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

Burke A. Cunha, MD, MACP[a,b,*]

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 *Legionella*. The isolate was believed to be the causative agent of the respiratory infection because antibodies to *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 *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.

---

[a] Infectious Disease Division, Winthrop-University Hospital, 259 First Street, Mineola, Long Island, NY 11501, USA
[b] State University of New York School of Medicine, Stony Brook, NY, USA
* Infectious Disease Division, Winthrop-University Hospital, 259 First Street, Mineola, Long Island, NY 11501.

id.theclinics.com

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% CO_2.[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
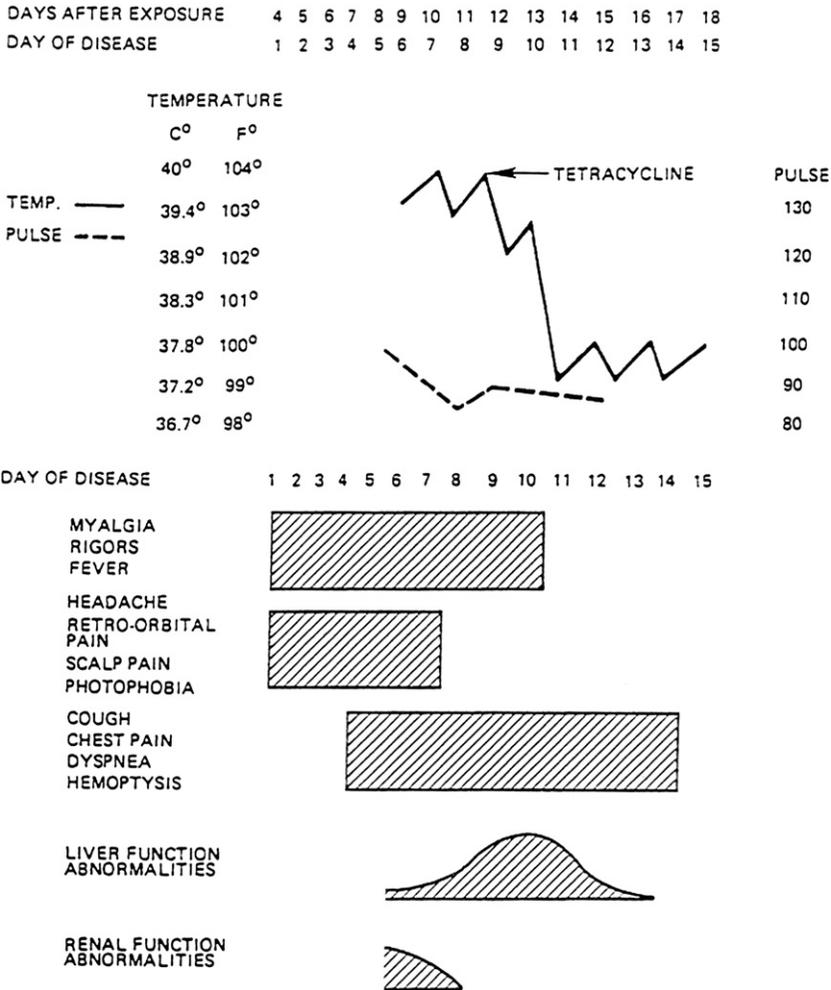
Fig. 1. Relative bradycardia, an early clinical clue, from an early case of Legionnaires' disease. (*Reprinted from* Lattimer GL, Ormsbee RA. Legionnaires' disease. New York: Marcel Dekker; 1981; with permission.)

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).[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.[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]).[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.[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.[17–19] There has been an unexplained increase in legionnaires' disease during the swine influenza (H1N1) pandemic.[20]

CLINICAL PRESENTATION
Overview

Legionella CAP and NP have the same clinical features.[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.[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.[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.[24–27] The radiographic and nonspecific laboratory findings that accompany legionnaires' disease overlap with typical and atypical pulmonary pathogens.[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*[a]	Legionnaires' Disease	*C pneumoniae*
Signs			
• Rash	±[b]	−	−
• Nonexudative pharyngitis	+	−	+
• Hemoptysis	−	±	−
• Wheezing	−	−	+
• Lobar consolidation	−	±	−
• Cardiac involvement	±[c]	−[d]	−
• 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 consolidation	"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	−	+[e]	−

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.

Table 2
Diagnostic features of the zoonotic atypical pneumonias

Key Characteristics	Psittacosis	Q fever	Tularemia
Symptoms			
Mental confusion	−	±	−
Prominent headache	+	+	+
Meningismus	−	−	−
Myalgias	+	+	+
Ear pain	−	−	−
Pleuritic pain	±	±	±
Abdominal pain	−	−	−
Diarrhea	−	−	−
Signs			
Rash	±[a]	−	−
Nonexudative pharyngitis	−	−	±
Hemoptysis	−	−	±
Lobar consolidation	+	+	+
Cardiac involvement	±[b]	±[c]	−
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 presents; −, usually absent; ↑, increased; ↓, decreased; ↑↑↑, markedly increased.
[a] Horder's spots (facial spots) resemble the abdominal rash of typhoid fever (Rose spots).
[b] Myocarditis.
[c] Endocarditis.
Adapted from Cunha BA, editor. Pneumonia essentials. 3rd edition. Sudbury (MA): Jones & Bartlett; 2010.

Table 3			
Clinical features of legionnaires' disease			
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[a]	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			
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.

[a] 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

Table 4
Differential diagnosis of relative bradycardia

Temperature-pulse Relationships

Temperature °F (°C)	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	Noninfectious
• Legionnaires' disease	• β-blockers
• Psittacosis	• Verapamil
• Q fever	• Diltiazem
• Typhoid fever	• Central nervous system disorders
• Typhus	• Lymphomas
• Babesiosis	• Factitious fever
• Malaria	• Drug fever
• Leptospirosis	
• Yellow fever	
• Dengue fever	
• Viral hemorrhagic fevers	
• Rocky Mountain spotted 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**).[35,49,50]

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.[32–35,51,52]

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.[33,35,49]

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
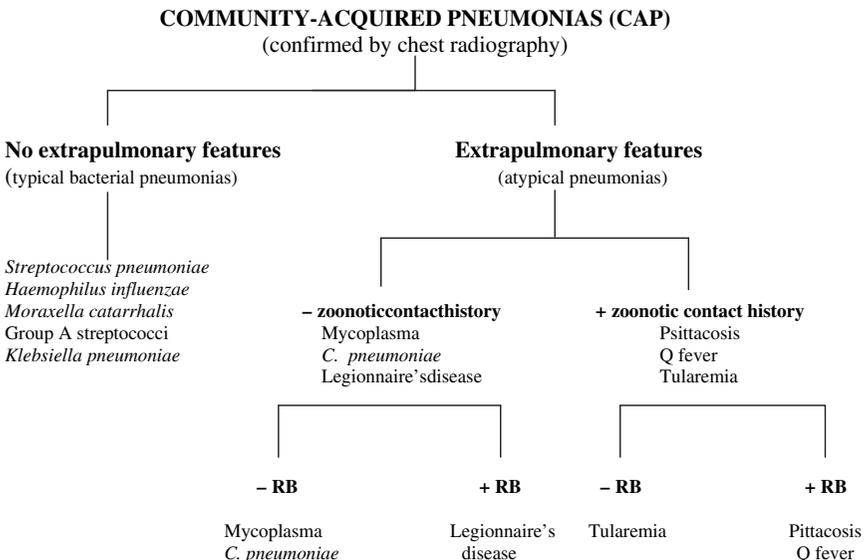

Fig. 2. Clinical approach to community-acquired pneumonias: the importance of the zoonotic contact history and relative bradycardia.

bradycardia should prompt the clinician to question the diagnosis. Relative brady-cardia 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.[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.[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 *M pneumoniae* or legionnaires' disease. The presence of abdominal pain with or without watery diarrhea limits differential diag-nostic possibilities to legionnaires' disease.[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 extrapul-monary manifestation of legionnaires' disease.[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 func-tion 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.[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 *M pneumoniae* is associated with skin manifestations (eg, erythema multiforme).[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 labo-ratory 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 micro-scopic hematuria.[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,

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 tuberculosis	• 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
	• Coronary bypass
	• Wegener granulomatosis
	• CHF
	• Acute pancreatitis
	• 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, 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 6
Differential diagnosis of hypophosphatemia

Infectious Causes	Noninfectious Causes
• Legionnaires' disease	• Alcoholism
• Malaria (acute)	• Diabetes mellitus
• Burkitt's lymphoma	• Primary hyperparathyroidism
	• Idiopathic hypercalciuria
	• Hypokalemia
	• Hypomagnesemia
	• Cushing's syndrome
	• Acute gout
	• Diabetes mellitus
	• RTA
	• Malabsorption
	• Hyperalimentation
	• Vitamin D deficiency
	• Malnutrition
	• Vomiting
	• Diarrhea
	• Alcoholism
	• Alkalosis (respiratory)
	• Acidosis
	• 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
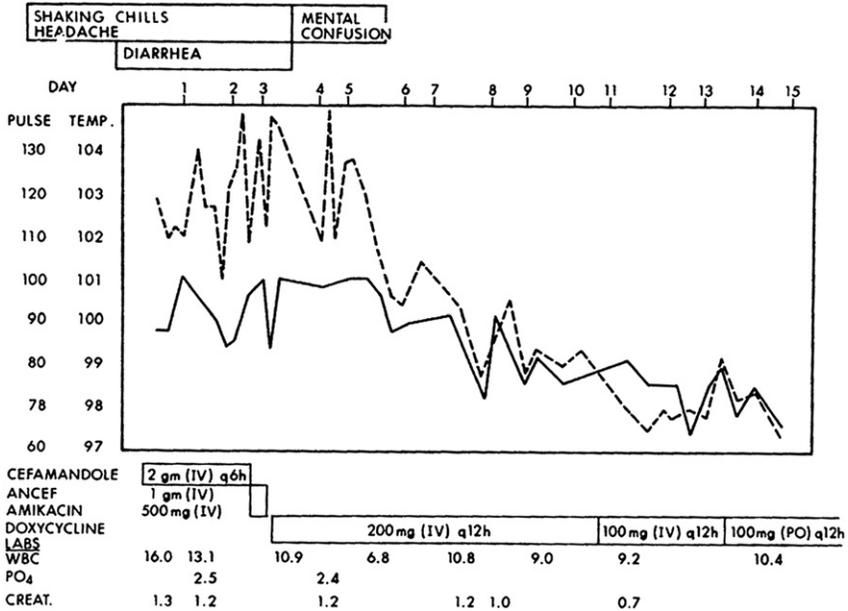
Fig. 3. Typical fever response (5–7 days) of legionnaires' disease to anti-*Legionella* antibiotic therapy with doxycycline (note lack of fever response to β-lactam therapy). (*Reprinted from* Cotton LM, Strampfer MJ, Cunha BA. Legionella and *Mycoplasma pneumonia*. A community hospital experience. Clin Chest Med 1987;8:441–53; with permission.)

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* or *C 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. Midly/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

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 • *M pneumoniae* • Adenovirus • Influenza Nonrespiratory pathogens • EBV • CMV • HCV • Malaria • Trypanosomiasis • Coxsackie viruses • Measles • Mumps • HIV	• SLE • Myeloma • Waldenström's macroglobulinemia • Lymphoma • CLL • Sinus histocytosis

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.

Table 8
Differential diagnosis of highly increased serum ferritin levels (>2× normal)

Infectious Causes	Noninfectious Causes
Acute	**Malignancies**
• Legionnaires' disease	• Preleukemias
• WNE	• Lymphomas
Chronic	• Multiple myeloma
• HIV	• Hepatomas
• CMV	• Breast cancer
• TB	• Colon cancer
	• Prostate cancer
	• Lung cancer
	• Liver/CNS metastases
	Myeloproliferative disorders
	Rheumatic/inflammatory disorders
	• Rheumatoid arthritis
	• Adult Still's disease
	• SLE
	• TA
	Renal disease
	• Acute renal failure
	• Chronic renal failure
	Liver disease
	• Hemochromatosis
	• Cirrhosis
	• α_1-antitrypsin deficiency
	• CAH
	• Cholestatic jaundice
	Miscellaneous
	• Sickle cell anemia
	• Multiple blood transfusions

Abbreviations: CAH, chronic acute hepatitis; CNS, central nervous system; SLE, systemic lupus erythematosus; TA, temporal arteritis; TB, active tuberculosis; WNE, West Nile encephalitis.

Adapted from Cunha CB. Differential diagnosis of infectious disease. In: Cunha BA, editor. Antibiotic essentials. 9th edition. Sudbury (MA): Jones & Bartlett; 2010.

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**).[35] Highly increased serum PCT levels may have prognostic significance in legionnaires' disease.[61]

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.[62–64] Such approaches do not work because critical parameters are not included (ie, hypophosphatemia, or relative bradycardia).[62–64] 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

Table 9
Differential diagnosis of increased PCT levels

Infectious Disorders	Noninfectious Disorders

• Bacterial pneumonias
  CAP
  NHAP
  NP
• Legionnaires' disease
• Bacteremias (gram-negative > gram-positive)
• TB
• Bacterial meningitis
• Fungal pneumonias
• Viral hepatitis
• Toxoplasmosis
• Osteomyelitis
• SBE
• Malaria (*Plasmodium falciparum*)
	• Renal insufficiency
	• Alcoholic hepatitis
	• Lung cancer (small cell)
	• Thyroid cancer
	• Surgery
	• Trauma
	• Burns
	• Cardiogenic shock
	• Goodpasture syndrome shock
	• GVHD
	• Hypotension
	• Hemorrhagic/necrotic pancreatitis
	• Normal variant (elderly)
	• 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
• Hemoptysis[a]	Mild/moderate	−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.

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 • New infiltrate on chest radiograph[a] • Negative recent/close zoonotic vector contact history	Fever >102°F with relative bradycardia[a]	• Hypophosphatemia[a] • Highly increased serum ferritin levels[a] (>2 × n) • Mildly/transiently increased serum transaminases[a] • Relative lymphopenia[a]

[a] 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.

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 possibility 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*
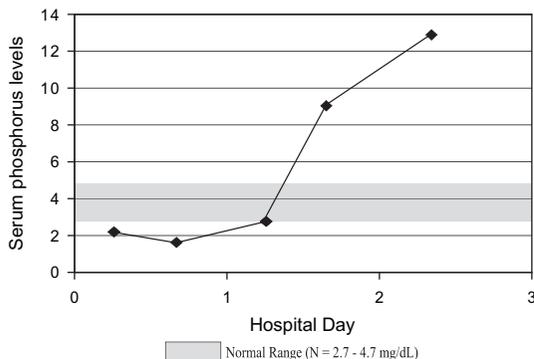

Fig. 4. Typical time course of early transient hypophosphatemia with legionnaires' disease. *From* Cunha BA. Hypophosphatemia: diagnostic significance in legionnaires' disease. Am J Med 2006;119:5–6.
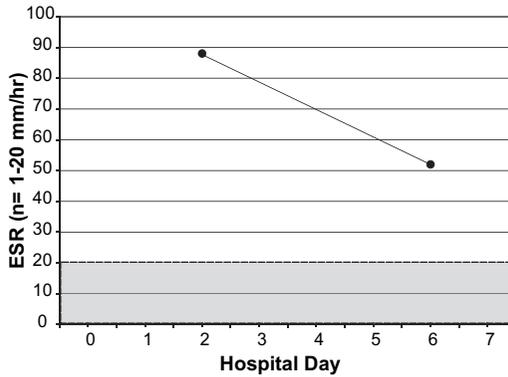
Fig. 5. Serial ESRs in a patient with *Legionella* CAP. (*From* Cunha BA, Mickail N, Syed U, et al. The rapid clinical diagnosis of Legionnaires' disease during the "herald wave" of the swine influenza (H1N1) pandemic: the Legionnaires' disease triad. Heart Lung 2010;39; in press; with permission.)

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
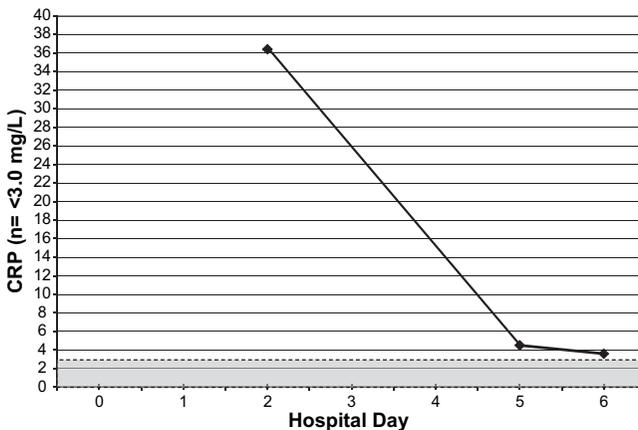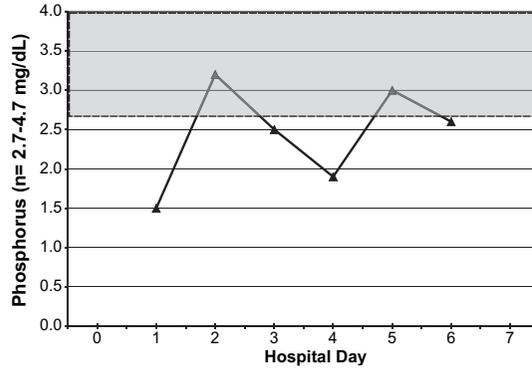

Fig. 6. Serial CRP levels in a patient with *Legionella* CAP. (*From* Cunha BA, Mickail N, Syed U, et al. The rapid clinical diagnosis of Legionnaires' disease during the "herald wave" of the swine influenza (H1N1) pandemic: the Legionnaires' disease triad. Heart Lung 2010;39; in press; with permission.)

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.)

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,
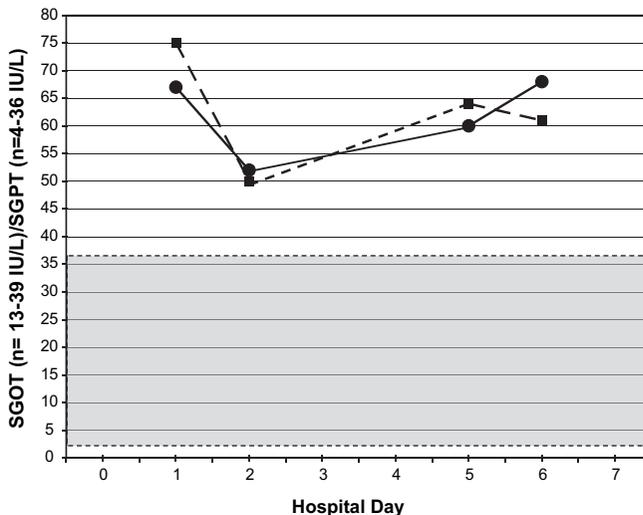

Fig. 8. Serial serum transaminase levels in a patient with *Legionella* CAP. (*From* Cunha BA, Mickail N, Syed U, et al. The rapid clinical diagnosis of Legionnaires' disease during the "herald wave" of the swine influenza (H1N1) pandemic: the Legionnaires' disease triad. Heart Lung 2010;39; in press; with permission.)
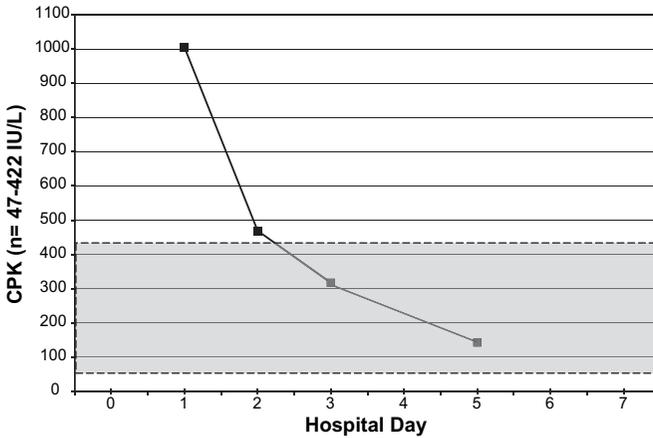
Fig. 9. Serial CPK levels in a patient with *Legionella* CAP. (*From* Cunha BA, Mickail N, Syed U, et al. The rapid clinical diagnosis of Legionnaires' disease during the "herald wave" of the swine influenza (H1N1) pandemic: the Legionnaires' disease triad. Heart Lung 2010;39; in press; with permission.)

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
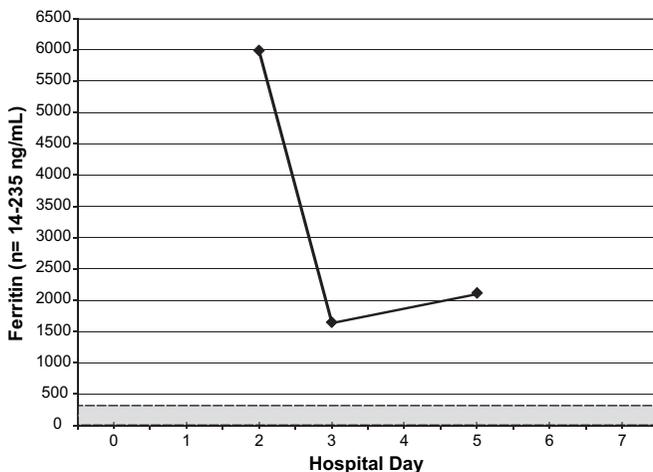

Fig. 10. Serial ferritin levels in a patient with *Legionella* CAP. (*From* Cunha BA, Mickail N, Syed U, et al. The rapid clinical diagnosis of Legionnaires' disease during the "herald wave" of the swine influenza (H1N1) pandemic: the Legionnaires' disease triad. Heart Lung 2010;39; in press; with permission.)

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 × 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.[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 *Legionella* sp titers (indirect fluorescent antibody [IFA]) are usually negative and serial determinations are usually needed to demonstrate an increase in *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 *Legionella* sp decreases rapidly with effective anti-*Legionella* antimicrobial therapy. *Legionella* antigen testing is also useful but may be negative early. *Legionella* antigenuria becomes progressively positive over time and antigenuria continues for weeks after the infection. Legionella urinary antigen testing only detects *Legionella pneumophila* serotypes 01–06.[2,5,35]

In patients with nonsevere CAP when *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.[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.[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 *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 supraserum concentrations in alveolar macrophages, treatment failures are not infrequent, even with parenteral erythromycin.[35,81–85]

Doxycycline

Prior to the quinolones, doxycycline was the mainstay of anti-*Legionella* therapy and remains highly effective against *Legionella pneumophila* as well as other *Legionella* species causing legionnaires' disease. Rifampin has in vitro activity against *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 ($t_{1/2}$ = 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.[14–16,35]

REFERENCES

1. Lattimer GL, Ormsbee RA. Legionnaires' disease. New York: Marcel Dekker, Inc; 1981.
2. Edelstein PH. *Legionella*. In: Murray PR, editor. Manual of clinical microbiology. 9th edition. Washington, DC: ASM Press; 2007. p. 835–49.
3. Forbes BA, Sahm DF, Weissfeld AS. *Legionella*. Bailey & Scott's diagnostic microbiology. 12th edition. St. Louis (MO): Mosby Elsevier; 2007. p. 424–8.
4. Edelstein PH. State of the art lecture. Laboratory diagnosis of legionnaire's disease. In: Thornsberry C, Balows A, Feeley JC, et al, editors. *Legionella*: proceedings of the 2nd international symposium. Washington, DC: ASM Press; 1984. p. 3–5.
5. Luck PC, Helbig JH, von Baum H, et al. Diagnostics and clinical disease treatment: usefulness of microbiological diagnostic methods for detection of *Legionella* infections. In: Cianciotto NP, Kwaik YA, Edelstein PH, et al, editors. *Legionella:* state of the art 30 years after its recognition. Washington, DC: ASM Press; 2006. p. 15–21.
6. Mykietiuk A, Carratal J, Fernandex-Sabe N, et al. Clinical outcomes for hospitalized patients with *Legionella* pneumonia in the antigenuria era: the influence of levofloxacin therapy. Clin Infect Dis 2005;15(40):794–9.
7. Marlow E, Whelan C. *Legionella* pneumonia and use of the *Legionella* urinary antigen test. J Hosp Med 2009;4(3):E1–2.
8. Olsen CW, Elverdal P, Jørgensen CS, et al. Comparison of the sensitivity of the *Legionella* urinary antigen EIA kits from Binax and Biotest with urine from patients with infections caused by less common serogroups and subgroups of *Legionella*. Eur J Clin Microbiol Infect Dis 2009;287:817–20.
9. Baltch AL, Bopp LH, Smith RP, et al. Antibacterial activities of gemifloxacin, levofloxacin, gatifloxacin, moxifloxacin and erythromycin against intracellular *Legionella pneumophila* and *Legionella micdadei* in human monocytes. J Antimicrob Chemother 2005;56:104–9.
10. Pedro-Botet L, Yu VL. *Legionella*: macrolides or quinolones? Clin Microbiol Infect 2006;12:25–30.
11. Hendrickson SE, Neil M. *Legionella* pneumonia and HIV infection: a case report. AIDS Read 2004;14:267–70.
12. Pedro-Botet ML, Sopena N, Garcia-Cruz A, et al. Community acquired pneumonia in human immunodeficiency virus-infected patients: comparative study of *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1. In: Cianciotto NP, Kwaik YA, Edelstein PH, et al, editors. *Legionella*: state of the art 30 years after its recognition. Washington, DC: ASM Press; 2006. p. 30–2.
13. Hamid NS, Mohan SS, Cunha BA. Fatal disseminated *Legionella* pneumonia in a neonate with severe combined immunodeficiency (SCID). Infect Dis Clin Pract 2006;14:116–8.

14. Albert C, Vandenbos F, Brocq O, et al. Legionellosis in patient treated with inflix-imab. Rev Med Interne 2004;25:167–8.

15. Wondergem MJ, Voskuyl AE, van Agtmael MA. A case of legionellosis during treatment with a TNF-alpha antagonist. Scand J Infect Dis 2004;36: 310–1.

16. Li Gobbi F, Benucci M, Del Rosso A. Pneumonitis caused by *Legionella pneumoniae* in a patient with rheumatoid arthritis treated with anti-TNF alpha therapy (infliximab). J Clin Rheumatol 2005;11:119–20.

17. Dubrou S, Guillotin L, Cabon S. Cooling towers and legionellosis: a large urban area experience. In: Marre R, Kwaik YA, Bartlett C, et al, editors. *Legionella*. Washington, DC: ASM Press; 2002. p. 291–4.

18. Nguyen TM, Ilef D, Harraud S, et al. A community-wide outbreak of legionnaires' disease linked to industrial cooling towers – how far can contaminated aerosols spread? J Infect Dis 2006;193:102.

19. Levy PY, Teysseire N, Etienne J, et al. A nosocomial outbreak of *Legionella pneumophila* caused by contaminated transesophageal echocardiography probes. Infect Control Hosp Epidemiol 2004;24:619–22.

20. Cunha BA, Mickail N, Syed U. Unexplained increase in legionnaires' disease during the "Herald Wave" of the swine influenza (H1N1) pandemic. Hosp Epidemiol Infect Control 2010;31, in press.

21. Forgie S, Marrie TJ. Healthcare-associated atypical pneumonia. Semin Respir Crit Care Med 2009;30:67–85.

22. Beaty HN. State of the art lecture. Clinical features of legionellosis. In: Thornsberry C, Balows A, Feeley JC, et al, editors. Legionella: proceedings of the 2nd international symposium. Washington, DC: ASM Press; 1984. p. 6–10.

23. Diederen BMW. *Legionella* spp. and Legionnaires' disease. J Infect 2008;56: 1–12.

24. Phares CR, Russell E, Thigpen MC, et al. Legionnaires' disease among residents of a long-term care facility: the sentinel event in a community outbreak. Am J Infect Control 2007;5:319–23.

25. Carbonara S, Monno L, Longo B, et al. Legionella is often overlooked as a cause of NHAP outbreaks. Curr Opin Pulm Med 2009;15:261–73.

26. Nakashima K, Tanaka T, Kramer MH, et al. Outbreak of *Chlamydia pneumoniae* infection in a Japanese nursing home, 1999–2000. Infect Control Hosp Epidemiol 2006;27:1171–7.

27. Roig J, Aguilar X, Ruiz Z, et al. Comparative study of *Legionella pneumophila* and other nosocomial-acquired pneumonias. Chest 1991;99:344–50.

28. Cunha BA, Quintiliani R. The atypical pneumonias, a diagnostic and therapeutic approach. Postgrad Med 1979;66:95–102.

29. Cunha BA, Ortega AM. Atypical pneumonia. Extrapulmonary clues guide the way to diagnosis. Postgrad Med 1996;99:123–8.

30. Cunha BA. The extrapulmonary manifestations of community-acquired pneumonias. Chest 1998;112:945.

31. Cotton LM, Strampfer MJ, Cunha BA. *Legionella* and *Mycoplasma pneumonia*: community hospital experience. Clin Chest Med 1987;8:441–53.

32. Cunha BA. The atypical pneumonias: clinical diagnosis and importance. Clin Microbiol Infect 2006;12:12–24.

33. Cunha BA. Atypical pneumonias: current clinical concepts focusing on Legionnaires' disease. Curr Opin Pulm Med 2008;14:183–94.

34. Cunha BA. Clinical diagnosis of Legionnaires' disease. Semin Respir Infect 1998; 13:116–27.

35. Cunha BA, editor. Pneumonia essentials. 3rd edition. Sudbury (MA): Jones & Bartlett; 2010.
36. Edelstein PH. Legionnaires' disease. Clin Infect Dis 1993;16:741–9.
37. Sugihara E, Dambara T, Aiba M, et al. Clinical characteristics of 8 sporadic cases of community-acquired Legionella pneumonia in advanced age. Intern Med 2007;46:461–5.
38. Pedro-Botet ML, Mateu L, Sopena N, et al. Hospital and community acquired Legionella pneumonia: two faces of the same disease. In: Cianciotto NP, Kwaik YA, Edelstein PH, et al, editors. *Legionella:* state of the art 30 years after its recognition. Washington, DC: ASM Press; 2006. p. 22–4.
39. Macfarlane JT, Miller AC, Morris AH, et al. Comparative radiologic features of Legionnaires' disease and other sporadic community-acquired pneumonias. In: Thornsberry C, Balows A, Feeley JC, et al, editors. *Legionella*: proceedings of the 2nd international symposium. Washington, DC: ASM Press; 1984. p. 12.
40. Coletta FS, Fein AM. Radiological manifestation of *Legionella/Legionella*-like organisms. Semin Respir Infect 1998;13:109–15.
41. Boermsa WG, Daniels JM, Lowernberg A, et al. Reliability of radiographic findings and the relation to etiologic agents in community-acquired pneumonia. Respir Med 2006;100:926–32.
42. Nambu A, Saito A, Araki T, et al. *Chlamydia pneumoniae*: comparison with findings of *Mycoplasma pneumoniae* and *Streptococcus pneumoniae* at thin-section CT. Radiology 2006;238:330–8.
43. Sakai F, Tokuda H, Goto H. Computed tomographic features of *Legionella pneumophilia* pneumonia in 38 cases. J Comput Assist Tomogr 2007;31:125–31.
44. Lee I, Kim TS, Yoon HK. *Mycoplasma pneumoniae* pneumonia: CT features in 16 patients. Eur Radiol 2006;16:719–25.
45. Okada F, Ando Y, Wakisaka M, et al. *Chlamydia pneumoniae* pneumonia and *Mycoplasma pneumoniae* pneumonia: comparison of clinical findings and CT findings. J Comput Assist Tomogr 2005;29:626–32.
46. Cunha BA, Pherez FM. Bilateral spontaneous pneumothoraces at the presenting finding in legionnaires' disease. Heart Lung 2008;37:238–41.
47. Sopena N, Sabria-Leal M, Pedro-Botet, et al. Comparative study of the clinical presentation of Legionella pneumonia and other community-acquired pneumonias. Chest 1998;113:1195–200.
48. Schneeberger PM, Dorigo-Zetsma JW, van der Zee A, et al. Diagnosis of atypical pathogens in patients hospitalized with community-acquired respiratory infection. Scand J Infect Dis 2004;36:269–73.
49. Strampfer MJ, Cunha BA. Legionnaires' disease. Semin Respir Infect 1987;2:228–34.
50. Cunha BA. Diagnostic significance of relative bradycardia. Clin Microbiol Infect 2000;6:633–4.
51. Sotgiu S, Pugliatti M, Rosati G, et al. Neurological disorders associated with *Mycoplasma pneumoniae* infection. Eur J Neurol 2003;10:165–8.
52. von Baum H, Welte T, Marre R, et al. *Mycoplasma pneumoniae* pneumonia revisited within the German Competence Network for Community-acquired pneumonia (CAPNETZ). BMC Infect Dis 2009;9:62.
53. Marrie TJ. Q fever pneumonia. Curr Opin Infect Dis 2004;17:137–42.
54. Cutler SJ, Bouzid M, Cutler RR. Q fever. J Infect 2007;54:313–8.
55. Parker NR, Barralet JH, Bell AM. Q fever. Lancet 2006;367:679–88.
56. Gregory DW, Schaffner W. Psittacosis. Semin Respir Infect 1997;12:7–11.
57. Cunha BA. Hypophosphatemia: diagnostic significance in legionnaires' disease. Am J Med 2006;119:5–6.

58. Cunha BA. Elevated serum transaminases in patients with *Mycoplasma pneumoniae* pneumonia. Clin Microbiol Infect 2005;11:1051–2.
59. Cunha BA, Nausheen S, Busch L. Severe Q fever mimicking Legionella community acquired pneumonia (CAP): the diagnostic importance of cold agglutinins, anti-smooth muscle antibodies, and thrombocytosis. Heart Lung 2009;38:354–62.
60. Cunha BA. Serum ferritin levels in *Legionella* community-acquired pneumonia. Clin Infect Dis 2008;46:1789–91.
61. Franzin L, Cabodi D. *Legionella* pneumonia and serum procalcitonin. Curr Microbiol 2005;50:43–6.
62. Miyashita N, Fukano H, Yoshid K, et al. Is it possible to distinguish between atypical pneumonia and bacterial pneumonia? Evaluation of the guidelines for community acquired pneumonia in Japan. Respir Med 2004;98:952–60.
63. Fiumefreddo R, Zaborsky R, Haeuptle J, et al. Clinical predictors for Legionella in patients presenting with community-acquired pneumonia to the emergency department. BMC Pulm Med 2009;9:4–7.
64. Masiá M, Gutiérrez F, Padilla S, et al. Clinical characterisation of pneumonia caused by atypical pathogens combining classic and novel predictors. Clin Microbiol Infect 2007;13:153–61.
65. Cunha BA. The clinical diagnosis of legionnaires' disease: diagnostic value of combining non-specific laboratory tests. Infection 2008;6:395–7.
66. Cunha BA. Severe legionella pneumonia: rapid diagnosis with Winthrop-University-Hospital's weighted point score system (modified). Heart Lung 2008;37:312–21.
67. 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.
68. Cunha BA, Pherez FM. *Mycoplasma pneumoniae* community acquired pneumonia (CAP) in the elderly: the diagnostic importance of acute thrombocytosis. Heart Lung 2009;38:444–9.
69. Cunha BA. Ambulatory community-acquired pneumonia: the predominance of atypical pathogens. Eur J Clin Microbiol Infect Dis 2003;2:579–83.
70. Cunha BA. Severe adenovirus community-acquired pneumonia mimicking Legionella. Eur J Clin Microbiol Infect Dis 2009;28:313–5.
71. Cunha BA, Klein NC, Strollo S, et al. Legionnaire's disease mimicking swine influenza (H1N1). Heart & Lung 2010;39, in press.
72. Lewis PF, Schmidt MA, Lu X, et al. A community-based outbreak of severe respiratory illness caused by human adenovirus serotype 14. J Infect Dis 2009;199:1427–34.
73. Cunha BA. Severe community acquired pneumonia. Crit Care Clin 1998;8:105–17.
74. Cunha BA, Gouzhva O, Nausheen S. Severe cytomegalovirus (CMV) community acquired pneumonia (CAP) precipitating a systemic lupus erythematosis (SLE) flare. Heart Lung 2009;38:249–52.
75. Sanford JP. Tularemia. JAMA 1983;250:3225–6.
76. Teutsch SM, Martone WJ, Brink EW, et al. Pneumonic tularemia on Martha's vineyard. N Engl J Med 1979;301:826–8.
77. Murdoch DR, Chambers ST. Atypical pneumonia–time to breathe new life into a useful term? Lancet Infect Dis 2009;9:512–9.
78. Cunha BA. Severe community acquired pneumonia in the CCU. In: Cunha BA, editor. Infectious diseases in critical care medicine. 3rd edition. New York: Informa Healthcare; 2010. p. 164–77.

79. Birteksoz AS, Zeybek Z, Cotuk A. In vitro activities of various antibiotics against *Legionella pneumophila*. In: Cianciotto NP, Kwaik YA, Edelstein PH, et al, editors. *Legionella*: state of the art 30 years after its recognition. Washington, DC: ASM Press; 2006. p. 43–6.

80. Cunha BA. Antibiotic pharmacokinetic considerations in pulmonary infections. Semin Respir Infect 1991;6:168–82.

81. Smith RP, Baltch AL, Franke M, et al. Effect of levofloxacin, erythromycin or rifampin pretreatment on growth of *Legionella pneumophila* in human monocytes. Antimicrob Agents Chemother 1997;40:673–8.

82. Baltch AL, Smith RP, Franke MA, et al. Antibacterial effects of levofloxacin, erythromycin, and rifampin in a human monocyte system against *Legionella pneumophila*. Antimicrob Agents Chemother 1998;42:3153–6.

83. Rudin JE, Evans TL, Wing EJ. Failure of erythromycin in treatment of *Legionella micdadei* pneumonia. Am J Med 1984;76:318–20.

84. Parker MM, Macher AM, Shelhamer JH, et al. Unresponsiveness of *Legionella bozemanii* pneumonia to erythromcyin administration despite in vitro sensitivity. Am Rev Respir Dis 1983;182:955–6.

85. Sabria M, Pedro-Botet ML, Gomez J, et al. Fluoroquinolones vs macrolides in the treatment of Legionnaires' disease. Chest 2005;128:1401–5.

86. Cunha BA, Sibley CM, Ristuccia AM. Doxycycline. Ther Drug Monit 1982;4:115–35.

87. Cunha BA. Doxycycline re-revisited. Arch Intern Med 1999;159:1006–7.

88. Cunha BA. Doxycycline for community acquired pneumonia. Clin Infect Dis 2003;37:870.

89. Dartois N, Castaing N, Gandjini H, et al. Tigecycline versus levofloxacin for the treatment of community-acquired pneumonia: European experience. J Chemother 2008;20:28–35.

90. Tanaseanu C, Milutinovic S, Calistru PI, et al. Efficacy and safety of tigecycline versus levofloxacin for community-acquired pneumonia. BMC Pulm Med 2009;9:44.

91. Mercatello A, Frappaz D, Robert D, et al. Failure of erythromycin/rifampicin treatment of Legionella pneumonia. J Infect 1985;10:282–3.

92. Amsden GW. Treatment of Legionnaires' disease. Drugs 2005;65:605–14.

93. Cunha BA. Fluoroquinolones in the treatment of Legionnaires' disease. Penetration 2000;3:32–9.

94. Ludlam HA, Enoch DA. Doxycycline or moxifloxacin for the management of community-acquired pneumonia in the UK? Int J Antimicrob Agents 2008;32:101–5.

95. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;1(44 Suppl 2):S27–72.

96. Cunha BA. Empiric antibiotic therapy for community-acquired pneumonia: guidelines for the perplexed? Chest 2004;125:1913–21.

97. Pedreo Botet ML, Yu VL. Treatment strategies for *Legionella* infection. Expert Opin Pharmacother 2009;10:1109–21.