Other full case

Management of *Legionella* in the intensive care settingNicholas John Harris,¹ Anna Claire Victoria Harris,² Michael Spiro³¹Whipps Cross University Hospital NHS Trust, London, UK;²The Homerton University Hospital NHS Trust, London, UK;³Anaesthetics & Intensive Care, University College Hospital, London, UK**Correspondence to** Dr Nicholas John Harris, n.j.harris@doctors.org.uk**Summary**

In August 2009, during the swine flu pandemic, a 55-year-old male presented to the Emergency Department (ED) with shortness-of-breath and chest pain. He had experienced diarrhoea and vomiting during the 3 weeks preceding admission, and so had sought the advice of his General Practitioner (GP) who had prescribed a course of oseltamivir (Tamiflu). Despite this, his symptoms had worsened, and on arrival in the ED he was found to be tachypnoeic, tachycardic, feverish, anuric and in type I respiratory failure with a compensated metabolic acidosis. He subsequently became hypotensive, and so was transferred to the Intensive Care Unit (ICU) for supportive treatment of three organ failures. Investigation revealed that he was suffering from Legionnaires disease. This required a prolonged inpatient stay owing to both disease and treatment related complications.

BACKGROUND

Legionnaires disease is the term employed to describe a pneumonia resulting from infection with the bacterium *Legionella pneumophila*. This species of bacterium is the commonest member of the *Legionellaceae* family, accounting for over 90% of cases of legionellosis.¹

Conventional teaching is that Legionnaires disease is a rare entity. This is supported on a national level by surveillance figures from the Health Protection Agency (HPA). During the period 1980–2009, the HPA recorded an average 236.5 cases of Legionnaires disease each year in the UK.² Since there are an estimated 261 000 cases of community acquired pneumonia each year in the UK,³ this accounts for just 0.1% of the total. However, our District General Intensive Care Unit (ICU) received four unrelated cases of Legionnaires disease over a 2-month period. The total number of cases with a primary diagnosis of community acquired pneumonia in this same period was 56, thus *Legionella* pneumonia accounted for 7.1% of admissions during this time. This led us to the conclusion that *Legionella* is an important and often overlooked aetiology in the pathogenesis of pneumonia.

The burden of this disease is significant; in the intensive care setting it is the second most common cause of pneumonia necessitating ICU admission after *Pneumococcus* (17.8% vs 21.6% respectively),⁴ and mortality are on the order of 30%.⁵ Outside the ICU, morbidity rates have been reported as high as 25%, and mortality varies between 5% for those in whom appropriate antibiotics are commenced immediately, and 11.1% for those in whom they are not.⁶ Therefore, it is clear that a delay caused by empirical treatment for more common pathogens, or in our case a presumptive diagnosis of swine flu, can have a profound impact on survival.

We believe that this case is important because of the significant mortality associated with Legionnaires disease, and because contrary to conventional teaching, this pathogen is relatively commonplace, at least in the intensive care setting.

CASE PRESENTATION

In August 2009, a 55-year-old civil servant presented to the Emergency Department (ED) of our District General Hospital, with a 3-day history of sudden onset, intermittent, non-radiating chest pain, associated with a non-productive cough and shortness-of-breath. There were no features of heart failure. On further questioning, he reported that he had also been suffering from a 3-week history of persistent diarrhoea and vomiting associated with fever. He had contacted his General Practitioner (GP) about this, who had started him empirically on oseltamivir, with a presumptive diagnosis of swine flu (H1N1). However, despite completing his course of treatment, his symptoms had progressed, and so he had seen fit to attend the ED.

His medical history included hypertension, for which he was taking amlodipine and lisinopril, renal calculi, ankylosing spondylitis and asthma. The patient's asthma had always been well controlled, requiring neither hospital nor ICU admission. He had no known drug allergies, nor any significant family history. He was independent in activities of daily living, and reported a 20 pack-year history of smoking. His predisposing risk factors for *Legionella* infection were therefore his gender, age, smoking history and chronic pulmonary condition.⁷ This was further complicated by the concomitant pandemic flu scare which served to delay his presentation to secondary care.

On initial examination, he appeared unwell and dehydrated. The observations were as follows:

Observation	Value
Respiratory rate	42 breaths/min
Saturations	97% on 5l O ₂ via Hudson mask
Heart rate	136 beats/min
Blood pressure	155/75
Temperature	38°C

INVESTIGATIONS

A diagnosis was sought from the point of admission through a process of history, examination and investigation. Initial investigations were carried out in the ED resuscitation room. The patient underwent routine baseline blood tests, an arterial blood gas (ABG), and a plain chest radiograph. His blood results were as follows:

Investigation	Result
Urea	21.8
Creatinine	504
CRP	446.1
White cell count	9.9
Neutrophils	9.1
Creatine kinase	9528

CRP, C reactive protein.

Admission ABG demonstrated a widened alveolar-arterial (A-a) gradient, type I respiratory failure and a compensated metabolic acidosis. Serial ABGs progressed as follows:

Parameter	Value	Normal values
Time	1100 h	1540 h
Oxygen	5l	5l
pH	7.453	7.439
pCO ₂	3.44	3.38
pO ₂	13.81	9.53
HCO ₃ ⁻	20.4	19.6
Base excess	-4.9	-5.9
Saturations	98%	94.7%
Lactate	1.74	1.38

pCO₂, partial pressure of carbon dioxide; pO₂, partial pressure of oxygen.

The initial plain chest radiograph was reported as having no gross lung lesion seen, although the right heart border and medial aspect of the right hemi-diaphragm was felt to be indistinct, indicating right middle and lower lobe involvement (figure 1).

On the basis of the patient's chest pain, cough and shortness of breath, and the results of these initial tests, he was diagnosed with a right lower lobe community acquired pneumonia on the background of a possible H1N1 infection, and acute renal failure secondary to diarrhoea and vomiting. A differential diagnosis was generated and further investigations were carried out accordingly.

DIFFERENTIAL DIAGNOSIS

The principle differential diagnoses at this time were the organisms which are responsible for causing typical and atypical pneumoniae. As such, blood cultures, sputum microscopy, culture and sensitivity, *Mycoplasma* serology and urinary *Legionella* and *Pneumococcus* antigen tests were performed in order to identify the offending pathogen. On day 1 post admission, antigens to *L pneumophila* were found in the patient's urine thereby giving the diagnosis. This was later confirmed by the results of sputum culture from samples taken on the same day.

TREATMENT

Although the patient had an admission CURB-65 score of 2, he was referred to the intensive care team because of his type I respiratory failure and acute renal failure. The admitting staff commenced him on intravenous benzylpenicillin and clarithromycin in line with the Trust's antibiotic policy for treatment of community acquired

Figure 1 Admission radiograph, day 1, 09:47. No gross lung lesion.

pneumoniae. He was also commenced on a trial of continuous positive airway pressure (CPAP), and aggressively fluid resuscitated. Despite this initial therapy, his blood pressure fell and he failed to tolerate the CPAP. He was therefore transferred directly to the ICU from the ED for supportive management of what was now three organ failures.

The patient remained on the Unit for 27 days. During this time, each organ failure was considered daily and the management plan altered according to response to treatment.

On day 1, his intravascular volume was optimised by fluid resuscitation targeted against oesophageal Doppler cardiac output monitoring. However, this alone proved inadequate to achieve desired blood pressures, and so he was started on a norepinephrine infusion with good effect. At this time, the results of *Legionella* urinary antigen tests taken on admission became available; they were positive for *L pneumophila* and this was later confirmed by sputum culture from samples obtained on the same day. As a result, his antibiotic therapy was changed immediately as per specialist microbiological advice with benzylpenicillin being stopped in favour of rifampicin.

Laboratory testing on day 2 showed worsening renal failure, and so haemofiltration was commenced. This continued on an intermittent basis until the patient's renal function returned to normal some 10 days later.

Unfortunately, the previous day's improvement in cardiovascular parameters did not persist, and he soon developed episodic cardiovascular instability fluctuating between extreme hypotension and hypertension. As a result of these fluctuations, the norepinephrine infusion could only be used intermittently, and indeed over a period of days this was ceased altogether. The hypotensive episodes then became controlled by colloid challenges alone with good effect. The hypertensive episodes, however, seemed to be largely resistant to treatment for the majority of his inpatient stay and was likely to be the causative agent for his subsequent pulmonary oedema and acute lung injury. The hypertension and pulmonary oedema were eventually stabilised on a cocktail of amlodipine, metoprolol and ramipril, as well as clonidine and glyceryl trinitrate infusions.

Over the next few days it became evident that the change to his antibiotic therapy was affording limited benefit. His ventilation and oxygenation parameters were not improving and his respiratory failure was difficult to manage owing to the production of large quantities of mucopurulent, blood streaked secretions. In order to maintain adequate saturations, we carried out frequent suctioning and recruitment manoeuvres, and used inverse I:E ratios during this early part of his admission.

A week after presentation, further organisms were cultured from the patient's respiratory tract. His sputum grew *Candida* and gram negative rods, while broncho-alveolar lavage (BAL) specimens grew coliforms. These were treated with fluconazole and gentamicin commenced on days 8 and 9 respectively. Several days after this, an imipenem resistant *Pseudomonas* was also identified. Despite being started on appropriate antibiotic therapy for both the *Legionella* and additional cultured

organisms, he failed to make any significant clinical improvement over the coming days. Therefore further specialist microbiological advice was sought, and on this basis rifampicin and gentamicin were discontinued on day 16, in favour of tazocin (in addition to the clarithromycin and fluconazole) to cover for a ventilator associated pneumonia. This proved extremely effective and the patient's ventilation parameters improved greatly. Eight days later and 24 days after being admitted to the hospital, he was able to self-ventilate; his tracheostomy was decannulated and he was commenced on oxygen via nasal cannulae.

OUTCOME AND FOLLOW-UP

The patient was fit for discharge to a general medical ward after 27 days in intensive care, and was discharged from the hospital after a 31-day inpatient stay. He had no residual problems from either the *Legionella* pneumonia or its complications, and as such did not require any follow-up by the intensive care team, although routine outpatient appointments were made for him under the respiratory physicians.

DISCUSSION

Diagnosis of atypical pneumoniae is often delayed. This maybe attributable to multiple factors, not least that while community acquired pneumoniae are common in the ED, atypical pathogens are rarely the responsible organisms, and so they are frequently forgotten in the differential. Moreover, the atypicals can easily be misdiagnosed as viral illnesses such as H1N1, owing to the non-specific way in which they can present. For example, *Legionella* predominantly causes respiratory symptoms such as a mild cough with blood streaked sputum, but it can also cause diarrhoea, nausea, vomiting and abdominal pain, as well as lethargy, headache, fever and myalgia.⁸ Furthermore, government advice during the international flu pandemic, was that patients with non-specific symptoms such as these, were to stay at home and have a friend or family member collect a prescription for oseltamivir on their behalf. In our patient's case, all of these factors combined to slow the timeliness of his diagnosis and instigation of appropriate treatment.

In keeping with the variable presentation described above, there is also a wide range of examination findings. For example, Legionnaires commonly cause fever with signs of pulmonary consolidation, but may also result in rashes, neuropathy and signs of disseminated intravascular coagulation and glomerulonephritis.⁹ The spectrum of disease exhibited by patients therefore ranges from a mild, self-limiting flu-like illness termed Pontiac fever, to multi-organ failure.¹⁰

Further investigation involves biochemical and microbiological tests, as well as blood gas analysis and radiology; many of these were initiated in our ED. Biochemical derangements include a low serum sodium (which is more common in Legionnaires disease than in other causes of community acquired pneumonia, and is secondary to the syndrome of inappropriate antidiuretic hormone secretion),¹¹ elevated creatinine, bilirubin, lactate dehydrogenase and C reactive protein. Microbiological

investigation relies on culture of respiratory secretions, for example, sputa and specimens obtained from BAL.⁴ These are the gold standard investigations for *Legionella*, because culture has a specificity of 100% and is deemed the 'only reliable method of detecting infection with non-pneumophila *Legionella* species'.⁴ However, culture is an involved process which takes time, and so the rapid '*Legionella* urinary antigen test' is often used as an adjunct. This test also benefits from the ease with which a specimen can be obtained, and the fact that the antigens persist in the urine several months after infection, regardless of treatment.¹² However, it can only be used to identify *L pneumophila* serogroup 1,^{4 11} and has variable sensitivity.⁴ *L pneumophila* accounts for approximately 90% of cases of legionellosis, and serogroup 1 for 80% of these,¹³ thus leaving a significant number of cases for which this test is not suitable.

ABG analysis typically shows an increased A-a gradient, consistent with pulmonary infection and suboptimal gas exchange, as demonstrated in this case. There are no diagnostic findings on plain chest radiograph,¹ although common features include unilateral, rapidly progressive pulmonary infiltrates primarily affecting the lower lobes, and pleural effusions.¹ As with other causes of pneumonia, there is a delay before the radiographic changes reflect the clinical status of the patient.^{1 4} This was striking in our patient's case because he was admitted with a respiratory rate of 42 breaths/min and type I respiratory failure, but with minimal changes on the initial film. Serial films, however, clearly demonstrated the speed with which his infection evolved (figures 2–6).

Since *Legionella* causes such a broad spectrum of symptoms, its differential diagnoses reflect this. The most likely alternative pathogens are those that affect several organ systems, such as *Mycoplasma pneumoniae*. Other differentials can be subcategorised based upon the organ systems affected:

Pneumonias	Respiratory failure	Acute renal failure
Atypical bacterial pneumonias, eg, <i>Mycoplasma</i> , <i>Chlamydia</i>	Pneumonia	Sepsis
Viral pneumonias, eg, influenzae A or B, H1N1	Pulmonary embolus	Dehydration, eg, due to diarrhoea and vomiting
Typical bacterial pneumonias, eg, <i>Streptococcus</i>	Acute asthma	Drugs
Fungal pneumonias	Pulmonary oedema Acute respiratory distress syndrome	

As the case above clearly demonstrates, the mainstay of treatment is early and effective antibiotic therapy, as well as appropriate organ support. Prompt administration of antibiotics to the septic patient is crucial.^{14 15} Many hospital antibiotic guidelines suggest macrolides as part of their community acquired pneumonia protocol. These provide some empirical treatment for both *Legionella* and the other atypicals from the outset, as macrolides are known to be efficacious in the treatment of these organisms. However, fluoroquinolones are the recommended treatment of choice; in severe cases these may be combined with a macrolide or rifampicin.⁴

Although we could find no similar case reports elsewhere, it is clear that supportive requirements may be

Figure 2 Repeat radiograph, day 1, 12:17. AP view. No evidence of pneumothorax.

Figure 3 Repeat radiograph in ICU, day 1, 20:29. There is homogeneous hazy shadowing in the right mid and lower zones, most consistent with a pleural effusion.

Figure 4 Repeat radiograph, day 3 post admission. Persistent, extensive, air space shadowing seen in the right mid and lower zones with a probable associated effusion. Relatively minor air space shadowing seen in the left lung base, with a probable associated small left effusion.

extensive and so intensive care management should be considered early. Supportive measures include:

- Respiratory support: non-invasive or invasive ventilation and tracheo-bronchial toilet
- Cardiovascular support: invasive monitoring, volume optimisation and inotropic support
- Renal support: targeted fluid administration, catheterisation and haemofiltration.

Figure 5 Repeat radiograph, day 6 post admission. As previously there is hazy opacification of the right lung and probable bilateral pleural effusions.

Figure 6 Repeat radiograph, day 8 post admission. Persistent air space shadowing seen in the bilateral mid and lower zones with the changes in the left lung having developed since the previous radiograph. There are bilateral pleural effusions, larger on the right side.

The follow-up of patients post-ICU is a developing area. Although follow-up per se is not required after infection with *L pneumophila*, as effective antibiotic treatment should eradicate the organism, patients may benefit from further consultation. This is because such serious illness can exacerbate co-morbidities, adversely affect a patient's baseline function, and because patients

who have been ventilated may benefit from pulmonary rehabilitation. Additionally, prolonged stay in intensive care has a profound psychological impact, and so follow-up may be useful to debrief the patient, offer support and explain aberrant experiences, for example incomplete/inaccurate memories as a result of medication or illness.

Learning points

- ▶ *Legionella* is an important and often overlooked cause of both community acquired and nosocomial pneumoniae.
- ▶ *Legionella* can easily be misdiagnosed as a viral infection, particularly during the early stages of its course.
- ▶ It has a significant mortality associated with it, reaching 30% in those requiring intensive care admission.
- ▶ Effective treatment relies upon early administration of antibiotics and appropriate supportive measures. These supportive measures can be extensive, so early transfer to the ICU should be considered.

Competing interests None.

Patient consent Obtained.

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