

A CASE OF AN ATYPICAL, COMMUNITY ACQUIRED PNEUMONIA: A CASE SUMMARY AND TOPIC REVIEW

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Case Report

A 59 year old gentleman with a past medical history of hypertension, hyperlipidemia, anxiety, depression, arthritis, and hypothyroidism presented with a five day history of fever to 102° F. He complained of a three-day history of nausea, vomiting, and non-bloody, loose diarrhea, all of which had been persistent and worsening over the past week. Over the past two days, the patient had felt short of breath, and presented in a state of severe dyspnea. He had experienced an indolent course of illness, but was now concerned with his tachynpea and wheezing, and he had developed a productive cough with a small amount of yellow-brown sputum. He denied any hemoptysis as well as recent travel or sick contacts. On admission, the patient was taking hydrochlorothiazide, lisinopril, atorvastatin, levothyroxine and fluoxetine. He was also using over-the-counter ibuprofen for arthritic pain.

The patient was a smoker with a ten pack-year history. He denied intravenous drug use and occasionally drank alcohol. Family history was significant for paternal obstructive lung disease and coronary artery disease. On review of systems, the patient denied having a sore throat or any nasal congestion.

Vital signs upon presentation were temperature 101.0° F, pulse 110 beats per minute, respiratory rate 40 breaths per minute, blood pressure 125/68 mmHg, and pulse oximetry of 86% on a non-rebreather mask. Upon physical examination, the patient was in moderate respiratory distress and unable to talk in complete sentences. He appeared mildly confused, but was awake, alert, and oriented. Jugular venous distention was not recognized. His cardiovascular exam was significant for tachycardia, but was without murmurs, rubs, or gallops. His pulmonary exam demonstrated coarse breath sounds bilaterally with diffuse, rhonchi throughout all lung fields. His abdomen was soft, mildly distended with moderate obesity, and was without hepato-splenomegaly. He had no lower extremity edema and his musculoskeletal exam was grossly normal. His skin was warm and moist, with good capillary refill (<2 sec).

Laboratory studies upon admission demonstrated electrolyte abnormalities, including a sodium of 125 mmol/L, chloride of 91 mmol/L, blood urea nitrogen of 83 mmol/L and creatinine of 5.6 mmol/L. His complete blood count was within normal limits. Blood gas demonstrated a pH of 7.22 carbon dioxide pressure of 45 mmHg, and oxygen pressure of 69 mmHg. Cardiac enzymes were negative and brain natriuretic peptide was 43.9 ng/L. His coagulation studies were within normal limits, as was his thyroid stimulating hormone. A urinalysis showed a slightly cloudy specimen with mild proteinuria. *Clostridium difficile* antigen was negative.

Figure 1. Imaging upon admission

Chest x-ray – A bilateral infiltrative process is seen consuming the majority of the right lung.

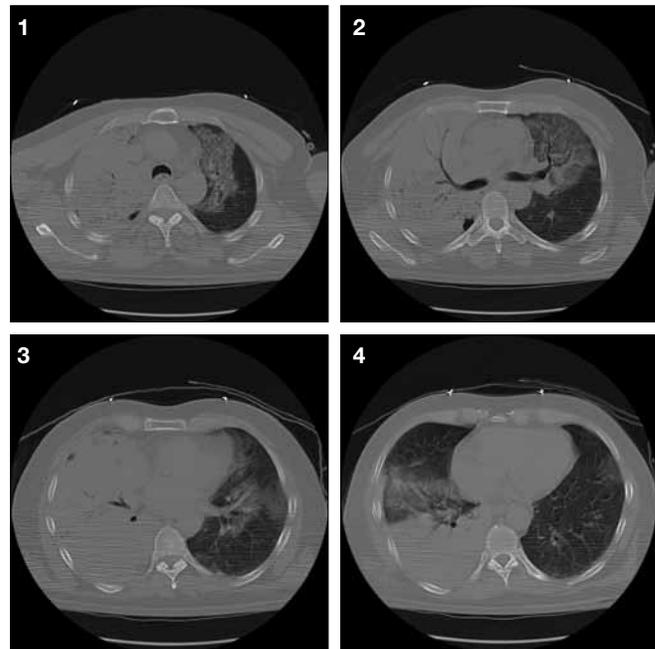
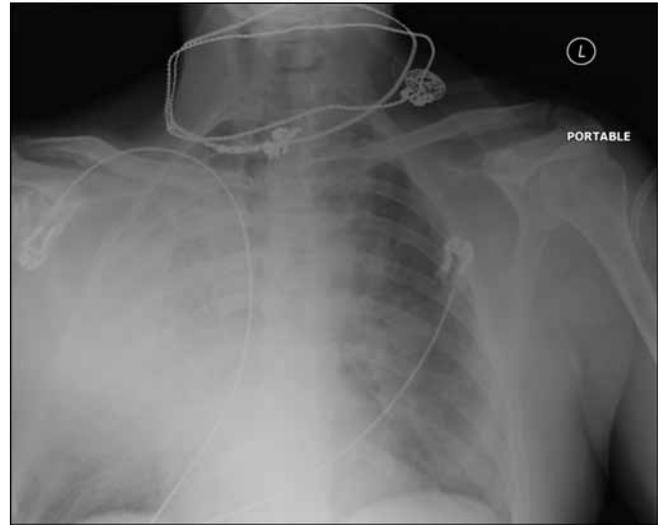


Figure 2. CT Chest without contrast – As the images move superiorly to inferiorly, note the dense consolidation of the right upper and lower lobes, as well as the groundglass appearance to the infiltrative process of the left upper lobe.

The patient was intubated in the Emergency Department due to severe dyspnea, hypoxia, and respiratory failure. Blood, urine and stool cultures were obtained. The patient was started on empiric antibiotic coverage for signs of possible systemic inflammatory response system with consolidative pneumonia with piperacillin-tazobactam, vancomycin, and azithromycin. Given the patient's history of diarrhea, dyspnea, mild confusion, and hyponatremia, a Legionella urine antigen was also sent. The patient was admitted to the medical Intensive Care Unit, and nephrology and infectious disease services were consulted.

The patient's urine Legionella antibody assay returned positive, and antibiotic coverage was then narrowed to azithromycin. Treatment was planned for 21 days. After nine days of ventilatory support, the patient was weaned and extubated without complication. Upon questioning, the patient explained that he had recently been working to remodel his bathroom, including removing a finished bath tub which was designed to lay a top the previous tub. The oldest tub was full of stagnate water which had been pooled there for approximately six months before this planned bathroom remodel. This added a potential source of Legionella infection to the overall clinical story.

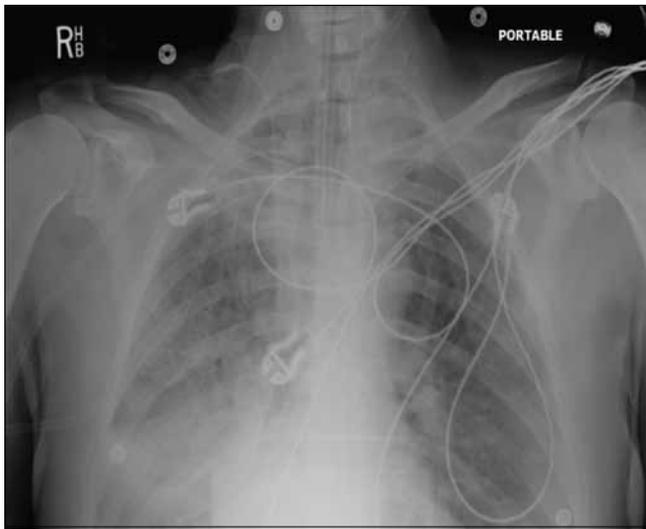


Figure 3. CXR upon extubation – There has been interval clearance of the infiltrative process of the right lung. Residual patchy infiltrates remain in the left lung base and right middle and lower lobes.

Introduction to Legionella and Legionnaire's Disease

Background

First identified in Philadelphia in 1976, Legionella has become recognized as a common atypical pathogen. Legionella is ubiquitous and classified as a fastidious gram-negative coccobacilli, representing a genus with over fifty subgroups. *L. pneumophila* comprises at least sixteen different subgroups, many of which require very specific culture growth media. Legionellosis refers to two clinical syndromes caused by the

genus Legionella: 1) Legionnaire's disease, a syndrome of pneumonia, and 2) Pontiac fever, an acute febrile illness that tends to be self-limited in nature.

Epidemiology

Legionella is noted as one of the top four causes of community acquired pneumonia (CAP) amongst the immunocompromised population, and is a common culprit of hospital-associated pneumonia. In fact, the incidence of Legionella as a cause of sporadic community-acquired pneumonia ranges from 2-15% of all cases requiring admission to a hospital.[□]

Transmission of Disease

Transmission of Legionella is accomplished by way of aerosol inhalation or by micro-aspiration of water contaminated with the organism.¹ Cooling towers, ultrasonic mist machines such as those used by grocery stores, respiratory equipment, and whirlpool baths have been commonly cited as vectors for disease transmission. Water distribution systems in nursing homes, workplaces, and private residences have each been implicated as primary sources of Legionellosis. Indeed, potable water sources have been associated with numerous reports of Legionella infection. The species *L. pneumophila* is capable of infecting and replicating in various protozoa found in soil and water, and may have increased virulence if replication occurs within amoeba.¹ Due to *L. pneumophila*'s virulence, Legionella pneumonia is recognized as manifesting a more severe pneumonia than other bacteria commonly associated with CAP.

The group of atypical CAP represents systemic infectious diseases that can primarily or secondarily infect the lungs. Atypical CAP differs from CAP in the way the specific bacteria infect host cells. Atypical bacteria are facultative intracellular organisms most susceptible to tetracyclines, macrolides, or quinolones. Indeed, Legionella species are capable of exponential multiplication within human monocytes and alveolar macrophages. An intact cellular immune response is thus necessary to inhibit intracellular replication, with use of activated macrophage and monocyte cell-mediated immunity. Patients with immune-suppression have neutrophil ingestion of the organisms after complement and antibody have targeted the organism, but often are unable to effectively kill the bacteria.² Typical pneumonias more commonly are comprised of organisms that invade interstitial spaces between cells and trigger neutrophil activation with cytokine release, thereby activating a generalized and immediate immune response.

Risk Factors and Disease Manifestations

Underlying disease is a major risk factor for acquisition of this disease. The risk factors most commonly implicated are cigarette smoking, chronic lung disease, and immunosuppression. Severely immunocompromised patients are said to fare worse in terms of disease severity, which may include lung abscess and bacteremia. They are also at risk for extra-pulmonary infections including sinusitis, pancreatitis, peritonitis, pyelonephritis, and most commonly, cardiac manifestations such as myocarditis,

Table 1. Common Clinical Features of Legionnaire's Disease

Organ Involved	Common Features	Argues Against Legionnaires' Disease
Central Nervous System	Confusion	Meningeal Signs
Upper Respiratory Tract	None	Sore throat, ear pain, bullous myringitis, otitis media
Cardiac	Relative bradycardia	Splenomegaly
Gastrointestinal	Loose, watery stools	Hepatic tenderness, RLQ pain, LUQ tenderness, peritoneal signs
Renal	Renal insufficiency	CVA tenderness, chronic renal failure

pericarditis, postcardiotomy syndrome, and endocarditis (Table 1).³ Nasogastric tubes have been implicated as sources of nosocomial legionellosis as well.¹ Also, patients who have recently undergone head and neck surgery, and therefore are susceptible to aspiration, have been noted as an at-risk population.¹ Common clinical features of community-acquired pneumonias include: cough, fever, pleuritic chest pain, sputum production, and dyspnea. Scant sputum production is more typical of atypical community-acquired pneumonias, whereas typical pneumonias contracted within the community are more commonly characterized by mucopurulent sputum production.

Differential Diagnosis

- Chlamydia pneumonia
- Mycoplasma pneumonia
- Fungal pneumonia
- Viral pneumonia
- Q Fever
- Psittacosis

Owing to its potential degree of severity and its resistance to beta-lactam antibiotic therapy, *Legionella* represents the most important nonzoonotic CAP pathogen to differentiate from CAP pathogens.² With observation of commonalities amongst patients infected with *Legionella*, it is possible to make presumptive diagnoses based on clinical presentation. Therefore, it is important to keep in mind the following differentiating features frequently seen with *Legionella* infection when narrowing a differential diagnosis:

- a. relative bradycardia in the context of a febrile illness
 1. limits diagnosis to *Legionella*, Q fever, and psittacosis
- b. unexplained mental confusion, including cerebellar ataxia
- c. loose, watery stools

Clinical Diagnosis

Pneumonia is the predominant clinical syndrome. The disease may represent a broad spectrum of illnesses though, ranging from mild cough to respiratory failure. Typically seen early in the disease course are non-specific symptoms and signs such as

fever, malaise, myalgias, headache, and anorexia.¹ Cough tends to be only slightly productive, and temperature commonly exceeds 104° F. Diarrhea may be seen in approximately 25% of cases, with complaints of watery rather than bloody stools;³ loose, watery diarrhea was reported in approximately 6% of other types of community-acquired pneumonias.³ Other common characteristic findings are relative bradycardia, which is most common among the elderly or those with advanced disease states and hyponatremia (serum sodium levels less than 130 mg/dL). Additionally, in patients demonstrating an increased cold agglutinin titer, which is commonly checked for suspected mycoplasma infections, the diagnosis of *Legionella* pneumonia is essentially ruled out. Due to the variance in severity of disease, as well as specialized lab tests required to confirm the diagnosis, Legionellosis is often underdiagnosed.⁵

The most important test for Legionnaire's disease is the isolation of the organism by culture on buffered charcoal yeast extract. Obtaining adequate sputum for culture can often be problematic in these patients however. When Legionnaire's is considered or suspected, a urine antigen test, *Legionella* culture, and a direct fluorescent antibody (DFA) staining from sputum or tissues should be considered. Indirect immunofluorescence assay (IFA) and/or enzyme-linked immunosorbent assay (ELISA) are also possible, but are not as useful in clinical decision making, as increased titers over four to eight weeks are required for confirmatory diagnoses (a fourfold rise in the titer of serum IgG antibody to *L. pneumophila* with final titer of at least 1/128 is commonly considered positive).⁶ The urine antigen test is an enzyme immunoassay with sensitivity of approximately 70%, and nearly 100% sensitivity;⁷ this test however applies to *L. pneumophila* serotype 1, which represents only 80-90% of *Legionella* infections.⁷ In contrast, the DFA test (sensitivity 33-68%, specificity 99-100%) can be performed in a manner of a few hours.⁸ ELISA tests are generally preferred over IFA tests nowadays, due to reportedly improved sensitivities (80% and 70%, respectively).^{8,9} Unfortunately this type of serum testing also lacks sensitivity for detecting serotypes other than serotype 1, as with the urine tests.

Treatment

Quinolones or doxycycline remain first-line therapy. Delay in initiation of treatment significantly increases mortality.¹

Table 2. Non-Specific Laboratory Tests

Nonspecific Laboratory Tests	Common Features	Argues Against Legionnaire's Disease
Gram stain (sputum)	Few mononuclear cells, few/no bacteria	Purulent sputum, single predominant organism
White Blood Cell Count	Leukocytosis, relative lymphopenia	Leucopenia, thrombocytosis, thrombocytopenia
Pleural Fluid	Exudative	Red blood cells, decreased pH, decreased glucose
Aminotransferases	Mildly elevated (2-5x normal)	Markedly elevated (10x normal)
Serum Phosphorus	Decreased (early)	Normal value does not rule out Legionnaire's Disease
Creatine Phosphokinase	Increased (early)	Normal value does not rule out Legionnaire's Disease
C-Reactive Protein	Increased (early)	Normal value does not rule out Legionnaire's Disease
Ferritin	Highly elevated (>2x normal)	Normal/slightly increased early. Normal value does not rule out Legionnaire's Disease
Cerebral Spinal Fluid	No pleocytes	Red blood cells, decreased glucose, decreased lactate
Urinalysis	Microscopic hematuria	Gross hematuria, pyuria, hemoglobinuria
Stool	Watery stools	Blood or mucus

Treatment duration is two weeks with quinolones, or two to four weeks with other antibiotics.¹ Another treatment option is macrolides, however there is variability between drug efficacy in this class for eradicating *Legionella*. For instance, erythromycin has been associated with therapy failures.¹ Other macrolides, such as azithromycin are said to have better in vitro activity and improved pulmonary tissue penetration.¹ Overall, quinolones have improved in vitro activity and intracellular penetration compared to macrolides. In patients who are severely ill, rifampin is recommended as an adjunct in combination therapy with a macrolide or quinolone, as it has high levels of activity against *Legionella*. Imipenem, trimethoprim-sulfamethoxazole, and clindamycin have all been proven efficacious for the treatment of *Legionella* pneumonia.⁹ Treatment of the underlying pneumonia will improve the associated diarrhea, electrolyte abnormalities, and other associated syndromes seen with Legionnaire's Disease.

Prognosis

Patients with Legionnaire's Disease usually experience symptomatic improvement within three to five days if treated early with an effective antibiotic. With early treatment and appropriate drug choice, the mortality rate for immunocompromised patients approaches that of immuno-competent patients.¹⁰ However, mortality can vary widely and is noted to be as high as 80% in cases, particularly in patients with underlying disease where lack of prompt recognition and

treatment initiation exist, and in nosocomial or large outbreaks. Decreasing mortality trends have been noted recently due to increased awareness and consideration of the disease as a possible infectious etiology.

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