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Could it be Legionella?

Background
Community acquired pneumonia is a common condition presenting to general practitioners and emergency departments across Australia. Legionella is one of many pathogens responsible for community acquired pneumonia. Cases of Legionella may occur sporadically or as part of an outbreak.

Objective
This article describes the clinical manifestations of Legionella infection and provides clinicians with an approach to its diagnosis and management.

Discussion
Legionella infection is typically associated with community acquired pneumonia, which can be severe. Features pointing to Legionella as a cause of pneumonia include the presence of gastrointestinal symptoms, especially diarrhoea; neurological symptoms, especially confusion; fever up to 40°C; hyponatraemia; and hepatic dysfunction. However, none of these is required to make the diagnosis. Sometimes nonrespiratory symptoms can predominate. Diagnosis requires the use of special tests specific for Legionella, the most clinically useful being urinary antigen tests and serology. Recommended treatments include macrolide therapy or doxycycline.

Legionella was first identified in 1976 after an outbreak of pneumonia in people who attended an American Legion Convention in Philadelphia.[1] The responsible organism was later identified as a Gram negative bacillus, and named 'Legionella'. Forty-one species have been identified in the *Legionellaceae* family, and 18 species have been reported to cause human infection. *Legionella pneumophila* (*Figure 1*) is responsible for the majority, with serotype 1 accounting for over 80% of cases. However, the epidemiology does vary in different regions. Other species include *L. longbeachae, L. micdadei, L. bozemanii* and *L. dumoffii*.[2] Legionella does not grow on routine bacterial culture media, which may lead to difficulties in diagnosis. Alternate methods of diagnosis are available.

The natural habitat for Legionella is water, including lakes and streams, and soil. Legionella bacteria are adaptable to a remarkably wide range of environmental conditions.[2] Infection in humans can be viewed to have been promoted by many of the activities related to modern civilisation. Growth of Legionella is particularly amplified in domestic and industrial water systems due to conditions such as warmth, stagnation, nutrition from sediment, and the presence of protozoa and other bacteria.[2]

Legionella is a relatively common cause of community acquired pneumonia (CAP). In published series analysing causative pathogens of CAP, Legionella accounts for 2–9% of all identified pathogens.[2] In a recent Australian study (where intensive investigations were undertaken to ascertain the cause of CAP) in six hospitals across three states, 3.4% of CAP was caused by Legionella.[3] Legionella was reported at a frequency of less than 1% in ambulatory patients with pneumonia, compared to much higher rates (up to 8%) in patients with CAP who required intensive care management.[4,5]

Many outbreaks have been associated with contamination of cooling towers used for the air-conditioning of large buildings such as offices and shopping centres. Australia's largest outbreak of Legionnaire disease was at the Melbourne Aquarium in April 2000, with 125 confirmed cases. The cooling towers at this location were found to be contaminated with high levels of Legionella bacteria.[6]

Legionella is also a cause of hospital acquired pneumonia. This phenomenon is increasingly being appreciated with the availability of

rapid diagnostic tests. Hospital associated cases have been linked to contaminated cooling towers and hot water distribution systems.[7] This necessitates careful environmental monitoring as a routine infection control measure.[1]

There have been many reports of patients with Legionella infection without an obvious epidemiological link to an environmental source. The origin of many of these sporadic cases has been speculated to be associated with exposure at home, with Legionella isolated from drinking water. However, the absolute risk to an individual person if Legionella is isolated in their water system appears very low.[8]

Risk groups and risk factors

Legionella infection typically originates from an environmental source. It is acquired by one of two main mechanisms:

- the inhalation of aerosols containing Legionella bacteria, or
- by micro-aspiration of ingested water containing the organism.[1]

Person-to-person transmission is not thought to be a risk.

Studies have demonstrated strong associations between Legionella infection and

- underlying chronic pulmonary disease
- a history of smoking, and
- age >50 years.[6,9]

In the Melbourne Aquarium outbreak, a case control study demonstrated an association with current smoking, as well as a significant association with visiting the aquarium on specific dates.[6]

Other patients at high risk of acquiring Legionella infection include the immunosuppressed (due to malignancy, transplantation or corticosteroid therapy).[10] However, infection can certainly occur in hosts without obvious risk factors; a large review described 14% of patients with Legionella infection being <55 years of age and previously well.[9]

Many surveillance reports have identified returned travellers with Legionella, and in the United States, up to 20% of cases are reported to be associated with travel.[11] Contaminated cooling towers and water systems in hotels and cruise ships have been proposed as likely sources. Poor standards of maintenance or extreme environmental conditions may contribute to Legionella overgrowth in these situations.

Infections have also occurred in long term care facilities such as nursing homes.[12] Contaminated cooling towers have been the cause in the majority of cases, but aspiration of water containing Legionella, such as in pureed food, has been also implicated.[13] Patients with swallowing disorders or receiving nasogastric feeding may also be at increased risk of infection via micro-aspiration.[1]

Infection with *L. longbeachae* has been associated with exposure to garden potting mix and hanging flower pots.[14]

Clinical features

Pneumonia caused by Legionella is sometimes referred to as 'Legionnaire disease'. The less common systemic illness without pneumonia is also sometimes termed 'Pontiac fever'.

The incubation period of Legionella pneumonia ranges 2–18 days. Clinical features vary widely and range from a mild pneumonia to severe pneumonia requiring intensive care admission (*Table 1*). Systemic symptoms tend to predominate early, including high grade fever, malaise, myalgia, anorexia and headache.[1] Localising respiratory symptoms then typically develop, including a dry cough, dyspnoea, and much less commonly, chest pain and haemoptysis. Gastrointestinal symptoms are common and include nausea, vomiting, abdominal pain and diarrhoea. Neurological symptoms are also common, particularly confusion, but collapse and focal neurological signs have also been reported.[15]

Figure 1. Dieterle's silver impregnation stain of a lung section showing pleomorphic bacilli of L. pneumophila

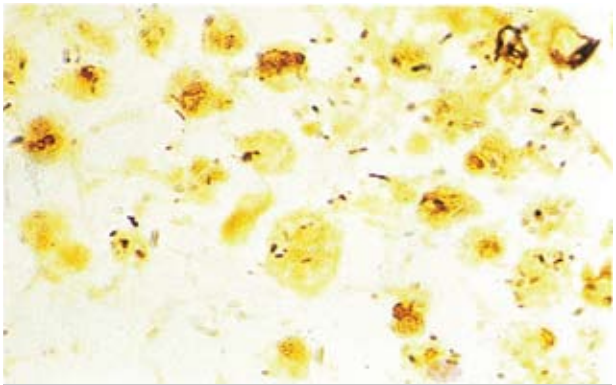

Photo courtesy Dorothy I Slater

Table 1. Main clinical syndromes caused by Legionella

Syndrome	Clinical features
Legionnaire disease	Pneumonia, commonly with systemic symptoms
Pontiac fever	Milder disease, prominent systemic symptoms without pneumonia
Rare manifestations	• Sinusitis • Cellulitis • Pancreatitis • Septic arthritis • Cardiac – myocarditis, pericarditis and endocarditis

Rapid clinical deterioration has been described, and at this point, the illness more resembles a 'typical pneumonia' with fever, productive cough, pleuritic pain and breathlessness.[16] A systemic inflammatory response syndrome or multi-organ failure may result in a minority of patients.

The majority of patients have an abnormal chest X-ray at presentation.[17] In some cases, however, this may be overlooked as clinicians may be distracted by early nonrespiratory symptoms and pursue alternate diagnoses.[15] In one case series, diagnoses such as presumed meningitis or acute cholecystitis were initially applied to patients in a hospital emergency department.[15] Legionnaire disease cannot be distinguished from other causes of CAP on radiological grounds alone. The majority of patients are said to have patchy or confluent consolidation (predominantly of the lung bases) and pleural effusions are common; described in up to 30% of cases.[17,18] Resolution of the radiological abnormalities may take up to several months.[1]

Laboratory abnormalities are common but nonspecific, and include renal and hepatic dysfunction, thrombocytopaenia and leucocytosis. Hyponatraemia is said to occur more commonly in Legionnaire disease than in other forms of pneumonia.[2]

Several clues may point to a diagnosis of Legionellosis, such as:

- fever up to 40ºC
- systemic symptoms preceding respiratory symptoms
- gastrointestinal or neurological symptoms
- hyponatraemia, and
- hepatic dysfunction.[1,2]

'Pontiac fever' is a milder form of infection caused by Legionella. It has a much shorter incubation period with a mean of 36 hours. This febrile syndrome is characterised by systemic symptoms such as malaise, chills, fatigue and headache, without manifestations of pneumonia. It is usually self limited and does not require treatment.[2]

The exact cause of these different manifestations is not known. Several varying explanations have been speculated, including the burden of initial infection, an allergic reaction to inhaled live or dead bacteria, inhaled bacterial endotoxin, or due to host factors.[19] Interestingly, outbreaks have been reported where a common source has resulted in cases of both Legionnaire disease and Pontiac fever.[20,21] A notable incident was after two workmen repaired the interior of a cooling tower; one developed Legionnaire disease and the other developed a febrile illness consistent with Pontiac fever.[20] Cases of Pontiac fever almost certainly go unrecognised. During the Melbourne Aquarium outbreak, many people who had visited the aquarium were tested via a urinary antigen test and returned positive results despite having mild, nonspecific clinical symptoms. These patients probably had Pontiac fever.[6]

Diagnosis

Specialised tests are required to diagnose Legionella infection, which must be specifically requested by the treating clinician (*Table 2*). Some guidelines have suggested that all patients requiring admission to hospital for CAP should have a diagnostic test for Legionella.[2] This is certainly most appropriate for severely ill patients where an accurate diagnosis is critical. More widespread testing may help provide epidemiological surveillance for Legionella infections.

Legionella urinary antigen test

In most cases Legionella urinary antigen is the appropriate test as it detects the majority of clinical disease caused by *L. pneumophila* serogroup 1 and obtaining an adequate sputum sample can be difficult. This test has a high sensitivity and specificity and a rapid turnaround time. Another benefit is that it remains positive for weeks and is not affected by antibiotic treatment. A limitation is that only *L. pneumophila* serogroup 1 is detected.

Table 2. Performance of specialised laboratory tests for the diagnosis of Legionella infection[1]

Test	Sensitivity (%)	Specificity (%)
Urinary antigen*	70	100
Sputum culture	80	100
PCR of sputum	As sputum culture	As sputum culture
Serology	40–60	96–99

* Detects only L. pneumophila serogroup 1

Culture

Specialised media is required to culture Legionella, although it is not routinely performed. It is important to check with the laboratory if ordering culture to ensure appropriate collection methods and culture media is used. Sputum may be cultured if a patient can produce a deep cough specimen, or from a bronchoscopy sample. This is the gold standard against which other tests are compared.

Legionella PCR

These assays have been used on specimens such as sputum, urine and serum. In general their specificity is good but sensitivity is no better than culture.[1] Culture and polymerase chain reaction (PCR) have the advantage over urinary antigen testing of being able to detect species other than *L. pneumophila*.

Serology

For accurate interpretation, acute and convalescent serology should be requested, 4 weeks apart. Criteria for positivity include a four-fold increase in titre to 1:128 or more. A single high titre IgG or positive IgM can only be diagnosed as presumptive. This test is generally only useful in retrospect but is worthwhile for epidemiologic information. It can also diagnose species of Legionella other than *L. pneumophila*.

Management

As treatment is commenced before a microbiological diagnosis in the majority of patients with CAP, empiric treatment is required. Guidelines usually recommend treatment covering both *Streptococcus pneumoniae*, the most common cause of CAP (which is usually treated with a beta lactam antibiotic) and the so-called 'atypical organisms'.[22] These are intracellular bacteria and include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *C. psittaci*, and Legionella species. Agents with activity against these organisms includes doxycycline, macrolides (eg. azithromycin, roxithromycin or clarithromycin) and quinolones (eg. moxifloxacin).[22]

Legionella organisms live within cells, so antibiotics that penetrate into cells at high levels have the best activity. Previously erythromycin was the treatment of choice, but this drug is poorly tolerated due to gastrointestinal adverse effects. More recently, the efficacy of newer macrolides and fluoroquinolones has been recognised. For directed therapy against Legionella infection, current guidelines suggest azithromycin (usually intravenously). This may be combined with a second active agent such as a quinolone or rifampicin in severe cases. Doxycycline is an option in milder disease. Treatment is

generally recommended for 14 days, except in an immunocompromised host where 14–21 days is recommended.[22]

Given the significant diagnostic challenges outlined above, it is the authors' view that every patient with CAP should receive empiric treatment active against Legionella in addition to therapy directed toward *S. pneumoniae* (eg. a beta lactam plus a macrolide). If this has not occurred and the patient has not responded as expected to treatment with a beta-lactam antibiotic alone, consideration should be given to performing diagnostic tests for Legionella and broadening antibiotics to include one of the agents listed. Obviously, if the clinical condition warrants, inpatient investigation and management should be undertaken.[22]

Public health issues

Confirmed or suspected cases of Legionella are required to be notified to the appropriate state (or territory) health authority. Patients' environmental exposures during the incubation period are established by interview and compared to other cases. Workplaces of confirmed cases are routinely investigated.[23] Infection can often then be epidemiologically linked to an environmental source such as a contaminated cooling tower. Regular maintenance and surveillance of all cooling towers is now required in Australia and local guidelines exist in all states.[23] Outbreaks or individual cases of Legionella infection have also been reported from a diverse range of other sources including humidifiers, spa baths, respiratory therapy devices and a decorative fountain.[24,25] Early detection and notification of cases allows potential sources to be detected, preventing further exposure to the public.

Residential hot water systems may play a role in sporadic cases of Legionella infection. It has been proposed that more emphasis should be placed on investigating water systems and practices around the home in such cases.[7] Recommendations to prevent gardeners from infection by Legionella include:[23]

- always wear a face mask and gloves when using compost and potting mix, including opening the bag
- moisten the contents of potting mix bags to avoid creating dust
- wear gloves and always wash hands after handling potting mix.

Summary of important points

- Exposure to contaminated aerosolised water is the most common source of Legionella infection.
- A spectrum of clinical presentation occurs including patients with a systemic febrile illness without prominent respiratory symptoms.
- A pattern of several days of illness with nonrespiratory symptoms (similar to 'atypical pneumonia'), followed by rapid clinical deterioration and symptoms suggestive of severe 'typical pneumonia' has been described.
- Clues to Legionellosis in CAP include gastrointestinal symptoms, especially diarrhoea; neurological symptoms especially confusion; fever up to 40ºC, hyponatraemia; and hepatic dysfunction.
- The urinary antigen test has high sensitivity and specificity, but only detects *L. pneumophila* serotype 1 (the most common serotype).
- Empiric treatment for CAP should include cover for Legionella.
- Problems may arise when an alternate diagnosis (eg. gastroenteritis) is initially made because of a lack of early respiratory symptoms, and appropriate antibiotics can therefore be delayed.

Conflict of interest: none declared.

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