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Acute respiratory distress syndrome in patients with Legionella pneumonia

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Objective. The relationship between specific causative organisms and development of ARDS in pneumonia patients has not been explored. Several case reports have described the development of ARDS in patients with *Legionella* pneumonia. The aim is of this study was to determine frequency and outcomes of ARDS in patients with *Legionella* Pneumonia. **Methods.** A retrospective cohort study of patients with *Legionella* pneumonia hospitalized at two Mayo Clinic Rochester hospitals was conducted. To identify the patients with *Legionella* pneumonia we searched the Mayo Clinic Life Sciences System (MCLSS) database from 01/01/2003 to 12/31/2007. Electronic medical records of patients with active Legionella pneumonia based on positive cultures and/or urinary antigen were reviewed. ARDS was diagnosed on the basis of the criteria of the North American/European consensus conference definition. **Results.** We identified 15 patients with microbiologically proven *Legionella* pneumonia of whom 11 were admitted to the intensive care unit (ICU), 6 required mechanical ventilation and 5 met the criteria for ARDS. Age (median 42 vs. 50 years, p=0.32) and gender (4/10 vs. 1/5 female, p=0.60) were similar in patients with and without ARDS. Septic shock was present in 4 of the 5 patients with ARDS and only 1 without. Patients with ARDS had longer ICU length of stay (median 9 vs. 1 days, P=0.03). Only one patient (from the ARDS group) died in the hospital. **Conclusion.** In this retrospective study ARDS occurred in one third of patients with microbiologically proven *Legionella* pneumonia and was associated with prolonged length of ICU stay.

Key words: Pneumonia, Legionella, ARDS.

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Introduction

Legionella is a Gram negative pathogen that causes legionellosis or Legionnaires' disease. Legionella has 50 species and 70 serogroups identified, most commonly L. pneumophila. Since the first breakout of Legionella in July 1976 that affected 221 persons, resulting in 34 deaths

(1), there have been numerous reported breakouts worldwide (2-9), often associated with severe presentations and substantial mortality. The incidence of Legionella pneumonia ranges from 2 to 15 percent of all community-acquired pneumonias (CAP) that require hospitalization (10) and is the second cause of severe CAP requiring ICU admission (11). So far, several case reports have described the development of ARDS in patients with Legionella pneumonia. In addition, a recent report demonstrated an increased risk for ARDS in pulmonary vs. non-pulmonary infection, as well as the relationship between Legionella infection and the development of ARDS in critically ill patients (12). To our knowledge, there is no study that has looked specifically at the features of hospitalized patients with Legionella pneumonia and its relation to ARDS.

The objective of this study was to determine the frequency, characteristics and outcome of ARDS among patients with sporadic Legionella pneumonia at Mayo Clinic Rochester over a five year period.

Patients and methods

In this retrospective cohort study, we reviewed electronic medical records of patients admitted to two Mayo Clinic Rochester hospitals between 01/01/2003 and 12/31/2007 with microbiologically confirmed Legionella pneumonia based on positive cultures and/or urinary antigen test. Patients were identified by using the Mayo Clinic Life Sciences System (MCLSS) database. Pneumonia was defined as new or progressive infiltrate as seen on a chest X-ray or CT scan along with a high clinical suspicion of pneumonia defined as at least one of the following: fever (>38°C or >100.4°F), leucopenia (<4000 WBC/mm^3) or leukocytosis (>12,000 WBC/mm^3), altered mental status with no other recognized cause (for adults >70 years old) and at least two of the following: new onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements, new onset or worsening cough, or dyspnea, or tachypnea, rales or bronchial breath sound and worsening gas exchange, increased oxygen requirements, or increased ventilation demand (13). The outcome measures were: development of ARDS, the length of ICU stay and overall mortality. ARDS was diagnosed based on the criteria by the North American/European consensus conference definition as acute hypoxemic respiratory failure (PaO_2/FIO_2<300) and development of bilateral pulmonary infiltrates in the absence of left atrial hypertension (14).

Statistical analysis

Continuous data are presented as median and interquartile range (IQR) and categorical data as counts and percentages. Continuous variables were compared using the Wilcoxon rank-sum test for non-normally distributed variables. The Fisher's exact tests were used to compare categorical variables. JMP statistical software (JMP Version 7, SAS Institute Inc., Cary, NC) was used for all statistical analyses.

Results

We identified 15 patients, 5 women, median age 46 years (interquartile range (IQR) 42-57) with microbiologically proven Legionella pneumonia, of whom 11 were admitted to the intensive care unit (ICU), 6 required mechanical ventilation and 5 met the criteria for ARDS. The median duration of mechanical ventilation was 5 days (IQR 4-8). The diagnosis was made by culture in 2, urinary antigen in 10 and both in 3 cases. Two patients had positive bronchoalveolar lavage by direct fluorescent antibody staining (DFA). Only 4 patients had no previous

medical history. The most frequent comorbidities were hypertension and diabetes. The majority of patients presented with bilateral chest infiltrates at the time of hospital admission, and four patients met the criteria for ARDS at the time of hospital admission. Figure 1 presents a portable chest radiograph appearance in patient with ARDS due to Legionella pneumonia. The mean time from symptom onset to appropriate antibiotic treatment was 6 days (2-10) (Table 1).

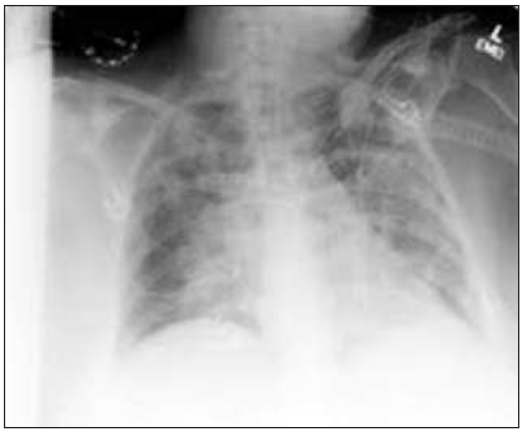

Figure 1 Acute respiratory distress syndrome in patient with Legionella pneumonia. Dense right middle lobe consolidation and bilateral alveolar infiltrates, endotracheal tube 2 cm above the carina

Age (median 42 vs. 50 years, p=0.32) and gender (4/10 vs. 1/5 female, p=0.60) were similar in patients with and without ARDS. ARDS developed in 4 patients with no comorbidities and 1 with past medical history of COPD and diabetes mellitus. Median time from symptom onset to initiation of appropriate antibiotic therapy was similar in patients with and without ARDS (6 vs.4 days, p=0.17). Septic shock was present in 4

Table 1 Characteristics of patients with Legionella pneumonia

Number of patient	Age (Years)	Gender	Comorbidities	Chronic Immuno-suppression	Symptom to AB (days)	Chest X ray (on admission)	ARDS
1	75	F	CAD, HTN, DM, PMR	Yes	2	Bilateral	No
2	46	M	HTN	No	14	Unilateral	No
3	51	M	None	No	14	Bilateral	Yes
4	42	F	HTN, DM	No	1	Bilateral	No
5	42	F	None	No	5	Bilateral, ARDS	Yes
6	10	F	IPH	Yes	6	Bilateral	No
7	68	M	Multiple myeloma	Yes	1	Unilateral	No
8	39	M	None	No	6	Bilateral, ARDS	Yes
9	74	M	Ulcerative colitis, CAD, DM	Yes	-	Unilateral, cavitary mass	No
10	57	M	COPD, DM	No	6	Bilateral, ARDS	Yes
11	50	M	Crohn's disease	Yes	2	Unilateral	No
12	54	M	Alcohol abuse	No	4	Bilateral	No
13	46	F	Bilateral lung transplant for emphysema	Yes	12	Unilateral	No
14	46	M	Alcohol abuse	No	6	Unilateral, pleural effusion	No
15	25	M	No	No	9	Bilateral, ARDS	Yes

AB-Antibiotics, CAD-Coronary artery disease, HTN-Hypertension, DM-Diabetes mellitus, PMR-Polymyalgia rheumatica, IPH-Idiopathic pulmonary hemosiderosis

of the 5 patients with ARDS and only 1 without. All ARDS patients were treated per protocol with lung protective (tidal volume 4-8 mL/kg predicted body weight) mechanical ventilation. Patients with ARDS had longer ICU length of stay (median 9 vs. 1 days, P=0.03). Only one patient (from the ARDS group) died in the hospital.

Discussion

The results of this study demonstrated the high frequency of ARDS among hospitalized patients with confirmed Legionella pneumonia and substantially lower mortality than previously reported. Comorbidities were common, including diabetes mellitus and immunologic diseases. This is in line with previous studies that showed increased risk for Legionnaires' disease in patients 50 years and older, with comorbidities including diabetes mellitus, chronic obstructive pulmonary disease, renal disease and immuno suppression (15, 16).

The mortality from Legionnaires' disease ranges from 5-17% in hospitalized patients (17, 18), up to 30% in patients requiring ICU admission. Considering most patients in this study had severe forms of Legionella pneumonia, mortality was considerably lower than previously reported (19, 20). Over the past decade there has been a substantial decline in mortality from Legionella infections in the US (21). Early initiation of empirical antimicrobial coverage for atypical bacteria, as well as the recent developments in critical care medicine, including the standardized protocols for lung protective ventilation(22), sedation (23), weaning (24), early goal directed therapy in sepsis (25) and conservative strategy of fluid management in patients with acute lung injury (26) could explain the lower mortality in the observed patients. Several factors have been shown to independently influence survival in critically ill patients with Legionella pneumonia, including the baseline severity of illness and hyponatremia (20). The majority of patients in our study presented with bilateral chest infiltrates and required ICU care, almost half of them were mechanically ventilated, and 30% developed septic shock. Although these features have been previously recognized to be associated with mortality in severe pneumonia patients, and are often associated with ARDS, the relationship between Legionella and ARDS has been mostly described in case reports. Interestingly, severe forms of Legionella pneumonia associated with ARDS were recorded not only in patients at risk (27-29), but also in previously healthy young adults (30, 31). In our study, majority of ARDS patients had no past medical history.

Experimental studies have shown that in macrophages, *L. pneumophila* inhibits phagolysosome fusion, multiplies and causes lysis of the host cell. Both, in macrophages and alveolar epithelial cells the virulent strain of *L. pneumophila* induces programmed cell death, DNA fragmentation and activation of various caspases (32, 33).

Delay in appropriate antibiotic treatment (34) has been associated with increased mortality in patients with Legionnaires' disease. In our study, patients who developed ARDS had longer time from symptom onset to initiation of appropriate antibiotic treatment although the difference was not statistically significant.

There are several limitations of the present study. Due to retrospective design and the fact that hospital database was used to select patients, it is likely that the frequency of Legionnaires' disease is largely underestimated, resulting in confirmed infections mostly in severely ill patients who underwent detailed microbiological evaluation. Legionella is rarely identified in pneumonia patients since the diagnosis requires the use of specific tests and the isolation is difficult due to organisms' fastidious nature. In addi-

tion, the study includes relatively low number of patients and was underpowered to detect all relevant differences between patients with and without the ARDS.

Conclusion

In conclusion, in this retrospective study ARDS occurred in one third of patients with microbiologically proven Legionella pneumonia and was associated with prolonged length of ICU stay. Only one patient with ARDS due to Legionella pneumonia died.

Authors' contributions: Conception and design: MK and OG; Acquisition, analysis and interpretation of data: MK and GL; Drafting the article: MK; Revising it critically for important intellectual content: GL and OG.

Conflict of interest: The authors declare that they have no conflict of interest. This study was not sponsored by any external organization.

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