

retrospective study of outcomes in a UK district hospital

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ABSTRACT – As the recent outbreaks in Edinburgh and Camarthen, UK, have shown, *Legionella pneumonia* (LP) remains a significant public health problem, which is not only confined to those who have travelled abroad. In both outbreaks and sporadic cases, diagnosis can go unrecognised. We reviewed the demographics, comorbidities, diagnosis, treatment and clinical outcome of LP cases over five years in a district general hospital in northwest England. Over half of LP cases were UK acquired and ‘classic’ clinical features were common. Clinical criteria for diagnosing LP were confirmed, but few sputum samples were sent to reference laboratories, limiting further essential epidemiological mapping of UK cases. Following current UK community-acquired pneumonia guidance would have missed nearly one quarter of LP cases in our series, potentially leading to further morbidity and mortality.

KEY WORDS: descriptive; atypical; *Legionella*; pneumonia; CURB-65; outcome

Introduction

Specific guidance on the investigation and early diagnosis of *Legionella pneumonia* (LP) is limited despite this infection comprising nearly 7% of all community-acquired pneumonias (CAP) in some series¹ and up to 13% of pneumonias dealt with in outpatient settings.² Rates of LP are increasing³ and it continues to cause high morbidity and mortality.⁴ Recent LP outbreaks, such as those in southwest Edinburgh and Camarthen, have been associated with acquisition of infection within the UK and are a stark reminder of the severity of the disease. UK Health Protection Agency (HPA) data have shown that, over the past 31 years (1980–2011), just over half of UK LP cases were associated with recent travel, mainly overseas.⁵ However, a travel history alone has little predictive value. Moreover, although presentation can include ‘classic’ features of atypical pneumonia, these features are not sufficient to accurately differentiate LP from pneumonia of other aetiology.⁶

Rapid testing for LP using *Legionella* urinary antigen (LUA) is now widely available and reporting of positive results to local public health authorities is not only recommended but is also a

legal requirement.⁶ The CURB-65 score⁷ enables severity assessment and can help optimise antibiotic therapy.

In 2011, in a report from the Cumbria and Lancashire Health Protection Unit of the HPA to the Department of Microbiology of Blackpool Teaching Hospitals, an uneven distribution of LP was noted in the Cumbria and Lancashire region, with clustering of 44% of total cases in the Blackpool area between 2001 and 2009 (Fig 1). This clustering did not appear to be either a UK-acquired community outbreak or related to the location of registered wet cooling systems (also known as industrial water coolants; Fig 2). When compared with other trusts serving similar-sized populations in the north west region, no increased frequency of LUA testing was found in Blackpool Teaching Hospitals that could have accounted for the apparent clustering of cases (Fig 3).

An observational, descriptive, retrospective analysis of all LP cases over the preceding five years was undertaken to examine the apparent clustering of cases in north-west England.

Methods

In total, 26 LP cases with a positive LUA test (BinaxNOW, Inverness Medical, UK) were identified from the pathology database of the Blackpool Teaching Hospitals between July 2006 and July 2011. This time period was chosen because microbiological reporting was standardised to the computerised pathology database from 2006 onwards.

Case-note review was undertaken to gather specific data on demographics, comorbidities, foreign travel history, clinical and microbiological findings, diagnosis, treatment and clinical outcome (Table 1). In addition, information on dates of symptom onset and delay before admission was collated from HPA data.

Statistical analysis involved comparisons of means using unpaired t-test for parametric data and Mann-Whitney U test for nonparametric data. Additional simple univariate logistic regression was performed using the STATA program (version 12).

Results

Demographics, history, comorbidity, duration of symptoms before admission and diagnosis, clinical findings, microbiological findings and outcome are summarised in Table 2.

Demographics

Of the patients, 20/26 (77%) were men, with a mean age of 66 years (median 66, range 41–87). Women had a higher mean age than

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men, but this was not significant (women 72 years, 95% confidence interval (CI) 60–87 vs men 63 years, 95% CI 57–68, $p=0.1$).

Of those that acquired LP in the UK, all residences were defined as ‘own home’ and no clustering was found between these postcodes.

Over half of the patients were current smokers, 14/26 (54%). Of those patients with documented data available, over two-thirds drank alcohol, 16/23 (70%), with over one third being moderate–heavy drinkers (alcohol unit intake >30 units per week).

Comorbidity

Three of the 26 patients (12%) were immunosuppressed: two patients were taking long-term steroids >15 mg daily and another patient with severe rheumatoid arthritis was taking adalimumab (an antitumour necrosis factor agent) and weekly methotrexate. In addition, four of the 26 patients (15%) had existing chronic kidney injury (CKI), with one of these patients being on regular dialysis before admission. Six of the 26 patients (23%) had diabetes.

Foreign travel

In total, 12/26 (46%) patients reported foreign travel within the previous month: 10/12 within Europe, with Italy and Spain being the most commonly visited destinations. Two patients had travelled beyond Europe (Fig 4).

Clinical and microbiological findings

In total, 96% (25/26) of patients had consolidation on chest X-ray: this was unilateral in 22/25 patients (88%) and bilateral in 3/25 (12%) patients. No patients had radiographic evidence of pleural effusions or pneumonitis.

Initial CURB-65 score was not documented in 15/26 patients (58%). Of the documented initial CURB-65 scores, the median was 3 (5/11, range 0–4). For those without a documented initial CURB-65 score, their score was subsequently calculated by the investigators using clinical documentation, blood results and physiological observations from case notes (see Discussion).

Of the 26 patients, 22 (85%) had new liver derangement, mainly hepatic with an isolated increase in aspartate transaminase (AST).

Mean serum sodium (Na) at diagnosis was 129.9 mmol/l (range 122–136), with 23/26 patients (88%) showing some degree of biochemical hyponatraemia. In addition, 9/26 (35%) of the patients had new-onset confusion or other neurological features. Mean serum Na in those with neurological features was 128.1 mmol/l

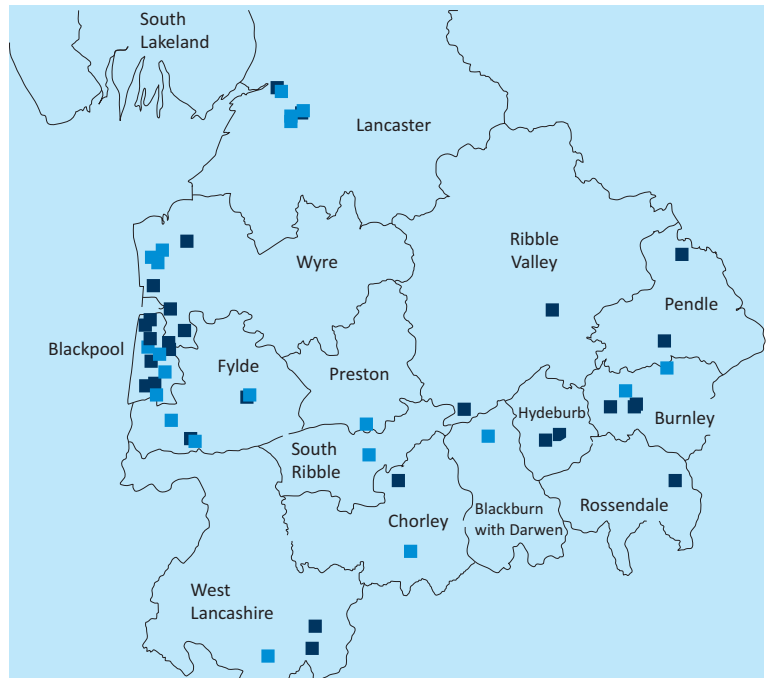


Fig 1. Geographical distribution of Legionella cases in northwest England, 2001–2009. Dark blue squares represent travel-associated cases, light blue squares represent community-acquired cases. © Crown copyright and database rights 2012, Ordnance Survey, 100016969.

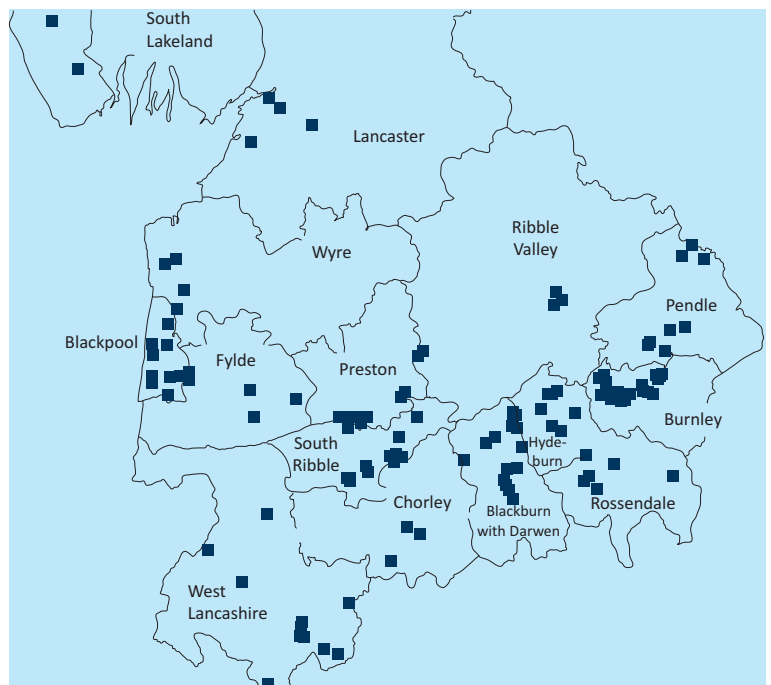


Fig 2. Geographical distribution of wet cooling systems in northwest England, 2001–2009. © Crown copyright and database rights 2012, Ordnance Survey, 100016969.

(n=9) and 131.7 mmol/l in those without neurological features (n=17); however, this trend was not statistically significant (p=0.09).

Diagnosis and treatment

Patients had a mean of four days between symptom onset and admission to hospital (range 0–14 days). LUA was identified a mean two days into admission (range 0–6 days), with results being phoned by laboratory scientists to the ward directly in all cases. The full time and date of the result given by telephone was documented in notes from 23/26 (88%) patients. The mean total number of days between symptom onset and diagnosis was six (range 1–15).

Antibiotic prescriptions in 6/26 patients (23%) did not conform to local or national guidance, with these patients receiving additional antibiotic groups or broader spectrum antibiotic cover than recommended at lower CURB-65 scores (data not shown). Of those who survived until discharge, 20/20 (100%) received appropriate antibiotic cover for LP (defined as 10–14 days of appropriate dose, route and choice of macrolide or quinolone). Antibiotic regimens after LP diagnosis are shown in Fig 5.

Outcome

The median length of stay (LOS) was five days (range 4–119, mean 18 days). Of the 26 patients, 15 (58%) were treated on a specific respiratory medicine ward. In addition, 7/26 (27%) of the patients required care in a high dependency (HDU) or intensive treatment (ITU) unit. Of the 26 patients, six (23%) died, five of whom died within the first five days of admission. Two of these patients died on ITU, one on HDU, and the remaining two on respiratory wards.

Those who died during admission were significantly older than those who survived to discharge (79 years (95% CI 70–88) vs 60 years (95% CI 55–66), p<0.001). Of those who died, five (83%) had UK community-acquired LP. The demographics of patients who died are shown in Table 3.

Of those surviving to discharge, 3/20 (15%) were readmitted within three months, all for unrelated medical conditions.

On univariate logistic regression analysis of the effect of demographic and clinical variables on outcome, only lower age was associated with a decreased likelihood of death (OR 0.83 (95% CI 0.72–0.97), p<0.02). There was a tendency towards lower CURB-65

Table 1. Data collection proforma and definitions

Data collected	Definition and explanation of collected data
Demographics and/or relevant history	<ul style="list-style-type: none"> Age (at time of presentation) and gender Postcode and type of residency: own home, residential and/or nursing home Smoking history: defined as current smoker yes or no Alcohol intake: 21–30 units defined as moderate, >30 units high Foreign travel to include destination and length of stay
Comorbidities	<ul style="list-style-type: none"> Immunosuppression: defined as primary immunodeficiency disorder or secondary disorder owing to HIV or medication including prednisolone >15 mg/day or other immunosuppressive agents Other severe chronic illness, including liver, lung and kidney disease: defined as disease requiring input from a secondary care specialist (ie consultant in renal, respiratory or gastroenterology medicine) Diagnosis of diabetes (data were not collected on duration or type of diabetes, recent diabetes control or type of diabetes treatment)
Clinical and microbiological findings	<ul style="list-style-type: none"> New neurological dysfunction or encephalopathy (any neurological presentation, such as nerve palsies, confusion or sensorineural deficit) Chest radiograph findings: none, unilateral consolidation, bilateral consolidation, pleural effusions or pneumonitis Documentation of CURB-65 score by admitting physician Recalculated CURB-65 score based on clinical documentation and physiological observations in case notes New liver derangement: data on peak aspartate transaminase levels, alkaline phosphatase levels and bilirubin taken using local normal ranges as standard, previous results examined if available Presence of new hyponatraemia on admission: using local normal range as standard, 135–145 mmol/l New AKI: defined as creatinine newly higher than local normal range or deterioration in baseline estimated glomerular filtration rate
Diagnosis and treatment	<ul style="list-style-type: none"> Time elapsed between admission and positive LP result being alerted to the ward (based on documentation in notes of the time at which the result was phoned through to the appropriate ward to be actioned) Other <i>Legionella</i> tests sent (sputum culture and serology) Confirmatory tests sent to reference laboratory Antibiotic choices initially (and whether they conformed to local and national guidelines relating to CURB-65 score) Antibiotic choices after LP diagnosis confirmed Duration of antibiotic therapy Ward on which patient was cared for Maximum level of care required during admission (level 1 care = ward based being, level 2 care = high dependency unit (HDU), level 3 care = intensive therapy unit (ITU))
Outcome	<ul style="list-style-type: none"> Length of stay (LOS) Death (including number of days into admission) Readmission within three months of discharge

AKI = acute kidney injury; HIV = human immunodeficiency virus; LP = *Legionella* pneumonia.

scores (0–2) being associated with decreased likelihood of death, but this did not reach statistical significance (OR 0.18 (95% CI 0.23–1.33), $p=0.09$). No other demographic or clinical factors were predictive of outcome, including days from symptom onset to admission and diagnosis (Table 4). Subsequently, no multiple logistic regression analysis was performed.

Discussion

After being alerted by the HPA that, between 2001 and 2009, there appeared to be an uneven distribution of the LP cases in the Lancashire and Cumbria region, with 44% being in the Blackpool area, we undertook an observational, descriptive, retrospective analysis of all LP cases in our trust, Blackpool Teaching Hospitals, between July 2006 and July 2011.

LP was first reported after an outbreak at an American Legion conference in 1976⁸ and, since then, the number of LP cases in high-resource settings has continued to increase.⁹ *Legionella pneumophila* comprises 90% of Legionellaceae family infections,¹⁰ with *L. pneumophila* serogroup 1 being most common.¹¹ *Legionella spp.* are heat-stable bacteria that have been associated with colonisation of sources as varied as wet cooling systems, pollution-relieving aerosols,³ asphalt-paving machines,¹² spa pools,¹³ showers, fountains and even windscreen-wiper fluid containers.¹⁴

With LP being the cause of up to 7% of CAP and hospital-acquired pneumonias (HAP),¹ and with mortality in outbreaks being as high as 20%,⁴ the disease continues to pose a significant public health risk. A recent outbreak of LP in southwest Edinburgh resulted in high levels of morbidity and three deaths, while a current outbreak in Camarthen, South Wales remains under investigation (www.bbc.co.uk/news/uk-wales-19654519).

The proportion of patients with LP requiring care in HDU or ITU facilities is significant. Nearly one-fifth of CAP cases in ITU were related to LP in some series, higher than was found in those with CAP but not admitted to ITU.^{15,16} However, with early recognition and appropriate treatment, it is estimated that mortality can be reduced to below 5%.^{17–19}

Patients with LP are more likely to be male²⁰ and smokers,²¹ a trend that was followed in our cohort (77% male, 54% smokers). Although *Legionella* is known to affect any age group,²² the mean average age in our series was 65 years, with affected women being older than men.

Little evidence exists as to the effect of comorbidities on either acquisition or severity of LP. British²³ and Spanish²⁴ studies have demonstrated chronic illness and worsening kidney function to be associated with poorer outcome, as is chronic lung disease. There is little evidence for the severity of LP in immunosuppressed patients, although one study following up patients with systemic lupus erythematosus taking infliximab reported a death secondary to LP.²⁵ However, only a small number in our series were immunosuppressed or had chronic kidney disease.

Over two-thirds of our cohort drank alcohol, 38% of whom were moderate to heavy drinkers. Alcoholism has previously been recognised as a predictor of more severe disease.²⁴

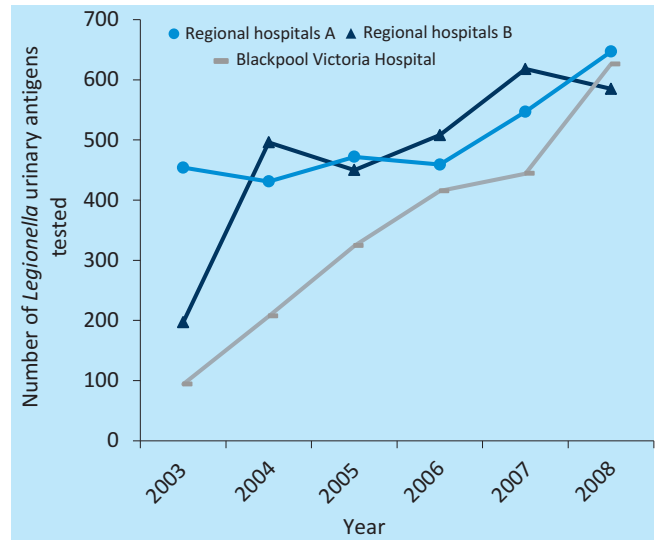


Fig 3. Number of Legionella urinary antigen (LUA) tests per regional hospital. Regional hospitals A (dark blue line) and B (light blue line) serve populations of a similar size to Blackpool Victoria Hospital (grey line). Data courtesy of the Cumbria and Lancashire Health Protection Unit.

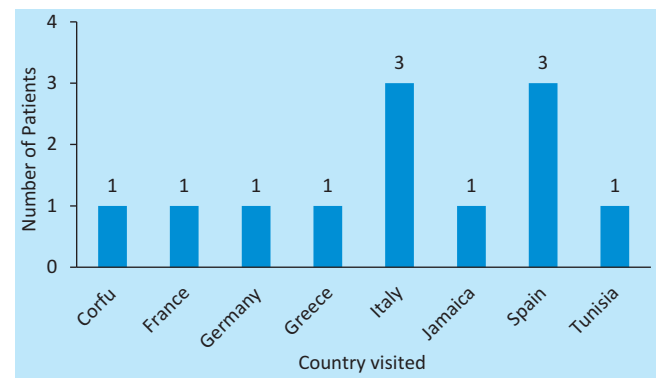


Fig 4. Destination of those patients with a relevant travel history (n=12).

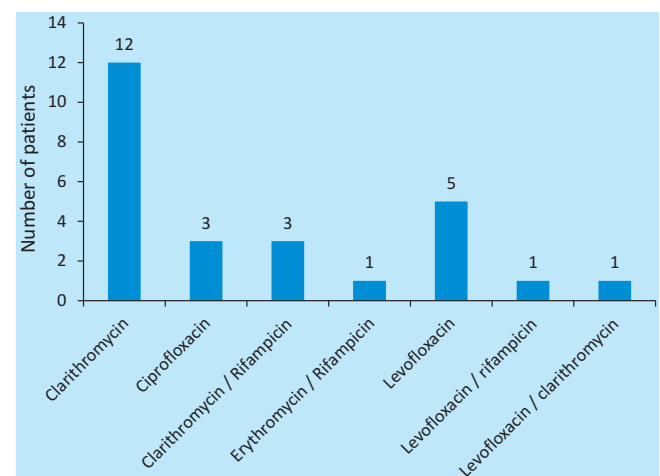


Fig 5. Choice of antibiotic for Legionella cover after diagnosis (n=26). Sputum samples were collected for reference laboratory confirmation in 5/26 patients (19%).

Table 2. Demographics, comorbidities, foreign travel history and clinical and/or microbiological findings.

Patient demographics (n=26)	Number (% or range)
General demographics and social history	
Mean age (years)	66 (41–87)
Male sex	20 (77%)
Active smoker	14 (54%)
Drink alcohol	16 (70%)
Comorbidities	
Immunosuppressed	3 (12%)
Chronic kidney disease	4 (15%)
Diabetes	6 (23%)
Duration of symptoms and time to diagnosis	
Days from symptom onset to admission	4 (0–14)
Days from admission to diagnosis	2 (0–6)
Total days from symptom onset to diagnosis	6 (1–15)
Foreign travel	
No foreign travel	14 (54%)
Foreign travel in Europe	10 (42%)
Foreign travel outside of Europe	2 (4%)
Clinical and microbiological findings	
Consolidation on chest X-ray	25 (96%)
No CURB-65 score documented	15 (58%)
New liver derangement	22 (85%)
New hyponatraemia	23 (88%)
New neurological features	9 (35%)
Acute kidney injury (AKI)	14 (54%)
Initial CAP treatment according to recognised guidelines	20 (77%)
LP treatment according to recognised guidelines	26 (100%)
Outcome	
Median length of stay (days)	5 (4–119)
Required HDU and/or ITU care	7 (27%)
Died	6 (23%)

CAP = community-acquired pneumonia; ITU = intensive treatment unit; HDU = high dependency unit.

In our study, 23% of patients had diabetes, which is higher than the 4.88% background local rate.²⁶ The apparent LP–diabetes association is biologically plausible, because diabetes impairs immune function²⁷ and has been linked with increasing susceptibility to other infections, such as tuberculosis.²⁸ However, it is more likely within our series that this association is confounded by age.

In patients with LP in the UK, infection is often associated with a travel history abroad (commonly to southern Europe).²⁹ Nearly half (46%) of our cohort had undergone foreign travel within the previous month (Fig 4), mostly within Europe, but with two

patients travelling further afield. Conversely, an interesting finding from our series was that 54% of patients had UK-acquired LP, none of whom had any relevant ‘within-UK’ travel history. This number is similar to that previously demonstrated in UK public health data. However, in contrast to these previous data, which had suggested that fewer than 10% of cases were related to travel inside the UK, none of the patients with UK-acquired LP in our series reported such travel.³⁰ This is likely to be biased by lack of documentation in clinical notes.

Recent evidence suggests that wider availability of LUA test has led to increased diagnosis of nosocomial LP that might otherwise have gone unnoticed;³¹ however, all patients in the current series had confirmed CAP. No postcode clustering was found in UK-acquired cases to account for a geographically linked pattern of LP acquisition or transmission (data not shown). In addition, after liaison with local environmental health department officers, who reviewed previous *Legionella* sources and their updated register of wet cooling systems, neither did the Cumbria and Lancashire Health Protection Unit find any associated geographical clustering of wet cooling systems in the region. However, it was acknowledged that it was unlikely that all wet cooling systems would be registered with the appropriate authorities for analysis. Other potential explanations, such as local weather patterns, were not examined within the confines of this study, and the HPA remains vigilant to new LP cases and continues to monitor the local situation.

A variety of well-recognised clinical and biochemical features are suggestive of LP, including fever, gastrointestinal disturbance, confusion, meningoencephalitis, new neurological features (such as nerve palsies, including Guillain–Barré syndrome), deranged liver function tests, hyponatraemia and kidney failure.^{8,32–34} Many of our cohort had a combination of these ‘classic’ features, indicating that they continue to be relevant in clinical assessment: 88% had biochemical hyponatraemia; 54% had AKI, as shown in other series;³³ 85% had hepatitis liver derangement (only 7% showed a cholestatic picture); and 35% had new-onset confusion or other neurological features. Although there was a trend in our series towards lower mean average serum Na in those patients presenting with neurological features than those without, this did not reach statistical significance.

Of note for the clinician, two patients with LP and neurological features presented with marked cerebellar syndrome, an uncommon but recognised presentation.³⁵

LUA testing is rapid, highly specific and recommended as a first-line diagnostic test for early *Legionella* diagnosis.³⁶ However, LUAs only identify *L. pneumophila* Serogroup 1 and have moderate overall sensitivity (74% in a recent meta-analysis),³⁷ which improves with greater disease severity.¹⁸ The mean average of two days until a positive LUA result in our study is likely to reflect ward-based delay in requesting the test, rather than a lab-based delay in reporting the result; however, it was not possible to verify this from analysis of patients’ case notes. Although on regression analysis no association between outcome and time from symptom onset to admission or diagnosis was found, this is likely to be related to the size of our patient cohort being too small to identify any possible effect.

Most patients (25/26, 96%) had consolidation on chest X-ray: in 22/25 patients (88%), this was unilateral, a propensity that has been noted in other studies.³⁸

Despite wide recognition in the UK of the CURB-65 score and its incorporation into both local and national CAP guidelines, admission CURB-65 score was not documented in over half of the patients. Furthermore, the antibiotic prescription was inappropriate for the severity of disease (as per documented CURB-65 score) in 23% of patients. Of particular note, a significant proportion of patients had a recalculated CURB-65 score of 0–2 (62%). Table 5 shows the demographics of this subgroup. Of these patients, who had either risk factors for, or travel history suggestive of, LP, 77% received appropriate *Legionella* cover. However, 23% of these patients with a CURB-65 score <2 had neither relevant travel history nor any documented evidence of high clinical *Legionella* suspicion, but still went on to have a LUA test sent and began treatment with antibiotics that included cover against *Legionella* (a macrolide in all cases). It is unclear whether the choice of macrolide in these cases was the result of suspicion of ‘atypical’ pneumonia, but it is clear that strict adherence to national CURB-65 guidance in these patients with low CURB-65 scores would have meant not testing or treating for atypical pneumonias, including *Legionella*. Current UK guidance recommends *Legionella* testing in ‘severe’ pneumonia (CURB-65 ≥3), when there is high clinical suspicion, or during outbreaks.⁶ There was no known acute outbreak of *Legionella* locally at this time and so guidance would have missed nearly one-quarter (6/26) of *Legionella* cases in our series. It may be postulated that, despite their low CURB-65 scores, these patients had other clinical features that made the ‘clinical suspicion’ for potential *Legionella* diagnosis high (eg failure to respond to first-line beta-lactam or aminoglycoside antibiotics in the community, profound hyponatraemia, deranged liver function tests, neurological signs or multisystem involvement). However, it was not possible to elicit this subjective ‘clinical suspicion’ from the patient case notes with any certainty.

Of those who survived until discharge, 20/20 (100%) received appropriate *Legionella* therapy as documented in Fig 5, and all of these patients had microbiology clinician involvement.

Full typing and resistance profiling of both the urine and sputum samples of LP patients at reference laboratories is recommended. However, sputum testing occurred in only 19% of our cases. LP remains a significant public health problem and acquisition of quality epidemiological data will require the vigilance of physicians to send further confirmatory tests that might not be of direct benefit to the patient but of benefit to the wider community. This issue could be brought to the clinician’s attention on reports of a positive diagnosis or through phone calls from the microbiology department to the patient’s attending physician.

Overall morbidity and mortality were high, with nearly one-third of patients requiring HDU or ITU care. Median LOS in those treated on HDU or ITU was 31 days, as opposed to five days if managed on a ward. Nearly one-quarter of the patients died, mostly early into admission, with five of the deaths being within the first five days. Although data from outbreak studies have shown mortality rates of up to 20%,⁴ the mortality rate seen in our cohort

Table 3. Demographic data for those patients who died during admission (n=6).

Category	Demographic	Patients with <i>Legionella pneumonia</i> who died (n=6)
Demographic	Age (mean years)	78.8
	Sex (male)	5
Travel history	Yes, foreign or other travel before admission	1
Smoker	Yes, active smoker	4
Comorbidity	Chronic kidney injury (CKI)	2
	Severe liver disease	0
	Severe lung disease	1

Table 4. Simple univariate logistic regression of the effect of demographic and clinical variables on outcome of survival to discharge in patients with *Legionella pneumonia*.

Variable	Odds ratio	Standard error	P value	95% CI
Age	0.83	0.06	<0.02	0.72–0.97
Male sex	0.6	0.73	0.673	0.56–6.44
Smoker	0.75	0.73	0.8	0.11–5.11
Alcohol drinker	3.25	3.24	0.3	0.46–22.90
Diabetic	1.67	2.02	0.7	0.16–17.90
Known chronic kidney injury (CKI)	0.22	0.25	0.2	0.02–2.10
Relevant travel history	6.11	7.24	0.1	0.6–62.2
Neurological features	1.08	1.06	0.9	0.2–7.4
Newly deranged liver function tests	4.5	5.14	0.2	0.5–42.3
CURB-65 <3	0.18	0.18	0.09	0.2–1.3
Days from symptom onset to admission	0.98	0.15	0.9	0.7–1.3
Days from admission to diagnosis	0.85	0.26	0.6	0.5–1.6
Total days from symptom onset to diagnosis	0.94	0.14	0.7	0.7–1.3

of unrelated cases is higher. The patients who died were older than the cohort average (79 vs 65 years, p=0.017), half had severe chronic illness and two-thirds were ongoing smokers. The difference in mortality rates between our cohort and those of outbreaks may relate to heightened clinical suspicion during outbreaks.

This study has several limitations. First, it describes a patient group of limited numbers, enabling only minimal statistical analysis. Second, its retrospective design means that it is reliant on data collection from documentation in clinical case notes. Finally, no comparison was made with demographic, clinical and outcome data of patients with non-*Legionella* pneumonias within the same study setting.

Conclusions

In our study, over half of *Legionella* infections were UK-acquired, indicating that a travel history alone is an insufficient clinical indicator for *Legionella* disease. Classic atypical features were common, as was the well-recognised association with hyponatraemia, a greater degree of which was seen in those with neurological derangement. Only a few sputum samples were sent to a reference laboratory, limiting further epidemiological mapping of UK *Legionella* cases. There was high morbidity and mortality, with nearly one-third of patients requiring HDU or ITU care and over one-quarter dying, mainly within the first week of admission. Although generally poorly documented, in patients for whom a CURB-65 score was recorded, over half had a score of 0–2, which would indicate neither requesting of a *Legionella* test nor empirical LP treatment, according to current UK guidelines; therefore, LP cases might be being missed, untreated or both.

Our study highlights the need for clinicians to consider a diagnosis of LP, be aware that travel history or low CURB-65 score do not preclude the diagnosis, treat suspected LP early and appropriately and be vigilant in collection of samples for essential epidemiological profiling.

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