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Legionnaires' disease: a review of 79 community acquired cases in Nottingham

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ABSTRACT Seventy nine cases of sporadic, community acquired legionnaires' disease have been reviewed. Annual and seasonal variation in incidence was noted. The mean age of the patients was 53 years and 50 (63%) were male. Pre-existing chronic diseases were present in only 23 (29%), including two patients receiving immunosuppressive treatment. Common symptoms included unproductive cough, dyspnoea, chest pain, headache, confusion, nausea, vomiting, and diarrhoea. Respiratory symptoms were absent, however, in 17 (22%). Localising chest signs were present in 74 (95%) cases. Frequent laboratory findings included lymphopenia, high erythrocyte sedimentation rate, hyponatraemia, raised urea and creatinine concentrations, abnormal liver function, hypophosphataemia, hypoalbuminaemia, proteinuria, and haematuria. Thirteen patients died (16%), including nine of 20 who received assisted ventilation. The mortality rate in patients treated with erythromycin (11%) was lower than in those who received other antibiotics (23%), but this difference was not statistically significant. Of the features noted on admission, only a high plasma urea concentration was significantly associated with death. Sporadic community acquired legionnaires' disease is a not uncommon disorder, which with appropriate treatment has a prognosis similar to that of other forms of community acquired pneumonia.

The discovery of legionnaires' disease in Philadelphia in 1976[1] was followed by several reports of the disease in Britain in both the medical and the popular press. It soon became apparent that legionnaires' disease was not a "new" disease, the first known case in the United States being diagnosed retrospectively in 1947[2] and the first in Britain in 1972.[3] Subsequently it has been recognised that legionnaires' disease is not uncommon and may account for a considerable proportion of all sporadic cases of pneumonia in the United States,[4] Britain,[5 6] and Europe.[7–11] Although sporadic community acquired pneumonia is probably the most common form of legionnaires' disease,[1 2] reported experience has largely concerned epidemic and nosocomial infections.[1 13 14] This paucity of information about community acquired legionnaires' disease has prompted us to review our experience in Nottingham.

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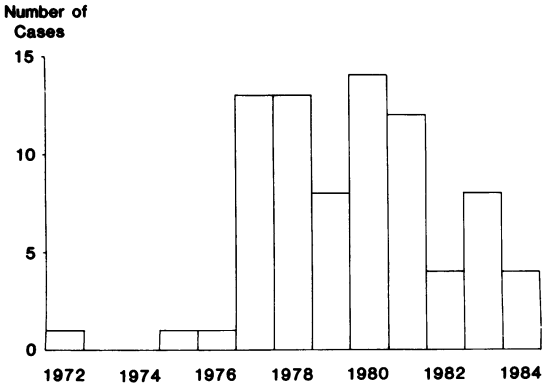
Methods

Cases of legionnaires' disease occurring in Nottingham from 1972 to 1984 were identified from the records of the department of Microbiology and Public Health Laboratory Service which serves the two district general hospitals in the city. The diagnosis of legionella pneumonia was accepted for any patient with a fourfold or greater rise in indirect immunofluorescent antibody titre or a single titre of $\geqslant 256$, formolised yolk sac legionella antigens being used[15] or if the legionella organism was cultured either during life or from post mortem tissues or the bacterium was demonstrated by direct immunofluorescent stains in body fluids or post-mortem lung tissue. Any patient becoming ill while a hospital inpatient or within two weeks of discharge from hospital was presumed to have acquired a nosocomial infection and was excluded. Information on all patients was extracted retrospectively from the case notes. The radiological features have been described elsewhere.[16]

Statistical analysis was performed using the χ^2 test.



Annual incidence of community acquired legionnaires' disease in Nottingham.

Results

Ninety confirmed cases of legionnaires' disease were identified during the 12 years. Four were nosocomial; case notes could not be found for five; and two patients were not admitted to hospital. Thus 79 community acquired cases form the basis for this study.

The annual incidence varied widely, most cases occurring during 1977–81 (figure). A seasonal variation was noted with 57 (72%) cases occurring in the months July to December.

The mean age of the patients was 53 (range 25–83) years and 50 (63%) were male. Seven patients had recently returned from abroad; one of them had been taken ill at the Rio Park Hotel in Benidorm, Spain. Five patients had been recently discharged from hospital, but in each case this was more than one month before the onset of legionnaires' disease. An additional six patients were known to have had recent hospital contact; four of these were currently employed in hospital.

Table 1 *Pre-existing chronic diseases (29 diseases in 23 patients) among 79 cases of community acquired legionnaires' disease*

	No
Cardiac disease	8
Respiratory diseases	6
Diabetes mellitus	3
Renal disease	2
Cancer	0
Immunosuppressive treatment	2
Others	8

Of 70 patients whose smoking history was known, 54 (77%) were current smokers or had recently stopped smoking and 33 of the 42 (79%) whose consumption was known smoked 20 or more cigarettes a day. Of 53 patients whose alcohol history was available, 40 (75%) took regular alcohol; of the 22 whose precise consumption was known nine (41%) regularly drank more than 50 units a week (one unit = one half pint of beer or one measure of spirit).

Twenty three (29%) patients had pre-existing chronic diseases and 32 (41%) were having regular drug treatment (table 1). Chronic cardiovascular and respiratory diseases occurred most frequently. There were no patients with cancer and only two patients were having immunosuppressive treatment—one was taking prednisolone for sarcoidosis, having previously had a splenectomy, and the other, who had systemic lupus erythematosus, was taking prednisolone and cyclophosphamide.

CLINICAL FEATURES

The mean duration of symptoms before admission to

Table 2 *Frequency of symptoms (%) for patients with community acquired legionella pneumonia compared with previous reported experience*

Symptom	*Nottingham (present study) (n = 78)**	*Community[20] acquired (USA) (n = 67)*	*Epidemic[1] (USA) (n = 123)*	*Epidemic[14] (Sweden) (n = 68)*
Respiratory	78	—	—	76
Cough	73	72	86	65
Expectoration	41	45	50	—
Haemoptysis	14	18	—	0
Dyspnoea	35	37	59	34
Chest pain	36	18	52	28
Upper respiratory tract infection	14	10	—	0
Neurological	54	33	—	44
Headache	27	34	53	56
Confusion	35	53	21	32
Gastrointestinal	40	—	—	57
Nausea/Vomiting	32	37	23	34
Diarrhoea	22	27	41	26
Abdominal pain	5	6	—	9

*Presenting symptoms not recorded in one patient.

hospital (73 cases) was seven (range 1–24) days and 66 (90%) patients had been admitted to hospital by seven days. Symptoms were recorded for all but one patient, who was moribund on admission (table 2). Although a non-productive cough was common, respiratory symptoms were absent in 17 (22%) of cases. Neurological symptoms, found in 42 (54%) cases, included not only headache in 21 (27%) and confusion in 27 (35%) but also dysarthria (four cases), gait disorder (five), diplopia (one), vertigo (one), and deafness of acute onset (one). Other symptoms noted on admission included rigors (11 cases), myalgia (five), rash (one). palpitations (one), and melaena (one).

Fever was the commonest abnormality found on initial examination, 51 of 71 (72%) patients having an oral temperature of 39°C or more and 17 (24%) of 40°C or more and only seven (10%) having a temperature below 37·5°C. Confusion was noted on examination in 32 of 74 cases (43%) and a depressed conscious level in 15 of 60 (25%). Tachycardia (pulse rate $\geqslant$100 beats/min) occurred in 56 of 73 cases (77%), with relative bradycardia (pulse rate $<$100 beats/min in the presence of temperatures of $\geqslant$39·4°C) noted in only 13 (18%) patients, three of whom were taking negatively chronotropic drugs. Hypotension (systolic blood pressure $<$100 mm Hg) on admission to hospital was noted in four patients. All patients were tachypnoeic (respiratory rate $\geqslant$20/minute in the 26 cases in which it was recorded). Localising chest signs were present in 72 of 76 (95%) cases. These included crepitations in 65 (86%) and dullness to percussion in 39 (51%). Bronchial breathing was present in only 17 (22%) and a pleural friction rub in six (8%). Herpes labialis was noted in three patients.

LABORATORY RESULTS

Common laboratory findings are shown in table 3. Creatine phosphokinase activity was increased in 11 of the 18 patients in whom it was measured, the highest activity being 1521 IU/l.

MICROBIOLOGY

The diagnosis was based on a fourfold rise in immunofluorescent antibody titre in 67 patients and a single titre of 256 or more in three. Of those showing a fourfold rise, 26 (39%) had an initial titre of 16 or more. Ten of these samples were taken at least five days after admission. *Legionella pneumophila* was cultured from only five patients—from sputum in one, from tracheal aspirates in three, and from bronchoscopic aspirates in one. The organism was demonstrated by immunofluorescent staining in postmortem lung tissue in eight cases. In 72 (91%) *L pneumophila* of serogroup 1 was responsible. There were only two serogroup 5 infections and one serogroup 4, and one each of *L micdadei, L gormanii, L bozemanii,* and *L dumoffii.*

Evidence of dual infection was found in eight patients. *Haemophilus influenzae* was grown from the sputum of one patient on admission to hospital and in another a fourfold rise in *Mycoplasma pneumoniae* antibody titre was detected. Pneumococcal antigen was detected in specimens from six patients by countercurrent immunoelectrophoresis,[17] from sputum in five and urine in two cases.

Table 3 *Laboratory findings on admission to hospital*

Feature	*Proportion of cases showing feature (%)*
Leucocyte count $\geqslant 10 \times 10^9$/l	46/73 (63)
$\geqslant 15 \times 10^9$/l	11/73 (15)
Lymphocyte count $<1{\cdot}0 \times 10^9$/l	34/61 (56)
Erythrocyte sedimentation rate $\geqslant$50 mm in 1 h	54/60 (90)
$\geqslant$100 mm in 1 h	26/60 (43)
Platelets $<100 \times 10^9$/l	4/64 (6)
Sodium $<$130 mmol/l	40/73 (55)
$<$135 mmol/l	59/73 (81)
Potassium $<3{\cdot}5$ mmol/l	18/71 (25)
Urea $\geqslant 7{\cdot}0$ mmol/l	43/72 (60)
$\geqslant 15{\cdot}0$ mmol/l	10/72 (14)
Creatinine $\geqslant$120 µmol/l	20/42 (48)
Abnormal liver function at some time*	24/41 (59)
Albumin $<$25 g/l at some time	30/48 (63)
Phosphate $<0{\cdot}8$ mmol/l at some time	6/13 (46)
Proteinuria present	30/54 (56)
Haematuria present	23/54 (43)

*Activity of two or more enzymes above the normal range.
Conversion: SI to traditional units (plasma concentrations)—Sodium, potassium: 1 mmol/l = 1 mEq/l; urea: 1 mmol/l = 6·0 mg/100 ml; creatinine: 1 µmol/l = 0·01 mg/100 ml; phosphate: 1 mmol/l = 3·1 mg/100 ml.

TREATMENT AND PROGRESS

Antibiotics had been given to 40 of 75 patients (53%) before admission to hospital. Six had received tetracycline but none erythromycin. In hospital, antibiotics were given to all but three patients, of whom one died immediately on arrival at hospital, one had a resolving pleural effusion after a febrile illness, and one was treated for ataxia and abdominal pain, the true diagnosis of pneumonia being recognised only in retrospect. The antibiotic treatment received by one patient was not known. Most patients received from one to three antibiotics, but eight were given up to six different antibiotics. Erythromycin was given to 45 (60%) of the 75 patients with known antibiotic treatment, and in 33 (73%) of these cases treatment was started within 48 hours of admission. Only 10 of the 34 patients (29%) seen before 1980 received erythromycin, compared with 35 of the 41 (85%) treated thereafter. Rifampicin was given to only six patients, four of whom only received it 14 days after admission.

In 24 of the 36 patients (67%) with detailed temperature records the temperature had settled by the fourth day, but in four a relapse associated with recrudescence of fever occurred between day 6 and day 12; one of these was already having erythromycin.

Twenty one patients (27%) required treatment in the intensive care unit, 20 of whom had assisted ventilation because of acute respiratory failure. Assisted ventilation was started electively in all but two, who requried emergency intubation. The period of ventilation ranged from one to 39 days with a mean of 11 days. Seven of the nine deaths occurring during the course of assisted ventilation happened within seven days of admission to hospital. Six of eight patients ventilated for longer than seven days survived. The length of stay in hospital varied from one to 76 days with 65% of the 66 survivors leaving hospital by 15 days and 75% by 20 days. Four patients, all of whom survived, were in hospital for more than 40 days.

Table 4 *Complications of legionnaires' disease*

System	*Complication*	*No of cases (deaths)*
Renal	Renal failure requiring dialysis	7 (3)
Respiratory	Respiratory failure*	20 (9)
	Pneumothorax	2 (1)†
	Pulmonary embolus	1 (0)
Cardiac	Tachyarrhythmias‡	5 (0)
	Unexpected cardiac arrest	3 (3)
Neurological	Epileptic fit	1 (0)
	Guillain-Barré syndrome	1 (0)
	Prolonged abnormal mental state	2 (0)
Gastrointestinal	Paralytic Ileus	1 (0)
	Haemorrhage	1 (1)
	Proctitis	1 (0)

*Requiring assisted ventilation.
†One after transbronchial lung biopsy.
‡Atrial fibrillation (2), atrial flutter (1), supraventricular tachycardia (1), paroxysmal atrial tachycardia (1).

OUTCOME

There were 13 deaths (16%) of which four occurred in the 59 patients (7%) who did not require assisted ventilation and nine in the 20 (45%) who did ($p < 0.001$). Three patients died as a result of an unexpected cardiac arrest in a general medical ward and one was found dead in bed 28 days after admission. Of the features noted on admission, only a high plasma urea concentration (≥ 15.0 mmol/l) (90 mg/100 ml) was significantly associated with risk of death ($p < 0.05$). Only 11% of the patients treated with erythromycin died compared with 23% of those who did not receive erythromycin, but this difference was not statistically significant. Fifty four per cent of deaths occurred in the first five days after admission and 77% has occurred by day 10.

Some recorded complications are shown in table 4. No specific visible abnormalities were detected through the three bronchoscopies performed for slow resolution of radiographic consolidation, and only one of four lumbar punctures revealed abnormal cerebrospinal fluid (a raised protein concentration in the patient with Guillain-Barré syndrome).

Discussion

About 150 epidemic and sporadic cases of legionella pneumonia are reported annually in Britain. A study in 1980–1 from Nottingham found legionnaires' disease to be responsible for 15% of all community acquired cases of pneumonia seen in hospital in that year.[5] In a smaller prospective investigation of consecutive cases of community acquired pneumonia in 1983 we found legionnaires' disease in only 5%. These figures are similar to published data from other parts of Europe.[7-11] Although legionnaires' disease accounted for only 2% of all community acquired pneumonia (3% of those in which a causal organism was identified) in a recent multicentre study in Britain,[18] there appear to be regional as well as annual variations.[6 19] The recent severe epidemic in Staffordshire has once again shown that legionnaires' disease should be considered as a potential cause of any severe pneumonia. Clinicians in Britain must therefore be aware of both the typical and the atypical features of the illness.

Although other studies have found a high frequency of pre-existing chronic diseases in patients with epidemic or nosocomial legionnaires' disease,[1 20] we have found the typical patient to be a previously fit middle aged man who is a regular smoker and drinker. Most have been ill for one week before admission to hospital. The initial suggestion of a unique clinical

picture in legionnaires' disease[21] has not been confirmed,[4 20] but the presence of unproductive cough and in particular features suggesting multisystem disease should alert doctors to the possibility of legionnaires' disease. Indeed, the absence of respiratory symptoms in nearly a quarter of patients may mask the true diagnosis of pneumonia, especially when neurological or gastrointestinal features are prominent.

The frequently occurring hyponatraemia, lymphopenia, a high erythrocyte sedimentation rate, abnormal results in liver function tests, hypophosphataemia, hypoalbuminaemia, proteinuria, and haematuria may be pointers to the diagnosis of legionnaires' disease, but are not specific. The frequency of these features in our series is similar to that noted in other published studies.[1 14 20]

The lack of a rapid and widely available diagnostic test for legionnaires' disease and the absence of a specific clinical presentation makes early diagnosis difficult. Few cases are diagnosed by culture of the organism and, as we found, only one third of those subsequently showing a fourfold rise in immunofluorescent antibody titre have titres of 16 or more at the first testing.[22] Bronchial lavage and transbronchial lung biopsy may be useful for early diagnosis in selected patients.[23] Simple methods for the detection of legionella antigen are under assessment[24 25] and may eventually be helpful for early diagnosis, but until these are widely available the initial diagnosis rests on clinical judgment. Failure to identify a pathogen from initial microbial cultures of blood and sputum may be a pointer to legionnaires' disease, especially where prior antibiotics have not been given. In a study of patients with severe community acquired pneumonia legionnaires' disease was eventually diagnosed in 52% of those in whom a pathogen had not been identified within 48 hours of admission.[3] Nevertheless the occurrence of dual infections in 10% of cases indicates that isolation of another pathogen does not preclude the diagnosis.

There have been no prospective studies of antibiotic treatment in legionnaires' disease in man; but animal studies[26 27] and in vitro work[28] as well as retrospective data in man[13 29] have supported the effectiveness of erythromycin. Our experience agrees with this. None of our patients received erythromycin before hospital admission, suggesting that its early use by general practitioners, especially during the course of an epidemic and in areas where legionnaires' disease is known to occur, may be of advantage. As legionnaires' disease is one of the few causes of severe community acquired pneumonia in Britain we would advocate the inclusion of erythromycin in the initial antibiotic treatment of any patient with severe pneumonia.[3]

Unusual features and complications of legionnaires' disease have been recorded, originating from many systems.[30] The most common complication is respiratory failure. Assisted ventilation was required in a quarter of our cases. The fact that over half of these patients survived, occasionally after prolonged ventilation, emphasises the importance of this form of management for community acquired legionnaires' disease. Sudden and unexpected cardiac arrests leading to death in three patients in general medical wards confirms the need for careful monitoring of any patient suspected of having legionnaires' disease. There should be a low threshold for admission to an intensive care unit for observation and early elective assisted ventilation if required. Acute renal failure was the most common non-respiratory complication, with a similar frequency to that found in another study of sporadic legionnaires' disease.[12] The pathogenesis of the widespread features of legionnaires' disease remains unexplained, but they are out of proportion to any biochemical or haemodynamic abnormalities. Bacterial dissemination,[31] toxin production,[32] and immunological effects[33] have all been described, but it remains to be shown which is most important in producing these effects.

Unlike nosocomial legionnaires' disease, community acquired legionnaires' disease does not have a high mortality rate. Our rate is similar to the overall reported mortality of 10% for community acquired cases in Britain.[34] With appropriate management the prognosis is similar to that of other forms of community acquired pneumonia seen in hospital,[5] although many patients may require assisted ventilation at some stage.

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