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Abnormal Radiological Findings and a Decreased Carbon Monoxide Transfer Factor Can Persist Long after the Acute Phase of *Legionella pneumophila* Pneumonia

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Pulmonary abnormalities may persist long after the acute phase of legionnaires disease (LD). In a cohort of 122 survivors of an outbreak of LD, 57% were still experiencing an increased number of symptoms associated with dyspnea at a mean of 16 months after recovery from acute-phase LD. For 86 of these patients, additional evaluation involving high-resolution computed tomography (HRCT) of the lung revealed pulmonary abnormalities in 21 (24%); abnormal HRCT findings generally presented as discrete and multiple radiodensities. Residual pulmonary abnormalities were associated with a mean reduction of 20% in the gas transport capacity of the lung. This latter sign could not be used to explain the increased symptoms of dyspnea reported by patients. Receipt of mechanical ventilation during the acute phase of LD, delayed initiation of adequate antibiotic therapy, and chronic obstructive pulmonary disease were identified as risk factors for the persistence of lung abnormalities.

In a survey of 31 survivors of the classic 1976 outbreak of legionnaires disease (LD) in Philadelphia, a considerable proportion still had respiratory symptoms or a reduced carbon monoxide diffusion capacity (DLCO) after a follow-up period of 2 years [1]. Additional information on the persistence of such pulmonary symptoms and signs in survivors of LD is scarce. In one study, abnormal radiological findings were observed for at least several months after recovery from acute-phase LD [2]. In 2 small series, analysis of lung biopsy specimens obtained shortly after acute-phase LD revealed structural changes and fibrosis of the lung parenchyma [3, 4]. Taken together, these observations suggest that

residual abnormalities in the lung parenchyma (hereafter, "pulmonary abnormalities") resulting in functional disturbances may persist long after the clinical resolution from the acute phase of LD. It is unknown which factors predispose patients to such long-term pulmonary abnormalities.

In March 1999, a large outbreak of LD occurred among individuals who visited a flower exhibition in The Netherlands [5]. This offered a unique opportunity to expand the knowledge on the long-term pulmonary sequelae of LD. We evaluated 122 survivors 13–19 months after resolution of the acute phase of LD for the presence of persistent abnormal radiological and functional findings and tried to correlate these with symptoms of shortness of breath. In addition, we tried to identify risk factors associated with the persistence of pulmonary abnormalities.

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PATIENTS AND METHODS

Patients. After detection of the outbreak, local municipal health services and hospitals were requested to

report every suspected case of LD. Six months after the outbreak, 318 patients with suspected LD had been reported. Written informed consent was obtained from 202 patients or their relatives; 161 had confirmed or probable LD. Our definitions of confirmed and probable cases of LD have been described elsewhere [6]. Eighteen patients died during the acute phase of the disease, and 1 died shortly thereafter. Of the remaining survivors, 130 were contacted for our follow-up study 13–19 months after the acute phase of the disease, and 122 participated. All participants completed a questionnaire, and 86 consented to visit our hospital for additional radiological examination and lung function testing. This study was approved by the medical ethics committee of the Academic Medical Center in Amsterdam, The Netherlands.

Radiological examination and lung function testing.

Participants were screened for pulmonary abnormalities using standard chest radiography and tests that measured the vital capacity (VC), the forced expiratory volume in 1 s (FEV₁), and the single-breath DLCO of the lung (expressed as a percentage of the predicted value). All chest radiographs were evaluated by 2 radiologists blinded to the patients' medical records; consensus was required for inclusion of findings in our analysis. Focal increases in radiodensity anywhere in the lung parenchyma were considered to be signs of residual abnormalities. Participants with no abnormal chest radiograph findings were suspected of having residual pulmonary abnormalities if either the VC or the DLCO was >1.64 SDs below the normal value [7, 8].

For participants in whom residual pulmonary abnormalities were suspected, an additional measurement of total lung capacity and a high-resolution CT (HRCT) scan (MX Twin; Elscint) of the whole chest were performed (1-mm-thick slices, with increments of 10 mm, at 120 kV and 220 mAs). HRCT scans were evaluated by the same 2 radiologists using a standardized scoring system (i.e., for all lung fields, an explicit search was made for specific abnormalities) (table 1). Abnormal findings were considered to be residual abnormalities due to LD if they were present focally and located mainly in areas of involvement revealed by chest radiography performed during the acute phase of LD. HRCTs were also evaluated for the presence or absence of findings suggestive of emphysema.

Questionnaire. The questionnaires were sent by mail or were distributed and completed during the hospital visit. Participants were asked to grade symptoms of shortness of breath that occurred during the period shortly before they developed LD and at the time of questionnaire completion and were also asked about their smoking history. Self-reported symptoms of shortness of breath were graded on a scale of 0–4: no complaints (0); shortness of breath associated with heavy (1), moderately heavy (2), or light (3) exercise; and shortness of breath at rest (4).

Table 1. Abnormal radiological findings in 33 survivors of an outbreak of legionnaires disease who underwent high-resolution CT scanning.

Finding	Detection of residual pulmonary abnormalities, no. (%) of survivors	
	Yes (n = 21)	No (n = 12)
Linear opacities	21 (100)	4 (33)
Segmental or subsegmental consolidation	8 (38)	0 (0)
Bronchiolectasis and/or bronchiectasis	7 (33)	2 (17)
Cysts	4 (19)	0 (0)
Emphysema	8 (38)	10 (83)

Statistical analysis. Continuous variables were compared using Student's *t* test for groups, and categorical variables were compared using χ^2 analysis or Fisher's exact test. A 2-tailed *P* value of <.05 was considered to be statistically significant. The association between potential risk factors present during the acute phase of LD and residual pulmonary abnormalities was evaluated by univariate regression analysis. Factors with a *P* value of \leq .10 were subsequently included in a multivariate logistic regression analysis. Factors with a *P* value of >.20 in the multivariate analysis were excluded from the final multivariate model.

RESULTS

General demographic and clinical characteristics of participants.

All 122 participants completed a questionnaire; 86 underwent the full evaluation (i.e., lung function testing and radiological examination). The latter group were mostly male, generally older, and had a high percentage of patients who were active smokers at the time of visiting the flower show and a high percentage of patients with any history of smoking (defined as smoking at least 1 pack of cigarettes/day for 5 years [\geq 5 pack-years]) (table 2). Among patients with a history of smoking, there was a high prevalence of chronic obstructive pulmonary disease (COPD), defined as an FEV₁/VC ratio of <0.7 after salbutamol inhalation [9]. Participants were evaluated 13–19 months (mean interval, 16 months) after the start of the acute phase of LD.

All participants had been treated with antibiotics for 2–3 weeks at the time of infection. For 79 of these 86 participants, data on antibiotic treatment received were available. For 24 of these 79 patients, adequate antibiotic therapy (a macrolide with or without rifampicin or fluoroquinolone) had been initiated >24 h after hospital admission for LD. In 33 of 86 participants, residual abnormalities were suspected after the first evaluation on the basis of abnormal chest radiograph findings either with

Table 2. Demographic and clinical characteristics of survivors of an outbreak of legionnaires disease who underwent lung function testing and chest radiography.

Characteristic	Presence of residual pulmonary abnormalities		
	Yes (n = 65)	No (n = 21)	Total (n = 86)
Sex, M/F	41/24	13/8	54/32
Age, mean years \pm SD	61 \pm 10	64 \pm 11	62 \pm 11
Smoking history			
Any ^a	53 (82)	18 (86)	71 (83)
Active	24 (37)	14 (67)	38 (44)
COPD ^b	10 (15 vs. 19)	8 (38 vs. 44)	18 (21 vs. 25)

NOTE. Data are no. (%) of patients, unless otherwise indicated. COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; VC, vital capacity.

^a Defined as \geq 5 pack-years (i.e., at least 1 pack of cigarettes/day for 5 years).

^b Data are no. of patients with an FEV₁/VC ratio of $<$ 0.7 after salbutamol inhalation (% of all participants vs. % of participants with any history of smoking).

(9 patients) or without (9 patients) a decreased DLCO or on the basis of a decreased DLCO only (15 patients) (figure 1). None of the 86 participants had a decreased VC.

The mean age of the 36 participants who completed the questionnaire only was greater than that of the 86 patients who also underwent the full evaluation (67 vs. 62 years; $P < .01$). The sex distribution among these 36 survivors was not significantly different from the group that also underwent the full evaluation (female:male ratios, 17:19 vs. 32:54; not significant [NS], by Fisher's exact test). The individuals who completed the questionnaire only were smoking an equal number of cigarettes per day at the time of the flower show visit (mean, 4 vs. 6 cigarettes/day; NS) and were equally likely to smoke \geq 10 cigarettes/day, but they had fewer pack-years of cigarette smoking than did the participants who underwent the full evaluation (mean, 12 vs. 22 pack-years of cigarettes; $P < .001$). Of these 36 participants, 3 (8%) had received mechanical ventilation during the acute phase of LD, compared with 9 (10%) of 86 of the participants who underwent the full evaluation, for a mean duration of 9 and 14 days, respectively (NS). None of the 122 participants were known to have any form of chronic interstitial lung disease or an altered immune status, except for 1 participant, who was HIV seropositive.

Radiological findings. For the 33 participants with abnormal chest radiograph findings and/or a decreased DLCO, an HRCT was performed (figure 1). In 21 participants, HRCT revealed abnormal findings that were likely attributable to their episode of LD. These abnormal findings were generally discrete and multiple (table 1 and figure 2). In 10 of the remaining 12 participants, HRCT revealed signs of significantly progressed emphysema, which explained the decreased DLCO that was observed (figure 1). In 5 of these 12 participants, HRCT also revealed abnormal findings other than emphysema (table 1 and figure 1). However, these findings were considered unlikely to

be associated with LD, because they were diffuse rather than localized in the areas involved during the acute phase of LD (2 participants), or because they were present only in areas other than and away from those involved during the acute phase of LD (3 participants).

Lung function measurements. None of the 33 participants who underwent additional lung function testing had a decreased total lung capacity. A total of 24 participants had a decreased DLCO (12 participants with and 12 without LD-related residual pulmonary abnormalities revealed by HRCT). COPD was present in 8 participants with and in 10 participants without residual abnormalities, all of whom were former or active smokers with a smoking history of at least 15 pack-years.

The mean VCs among participants with and participants without residual pulmonary abnormalities revealed by HRCT were not different ($105\% \pm 13\%$ vs. $109\% \pm 14\%$; NS). The mean DLCOs in the 2 groups, however, were significantly different ($70\% \pm 12\%$ vs. $84\% \pm 16\%$; $P < .001$). When the groups were further subdivided on the basis of HRCT-confirmed emphysema, the latter appeared to be a confounding factor (table 3). Taking this into account, in the subgroup of participants without emphysema, those with residual abnormalities also had a lower mean DLCO than did those without residual abnormalities (72% vs. 89% ; $P < .001$).

Risk factors for the presence of residual pulmonary abnormalities. Univariate analysis revealed that receipt of mechanical ventilation during the acute phase of LD, smoking \geq 10 cigarettes/day at the time of the flower show visit, initiating appropriate antibiotic therapy $>$ 24 h after hospital admission for LD, and having COPD were statistically significantly associated with the presence of residual pulmonary abnormalities (table 4). In the final multivariate logistic regression model, the ORs for receipt of mechanical ventilation and delayed receipt of appropriate antibiotic therapy were statistically significant

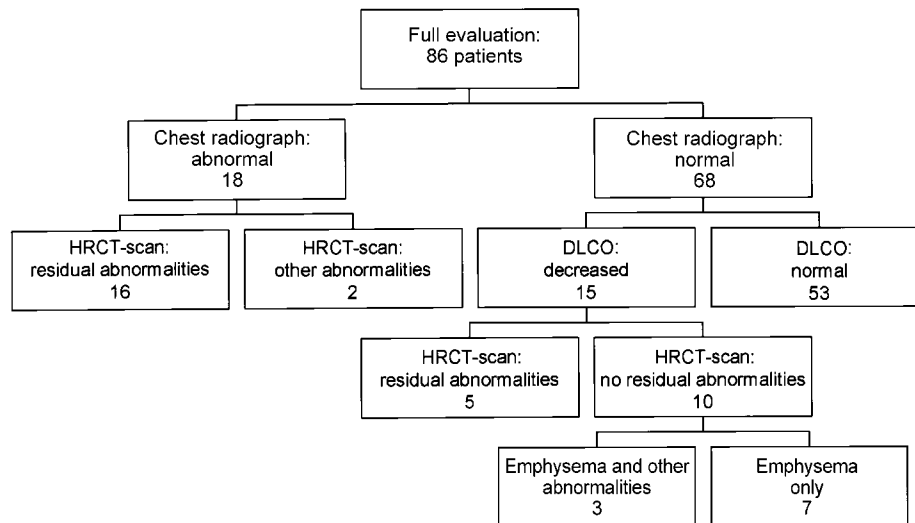


Figure 1. Flow chart illustrating the results of chest radiography, high-resolution CT (HRCT) scanning, and lung function testing for 86 survivors of legionnaires disease who consented to undergo full evaluation. DLCO, single-breath carbon monoxide diffusion capacity.

($P = .027$ and $P = .044$, respectively), and the OR for having COPD was nearly statistically significant ($P = .072$) (table 4). Receipt of mechanical ventilation was numerically the strongest predictor of residual pulmonary abnormalities (table 4). In this cohort of generally older individuals—among whom there was a high number of former smokers—age and cardiovascular comorbidities could not be identified as risk factors for residual abnormalities.

Self-reported shortness of breath symptoms. The reported severity of shortness of breath symptoms was greater at the time of the full evaluation than before the onset of LD. More-severe shortness of breath symptoms were reported by 37 (57%) of 65 participants without residual pulmonary abnormalities and by 13 (62%) of 21 of those with residual abnormalities revealed by HRCT (NS). In addition, the relative severity of shortness of breath symptoms before and after onset of LD and the increase in severity of shortness of breath symptoms did not differ between the subgroups of participants with and participants without residual abnormalities (NS), nor did they differ between participants who completed the questionnaire and underwent full evaluation and those who completed the questionnaire only. Overall, the severity of shortness of breath symptoms after LD in the group of participants who underwent full evaluation correlated statistically significantly but weakly with DLCO values ($r = -0.24$; $P = .03$).

DISCUSSION

In 21 (24%) of 86 survivors who recovered from acute-phase LD >1 year earlier, we found residual structural and functional pulmonary abnormalities, as established by HRCT findings and results of lung function tests. Taking into account the con-

founding effect of the presence of emphysema, these abnormalities were associated with a mean DLCO that was 20% lower than the normal value. Several risk factors were associated with the persistence of residual abnormalities, but, only for mechanical ventilation and a delay in starting appropriate antibiotic therapy during acute LD, and a diagnosis of COPD the association was statistically significant in a multivariate model. In ~60% of the participants, greater severity of self-reported shortness of breath symptoms associated with the episode of LD were observed, but this was independent of the presence or absence of residual pulmonary abnormalities. Decreased DLCO contributed only marginally to the explanation of the symptoms of shortness of breath reported in the questionnaire.

With respect to the study design, it must be realized that, because of its retrospective character, some uncertainty as to whether the abnormal HRCT findings were really the result of the acute LD the study participants had had 16 months earlier is unavoidable. On the other hand, in identifying residual abnormalities, our radiologists strictly applied a definition that allowed them to distinguish between post- and preinfection abnormalities with high precision. Only participants with signs of residual abnormalities revealed by plain chest radiography or participants with decreased lung function were subjected to HRCT. This way, we limited exposure to the ionizing radiation of the HRCT to participants who were most likely to have clinically relevant residual abnormalities. We realize that, because of this approach, minor residual abnormalities in some individuals may have remained undetected.

The outcome of our analysis may have been biased by selection, because only 86 (61%) of the total cohort of 142 survivors with confirmed or probable LD participated in the full evaluation. An indication of the presence of such bias can be

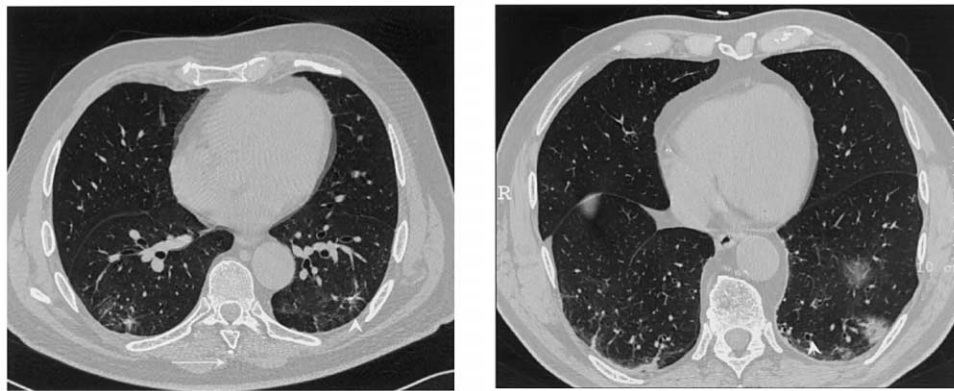


Figure 2. High-resolution CT scans of the lungs of 2 survivors of acute legionnaires disease who underwent full evaluation (i.e., lung function testing and radiological examination), illustrating representative residual pulmonary abnormalities. *Left*, Linear opacities and small consolidations in both lower lobes of the lung. *Right*, Subsegmental consolidations in the subpleural regions of both lower lobes of the lung, in combination with some linear opacities and a bronchiectatic airway (*arrowhead*).

obtained by comparing the presence of symptoms and risk factors for the 86 participants who underwent the full evaluation with those for the 36 who only completed questionnaires, who together comprised 86% of all survivors with confirmed or probable LD. Shortness of breath symptoms were similar in these 2 subgroups. Furthermore, the percentage of patients who received mechanical ventilation and for whom initiation of adequate antibiotic therapy was delayed during acute-phase LD—both of which were identified as risk factors for the presence of residual abnormalities—was similar in the 2 groups of participants investigated. A potentially relevant difference may be, however, that the participants who only answered the questionnaire had fewer pack-years of cigarette smoking. This may have rendered them less likely to have developed COPD, which we identified as a risk factor for the persistence of pulmonary abnormalities. These latter factors indicate that the group of participants who underwent full evaluation may have been biased toward a higher prevalence of residual abnormalities.

Previous information on the persistence of pulmonary abnormalities and associated functional abnormalities after LD is limited. In a study of survivors of acute LD, a variety of abnormal radiological findings were still observed in 70% of individuals after a mean follow-up period of 104 days [2]. In a study involving 30 of the 153 survivors 2 years after the original 1976 Philadelphia outbreak, a decreased DLCO was found in 2 of 5 nonsmoking and 12 of 25 smoking participants [1]. Fractionally, these numbers are considerably higher than those in the present study. Selection bias on the basis of symptoms is not a likely explanation for these differences, because, in the Philadelphia outbreak, 42% of the participants reported experiencing dyspnea on exertion (equivalent to grades 1–3 on our questionnaire), compared with 60% in our study.

We can only partially explain the persistent shortness of breath in more than one-half of the survivors, in view of the

relatively modest residual abnormalities detected. Two additional factors about which we were not informed may have contributed to these findings. First, cardiovascular factors and general physical condition also determine exercise capacity and the development of shortness of breath during exercise. Most patients had been immobilized for some time during the acute phase of LD, and, particularly at an older age, it may be difficult to regain a good general physical condition after such a period of immobilization. Second, the perception of shortness of breath before LD was graded retrospectively. This carries a risk for the introduction of recall bias [10]. A factor that we had some information on is psychological in nature. We have reported elsewhere that, in the present cohort of survivors of LD, a significant decrease in several dimensions of health-related quality of life was present at the time of this investigation [6]. Fifteen percent of the survivors experienced a clinically significant degree of posttraumatic stress disorder. It is conceivable that the subjective basis of the participants' judgment of their general state of health influenced the way in which they graded their symptoms of shortness of breath, resulting in a dissociation between these subjective symptoms and the objective lung function test results.

Table 3. Single-breath carbon monoxide diffusion capacity, according to the presence/absence of emphysema and residual pulmonary abnormalities.

Presence of emphysema	Presence of residual pulmonary abnormalities, % of predicted value \pm SD (no. of survivors)		
	No	Yes	Total
No	89 \pm 16 ^a (55)	72 \pm 17 ^a (13)	85 \pm 15 ^b (68)
Yes	58 \pm 16 (10)	66 \pm 8 (8)	62 \pm 4 ^b (18)

^a $P < .001$.

^b $P < .001$.

Table 4. Univariate and multivariate analysis of residual pulmonary abnormalities in survivors of an outbreak of acute legionnaires disease.

Factor	Type of statistical analysis			
	Univariate		Multivariate	
	OR (95% CI)	P	OR (95% CI)	P
Receipt of mechanical ventilation ^a	4.77 (1.15–19.8)	.022	5.55 (1.21–25.4)	.027
Smoking \geq 10 cigarettes/day	3.66 (1.19–11.3)	.020
Chronic obstructive pulmonary disease	3.39 (1.12–10.3)	.026	2.96 (0.91–9.65)	.072
Smoking 1–9 cigarettes a day	2.93 (0.69–12.40)	.13
Delayed initiation of adequate antibiotic therapy ^b	2.86 (1.00–8.14)	.045	3.17 (1.03–9.75)	.044
History of smoking ^c	1.36 (0.34–5.37)	.66

^a During the acute phase of legionnaires disease.

^b Initiation of therapy $>$ 24 h after hospital admission for acute legionnaires disease.

^c Defined as \geq 5 pack-years (i.e., at least 1 pack of cigarettes/day for 5 years).

Receipt of mechanical ventilation during the acute phase of LD, delayed initiation of adequate antibiotic treatment, and COPD were identified as factors associated with an increased risk for residual pulmonary abnormalities. In our view, receipt of mechanical ventilation is merely an indicator for the severity of acute LD, rather than a risk factor per se. It must be recognized, however, that mechanical ventilation itself can cause injury to lung tissue. Long-term persistence of pulmonary abnormalities revealed by CT have been described after prolonged receipt of mechanical ventilation in survivors of acute respiratory distress syndrome [11]. These abnormalities presented as reticular changes and ground-glass attenuations and were confined to those parts of the lung that were unaffected by consolidation in the acute phase of the disease [11]. These data contrast with our findings in several ways. The participants in the present study received ventilation for only short periods of time. In addition, the abnormal radiological findings we observed were of a different kind and, in almost all cases, were restricted to the areas of the lung that showed signs of pneumonia during the acute phase of LD. Our results show that, in addition to a worse prognosis for LD in terms of increased mortality and risk of admission to an intensive care unit [12], a delay in initiating appropriate antibiotic therapy [13–15] also increases the risk of persistent pulmonary abnormalities.

In a number of previous studies, a history of smoking was identified as an apparent risk factor for acquiring community-acquired pneumonia, in general [16–18], and LD, in particular [19, 20]. Cigarette smoking is associated with invasive disease in pneumococcal pneumonia [21], and appearance of radiographic evidence of community-acquired pneumonia in general is delayed in smokers [22]. The mechanisms by which smoking increases the susceptibility for acquiring pneumonia and leads to a more severe course of pneumonia are not well known. Because smoking is a major etiologic factor in COPD, it might be hypothesized that COPD is the factor that links smoking to a different course of at least some forms of pneumonia.

Assuming that COPD is indeed a risk factor for residual pulmonary abnormalities after LD, it is tempting to speculate on the mechanisms underlying this association. According to current views, one of the pivotal factors in the development of COPD is an imbalance in protease and antiprotease activity in the lungs of susceptible smokers [23, 24]. *Legionella pneumophila* produces a tissue-destructive metalloproteinase that, on the basis of results of animal studies, has been attributed an important role in the pathogenesis of LD [25–32]. A plausible hypothesis would be that the inability to counterbalance tissue-destructive metalloproteinases predisposes to the development of COPD and to more damage to the lung tissue during *Legionella* pneumonia, leading to an incomplete resolution of disease.

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