causes 3.5% to 10.0% of cases of community-acquired pneumonia. Like *Mycoplasma pneumoniae*, infection occurs mainly in children and young adults and is associated with close community settings.[1] [3] [6] [9] [10] A Dutch study identified *Chlamydia psittaci* by polymerase chain reaction (PCR) of sputum (when available) as a cause of community-acquired pneumonia in 4.8% of cases, higher than that previously reported (2.1%).[11]

*Legionella pneumophila* is responsible for a low percentage of community-acquired pneumonia cases (around 2.7%),[1] but it is responsible for up to 16% of cases that require hospitalization. It is generally associated with exposure to a new source of aerosolized water in showers or from cooling systems. Smoking, chronic lung disease, immunosuppression, and immunomodulatory drugs are known risk factors.[12] It may be associated with recent travel and may have a male predilection.[6] [13] [14] [15]

Viruses (including influenza, adenovirus, respiratory syncytial virus, as well as others) may cause pneumonia that can fit atypical bacterial pneumonia features in up to 25% of the community-acquired pneumonia patients.[16] [17] [18] [19] Influenza was the most frequently identified virus in adults with community-acquired pneumonia in one systematic review, accounting for 9% of cases.[20]

*Coxiella burnetii* accounts for approximately 1% of pneumonia cases; however, higher incidence occurs in regions where there is high exposure to aerosols originated from livestock. It is a more common cause of pneumonia in Europe and certain regions of Canada.[21]

The specific cause of community-acquired pneumonia can vary by season, location, and age.[3] [22] [23] [24]

Etiology

The major causes of atypical bacterial pneumonia are *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila*. Other common pathogens that may cause similar presentation include viruses (e.g., influenza virus, adenovirus, and hantavirus), other bacteria (such as other *Legionella* species and other *Chlamydophila* species), and zoonotic pathogens, such as *Coxiella burnetii*. [8]

*M pneumoniae* is a small, free-living bacterium with one of the smallest known genomes. Unlike many other bacteria, it does not have a cell wall. Humans are thought to be the only hosts.[5] *C pneumoniae* is an obligate intracellular gram-negative bacterium. Humans are thought to be the only host.[9] *L pneumophila* is a gram-negative bacterium with the ability to live both in extracellular and intracellular environments. In nature it infects amoeba. Humans are accidental hosts through exposure to contaminated water.[25] *C burnetii* is an obligate intracellular bacteria with gram-negative cell wall. This zoonotic pathogen has a wide
range of hosts, which includes arthropods, fish, birds, and mammals. It has a spore-like formation that is resistant to environmental stress and thus promotes its virulence either by inhalation or ingestion.[21]

**Pathophysiology**

Transmission of *Mycoplasma pneumoniae* occurs from human to human. This pathogen has a unique organelle that allows it to attach to respiratory ciliated epithelia. It also exhibits gliding motility on surfaces, which is thought to promote infection.[5] It may produce toxins that cause persistent cough.[26] Another suggested feature is that the immunologic response to this pathogen might promote acute exacerbations of asthma.[27]

*Chlamydia pneumoniae* is also transmitted from human to human. Upon infection, its intracellular lifestyle enables it to grow in many cell types, such as macrophages and smooth muscle and endothelial cells. Its ability to inhibit ciliary action is thought to promote persistent cough.[9] As with *M pneumoniae*, immunologic response to infection may promote acute exacerbations of asthma.[27]

Infection with *Legionella pneumophila* occurs when humans are exposed to infested water. No human-to-human transmission was thought to occur, but cases suggestive of human transmission were reported in 2016.[28] Within the host, *L pneumophila* invades phagocytic cells and exploits the host's response to its own benefit, evading degradation and killing.[25, 29]

*Coxiella burnetii* is transmitted either by inhalation, or by ingestion of contaminated animal products. Human-to-human transmission is rare. Although *C burnetii* causes pneumonia, in many cases it causes acute hepatitis with or without pneumonia or chronic systemic infections.[21]

**Case history**

**Case history #1**

A 20-year-old college student presents with a 3-day history of cough, fever, malaise, and headache. On examination, he is febrile to 101°F and he has crackles in the right-lower lung field.

**Other presentations**

Presence of bullous myringitis on ear examination is not a common sign, but it suggests infection with *Mycoplasma pneumoniae*. Although most patients infected with *M pneumoniae* and *Chlamydia pneumoniae* have relatively mild pneumonia, some will present with severe pneumonia requiring hospitalization or even intensive care unit admission.
Approach

During the pandemic, consider all patients with cough and fever or suggestive symptoms to have COVID-19 until proven otherwise. See our topic Coronavirus disease 2019 (COVID-19).

The first step is to evaluate the pneumonia patient with detailed history and physical exam. The diagnosis may be made clinically in the appropriate setting, although blood counts, blood biochemistry, and chest x-ray are usually performed as well. In more severe illness, especially when admission is needed and in order to identify a possible typical bacterial pathogen, cultures of blood and sputum may be required, as well as specific cultures and urine antigen tests for Legionella and Streptococcus pneumoniae. Some authors even advocate the use of specific tests for the identification of atypical bacterial and viral pathogens in such settings to guide specific targeted therapy. In some cases (up to 25%) mixed infections can be identified. If available, virological diagnostics should be performed to guide possible treatment for influenza.

History and clinical examination

Key risk factors include close community settings (e.g., boarding schools, college dormitories, army basic training camps, or even hospitals) and immunosuppression. A history of exposure to someone with respiratory infection is also a risk factor for atypical bacterial pneumonia. Many patients with atypical bacterial pneumonia are younger than 50 years.

Typically, patients complain about a persistent cough that does not resolve with time. The presence of a dry cough and a prolonged time from onset of symptoms to the presentation should prompt suspicion that an atypical pathogen is present. Fever, if present, is usually low grade. In many cases of Mycoplasma pneumoniae and Chlamydophila pneumoniae, pharyngitis, hoarseness, and headache may also be present. Diarrhea may accompany Legionella infections. Bullous myringitis is rare sign that suggests M pneumoniae infection. Rash, mainly a self-limited maculopapular or vesicular rash can accompany M pneumoniae pneumonia. In some cases, a more severe form of Stevens-Johnson syndrome affecting the oral mucosa or other parts can be seen.

Clinical signs of pneumonia such as rales/crepitations may be mild or absent.

Suspected atypical pathogen

Treatment guidelines for managing patients with community-acquired pneumonia are designed to cover atypical pathogens. Nonetheless, it is best to confirm the diagnosis if an atypical pathogen is suspected because this may have implications for duration of therapy.

The chest x-ray confirms infiltrates and may show more extensive abnormalities than physical exam suggests. A low oxygen saturation indicates a more severe course of disease requiring hospitalization.

A white blood cell (WBC) count should be done for patients requiring hospitalization. Relatively minor elevations in WBC counts are seen (usually <13,000/microliter). A relative lymphocytosis is observed if infection is viral. A low hemoglobin count may accompany M pneumoniae infections. Elevated liver enzymes suggest M pneumoniae or Legionella pneumophila. Liver function tests should be ordered in hospitalized patients. An elevation in blood urea nitrogen (>198 mg/dL) suggests more severe disease.

Molecular-based diagnostic tests for M pneumoniae from throat swabs are now available in many formats, including in-house and commercial assays. Molecular based diagnostics for C pneumoniae are available, either from sputum or throat swabs. However, lack of standardization between many
of the tests may affect the rate of diagnosis and validity.[33] A study from the Netherlands has raised concerns over the interpretation of positive polymerase chain reaction results in patients younger than 16 years because of the high carriage rate of *M pneumoniae* in the upper respiratory tracts of healthy children.[34] But another study from the US failed to support this observation.[3] New, validated tests that are becoming commercially available may facilitate an increased understanding of the etiology of atypical pneumonia.[35]

Serology for both *M pneumoniae* and *C pneumoniae* may also be conducted, although such tests will not influence treatment, given that the diagnosis will be confirmed retrospectively, based on convalescent serology. It requires blood from early in the course of disease and a second blood specimen at least 10 days later. Lack of standardization between many of the tests might affect also rate of diagnosis. It may also be used to confirm diagnosis of many atypical pathogens and some viruses. In most cases, serology will be the main diagnostic test for *Coxiella burnetii* pneumonia.[36]

Where there is uncertainty regarding whether patients with community-acquired pneumonia have typical or atypical pathogen disease, they should undergo a sputum Gram stain and culture. Urine for a *Legionella* antigen test may also be sent.[18] Nasopharyngeal viral cultures may be difficult to culture and results may take many days to return. However, molecular diagnostics on nasopharyngeal viral swabs are widely available.

### History and exam

**Key diagnostic factors**

**age <50 years (common)**
- Many patients with atypical bacterial pneumonia will be younger than 50 years.

**persistent cough (common)**
- In many cases, patients will complain about persistent cough that does not resolve with time.

**dry cough (uncommon)**
- The presence of a dry cough should prompt suspicion that an atypical pathogen is present.

**long duration of symptoms (uncommon)**
- Prolonged time from onset of symptoms to the presentation can suggest atypical bacterial pneumonia.

**Other diagnostic factors**

**recent community exposure (common)**
- A history of exposure to someone with respiratory infection is a risk factor for atypical bacterial pneumonia.

**throat involvement (common)**
- In many cases of pneumonia due to *Mycoplasma pneumoniae* and *Coxiella burnetii* pneumonia, pharyngitis and hoarseness will be present as well.

**fever (uncommon)**
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**Diagnosis**

- Fever, if present, is usually low grade.

**headache (uncommon)**
- Headache may accompany *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* infections.

**diarrhea (uncommon)**
- Diarrhea may accompany *Legionella* infections.

**bullous myringitis (uncommon)**
- Bullous myringitis is a rare sign that suggests *Mycoplasma pneumoniae* infection.

**lung rales/crepitations (uncommon)**
- Clinical signs of pneumonia may be mild or absent.

**rash (uncommon)**
- A mainly self-limited maculopapular or vesicular rash can accompany *Mycoplasma pneumoniae* pneumonia.

**Risk factors**

**Strong**

**close community settings**
- Many studies have shown that exposure to *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* in close community settings such as boarding schools, college dormitories, army basic training camps, or even hospitals can lead to outbreaks of infection with these pathogens.[5] [30] This takes place mainly by person-to-person transmission among people in close proximity to each other.

**immunosuppression**
- Immunosuppression is associated with *Legionella pneumophila* infection. Affected patients seem to be highly susceptible to the disease, probably because of reduced ability to eradicate the intracellular pathogen.[14] [15] [31]

**Weak**

**cigarette smoking**
- A few studies have shown that people who smoke are at greater risk for developing pneumonia due to infection with *Mycoplasma pneumoniae*, *Legionella pneumophila*, and probably *Coxiella burnetii*. [7] [8] [13] [21] This may be related to damage to ciliated epithelium and/or modification of the host immune response.

**chronic lung disease**
- Chronic lung disease is mainly associated with *Legionella pneumophila* infection.[14] [15] [31]
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**Diagnosis**

**travel**
- Travel is associated with heightened risk for infections, probably related to exposure to new water sources that have not been used for a while. Standing water has a higher *Legionella pneumophila* load.[14] [15] [31] Risk factor for influenza and severe acute respiratory syndrome.

**male sex**
- Men are at greater risk for infection, mainly with *Legionella pneumophila*. [14] [15] [31]

**immunomodulating drugs**
- One prospective incidence study has shown a possible association between patients receiving tumor necrosis factor (TNF)-alpha antagonists and *Legionella pneumophila* pneumonia.[10]

**Investigations**

**1st test to order**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>chest x-ray</td>
<td>May show more extensive abnormalities than physical exam would suggest.</td>
</tr>
<tr>
<td>WBC count</td>
<td>Should be done for patients requiring hospitalization. Relatively minor elevations in WBC counts (usually &lt;13,000/microliter) in patients with pneumonia suggest an atypical pathogen.</td>
</tr>
<tr>
<td>hemoglobin</td>
<td>May accompany <em>Mycoplasma pneumoniae</em> infections.</td>
</tr>
<tr>
<td>LFTs</td>
<td>Ordered for inpatients; elevated LFTs suggest <em>Mycoplasma pneumoniae</em> or <em>Legionella pneumophila</em>.</td>
</tr>
<tr>
<td>oxygen saturation in air</td>
<td>Low saturation indicates a more severe course of disease requiring hospitalization.</td>
</tr>
<tr>
<td>BUN level</td>
<td>Elevation in blood urea nitrogen suggests more severe disease favoring hospitalization.</td>
</tr>
<tr>
<td>real-time reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2</td>
<td>Molecular testing is required to confirm the diagnosis. Nucleic acid sequencing may be required to confirm the diagnosis.[37] Priorities for testing depend on local guidelines and available resources.</td>
</tr>
<tr>
<td></td>
<td>During the pandemic, consider all patients with cough and fever or suggestive symptoms to have COVID-19 until proven otherwise. See our topic Coronavirus disease 2019 (COVID-19).</td>
</tr>
</tbody>
</table>

**RT-PCR for SARS-CoV-2**
- Positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA
## Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>urinary Legionella antigen</td>
<td>may be positive with Legionella antigen</td>
</tr>
<tr>
<td>• Indicated in cases of severe pneumonia and when <em>L pneumophila</em> infection is suspected.</td>
<td></td>
</tr>
<tr>
<td>sputum culture for Legionella</td>
<td>may be positive with Legionella</td>
</tr>
<tr>
<td>• Indicated in cases of severe pneumonia and when <em>L pneumophila</em> infection is suspected.</td>
<td></td>
</tr>
<tr>
<td>molecular diagnosis of Mycoplasma pneumoniae or Chlamydophila pneumoniae</td>
<td>may be positive with <em>M pneumoniae</em> or <em>C pneumoniae</em></td>
</tr>
<tr>
<td>• Either from sputum or throat swabs.</td>
<td></td>
</tr>
<tr>
<td>serology for atypical pathogens</td>
<td>rise in titer on convalescent serum</td>
</tr>
<tr>
<td>• Requires blood from early in the course of disease and a second blood specimen at least 10 days later. May be used to confirm diagnosis of many atypical pathogens and some viruses. In most cases, serology will be the main diagnostic test for <em>Coxiella burnetii</em> pneumonia.[36]</td>
<td></td>
</tr>
<tr>
<td>nasopharyngeal viral cultures</td>
<td>may be positive with viral pneumonia</td>
</tr>
<tr>
<td>• Viruses can cause atypical pneumonia but may be difficult to culture and results may take days to return.</td>
<td></td>
</tr>
</tbody>
</table>
## Atypical pneumonia (non-COVID-19)

### Diagnosis

#### Differentials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronavirus disease 2019 (COVID-19)</strong></td>
<td>• Residence in/travel to a country/area or territory with local transmission, or close contact with a confirmed or probable case of COVID-19, in the 14 days prior to symptom onset. • Signs and symptoms are similar so it may be difficult to differentiate between the conditions clinically. The situation is evolving rapidly; see our COVID-19 topic for further information.</td>
<td>• Real-time reverse transcription polymerase chain reaction (RT-PCR): positive for SARS-CoV-2 RNA. • It is not possible to differentiate COVID-19 from other causes of pneumonia on chest imaging.</td>
</tr>
<tr>
<td><strong>Typical bacterial pneumonia</strong></td>
<td>• Acute onset with a chill followed by a high fever and pleuritic chest pain suggests pneumococcal pneumonia.</td>
<td>• Sputum cultures and blood cultures may be positive for <em>Streptococcus pneumoniae</em> or other bacterial pathogens.</td>
</tr>
<tr>
<td><strong>Viral pneumonia</strong></td>
<td>• Symptoms of dry cough, fever, myalgia, and malaise, which are clinically difficult to differentiate from atypical bacterial pneumonia.</td>
<td>• Nasopharyngeal viral cultures may be positive. Relative lymphocytosis on CBC may be detected.</td>
</tr>
<tr>
<td><strong>Tuberculosis</strong></td>
<td>• A history of immunosuppression or prolonged course that is not responding to antibacterial therapy suggests tuberculosis.</td>
<td>• Sputum cultures and acid fast bacilli stains positive. A cavity on the chest x-ray may be observed.</td>
</tr>
<tr>
<td><strong>Fungal pneumonia</strong></td>
<td>• Travel or exposure in endemic area. • There may be extrapulmonary symptoms (e.g., rheumatologic).</td>
<td>• Sputum culture and stain may demonstrate hyphae or yeasts. • Antigen detection assays or polymerase chain reaction may identify specific mycoses (e.g., aspergillosis).</td>
</tr>
<tr>
<td><strong>Pneumocystis jirovecii pneumonia</strong></td>
<td>• History of HIV or risk factors should raise suspicion.</td>
<td>• Special stain of sputum or bronchoalveolar lavage will be positive for <em>Pneumocystis jirovecii</em>.</td>
</tr>
<tr>
<td><strong>Pulmonary embolism</strong></td>
<td>• Absence of fever and/or lack of response to antimicrobial therapy support a diagnosis of pulmonary embolism.</td>
<td>• The ventilation-perfusion scan will be positive in pulmonary embolism.</td>
</tr>
</tbody>
</table>
### Condition | Differentiating signs / symptoms | Differentiating tests
---|---|---
**Inhalation/occupational lung injury** | • A history of exposure to chemicals or special work conditions should raise suspicion of inhalation/occupational lung injury. | • Cultures will be negative. There may be diffuse disease on the chest x-ray.

**Anthrax** | • Course of disease may be rapid with respiratory problems; might present with mediastinal masses. Clusters of cases may occur. | • Cultures will be positive for *Bacillus anthracis*. Mediastinal widening may present in the respiratory forms of the disease.

**Plague** | • Course of disease may be rapid with respiratory problems; might present with mediastinal masses. Clusters of cases may occur. | • Cultures will be positive for *Yersinia pestis*. Chest x-ray will show unilateral or bilateral consolidation or alveolar infiltrates.

**Tularemia** | • Course of disease may be rapid with respiratory problems; might present with mediastinal masses. Clusters of cases may occur. | • Cultures will be positive for *Francisella tularensis*. Hilar adenopathy may present in the respiratory forms of the disease.
## Approach

During the pandemic, consider all patients with cough and fever or suggestive symptoms to have COVID-19 until proven otherwise. See our topic Coronavirus disease 2019 (COVID-19).

Initial treatment for any patient with pneumonia is guided by the severity of the disease and presence of comorbidities, prior hospitalizations, and resistant bacteria in the community.[18]

Patients should be assessed for hydration status, adequacy of gas exchange, and hemodynamic stability. Oxygen and ventilation should be started immediately if needed.

### Antibiotic therapy

Atypical bacterial pneumonia pathogens generally do not respond to beta-lactam antibiotics and require treatment with a macrolide, tetracycline, or fluoroquinolone. The current pneumonia treatment guidelines recommend considering empiric use of a macrolide or doxycycline for uncomplicated community-acquired pneumonia to ensure coverage of atypical organisms.[18] [39] [43] [44] Coverage of atypical organisms is also recommended in more severe disease and patients with comorbidities.[18] [39] [45] The recommendation to cover atypical pathogens in the empiric antibiotic regimen is debated;[46] [47] [48] however, the recommendation is supported by current data.[49] [50]

Tetracyclines and fluoroquinolones are generally not recommended in children or pregnant women; however, their use may be considered in these patients when the benefits of using these drugs outweigh the risks, and there are no other suitable treatment options available, especially in cases of macrolide resistance.

When a specific etiology for the pneumonia is found using a reliable method, antimicrobial therapy should be directed at that pathogen.[18] However, in the last few years an increasing frequency (up to 80%) of macrolide-resistant *Mycoplasma pneumoniae* cases have been reported in Asia,[51] whereas rates are lower in the Middle East (30%),[52] Europe (10%),[53] [54] [55] and the US (10%).[56] This is likely due to overuse of macrolides for the treatment of community-acquired pneumonia. Tetracyclines and fluoroquinolones are highly effective for macrolide-resistant strains of *M pneumoniae*. [57] [58] When *Legionella pneumophila* is diagnosed, either macrolides or fluoroquinolones should be used without preference to any of the agents.[59]

The use of procalcitonin (a biomarker) to guide initiation and duration of antibiotic treatment has been found to result in a lower risk of mortality, lower antibiotic consumption, and lower risk of side effects in patients with acute respiratory infections.[60] [61] However, one review found no difference in short-term mortality in critically ill patients specifically, while another study found that procalcitonin-guided therapy did not result in decreased use of antibiotics in patients with suspected lower respiratory tract infection.[62] [63]

### Outpatient care or hospitalization

Scoring the severity of illness can help to determine whether the patient can be treated as an outpatient or requires hospitalization or intensive care. It is most commonly determined using the Pneumonia Severity Index (PSI).[64] The PSI, also referred to as the Pneumonia Patient Outcomes Research Team Model, has been repurposed as an online tool. Twenty factors are assessed, including age, respiratory rate, pulse, blood pressure, and temperature, and total points are added together. CURB-65 is another severity scoring system developed by the British Thoracic Society.[39]
New scoring systems might have some advantage on the PSI and the CURB-65, in identifying patients who need intensive care and hospital admission.[65] [66] [67] [68] Two studies suggest that saturation below 92% is associated with adverse effects and more severe disease, thus requiring admission.[67] [69]

Role of corticosteroids

The use of corticosteroids in patients with severe community-acquired pneumonia has been a long-debated issue. Current guidelines generally recommend against the use of corticosteroids in patients with nonsevere or severe community-acquired pneumonia; although; Surviving Sepsis Campaign guidelines acknowledge that they may be considered in patients with refractory septic shock and can be used as clinically appropriate for comorbid conditions (e.g., COPD, asthma, autoimmune diseases). This recommendation is based on the fact that there are no data suggesting benefit in patients with nonsevere community-acquired pneumonia with respect to mortality or organ failure, and only limited data to support their use in patients with severe community-acquired pneumonia.[18]

Meta-analyses of studies of hospitalized adults with community-acquired pneumonia found that the use of corticosteroids was associated with reduced need for mechanical ventilation, reduced hospital stay, lower clinical failure rates, fewer complications (including septic shock), decreased C-reactive protein (CRP) levels, and reduced all-cause mortality. However, it appears that the reduction in mortality applies only to patients with severe community-acquired pneumonia. In patients with nonsevere disease, adjunctive corticosteroids reduce morbidity, but not mortality.[70] [71] [72] [73] [74] [75] [76] A study from Japan suggests that corticosteroids may not offer any advantage in the treatment of \textit{M} \textit{pneumoniae} pneumonia.[77]

Patients treated with corticosteroids have an increased risk for hyperglycemia.[72] [73] Other adverse effects include super infection and upper gastrointestinal bleeding.

Adjunctive corticosteroid therapy has not been studied in pregnant or pediatric populations and cannot currently be recommended.

Safety of fluoroquinolone antibiotics

Consider safety issues before prescribing fluoroquinolones. The Food and Drug Administration has issued warnings about the increased risk of aortic dissection, significant hypoglycemia, and mental health adverse effects in patients taking fluoroquinolones.[78] [79]

The European Medicines Agency completed a review of serious, disabling, and potentially irreversible adverse effects associated with fluoroquinolones in 2018. These adverse effects included tendonitis, tendon rupture, arthralgia, neuropathies, and other musculoskeletal or nervous system effects. Patients who are older, have renal impairment, or have had a solid organ transplant, and those being treated with a corticosteroid are at a higher risk of tendon damage. Co-administration of a fluoroquinolone and a corticosteroid should be avoided if possible. This review resulted in prescribing restrictions in Europe, limiting the use of fluoroquinolones to severe infections only.[80]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
### Acute

<table>
<thead>
<tr>
<th>Presumed atypical bacterial pneumonia: nonpregnant adult</th>
<th>1st</th>
<th>2nd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presumed atypical bacterial pneumonia: pregnant or child</td>
<td>1st</td>
<td>2nd</td>
</tr>
</tbody>
</table>

#### Acute (summary)

- **Presumed atypical bacterial pneumonia: nonpregnant adult**
  - 1st: macrolide
  - plus: supportive care
  - 1st: doxycycline
  - plus: supportive care
  - 2nd: fluoroquinolone
  - plus: supportive care
  - Severe community-acquired disease
  - plus: beta-lactam antibiotic plus hospitalization
  - Adjunct: corticosteroid

- **Presumed atypical bacterial pneumonia: pregnant or child**
  - 1st: macrolide
  - plus: supportive care
  - 2nd: doxycycline or a fluoroquinolone
  - plus: supportive care
  - Severe community-acquired disease
  - plus: beta-lactam antibiotic plus hospitalization
Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer
### Acute

**atypical pneumonia (non-COVID-19)**

#### Management

**presumed atypical bacterial pneumonia: nonpregnant adult**

<table>
<thead>
<tr>
<th>1st</th>
<th>macrolide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» azithromycin: 500 mg orally once daily on the first day, followed by 250 mg once daily for 4 days; 500 mg intravenously once daily for at least 5 days</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» clarithromycin: 500 mg orally (immediate-release) twice daily for 14-21 days</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» erythromycin base: 500 mg orally four times daily for 14-21 days; 1000 mg intravenously four times daily for 14-21 days</td>
<td></td>
</tr>
</tbody>
</table>

» Macrolides cover all common atypical pathogens as well as many of the other causes of community-acquired pneumonia. If the patient is unable to take drugs orally, intravenous formulations are available.

#### plus supportive care

**Treatment recommended for ALL patients in selected patient group**

» Patients should be assessed for hydration status, adequacy of gas exchange, and hemodynamic stability. Oxygen and ventilation should be started immediately if needed.

<table>
<thead>
<tr>
<th>1st</th>
<th>doxycycline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» doxycycline: 100 mg orally twice daily for 14 days</td>
<td></td>
</tr>
</tbody>
</table>

» Doxycycline covers common atypical pathogens as well as many of the other causes of community-acquired pneumonia. It is considered to be the first-line treatment for less common zoonotic atypical pathogens, such as *Chlamydia psittaci* (psittacosis) and *Coxiella burnetii* (Q fever).

#### plus supportive care

**Treatment recommended for ALL patients in selected patient group**

» Patients should be assessed for hydration status, adequacy of gas exchange, and
## Acute Management

**2nd 2nd fluoroquinolone**

**Primary options**

- **levofloxacin**: 750 mg orally/intravenously once daily for 5 days
- **moxifloxacin**: 400 mg orally/intravenously once daily for 7-14 days
- **gemifloxacin**: 320 mg orally once daily for 5-7 days

> These agents provide coverage for all atypical pathogens, although less evidence exists for *Chlamydia* species. They are the drug of choice for patients with comorbidities such as diabetes, alcoholism, chronic heart, lung, liver, or renal disease.

> These agents can be given orally or intravenously and they generally provide broader spectrum coverage than is needed for atypical bacterial pneumonia.

> Their use may promote emergence of fluoroquinolone resistance, and so widespread use in the community is discouraged.[18]

> Consider safety issues before prescribing fluoroquinolones. The Food and Drug Administration has issued warnings about the increased risk of aortic dissection, significant hypoglycemia, and mental health adverse effects in patients taking fluoroquinolones.[78] [79] The European Medicines Agency completed a review of serious, disabling, and potentially irreversible adverse effects associated with fluoroquinolones in 2018. These adverse effects included tendonitis, tendon rupture, arthralgia, neuropathies, and other musculoskeletal or nervous system effects.[80]

**plus supportive care**

Treatment recommended for ALL patients in selected patient group

> Patients should be assessed for hydration status, adequacy of gas exchange, and hemodynamic stability. Oxygen and ventilation should be started immediately if needed.
### Acute

<table>
<thead>
<tr>
<th>Severe community-acquired disease</th>
<th>Plus</th>
<th>Beta-lactam antibiotic plus hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Treatment recommended for ALL patients in selected patient group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In severe community-acquired pneumonia, guidelines recommend empirical treatment with a beta-lactam antibiotic, as well as coverage for atypical pathogens. [18] [39] Antibiotic treatment should be directed at the causative organism once etiology is established. Consult local guidelines for guidance on antibiotic regimen selection and doses.</td>
</tr>
<tr>
<td>Adjunct</td>
<td>Corticosteroid</td>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The use of corticosteroids in patients with severe community-acquired pneumonia has been a long-debated issue. Current guidelines generally recommend against the use of corticosteroids in patients with nonsevere or severe community-acquired pneumonia; although; Surviving Sepsis Campaign guidelines acknowledge that they may be considered in patients with refractory septic shock and can be used as clinically appropriate for comorbid conditions (e.g., COPD, asthma, autoimmune diseases). This recommendation is based on the fact that there are no data suggesting benefit in patients with nonsevere community-acquired pneumonia with respect to mortality or organ failure, and only limited data to support their use in patients with severe community-acquired pneumonia. [18]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A study from Japan suggests that corticosteroids may not offer any advantage in the treatment of <em>M pneumoniae</em> pneumonia. [77]</td>
</tr>
</tbody>
</table>

### Presumed atypical bacterial pneumonia: pregnant or child

<table>
<thead>
<tr>
<th>1st</th>
<th>Macrolide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary options</td>
<td></td>
</tr>
<tr>
<td>Azithromycin: children ≥3 months of age: 10 mg/kg orally once daily on day 1, followed by 5 mg/kg once daily on days 2-5, maximum 500 mg/day; adults: 500 mg intravenously/orally once daily on day 1, followed by 500 mg intravenously once daily or 250 mg orally once daily on days 2-5</td>
<td>OR</td>
</tr>
</tbody>
</table>
### Management

#### Acute

<table>
<thead>
<tr>
<th>Option</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>erythromycin lactobionate</strong>:</td>
<td>children and adults: 20 mg/kg/day intravenously given in divided doses every 6 hours, maximum 4000 mg/day</td>
</tr>
<tr>
<td><strong>erythromycin base</strong>:</td>
<td>children: 40 mg/kg/day orally given in 4 divided doses, maximum 2000 mg/day; adults: 500 mg orally four times daily</td>
</tr>
<tr>
<td><strong>clarithromycin</strong>:</td>
<td>children ≥3 months of age: 7.5 mg/kg orally twice daily, maximum 1000 mg/day; adults: 500 mg orally (immediate-release) twice daily</td>
</tr>
</tbody>
</table>

- Macrolides cover all common atypical pathogens as well as many of the other causes of community-acquired pneumonia.
- If the patient is unable to take drugs orally, intravenous formulations of erythromycin and azithromycin are available; however, the patient should be switched to oral therapy when possible.
- Treatment course: 5 days (azithromycin); 14-21 days (erythromycin, clarithromycin).

**plus** **supportive care**

- Treatment recommended for ALL patients in selected patient group
- Patients should be assessed for hydration status, adequacy of gas exchange, and hemodynamic stability. Oxygen and ventilation should be started immediately if needed.

**2nd** **doxycycline or a fluoroquinolone**

**Primary options**

<table>
<thead>
<tr>
<th>Option</th>
<th>Guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>doxycycline</strong>:</td>
<td>consult specialist for guidance on dose</td>
</tr>
<tr>
<td><strong>levofloxacin</strong>:</td>
<td>consult specialist for guidance on dose</td>
</tr>
<tr>
<td><strong>moxifloxacin</strong>:</td>
<td>consult specialist for guidance on dose</td>
</tr>
</tbody>
</table>
### Acute

<table>
<thead>
<tr>
<th>Severe community-acquired disease</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>plus</strong> beta-lactam antibiotic plus hospitalization</td>
</tr>
<tr>
<td></td>
<td>Treatment recommended for ALL patients in selected patient group</td>
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<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>» If a patient has a macrolide resistant <em>Mycoplasma pneumoniae</em> infection, doxycycline or a fluoroquinolone may be considered as an alternative treatment.</td>
</tr>
<tr>
<td></td>
<td>» Doxycycline is generally not recommended in children &lt;8 years of age due to the ability of tetracycline antibiotics to cause permanent discoloration of developing teeth. Fluoroquinolones are generally not recommended in children due to their adverse effects on joints. However, these drugs may be used with caution in children provided the benefits of using them outweigh the risks, and there are no other appropriate treatment options available.</td>
</tr>
<tr>
<td></td>
<td>» Doxycycline is not recommended in pregnant women due to its detrimental effect on fetal skeletal development and bone growth. However, it may be used in situations where there is no alternative option and the benefits outweigh the risks. Likewise, fluoroquinolones should not be used in pregnancy unless the potential benefits outweigh the risks.</td>
</tr>
<tr>
<td></td>
<td>» Consider safety issues before prescribing fluoroquinolones. The Food and Drug Administration has issued warnings about the increased risk of aortic dissection, significant hypoglycemia, and mental health adverse effects in patients taking fluoroquinolones.[78] [79] The European Medicines Agency completed a review of serious, disabling, and potentially irreversible adverse effects associated with fluoroquinolones in 2018. These adverse effects included tendonitis, tendon rupture, arthralgia, neuropathies, and other musculoskeletal or nervous system effects.[80]</td>
</tr>
</tbody>
</table>

**plus** supportive care

Treatment recommended for ALL patients in selected patient group

» Patients should be assessed for hydration status, adequacy of gas exchange, and hemodynamic stability. Oxygen and ventilation should be started immediately if needed.
### Acute

Once etiology is established, consult local guidelines for guidance on antibiotic regimen selection and doses.
Lefamulin

A first-in-class pleuromutilin antibiotic available in oral and intravenous formulations. It inhibits bacterial protein synthesis via interactions with the A- and P- sites of the peptidyl transferase center of the 50S subunit. Lefamulin offers a unique spectrum of activity covering *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* (including MRSA), beta-hemolytic streptococci (including *Streptococcus pyogenes* and *Streptococcus agalactiae*), and *Enterococcus faecium* (including vancomycin-resistant enterococci). It also covers *Legionella pneumophila*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*, the most common atypical organisms that cause community-acquired pneumonia.84] [85] [86] The safety and efficacy of lefamulin has been evaluated in two phase 3 clinical trials where it was found to be noninferior to moxifloxacin (with or without linezolid) in terms of primary efficacy end points (early clinical response, investigator assessment of clinical response). It was considered safe and well tolerated.87] [88] However, it has the potential to cause QT interval prolongation and should not be used in patients with known prolongation of the QT interval, ventricular arrhythmias, or who are on other drugs that prolong the QT interval. Lefamulin is approved by the Food and Drug Administration (FDA) for the treatment of community-acquired pneumonia in adults; however, its exact place in management is not clear as yet.

Delafloxacin

A new fluoroquinolone antibiotic approved by the FDA for the treatment of adults with community-acquired pneumonia caused by designated susceptible bacteria. It covers *L pneumophila*, *C pneumoniae*, and *M pneumoniae*, the most common atypical organisms that cause community-acquired pneumonia. The approval is based on results from a phase 3 study that found it was noninferior to moxifloxacin.89]

Omadacycline

A new modernized tetracycline antibiotic (aminomethylcycline) with broad-spectrum activity, designed to overcome tetracycline resistance. It covers *L pneumophila*, *C pneumoniae*, and *M pneumoniae*, the most common atypical organisms that cause community-acquired pneumonia. It is available in oral and intravenous formulations. Like other antibiotics in the tetracycline class, omadacycline may cause discoloration of deciduous teeth, and inhibition of fetal bone growth when administered during pregnancy. It has been found to be noninferior to moxifloxacin in terms of efficacy in adults with community-acquired pneumonia.90] Omadacycline is approved by the FDA for the treatment of community-acquired pneumonia in adults; however was refused approval for this indication in Europe in October 2018.

Solithromycin

In a randomized controlled trial oral solithromycin, a macrolide, was noninferior to oral moxifloxacin for the treatment of patients with community-acquired bacterial pneumonia.91] Studies demonstrate that the efficacy, tolerability, and safety profile make it a promising treatment.92] [93] Solithromycin is currently in phase 3 development for the treatment of community-acquired bacterial pneumonia.

Secondary prevention

Respiratory hygiene measures, such as the use of hand hygiene and tissues for patients who cough are recommended to reduce the risk of spread.

Epidemiological investigation is generally warranted (either by the local infection control team or by official epidemiological investigation) in cases where *Legionella pneumophila* infection has been diagnosed to prevent further exposure and infections.[29] [102] [103] and to improve water *Legionella* disinfection measures.[104]
Patient discussions

Smokers should be advised to quit. Respiratory hygiene measures, such as the use of hand hygiene and tissues for patients who cough are recommended to reduce the risk of spread.
Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>pleural/parapneumonic effusion</td>
<td>short term</td>
<td>medium</td>
</tr>
</tbody>
</table>

Pleural/parapneumonic effusion is an accumulation of fluid and inflammatory cells caused by adjacent lung infection or due to invasion of the pleural space by the pathogen. It occurs in up to 30% of cases of *Legionella pneumophila* pneumonia and in rare cases of *Mycoplasma pneumoniae* pneumonia. [7] [96]

Appropriate antibiotic treatment is essential. If fluid accumulates or does not resolve, then thoracentesis and drainage may be indicated. In severe nonresolving cases, pleural decortication may be required.

| rash                                       | short term | medium     |

May occur in up to 25% of *M pneumoniae* patients and is mainly self-limited maculopapular or vesicular rash. [5]

Severe cases may include Stevens-Johnson syndrome and ulcerative stomatitis. The term Mycoplasma-induced rash and mucositis has been used to describe the rash as it can be difficult to classify it as erythema multiforme or Stevens-Johnson syndrome. [97]

Because the main cause for the rash is probably systemic spread of the pathogen to the skin, appropriate antibiotic treatment is the treatment of choice.

| neurologic complications                    | short term | low         |

In up to 7% of patients hospitalized with *M pneumoniae*, a neurologic complication develops. These occur up to 2 weeks after the onset of infection and may include encephalitis, meningitis, cerebellar syndrome, cranial nerve palsies, and Guillain-Barre syndrome. [5]

Because some of these complications have autoimmune features, any treatment for each individual patient should be tailored according to the specific neurologic syndrome.

| pericarditis                                | short term | low         |

Pericarditis is an accumulation of fluid in the pericardial space that is mainly seen in *M pneumoniae* and *L pneumophila* infections. [5] [98] If abnormalities do not resolve with antibiotic treatment, then the patient may require pericardiocentesis and drainage.

| atherosclerosis                             | long term  | low         |

For more than a decade, studies have suggested a possible role of atypical pathogens, mainly *Chlamydia pneumoniae*, in progression of atherosclerosis. Further study is needed. [99] [100] [101]

Prognosis

Generally, the clinical outcome in patients with community-acquired pneumonia (including those with atypical bacterial pneumonia) can be predicted according to the initial severity of illness. Mortality rates in patients with less serious disease who are managed as outpatients are under 1%. However, patients with more
serious disease, especially those who do not respond to initial therapy, may have mortality rates as high as 50%.[18]

Additionally, patients in long-term care facilities may be prone to respiratory disease outbreaks and mortality.[94]
Diagnostic guidelines

International

Diagnosis and treatment of adults with community-acquired pneumonia (https://www.idsociety.org/practice-guideline/alphabetical-guidelines)  [18]

Published by: Infectious Diseases Society of America; American Thoracic Society  Last published: 2019

The management of community-acquired pneumonia in infants and children older than 3 months of age (https://www.idsociety.org/practice-guideline/alphabetical-guidelines)  [38]

Published by: Pediatric Infectious Diseases Society; Infectious Diseases Society of America  Last published: 2011

Guidelines for the management of community acquired pneumonia in adults (https://www.brit-thoracic.org.uk/quality-improvement/guidelines)  [39]

Published by: British Thoracic Society  Last published: 2009

The JRS guidelines for the management of community-acquired pneumonia in adults: an update and new recommendations (https://www.jstage.jst.go.jp/article/internalmedicine/45/7/45_7_419/_article)  [40]

Published by: Japanese Respiratory Society  Last published: 2006

Treatment guidelines

International

Diagnosis and treatment of adults with community-acquired pneumonia (https://www.idsociety.org/practice-guideline/alphabetical-guidelines)  [18]

Published by: Infectious Diseases Society of America; American Thoracic Society  Last published: 2019

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Atypical pneumonia (non-COVID-19)  References

**Key articles**


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Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

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Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style
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DISCLOSURES: At the time of the peer review, Professor Rubinstein declared no competing interests. We were made aware that Professor Rubinstein is now deceased.