The effect of a large Legionnaires' disease outbreak in Southwest Edinburgh on acute and critical care services

J.F. IRONS1,2, M.J.G. DUNN1,2, K. KEFALA1,2, S. THORN3, F. LAKHA3, D. CAESAR2,4, D.D. CAMERON1,2, D. MCCORMICK3, A. MCCALLUM3, K.O. HELGASON2,5, I.F. LAURENSON2,5, R.L. PATERSO1,6, A. GREENING6,7, M. FRIED1,8, A.T. HILL2,7, M. HANSON5,6 and M.A. GILLIES1,2

From the 1Department of Anaesthesia, Critical Care and Pain Medicine, 2The Royal Infirmary of Edinburgh, Edinburgh, UK, 3Department of Public Health, NHS Lothian, 4Department of Emergency Medicine, 5Department of Microbiology, The Royal Infirmary of Edinburgh, Edinburgh EH16 4SA, UK, 6The Western General Hospital, Edinburgh EH4 2XU, UK, 7Department of Respiratory Medicine, The Royal Infirmary of Edinburgh, Edinburgh, UK and 8St John’s Hospital, Livingston EH54 6PP

Address correspondence to M.A. GILLIES, Department of Anaesthesia, Critical Care and Pain Medicine, Royal Infirmary of Edinburgh, Edinburgh, EH16 4SA, UK. email: michael.gillies@ed.ac.uk

Received 16 June 2013 and in revised form 26 July 2013

Summary

Objective: The largest outbreak of Legionnaires Disease (LD) in the UK for a decade occurred in Edinburgh in June 2012. We describe the clinical and public health management of the outbreak.

Setting: Three acute hospitals covering an urban area of ~480,000.

Methods: Data were collected on confirmed and suspected cases and minutes of the Incident Management Team meetings were reviewed to identify key actions.

Results: Over 1600 urine samples and over 600 sputum samples were tested during the outbreak. 61 patients with pneumonia tested positive for Legionella pneumophila serogroup 1 by urinary antigen detection, culture, respiratory PCR or serology. A further 23 patients with pneumonia were treated as suspected cases on clinical and epidemiological grounds but had no microbiological diagnosis. 36% of confirmed and probable cases required critical care admission. Mean ICU length of stay was 11.3 (±7.6) days and mean hospital length of stay for those who were admitted to ICU was 23.0 (±17.2) days. For all hospitalized patients the mean length of stay was 15.7 (±14) days. In total there were four deaths associated with this outbreak giving an overall case fatality of 6.5%. Hospital and critical care mortality was 6.1% and 9.1%, respectively.

Conclusions: A significant proportion of patients required prolonged multiple organ support or complex ventilation. Case fatality compared favourably to other recent outbreaks in Europe. Access to rapid diagnostic tests and prompt antibiotic therapy may have mitigated the impact of pre-existing poor health among those affected.

Introduction

Legionella pneumophila is commonly present in natural water sources (e.g. rivers, lakes) as well as in man-made systems, e.g. cooling towers, condensers, water tanks and shower/sprinkler systems. Under certain conditions: water temperatures of 20–45°C; stored/recirculated water; where there is a source of nutrients (e.g. sludge, scale or fouling) they may grow in increasing numbers. Outbreaks of Legionnaires Disease (LD) occur when water containing high concentrations of Legionella bacteria is aerosolized and inhaled. Legionella species are implicated in two clinical syndromes: LD, a serious
bacterial pneumonia and Pontiac Fever, a self-limiting, influenza-like illness. The incubation period for LD is 4–19 days.1

Between the 28 May 2012 and the 13 July 2012 a large outbreak of LD occurred in Edinburgh, the capital city of Scotland with a population of ~480 000. This outbreak was identified on the 3 June 2012 after four patients admitted to critical care with severe community-acquired pneumonia (CAP) within a 4-day period tested positive for L. pneumophila.

An Incident Management Team (IMT) was convened on the 3rd of June, in line with the Scottish Government framework for managing public health incidents. The IMT included representation from: Microbiology, Public Health, critical care, Respiratory Medicine, Primary Care, The Health and Safety Executive (HSE), Environmental Health, Health Protection Scotland and the Scottish Government. Case definitions were developed by the IMT in accordance with European Guidance.2,3 Three acute hospitals in NHS Lothian were involved in this outbreak: The Royal Infirmary of Edinburgh (RIE), a 900 bedded hospital with a 18 bedded general Intensive Care Unit (ICU) and a 12 bedded general High Dependency Unit (HDU), the Western General Hospital (WGH), Edinburgh a 600 bedded with 9 ICU and 5 HDU beds and St John’s Hospital (SJH), Livingston a 500 bedded hospital with 3 ICU and 2 HDU beds. All are university affiliated teaching hospitals and cover a population of ~850 000.

This article describes the demographic and clinical features of the patients affected by this outbreak, the clinical and public health management of the outbreak and its impact on acute and critical care services.

Methods

The proposed study protocol was reviewed by the Chairs of South East Scotland Research Ethics Committees 01 and 02; as a management of a disease outbreak study, was deemed as not requiring NHS ethical review. The NHS Lothian Caldicott Guardian advised on the data flows, reviewed the collected data for disclosivity and approved the final manuscript. Written consent was obtained from one patient, where there was potential for disclosure secondary to media coverage.

Case definitions of LD

The following case definitions were developed by the IMT at the initial meetings and used throughout the outbreak and afterwards to categorize associated cases. These definitions are based on the European Working Group for Legionella Infection (EWGLI) definitions.4

A confirmed case was defined as an individual with an acute lower respiratory infection with focal signs of pneumonia on clinical examination and/or radiological evidence of pneumonia and one or more of the following: isolation of any Legionella organism from respiratory secretion, lung tissue or blood; a 4-fold or greater rise in specific serum antibody titre to L. pneumophila (serogroup 1); the detection of specific Legionella antigen in urine using validated reagents and methods.

A probable case was defined as an individual with a diagnosis of CAP and microbiological evidence of L. pneumophila infection which did NOT meet the definition of laboratory confirmation.

A possible case was defined as an individual with diagnosis of CAP.

In all cases disease onset was on or after 14 May 2012 and the patient had links to South West Edinburgh, i.e. lived or worked in the area or visited in the 2 weeks preceding symptoms. This was ascertained by interviewing all patients or their relatives.

Clinical management

Antibiotic guidance was produced on by the IMT (based on the British Thoracic Society (BTS) guidelines):5

Severe pneumonia: Either CURB65 score ≥ 3, hypoxaemia or hypotension. Patients received empirical treatment with intravenous (IV) levofloxacin 500 mg twice daily. IV or oral clarithromycin (500 mg twice daily) was added at the discretion of the treating clinician. If therapy with both levofloxacin and clarithromycin was given, it was recommended that patient’s liver function tests and QT interval were monitored. Moderate pneumonia: This was defined as patients who required hospitalization but who did not meet the criteria for severe disease. These patients were treated empirically with IV or oral levofloxacin (500 mg 1–2 times daily). If oral levofloxacin was not available then oral ciprofloxacin (750 mg twice daily) plus amoxicillin (or co-amoxiclav) was advised as a suitable alternative regimen. Mild pneumonia: This was broadly defined as patients who did not require hospital admission and patients were treated empirically with oral clarithromycin (500 mg twice daily).

Data collection

Active surveillance was established to detect patients who could potentially be suffering from LD on the 3 June 2012. 57 cases were interviewed and completed an epidemiological questionnaire after diagnosis to obtain ‘travel diaries’ and ascertain
place of residence and work, date of symptom onset, co-morbidities, age and gender. Following the outbreak, data on all confirmed and probable cases were extracted from patients’ medical records. This data included age, gender, co-morbidities, hospital length of stay and hospital outcome. Documented cardiovascular disease (including a history of ischaemic or valvular heart disease or heart failure) respiratory disease (asthma, chronic obstructive pulmonary disease or lung fibrosis), chronic kidney disease, chronic liver disease or immunosuppression (systemic steroids or immunosuppressant therapy) was recorded.

Where patients were admitted to critical care, data on demographics, acute physiology, therapeutic interventions and outcome were extracted using the Scottish Intensive Care Society Audit Group’s data collection programme ‘Wardwatcher’.

Five of the confirmed cases and one suspected case received treatment in hospitals outside Lothian. Although local teams were contacted to obtain as much information as possible, these patients’ data were incomplete.

Microbiological testing and laboratory diagnostic methods

Clinicians treating suspected cases were advised to submit urine for detection of L. pneumophila serogroup 1 urinary antigen, sputum or bronchoalveolar lavage samples for molecular testing and culture, and paired sera for specific antibody detection from patients suspected of suffering from Legionella pneumonia. In addition, respiratory samples were processed to detect: Influenza virus A and B, respiratory syncitial virus (RSV), parainfluenza virus types 1-4, adenovirus, Mycoplasma pneumoniae, metapneumovirus and rhinovirus.

Detection of L. pneumophila serogroup 1 urinary antigen was performed using a rapid, specific immunochromatographic assay (BinaxNOW™ Legionella Urinary Antigen Test, Alere, Stockport, UK). An in-house multiplex real-time polymerase chain reaction (PCR) assay was used to detect both L. pneumophila and Legionella species in respiratory samples. Extra laboratory resources were urgently made available during the outbreak. Samples positive by PCR at the Department of Laboratory Medicine in the RIE were referred to the Scottish Haemophilus, Legionella, Meningococcus and Pneumococcus Reference Laboratory (SHLMPRL) for culture and typing. Cultures of L. pneumophila from post-mortem lung tissue from three critical care patients were also sent to SHLMPRL for confirmation and typing.

A confirmed case was defined as a case of CAP with either a positive culture, L. pneumophila serogroup 1 urinary antigen test, or 4-fold or greater rise in specific serum antibody. A positive respiratory PCR only was used to define a probable case.

Statistical analysis

Descriptive statistics were carried out using STATA v12 (Statcorp, TX, USA).

Results

Laboratory results

During the outbreak period 1680 urine samples and respiratory samples were tested. Sixty-one patients with pneumonia tested positive for L. pneumophila by urinary antigen detection, culture, respiratory PCR or serology: 54 were confirmed cases and a further 7 were probable (i.e. positive PCR only). A further 23 patients with pneumonia were treated as suspected cases on clinical and epidemiological grounds but were not microbiologically confirmed. 1626 urine samples and 572 sputum samples tested negative.

Infection with L. pneumophila serogroup 1 was confirmed by urinary antigen detection in 19 critical care patients. Overall, 15 patients had culture positive respiratory samples, and the causative organism was identified as L. pneumophila serogroup 1, monoclonal subtype Knoxville, sequence type ST 191.

Eight patients with positive PCR results on respiratory secretions tested negative for L. pneumophila by urinary antigen in our laboratory. Six had samples sent to the reference laboratory in Glasgow for further testing and of these, four were subsequently confirmed with Legionella infection. The reference laboratory uses Binax™ Legionella Urinary Antigen EIA (Alere), an enzyme immunoassay which is more sensitive than the Binax™ immunochromatographic assay.

Descriptive epidemiology

Initially a total of 101 cases of pneumonia were associated with this outbreak over a 6-week period, however the final number of cases based on the case definitions was 54 confirmed cases, 7 probable cases and 23 possible cases.

Figure 1 shows the mapping of cases as of 29 June 2012. Based on clustering of cases, location of cooling towers and the prevailing wind, the IMT hypothesized that the most likely source of infection was cooling towers to the north-east of the affected
area. Figure 2 shows the temporal distribution of cases over the 6 weeks of the outbreak by onset of symptoms, hospital and critical care admission. It was postulated that a common airborne exposure occurred during the period 12–28 May. Peak presentation occurred over the week commencing 4 June 2012.

Public health management
Potential sources of the outbreak were sampled, and immediate action was taken to disinfect cooling towers with chlorine. Much of the public health management is described elsewhere.3

Hospital and critical care resource management
Forty-nine (80.3%) of the confirmed or probable cases were admitted to hospital. Twenty-two patients (44.5% of those admitted to hospital) required critical care admission; 19 were admitted to ICU and 3 to HDU.

The IMT met daily for the first 2 weeks of the outbreak and every 2 or 3 days thereafter (a total of 15 times) to review the progression of the outbreak, including: information from Environmental Health, numbers of patients presenting at general practice surgeries and emergency departments and acute and critical care beds. In addition it disseminated advice on testing and clinical management to all staff in NHS Lothian. Antimicrobial and testing guidance was issued to all staff on Tuesday 5 June and updated on Friday 8 June 2012. Beds occupied by patients with LD as a percentage of total critical care beds on each site for the month of June is shown in Figure 3. Four critical care transfers between hospitals in NHS Lothian occurred. At the WGH a four-bedded HDU area was created on a surgical ward to facilitate discharge of patients from ICU to HDU.

Demographic and clinical features
Demographic information on all confirmed and probable cases admitted to hospitals in NHS Lothian is presented in Table 1. The confirmed cases were typical of LD: predominantly males, smokers, aged over 50 and with other cardiorespiratory co-morbidities or impaired immunity. Twenty-two patients, 36% of the total confirmed and probable cases or 45% of hospitalized cases required admission to critical care.
Critical care management

Definitions of critical care are in line with UK Intensive Care Society definitions, i.e. Level 2 (HDU) Care being more detailed observation or intervention including support for a single failing organ system and Level 3 (ICU) Care being patients requiring advanced respiratory support alone or basic respiratory support together with support of at least two organ systems.

Of those patients admitted to critical care, 17 (77%) required mechanical ventilation. In those patients who were ventilated, the mean duration of ventilation was 10.3 (±6.0) days. Three patients (17.7%) required prone ventilation for severe Acute Respiratory Distress Syndrome (ARDS), two (11.8%) required treatment with inhaled nitric oxide, one (5.9%) required high frequency oscillatory ventilation (HFOV) and one (5.9%) referral for extra-corporeal membrane oxygenation (ECMO). Six patients (29%) required renal replacement therapy for acute kidney injury.

Length of stay and outcome

Mean ICU length of stay was 11.3 (±7.6) days and mean hospital length of stay for those who were admitted to ICU was 23.0 (±16.9) days. For all hospitalized patients the mean length of stay was 15.7 (±14) days.

In total there were four deaths associated with this outbreak giving an overall case fatality of 6.5%. The mortality among hospitalized cases was 6.1%. Critical care mortality was 9.1% overall and 13.6% for those cases admitted to ICU only.

Discussion

The United States Centre for Disease Control (US CDC) initially described LD as a cause of epidemic CAP following an outbreak at an American Legion convention in Philadelphia in 1976. Since 2003 there has been an abrupt rise in the incidence of LD, the reasons for which are unclear. The majority of cases of LD worldwide are caused by \textit{L. pneumophila} serogroup 1, the organism involved in this outbreak.
To date the largest UK outbreak occurred in Barrow-in-Furness in 1999 with 170 confirmed cases and the largest worldwide in Murcia, Spain with 449 cases. In Scotland 15–40 cases of LD occur annually of which approximately half are travel associated. This outbreak of LD is the largest in Scotland and the largest in the UK for a decade.

Epidemiological data from the US CDC suggests that LD predominantly affects males aged 45–64 years. In our group 72% cases were men and the mean age was 56.1 (±12.0). Co-existing cardio-respiratory disease, smoking, immunosuppression, diabetes and renal disease are all also known to be risk factors. LD is associated with low serum sodium, high fever, confusion, deranged liver function tests and absence of a productive cough. However, there is no single clinical feature that makes the presence of LD more likely than other causes of severe CAP. Fiemefreddo proposed a score based on six clinical and laboratory variables: temperature, absence of sputum production, serum sodium, lactate dehydrogenase, C-reactive protein and platelet count; however this score performed poorly in a case-control study.

In this outbreak over a third of patients required admission to critical care, similar to other reports. The mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score of those admitted to critical care was 23, suggestive of a high severity of illness in those patients. Significant proportions required renal replacement therapy and complex ventilation; one patient required transfer to a specialist centre for ECMO.

Case fatality rates for LD have decreased over the last three decades; the US CDC data reported a decline from 34% to 12% for all cases and from 26% to 9.1% for those requiring critical care.

| Table 1 Demographic, clinical and outcome data of confirmed and probable cases |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | All confirmed  | All confirmed  | Hospitalized   | Admitted       |
|                  | and probable   |                 |                 | critical care  |
| N                | 61             | 54              | 49              | 22             |
| Gender           |                |                 |                 |                |
| Male n (%)       | 44 (72%)       | 40 (78%)        | 36 (73%)        | 18 (82%)       |
| Female n (%)     | 17 (28%)       | 14 (22%)        | 13 (27%)        | 4 (18%)        |
| Age (mean ± SD)  | 56.1 (±12.0)   | 57.4 (±11.6)    | 57.5 (±12.1)    | 57.5 (±13.3)   |
| CURB65 ≥3        | 11 (18%)       | 10 (19%)        | 11 (22%)        | 8 (36%)        |
| Highest temp 1st 24 h C (mean ± SD) | 39.0 (±0.8) | 39.0 (±0.8) | 39.0 (±0.8) | 39.0 (±0.8) |
| APACHE II (mean ± SD) | 23 (±6.7) | 23 (±6.7) | 23 (±6.7) | 23 (±6.7) |
| Co-morbidities   |                |                 |                 |                |
| Chronic respiratory disease n (%) | 6 (9.8%) | 3 (5.6%) | 4 (9.8%) | 2 (9.1%) |
| Smoker n (%)     | 20 (32.8%)     | 17 (31.5%)      | 19 (38.8%)      | 8 (36.4%)      |
| Cardiovascular disease n (%) | 13 (21.3%) | 12 (22.2%) | 13 (26.5%) | 6 (27.3%) |
| Diabetes n (%)   | 5 (8.2%)       | 4 (7.4%)        | 5 (10.2%)       | 3 (13.6%)      |
| Liver disease n (%) | 5 (8.2%) | 4 (7.4%) | 5 (10.2%) | 3 (13.6%) |
| Immunosuppressed n (%) | 3 (4.9%) | 3 (5.6%) | 3 (6.1%) | 0 |
| Renal disease n (%) | 5 (8.2%) | 5 (22.7%) | 5 (10.2%) | 1 (4.5%) |
| Laboratory investigations |                |                 |                 |                |
| Na mean (±SD) mmol/l | 130.4 (±5.5) | 130.3 (±5.5) | 130.4 (±5.5) | 129.8 (±5.2) |
| Urea mean (±SD) mmol/l | 10.5 (±8.6) | 10.9 (±8.7) | 10.5 (±8.6) | 13.2 (±11.4) |
| Creatinine mean (±SD) μmol/l | 105 (±56.8) | 106.5 (±52.8) | 105 (±49.8) | 174.4 (±204.8) |
| WCC mean (±SD) 10⁹/mm³ | 12.3 (±4.7) | 12.4 (±4.7) | 12.3 (±4.7) | 11.4 (±5.0) |
| ALT mean (±SD)IU/L | 30.5 (±53.3) | 31 (±53) | 30.5 (±36.8) | 69.3 (±68.1) |
| Outcome data    |                |                 |                 |                |
| Duration of ventilation (mean ± SD) |                |                 | 10.3 (±6.0) |                |
| Critical care length of stay (mean ± SD) |                |                 | 11.3 (±7.6) |                |
| ICU length of stay (mean ± SD) |                |                 | 12.3 (±7.6) |                |
| Critical care mortality n (%) | 2/22 (9.1%) |                |                |                |
| ICU mortality n (%) | 2/19 (10.5%) |                |                |                |
| Hospital LoSa (±SD) | 15.7 (±14) | 23.2 (±16.9) |                |                |
| Overall mortality n (%) | 4/61 (6.5%) | 4/54 (7.4%) | 3/49 (6.1%) | 3/22 (13.6%) |

*Length of stay
to 10% for community-acquired cases between 1980 and 1998. Reasons postulated for this are rapid diagnosis and more effective antibiotics. There is evidence that delay in initiating antibiotic therapy leads to increased risk of death. Levofoxacin is considered by some to have superior activity against \textit{L. pneumophila} compared with macrolides both \textit{in-vitro} and in comparative clinical studies. Its use is recommended in the most recent BTS guidelines for management of CAP. 

In this outbreak, availability of PCR testing allowed more rapid identification of probable cases. This was often the first test to become positive and was used to guide therapy. Where PCR testing of respiratory samples was positive and urinary antigen testing negative, four out of the six samples subsequently tested in the reference laboratory using a more sensitive assay were positive. This adds some confidence to the diagnosis of probable cases and the validity of positive PCR results on respiratory secretions. Large outbreaks in Europe in the last decade have quoted mortality rates of 3–13% and ICU mortality of 36%. The European average case fatality rate was 10.1% in 2010. Our case fatality rate was 6.5% and ICU mortality 10.5%. Several factors may have contributed to this including: access to rapid diagnostic tests such as urinary antigen detection and PCR on respiratory samples, possible features of the infecting strain, well organized critical care support and rapid initiation of effective antibiotic therapy.

**Conclusion**

Case fatality rate and ICU mortality in this outbreak was lower than the European average and comparable to other recent outbreaks in Europe. Access to rapid diagnostic tests, interventions to control potential environmental sources, prompt antibiotic therapy and access to critical care were the key to controlling and managing the outbreak. Characteristics of the infecting strain may have also played a role in the evolution and outcomes of infection.

**Acknowledgements**

NHS Lothian Incident Management Team: Alison McCallum, Director of Public Health and Health Policy, NHS Lothian; Sian Tucker, Acting Clinical Director, Lothian Unscheduled Care Service (LUCS), NHS Lothian; Lynn Cree, Environmental Health Adviser, Health Protection Scotland; Alison Smith-Palmer, Epidemiologist, Health Protection Scotland; Steve Harvey, Emergency Planning Officer, NHS Lothian; Mary Hanson, Consultant Microbiologist, NHS Lothian; Andrew Campbell, Environmental Health Officer, City of Edinburgh Council; Sue Payne, Consultant in Public Health Medicine, NHS Lothian; Michael Gillies, Clinical Director of critical care, NHS Lothian; Christine Evans, Consultant in Public Health Medicine, NHS Lothian; Alison Potts, Epidemiologist, Health Protection Scotland; Robbie Beattie, Scientific and Environmental Services Manager, City of Edinburgh Council; Dona Milne, Specialist in Public Health, NHS Lothian; Alistair McNab, Head of Operations, Health and Safety Executive; Simone Thorn, Lead Health Protection Nurse, NHS Lothian; Fatim Lakha, Specialist Registrar, Public Health Medicine, NHS Lothian; Carol Harris, Communications Manager, NHS Lothian; Stuart Wilson, Director of Communications, NHS Lothian.

**Conflict of interest:** None declared.

**References**


