Case Report

Two cases of community acquired *Legionella pneumophila* non-serogroup 1 in patients undergoing extra corporeal membrane oxygenation for severe respiratory failure

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Introduction: The *Legionellaceae* are fastidious Gram-negative bacteria that reside in aquatic environments. They are a cause of severe community acquired pneumonia. *Legionella pneumophila* serogroup 1 is responsible for 70–90 % of human infection, with cases caused by some of the other 15 serogroups accounting for the rest. Most hospitals use the *Legionella* urinary antigen test for detection of legionellosis; however, this will only reliably detect *L. pneumophila* serogroup 1.

Case presentation: We report two cases of severe community acquired pneumonia in patients requiring extracorporeal membrane oxygenation, referred to our adult Severe Respiratory Failure Unit. Legionella urinary antigen was negative in both cases. As clinical presentation strongly suggested Legionnaires’ disease (LD), respiratory samples were sent to the reference laboratory for PCR, which confirmed *L. pneumophila* non-serogroup 1 in both cases. Case 1 was subsequently confirmed by culture and confirmed as *L. pneumophila* serogroup 5. Case 2 was culture-negative.

Conclusion: *Legionella* is an important pathogen. Recognition of the potential for non-serogroup 1 strains to cause severe LD should prompt requests for further investigations including *Legionella* PCR in patients who present with suggestive symptoms when the urine antigen is negative. Reliance on the urine antigen test may result in a potentially serious under-recognition of *L. pneumophila* non-serogroup 1 and lead to mis-diagnoses and inappropriate antimicrobial treatment.

Keywords: Disease/indication: Legionnaires’ disease; pathology/symptoms: severe community acquired pneumonia; treatment: extra corporeal membrane oxygenation (ECMO).

Introduction

The *Legionellaceae* are fastidious Gram-negative bacteria that reside in aquatic environments. They have been recognized as an important cause of severe community acquired pneumonia (CAP) (Phin et al., 2014). The family *Legionellaceae* consists of a single genus, *Legionella*. This genus includes the species *Legionella pneumophila*, the most frequent cause of human legionellosis, better known as Legionnaires’ disease (LD). The disease was first described after an outbreak affecting war veterans (Legionnaires) at the 1976 American Legion convention in Philadelphia. LD is characterized by pneumonia that can be associated with multi-organ involvement. Within
the species *L. pneumophila*, serogroup 1 is responsible for 70–90 % of human infection, with cases caused by the other 15 serogroups accounting for most of the remainder.

Many hospitals use the *Legionella* urinary antigen test for detection of legionellosis. Advantages include speed of results, obtained in a matter of hours rather than the up to 10 days required for culture. In addition, a urine specimen is more easily obtained than a sputum specimen. Disadvantages, however, are that the urine antigen test will only reliably detect *L. pneumophila* serogroup 1 and tends to yield positive results more frequently in patients with more severe pneumonia (Yzerman et al., 2002). Reliance on the urine antigen test may result in a potentially relevant under-recognition of non-serogroup 1 *L. pneumophila* and may explain the lack of population data for non-serogroup 1 infections.

Extracorporeal membrane oxygenation (ECMO) is an extracorporeal technique for providing cardiac and respiratory support to patients with severe acute cardiac or pulmonary failure that is potentially reversible but unresponsive to conventional management. The ECMO circuit provides oxygenation and rests the lungs and so decreases the insult caused by mechanical ventilation (Gaffney et al., 2010). Published cases of LD secondary to non-serogroup 1 in patients requiring ECMO are rare.

We report two cases of LD in patients requiring ECMO for severe respiratory failure. In both cases the *Legionella* urinary antigen test was negative. We highlight the growing importance of non-serogroup 1 infection in this cohort of patients.

**Case report**

We report two cases of severe CAP in patients referred for ECMO to our adult Severe Respiratory Failure Unit. Case 1 was a 60-year-old, previously fit and well man, who presented with increased shortness of breath and a history of feeling generally unwell for 5 days. He had recently visited Dubai for a 10 day holiday and felt unwell on his return. He became acutely short of breath 24 hours before his admission, with an associated dry cough, malaise and lethargy. He presented to his local Accident and Emergency Department and required admission to Intensive Care for mechanical ventilation. He continued to deteriorate from a respiratory perspective and was referred for ECMO.

Case 2 was a 60-year-old, previously well man who presented to Accident and Emergency with a fever, shortness of breath, diarrhoea and vomiting, lethargy and collapse. He had recently returned from a holiday to Malta. He was diagnosed with CAP, supported by chest X-ray findings. On admission to his local hospital he was transferred to Intensive Care but failed mechanical ventilation and required referral for ECMO.

**Diagnosis**

A urinary antigen test (Alere BinaxNOW) was carried out as part of an ECMO admission septic screen, which also included an atypical serology test (including *Mycoplasma* and *Chlamydia*), a viral PCR screen for respiratory viruses (influenza A and B, parainfluenza 1, 2 and 3, respiratory syncytial virus, metapneumovirus, adenovirus and rhinovirus) and a human immunodeficiency virus (HIV) test. In both cases, all investigations were negative. As the clinical presentation, supported by a history of travel abroad in each case, strongly suggested LD, respiratory samples (bronchoalveolar lavage) were sent to the reference laboratory for PCR. This was positive for *L. pneumophila* non-serogroup 1 in both cases. Case 1 was subsequently confirmed by culture as *L. pneumophila* serogroup 5. Case 2 was culture-negative.

**Outcome and follow-up**

Case 1 required nine days of ECMO support but responded well to dual therapy with levofloxacin and clarithromycin. Case 2 had a stormy course while on ECMO and developed multiple secondary infections, including ventilator-associated pneumonia with bacteremia due to *Burkholderia cepacia*. Despite triple therapy for the management of LD with levofloxacin, clarithromycin and rifampicin he passed away after 28 days of ECMO support.

**Discussion**

LD is a relatively rare (5.33 per million population in England and Wales) (Public Health England, 2012) but important cause of severe CAP, more common in men. Although it was first recognized more than three decades ago, there has been little progress in defining the burden of disease, the virulence potential of the different strain types and the optimal treatment (Phin et al., 2014). LD is a potentially reversible infection but in both LD cases reported here, patients proved unresponsive to conventional management. They presented with severe acute respiratory failure, which was refractory to mechanical ventilation. In addition to conventional antimicrobial therapy they required rescue therapy in the form of ECMO. This suggests that *Legionella* strains other than *L. pneumophila* serogroup 1 can cause severe disease in previously healthy subjects. To our knowledge, LD secondary to *L. pneumophila* non-serogroup 1 in patients requiring ECMO has not been previously reported.

The introduction of the urinary antigen test was described as a turning point in the diagnostic evaluation of *Legionella* pneumonia (von Baum et al., 2008). The rate of detection by urine antigen testing increased from 0 to 69 % in the USA, constitutes 73 % of diagnostic procedures for *Legionella* in Europe and has resulted in a substantial increase in the diagnosis of *Legionella* infections (Ricketts
& Joseph, 2005; Benin et al., 2002). A recent study reviewed the management and outcome of 19 patients who required ECMO for LD, over a ten-year period. In each case the diagnosis was made using the urinary antigen test (Noah et al., 2013).

However, as we know, the urine antigen test will only reliably detect L. pneumophila serogroup 1, which accounts for no more than 80% of reported cases. LD is associated with substantial morbidity and mortality, is widespread in the environment and still associated with major outbreaks. This emphasizes the need for further work to support early diagnosis, better molecular diagnostic tests and improved clinical management (Phin et al., 2014). In order to better understand the epidemiology of LD, the potential for non-serogroup 1 to cause clinical infection must be recognized. Under-detection can potentially result in inappropriate antimicrobial treatment and increased morbidity. It may also bias epidemiological data.

Although infection specialists are aware of the limitation of urinary antigen testing in Legionella infection, we suggest that there is a reliance on the urine antigen test alone, and this may result in a significant under-recognition of L. pneumophila non-serogroup 1, and other Legionella species such as Legionella longbeachae (Potts et al., 2012). Culture is not always feasible because it requires specialized media and sensitivity is low, depending on disease severity, and is in any case slow, taking from 3–10 days for a positive result. We therefore recommend that further investigations including Legionella PCR should be undertaken in patients who present with symptoms suggestive of Legionnaires’ disease when the urine antigen is negative. We suggest that this be part of an initial screening repertoire for investigating all patients with severe pneumonia requiring ventilatory support, in addition to those that require referral for respiratory ECMO.

References


