Legionnaires’ Disease: Clinical Differentiation from Typical and Other Atypical Pneumonias

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KEYWORDS
- Clinical syndromic diagnosis
- Relative bradycardia
- Ferritin levels
- Hypophosphatemia

HISTORY
An outbreak of a severe respiratory illness occurred in Washington, DC, in 1965 and another in Pontiac, Michigan, in 1968. Despite extensive investigations following these outbreaks, no explanation or causative organism was found. In July 1976 in Philadelphia, Pennsylvania, an outbreak of a severe respiratory illness occurred at an American Legion convention. The US Centers for Disease Control and Prevention (CDC) conducted an extensive epidemiologic and microbiologic investigation to determine the cause of the outbreak. Dr Ernest Campbell of Bloomsburg, Pennsylvania, was the first to recognize the relationship between the American Legion convention in 3 of his patients who attended the convention and who had a similar febrile respiratory infection. Six months after the onset of the outbreak, a gram-negative organism was isolated from autopsied lung tissue. Dr McDade, using culture media used for rickettsial organisms, isolated the gram-negative organism later called \textit{Legionella}. The isolate was believed to be the causative agent of the respiratory infection because antibodies to \textit{Legionella} were detected in infected survivors. Subsequently, CDC investigators realized the antecedent outbreaks of febrile illness in Philadelphia and in Pontiac were caused by the same organism. They later demonstrated increased \textit{Legionella} titers in survivors’ stored sera. The same organism was responsible for the pneumonias that occurred after the American Legionnaires’ Convention in Philadelphia in 1976.

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Legionnaires’ disease had existed before the outbreaks but was never recognized as a cause of community-acquired pneumonia (CAP). Clustering of cases and outbreaks is useful in recognizing common epidemiologic and clinical features and is helpful in initiating investigative efforts to determine the cause of such outbreaks. Without the large number of cases in the Philadelphia 1976 outbreak, the eventual identification of *Legionella pneumophila* as the cause of legionnaires’ disease would have taken longer. A key clinical finding in legionnaires’ disease (ie, relative bradycardia) was noted in early descriptions. Subsequently, because the criteria for relative bradycardia was not defined, the clinical importance of relative bradycardia has been overlooked and underestimated (Fig. 1).1,2

Pneumonia caused by any *Legionella* species is termed legionnaires’ disease. The outbreak in Pontiac, Michigan, known as “Pontiac fever,” had an acute febrile illness but did not have pneumonia as in the Philadelphia outbreak. The isolation of *Legionella* was the first crucial step in understanding legionnaires’ disease. The initial isolation of *Legionella pneumophila* paved the way for ecological/epidemiologic studies, various direct and indirect diagnostic tests, and refining our therapeutic approach to legionnaires’ disease.

**MICROBIOLOGY**

The family Legionellae consists of more than 70 serogroups. *Legionella pneumophila* serotypes 1 to 6 account for most human infections. *Legionella* organisms are small obligate aerobic gram-nonfermenting gram-negative bacilli. *Legionella* are motile by bipolar flagella and stain poorly by Gram stain. *Legionella* seem to be filamentous in culture, but in tissue appear as small gram-negative coccobacilli. *Legionella* grow on buffered charcoal yeast extract (BCYE) and do not grow on standard media. *Legionella* require L-cysteine, and iron salts enhance their growth. BCYE is supplemented with L-cysteine, α-ketoglutarate and ferric pyrophosphate. *Legionella* colonies on BCYE develop a “ground glass” appearance with magnification. *Legionella* may be inhibited on artificial media by 0.6% sodium chloride peroxidides. Optimal pH for growth is 6.7 to 6.9. Colonies appear to be grayish white after 72 hours’ incubation at 35°C with 5% CO₂.3

*Legionella* are better seen on Giemsa stain than Gram stain. Silver stains (ie, Dieterle and Warthin-Starry silver stains) demonstrate *Legionella* in fixed tissue preparations. The best way to demonstrate *Legionella* is by monoclonal or polyclonal immunofluorescent antibody staining. *Legionella micdadei* is weakly acid fast using Ziehl-Nielsen staining. *Legionella* may be extracellular or intracellular. In the lung, *Legionella* cells infect mononuclear cells (eg, alveolar macrophages). To demonstrate *Legionella* in respiratory secretions, monoclonal antibody staining is preferred to polyclonal antibody staining. With polyclonal antibodies, false positives (ie, cross-reactions with *Pseudomonas aeruginosa, Pseudomonas fluorescens, Bordetella pertussis, Staphylococcus aureus, Bacteroides fragilis, and Bacillus sp*) may occur. Cross-reactions with a monoclonal antibody are infrequent but may occur with *S aureus* or *Bacillus* species. Colonies of *Legionella* appear on *Legionella* solid culture media after approximately 3 days but some *Legionella* species may require 2 weeks to develop visible colonies. Between days 1 and 3, *Legionella* colonies are best detected on plates using magnification.4,5

Legionnaires’ disease may be diagnosed by *Legionella* or acute/convalescent high rising titers. Seroconversion usually take 4–6 weeks. Monoclonal direct fluorescence assay (DFA) staining respiratory secretions/lung is diagnostic, but DFA positivity decreases rapidly with anti-*Legionella* therapy. *Legionella* antigenuria detects
L pneumophila serogroups 1 to 6 only. Seroconversion occurs in less than 50% of patients within 2 weeks of the onset of legionnaires’ disease.4–8 Antimicrobial susceptibility testing of L pneumophila should not be performed because the organism is an intracellular alveolar macrophage pathogen. In vitro susceptibility tests of Legionella must be used in an intracellular model (eg, alveolar macrophage) that takes into account pH and intracellular concentrations of the antimicrobials being tested.2,9,10

EPIDEMIOLOGY

The natural habitat of Legionella species is fresh water. With Legionella CAP, there is a seasonal peak in the late summer and early fall. Sporadic cases occur throughout
the year. Sporadic cases and outbreaks of Legionella CAP are often related to exposure to water colonized by Legionella (eg, during air travel or in water puddles, excavation, or construction sites).\textsuperscript{1,2} Outbreaks of Legionella nosocomial pneumonia (NP) are related to exposure of water sources containing Legionella sp (eg, ice cubes, shower water). Legionella CAP occurs in all age groups but is most common in adults more than 50 years of age.\textsuperscript{1,4,5}

Epidemiologically, the distribution of Legionella is reflective of the presence or absence of Legionella sp in local aquatic sources. Because Legionella sp are intracellular pathogens, patients with impaired cellular immunity (CMI) are particularly predisposed to legionnaires’ disease (eg, patients infected with the human immunodeficiency virus [HIV]).\textsuperscript{11,12} Legionella CAP caused by various Legionella spp has been described in transplant patients. Less commonly, legionnaires’ disease may cause CAP in non-transplant immunocompromised hosts with impaired CMI. Patients on immunomodulating/immunosuppressive agents (eg, G-CSF) have an increased incidence and increased severity of legionnaires’ disease.\textsuperscript{13–16} Epidemiologic investigations of CAP outbreaks, like Legionella NP, have had in common a water source colonized by Legionella (eg, legionnaires’ disease following gardening or hot tub exposure). Legionnaires’ disease is endemic in some areas but not in others if Legionella is not in the water supply.\textsuperscript{17–19} There has been an unexplained increase in legionnaires’ disease during the swine influenza (H1N1) pandemic.\textsuperscript{20}

**CLINICAL PRESENTATION**

*Overview*

Legionella CAP and NP have the same clinical features.\textsuperscript{21–23} Like other atypical pulmonary pathogens, legionnaires’ disease is associated with extrapulmonary manifestations. Legionnaires’ disease, like other causes of atypical CAP, is characterized by its own pattern of extrapulmonary organ involvement.\textsuperscript{22–30} Individual findings or specific organ involvement may occur with other atypical CAPs but it is the pattern of extrapulmonary organ involvement rather than individual findings characteristic of legionnaires’ disease which permits a syndromic clinical diagnosis. The syndromic diagnosis of Legionella CAP is based on recognizing, when present, a constellation of key clinical findings that are suggestive of Legionella CAP. In legionnaires’ disease, extrapulmonary clinical and laboratory findings have different clinical significance or diagnostic importance. By appreciating the relative diagnostic importance of various signs, symptoms, and laboratory tests, clinicians can apply these principles using a weighted diagnostic point score system that permits a rapid presumptive clinical diagnosis. With this approach, the clinicians can not only differentiate legionnaires’ disease from typical bacterial CAPs but can also differentiate legionnaires’ disease from other atypical CAPs.

Legionnaires’ disease may present subacutely for days or a week but more commonly presents acutely. In normal hosts, Legionella often presents as severe CAP. Legionnaires’ disease is in the differential diagnosis of atypical CAP and severe CAP. In the nosocomial setting, legionnaires’ disease, although it has the same clinical findings as sporadic Legionella CAP, usually presents in clusters or outbreaks caused by exposure to contaminated water in the hospital.\textsuperscript{24–27} Except for C pneumoniae outbreaks occurring in chronic care facilities or nursing homes (ie, nursing home-acquired pneumonia [NHAP]), legionnaires’ disease is the most common atypical CAP pathogen in hospital outbreaks or in intensive care units.\textsuperscript{24–27} The radiographic and nonspecific laboratory findings that accompany legionnaires’ disease overlap with typical and atypical pulmonary pathogens.\textsuperscript{28–37} The pulmonary
manifestations of *Legionella* CAP (ie, productive cough, shortness of breath, rales, sometimes accompanied by consolidation or pleural effusion) are nonspecific. In legionnaires’ disease pleuritic chest pain may be present if the infiltrates are pleural based.2,3,34,38

**Radiologic Manifestations**

**Chest film findings**
Chest radiograph (CXR) findings in legionnaires’ disease are not specific.35,36 However, certain radiological features may suggest the diagnosis or argue against the diagnosis. Although virtually every radiological manifestation of legionnaires’ disease has been described, certain findings argue strongly against the diagnosis of *Legionella* CAP (ie, rapid cavitation within 72 hours, hilar adenopathy, or massive or bloody pleural effusion). Cavitation or abscess formation is rare with legionnaires’ disease. Most characteristic of legionnaires’ disease radiographically are rapidly progressive asymmetrical patchy infiltrates on CXR.39,40 The rapid asymmetric progression of CXR infiltrates even with appropriate anti-*Legionella* sp therapy is usual with legionnaires’ disease. When *Legionella* presents as severe CAP, the CXR is important in limiting/eliminating other diagnostic possibilities. Severe CAP with no/ minimal infiltrates and profound hypoxemia should suggest a viral cause (eg, influenza [human, avian, swine], hantavirus pulmonary syndrome [HPS], severe acute respiratory syndrome [SARS], or cytomegalovirus [CMV]). The differential diagnosis of severe CAP with focal segmental/lobar infiltrates includes *Streptococcus pneumoniae* (in patients with impaired splenic function), legionnaires’ disease and zoonotic atypical pathogens (eg, Q fever, tularemia, or adenovirus).35 Because rapid asymmetrical progression of infiltrates on CXR may occur despite appropriate anti-*Legionella* therapy, the unwary clinician may be misled into thinking that the CAP is not caused by legionnaires’ disease.28–30,32–35

**Chest computed tomography findings**
Frequently, chest computed tomography (CT) scans are performed when there is a discordance between radiological and clinical findings or when the CXR features would benefit from the enhanced definition of a chest CT scan.

**Chest CT: *S pneumoniae*** If *S pneumoniae* is in the differential diagnosis of CAP, the typical findings of *S pneumoniae* CAP on chest CT include peribronchovesicular/centrilobular nodules or bronchovascular bundle thickening. With *S pneumoniae*, the hallmark finding on CXR/chest CT is consolidation (present on chest CT in 90%). These findings are less frequently found on chest CT with *Chlamydophila pneumoniae* or *Mycoplasma pneumoniae* CAP.41

In general, atypical CAP pathogens often show centrilobular/acinar infiltrates with air space consolidation and “ground glass” attenuation in a lobar distribution. *Streptococcus pneumoniae* bronchopneumonia radiologically may resemble *Legionella* CAP. Although *S pneumoniae* CAP may, like legionnaires’ disease, have consolidation with “ground glass” opacification/attenuation, the “ground glass” attenuation occurs only in the peripheral portions of the consolidation. The consolidation with *S pneumoniae* is usually not sharply demarcated in contrast to legionnaires’ disease with sharp demarcation of consolidation.42

**Chest CT: legionnaires’ disease** The characteristic appearance of *Legionella* CAP often shows chest CT multiple foci of sharply demarcated areas of consolidation intermingled with “ground glass” opacities. Another differential diagnostic point on chest CT is that the segmental/subsegmental consolidation in legionnaires’ disease is more
prominent in the perihilar areas rather than the peripheral regions of the lung. Other chest CT *Legionella* CAP findings include a bilateral diffuse interstitial pattern mimicking acute pulmonary edema/noncardiogenic pulmonary edema. Another specific feature of legionnaires’ disease on chest CT is the “reversed halo sign.” Although not apparent on CXR, legionnaires’ disease on chest CT may show unilateral hilar or mediastinal minimal adenopathy. The “bulging fissure sign” is a manifestation of an increase in lobar volume and is typically associated with *Klebsiella pneumoniae* CAP but is not an infrequent finding with *S pneumoniae* CAP and may also occur rarely in legionnaires’ disease. With legionnaires’ disease, small pleural effusions may be present on chest CT that were not visible on CXR.41–43

**Chest CT: *M pneumoniae*** The advantage of chest CT is to demonstrate more accurately “ground glass” opacities and thickening/nodules of bronchovascular bundles. These findings are important in the differential diagnosis of atypical CAP. Clinically, *M pneumoniae* CAP is often in the differential diagnosis of *Legionella* CAP. Radiologically, both may have bilateral patchy infiltrates on CXR, but chest CT demonstrates differential radiographic features on legionnaires’ disease compared with *M pneumoniae*. In nearly all patients with *M pneumoniae* CAP, diffuse bronchial wall thickening is the most characteristic finding on chest CT. Although the most common radiological feature of *M pneumoniae* CAP is central lobular nodules, the finding of generalized bronchial wall thickening is characteristic of *M pneumoniae* CAP.35,41–44

**Chest CT: *C pneumoniae*** Although the typical bacterial CAPs present with unilateral radiographic findings, bilateral infiltrates are common in CAP caused by *C pneumoniae, M pneumoniae*, and legionnaires’ disease. Although bronchovesicular thickening is the hallmark of *M pneumoniae* CAP, it may also be present in *C pneumoniae* CAP. The chest CT finding that differentiates *C pneumoniae* from *M pneumoniae* CAP is airway dilatation. Diffuse bronchovesicular bundle thickening may be present with either *C pneumoniae* or *M pneumoniae* but the presence of peripheral airway dilatation favors the diagnosis of *C pneumoniae* CAP.44,45

Branching central lobular nodules are usually reported as having a “tree-in-bud” appearance is a nonspecific finding. “Tree-in-bud” appearance may be seen with *C pneumoniae* and *M pneumoniae* CAP but argues against the diagnosis of legionnaires’ disease.41–45

Many radiological features of CAP are common to typical and atypical organisms on CXR. Enhanced definition visible of chest CT scans can help to further limit differential diagnostic possibilities, particularly with *M pneumoniae, C pneumoniae*, and legionnaires’ disease. However, the presumptive diagnosis of *Legionella* CAP must be based on clinical and not radiologic criteria.41–46

**Clinical Extrapulmonary Features**

As with all atypical causes of CAP, presumptive diagnosis is based on the pattern of extrapulmonary findings, which is distinctive for each atypical CAP pathogen.33–35 The zoonotic atypical CAP pathogens (ie, tularemia, psittacosis, and Q fever) may be eliminated from further diagnostic consideration by a negative history of recent contact with a zoonotic vector. In patients with CAP with extrapulmonary findings and a negative history of contact with a zoonotic vector, differential diagnostic possibilities are limited to the nonzoonotic atypical CAP pathogens (ie, *M pneumoniae, C pneumoniae*, and legionnaires’ disease) (Tables 1–3).47–49
Table 1
Diagnostic features of the nonzoonotic atypical pneumonias

| Key Characteristics | M pneumoniae | Legionnaires’ Disease | C pneumonia |
|---------------------|--------------|-----------------------|-------------|
| **Signs**           |              |                       |             |
| Rash                | ±            | –                     | –           |
| Nonexudative pharyngitis | +        | –                     | +           |
| Hemoptyis           | –            | ±                     | –           |
| Wheezing            | –            | –                     | +           |
| Lobar consolidation | –            | ±                     | –           |
| Cardiac involvement | ±            | –                     | –           |
| Splenomegaly        | –            | –                     | –           |
| Relative bradycardia| –            | +                     | –           |
| **Laboratory abnormalities** |         |                       |             |
| WBC count           | ↑/N          | ↑                     | N           |
| Acute thrombocytosis| ±            | –                     | –           |
| Hyponatremia        | –            | +                     | –           |
| Hypophosphatemia    | –            | +                     | –           |
| ↑ AST/ALT           | –            | +                     | –           |
| ↑ CPK               | –            | +                     | –           |
| ↑ CRP (>30)         | –            | +                     | –           |
| ↑ Ferritin (>2 × n) | –            | +                     | –           |
| ↑ Cold agglutinins  | (+ ≥1:64)    | +                     | –           |
| Microscopic hematuria| –         | ±                     | –           |
| **Chest radiograph** |            |                       |             |
| Infiltrates         | Patchy      | Patchy or consolidated| *Circumscribed* lesions |
| Bilateral hilar adenopathy | –       | –                     | –           |
| Pleural effusion    | ± (small)   | ±                     | –           |
| **Diagnostic tests** |            |                       |             |
| Direct isolation (culture) | ±      | +                     | ±           |
| Serology (specific) | CF          | IFA                   | CF          |
| Legionella IFA titers| –         | ↑↑↑                   | –           |
| Legionella DFA      | –            | +                     | –           |
| Legionella urinary antigen | –     | +*                    | –           |

Abbreviations: CF, complement fixation; CPK, creatinine phosphokinase; CRP, C-reactive protein; CYE, charcoal yeast agar; DFA, direct fluorescent antibody; IFA, indirect fluorescent antibody; N, normal; WBC, white blood cell; +, usually present; ±, sometimes present; –, usually absent; ↑, increased; ↓, decreased; ↑↑↑, markedly increased.

a Mental confusion only if meningoencephalitis.
b Erythema multiforme.
c Myocarditis, heart block, or pericarditis.
d Unless endocarditis.
e Often not positive early, but antigenuria persists for weeks. Useful only to diagnose L pneumophila (serogroups 01–06), not other species/serogroups.

Adapted from Cunha BA, editor. Pneumonia essentials. 3rd edition. Sudbury (MA): Jones & Bartlett; 2010.
| Key Characteristics | Psittacosis | Q fever | Tularemia |
|---------------------|------------|---------|-----------|
| **Symptoms**        |            |         |           |
| Mental confusion    | –          | ±       | –         |
| Prominent headache  | +          | +       | +         |
| Meningismus         | –          | –       | –         |
| Myalgias            | +          | +       | ±         |
| Ear pain            | –          | –       | –         |
| Pleuritic pain      | ±          | ±       | ±         |
| Abdominal pain      | –          | –       | –         |
| Diarrhea            | –          | –       | –         |
| **Signs**           | ±          | –       | –         |
| Rash                | –          | ±       | –         |
| Nonexudative pharyngitis | –   | –       | ±         |
| Hemoptyysis         | –          | ±       | –         |
| Lobar consolidation | +          | +       | +         |
| Cardiac involvement | ±          | ±       | ±         |
| Splenomegaly        | +          | +       | –         |
| Relative bradycardia| +          | +       | –         |
| **Chest radiograph**|           |         |           |
| Infiltrates         | Patchy or consolidation | Patchy or consolidation | *Ovoid* or round infiltrates |
| Bilateral hilar adenopathy | –       | –       | ±         |
| Pleural effusion    | –          | –       | Bloody    |
| **Laboratory abnormalities** |         |         |           |
| WBC count           | ↓          | ↑/N     | ↑/N       |
| Acute thrombocytosis| –          | +       | –         |
| ↓ Na⁺               | ±          | ±       | ±         |
| Hypophosphatemia    | –          | –       | –         |
| ↑ AST/ALT           | +          | +       | –         |
| ↑ Cold agglutinins  | –          | ±       | –         |
| ASM antibodies      | –          | ±       | –         |
| Microscopic hematuria| –        | –       | –         |
| **Diagnostic tests**|           |         |           |
| Direct isolation (culture) | –      | –       | –         |
| Serology (specific) | CF         | CF      | TA        |

**Abbreviations:** ASM, anti-smooth muscle; CF, complement fixation; N, normal; TA, tube agglutinins; WBC, white blood cells; +, usually present; ±, sometimes present; –, usually absent; ↑, increased; ↓, decreased; ↑↑↑↑, markedly increased.

* Horder’s spots (facial spots) resemble the abdominal rash of typhoid fever (Rose spots).
* Myocarditis.
* Endocarditis.

*Adapted from* Cunha BA, editor. Pneumonia essentials. 3rd edition. Sudbury (MA): Jones & Bartlett; 2010.
| Organ Involvement | Common Features | Uncommon Features | Argues Against Legionnaires’ Disease |
|------------------|----------------|------------------|--------------------------------------|
| CNS              | Mental confusion, encephalopathic, headache | Lethargy, stupor, dizziness | Meningeal signs, seizures, CN palsies |
| Upper respiratory tract | None | Vertigo | Sore throat, ear pain, bullous myringitis, otitis media |
| Cardiac          | Relative bradycardia | Myocarditis, endocarditis<sup>a</sup> | Pericarditis, no relative bradycardia |
| GI               | Loose stools/watery diarrhea | Abdominal pain | Hepatomegaly, hepatic tenderness, peritoneal signs |
| Renal            | Microscopic hematuria, renal insufficiency | Decreased urine output, acute renal failure | CVA tenderness, chronic renal failure |

**Laboratory tests**

| Test                        | Common Features | Uncommon Features | Argues Against Legionnaires’ Disease |
|-----------------------------|----------------|------------------|--------------------------------------|
| Gram stain (sputum)         | Few mononuclear cells, few/no bacteria | PMN predominance, mixed flora | Purulent sputum, single predominant organism |
| WBC count                   | Leukocytosis, relative lymphopenia | Lymphocytosis | Leukopenia, atypical lymphocytes, thrombocytosis, thrombocytopenia |
| Pleural fluid               | Exudative | ↑ WBCs | RBCs, ↓ pH, ↓ glucose |
| AST/ALT                     | Mildly increased (2–5 × n) | Moderately increased (5–10 × n) | Markedly increased (>10 × n) |
| Serum phosphorus            | Decreased transiently (early) | Decreased (later) | Increased/normal |
| CPK                         | Increased (early) | Rhabdomyolysis | Normal levels do not rule out legionnaires’ disease |
| CRP                         | ↑ >35 (early) | ↓ >35 (later) | Normal levels does not rule out legionnaires’ |
| Ferritin                    | Highly increased (>2 × n) | Moderately increased (<2 × n) | Normal ferritin levels early |
| CSF                         | Normal | Mild pleocytosis | RBCs, ↓ glucose, ↑ lactic acid |
| Urine analysis              | RBCs | Myoglobinuria, gross hematuria | Pyuria, hemoglobinuria |

*Abbreviations:* CN, cranial nerve; CNS, central nervous system; CPK, creatinine phosphokinase; CRP, C-reactive protein; CSF, cerebrospinal fluid; CVA, costovertebral angle; GI, gastrointestinal; PMN, polymorphonuclear leukocyte (neutrophil); RBC, red blood cell; WBC, white blood cell.

*<sup>a</sup> Culture negative.*

*Adapted from Cunha BA, editor. Pneumonia essentials. 3rd edition. Sudbury (MA): Jones & Bartlett; 2010.*
Diagnostic significance of relative bradycardia

As mentioned earlier, some clinical findings have more diagnostic importance than others and therefore have more diagnostic value when present. The specificity of findings is enhanced when key findings are combined in a syndromic diagnosis. In a patient with CAP with extrapulmonary findings and a negative history of recent zoonotic contact, the presence or absence of a pulse temperature (ie, relative bradycardia) is a key diagnostic sign. This key sign was present in early reports on legionnaires’ disease (see Fig. 1). Most physicians are unaware of the criteria of relative bradycardia. In normal hosts, a temperature of 102°F should be accompanied by an appropriate pulse response of 110/min. In such a patient, if the pulse is less than 100/min, relative bradycardia is said to be present. Pulse-temperature relationships for different degrees of fever and the pulse diagnostic of relative bradycardia for given temperatures are presented in Table 4.35,50 If the patient with nonzoonotic CAP is not on β-blockers, diltiazem, or verapamil, or does not have a pacemaker or heartblock, relative bradycardia points to legionnaires’ disease. None of the typical bacterial

| Temperature-pulse Relationships |
|-------------------------------|
| Temperature °C (°F) | Appropriate pulse response (beats/min) | Relative bradycardia (pulse deficit) pulse (beats/min) |
|------------------------|-----------------|------------------|
| 106 (41.1) | 150 | <140 |
| 105 (41.1) | 140 | <130 |
| 104 (41.1) | 130 | <120 |
| 103 (41.1) | 120 | <110 |
| 102 (41.1) | 110 | <100 |

Criteria for relative bradycardia

Inclusive
1. Patient must be an adult
2. Temperature ≥ 102°F
3. Pulse must be taken simultaneously with the temperature

Exclusive
1. Patient has normal sinus rhythm without arrhythmia, second/third-degree heart block or pacemaker-induced rhythm
2. Patient must not be on a β-blocker, verapamil, or diltiazem

Causes of Relative Bradycardia

Infectious
- Legionnaires’ disease
- Psittacosis
- Q fever
- Typhoid fever
- Typhus
- Babesiosis
- Malaria
- Leptospirosis
- Yellow fever
- Dengue fever
- Viral hemorrhagic fevers
- Rocky Mountain spotted fever

Noninfectious
- β-blockers
- Verapamil
- Diltiazem
- Central nervous system disorders
- Lymphomas
- Factitious fever
- Drug fever

Adapted from Cunha CB. Differential diagnosis of infectious disease. In: Cunha BA. Antibiotic essentials. 9th edition. Sudbury (MA): Jones & Bartlett; 2010; with permission.
CAPs are associated with relative bradycardia nor is *M. pneumoniae* or *C. pneumoniae* (Fig. 2).

**Central nervous system manifestations** Some patients with CAP complain of headache, which is also the case with legionnaires’ disease. However, among the atypical pathogens, *Legionella* is most likely to present with CAP with encephalopathy. Mental confusion may accompany headache in patients with legionnaires’ disease. Among the nonzoonotic atypical pathogens, *M. pneumoniae* (if CAP is accompanied by *M. pneumoniae* meningoencephalitis) or Q fever CAP may rarely present with mental confusion. Such cases should be readily differentiated from legionnaires’ disease by cold agglutinin titers. Increased cold agglutinin titers are not a feature of legionnaires’ disease but may occur in low titer with various viral pathogens or with Q fever. *Mycoplasma pneumoniae* CAP may be accompanied by higher levels of cold agglutinins that when present are helpful diagnostically if the titer is 1:64 or higher. In CAP with mycoplasma meningoencephalitis, the cold agglutinin titers are usually high (ie, >1:512 and not uncommonly >1:1052). Excluding encephalopathy and headache, there are no other neurologic manifestations that suggest legionnaires’ disease.

**Head, eyes, ears, nose, and throat manifestations** There are no head, eyes, ears, nose, and throat (HEENT) manifestations of *Legionella* CAP. The presence of otitis/bullous myringitis or nonexudative pharyngitis should suggest *M. pneumoniae* or less commonly *C. pneumoniae* CAP.

**Cardiac manifestations** The characteristic cardiac manifestation of legionnaires’ disease is a pulse-temperature deficit, (ie, relative bradycardia). Diagnostic possibilities in patients who have otherwise unexplained relative bradycardia with CAP are limited to legionnaires’ disease, Q fever, and psittacosis. Relative bradycardia is a nearly universal finding in legionnaires’ disease and the absence of relative

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**COMMUNITY-ACQUIRED PNEUMONIAS (CAP)**

(confirmed by chest radiography)

**No extrapulmonary features**
(typical bacterial pneumonias)

*Streptococcus pneumoniae*

*Haemophilus influenzae*

*Moraxella catarrhalis*

Group A streptococci

*Klebsiella pneumoniae*

**Extrapulmonary features**
(atypical pneumonias)

− zoontotic contact history

Mycoplasma

*C. pneumoniae*

Legionnaire’s disease

+ zoontotic contact history

Psittacosis

Q fever

Tularemia

− RB

+ RB

− RB

+ RB

Mycoplasma

*C. pneumoniae*

Legionnaire’s disease

Tularemia

Psittacosis

Q fever

Fig. 2. Clinical approach to community-acquired pneumonias: the importance of the zoontotic contact history and relative bradycardia.
bradycardia should prompt the clinician to question the diagnosis. Relative bradycardia is a characteristic feature of legionnaires' disease but may be found less frequently in patients with Q fever or psittacosis CAP. Rarely, legionnaires' disease may present as “culture-negative” endocarditis. Culture-negative endocarditis may occur on normal or prosthetic heart valves. Myocarditis is rare with legionnaires' disease.\textsuperscript{35,50,53–55}

**Hepatic manifestations** The hepatic manifestations of legionnaires’ disease are mildly transiently increased serum transaminase (aspartate aminotransferase [AST]/alanine aminotransferase [ALT]) levels. The alkaline phosphatase level is occasionally increased in legionnaires’ disease but is much less frequent than increased serum transaminase levels, which are present in nearly all patients. Hepatic enlargement or tenderness is not a feature of legionnaires' disease. Hepatomegaly, if present in a patient with CAP, should suggest an underlying disorder or an alternate diagnosis. Similarly, splenomegaly is not a clinical feature of legionnaires’ disease. In a CAP patient with splenomegaly, legionnaires’ disease is effectively ruled out and alternate diagnoses (eg, Q fever or psittacosis) should be considered instead.\textsuperscript{35,53–55}

**Gastrointestinal manifestations** Atypical CAP gastrointestinal manifestations are loose or watery stools with or without abdominal pain. Loose stools or watery diarrhea in a patient with atypical CAP should suggest \textit{M pneumoniae} or legionnaires’ disease. The presence of abdominal pain with or without watery diarrhea limits differential diagnostic possibilities to legionnaires’ disease.\textsuperscript{2,33,35}

**Musculoskeletal manifestations** Legionnaires’ disease is usually accompanied by fever, often with chills. Myalgias may accompany fever and chills in legionnaires’ disease, but are usually not severe. Myalgias may be present with typical or atypical pathogens and are diagnostically unhelpful.

Severe myalgias should suggest an alternate diagnosis (eg, human, avian, or swine influenza). Some patients with legionnaires’ disease develop rhabdomyolysis. In this patient subgroup, myalgias are not only severe but may be the predominant extrapulmonary manifestation of legionnaires’ disease.\textsuperscript{20,35,39,47}

**Renal manifestations** Otherwise unexplained microscopic hematuria is the most frequent renal manifestation of legionnaires’ disease. The presence of gross hematuria in a patient with CAP should suggest an alternate diagnosis. A decrease in renal function manifested by an increased in the serum creatinine has been noted in some patients with legionnaires’ disease but a causal relationship has not been convincingly demonstrated.\textsuperscript{35,39,49}

**Dermatologic manifestations** In a patient with CAP, dermatologic findings argue against the diagnosis of legionnaires’ disease. Among the atypical nonzoonotic causes of CAP, only \textit{M pneumoniae} is associated with skin manifestations (eg, erythema multiforme).\textsuperscript{35,49}

**Nonspecific Laboratory Findings**

**Overview**
Nonspecific laboratory tests are helpful, particularly when combined, in suggesting legionnaires’ disease or an alternate diagnosis. The most important nonspecific laboratory findings that suggest legionnaires’ disease versus other CAP pathogens are otherwise unexplained early/transient hypophosphatemia, highly increased serum ferritin levels, mildly/transiently early increases of serum transaminases, and microscopic hematuria.\textsuperscript{35,49}
**Complete blood count**
Leukocytosis is a standard feature in patients with legionnaires’ disease. In a patient with CAP the presence of leukopenia should suggest an alternate diagnosis (eg, adenoviral CAP). Legionnaires’ disease does not affect the platelet count. Therefore, in a patient with CAP with either thrombocytosis or thrombocytopenia, an alternate diagnosis besides legionnaires’ disease should be considered.33–35

**Relative lymphopenia**
Otherwise unexplained relative lymphopenia is a nearly universal nonspecific laboratory finding in legionnaires’ disease. However, there are many infectious and noninfectious disorders associated with relative lymphopenia. Before ascribing relative lymphopenia to legionnaires’ disease, the clinician must be careful to exclude other disorders associated with relative lymphopenia. Relative lymphopenia may occur with other causes of CAP, particularly CMV, influenza (human, avian, swine) pneumonia, and *Pneumocystis (carinii) jiroveci* pneumonia (PCP). Because otherwise unexplained relative lymphopenia is such a frequent finding in legionnaires’ disease, clinicians should question the diagnosis of legionnaires’ disease in a patient with CAP if relative lymphopenia is not present. Relative lymphopenia in legionnaires’ disease, if present, is often profound and prolonged and also has prognostic significance (Table 5).35,36,49

**Erythrocyte sedimentation rate/C-reactive protein**
The erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level are nonspecific indicators of inflammation, infection, or neoplasm. Most patients acutely ill with CAP have an increased ESR or CRP. The ESR and CRP levels tend to be highly increased in legionnaires’ disease but are nonspecific findings. Highly increased ESR or CRP level is consistent with but not characteristic of the diagnosis of legionnaires’ disease. With legionnaires’ disease, the ESR may be high and in some cases exceed 100 mm/h, and CRP values may exceed 35. Other nonspecific laboratory tests are better indicators of legionnaires’ disease than are a highly increased ESR or CRP.2,5,35,49

**Hyponatremia**
Hyponatremia is commonly associated with CAP of any cause, but is most frequently associated with *Legionella* CAP. Because hyponatremia is a nonspecific finding, it is an unhelpful discriminant parameter in differentiating *Legionella* from other causes of CAP. Hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone (SIADH) may occur with various infectious and noninfectious pulmonary disorders. Although hyponatremia is a frequent but nonspecific finding in legionnaires’ disease, if present in legionnaires’ disease, it is usually greater than in other pulmonary conditions associated with hyponatremia.1–4 Many physicians ascribe undue diagnostic significance to hyponatremia, which, in addition to being secondary to SIADH, may represent dilutional hyponatremia. With legionnaires’ disease, hyponatremia is a less specific laboratory test than is otherwise unexplained hypophosphatemia. In a patient with CAP, otherwise unexplained hypophosphatemia should suggest the diagnosis of legionnaires’ disease.33–35,39,49

**Hypophosphatemia**
In contrast to hyponatremia, hypophosphatemia, if present in CAP, limits diagnostic possibilities to legionnaires’ disease. Most nonspecific laboratory markers of legionnaires’ disease may occur (eg, highly increased ESR, highly increased CRP levels,
mildly increased serum transaminase levels, highly increased serum ferritin levels) with other causes of CAP. Otherwise unexplained hypophosphatemia is an important nonspecific laboratory marker for legionnaires’ disease because it is not associated with any other CAP pathogen. Hypophosphatemia occurs commonly with legionnaires’ disease. Hypophosphatemia, when present in legionnaires’ disease, may occur at any time during the in-hospital clinical course (Table 6). Although hypophosphatemia of legionnaires’ disease may be prolonged in duration, more frequently it may be transiently present early and easily missed. It is not uncommon for the hypophosphatemia in legionnaires’ disease to resolve spontaneously within the first day or 2 of hospitalization (Fig. 3). Unless serum phosphorus levels are obtained on admission or in the first few days of hospital admission, hypophosphatemia may be missed. Because serum phosphorus levels are not always ordered on admission by physicians in patients with CAP, an important clue to legionnaires’ disease in a patient with CAP is often missed or its clinical significance overlooked (see Fig. 3 and Table 6).35,49,56

Table 5
Differential diagnosis of relative lymphopenia ≤21% (n = 21%-52%)

| Infectious Causes                                | Noninfectious Causes                                      |
|--------------------------------------------------|----------------------------------------------------------|
| • CMV                                            | • Cytoxic drugs                                          |
| • HHV-6                                          | • Steroids                                               |
| • HHV-8                                          | • Sarcoidosis                                            |
| • HIV                                            | • SLE                                                    |
| • Miliary tuberculous                            | • Lymphoma                                               |
| • Legionnaires’ disease                          | • Rheumatoid arthritis                                   |
| • Typhoid fever                                  | • Radiation                                              |
| • Q fever                                        | • Wiskott-Aldrich syndrome                               |
| • Brucellosis                                    | • Whipple’s disease                                      |
| • Malaria                                        | • Severe combined immunodeficiency disease (SCID)        |
| • Babesiosis                                     | • Common variable immune deficiency (CVID)               |
| • SARS                                           | • DiGeorge’s syndrome                                    |
| • Influenza                                      | • Nezelof’s syndrome                                     |
| • Avian influenza                                | • Intestinal lymphangiectasia                            |
| • Swine influenza                                | • Ataxia telangiectasia                                  |
| • Rocky Mountain spotted fever                   | • Constrictive pericarditis                              |
| • Histoplasmosis                                 | • Tricuspid regurgitation                                |
| • Dengue fever                                   | • Kawasaki’s disease                                     |
| • Chikungunya fever                              | • Idiopathic CD4 cytopenia                               |
| • Ehrlichiosis                                   | • Acute/chronic renal failure                            |
| • Parvovirus B19                                 | • Hemodialysis                                           |
| • HPS                                            | • Myasthenia gravis                                      |
| • WNE                                            | • Celiac disease                                         |
| • Viral hepatitis (early)                         | • Alcoholic cirrhosis                                    |
| • Viral hepatitis (early)                         | • Coronary bypass                                        |
| • Viral hepatitis (early)                         | • Wegener granulomatosis                                 |
| • Viral hepatitis (early)                         | • CHF                                                    |
| • Viral hepatitis (early)                         | • Acute pancreatitis                                     |
| • Viral hepatitis (early)                         | • Carcinomas (terminal)                                  |

Abbreviations: CHF, congestive heart failure; CLL, chronic lymphocytic leukemia; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HHV, human herpesvirus; HPS, hantavirus pulmonary syndrome; SARS, severe acute respiratory syndrome; SLE, systemic lupus erythematosus; WNE, West Nile encephalitis.

Adapted from Cunha CB. Infectious disease differential diagnosis. In: Cunha BA, editor. Antibiotic essentials. 9th edition. Sudbury (MA): Jones & Bartlett; 2010.
Mildly increased serum transaminase levels are a common and consistent finding in Legionella CAP. Hepatic involvement (ie, mild increases of the serum transaminases) is not a feature of M pneumoniae or C pneumoniae CAP. Atypical CAP with mildly increased AST/ALT levels are sufficient to effectively rule out C pneumoniae or M pneumoniae from further diagnostic consideration. Hepatic involvement is one of the usual extrapulmonary manifestations of legionnaires’ disease. Because serum transaminase (eg, AST/ALT) levels are mildly or transiently increased early in the course of legionnaires’ disease, the presence and clinical significance of this laboratory finding is often overlooked. Physicians often regard mild transient increases of AST/ALT levels as nonspecific and do not appreciate its clinical significance in the context of the patient with CAP. Patients with typical bacterial CAPs do not have increased AST/ALT levels. The atypical CAP pathogens with mild/transiently

| Infectious Causes                      | Noninfectious Causes                                      |
|----------------------------------------|----------------------------------------------------------|
| • Legionnaires’ disease                | • Alcoholism                                             |
| • Malaria (acute)                      | • Diabetes mellitus                                      |
| • Burkitt’s lymphoma                   | • Primary hyperparathyroidism                             |
|                                        | • Idiopathic hypercalcuiura                              |
|                                        | • Hypokalemia                                            |
|                                        | • Hypomagnesemia                                         |
|                                        | • Cushing’s syndrome                                      |
|                                        | • Acute gout                                              |
|                                        | • Diabetes mellitus                                      |
|                                        | • RTA                                                     |
|                                        | • Malabsorption                                          |
|                                        | • Hyperalimentation                                       |
|                                        | • Vitamin D deficiency                                   |
|                                        | • Malnutrition                                           |
|                                        | • Vomiting                                                |
|                                        | • Diarrhea                                                |
|                                        | • Alcoholism                                              |
|                                        | • Alkalosis (respiratory)                                 |
|                                        | • Acidosi                                                 |
|                                        | • Nutritional recovery syndrome                           |
|                                        | • Salicylate poisoning                                    |
|                                        | • Multiple myeloma                                        |
|                                        | • Dialysis                                                |
|                                        | • AML                                                     |
|                                        | • Histiocytic lymphomas                                   |
|                                        | • Malignant neuroleptic syndrome                          |
|                                        | • Burns (severe)                                          |
|                                        | • Drugs                                                   |
|                                        | • Diuretics                                               |
|                                        | • Corticosteroids                                         |
|                                        | • Phosphate binding antacids                              |
|                                        | • Cisplatin                                               |
|                                        | • Acetaminophen toxicity                                  |
|                                        | • Foscarnet                                               |

Abbreviations: AML, acute myeloid leukemia; RTA, renal tubular acidosis.
Adapted from Cunha CB. Differential diagnosis of infectious disease. In: Cunha BA, editor. Antibiotic essentials. 9th edition. Sudbury (MA): Jones & Bartlett; 2010; with permission.

**Elevated serum transaminase levels**

Mildly increased serum transaminase levels are a common and consistent finding in Legionella CAP. Hepatic involvement (ie, mild increases of the serum transaminases) is not a feature of M pneumoniae or C pneumoniae CAP. Atypical CAP with mildly increased AST/ALT levels are sufficient to effectively rule out C pneumoniae or M pneumoniae from further diagnostic consideration. Hepatic involvement is one of the usual extrapulmonary manifestations of legionnaires’ disease. Because serum transaminase (eg, AST/ALT) levels are mildly or transiently increased early in the course of legionnaires’ disease, the presence and clinical significance of this laboratory finding is often overlooked. Physicians often regard mild transient increases of AST/ALT levels as nonspecific and do not appreciate its clinical significance in the context of the patient with CAP. Patients with typical bacterial CAPs do not have increased AST/ALT levels. The atypical CAP pathogens with mild/transiently
increased AST/ALT levels are legionnaires' disease, Q fever, and psittacosis. From a differential diagnostic perspective liver involvement manifested by mildly increased serum transaminase levels is not a feature of tularemia or *M pneumoniae* CAP. Highly elevated AST/ALT levels should suggest a non-CAP diagnosis.1–3,35,56–58

**Antismooth muscle antibodies**

Antismooth muscle (ASM) antibodies are not ordinarily part of the laboratory tests ordered in a patient with CAP. The only cause of CAP associated with increased ASM antibody titers is Q fever. Because coinfections are rare, the finding of ASM antibodies in a patient with CAP argues against other diagnostic possibilities including legionnaires’ disease and should suggest the diagnosis of Q fever CAP.35,59

**Increased cold agglutinin titers**

In a CAP patient there are nonspecific laboratory tests that, when present, should suggest a diagnosis other than legionnaires’ disease. Because copathogens in CAP are rare, the presence of highly elevated cold agglutinin titers should suggest an alternative diagnosis to legionnaires’ disease. Mildly increased cold agglutinin titers may occur with various viral respiratory infections. Increased cold agglutinin titers, excluding influenza (human, avian, swine), CMV, and adenovirus, are not associated with extrapulmonary clinical features. Being aware of the pattern of extrapulmonary organ involvement with various pulmonary pathogens, clinicians should have no difficulty in evaluating the clinical significance of mild/moderately increased serum cold
agglutinin titers. Highly increased cold agglutinin titers in a patient with CAP points to the diagnosis of *M pneumoniae* CAP. Mild to moderate increases of cold agglutinins may also be present in patients with Q fever CAP. In a patient with CAP, the higher the cold agglutinin titer is over 1:64, the more likely it is that the patient has *M pneumoniae*. CAP with highly increased cold agglutinin titers (ie, >1:256) is virtually diagnostic of *M pneumoniae* CAP. Because coinfection in CAP is rare, cold agglutinin titers are important because increased cold agglutinins effectively rule out *Legionella* CAP (Table 7).35,52,59

**Increased serum ferritin levels**
Otherwise unexplained highly elevated serum ferritin levels are a characteristic laboratory finding in legionnaires’ disease. In legionnaires’ disease, highly elevated serum ferritin levels are usually, but not always, present on admission. However, during the course of legionnaires’ disease, serum ferritin levels become highly and persistently elevated. Mildly/transiently elevated serum ferritin may represent an acute phase reactant. However, the magnitude/duration of ferritin level elevations in legionnaires’ disease is due to the infection and not an acute phase phenomenon. Highly elevated serum ferritin levels are such a consistent finding in legionnaires’ disease, that with un-elevated/minimally elevated serum ferritin levels the diagnosis of Legionnaires’ disease should be questioned (Table 8).35,60

**Increased serum creatinine phosphokinase levels**
Creatinine phosphokinase (CPK) levels are often increased in patients with legionnaires’ disease. Highly elevated CPK levels may also be a manifestation of

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**Table 7**

Differential diagnosis of increased cold agglutinin titers

| Infectious Causes | Non-infectious Causes |
|-------------------|-----------------------|
| High cold agglutinin titers (≥1:64) | High cold agglutinin titers high (≥1:64) |
| • *Mycoplasma pneumoniae* | • Cold agglutinin disease |
| Elevated cold agglutinin titers (<1:64) | Elevated cold agglutinin titers (<1:64) |
| Respiratory pathogens | Nonrespiratory pathogens |
| • *M pneumoniae* | • EBV |
| • Adenovirus | • CMV |
| • Influenza | • HCV |
| • Malaria | • Malaria |
| • Trypanosomiasis | • Trypanosomiasis |
| • Coxsackie viruses | • Coxsackie viruses |
| • Measles | • Measles |
| • Mumps | • Mumps |
| • HIV | • HIV |

Abbreviations: CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HIV, human immuno deficiency virus; SLE, systemic lupus erythematosus.

Adapted from Cunha BA. The clinical diagnosis of *Mycoplasma pneumoniae*: the diagnostic importance of highly elevated serum cold agglutinins. Eur J Clin Microbiol Infect Dis 2008;27:1017–9.
rhabdomyolysis. Mild to moderate increases of CPK may occur with various infectious and noninfectious disorders. Rhabdomyolysis may accompany various CAPs, particularly influenza (human, avian, swine) pneumonia and legionnaires’ disease. In a CAP patient in whom influenza (human, avian, swine) is not a diagnostic consideration, the clinician should order _Legionella_ sp diagnostic tests to confirm or rule out the diagnosis.33,35

Lactate dehydrogenase
Lactate dehydrogenase (LDH) levels are variably increased in legionnaires’ disease. Mild increases in serum LDH levels may occur with various disorders and are diagnostically unhelpful in patients with CAP. Highly increased LDH levels in a patient with CAP and with shortness of breath/hypoxemia with a clear CXR or a CXR with bilateral patchy interstitial infiltrates should suggest the diagnosis of _Pneumocystis (carinii) jiroveci_ CAP.2–4,35

Increased serum procalcitonin levels
Serum procalcitonin (PCT) levels have been used as a marker for bacterial CAP. Serum PCT levels are not increased in viral infections including influenza (human,
avian, swine). In legionnaires’ disease, serum PCT levels may be increased. Various disorders are associated with increased PCT levels. Like other nonspecific laboratory tests, the clinical significance of increased serum PCT must be interpreted in the appropriate clinical setting. With the exception of legionnaires’ disease, serum PCT levels are not increased with the other atypical CAPs. Serum PCT levels offer no additional diagnostic information in diagnosing CAP other than what may be learned from the CXR. The CXR remains the best way to identify bacterial pneumonias and eliminate other disorders that may mimic radiologically bacterial CAPs. In CAPs, serum PCT levels are expensive and offer no additional diagnostic information than can be obtained by a CXR (Table 9). Highly increased serum PCT levels may have prognostic significance in legionnaires’ disease.

**Clinical Syndromic Diagnosis**

In the clinical diagnosis of legionnaires’ disease, individual clinical and nonspecific laboratory and radiologic findings have little diagnostic specificity. Studies reporting the inability clinically to differentiate typical from atypical CAP pathogens usually are based on comparing single parameters, such as fever or hyponatremia. Such approaches do not work because critical parameters are not included (ie, hypophosphatemia, or relative bradycardia). The diagnostic usefulness of selecting key nonspecific findings is enhanced when they are combined to increase diagnostic specificity, which is the basis of clinical syndromic diagnosis. In CAP patients with extrapulmonary findings and a negative history of zoonotic contact who present with relative bradycardia, hypophosphatemia, or increased serum ferritin levels, the

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**Table 9**

Differential diagnosis of increased PCT levels

| Infectious Disorders | Noninfectious Disorders |
|----------------------|------------------------|
| - Bacterial pneumonias | - Renal insufficiency |
| - CAP | - Alcoholic hepatitis |
| - NHAP | - Lung cancer (small cell) |
| - NP | - Thyroid cancer |
| - Legionnaires’ disease | - Surgery |
| - Bacteremias (gram-negative > gram-positive) | - Trauma |
| - TB | - Burns |
| - Bacterial meningitis | - Cardiogenic shock |
| - Fungal pneumonias | - Goodpasture syndrome shock |
| - Viral hepatitis | - GVHD |
| - Toxoplasmosis | - Hypotension |
| - Osteomyelitis | - Hemorrhagic/necrotic pancreatitis |
| - SBE | - Normal variant (elderly) |
| - Malaria (*Plasmodium falciparum*) | - Febrile neutropenia |
| | - Drug fever |
| | - HD (not PD) |
| | - Immunosuppression/steroids |
| | - BMT |
| | - Tumor fever |

_Abbreviations: BMT, bone marrow transplant; CAP, community acquired pneumonia; GVHD, graft-versus-host disease; HD, hemodialysis; NHAP, nursing home acquired pneumonia; NP, nosocomial pneumonia; PD, peritoneal dialysis; SBE, subacute bacterial endocarditis; TB, tuberculosis._

_Data from_ Cunha CB. Differential diagnosis of infectious disease. In: Cunha BA, editor. Antibiotic essentials. 9th edition. Sudbury (MA): Jones & Bartlett; 2010._
likelihood of legionnaires’ disease is high. Clinically, given these findings in a CAP patient, there is no alternative diagnosis that would be readily confused with legionnaires’ disease (Tables 10 and 11).35,65–67

Legionnaires’ disease often progresses within 2 to 3 days despite anti-Legionella antimicrobial therapy. This progress may be related to the intracellular location of Legionella in the alveolar macrophage. If the clinical syndromic diagnosis suggests legionnaires’ disease based preferably on a weighted diagnostic index, clinicians should not add another antimicrobial therapy or consider alternative diagnoses. As the patient begins to improve, usually after 3 to 5 days, a decrease in temperature is accompanied by a disappearance of relative bradycardia (Fig. 4). Most clinical and laboratory abnormalities resolve quickly but fever and mental confusion may persist for 2 to 3 days. CXR may show legionnaires’ disease infiltrates for weeks after clinical improvement (Figs. 5–10).35

Differential Diagnosis

Mimics of legionnaires’ disease

Legionella CAP may resemble any one of the typical bacterial CAP pathogens radiologically. On CXR, Legionella pneumophila often presents with a lobar infiltrate that may or may not be accompanied by consolidation or pleural effusion, which are the radiological hallmarks of typical bacterial CAP pathogens. Radiologically, Legionella may also resemble some of the zoonotic atypical pulmonary pathogens, particularly Q fever and psittacosis. Psittacosis and Q fever, like legionnaires’ disease, may present with lobar infiltrates with or without consolidation/pleural effusion. In patients with an appropriate history of recent epidemiologic or vector contact, either Q fever or psittacosis should be included in the differential diagnosis of CAP. The viral CAPs that may be confused with legionnaires’ disease are adenoviral and swine influenza (H1N1) pneumonias. Adenovirus radiologically may present with lobar infiltrates with or without pleural effusion, resembling a typical bacterial CAP or legionnaires’ disease. Mimics of legionnaires’ disease may be diagnosed by ordering specific acute/convalescent serology appropriate to the pathogens that are clinically relevant in the differential diagnosis.35,53,56

Mycoplasma pneumoniae CAP

Clinically, legionnaires’ disease and M pneumoniae CAP are the commonest nonzoonotic atypical CAP pathogens. Atypical CAP pathogens may be clinically differentiated from typical CAP pathogens by the presence or absence of extrapulmonary clinical and laboratory findings. Similarly, among the atypical CAPs a presumptive clinical diagnosis based on the characteristic pattern of extrapulmonary organ involvement of each individual pathogen is relatively straightforward. The zoonotic atypical CAP pathogens may be eliminated from consideration with a negative recent zoonotic contact history. If the patient has CAP and extrapulmonary findings ie, has an atypical CAP with zoonotic atypical pathogens eliminated by history, the differential diagnosis is limited to the nonzoonotic atypical CAP pathogens. Mycoplasma and legionnaires’ disease are often in the differential diagnosis of non-zoonotic atypical CAPs, not because they resemble each other but because the M pneumoniae CAP is so common. Clinically, in terms of pattern of organ involvement and nonspecific laboratory tests, legionnaires’ disease and M pneumoniae CAP are easily differentiated. The key cardinal findings that serve to differentiate legionnaires’ disease from M pneumoniae are relative bradycardia, mildly increased serum transaminase levels, early/transient hypophosphatemia, highly increased ferritin levels, and microscopic hematuria. Although all of these findings are not present in every patient with Legionella CAP,
Table 10
Winthrop-University Hospital Infectious Disease Division’s diagnostic weighted point score system for diagnosing legionnaires’ disease in adults (modified)

| Presentation | Qualifying Conditions b | Point Score |
|--------------|-------------------------|-------------|
| **Clinical features** | | |
| Temperature >102°F a | With relative bradycardia a | +5 |
| Headache a | Acute onset | +2 |
| Mental confusion/lethargy a | Not drug-induced or toxic/metabolic | +4 |
| Ear pain | Acute onset | −3 |
| Nonexudative pharyngitis | Acute onset | −3 |
| Hoarseness | Acute not chronic | −3 |
| Sputum (purulent) | Excluding AECB | −3 |
| Chest pain | Pleuritic | −3 |
| Loose stools/watery diarrhea a | Not drug induced | +3 |
| Abdominal pain a | With/without diarrhea | +5 |
| Renal failure a | Acute (not chronic) | +3 |
| Shock/hypotension a | Excluding cardiac/pulmonary causes | +1 |
| Splenomegaly a | Excluding non-CAP causes | −5 |
| Lack of response to β-lactam antibiotics | after 72 h | +5 |
| **Laboratory tests** | | |
| Chest radiograph | Rapidly progressive asymmetric infiltrates a (excluding influenza, CMV, HPS, SARS) | +3 |
| Severe hypoxemia (↑ A-a gradient >35) a | Acute onset (excluding influenza HPS, SARS) | −2 |
| Hyponatremia a | Acute onset | +1 |
| Hypophoshatemia a | Acute onset | +5 |
| ↑ AST/ALT (early/mild/transient) a | Acute onset | +2 |
| ↑ Total bilirubin | Acute onset | +1 |
| ↑ LDH (>400) a | Acute onset | −5 |
| ↑ CPK a | Acute onset | +3 |
| ↑ CRP >35 a | Acute onset | +5 |
| ↑ Cold agglutinin titers (≥ 1:64) a | Acute onset | −5 |
| Severe relative lymphopenia (<10%) a | Acute onset | +5 |
| ↑ Ferritin (>2 × n) a | Sustained elevations | +5 |
| Microscopic hematuria a | Excluding trauma, BPH, Foley catheter, bladder/renal neoplasms | +2 |
| **Likelihood of Legionella** | | |
| Total point score | >15 Legionnaires’ disease very likely | |
| | 5–15 Legionnaires’ disease likely | |
| | <5 Legionnaires’ disease unlikely | |

*Abbreviations: AECB, acute exacerbation of chronic bronchitis; BPH, benign prostatic hyperplasia; LDH, lactate dehydrogenase.

a Otherwise unexplained.
b In adults, otherwise unexplained, acute and associated with the pneumonia.

Adapted from Cunha BA, editor. Pneumonia essentials. 3rd edition. Sudbury (MA): Jones & Bartlett; 2010; with permission.
sufficient findings will be present to permit a presumptive clinical diagnosis, and
prompt specific laboratory testing for *Legionella*. *Mycoplasma pneumoniae* CAP has
none of these features. Because *M pneumoniae* CAP is not accompanied by a
pulse-temperature deficit (eg, relative bradycardia, hypophosphatemia, highly
increased ferritin levels, or renal involvement), the presence of several of these findings
eliminates *M pneumoniae* CAP from further diagnostic consideration. Conversely, the
hallmark laboratory abnormality present in approximately 75% of *M pneumoniae*
patients is increased cold agglutinin titers. Although low titers of cold agglutinins
may be associated with some viral infections and may be associated with a variety
of medical disorders. Highly increased cold agglutinin titers should suggest the possi-
bility of *M pneumoniae* in a patient with CAP. The only other pathogens that could be
confused with *M pneumoniae* CAP are Q fever and adenovirus. Excluding other
causes of highly increased cold agglutinins (eg, cold agglutinin disease) with CAP
patients with highly increased cold agglutinin titers (ie, ≥1:64) should be considered
as having *M pneumoniae* CAP until proven otherwise. The cold agglutinin titers with
*M pneumoniae* may not be present on clinical presentation but may be elevated in
the course of the infection. Although the diagnosis of *M pneumoniae* is likely in
a patient with CAP and highly increased cold agglutinin titers, (ie, >1:64); elevated
cold agglutinin titers occur in only 75% of patients. The diagnosis of *M pneumoniae*

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**Table 11**

Rapid clinical diagnosis of legionnaires’ disease: *Legionella* diagnostic triad

| Entry Criteria | Key Clinical Features | Key Laboratory Features (any 3) |
|----------------|-----------------------|---------------------------------|
| * Signs and symptoms of CAP plus | Fever >102°F with relative bradycardia<sup>a</sup> | * Hypophosphatemia<sup>a</sup> |
| * New infiltrate on chest radiograph<sup>a</sup> | | * Highly increased serum ferritin levels<sup>a</sup> (>2 × n) |
| * Negative recent/close zoonotic vector contact history | | * Mildly/transiently increased serum transaminases<sup>a</sup> |

<sup>a</sup> Otherwise unexplained.

*From* Cunha BA, Mickail N, Syed U, et al. The rapid clinical diagnosis of Legionnaires’ disease during the “herald wave” of the swine influenza (H1N1) pandemic: the Legionnaires’ disease triad. Heart Lung 2010;39; in press; with permission.

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**Fig. 4.** Typical time course of early transient hypophosphatemia with legionnaires’ disease. *From* Cunha BA. Hypophosphatemia: diagnostic significance in legionnaires’ disease. Am J Med 2006;119:5–6.
CAP is confirmed by demonstrating elevated *M pneumoniae* IgM titers acutely and increasing IgG titers during convalescence.\(^{33,35,50,68,69}\)

**Q fever CAP**

Q fever is an uncommon cause zoonotic atypical CAP. CAP in patients with a recent history of close contact with a zoonotic vector is often overlooked or not appreciated. An initial history regarding zoonotic contact vectors is often not elicited in patients presenting with Q fever CAP. Although patients can recall contact with sheep, they often overlook the potential clinical significance of a neighbor with a parturient cat. Q fever may mimic legionnaires’ disease in onset of clinical presentation. Although legionnaires’ disease may have a subacute onset, legionnaires’ disease onset is acute when presenting as severe CAP. Q fever CAP usually has a subacute onset, as with most cases of legionnaires’ disease. Relative bradycardia may be present with Q

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**Fig. 5.** Serial ESRs in a patient with *Legionella* CAP. *(From Cunha BA, Mickail N, Syed U, et al. The rapid clinical diagnosis of Legionnaires’ disease during the “herald wave” of the swine influenza (H1N1) pandemic: the Legionnaires’ disease triad. Heart Lung 2010;39; in press; with permission.)*

**Fig. 6.** Serial CRP levels in a patient with *Legionella* CAP. *(From Cunha BA, Mickail N, Syed U, et al. The rapid clinical diagnosis of Legionnaires’ disease during the “herald wave” of the swine influenza (H1N1) pandemic: the Legionnaires’ disease triad. Heart Lung 2010;39; in press; with permission.)*
fever, as with legionnaires’ disease. Among the extrapulmonary manifestations that overlap with legionnaires’ disease are headache and less commonly mental confusion. The cardinal clinical finding in Q fever CAP is the presence of splenomegaly. In a patient with CAP and splenomegaly, Q fever is the most likely diagnostic possibility; alternatively, psittacosis should be considered in those with a recent exposure to psitticine birds. Splenomegaly is not a feature of legionnaires’ disease but may be easily overlooked or may not yet be detectable on physical examination. In patients with CAP, splenomegaly is usually detected as an incidental finding if the abdomen is included in the CXR or chest CT. Among the nonspecific laboratory tests, mild increases of the serum transaminase levels occur with Q fever, legionnaires’ disease,

Fig. 7. Serial serum phosphorus levels in a patient with Legionella CAP. (From Cunha BA, Mickail N, Syed U, et al. The rapid clinical diagnosis of Legionnaires’ disease during the “herald wave” of the swine influenza (H1N1) pandemic: the Legionnaires’ disease triad. Heart Lung 2010;39; in press; with permission.)

Fig. 8. Serial serum transaminase levels in a patient with Legionella CAP. (From Cunha BA, Mickail N, Syed U, et al. The rapid clinical diagnosis of Legionnaires’ disease during the “herald wave” of the swine influenza (H1N1) pandemic: the Legionnaires’ disease triad. Heart Lung 2010;39; in press; with permission.)
and psittacosis. Increased serum ferritin levels may also occur with Q fever CAP, although they are less frequent and not as highly elevated as with legionnaires’ disease. If ASM antibodies are present in a patient with atypical CAP, it points to the diagnosis of Q fever. In patients with an atypical CAP, otherwise unexplained thrombocytosis occurring during hospitalization is an important clue to Q fever CAP. Although thrombocytosis may occur with *M pneumoniae* CAP, it is more common, pronounced, and prolonged with Q fever CAP. Other nonspecific laboratory features (ie, increased serum transaminases) readily differentiate Q fever from *M pneumoniae* CAP. Although there are no pathognomonic radiologic features that clearly differentiate legionnaires’ disease from Q fever, round opacities or infiltrates, if

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**Fig. 9.** Serial CPK levels in a patient with *Legionella* CAP. (*From* Cunha BA, Mickail N, Syed U, et al. The rapid clinical diagnosis of Legionnaires’ disease during the “herald wave” of the swine influenza (H1N1) pandemic: the Legionnaires’ disease triad. Heart Lung 2010;39; in press; with permission.)

**Fig. 10.** Serial ferritin levels in a patient with *Legionella* CAP. (*From* Cunha BA, Mickail N, Syed U, et al. The rapid clinical diagnosis of Legionnaires’ disease during the “herald wave” of the swine influenza (H1N1) pandemic: the Legionnaires’ disease triad. Heart Lung 2010;39; in press; with permission.)
present, are most helpful. The presence of so-called ovoid or round infiltrates should suggest the presence of Q fever in a patient with atypical CAP. Round or nodular infiltrates are not usually present in legionnaires’ disease but may be present with *Legionella micdadei* CAP.\(^{35,53–55,69}\)

Doxycycline is equally effective in treating legionnaires’ disease and Q fever. If a loading regimen of doxycycline is not used (ie, 200 mg intravenously [IV]/by mouth [PO] every 12 h x 3 days, followed by 100 mg IV/PO every 12 h), then a therapeutic response may not be evident for 4–5 days. Legionnaires’ disease responds in 2–3 days to treatment with a fluoroquinolone but Q fever responds less rapidly and less well to doxycycline therapy. Q fever may be diagnosed or ruled out by acute/convalescent phase I phase II Q fever titers.\(^{28,35,53–55,59}\)

**Adenovirus CAP**

Adenoviral CAP may be confused with legionnaires’ disease radiographically. Although there is no pathognomonic radiographic presentation of legionnaires’ disease, the radiographic behavior of the infiltrates is characteristic. Rapidly asymmetrical progression of infiltrates is characteristic of legionnaires’ disease on CXR, which is not usual with adenoviral CAP. Adenoviral CAP often presents with a focal segmental/lobar infiltrate mimicking legionnaires’ disease, Q fever, psittacosis, or typical bacterial CAPs. Although adenoviral CAP is not accompanied by relative bradycardia, many of the nonspecific laboratory findings associated with legionnaires’ disease may be present in patients with adenoviral CAP. Most commonly, adenoviral CAP may be accompanied by a mild increase of AST/ALT levels, most commonly mimicking legionnaires’ disease and less commonly, Q fever or psittacosis. Increased CPK levels are also frequently present in adenoviral CAP and legionnaires’ disease. The key nonspecific markers of legionnaires’ disease (ie, increased serum ferritin levels, hypophosphatemia, microscopic hematuria) are not features of adenoviral CAP. Of course, adenoviral CAP does not respond to anti-*Legionella* antibiotic therapy. Mild increases of cold agglutinin titers may be present, which would argue against the diagnosis of legionnaires’ disease. Diagnosis is confirmed or ruled out by acute/convalescent adenoviral titers.\(^{35,70}\)

**Severe CAP**

Legionnaires’ disease not infrequently presents as severe CAP. In the differential diagnosis of severe CAP, common diagnostic considerations include influenza (human, avian, swine), SARS, HPS, CMV, and adenovirus. In compromised hosts (eg, patients with impaired CMI), *Pneumocystis (carinii) jiroveci* may present as severe CAP. Similarly, in transplant patients, CMV CAP is an important diagnostic consideration. Excluding zoonotic pathogens, the severity of CAP depends primarily on host factors rather than to the inherent virulence of the pathogen. In a patient presenting with severe CAP with focal segmental/lobar infiltrates on CXR, the differential diagnosis is often between legionnaires’ disease, *S pneumoniae*, and adenovirus. Patients with *S pneumoniae* CAP do not usually present as severe CAP unless there is impaired humoral immunity (HI) (ie, impaired splenic function).\(^{35}\) Adenovirus is the “great imitator” of bacterial CAP. Unlike other viral CAPs presenting as severe pneumonia, adenovirus on the CXR may have focal segmental/lobar infiltrates without bilateral symmetric diffuse patchy infiltrates as with other viral pathogens (eg, influenza [human, avian, swine], CMV, HPS, or SARS). Patients with legionnaires’ disease presenting with severe CAP, like patients with adenovirus, may be accompanied by various degrees of hypoxemia. Legionnaires’ disease should always be considered in the differential diagnosis of severe CAP. The likelihood of legionnaires’ disease in patients presenting as severe
CAP is enhanced with otherwise unexplained relative bradycardia, hypophosphatemia, increased AST/ALT levels, or highly increased ferritin levels.\textsuperscript{35,71–78}

In patients with severe CAP with these nonspecific laboratory features, clinicians should order specific tests to rule in or rule out legionnaires’ disease. Initial \textit{Legionella} sp titers (indirect fluorescent antibody [IFA]) are usually negative and serial determinations are usually needed to demonstrate an increase in \textit{Legionella} sp IFA titers. DFA techniques may be used if the patient has sputum; although they are not often positive, they are most likely to be positive early in the course of the illness. Sputum DFA positivity for \textit{Legionella} sp decreases rapidly with effective anti-\textit{Legionella} antimicrobial therapy. \textit{Legionella} antigen testing is also useful but may be negative early. \textit{Legionella} antigenuria becomes progressively positive over time and antigenuria continues for weeks after the infection. Legionella urinary antigen testing only detects \textit{Legionella pneumophila} serotypes 01–06.\textsuperscript{2,5,35}

In patients with nonsevere CAP when \textit{Legionella} is a reasonable diagnostic consideration, atypical pathogen coverage should be included in empiric antimicrobial therapy. Patients presenting with severe CAP and focal infiltrates with one or more of the extrapulmonary findings characteristic of legionnaires’ disease should be treated for legionnaires’ disease.\textsuperscript{35,75–78}

**THERAPY**

**Overview**

When legionnaires’ disease was recognized as an infectious disease after the Philadelphia outbreak in 1978, it was quickly appreciated that cell wall active antibiotics were ineffective against the causative organism of the disease. Subsequently, it was realized that legionnaires’ disease was caused by an intracellular pathogen in alveolar macrophages. The organism responsible for legionnaires’ disease was found to be susceptible in vivo to macrolides and tetracyclines.\textsuperscript{1,2,9,35,79–82}

**Macrolides**

In the years following the Philadelphia outbreak, sporadic cases of legionnaires’ disease were treated with variable effectiveness with macrolides. However, tetracycline was more consistently effective against \textit{Legionella} sp than macrolides. Tetracycline for treatment of legionnaires’ disease has been gradually replaced by doxycycline. There have been reports of erythromycin failures in legionnaires’ disease. Although erythromycin, like other macrolides, concentrates to suprasealer concentrations in alveolar macrophages, treatment failures are not infrequent, even with parenteral erythromycin.\textsuperscript{35,81–85}

**Doxycycline**

Prior to the quinolones, doxycycline was the mainstay of anti-\textit{Legionella} therapy and remains highly effective against \textit{Legionella pneumophila} as well as other \textit{Legionella} species causing legionnaires’ disease. Rifampin has in vitro activity against \textit{Legionella} sp and has been used in combination with tetracycline with no demonstrable clinical advantage compared to doxycycline monotherapy. When doxycycline is used for any serious systemic infection (eg, legionnaires’ disease), optimally it should be administered using a loading regimen (not a loading dose). Because doxycycline is highly lipid soluble and has a long half-life (t\textsubscript{1/2} = 21–24 hours), it takes 4 to 5 days with IV/PO dosing to achieve steady state concentrations. Therefore, doxycycline therapy should be instituted using a 200 mg (IV/PO) dose every 12 hours for 72 hours, followed by 100 mg (IV/PO) every 12 hours for the remainder of therapy. Using a loading regimen
provides rapid therapeutic concentrations of doxycycline in serum and lung. Like the fluoroquinolones, doxycycline has excellent bioavailability and may be administered with equal efficacy IV or PO.35,86–88

**Tigecycline**
Tigecycline is active against typical CAP pathogens and legionnaires’ disease. Tigecycline concentrates well in lung tissue and alveolar macrophages and is useful for treating legionnaires’ disease in patients intolerant to fluoroquinolone.35,89,90

**Rifampin**
Although rifampin concentrates in alveolar macrophages, it should not be used as monotherapy. Combination therapy with rifampin plus erythromycin or doxycycline is no more effective than erythromycin or doxycycline monotherapy. There are few studies on the effectiveness of erythromycin plus rifampin to base any potential benefit of rifampin compared to the activity of erythromycin or erythromycin/rifampin combination therapy.35,91,92

**Quinolones**
After doxycycline, the next most important therapeutic advance in the therapy of legionnaires’ disease was the introduction of the fluoroquinolones. All quinolones are highly active in vitro and in vivo against all *Legionella* species. Although doxycycline is highly active against the common typical CAP pathogens (ie, *S pneumoniae*, *H influenzae*, and *M catarrhalis*), the “respiratory quinolones” have even higher activity against these pathogens. Doxycycline is highly active against penicillin-resistant *S pneumoniae* and most strains of multidrug-resistant (MDR) *S pneumoniae*, but “respiratory quinolones” are preferred for MDR *S pneumoniae*. Like doxycycline, quinolones are effective against typical and atypical CAP pathogens (eg, *Legionella* sp). “Respiratory quinolones,” like macrolides and doxycycline, penetrate well into alveolar macrophages and concentrate intracellularly to supraserum concentrations. “Respiratory quinolones” provide optimal monotherapy for CAP caused by either typical or atypical pathogens. In patients who are quinolone intolerant doxycycline remains a highly effective agent for all *Legionella* species that cause legionnaires’ disease. “Respiratory quinolones” have excellent bioavailability (ie, more than 90% absorption) and are ideal for PO or IV to PO switch therapy for CAP. Because of their excellent absorption, even in seriously ill patients, “respiratory quinolones” may be used to treat legionnaires’ disease entirely by the oral route.35,70,93–97

**Duration of Therapy**
The duration of therapy for legionnaires’ disease initially was 2 to 4 weeks. Relapse was common with erythromycin therapy, and for this reason the duration of therapy was extended to prevent relapse. Currently, the duration of therapy with doxycycline or respiratory quinolones is usually 2 weeks. Normal hosts with good cardiopulmonary function and mild to moderate legionnaires’ disease may be treated with shorter courses of therapy but those with severe disease, impaired CMI, or severely limited cardiopulmonary function may require longer courses of therapy. With properly dosed anti-*Legionella* therapy with doxycycline or respiratory quinolones, relapses are rare.35,95–97

**COMPLICATIONS AND PROGNOSIS**
Because legionnaires’ disease occurs primarily in older individuals, the prognosis in patients depends largely on the host’s underlying cardiopulmonary function and
disorders that impair CMI (T-lymphocyte function). Prognosis with *Legionella* CAP is also directly related to inoculum size, and early administration of effective anti-*Legionella* antibiotic therapy. Legionnaires’ disease may be fatal in compromised hosts with impaired T-cell function and in those on immunosuppressive therapy, particularly monoclonal antibody or anti-tumor necrosis factor agents. If cardiopulmonary function is good, early treatment of *Legionella* CAP, even in compromised hosts, has a good prognosis.\textsuperscript{14–16,35}

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