

Legionellosis

Clinical Picture & Treatment

Jantjie Taljaard
Division of Infectious Diseases
Department of Medicine – Tygerberg Academic Hospital
CID – University of Stellenbosch

Legionellosis refers to two clinical syndromes:

- Legionnaires' disease:
 - More common
 - Syndrome of pneumonia

- Pontiac fever:
 - Less common
 - An acute, febrile, self-limited illness

Legionnaires' disease

- Initial clinical descriptions:
 - Toxic patients with high fever and gastrointestinal symptoms accompanying pneumonia.
- Currently:
 - Diagnostic tests more widely available.
 - Clinical presentation more varied and nonspecific.

Symptoms

Incubation period 2 - 18 days

- Respiratory symptoms initially not prominent;
 - cough at first is mild and only slightly productive.
 - sputum may be blood-streaked, but gross hemoptysis is rare.
 - chest pain can occur in some patients
- Gastrointestinal symptoms often prominent:
 - diarrhea, nausea, vomiting, and abdominal pain.
- Patients are commonly lethargic with headache and occasionally stupor.

Physical examination

Non specific

- Fever
 - virtually always present
- Bradycardia relative to temperature elevation
- Auscultation
 - Crackles with subsequent signs of consolidation.
- Miscellaneous findings include:
 - DIC, glomerulitis, rhabdomyolysis, various rashes, and neuropathies;
 - nonspecific findings that may be related to the severity of infection, underlying disease, or perhaps side effects of drug therapies.

Frequency of the symptoms of Legionnaires' disease

Cough	41 – 92%
Chills	42 – 77%
Fever	
>38.8°C	88 – 90%
40°C	20 – 62%
Dyspnea	25 – 62%
Headache	40 – 48%
Myalgia/arthralgia	20 – 40%
Diarrhea	21 – 50%
Nausea/vomiting	8 – 49%
Neurologic abnormalities	4 – 53%
Chest pain	13 – 35%

Laboratory findings

- Laboratory abnormalities are common, but also nonspecific:
 - Renal and hepatic dysfunction
 - Thrombocytopenia and leukocytosis
 - Hypophosphatemia
 - Hyponatremia (serum sodium <130 mmol/L)
 - Hematuria and proteinuria are common.
 - High serum ferritin levels (>2 x the normal value)

Chest radiograph

- Almost all patients have radiographic abnormalities by day 3
- While abnormal, there is no characteristic CXR finding.
 - A patchy unilobar infiltrate that progresses to consolidation (most common)
 - But all types of infiltrates have been reported including diffuse, interstitial infiltrates.
 - Pleural effusions are commonplace.
- In the immunosuppressed patient
 - Initial densities may appear as rounded opacities, often pleural based
 - Nodular infiltrates may progress to cavitation
- CXR abnormalities often progress while receiving therapy
 - Radiographic improvement lags several days behind clinical response
 - Complete resolution over one to many months.

Clinical clues for the diagnosis

- Clinical clues in a patient with pneumonia that may increase the index of suspicion for Legionnaires' disease:
 1. Presence of gastrointestinal symptoms, especially diarrhea
 2. Neurologic findings, especially confusion
 3. Fever $>39^{\circ}\text{C}$, relative bradycardia
 4. The Gram stain of respiratory secretions shows many neutrophils, but few, if any, microorganisms
 5. Hyponatremia and hypophosphatemia
 6. Hepatic dysfunction
 7. Hematuria
 8. Failure to respond to beta-lactam and/or aminoglycoside antibiotics
 9. Patients at risk for Legionella infection: smokers, chronic lung disease, immunosuppressed

Pontiac fever

- Symptoms include fever, malaise, chills, fatigue and headache, without any respiratory complaints.
- Chest radiograph is unrevealing.
- The mean incubation period is 36 hours
- The illness is usually self-limited and typically does not require treatment.
- Why Pontiac fever has a shorter incubation period and less severe manifestations than Legionnaires' disease is not understood.

Extrapulmonary disease

- Extremely rare
 - Bacteremia leads to dissemination of the organism to other sites.
 - Most common extrapulmonary site is the heart:
 - Numerous reports of myocarditis, pericarditis, and even prosthetic valve endocarditis.
 - Surgical site infections have occurred after contamination of the wound by water.
 - Immunosuppressed patients
 - Cellulitis, sinusitis, septic arthritis, perirectal abscess, pancreatitis, peritonitis, and pyelonephritis

Treatment & Prognosis

- Mortality
 - 16 – 30% if untreated or Rx with inactive antibiotics
 - Can approach 50% given the underlying illness
- Reduced to 10%
 - improved diagnostic methods leading to earlier diagnosis and more potent therapies

Management

- Legionnaires' disease is not transmitted from person-to-person; thus, isolation for hospitalised patients is unnecessary.

SUSCEPTIBILITY TESTING

- In vitro susceptibility results are not readily interpretable:
 - Methods not standardised.
 - Conventional in vitro susceptibility methods in broth and agar have proven unreliable.
- The intracellular location of the pathogen is relevant to the efficacy of the antibiotic.
 - Effective antibiotics must achieve intracellular concentrations higher than the MIC.
 - Antibiotics with good intracellular penetration:
 - macrolides, quinolones, tetracyclines, and rifampicin.

SELECTION OF ANTIMICROBIAL AGENTS

- Comparative antibiotic trials have established that the newer macrolides (especially [azithromycin](#)) and the respiratory tract quinolones (especially [levofloxacin](#)) are effective.
- The newer macrolides and quinolones are superior to [erythromycin](#):
 - More potent intracellular activity
 - Superior penetration into lung tissue, alveolar macrophages, and WBC
 - Improved pharmacokinetic properties, allow once / twice daily dosing
 - Significantly reduced gastrointestinal toxicity
- Other drugs used successfully include [tetracycline](#), [doxycycline](#) and [tigecycline](#).

Quinolones versus macrolides

- There are no randomized, controlled trials comparing fluoroquinolones and macrolides.
- In 4 studies that included a total of nearly 600 patients, outcomes were similar.
- However, more rapid defervescence, fewer complications and/or shorter hospital stay seen with the quinolones.

Oral versus IVI

- IVI preferred
 - possibility of incomplete gastrointestinal absorption, given the prominent gastrointestinal manifestations in some patients.

Duration of therapy

- When an objective clinical response can be documented, treatment can be concluded with oral agents for a total of 10 - 14 days.
- The total duration of azithromycin administration can be shorter (7 - 10 days).
- A 21-day course is often recommended for immunosuppressed patients, especially if critically ill at onset of therapy.

Response to therapy

- Usually defervesce and symptomatic improvement within 3 - 5 days
 - if treated early with an active antibiotic.
- CXR not useful for monitoring response.

Prognosis

- Mortality of Legionnaires' disease is now $\leq 5\%$ in immunocompetent patients.
- The prognosis is dependent upon expeditious administration of appropriate antibiotics.
- Treatment failures do occur:
 - Immunosuppressive illness
 - Severe disease at the onset of therapy.

Longterm effects

- An uncontrolled study of 122 survivors of a community-acquired Legionnaires' disease,
- Impairment of health-related quality of life was found in most patients.
- At 17 months follow-up
 - fatigue (75%) and neurologic symptoms (66%) were the most common persisting symptoms.

Thank you

Dr Jantjie Taljaard
Division of Infectious Diseases
Tygerberg Academic Hospital
jjt@sun.ac.za

Empiric therapy for community-acquired pneumonia

- Clinical signs of pneumonia will precede definitive laboratory diagnosis of Legionella in most patients, necessitating empiric coverage for many microorganisms including Legionella.
- The broad spectrum of the newer macrolides and the respiratory tract quinolones usually provide coverage against the other common pathogens of CAP including both typical pathogens (eg, Streptococcus pneumoniae) and "atypical" pathogens (eg, Mycoplasma pneumoniae, Chlamydia pneumoniae).

Nosocomial pneumonia

- For nosocomial pneumonias and pneumonias acquired in an institution such as a nursing home in which Legionella is a potential pathogen, a quinolone, especially [levofloxacin](#) or [ciprofloxacin](#), may be the empiric drug of choice.
- The quinolones also provide coverage against the gram-negative bacilli, which are more common pathogens in these settings than in the community.

Transplant recipients

- In transplant recipients with Legionella infection, we recommend treatment with a quinolone, especially [ciprofloxacin](#) or [levofloxacin](#).
- The macrolides interact with the immunosuppressive agents [cyclosporine](#) and [tacrolimus](#) that are commonly used in transplantation

Endocarditis and extrapulmonary legionellosis

- For patients with endocarditis caused by Legionella, we recommend that combination therapy of a quinolone plus [azithromycin](#) be considered. The optimal duration of therapy is unknown, but we would administer at least three months of therapy if the infected valve is resected and three to six months if the valve is not resected.
- For patients with other forms of extrapulmonary disease (eg, skin and soft tissue infections, septic arthritis etc.), the source and portal of entry needs to be delineated. In general, we would recommend a newer macrolide or quinolone for 14 to 21 days.

HIV infection

- Legionnaires' disease is uncommon in AIDS patients, but when it occurs, extrapulmonary complications and mortality are relatively high.
- Cavitory pneumonia and persistent bacteremia have been observed.
- Relapse is also more common.
- Thus, we recommend continuing oral maintenance antibiotic therapy for several weeks until infiltrates resolve on chest radiography.

Pontiac fever

- This febrile, self-limited form of Legionella infection requires only symptomatic therapy, such as analgesics for headache.
- Antibiotics are not indicated.

Recommendations

- Suspected or proven Legionella pneumonia should be treated in most patients with [levofloxacin](#) or [azithromycin](#). Patients from long-term care facilities, those with nosocomial infection, or those who have received transplants should be treated with a fluoroquinolone to provide better coverage of other gram-negative bacilli and, in the case of transplant recipients, to avoid interactions between macrolides and immunosuppressive drugs.
- We recommend parenteral treatment initially for all patients with suspected Legionella pneumonia, given gastrointestinal dysfunction in some patients. A switch to oral therapy can be made after the patient defervesces.
- The total duration of therapy for Legionella pneumonia is 7 to 10 days for [azithromycin](#) and 10 to 14 days for other regimens. A longer course of 21 days might be considered for patients who are severely ill upon presentation or immunocompromised.
- Combination antibiotic therapy of a quinolone plus [azithromycin](#) might be considered for severely ill patients with extrapulmonary legionellosis. We also use [rifampin](#) as part of combination therapy with quinolones in selected patients, but drug interactions can be problematic.

Co-infection

- Co-infection with other pathogens responsible for community-acquired pneumonia has been a topical issue.
- However, most studies reporting co-infection have used serologic tests as the basis for diagnosis, and such tests may be nonspecific.
- On the other hand, one group described five patients with *Streptococcus pneumoniae* bacteremia who had co-infection with *Legionella* as defined by urine antigen or antibody seroconversion [[23](#)].

SPECIFIC LABORATORY DIAGNOSIS

- The prompt diagnosis of Legionnaires' disease can save lives. Early initiation of appropriate therapy is associated with improved outcome [[24,25](#)]. Because the clinical presentation of Legionnaires' disease is nonspecific, specialized diagnostic laboratory tests are the key feature for diagnosing Legionnaires' disease. Hospitals where Legionella diagnostic tests were available on-site were more likely to identify hospital-acquired Legionnaires' disease [[26](#)]. Among the species in the Legionellaceae family, *L. pneumophila* is responsible for 90 percent of infections [[27,28](#)].

Culture on selective media

- The single most important test for Legionnaires' disease is isolation of the organism by culture. When Legionnaires' disease is suspected, both a urinary antigen test and Legionella culture of a respiratory specimen should be ordered. The availability of the clinical isolate from culture can be critical for subsequent epidemiologic investigations [[29](#)].
- The standard media for Legionella isolation from contaminated clinical specimens is buffered charcoal yeast extract agar (BCYE) supplemented with polymyxin, anisomycin, [vancomycin](#), and dyes ([figure 1](#)); the antimicrobial agents prevent the overgrowth of Legionella by competing organisms, while the dyes impart a distinctive color to the Legionella organisms [[28](#)]. The presence of the dyes makes identification of *L. micdadei* and *L. maceachernii* easier. Their colonies will appear blue due to uptake of the dye bromothymol blue, whereas *L. pneumophila* will appear apple-green [[30](#)]. Maximal sensitivity is achieved by the simultaneous use of three media: BCYE; BCYE with polymyxin, anisomycin, and cefamandole (PAC); BCYE with polymyxin, anisomycin, vancomycin and dyes (PAV). All three media (BCYE, PAV, and PAC) are commercially available.

Urinary antigen testing

- Among reported cases of Legionnaires' disease, there has been a significant increase in the proportion diagnosed by the urinary antigen test [31]. In many hospitals, cases of Legionnaires' disease due to *L. pneumophila*, serogroup 1 are often diagnosed by urinary antigen rather than by direct fluorescent antibody (DFA) staining or culture (table 1). In addition, the introduction of the urinary antigen test into many hospital laboratories has resulted in the detection of unrecognized endemic nosocomial outbreaks of Legionnaires' disease [24,32].
- The urinary antigen test has several advantages over culture:
- For many patients with Legionnaires' disease, obtaining an adequate sputum specimen can be difficult.
- The fact that test positivity can persist for days even during administration of antibiotic therapy makes it useful in patients who receive empiric anti-*Legionella* therapy.
- The results of the urinary antigen test can be available within hours, whereas culture results require three to five days [33].
- The major disadvantage of the urinary antigen test is that it is specific for *L. pneumophila* serogroup 1 only. However, the vast majority of Legionnaires' disease cases from the community are caused by this species and serogroup [34-36].
- The test format is an enzyme immunoassay (EIA). A high sensitivity and specificity for the assay has been reported by the manufacturers. However, sensitivity may vary with severity of disease. Test performance can be illustrated by the following observations:
- In a study conducted during a large outbreak (295 cases) of *Legionella pneumoniae* in Spain, the overall sensitivity of the test was only 48 percent (case confirmed by a positive culture for *Legionella* or fourfold rise in antibody titer) [37]. Sensitivity was significantly higher in patients with severe compared with mild pneumonia (86 versus 38 percent). Thus, many patients with mild pneumonia may go undiagnosed if the urinary antigen test is used alone.
- In a large outbreak in Oklahoma resulting from exposure in an indoor pool and hot tub area, 101 of 107 patients had Pontiac fever, the milder form of *L. pneumophila* serogroup 1 infection [17]. (See '[Pontiac fever](#)' above.) The urine antigen test had a sensitivity of 36 percent and specificity of 100 percent, whereas prior small studies had a sensitivity less than 10 percent [7].
- There have been reports of positive urine antigen test results in Legionnaires' disease due to non-serogroup 1 *L. pneumophila* and other species [38]. However, the sensitivity and specificity of the urine test for detecting other serogroups and species is currently unknown.
- A rapid urinary antigen test is commercially available that yields a result in less than 15 minutes. This test is the Binax NOW *Legionella* Urinary Antigen Test. It is an immunochromatographic membrane (ICT) assay that is performed using a swab that has been dipped in urine and inserted into the card-type test device. The reaction is read as the presence or absence of a visually detectable pink-to-purple colored line that results from the antigen-antibody reaction. The ICT assay has been shown to be comparable to the EIA assay, with a sensitivity of 80 percent and specificity of 97 to 100 percent [39,40].

DFA staining

- The reported sensitivity of DFA stains has ranged from 25 to 75 percent. It is highly specific, and the monoclonal antibody test has eliminated the rare occurrence of cross-reactivity with other gram-negative bacilli. DFA may be performed if the direct culture of the specimen is overgrown by competing microflora. We have found the monoclonal antibody DFA reagent (MONOFLUO, Bio-Rad Laboratories, Redmond, WA) to be superior to polyclonal reagents for detecting *L. pneumophila* in respiratory specimens because background fluorescence is reduced, and cross-reactivity with non-*Legionella* bacteria has not occurred in our experience.

Serology

- Antibody tests have become less important with the advent of rapid diagnostic tests, such as urinary antigen testing, DFA staining, and polymerase chain reaction. Because the definitive criterion for diagnosis is a fourfold rise in antibody titer, repeat serology is required 8 to 12 weeks after the onset of infection. Maximal sensitivity requires detection of both immunoglobulin G (IgG) and IgM antibody. Effective antibiotics and suboptimal timing of specimen collection are possible reasons for the decrease in reported sensitivity of this test. Indirect fluorescent antibody (IFA) and enzyme-linked immunosorbent assays (ELISA) have been the most commonly used methodologies for *L. pneumophila* serology.
- Diagnosis is made based upon a fourfold rise in antibody titer to $\geq 1:128$; thus, both acute and convalescent sera are required [41]. The optimal period for seroconversion is 12 weeks. Use of both IgM and IgG assays gives maximal sensitivity, and 25 to 40 percent of patients may have elevated titers in the first week of disease [30]. Some patients never demonstrate a fourfold increase in titer [41]. Sensitivity and specificity have been reported to be approximately 75 and 95 percent, respectively [30].
- Serology is useful in epidemiologic studies but is less helpful to the clinician in making an immediate diagnosis of Legionnaires' disease for an individual patient. On the other hand, if the seroprevalence of *L. pneumophila* antibody titers within the community is known to be low, a single elevated titer (1:256) may indicate the presence of acute disease. However, in one study, acute phase antibody titers of ≥ 256 failed to discriminate between definitive cases of Legionnaires' disease and nondefinitive cases [42]. Also, a single elevated titer does not confirm a case of Legionnaires' disease because IFA titers of $\geq 1:256$ have been found in 1 to 16 percent of healthy adults [43], and the positive predictive value of a convalescent-phase titer is unacceptably low [42]. False-positive results can rarely occur as a result of cross-reacting antibody to other gram-negative organisms.
- Taken together, these facts show that the utility of serology as a diagnostic tool is limited. Serologic results are presumptive if results are available for only a single specimen. A fourfold rise to ≥ 128 in titer between the acute and convalescent titer is required for a definitive serologic diagnosis [43].

Polymerase chain reaction

- DNA amplification by polymerase chain reaction (PCR) of Legionella has been reported from patients with pneumonia using throat swab specimens, bronchoalveolar lavage (BAL), urine, and serum [[20,44-47](#)]. To date, clinical experience has not shown PCR to be more sensitive than culture, and therefore the Centers for Disease Control and Prevention (CDC) does not recommend the routine use of genetic probes or PCR for the detection of Legionella in clinical samples [[26](#)].

Recommendations

- While a number of prominent clinical manifestations are distinctive for Legionella infection, none of them are pathognomonic or highly specific. Thus, laboratory testing using specialized tests for Legionella should be performed on all patients hospitalized with community-acquired pneumonia.
- Culturing for Legionella spp is the single most important laboratory test. Given the frequency of Legionella as a pathogen in both community- and hospital-acquired pneumonia, this test should be routinely available in all clinical microbiology laboratories.
- Urinary antigen testing is rapid, sensitive, specific, and not costly, but is only useful for the diagnosis of *L. pneumophila* type 1 infection (accounts for 90 percent of community-acquired Legionella infections in the United States).
- The combination of culture of an appropriate respiratory specimen and urinary antigen testing are optimal as a diagnostic approach.
- Serologic tests are generally far less useful for the diagnosis of an individual patient.
- While PCR-based tests exist, to date they do not exceed the sensitivity of culturing the organism.

Monotherapy versus combination therapy

- Anecdotal cases and selected laboratory studies have suggested possible benefit with combination therapy of a quinolone plus [azithromycin](#) or a quinolone plus [rifampin](#).
- However, observational studies of antibiotic therapies for Legionnaires' disease have not validated this approach.

Current Opinion in Infectious Diseases

2010, 3:152–157

An update on Legionella

Jordi Carratala` and Carolina Garcia-Vidal

Introduction

- Recognized as a significant cause of sporadic and epidemic community-acquired pneumonia (CAP) and nosocomial acquired pneumonia in both healthy and immunosuppressed hosts.
- The majority of cases of Legionnaires' disease are caused by *L. pneumophila* serogroup 1, but other serogroups and other species are also pathogenic

Epidemiology

- The increased use of the Legionella urinary antigen test in many laboratories and the obligatory reporting in a growing number of countries has led to a remarkable increase in the prevalence of community-acquired and nosocomial-acquired Legionnaires' disease.
- During 2000–2005, legionellosis cases were most commonly reported in persons aged 45–64 years. Age-adjusted incidence rates in men exceeded those in women for all age groups and years.
- Legionellosis incidence showed marked seasonality in eastern states, with most cases reported in the summer or fall.

- The fact that Legionnaires' disease can be both mild and severe and the fact that it is occurring more often raises the question about whether the use of more sensitive diagnostic methods have changed the nature of the disease.
- It can be hypothesized that the prompt diagnosis and appropriate treatment of Legionnaires' disease may avoid the development of a more severe disease. In this regard, it has been suggested that early recognition of Legionella pneumonia by means of urinary antigen testing may have contributed to decreasing mortality observed over the last years [2,4,6].
- Nevertheless, the declines in mortality rates may also result from more widespread use of empiric therapy for pneumonia that includes drugs active against Legionella.

- Legionella species have been detected in virtually all sources of fresh water, including lakes, ponds, and rivers [11].
- However, these natural water supplies are rarely identified as sources of human infection.
- Cooling towers continue to be the most frequently suspected sources in reported community-acquired outbreaks [12].
- Potable water may also be an important source of sporadic and also epidemic legionellosis [13].

Pathogenesis

- Legionella infection usually occurs through inhalation of contaminated aerosols produced by water systems such as cooling towers, showers, hot water distribution systems, and faucets [12,14–17].
- Other modes of transmission of Legionella are aspiration and direct instillation into the lung during respiratory tract manipulations.
- The survival and proliferation of *L. pneumophila* in the warm-humid environment depends on several factors.
- Among them, the formation of biofilms has been recognized as one of the most important key factors [4].
- Legionella species have developed mechanisms to acquire nutrients by residing in relatively nutrient-rich biofilms [18].
- Recent research provides an insight into the resistance afforded to *L. pneumophila* against high levels of chlorine by the formation of biofilms and has implications for the delivery of potable water [19].

- In the biofilm environments, Legionella species are subjected to protozoan predation and, therefore, have countered this act by developing means of parasitizing and residing within at least 20 species of amoebae, two species of ciliated protozoa, and one species of slime mould [20].
- The ability of Legionella to survive and grow within protozoa has been implicated in the selection of virulent strains well suited for causing human disease.
- It has been demonstrated that *L. pneumophila* can survive for at least 6 months in association with *Acanthamoeba castellanii* [21], whereas free-living Legionella within biofilms may be inactivated within a few weeks [22].
- Elucidating the putative role of biofilms and amoebae in the proliferation, development, and dissemination of potentially pathogenic Legionella species will aid in more effective elimination strategies [20].

Clinical diagnosis

- Although there is no single clinical manifestation that distinguishes Legionnaires' disease from other types of pneumonia, it has been suggested that there is a characteristic clinical profile that increases the likelihood of the diagnosis.
- Fiumefreddo et al. [23] conducted a study to identify clinical predictors for Legionella in patients presenting with CAP to the emergency department.
- The investigators retrospectively compared clinical and laboratory data of 82 consecutive patients with Legionella CAP with 368 consecutive patients with non-Legionella CAP included in two studies at the same institution.
- Independent predictors of Legionella pneumonia were high body temperature, absence of sputum production, low serum sodium concentration, high levels of lactate dehydrogenase and C-reactive protein, and low platelet counts.
- With these clinical and laboratory parameters, they elaborated a diagnostic score for Legionella CAP.
- Of the 191 patients (42%) with a score of 0 or 1 point, only 3% had Legionella pneumonia. Conversely, of the 73 patients (16%) with at least 4 points, 66% of patients had Legionella CAP.
- If validated in future studies, this score might aid in the management of suspected Legionella pneumonia.

- By means of a multivariate analysis, the Community-Based Pneumonia Incidence Study (CBPIS) group found that certain clusters of clinical signs were more likely to be associated with Legionella pneumonia than with other types of CAP.
- This group suggested that an-easy-to-perform scoring system that was based on their findings might be used to identify most patients with Legionella pneumonia.
- Ferná'ndez-Sabe' et al. [25] performed a prospective study aimed at assessing the ability of physicians to recognize Legionella pneumonia at admission and validating the CBPIS group scoring system for Legionella pneumonia diagnosis.
- Physicians considered Legionella to be the most likely diagnosis in 52 (64%) of 81 Legionella pneumonia cases and in eight (6%) of 136 cases of bacteremic pneumococcal pneumonia.
- The CBPIS score did not differentiate reliably between Legionella pneumonia and bacteraemic pneumococcal pneumonia.
- Therefore, although some presenting clinical features may allow recognition of Legionella pneumonia, it appears that it is difficult to express them in a reliable scoring system.

- In an observational analysis of a cohort of 1383 nonimmunosuppressed adults with CAP, Roso'n et al. [26] aimed to identify causes and factors associated with early treatment failure.
- They found that Legionella pneumonia was independently associated with early failure.
- Significantly, L. pneumophila was the causative organism most frequently associated with early failure.
- Treatment failure in CAP is associated with high morbidity and mortality rates [27].
- Therefore, given the limitations of the clinical diagnosis of Legionnaires' disease, the routine use of Legionella testing, especially the Legionella urinary antigen test, for all patients with CAP is recommended [28].

Legionellosis in immunosuppressed patients

- Immunosuppression, some forms of cancer, organ transplantation, corticosteroids administration, and treatment with tumor necrosis factor- α (TNF α) antagonists have all been found to be important host risk factors for Legionnaires' disease.
- Jacobson et al. [31] recently reviewed their experience with 49 cancer patients with a positive Legionella culture or direct fluorescent antibody (DFA) documented over a 13-year period (1991–2003).
 - The majority of patients (82%) had an underlying hematologic malignancy, and 37% were bone marrow transplant recipients.
 - Lymphopenia (47%), use of systemic corticosteroids (41%), and chemotherapy (63%) were the most common underlying conditions.
 - There was no temporal or geographic clustering of cases.
 - The majority of the patients had multilobar (61%) or bilateral (55%) pulmonary involvement.
 - The mean time to response to therapy was 8 days; 18 patients (37%) developed complications requiring prolonged duration of treatment (mean 25 days).
 - The case fatality rate was 31%.
 - Two patients had relapse of Legionella pneumonia despite appropriate therapy.
- Accordingly, treatment of Legionella pneumonia in cancer patients may require a prolonged course with a regimen that includes a newer macrolide or quinolone.

- Solid organ transplant (SOT) recipients are classically considered to be at increased risk for acquiring Legionnaires' disease because of immunosuppressive therapy related deficiencies in cellular immune function.
- In a recent retrospective study [33], 14 cases (0.5%) of Legionnaires' disease occurring in 2946 SOT recipients from 1985 to 2007 were documented.
 - A significant number of patients developed the disease during allograft rejection, while they were receiving more than one immunosuppressive drug, with prednisone being the most frequently used.
 - Most cases were sporadic and community acquired. *L. pneumophila* serogroup 1 was the species involved in all cases.
 - High fever, chills, cough, and multilobar pneumonia were the most frequent manifestations.
 - Two patients had dual infections (cytomegalovirus and nocardiosis, respectively).
 - The diagnosis was obtained by culture in the first eight patients who were treated with erythromycin. The last six patients were diagnosed by urinary antigen test and were treated with
 - levofloxacin.
 - Mean time from onset of symptoms to diagnosis was significantly shorter in patients diagnosed using urinary antigen test. The rapid diagnosis allowed a prompt initiation of levofloxacin. This agent has fewer interactions than erythromycin with certain commonly used drugs in transplant recipients, such as cyclosporine and tacrolimus.
 - The overall case fatality rate was 14.3%.

- Finally, it has recently been suggested that patients treated with TNFa antagonists may have an increased risk of Legionella pneumonia [34,35].
- A registry involving 486 clinical departments in France was designed to collect data on opportunistic and severe infections occurring in patients treated with TNFa antagonists [34].
- The relative risk of legionellosis when receiving treatment with a TNFa antagonist, compared with the relative risk in France overall, was estimated to be between 16.5 and 21.0.
- It should be noted that some patients were also receiving corticosteroids or methotrexate that might have played a role in the infection.
- However, the hypothesis of an increased risk of L. pneumophila infection among patients treated with TNFa antagonists is reinforced by in-vitro data from mice demonstrating that TNFa is critical for clearing macrophage infection with the bacterium [35].

Microbiological diagnosis

- Diagnosis of Legionnaires' disease depends on a high index of suspicion and special laboratory tests [4,36].
- Definitive diagnosis of legionellosis is based on culture of the microorganism from respiratory secretions or pleural fluid on buffered charcoal yeast extract (BCYE) agar.
- The isolation of Legionella allows microbiological identification and subtyping by DNA studies to determine the environmental source of infection.
- DFA staining can identify Legionella antigens in respiratory specimens and tissue with a high degree of specificity, but as with other tests, the DFA staining is not sensitive (<60%).
- Diagnosis by serology requires a four-fold rise in antibody titers to at least 1 : 128 in acute and convalescent sera. A single titer of 1 : 256 is considered not specific enough of Legionnaires' disease.
 - Clinical utility of serologic diagnosis is limited, and the test is mainly useful as an epidemiological tool.

- The Legionella urinary antigen is a relatively inexpensive rapid test that detects antigens of *L. pneumophila* serogroup 1 in urine.
- Urinary antigen assays (enzyme immunoassay and immunochromatographic assay) offer simplicity and rapidity in diagnosis of Legionnaires' disease, though studies report a range of sensitivities.
- Recently, a systematic review of studies in the English language has been performed to assess test characteristics of Legionella urinary antigen [37].
- Two investigators independently reviewed articles and extracted data.
- Thirty studies met inclusion criteria. All but two studies focused on serotype 1 Legionella. The pooled sensitivity was 0.74 [95% confidence interval (CI) 0.68–0.81] and specificity was 0.991 (95% CI 0.984–0.997).
- The major disadvantage with Legionella urinary antigen tests is their inability to detect organisms other than *L. pneumophila* serogroup 1 reliably.
- Rapidity of diagnosis is an important advantage of the urine antigen test, as it means that patients can be detected early in the course of infection, when treatment decisions can be affected.
- In recent years, diagnosis of Legionnaires' disease by culture has decreased significantly, impairing outbreak investigation [38].
- Therefore, the use of both urine antigen testing and sputum culture, whenever available, should be regarded as the best diagnostic combination.
- DNA amplification by PCR has promise for the rapid diagnosis of Legionella infection.
- PCR-based assays for the detection of Legionella in clinical samples are highly specific and more sensitive than cultures [39,40]. An important benefit of PCR is the capability to detect Legionella rapidly and to detect species other than *L. pneumophila* [41]. Nevertheless, more experience is needed in the clinical use of PCR techniques.

Antibiotic therapy

- A reduction in case fatality rates among patients with Legionnaires' disease has recently been observed, suggesting that new management strategies may result in improved outcomes [42,43].
- These new approaches include the use of urinary antigen testing for the diagnosis in combination with highly active antimicrobial agents against Legionella, for example, azithromycin and fluoroquinolones.
- These agents have been shown to be superior to erythromycin in inhibiting the intracellular growth of *L. pneumophila* both in in-vitro and in
- animal models [6,44].
- Moreover, recent observational studies [45–48] provide useful information regarding the current utility of azithromycin and levofloxacin in the treatment of Legionnaires' disease.
- In a prospective, open-label, noncomparative study [45], azithromycin was well tolerated and efficacious in the treatment of 25 hospitalized patients with community-acquired Legionella pneumonia.
- The overall cure rate among clinically evaluable patients was 95% at 10–14 days after therapy and 96% at 4–6 weeks after therapy.
- Although in-vitro and in-vivo studies have demonstrated that the efficacy of azithromycin is comparable to that of quinolones, no comparative clinical studies have ever been performed.

- Recently, three observational studies [46–48] comparing levofloxacin versus older macrolides in the treatment of Legionnaires' disease have been reported.
- In these studies, levofloxacin was associated with better clinical response, including a faster resolution of pneumonia symptoms, a more rapid achievement of clinical stability, and shorter length of hospital stay compared with older macrolides.
- Nevertheless, it should be emphasized that none of the studies were randomized trials, so biases cannot be ruled out.

- Combined therapy has been used in mostly severe unresponsive disease.
- However, there is no convincing evidence of its effectiveness, and combinations may risk additional toxicity and drug interactions.
- In this regard, in some studies [47,49], adding rifampin to levofloxacin or clarithromycin provided no additional benefit.
- Moreover, patients receiving combination therapy experienced more complications.
- Although some in-vitro data support the combination of azithromycin and fluoroquinolones, clinical experience is scarce [50].

- In light of the current data, we recommend the use of levofloxacin (or other fluoroquinolone such as moxifloxacin) or azithromycin as drugs of choice for *Legionella pneumoniae*.
- In hospitalized patients, parenteral antibiotic therapy should be given until clinical stability is reached.
- Then, oral therapy should be administered.
- The total duration of antibiotic therapy is 7–10 days for patients who respond expeditiously, but a 21-day course has been recommended for severely immunosuppressed patients.

Conclusion

- *L. pneumophila* is increasingly recognized as a significant cause of pneumonia in ambulatory and hospitalized patients, including those with cancer, SOT, corticosteroids administration, and treatment with TNF α antagonists.
- Given the nonspecific clinical manifestations of Legionnaires' disease, the routine use of Legionella testing for all patients with pneumonia is recommended.
- Urinary antigen test is a valuable tool for the rapid diagnosis of Legionnaires' disease.
- Azithromycin and fluoroquinolones have been found to be superior to older macrolides in inhibiting the intracellular growth of *L. pneumophila* both in in-vitro and in animals models.
- Improved clinical response has been documented for patients with Legionnaires' disease treated with levofloxacin.
- The use of levofloxacin (or other fluoroquinolone) or azithromycin is the current treatment of choice for Legionnaires' disease.

Infect Dis Clin N Am 24 (2010) 73–105

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

Burke A. Cunha

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.
- 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 35C with 5% CO₂.

- 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, crossreactions 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).^{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 Chlamydomphila 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}

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 102F 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 b-blockers, diltiazem, or verapamil, or does not have a pacemaker or heartblock, relative bradycardia points to legionnaires' disease.
- None of the typical bacterial CAPs are associated with relative bradycardia nor is M pneumoniae or C pneumoniae.

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 non-zoonotic 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 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.^{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 diagnostic 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 extrapulmonary 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 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.^{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 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.^{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}

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 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 coldagglutinin 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 hasMpneumoniae.
- 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 unelevated/ minimally elevated serum ferritin levels the diagnosis of Legionnaires' disease should be questioned (Table 8).^{35,60}

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

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 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}

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 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, 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, R1:64) 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 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 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 psittacine 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, 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 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 ($t_{1/2}$ 5 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}

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)

- zoonotic contact history
Mycoplasma
C. pneumoniae
Legionnaire's disease

+ zoonotic contact history
Psittacosis
Q fever
Tularemia

- RB

+ RB

- RB

+ RB

Mycoplasma
C. pneumoniae

Legionnaire's
disease

Tularemia

Psittacosis
Q fever