Incidence and clinical features of community-acquired legionellosis in hospitalized patients


ABSTRACT: In a two-year prospective study of patients hospitalized because of community-acquired pneumonia, the incidence of legionellosis was found to be 3.8% (17/442 cases). After S. pneumoniae, M. pneumoniae and influenza viruses, Legionellae were the fourth most frequently identified pneumonia agents. We evaluated the clinical data from 41 cases with legionellosis, 17 diagnosed in this prospective study and 24 prior to the study. The age range of all patients (22 women, 19 men) was 24-78 yrs (median 61.3 yrs), 14 of 41 cases (34.1%) had extrapulmonary organ involvement. Twelve patients (29.3%) died. The fatality rate was 4.5% (1/22 cases) in patients treated with erythromycin, and 57.9% (11/19 cases) in patients treated with other antibiotics. Antibiotics effective in legionellosis should be added to the routine therapy of community-acquired pneumonia when this aetiology can not be excluded.

Patients and methods

Patients

This prospective study was performed from January 1, 1984, to December 31, 1985, at the Rudolf Virchow University Hospital. In these hospital patients with community-acquired pneumonia are either treated in the department of infectious diseases or in the medical intensive care unit. Thus, patients who were admitted to or treated in one of these facilities were included in this study.

Microbiological examinations

We examined serum, respiratory secretions, urine and lung tissue specimens obtained at autopsy. Legionellae were detected by the following laboratory procedures:

1) Demonstration of legionella serum antibodies in patients with pneumonia was achieved by the indirect immunofluorescence assay (IFA) [15, 16]. The antigens...
used were heat-inactivated *L. pneumophila* serogroups 1-6, *L. micdadei* and *L. dumoffii*.

2) Culture of bronchial secretions were pretreated with acid buffer in order to reduce growth of contaminating organisms [17]. Tissue homogenates were prepared according to the literature [18]. Buffered charcoal-yeast extract agar supplemented with alpha-ketoglutarate [19-21] and media described by EDELESTEIN [21] and WADOWSKY and Lee [22], the latter being modified [23], were used simultaneously to culture the organism.

3) Direct immunofluorescence (DFA) described by CHERRY et al. [24] was used to detect *Legionellae* species in sputum and deparaffinized lung tissue sections. Both polyclonal and monovalent fluorescent antibody reagents were used. The reagents were kindly supplied by the Centers for Disease Control (CDC), Atlanta, GA, USA. The conjugates were specific for the identification of *L. pneumophila* serogroups 1-6, *L. longbeachae* serogroups 1 and 2, *L. gormanii*, *L. micdadei*, *L. dumoffii* and *L. bozemanii*.

4) Detection of *L. pneumophila* serogroup 1 antigen in urine was carried out using the radioimmunoassay (RIA) as outlined by KOHLER et al. [25] and FEHRENBACH et al. [26].

**Case definition.** Legionellosis was defined by at least one of the following criteria: i) a four-fold or greater rise in serum antibody titres for confirmed diagnosis; ii) cultural growth of *Legionellae* from respiratory secretions; iii) demonstration of the organism in lung tissue by culture and/or DFA; and iv) detection of legionella antigen in urine.

The aetiologies of non-legionella pneumonias were established according to the following criteria:

**Bacterial agents.** Consistent isolation of bacteria in pure culture or one predominant bacterium in multiple cultures from leucocyte-containing respiratory secretions and isolation of bacteria from blood culture. Patients with isolation of multiple bacteria or with different predominant bacteria in multiple respiratory secretions were classified as aetiologically uncertain. Infections with *Mycoplasma pneumoniae* or *Chlamydia psittaci* were diagnosed through a significant rise of serum antibodies (complement fixation test). The *C. psittaci* diagnostic test was performed in selected cases only.

**Non-bacterial agents.** Various diagnostic tests were carried out in selected cases to evaluate non-bacterial aetiologies. Results were considered positive when a significant rise in serum antibody titres was found against: cytomegalovirus; influenza virus A or B and adenovirus (complement fixation test); echovirus and coxsackie virus (neutralization reaction); or when a virus was isolated from throat washings or throat swabs using standard techniques.

Statistical analysis was performed using the Chi-squared test.

**Results**

In the two-year prospective study 442 patients with pneumonia, of whom 35 patients (7.9%) died, were investigated. *Legionellae* were identified as the causative pneumonia agents in 17 (3.8%) patients. The incidence of legionellosis was 5.1% (12/236 cases) in 1984 and 2.4% (5/206 cases) in 1985. The difference of incidence in the two years was not significant (p=0.15). Three of 17 patients (17.6%) with legionellosis died. Another 24 cases of legionellosis were diagnosed before the prospective study was started through 1978–1983.

**Microbiological examinations**

The number of diagnostic tests positive for legionella in the prospective study carried out on variable numbers of specimens is shown in table 1 for the total of 442 patients with pneumonia and for the 17 patients with legionellosis. The diagnosis was established by three positive tests in one patient, by two positive tests in four and by one positive test in twelve patients.

Serology was positive in 7 of the 17 (41%) cases with legionellosis. Of the 17 cases, 6 had single and 11 paired serum samples examined. Three patients had positive titres (1:256 in two cases, 1:512 in one case) when the first sample was examined. The rate of positive results increased to 63% (7/11 cases) on the basis of paired serum samples (table 1). The maximum titres were 1:256, 1:512 and 1:2048 in two cases each and in one case 1:1024 (in 5 cases against *L. pneumophila* serogroup 1 and in one case each against serogroup 4 and 6).

### Table 1. Results of legionella diagnostic tests for 442 pneumonia cases and for 17/442 patients with legionella pneumonia

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Pneumonia n</th>
<th>Legionellosis n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Total</td>
</tr>
<tr>
<td>Serum (total)*</td>
<td>7</td>
<td>442 (1.6)</td>
</tr>
<tr>
<td>Serum (initial sample)</td>
<td>3</td>
<td>442 (0.7)</td>
</tr>
<tr>
<td>Serum (paired samples)</td>
<td>7</td>
<td>347 (2.0)</td>
</tr>
<tr>
<td>Sputum</td>
<td>6</td>
<td>335 (1.6)</td>
</tr>
<tr>
<td>Urine</td>
<td>9</td>
<td>290 (3.1)</td>
</tr>
<tr>
<td>Lung tissue</td>
<td>2</td>
<td>34 (5.9)</td>
</tr>
</tbody>
</table>

* Patients with single and paired serum samples; *a* six specimens were positive with the DFA, 2/6 specimens by culture; *b* positive both with DFA and culture.
L. pneumophila serogroup 1 antigen detection in urine was positive in 9 of 11 cases (82%) with L. pneumophila serogroup 1 pneumonia (table 1). In 5 cases with negative serology, the diagnosis was established through urinary antigen detection. Sputum and lung tissue were positive in 6 and 2 cases, respectively, (table 1).

In 204 of 442 patients (46.2%) an aetiological agent was identified (table 2). Legionella was the fourth most commonly identified agent, S. pneumoniae was isolated from sputum in 59 (16.7%) out of 335 cases and from blood cultures in 12 (3.4%) out of 352 cases. In nine cases dual infections were established, in 7 cases with influenza virus A or B and S. aureus and in two cases with M. pneumoniae and S. pneumoniae. In all cases of legionellosis, Legionellae spp. were the only agents identified.

From 1978 to 1983, when the legionella diagnostic tests were applied sporadically in pneumonia cases, 24 cases of legionellosis were diagnosed. Nine cases were discovered by examination of deparaffinized lung tissue sections with DFA; in four of them lung tissue specimens were available for culture and in three cases growth was obtained. Of the remaining 15 cases, 12 had a four-fold or greater rise in serum antibody titre (maximum titres 1:256 in 1 case, 1:512 in 4 cases, 1:1024, 1:2048, 1:4096 in 2 cases each and 1:8192 in 1 case) and in 11 legionella antigen was detected in urine. DFA of respiratory secretions was positive in two cases, with additional positive results in serological and urinary antigen detection tests in one case each. In ten of these 15 cases more than one method showed positive results.

Between 1978–1985, no Legionellae spp. species other than L. pneumophila are found. Of the 41 cases, serogroup 1 was responsible for 37 cases, serogroup 4 and 5 for one case each and serogroup 6 for 2 cases.

Clinical features and laboratory findings

All 41 cases were sporadic. The female/male ratio was 22:19. The median age was 61.3 yrs (range 24–68 yrs). Twenty of 41 patients (48.8%) suffered from one of more serious underlying diseases: chronic obstructive lung disease, (n=10); cardiac disease (n=7); malignancies (n=6); immunosuppressive states (n=5); diabetes mellitus (n=4); and chronic renal insufficiency (n=1). The initial chest X-ray revealed patchy infiltrations in all cases, with segmental or lobar distribution in about two-thirds of patients. The lower lobes were most frequently afflicted and cavitation was absent. The body temperature ranged from 38.2–40.1°C. Respiratory symptoms were seen in 33 cases (81%) and symptoms of extrapulmonary organs in 14 cases (34%). The clinical symptoms and laboratory findings are shown in tables 3 and 4.

Twelve patients (29.1%) died, all of them with underlying diseases. Of these patients, one was treated with erythromycin for two days, seven with cephalosporins and/or aminoglycosides for 2–5 days, two with chloramphenicol for 2–4 days, and two with amoxicillin for three and four days, respectively.

Twenty-nine patients (71%) survived. Twenty-one of them were treated with erythromycin for 7–21 days (initially in combination with chloramphenicol for up to 5 days), in five cases amoxicillin was given for 5–7 days and three were treated with tetracycline for 5–7 days.

Of the total of 22 patients (eight with underlying
diseases) treated with erythromycin, one died (4.5%).
Of the 19 patients (12 with underlying diseases) treated
with other antibiotics, 11 (57.9%) died.
In the group of patients with underlying diseases, the
mortality was lower in patients treated with erythro-
mycin (1/8 patients died) compared to patients treated
with other antibiotics (11/12 patients died) (p=0.0004).
In the group of patients without underlying diseases all
patients survived irrespective of the antibiotics admini-
stered.

Discussion

The diagnosis of legionellosis ranged from 0–32% of
community-acquired pneumonia cases in hospital based
studies [5–7, 11–14, 27–31]. The incidence of 3.8%
found in our study is in the lower range of incidences
reported.

Various reasons have been considered to account for
the great differences in incidence [1, 2]. High incidences
have been explained as the result of hyperendemic
situations [1, 2, 12]. Recently, considerable annual and seasonal variations have been found [12, 28]. Selection of pneumonia cases may also have an
effect on the incidence. Legionellosis frequently develop-
ing as a severe illness requires hospitalization in most
cases and its frequency seems to be higher when only severe pneumonia cases are evaluated [12, 28, 30]. The
low incidence in our study may partly be due to the
fact that there was no selection of pneumonia cases and
no endemic upsurge.

Legionella was the fourth most commonly identified
agent. The fact that legionellosis ranged in most stud-
ies among the five most frequently established pneumo-
nia aetiologies supports its importance [5, 7, 13, 14, 31]. The highest percentage of 53.8% of pneumonias
without established cause is in accordance with other
studies [6, 11, 31]. Partly, this may be due to the
frequently administered antibiotic therapy prior to
admission [13] and to the strict criteria in establishing
an aetiological agent.

Diagnosis of legionellosis is being handicapped by
drawbacks in conventional diagnostic tests [2, 16, 25, 26]. Serology, which is frequently the only diagnostic
test performed, is not suitable for diagnosis in the acute
phase [2, 16, 26]. A rise of serum antibodies can also
simply fail to appear [16, 23]. In our prospective study,
10 of 17 cases (59%) would not have been detected
using serology only. Negative results by examining
respiratory secretions does not exclude legionellosis since
representative specimens, especially when sputum is
examined, are frequently difficult to obtain [2, 16].
Legionella antigen detection in urine, which is
currently not generally available and is established for
L. pneumophila serogroup 1 only, has emerged as an
important diagnostic tool. This test frequently allows
the diagnosis to be made as early as 24 h after the onset
of symptoms and gives positive results in up to 93%
of cases [25, 26]. With five patients this was the only
positive test.

Our results underscore the necessity to employ a
broad spectrum of diagnostic tests to overcome "blind
spots" which are inherent in each of the examinations.
Postmortem examination of lung tissue is necessary to
gain reliable data on the importance of legionellosis,
since a number of fatal cases remained undiagnosed
during life [1, 2].

All cases were due to L. pneumophila, which is by
far the most frequently identified Legionella species
worldwide, with serogroup 1 being most important [16,
32, 33]. However, in some studies a high share of other
Legionella spp. species was found, sometimes even
outnumbering cases with L. pneumophila [7, 13, 14].
Currently, 23 Legionella spp. species are known [16],
but the vast majority of cases are due to a limited num-
ber of species only [16, 32, 33].

Clinical and laboratory findings of patients with
legionellosis are not specific enough to allow differen-
tiation from other pneumonias [5, 13]. However, in-
volve ment of extrapulmonary organ systems was also
mentioned to provide helpful clues and to sometimes
support the suspicion of legionellosis on clinical
grounds [2]. In our patients extrapulmonary involvement
was observed in an even lower range than in other
series, whereas respiratory symptoms were seen in simi-
lar proportions [34, 35]. The spectrum of laboratory
value alterations was similar to other studies [13, 35].
Low sodium values which were found to be frequently
associated with legionellosis, were found less often than
in other studies [13, 35].

Therapy with erythromycin has been reported to be
associated with the lowest fatality rate in legionellosis
[2, 34]. In our patients with underlying diseases, the fa-
tality rate of patients treated with erythromycin was
significantly lower compared to patients treated with
other antibiotics, whereas all patients without underly-
ing diseases survived irrespective of the antibiotics
administered.

Presently, erythromycin (2–4 g·day⁻¹) is recommended
for at least three weeks in order to prevent relapses [2, 36].
Recently, it has been mentioned that a shorter
course therapy may be sufficient in immunocompetent
patients with a mild case of legionellosis [36]. Our ex-
perience shows that antibiotics effective in legionellosis
should be part of the antibiotic therapy, especially in
patients with underlying diseases, when legionellosis
cannot be excluded.

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Résumé: Une étude prospective de deux ans chez des patients hospitalisés pour des pneumonies acquises dans la collectivité, a montré une incidence de légionnelle de 3.8% (17/442 cas). Les Legionella apparaissent ainsi comme le quatrième agent identifié de la pneumonie par ordre de...
fréquence après le Pneumocoque, le Mycoplasme et les virus de l'Influenza. Les données cliniques des 41 cas de légionellose ont été évaluées, 17 provenant de l'étude prospective et 24 antérieurs à l'étude. L'âge médian des patients était de 61,3 ans (extrêmes: 24 à 78). Il y avait 22 femmes et 19 hommes. 14 des 41 cas avaient une atteinte organique extra-pulmonaire (34,1%). 12 patients (29,3%) sont décédés. Le taux de mortalité s'élève à 4,5% (1/22) en cas de traitement par l'érythromycine, et à 57,9% (11/19) pour les patients traités par d'autres antibiotiques. Des antibiotiques efficaces dans les légionelloses devraient être joints au traitement de routine des pneumonies acquises dans la collectivité lorsque cette étiologie ne peut pas être exclue. *Eur Respir J.*, 1989, 2, 257–262.