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Original article

Severe Legionnaire's disease requiring intensive care treatment

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Abstract

Background: Legionnaire's disease is well known as severe pneumonia requiring intensive care treatment in many cases. In this study the clinical course is described of patients admitted to the medical ICU of the University Hospital of Rotterdam for respiratory distress due to Legionnaire's disease.

Methods: From the register of admissions to the medical ICU all patients suffering from Legionnaire's disease were identified. All data on clinical signs and symptoms present on admission were collected. The circumstances in which the infections were contracted were sought, as well as the tests establishing the diagnosis. The occurrence of various organ failures and complications were noted, as were the causes of death on the ICU.

Results: From 1978 till 1995 the diagnosis of *Legionella* pneumonia was made in 17 patients admitted to the ICU: in 13 patients a community-acquired infection was established. As in 12 patients Legionnaire's disease was diagnosed on serological tests, it took several weeks before the diagnosis could be established in these patients. In all patients the circumstances predisposing to Legionnaire's disease were noted. Respiratory distress was present in all patients, ventilatory support was required in 14. Apart from this, both profound shock and renal failure were commonly encountered. As complications jaundice, rhabdomyolysis and polyneuropathy were frequently noted. Three patients died: 2 due to irreversible shock and 1 due to hospital-acquired sepsis.

Conclusion: Legionnaire's disease can develop into life-threatening pneumonia requiring intensive care treatment in previously healthy subjects. As the clinical features are aspecific, careful search for predisposing circumstances such as recent travel or use of a contaminated water-supply is mandatory. As the diagnosis required positive serological tests in most patients, a considerable delay in diagnosis was noted. Despite the frequent occurrence of multiple organ failure, a favourable outcome can be anticipated in most cases.

Keywords: *Legionella*; Critical care; Multiple organ failure

1. Introduction

Legionella pneumophila is the causative agent of Legionnaire's disease, a severe pneumonia requiring

in many cases intensive care treatment [1,2]. The incidence of Legionnaire's disease has been reported to vary from 0–23% of all community-acquired pneumonias requiring intensive care [3–6]. Differences in population as well as geographical and seasonal data are assumed to account for the variability reported [2]. In some studies *Legionella* ranks

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second after *Pneumococcus* on the list of community-acquired pneumonias on the intensive care unit [2,5].

In the Netherlands all established cases of Legionnaire's disease are registered. After an initial decrease in the number of cases from 1988 to 1992 (from 60 to 21 cases per year), a gradual increase has been noted in subsequent years (43, 52 and 42 cases for 1993, 1994 and 1995, respectively). Over the years, predominantly isolated cases have been reported with the exception of one epidemic affecting Dutch tourists in Spain [7].

The aim of the study is to describe the clinical course of patients who were admitted to the medical intensive care unit of the University Hospital of Rotterdam for acute respiratory distress due to the Legionnaire's disease. Clinical data on the presentation, the complications during stay on the intensive care unit, and the course of the patients will be presented.

2. Patients and methods

From the register of all admissions to the medical intensive care unit of the University Hospital of Rotterdam since 1972, patients in whom Legionnaire's disease had been diagnosed were identified. In addition, all patients with Legionnaire's disease were identified from the files of all admissions to this hospital, registered under the heading 'pneumonia due to other specified bacteria' (ICD9). From the patients' files all clinical signs and symptoms present on admission to the ICU were noted. The various items suggestive of the circumstances in which the infections were contracted were sought in the case notes. On admission to the ICU the APACHE-II score was obtained for each patient [8]. Results of routine laboratory studies (liver and kidney function tests) were collected. Chest X-rays obtained on admission were reviewed. The diagnosis of Legionnaire's disease was established by serological testing, immunofluorescence or culture of sputum. A 4-fold rise in antibody titre to at least 128 was considered evidence of acute infection [1]. The starting date and the duration of antibiotic therapy were noted. For each patient the number of days between the onset of

the illness and the development of various organ failures and complications was calculated. As organ failures respiratory, renal and circulatory insufficiency were considered. Respiratory failure was defined as hypoxaemia ($\text{PaO}_2/\text{FiO}_2 < 100$) and/or the need for ventilatory support. Renal failure was defined as anuria/oliguria associated with serum creatinine levels of $> 600 \mu\text{mol/l}$. Circulatory failure was defined as a systolic blood pressure of ≤ 90 mmHg in the presence of an adequate fluid challenge. Jaundice, skeletal muscle damage, acute abdomen, upper gastrointestinal bleeding and polyneuropathy were considered as complications.

Discharge from the ICU to the ward or death on the ICU was noted. Data on follow-up of the period following stay on the ICU were collected.

3. Results (Table 1)

From 1978 to 1995, 17 patients suffering from *Legionella* pneumonia were admitted to the intensive care unit. At the same time another 10 patients with Legionnaire's disease admitted to the wards were identified. Twelve of 17 patients were admitted to the ICU in the summertime (June–September). The mean age of the patients was 52 years (range 25–69); 14 were male. Three patients died, all male, with a mean age of 60 years.

The mean duration of intensive care treatment amounted to 22 days (range 4–99); no difference

Table 1
Organ failures and complications in 17 patients with Legionnaire's disease requiring intensive care treatment

	Number of patients
Respiratory distress	17
Respiratory failure	14
Circulatory shock	5
Renal failure	8
Renal replacement therapy	7
Jaundice	8
Rhabdomyolysis	3
Suspected peritonitis	3
Upper gastro-intestinal haemorrhage	4
Polyneuropathy	8

For definitions of the various items, see text.

was established between survivors and non-survivors in the duration of IC treatment.

3.1. Circumstances in which the infections were contracted

In all patients a predisposing condition suggesting the circumstances in which the infection had been contracted was noted. Eleven patients had travelled abroad for holidays within a week before the onset of their illness. Eight patients had visited Mediterranean countries, 2 patients had stayed in Paris and 1 patient had made a boat trip along the river Rhine. Two patients had used water from reservoirs supposed to be contaminated with *Legionella*; both reservoirs were located on canal boats. Four patients were assumed to be infected in hospital: all had been admitted between 2 and 4 weeks before the onset of the illness. The 4 patients were all considered immunocompromised: 2 patients received corticosteroids and azathioprine for parapneumonia and dermatomyositis, respectively. One patient received a high dose of corticosteroids for temporal arteritis. One patient suffered from angioimmunoblastic lymphadenopathy. The last time a nosocomial *Legionella* infection was diagnosed in our hospital was in 1992: at that time *Legionella* was again cultured from the water supply system after years of absence. Infection control measures were successful in eradication of the organism.

3.2. Clinical features

The clinical features on admission were aspecific. All patients presented with dyspnea and high fever ($> 39.5^{\circ}\text{C}$). Abdominal discomfort as nausea and diarrhoea (13 patients) and mental confusion were frequently encountered (11 patients). The majority of the patients had been admitted to the ward before being transferred to the intensive care unit. As the diagnosis of Legionnaire's disease was not considered on admission to the hospital in all patients, a considerable delay in the institution of the appropriate antibiotic therapy was noted in several cases. In all patients intravenous erythromycin was administered for at least 2 weeks. The time between the

onset of the disease and the start of erythromycin varied from 2 to 14 days with a mean of 6 days. In 6 patients rifampicin was added to the erythromycin.

The Apache II score was obtained for each patient from the first 24 h on the ICU: the score amounted to 18 (mean, range 11–31). The actual death rate (18%) could be considered to be in agreement with the predicted death rate (25%) as previously published [9].

All patients presented with infiltrates in one or both lungs on the chest X-ray. In 9 patients both lungs were involved, in 6 the right lung (mostly more than 1 lobe), and in only 2 patients the left lung was involved.

3.3. Bacteriology

In 13 of the 17 patients sputum obtained on admission was examined. In 5 patients the organism was cultured from respiratory secretions; in one patient the immunofluorescence of the sputum was positive with a negative result of the culture. In all patients a 4-fold or greater rise in antibody titre or a single antibody titre of 128 or greater by immunofluorescent test was obtained. In 2 patients a single antibody titre of 128 was encountered: both patients were immunocompromised. In one of them a positive immunofluorescence of the sputum was noted. The time between onset of illness and the positive serological test amounted to 16 days (mean, range 10–23 days).

3.4. Respiratory failure

All patients were admitted to the ICU for respiratory distress. Life-threatening respiratory failure requiring mechanical ventilation was encountered in 14 patients. The time between onset of disease and the start of ventilatory support varied from 1 to 15 days with a mean of 6 days.

As ventilatory mode, pressure-controlled ventilation with a positive end-expiratory pressure of at least 5 cmH_2O was applied in all patients. High inspiratory oxygen concentrations were required to achieve adequate oxygenation ($\text{FiO}_2 > 40\%$). The mean duration of mechanical ventilation was 18 days (range 6–51 days).

In 3 patients no ventilatory support was required. They were treated with oxygen delivered by face-masks.

3.5. Circulatory failure and shock

On admission to the ICU 5 patients were in shock, requiring positive inotropic drugs such as dopamine and norepinephrine to restore the circulation. In all patients a diagnosis of septic shock was made [10]. Four patients had concomitant renal failure. In these patients the administration of inotropic drugs had to be continued for prolonged periods of time (mean 11 days, range 3–17 days). Two patients died without recovering from circulatory shock after 13 and 16 days of intensive care treatment, respectively.

3.6. Acute renal failure

Eight patients developed acute severe renal failure within 16 days after onset of the illness. In 7 patients renal replacement therapy was applied by means of continuous arterio-venous haemodiafiltration (CAVHD). All but one regained normal renal function after 1 to 5 weeks (mean 3 weeks). None of the patients underwent a renal biopsy to determine the pathophysiology of the renal failure. One patient with renal failure requiring renal replacement therapy died.

3.7. Jaundice

In 8 patients jaundice (defined as serum bilirubin $> 35 \mu\text{mol/l}$) was observed. In all patients elevated levels of alkaline phosphatase, glutamyl-transferase and/or aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were observed during stay on the ICU. No relation between circulatory failure and disturbed liver tests could be established. No difference in the severity of hyperbilirubinaemia was observed between patients who were treated with erythromycin and rifampicin or with erythromycin alone.

Ultrasound studies were performed in all patients. Using this technique extrahepatic bile duct obstruction could be excluded and a normal liver parenchyma

was observed in all patients. All survivors had normal liver function tests at discharge from hospital.

3.8. Skeletal muscle damage

In most patients elevated creatine kinase (CK) levels were encountered at admission to the ICU. In 3 patients CK levels exceeding 1000 U/l (normal values 0–110 U/l) were noted. No relation could be established between the high CK levels and the development of renal failure. CK levels normalized within 7 days in all patients.

4. Acute abdomen and gastro-intestinal bleeding

In 3 patients peritonitis was suspected on admission to the ICU. Two patients underwent a laparotomy; no abdominal pathology was found in either case.

During their stay in the ICU in 4 patients gastro-intestinal haemorrhage developed due to bleeding gastric or duodenal ulcers. These patients were all mechanically ventilated and bleeding was at first detected between the 2nd and 4th week after onset of the disease. Stress ulcer prophylaxis was not routinely provided. All patients underwent endoscopy with local injection therapy with etoxysclerol and epinephrine and were treated with systemic anti-ulcer therapy.

4.1. Polyneuropathy

Eight patients suffered from severe polyneuropathy (PNP), varying from mono- to tetraparesis. It developed slowly but progressively in the first 2 weeks of the illness. In all patients with PNP ventilatory support was applied.

In 3 patients a diagnosis of axonal PNP was confirmed by electromyography.

Long-term rehabilitation was required in all patients and resulted in full recovery in all but one.

4.2. Mortality

Three patients died on the ICU. Two patients were previously healthy and had community ac-

quired pneumonia. Both were in shock on admission to the ICU and died without recovering from circulatory failure. In both cases blood cultures at the time of death revealed *Pseudomonas aeruginosa*. One patient with a nosocomial pneumonia died. In this patient temporal arteritis had been diagnosed and high-dose corticosteroids had been started 4 weeks before the onset of the pneumonia. Eleven days after admission to the ICU the patient died of cardiac arrest related to severe sepsis.

5. Discussion

In this retrospective study the clinical course of patients admitted to the ICU for Legionnaire's disease has been reviewed. The 17 patients described in this study could be divided into two groups: 13 patients with community-acquired pneumonia and 4 patients with nosocomial pneumonia. In this patient group recent travel to the southern part of Europe proved to be the most frequent predisposing circumstance for community-acquired Legionnaire's disease. All patients with nosocomial Legionnaire's disease were immunocompromised, underlining the immunocompromised state as a risk factor for this type of infection.

Although advanced age is considered a risk factor in the literature, we encountered predominantly middle-aged subjects [1]. In accordance with the literature a male preponderance (M/F ratio 14:3) was established.

In the literature a mortality of 27% in patients with *Legionella* pneumonia requiring intensive care treatment is reported [11]. The overall mortality in this study group amounted to 18%, which compared favourably with the mortality of all community-acquired pneumonias admitted to the ICU (22–48%) [3–6].

All patients were admitted to the ICU for respiratory distress; in 14 mechanical ventilatory support was required. Although high inspiratory oxygen levels and high positive end-expiratory pressures were temporarily required, adequate oxygenation could be achieved in all patients.

Circulatory shock in Legionnaire's disease is related to a poor prognosis with mortality rates up to 60% [11]. In both patients in this study who died of

irreversible shock, secondary infections with *Pseudomonas* were implicated. This underlines the risks of nosocomial infections in these patients.

Acute renal failure is reported in 30–40% of severe *Legionella* pneumonia and is associated with a poor prognosis [4,11,12]. Mortality rates up to 50% in patients with Legionnaire's disease complicated by acute renal failure have been reported [12]. In this study continuous arterio-venous haemodiafiltration (CAVHD) was applied for acute renal failure. As only 1 of the 8 patients with renal failure died, it is suggested that the early start of CAVHD contributed to the favourable outcome. Continuous haemodiafiltration techniques are today the first choice of renal replacement therapy in critically ill patients with severe sepsis. CAVHD may improve the outcome of these patients due to the removal of inflammatory agents such as cytokines, interleukins and tumour necrosis factor [13].

Jaundice and disturbed liver tests are common in severe *Legionella* infections. The incidence varies from 40 to 60% [4,11,14]. In 8 patients in this study jaundice was noted, all without signs of liver failure. Although hyperbilirubinaemia has been closely related to rifampicin use in the literature, in this study no difference in bilirubin levels was found between patients treated with or without rifampicin [11].

Muscular damage and rhabdomyolysis have been described in case reports of Legionnaire's disease [15]. In this study elevated creatine kinase (CK) levels were frequently encountered; in 3 patients CK levels in the range of rhabdomyolysis were noted on admission to the intensive care. Skeletal muscle damage was not found to result in renal failure: ample intravenous fluid infusion, routinely applied in the ICU from the first day of admission, may have prevented renal failure to develop [16].

Gastro-intestinal symptoms such as nausea, vomiting and diarrhoea are commonly reported in Legionnaire's disease [1]. In this study the clinical diagnosis of peritonitis in 2 patients prompted a laparotomy that did not reveal any abdominal pathology. In 4 patients gastro-intestinal haemorrhage due to stress ulcers was noted. The incidence of stress-ulcer bleeding in this patient group is considered high compared to recently published studies [17,18]. In all patients bleeding gastric or duodenal ulcers were found, in agreement with this finding the bleeding

developed late in the course of the disease.

Severe polyneuropathy leading to a prolonged stay on the ICU and long-term ventilatory support was encountered in 8 patients. Acute polyneuropathy is well described in critically ill patients: electromyographic studies reveal a primary axonal degeneration of motor and sensory fibres, mainly distally with relative sparing of cranial nerves [19].

With respect to the causes of death in this study, it should be underlined that mortality was related to circulatory failure in all cases. Respiratory failure with progressive lung damage leading to intractable hypoxaemia was not encountered.

This study emphasizes that Legionnaire's disease can develop into a severe pneumonia requiring intensive care treatment in previously healthy subjects. A careful search for predisposing conditions is mandatory when making a diagnosis. Despite frequently encountered extrapulmonary involvement and the need for prolonged ICU treatment, a favourable outcome can be anticipated in most patients.

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