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

B. Ruf*, D. Schürmann*, I. Horbach**, F.J. Fehrenbach**, H.D. Pohle*

Incidence and clinical features of community-acquired legionellosis in hospitalized patients. B. Ruf, D. Schürmann I. Horbach, F.J. Fehrenbach, H.D. Pohle.
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 influenzae 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.
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* 2nd Dept of Internal Medicine, Rudolf Virchow University Hospital - Wedding, Freie Universität Berlin, Augustenburger Platz 1, D 1000 Berlin 65.
** Dept for Microbiology, Robert Koch Institute, Nordufer 20, D 1000 Berlin 65.

It has been well established that *Legionella spp.* are a cause of hospital- and community-acquired pneumonia worldwide [1, 2]. Epidemic outbreaks, especially in hospitals, have been a frequent topic for research [1–4]. Legionella has emerged as important aetiology in the spectrum of nosocomial pneumonias [2, 5–7], and in recent studies interest has mainly been focused on the control and prevention of hospital-acquired legionellosis [8–10]. However, it has been recognized in hospital-based pneumonia studies, that sporadically occurring community-acquired legionellosis may account for up to 32% of pneumonia cases [6]. Yet the incidences reported vary widely [6, 11–13], and in one study no case of legionellosis was detected [14].

We performed a two-year prospective study to gain further data on the incidence of community-acquired legionellosis in patients hospitalized for pneumonia. In addition, clinical data of patients with a diagnosed legionellosis, either during the prospective study or earlier, were evaluated.

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.

Diagnosis of community-acquired pneumonia was based on the patient's history, physical findings (pulmonary findings, fever) and pneumonic infiltration on chest X-ray. Patients with pulmonary tuberculosis and with pneumonia following pulmonary infarction or tumour stenosis as well as patients with human immunodeficiency virus (HIV) infection were excluded. Emphasis was given to the detection of legionellosis. Therefore, the evaluation of clinical data was restricted to patients in whom legionellosis had been diagnosed. In addition, cases in whom legionellosis had been diagnosed prior to this prospective study (1978–1983), when diagnostic tests for legionella were applied only occasionally, were evaluated retrospectively.

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 EDELSTEIN [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 polyvalent 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 and a single or standing titre of >1:256 for presumptive 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

	Pneumonia n			Legionellosis n		
Specimen	Positive	Total	%	Positive	Total	%
Serum (total)[a]	7	442	(1.6)	7	17	(41)
Serum (initial sample)	3	442	(0.7)	3	17	(18)
Serum (paired samples)	7	347	(2.0)	7	11	(64)
Sputum	6	335	(1.8)	6[b]	12	(50)
Urine	9	290	(3.1)	9	11	(82)
Lung tissue	2	34	(5.9)	2[c]	2	(100)

[a]: patients with single and paired serum samples; [b]: six specimens were positive with the DFA, 2/6 specimens by culture; [c]: 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

Table 2. – Results of microbiological examinations in 442 patients with community-acquired pneumonia

Aetiology	n	%[a]
Streptococcus pneumoniae	68	(15.4)
Mycoplasma pneumoniae	41	(9.3)
Influenza virus (A and B)	18	(4.0)
Legionella pneumophila	17	(3.8)
Chlamydia psittaci	14	(3.2)
Staphylococcus aureus	12	(2.7)
Haemophilus influenzae	11	(2.5)
Other gram-negative aerobes[b]	11	(2.5)
Other agents[c]	21	(4.8)
Uncertain or unknown	238	(53.8)

[a]: total number of aetiologies exceeds number of pneumonia cases with established cause since dual infections were diagnosed in nine cases; [b]: *Escherichia coli, Proteus spp., Klebsiella spp.,* [c]: cytomegalovirus, other viruses.

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 1:8182 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 two 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

Table 3. – Frequency of symptoms in 41 patients with legionellosis

Symptom	n	%
Respiratory	33	(80)
cough	29	(71)
productive cough	15	(37)
dyspnoea	13	(32)
chest pain	8	(20)
Gastrointestinal	12	(29)
nausea/vomiting	10	(24)
diarrhoea	5	(12)
Neurological	11	(27)
headache	9	(22)
confusion	4	(10)
ataxia	1	(2)

Table 4. – Laboratory findings on admission to hospital in 41 patients with legionellosis (modified according to WOODHEAD *et al.* [35])

Feature		n	%
Leucocyte count	$>10 \times 10^9 \cdot l^{-1}$	33	(80)
	$>15 \times 10^9 \cdot l^{-1}$	10	(24)
Lymphocyte count	$<1 \times 10^9 \cdot l^{-1}$	8	(20)
Erythrocyte sedimentation rate	>50 mm in 1 h	36	(88)
	>100 mm in 2 h	6	(15)
Thrombocytes	$<100 \times 10^9 \cdot l^{-1}$	3	(7)
Sodium	<135 mmol·l^{-1}	19	(46)
Sodium	<130 mmol·l^{-1}	7	(17)
Potassium	<3.5 mmol·l^{-1}	8	(20)
Urea	>7 mmol·l^{-1}	20	(49)
	>15 mmol·l^{-1}	5	(12)
Creatinine	>120 μmol·l^{-1}	11	(27)
Elevation of liver enzymes		17	(42)
Proteinuria		14	(34)
Haematuria		7	(17)

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 amoxycillin for three and four days, respectively.

Twenty-nine patients (71%) survived. Twenty-one of them were treated with erythromycin for 7–21 days (16 initially in combination with chloramphenicol for up to 5 days), in five cases amoxycillin 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 erythromycin (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 administered.

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 developing 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 studies among the five most frequently established pneumonia aetiologies supports its importance [5, 7, 13, 14, 31]. The higher 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 *Legionellae 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 number of species only [16, 32, 33].

Clinical and laboratory findings of patients with legionellosis are not specific enough to allow differentiation from other pneumonias [5, 13]. However, involvement 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 similar 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 fatality rate of patients treated with erythromycin was significantly lower compared to patients treated with other antibiotics, whereas all patients without underlying 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 experience 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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Incidence et aspects cliniques des légionelloses acquises dans la collectivité chez les patients hospitalisés. B. Ruf, D. Schürmann, I. Horbach, F.J. Fehrenbach, H.D. Pohle.
RÉSUMÉ: Une étude prospective de deux ans, chez des patients hospitalisés pour des pneumonies acquises dans la collectivité, a montré une incidence de légionellose de 3.8% (17/442 cas). Les Legionellae apparurent 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.