

ORIGINAL ARTICLE

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An outbreak of Legionnaires' disease associated with a circulating bathwater system at a public bathhouse. I: a clinical analysis

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Abstract Few reports have analyzed the clinical manifestations of patients with Legionnaires' disease in large outbreaks throughout the world. We retrospectively evaluated the clinical presentation and prognostic factors in 76 patients with Legionnaires' disease, reported by local physicians, in a large outbreak resulting from contamination of the water in a public bathhouse in Miyazaki, Japan. Fever, gastrointestinal tract symptoms, and abnormal neurological findings were seen in 95%, 35%, and 21% of the 76 patients, respectively. Respiratory tract symptoms were seen in only 42% of the patients, although all of these patients revealed pneumonia on chest X-ray. Only 20 (31%) of the 64 patients who had microbiological tests were reported to have positive results for one of the three microbiological tests (sputum culture, serology, and urinary antigen) which are specific for *Legionella* infection. Based on univariate analysis, the existence of neurological symptoms, elevated levels of C-reactive protein and transaminases, hyponatremia, a positive urinary antigen test, and serological evidence of *Legionella* infection were independent risk factors for poor clinical courses in patients with Legionnaires' disease. Patients treated with antimicrobial agents, such as macrolides, tetracyclines, and/or fluoroquinolones, within 3 days of onset of illness exhibited significantly better outcomes, when assessed by a multivariate logistic-regression model,

after adjusting for the severity of pneumonia. Taking a careful history and documenting potential *Legionella* exposure, as well as microbiological testing, is important for an accurate diagnosis of Legionnaires' disease. Antimicrobials effective against *Legionella* bacteria should be administered without delay in subjects with suspected Legionnaires' disease.

Key words Legionnaires' disease · *Legionella* bacteria · Outbreak · Bath house · Antimicrobials

Introduction

Nearly all cases of Legionnaires' disease result from the contamination of constructed warm-water reservoirs, such as air-conditioning units, cooling towers, warm-water baths, and re-circulating water systems.¹ Legionnaires' disease was first recognized in 1976 as the cause of a pneumonia outbreak at a Pennsylvania State American Legion convention in Philadelphia.² The first case of Legionnaires' disease in Japan was reported in 1981 by Saito et al.³ Since these reports, there have been multiple outbreaks of Legionnaires' disease linked to hospitals, hotels, and spas.^{4–8} In Japan, although the maintenance of residual chlorine concentrations in re-circulating bathwater has been promoted for the prevention of *Legionella* bacteria growth, outbreaks of Legionnaires' disease linked to public bathhouses have continued, even recently.^{9–12}

In July 2002, one of the largest outbreaks of Legionnaires' disease associated with a public bathhouse in Japan occurred in Miyazaki. The local government and the University of Miyazaki performed a retrospective investigation of individuals who were considered to have been exposed to *Legionella* bacteria. This investigation provided a unique opportunity to analyze the clinical presentation of patients with outbreak-associated Legionnaires' disease. We evaluated the clinical pictures of the patients, the usage of diagnostic tools, and differences in clinical courses, based on the medical records of local physicians.

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Patients and methods

Outbreak in Miyazaki, Japan

On July 18, 2002, the local governmental health center received a report of multiple cases of severe pneumonia in individuals who had visited a single public bathhouse that had opened in June 2002. The bathhouse was closed on July 24. *Legionella pneumophila* serogroup (SG) 1 was isolated from the sputa of one of the reported patients. Pulse-field gel electrophoresis showed that the isolated *L. pneumophila* was identical to that discovered in the water of the bathhouse. In addition, *L. dumoffii* as well as *L. pneumophila* SG8 were isolated from the water of the bathhouse. The local population and doctors were alerted to the outbreak of Legionnaires' disease by the local government. Officials recommended that any suspected cases should be registered with the health center. According to the records of the bathhouse, 19773 individuals had visited the bathhouse at least once between June 20 and July 23. Eventually, 295 individuals were registered by local physicians as representing potential cases of Legionnaires' disease.

Study protocol and data collection

A research team was established, as a collaborative endeavor between the local government and the University of Miyazaki, to perform an epidemiological study of this outbreak. The study protocol was approved by the institutional review board of the University of Miyazaki. All 295 registered subjects who were suspected of having Legionnaires' disease by the local doctors were invited to participate in the study. Of these, 162 individuals agreed to participate in this study and provided written informed consent. Participating individuals provided responses to a questionnaire given during face-to-face interviews conducted by public health nurses. Clinical data, including the medical records from regional hospitals and chest X-ray/chest computed tomography (CT) films, were available for 142 of the 162 subjects. The films were assessed independently by two doctors whose specialties are respiratory diseases.

The following criteria were used to identify patients with probable Legionnaires' disease: (1) visit to the bathhouse between June 20 and July 24, 2002, (2) the occurrence of symptoms within 14 days of visiting the bathhouse (if any subject had had more than one visit, the final visit was used for the analysis), and (3) the presence of new pulmonary infiltrates suggestive of Legionnaires' disease by chest X-ray and/or chest CT at the time of patient consultation. Of the 142 subjects enrolled in this study, 76 met these criteria.

The following data were collected from medical charts: (1) premorbid conditions and characteristics, such as age, sex, previous history of smoking, alcohol use, and other underlying diseases; (2) date of bathhouse visit, date of the first day of illness, and the dates of admission to and discharge from the hospital; (3) symptoms, signs, and the results of routine biochemical and hematological testing at

initial consultation; (4) the degree of pulmonary infiltration seen on chest X-ray and/or CT, scored according to the criteria proposed by the Working Party for Legionellosis, Japanese Ministry of Health and Welfare;¹³ (5) microbiological testing for *Legionella* bacteria by local doctors, including sputum cultures, antibody titers, and urinary antigen tests; and (6) antimicrobial treatment.

Assessment of clinical course and statistical analysis

Of the 76 patients enrolled in this study, 22 were treated exclusively as outpatients. Fifty-four patients were admitted to the hospital, with a median admission period of 17 days. Four patients died of Legionnaires' disease; another patient died of underlying colon cancer. We divided the 75 patients (excluding the patient who died of colon cancer) into four groups and categorized their clinical courses: group 1 consisted of the 22 outpatients, group 2 consisted of 27 patients who were admitted to hospital for less than 17 days (median admission period), group 3 consisted of 27 patients who were admitted to hospital for equal to or longer than 17 days, and group 4 consisted of the 4 patients who died of Legionnaires' disease.

Associations between markers and clinical course were assessed by univariate analysis, using the Wilcoxon signed-ranks test and Spearman's rank correlation coefficient. The independent association between antimicrobial treatment and clinical course was assessed by multivariate logistic regression analysis after adjusting for sex, age, and the severity of pneumonia at the time of initial consultation, based on the scores determined from chest X-rays.¹³ Values of $P \leq 0.05$ were considered to be statistically significant. All statistical analyses were evaluated using SPSS for Windows software (version 10.0.5J, SPSS Japan, Tokyo, Japan) and based on two-tailed probabilities.

Results

Clinical picture of patients

The average age of the 76 patients with probable Legionnaires' disease was 65 years, ranging from 9 to 95 years. In the 69 patients for whom information about smoking was available, a history of smoking was present in 35 patients (51%). We noted the presence of additional underlying diseases, including hypertension (22 patients), cardiovascular disease (7 patients), diabetes (5 patients), renal disease (4 patients), chronic respiratory disease (3 patients), malignancy (2 patients), and other minor diseases (13 patients) in 39 of the 76 patients (51%; Table 1).

The median incubation period from the date of the bathhouse visit to the onset of initial symptoms was 6 days (Fig. 1). The distribution curve of incubation periods exhibited one peak similar to a normal distribution. Of the initial signs and symptoms, high fever with or without chills was observed in 72 patients (95%). Symptoms of respiratory tract illness (cough, sputum, and dyspnea) were seen in 32 patients

(42%). Symptoms of digestive tract distress (nausea, vomiting, diarrhea, and abdominal pain) were present in 27 patients (35%), and neurological symptoms (unconsciousness and delirium) were documented in 16 patients (21%).

Table 1. Background characteristics of the 76 subjects in this study

Age (years)	64.9 ± 12.2
Sex (male/female)	49/27
Patients with underlying diseases	39
Hypertension	22
Cardiovascular disease	7
Diabetes mellitus	5
Renal disease	4
Chronic respiratory disease	3
Malignancy	2
Other diseases	13

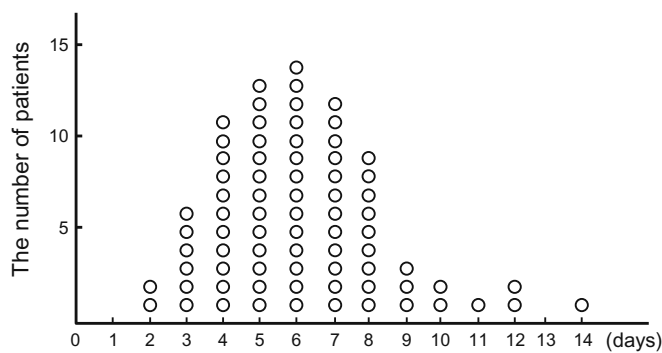
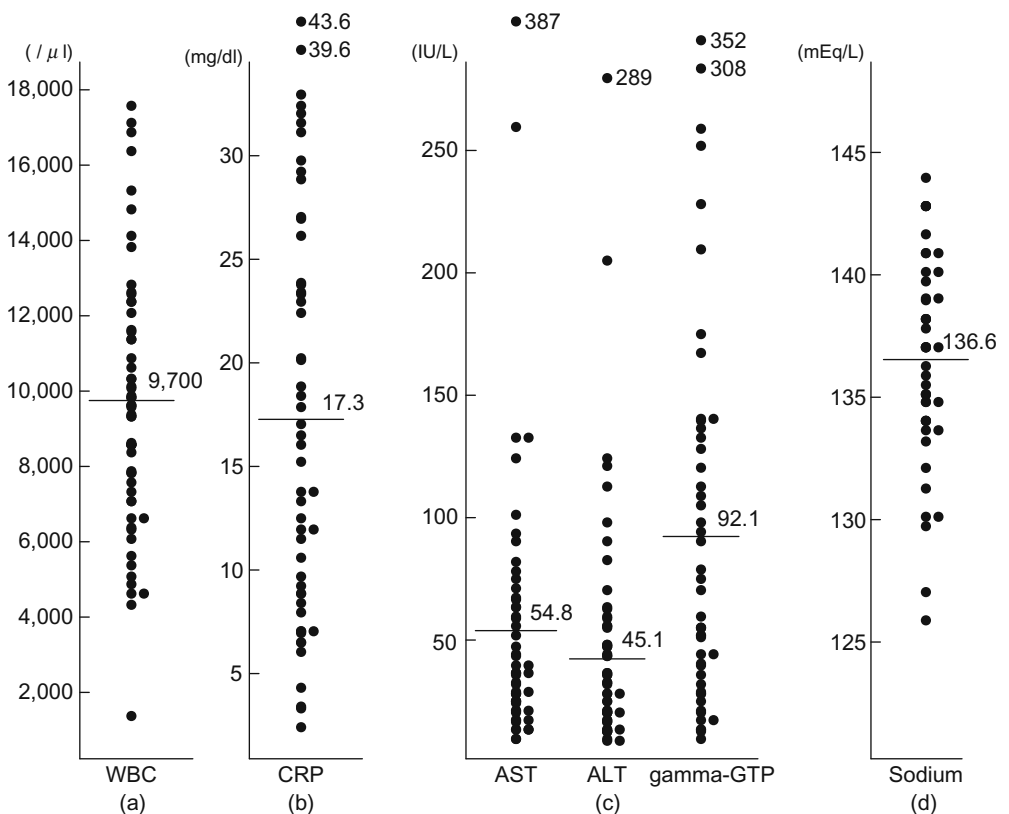


Fig. 1. Incubation periods (horizontal axis) in 76 patients with Legionnaires' disease in this outbreak

Fig. 2. Laboratory data for patients with Legionnaires' disease on initial presentation to hospital. *Panel a*, Number of white blood cells (WBC) in peripheral blood (number of patients, 62); *panel b*, serum concentrations of C-reactive protein (CRP; number of patients, 53); *panel c*, serum concentrations of aspartate aminotransferase (AST; number of patients, 59), alanine aminotransferase (ALT; number of patients, 59), and gamma-glutamyl transpeptidase (gamma-GTP, number of patients, 51); *panel d*, serum concentrations of sodium (number of patients, 48). Bars indicate the mean value



Only 42% of the patients complained of respiratory tract symptoms, despite the confirmation of pneumonia by chest X-ray in all 76 patients.

Routine biochemical and hematological tests, performed within 7 days of onset of illness and prior to the administration of any antimicrobial medication, were available for 64 patients. White blood cell counts, and serum levels of C-reactive protein (CRP), transaminases, and sodium were analyzed (Fig. 2a–d). White blood cell counts and CRP levels were elevated in 55% and 100% of the patients, respectively. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GTP) levels were elevated in 50%–60% of the patients. Mild hyponatremia ($\text{Na} \leq 137$ mEq/l) was observed in 60% of the patients.

Based on the medical records, at least one microbiological test to detect *Legionella* infection had been performed in 64 of the 76 patients at some point in their clinical course (Fig. 3). The medical records indicated that sputum cultures for *Legionella* were positive in 4 (22%) of the 18 patients tested. None of the common pathogens of pneumonia, such as *Streptococcus pneumoniae*, were isolated from the sputa of these patients. *Legionella* infection was confirmed by serological testing (indirect immunofluorescent antibody test and/or microplate agglutination test) in 7 (13%) of 52 patients, in whom titers were greater than or equal to 1:512 at a single measurement or exhibited a fourfold rise in paired measurements. Retrospective serological tests of preserved serum samples for *Mycoplasma pneumoniae* (particle agglutination test) and *Chlamydophila pneumoniae* (enzyme immunoassay) were also negative (data not

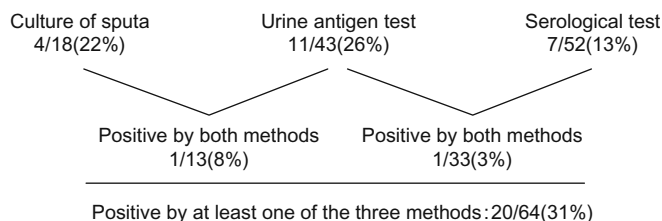


Fig. 3. *Legionella*-specific microbiological test results reported by local physicians for 64 patients

shown). Although the method used for urinary antigen testing could not be confirmed, the *Legionella* Urine Antigen EIA (Biotest AG, Dreieich, Germany) was the only commercial kit available to the laboratories in this area at the time of the outbreak. In 11 (26%) of the 43 patients tested for urinary antigen, results were reported as positive. In total, *Legionella* infection was confirmed in 20 (31%) of 64 patients, based on at least one positive *Legionella*-specific test.

Factors affecting clinical outcome

Of the 76 patients enrolled in this study, the number of patients who died of Legionnaires' disease was 4. Thus, it was difficult to evaluate the disease outcome by mortality rate in the present study. Therefore, we evaluated the clinical courses of 75 patients (excluding the patient who died of colon cancer) categorized in four groups: group 1, outpatients ($n = 22$); group 2, patients with a short hospital admission ($n = 27$); group 3, patients with extended hospital admission ($n = 22$); and group 4, patients who had died of the disease ($n = 4$). Groups with lower number were considered to have a less severe clinical course than groups with higher number. Based on univariate analysis, neurological symptoms; elevated CRP, AST, and ALT levels; hyponatremia; positive urinary antigen test; and serological evidence of *Legionella* infection were independent risk factors for a more severe clinical course (Table 2).

Of the 70 patients for whom information about medications was available, 42 patients (60%) were initially treated with antimicrobial agents (macrolides, tetracyclines, or fluoroquinolones) that are considered to be effective against intracellular bacteria,¹⁴ regardless of beta-lactam administration. Even in the 28 patients initially treated with beta-lactams alone, antimicrobial agents that were effective against intracellular bacteria were given to all but 4 patients at some point later in their clinical course.

To determine whether the initial treatment with a macrolide, tetracycline, or fluoroquinolone was an important factor in improving the outcome of disease, we evaluated a multivariate logistic-regression model after adjusting for the severity of pneumonia, determined from the chest X-ray scores. Patients treated with these antimicrobial agents tended to exhibit better clinical outcomes (Table 3). This trend was statistically significant when these agents were administered within 3 days of the onset of illness.

Table 2. Univariate analysis of factors associated with poorer outcomes in 75 patients with Legionnaires' disease

	<i>P</i> value
Background	
Male ^a	0.244
Older age ^b	0.210
History of smoking ^a	0.326
Current use of alcohol ^a	0.635
History of underlying diseases ^a	0.973
Shorter incubation time ^b	0.062
Symptoms	
Fever ^a	0.210
Cough ^a	0.937
Dyspnea ^a	0.563
Neurological symptoms ^a	0.005
Digestive symptoms ^a	0.416
Laboratory data	
Elevated white blood cell count ^b	0.252
Elevated C-reactive protein level ^b	0.026
Elevated aspartate aminotransferase level ^b	0.043
Elevated alanine aminotransferase level ^b	0.016
Elevated gamma-glutamyl transpeptidase level ^b	0.048
Lower than normal sodium level ^b	0.039
Positive <i>L. pneumophila</i> -specific microbiological test results	
Sputum culture ^a	0.454
Urinary antigen ^a	0.013
Antibody ^a	0.011

^aWilcoxon signed-ranks test

^bSpearman's rank correlation coefficient

Table 3. Multivariate analysis of factors associated with a poorer outcome in 75 patients with Legionnaires' disease

Treatment	Odds ratio	(95% CI)
Administration of ML, ^a FQ, ^b or TC ^c	0.44	(0.06, 3.01)
Within 3 days of onset	0.19	(0.0, 0.83)
Within 7 days of onset	0.55	(0.17, 1.78)

^aMacrolide

^bFluoroquinolone

^cTetracycline

Discussion

Since the first outbreak of Legionnaires' disease in Philadelphia, there have been several reports of large outbreaks associated with hotels, whirlpool spas, and cooling towers.⁴⁻⁸ Few reports, however, have analyzed the clinical presentation of affected individuals. The present study details the entire spectrum of the Legionnaires' disease in a group of people known to have been exposed to contamination in one of the largest outbreaks of Legionnaires' disease associated with a public bathhouse in Japan.

This study was performed retrospectively, based on subject interviews and an evaluation of medical records and chest X-ray/CT films. Therefore, there are several limitations to this study. First, of the 142 patients reported as having Legionnaires' disease by the local physicians, 66 patients were excluded from the analysis due to insufficient data or the absence of infiltration on chest X-rays. Secondly, Legionnaires' disease was confirmed in only 31% of the 64 patients for whom *Legionella*-specific microbiological test results were available. Therefore, the possibility exists that some patients who did not have Legionnaires' disease were

mistakenly categorized as having probable cases of Legionnaires' disease.

However, there seem to be several reasons for the low positivity of the *Legionella*-specific microbiological tests in the present study. The sensitivity of sputum culture testing for *Legionella* bacteria has been reported to be low, even when a suitable culture medium is used.^{1,14} In addition, sputum samples were often obtained after patients had received antimicrobials. The rate of positive antibody titers to *L. pneumophila* in this study was also low. The time at which blood samples for serological diagnosis were acquired varied from patient to patient. It is possible that *Legionellae* infection could have been confirmed if the most recently obtained serum sample had been available. However, the study design did not allow this. The urine antigen test is a useful diagnostic tool for Legionnaires' disease. The sensitivity of this test has been reported to be 80%–90% in Legionnaires' disease when infection is confirmed by an additional microbiological method.¹⁵ In the present study, only 26% of the patients evaluated were positive for the urine antigen test. Nakamura et al.¹² have also reported a low positive rate for the urine antigen test in patients with Legionnaires' disease in a large outbreak. The urine antigen test may fail to detect bacterial antigens in all patients with Legionnaires' disease, especially when samples are obtained just after the development of the disease.¹⁵ Kawano et al.¹⁶ reported that serum antibodies to *L. pneumophila* SG1, without any other serogroups, were detected in 5 of 66 patients in the same outbreak. They¹⁶ also reported that several other patients were positive for the antibody to *L. dumoffii*, which is not detectable by the urinary antigen test. In the outbreak in the present study, *L. pneumophila* SG8 was also isolated from the bathwater. Thus, there is a possibility that the pneumonia in some patients was caused by serogroups other than SG1, which are not detectable by the urinary antigen test.

The distribution of the incubation period for the 76 patients in our study, which was similar to a normal one-peak distribution, may suggest a single exposure to a pathogen in this population. The pneumonia occurred in the subjects exposed to *Legionella* bacteria during a short period in the middle of summer when we do not normally see many patients with pneumonia. There was no evidence of infection by other pathogens, such as *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, or *Chlamydophila pneumoniae* in the patients for whom data were available. Taking these results into consideration, we believe that the majority of these 76 patients, if not all, represented true cases of Legionnaires' disease.

An evaluation of the background information of these 76 patients revealed a predominance of disease in middle-aged or older (age, 65 years) men (64%). This is similar to results seen in previous reports.¹⁷ Despite a history of smoking and underlying disease in half of the patients, the number of patients with severe underlying disease, such as nephropathy, chronic heart and lung diseases, and diabetes was not large. This result demonstrated that even healthy people may develop Legionnaires' disease following significant exposure to the pathogen. Although pneumonia was

confirmed radiologically in all the patients, the incidence of respiratory symptoms in the patients was only 42%. The incidences of digestive tract and central nervous system symptoms were 35% and 21%, respectively, data which are consistent with rates reported in previous studies by Fernandez et al.¹⁸ and Falco et al.¹⁹ These rates are of importance when the diagnosis of Legionnaires' disease from patient symptoms is considered.

All the patients examined in our study displayed markedly elevated serum CRP levels (average value, 17.3 mg/dl). This observation is consistent with the conclusions of Vazquez et al.,²⁰ who demonstrated that CRP levels in patients with Legionnaires' pneumonia were significantly higher than those seen in non-Legionnaires' pneumonia. In our study, AST, ALT, and gamma-GTP levels were elevated in 50%–60% of the patients. Although elevations in transaminase levels have previously been reported for Legionnaires' disease, no report has detailed the effects of this disease on the gamma-GTP level. Gamma-GTP elevation is commonly observed in liver diseases, especially in alcoholic injury.²¹ The history of current alcohol use in the patients was examined for possible connection with the gamma-GTP elevation. However, no relationship was observed (data not shown). Therefore, it is possible that gamma-GTP elevation and mild hyponatremia, both of which were seen in 60% of the patients, are characteristics of Legionnaires' disease.

As a severe outcome is not uncommon in patients with Legionnaires' disease, we evaluated the impact of the initial symptoms and signs, the results of laboratory tests, and the background information on the clinical course of the patients in our study. Capelastegui et al.²² evaluated the outcome of patients with community-acquired pneumonia by the length of hospital stay. They also reported that the CURB-65 score (Confusion, Urea > 7 mmol·L⁻¹, Respiratory rate ≥ 30 min⁻¹, low Blood pressure, and age ≥ 65 years), which is used to evaluate the severity of pneumonia, was significantly associated with the length of hospital stay. Therefore, we evaluated the outcomes of the patients enrolled in this study by categorizing their hospital stay, using four categories: outpatients, patients with a short hospital stay, patients with a longer hospital stay, and patients who died as a result of Legionnaires' disease. Univariate analysis showed neurological symptoms; elevated CRP, AST, and ALT levels; hyponatremia; and positive urinary antigen and *Legionella*-specific antibody test results to be associated with severe clinical courses. These factors appear to be related to the initial severity of Legionnaires' disease. Supporting this possibility is the connection in this study of a number of these markers with the severity of pneumonia assessed by chest X-ray.²³

Next, we evaluated the ability of initial antimicrobial administration to improve the clinical course of patients with Legionnaires' disease. Patients were treated with several antimicrobials in various combinations during this outbreak. We evaluated the impact of initial treatment with macrolides, tetracyclines, or fluoroquinolones, which are reported to be effective against *Legionella*. Assessment using a multivariate logistic-regression model, after adjust-

ing for the severity of the disease based on the extent of pulmonary infiltration on chest X-ray, revealed that patients treated with these antimicrobial agents tended to have better clinical outcomes. This trend was statistically significant when these agents were given to the patients within 3 days of onset of illness. The importance of early administration of effective antimicrobials has also been emphasized in reports by Marston et al.¹⁷ and Heath et al.²⁴ Our findings support these conclusions for the treatment of Legionnaires' disease during a large outbreak.

In conclusion, patients with Legionnaires' disease due to a large outbreak associated with a contaminated public bathhouse were analyzed in the present study. Respiratory tract symptoms were seen in only 42% of the individuals, despite the confirmation of pneumonia in all of these patients by chest X-ray. *Legionella*-specific tests, including urine antigen testing, yielded positive results in only a small proportion of the patients. Therefore, a careful history documenting travel, lodging, and public bathhouse patronage (especially in Japan) is necessary to identify potential sources of *Legionella* exposure and for the diagnosis of this disease. In addition, providing information on an outbreak of Legionnaires' disease to residents and doctors in the affected area is of great importance when there is a large outbreak. Antimicrobials effective against *Legionella* should be administered as soon as possible when Legionnaires' disease is suspected, even if the infection is not confirmed by microbiological testing.

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References

- Fields BS, Benson RF, Besser RE. *Legionella* and Legionnaires' disease: 25 years of investigation. *Clin Microbiol Rev* 2002;15: 506–26.
- Fraser DW, Tsai TR, Orenstein W, Parkin WE, Beecham HJ, Sharrar RG, et al. Legionnaires' disease: description of an epidemic of pneumonia. *N Engl J Med* 1977;297:1189–97.
- Saito A, Shimoda T, Nagasawa M, Tanaka H, Ito N, Shigeno Y, et al. The first case of legionnaire's disease in Japan (in Japanese). *Kansenshougaku Zasshi* 1981;55:124–8.
- Carratara J, Gudiol F, Pallares R, Dorca J, Verdaguer R, Ariza J, et al. Risk factors for nosocomial *Legionella pneumophila* pneumonia. *Am J Respir Crit Care Med* 1994;149:625–9.
- Joseph CA, Watson JM, Harrison TG, Bartlett CLR. Nosocomial Legionnaires' disease in England and Wales, 1980–92. *Epidemiol Infect* 1994;112:329–45.
- Lettinga KD, Verbon A, Weverling GJ, Schellekens JFP, Boer JWD, Yzerman EPF, et al. Legionnaires' disease at a Dutch flower show: prognostic factors and impact of therapy. *Emerg Infect Dis* 2002;8:1448–54.
- Jernigan DB, Hofmann J, Cetron MS, Genese CA, Nuorti JP, Fields BS, et al. Outbreak of Legionnaires' disease among cruise ship passengers exposed to a contaminated whirlpool spa. *Lancet* 1996;347:494–9.
- Gotz HM, Tegnell A, De Jong B, Broholm KA, Kuusi M, Kallings I, et al. A whirlpool associated outbreak of Pontiac fever at a hotel in Northern Sweden. *Epidemiol Infect* 2001;126:241–7.
- Tominaga M, Aoki Y, Haraguchi S, Fukuoka M, Hayashi S, Tamesada M, et al. Legionnaires' disease associated with habitual drinking of hot spring water. *Intern Med* 2001;40:1064–7.
- Chiba Y, Okamoto H, Nagatomo A, Kunikane H, Watanabe K. Legionnaires' disease diagnosed by bronchoalveolar lavage. *Intern Med* 1998;37:153–6.
- Miyamoto H, Jitsurong S, Shiota R, Maruta K, Yoshida S, Yabuuchi E. Molecular determination of infection source of a sporadic *Legionella* pneumonia case associated with a hot spring bath. *Microbiol Immunol* 1997;41:197–202.
- Nakamura H, Yagyu H, Kishi K, Tsuchida F, Oh-ishi S, Yamaguchi K, et al. A large outbreak of Legionnaires' disease due to an inadequate circulating and filtration system for bath water: epidemiologic manifestations. *Intern Med* 2003;42:806–11.
- Taguchi Y, Nakahama C, Inamatsu T, Arakawa M, Saito A, Hara K, et al. Analysis of chest radiographs of culture positive *Legionella* pneumonia in Japan, 1980–1990 (in Japanese). Working Party for Legionellosis, Japanese Ministry of Health and Welfare. *Kansenshougaku Zasshi* 1992;66:1580–6.
- Stout JE, Yu VL. Legionellosis. *N Engl J Med* 1997;337:682–7.
- Kohler RB, Winn WC, Wheat LJ. Onset and duration of urinary antigen excretion in Legionnaires disease. *J Clin Microbiol* 1984; 20:605–7.
- Kawano F, Okada M, Kura F, Maekawa J, Watanabe H. Largest outbreak of legionellosis associated with spa baths: comparison of diagnostic tests (in Japanese). *Kansenshougaku Zasshi* 2007;81: 173–82.
- Marston BJ, Lipman HB, Breiman RF. Surveillance for Legionnaires' disease: risk factors for morbidity and mortality. *Arch Intern Med* 1994;154:2417–22.
- Fernandez JA, Lopez P, Orozco D, Merino J. Clinical study of an outbreak of Legionnaire's disease in Alcoy, southeastern Spain. *Eur J Clin Microbiol Infect Dis* 2002;21:729–35.
- Falco V, Sevilla TF, Alegre J, Ferrer A, Vazquez JMM. *Legionella pneumophila*. A cause of severe community-acquired pneumonia. *Chest* 1991;100:1007–11.
- Vazquez EG, Martinez JA, Mensa J, Sanchez F, Marcos MA, Roux AD, et al. C-reactive protein levels in community-acquired pneumonia. *Eur Respir J* 2003;21:702–5.
- Pratt DS, Kaplan MM. Evaluation of the liver: laboratory tests. In: Schiff ER, Sorrell MF, Maddrey WC, editors. *Schiff's diseases of the liver*. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 221–55.
- Capelastegui A, Espana PP, Quintana JM, Areitio I, Gorordo I, Egurrola M, et al. Validation of a predictive rule for the management of community-acquired pneumonia. *Eur Respir J* 2006;27: 151–7.
- Matsumoto N, Sasaki S, Nakao H, Katoh T, Fukuda Y, Nakazato M, et al. An outbreak of Legionnaires' disease associated with a circulating bathwater system at a public bathhouse II: radiological findings of pneumonia. *J Infect Chemother* 2008;14:123–9.
- Heath CH, Grove DI, Looke DFM. Delay in appropriate therapy of *Legionella* pneumonia associated with increased mortality. *Eur J Clin Microbiol Infect Dis* 1996;15:286–90.