

Lower serum phosphate levels in patients with Legionella pneumonia relative to patients with non-Legionella pneumonia

Mikio Wada¹, Atsushi Kawashima²

¹Fukuchiyama City Hospital Ooe Branch, Ooecho, Fukuchiyama City, Kyoto, Japan, ²Department of General Internal Medicine, Fukuchiyama City Hospital, Atsunakacho, Fukuchiyama City, Kyoto, Japan

ABSTRACT

Introduction: Few studies have evaluated serum phosphate levels in patients with Legionella pneumonia admitted to hospitals in Japan. This study aimed to assess serum phosphate levels among inpatients with Legionella pneumonia on admission and compare them to those of inpatients with non-Legionella community-acquired pneumonia. **Methods:** This case-control study included patients aged ≥ 16 years who were treated for Legionella pneumonia from April 2011 through March 2017 and those aged ≥ 16 years who were treated for non-Legionella community-acquired pneumonia from August 2014 through July 2015. Legionella pneumonia was diagnosed based on a positive result on the urinary antigen test, as well as radiographic examinations. Serum phosphate levels on admission were compared between Legionella and non-Legionella patients. In addition, serum phosphate levels on admission and on hospital day 5-7 were compared in Legionella patients. **Results:** We evaluated 8 Legionella patients and 61 non-Legionella patients. Median serum phosphate levels on admission were 1.90 and 2.80 mg/dL in Legionella and non-Legionella patients, respectively ($P = 0.008$). By hospital day 5-7, serum phosphate levels in Legionella patients had increased to 2.61 mg/dL ($P = 0.029$, relative to admission), which did not significantly differ from those of non-Legionella patients on admission ($P = 0.372$). **Conclusion:** Serum phosphate levels on admission were approximately 32% lower in Legionella pneumonia patients compared to non-Legionella pneumonia patients, but both were comparable by hospital day 7.

Keywords: Inpatient, Legionella pneumonia, serum phosphate level

Introduction

Legionellosis is an important cause of community-acquired pneumonia (CAP). In Japan, about 1% of CAP cases are reportedly Legionella pneumonia.^[1] Mortality rates from Legionella pneumonia are high ($\sim 10\%$), and can be as high as 27% in patients without adequate antimicrobial agent treatment.^[2] Antibiotics such as beta-lactam antibiotics, prescribed to treat

typical bacterial pneumonia, are not effective against Legionella pneumonia. Moreover, the standard culture used to identify typical bacterial pneumonia cannot be used for Legionella pneumonia. Clinicians should address pneumonia cases with thoughtful consideration of the possibility for Legionella pneumonia and promptly issue a test specific to Legionella.^[3]

Patients with bacterial pneumonia occasionally develop laboratory abnormalities.^[4] If Legionella pneumonia is suspected based on data readily available with safety in typical clinical settings, then a more specific and quick diagnostic procedure for Legionella pneumonia can be developed. For example, hypophosphatemia is said to be an important laboratory abnormality in Legionnaires'

Address for correspondence: Dr. Mikio Wada,

Fukuchiyama City Hospital Ooe Branch, Koumori-180, Ooecho, Fukuchiyama City, Kyoto, 620-0301, Japan.
E-mail: mwada@d6.dion.ne.jp

Received: 20-04-2021

Revised: 03-07-2021

Accepted: 30-07-2021

Published: 29-11-2021

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_728_21

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Wada M, Kawashima A. Lower serum phosphate levels in patients with Legionella pneumonia relative to patients with non-Legionella pneumonia. J Family Med Prim Care 2021;10:4272-6.

disease.^[5] However, most published studies have not focused on serum phosphate levels on admission among patients with Legionella pneumonia. In fact, only a few case reports on Legionella pneumonia have assessed serum phosphate levels. The present study aimed to assess serum phosphate levels on admission among inpatients with Legionella pneumonia and compare them with levels in non-Legionella CAP inpatients.

Materials and Methods

Subjects of this case-control study were inpatients of the Department of General Internal Medicine (DGIM) at Fukuchiyama City Hospital. Fukuchiyama City Hospital is a regional center hospital that has 354 beds (310 beds for inpatients with acute illnesses and 44 beds in a sub-acute rehabilitation unit) and an emergency medical care center. This hospital covers a medical district comprising roughly 100,000 residents. As there is no other central hospital in this district, many patients in this medical district visit the hospital seeking inpatient treatment for acute illnesses. The hospital did not have a residing pulmonologist or infectious disease specialist during the study period, and almost all pneumonia patients who required hospitalization were treated in DGIM.

Given the low prevalence of Legionella pneumonia, we defined case and control patients as follows. Case subjects were patients aged ≥ 16 years who were hospitalized to undergo treatment for Legionella pneumonia from April 2011 through March 2017 (6 years), and control subjects were those aged ≥ 16 years who were hospitalized for the treatment of non-Legionella pneumonia from August 2014 through July 2015. Control patients were registered in the database of the “Exploring infectious diseases in DGIM inpatients over the course of one year” project, which examined the characteristics of infectious diseases in DGIM inpatients over the course of a year. Patients registered in this database also included some who had nursing and healthcare-associated pneumonia or hospital-acquired pneumonia (HAP/NHCAP). When creating the database, we asked patients and/or their family members about living conditions, use of nursing services, and hospital discharge in the past 90 days. We selected patients who lived in their own house, did not use nursing services (e.g., daycare and/or short stays in a nursing home), and were not discharged from a hospital in the past 90 days.

We excluded patients for whom both Gram stain of sputum and its standard culture were not performed, and those for whom serum phosphate levels were not evaluated. We also excluded pneumonia patients who had swallowing issues and never ate a normal meal during hospitalization, given the higher possibility that these patients had aspiration pneumonia and malnutrition.

This study was approved by the ethics committee of Fukuchiyama City Hospital (No. 30-1). We provided patients and their relatives with the opportunity to opt out, and this information was provided on the Fukuchiyama City Hospital website.

Diagnosis of pneumonia

Bacterial pneumonia was diagnosed by several physicians on admission and was based on patient history, physical examination, chest X-ray (or chest computed tomography scan), laboratory findings, and Gram stain of sputum and its standard culture. Gram stain of sputum and its standard culture were performed for all study participants. Urinary antigen detection was performed within 3 days of admission using the Immunocatch Legionella (Eiken Chemical Co., Ltd.) in patients suspected of having Legionella pneumonia. The patient was diagnosed for Legionella pneumonia when the urinary antigen test yielded a positive result. The detection kit used in this study targets the antigen of *Legionella pneumophila* serogroup 1. Thus, *L. pneumophila* serogroup 1 is considered the causative agent of Legionella pneumonia in our patients. All diagnoses were confirmed at DGIM conferences, which were held every 3 or 4 days.

Laboratory test and evaluation

Serum phosphate measurements included those obtained from the standard laboratory test on admission (performed within the first 48 hours since entering the hospital; “serum phosphate level on admission”). If multiple serum phosphate measurements were taken within the first 48 hours, the earliest data were used. Patient characteristics, including age, sex, albumin, glucose, blood urea nitrogen, serum creatinine, sodium, and calcium, were also noted. Consciousness level, respiratory rate, and blood pressure were also obtained, and CURB-65 scores were calculated. For Legionella pneumonia cases, serum phosphate levels were also evaluated between hospital day 5 and 7 (“serum phosphate level on hospital day 5–7”). If more than one serum phosphate measurement was taken between hospital day 5 and 7, the value obtained nearest to day 7 had priority.

We compared serum phosphate levels on admission for Legionella pneumonia cases with those for non-Legionella pneumonia cases. In Legionella pneumonia cases, serum phosphate levels on admission were compared to serum phosphate levels on hospital day 5–7.

Subgroup analysis

In general, patients with severe infections present with hypophosphatemia.^[6] We selected patients whose CURB-65 scores were ≥ 2 and compared serum phosphate levels in this group for Legionella and non-Legionella pneumonia cases.

Statistical analysis

Serum phosphate levels, age, total protein, albumin, blood urea nitrogen, serum creatinine, sodium, and calcium were compared between Legionella and non-Legionella pneumonia patients with the Wilcoxon rank-sum test. Serum phosphate levels on admission and hospital day 5–7 of Legionella pneumonia patients were compared with the Wilcoxon signed-rank test. Sex was compared with Fisher’s exact test. Statistical analyses were performed using STATA software, version 15.0 (StataCorp LLC, Texas, USA).

Results

We identified 8 patients with Legionella pneumonia (mean age: 68.9 years), all of whom lived in their own house, did not use nursing services, were not discharged from a hospital in the past 90 days, and were able to eat normal meals. Of the 363 patients in the “Exploring infectious diseases in DGIM inpatients over the course of one year” project, 239 were inpatients hospitalized for the treatment of pneumonia. Among these patients, 113 lived in their own house, did not use nursing services, and were not discharged from a hospital in the past 90 days. One patient was treated for Legionella pneumonia. Six patients were excluded because the Gram stain of sputum and its standard culture were not performed, and 9 patients were excluded as they lacked serum phosphate measurements. In addition, 36 patients were excluded because they had swallowing issues and never ate a normal meal during hospitalization. The remaining 61 patients (mean age: 72.0 years) were evaluated as cases of non-Legionella CAP with minor swallowing issues [Figure 1]. Table 1 summarizes the characteristics of these patients.

Median serum phosphate levels on admission were 1.90 and 2.80 mg/dL in Legionella and non-Legionella pneumonia patients, respectively [$P = 0.008$; Figure 2]. Serum phosphate levels for Legionella pneumonia patients were roughly 32% lower than that of non-Legionella pneumonia patients. The median serum phosphate level of Legionella pneumonia patients during hospital day 5–7 was 2.61 mg/dL, which was higher than the median serum phosphate level on admission ($P = 0.029$). No significant difference was observed between serum phosphate levels on hospital day 5–7 for Legionella pneumonia patients and serum phosphate levels for non-Legionella pneumonia patients on admission ($P = 0.372$).

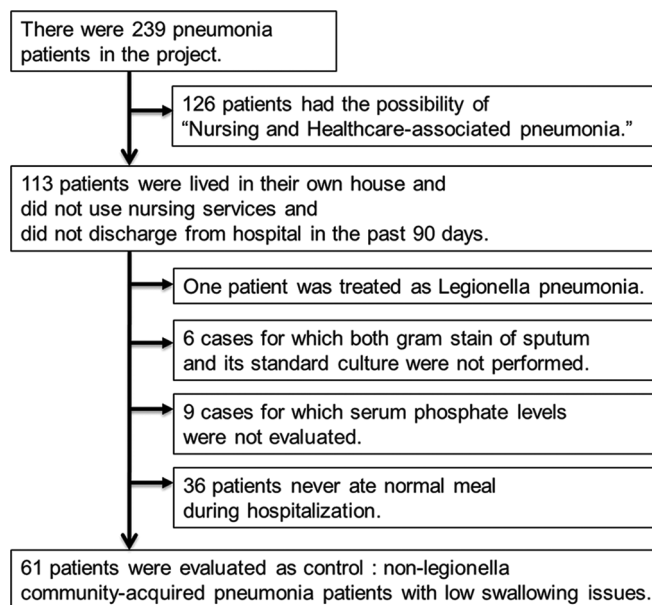


Figure 1: Flowchart of patient recruitment for non-Legionella pneumonia patients

In the subgroup analysis focusing on patients with a CURB-65 score ≥ 2 , median serum phosphate level was 1.90 mg/dL in Legionella pneumonia patients ($n = 6$) and 2.80 mg/dL in non-Legionella pneumonia patients ($n = 20$) ($P = 0.011$).

Discussion

Serum phosphate levels in Legionella pneumonia patients were lower than those of non-Legionella pneumonia patients on admission, but the differences disappeared by hospital day 5–7. Previous studies have reported that Legionella spp. is rarely the causative organism for HAP/NHCAP.^[7,8] Our present findings are consistent with these reports. Hypophosphatemia in Legionella pneumonia patients on admission was also confirmed in the subgroup analysis of patients with a CURB-65 score of ≥ 2 .

Legionella pneumonia patients develop hypophosphatemia early on, although it subsides within a few days.^[5] In the present study, we observed relatively low levels of serum phosphate on admission in Legionella pneumonia patients, with a subsequent increase to levels comparable to those of non-Legionella

Table 1: Characteristics of patients

	Legionella pneumonia patients	non-Legionella pneumonia patients	p-value
n	8	61	
Age mean	68.9	72.0	
Median	67.5	73.0	0.425
Sex male n (%)	7 (87.5)	32(52.5)	0.063
Alb[g/dl]	3.30	3.55	0.173
Glu[mg/dl]	158.0	130.0	0.070
BUN[mg/dl]	24.0	15.0	0.016
Cre[mg/dl]	0.96	0.65	0.007
Na[mEq/l]	132.5	137.0	0.025
Ca[mg/dL]	8.20	8.40	0.218
CURB-65(n)			
0 or 1	2	41	
2	6	17	
3, 4, 5	0	3	

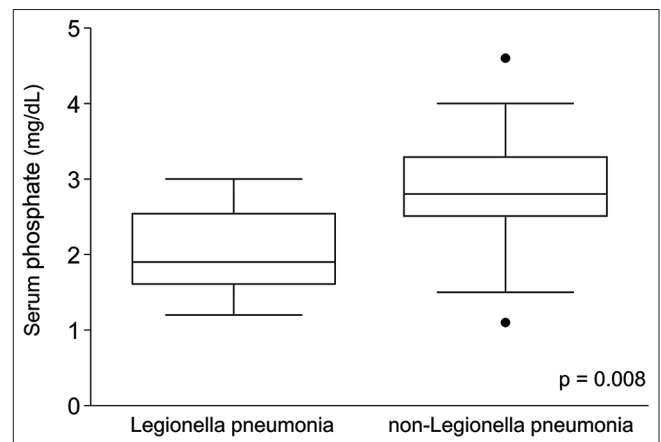


Figure 2: Serum phosphate levels in Legionella and non-Legionella pneumonia patients on admission

pneumonia patients by hospital day 5–7. Previous reports have shown that acquired Fanconi syndrome could occur in acute phase patients with Legionella pneumonia.^[9,10] Another study reported that proximal renal tubular dysfunction may occur transiently in cases of Legionella pneumonia.^[11] These observations may explain the onset of hypophosphatemia and improvement within a few days.

Legionella pneumonia patients reportedly have some laboratory abnormalities, such as levels of sodium, lactate dehydrogenase, C-reactive protein, and platelet counts.^[12] Low sodium was noted in patients of the present study as well. Meanwhile, hyponatremia, for example, is often observed in elderly patients, including those with syndrome of inappropriate secretion of antidiuretic hormone and mineralocorticoid-responsive hyponatremia of the elderly. Thus, low sodium levels cannot be used as the only test for differential diagnosis. Some authors have investigated diagnostic score models for the prediction of Legionella pneumonia.^[13-15] These prediction rules are very useful for diagnosing Legionella pneumonia and allow doctors to review the necessity of specific Legionella cultures, leading to correct diagnoses. On the contrary, their prediction rules have several parameters; thus, it may not be easy to use and evaluate prediction rules in all cases without any suspicion of Legionella pneumonia. Although medical history is an important component required in the diagnostic process of Legionella pneumonia, it is not easy to obtain past medical histories when there is no suspicion of the disease. In contrast, serum phosphate levels can easily be measured with safety in typical clinical settings, and lower serum phosphate levels may indicate suspicion of Legionellosis.^[5] Therefore, any patient with a suspicion of pneumonia would benefit from an evaluation of serum phosphate levels.

Some Legionella pneumonia outbreaks are still reported also in these days.^[16-18] Mortality rates from Legionella pneumonia are not enough low, especially in cases without proper treatment. Excess pneumonia deaths were reported during an outbreak of Legionnaires' disease.^[19] In the primary care setting, clinicians should address pneumonia cases with thoughtful consideration for the causative organism, especially for Legionella pneumonia. By measuring serum phosphate levels in cases of pneumonia, clinicians can consider Legionella pneumonia, a life-threatening disease without proper judgment, as a differential diagnosis.

There are some limitations of this study. First, the study population, especially Legionella pneumonia patients, was relatively small, and future studies of larger populations are needed. Second, not all patients with non-Legionella pneumonia were tested for Legionella pneumonia using the urinary antigen detection kit. The detection kit used in this study targets the antigen of *L. pneumophila* serogroup 1. Some patients with Legionella pneumonia might have remained undiagnosed and categorized as non-Legionella pneumonia patients. However, as such cases contribute to reduced statistical differences, the results of this study are unlikely to be affected. Third, we did not consider nutrition status before and after admission, although all

patients in this study had minor swallowing issues. Fourth, we did not consider medications taken prior to admission which may have affected serum phosphate levels. Finally, subjects of our study were limited to inpatients; mildly ill patients such as those with Pontiac fever were not taken into consideration.

Conclusion

This study revealed that serum phosphate levels of Legionella pneumonia patients were lower than those of non-Legionella pneumonia patients on admission but were comparable by hospital day 7.

Acknowledgement

We thank all staff members of the Department of General Internal Medicine, the Clinical Laboratory Department, and the Medical Information Management Division for their support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. The JRS Guidelines for the Management of Pneumonia in Adults. The Japanese Respiratory Society, 2017.
2. Falco V, Fernandez de Sevilla T, Alegre J, Ferrer A, Martinez Vazquez JM. *Legionella pneumophila*. A cause of severe community-acquired pneumonia. *Chest* 1991;100:1007-11.
3. Cunha BA, Cunha CB. Legionnaire's disease: A clinical diagnostic approach. *Infect Dis Clin North Am* 2017;31:81-93.
4. Sankaran RT, Mattana J, Pollack S, Bhat P, Ahuja T, Patel A, *et al*. Laboratory abnormalities in patients with bacterial pneumonia. *Chest* 1997;111:595-600.
5. Cunha BA. Hypophosphatemia: Diagnostic significance in Legionnaires' disease. *Am J Med* 2006;119:e5-6.
6. Geerse DA, Bindels AJ, Kuiper MA, Roos AN, Spronk PE, Schultz MJ. Treatment of hypophosphatemia in the intensive care unit: A review. *Crit Care* 2010;14:R147.
7. Shindo Y, Sato S, Maruyama E, Ohashi T, Ogawa M, Hashimoto N, *et al*. Health-care-associated pneumonia among hospitalized patients in a Japanese community hospital. *Chest* 2009;35:633-40.
8. Ishida T, Tachibana H, Ito A, Yoshioka H, Arita M, Hashimoto T. Clinical characteristics of nursing and healthcare-associated pneumonia: A Japanese variant of healthcare-associated pneumonia. *Intern Med* 2012;51:2537-44.
9. Kinoshita-Katahashi N, Fukasawa H, Ishigaki S, Isobe S, Imokawa S, Fujigaki Y, *et al*. Acquired Fanconi syndrome in patients with Legionella pneumonia. *BMC Nephrol* 2013;14:171.
10. Koda, R, Itoh R, Tsuchida M, Ohashi K, Iino N, Takada T, *et al*. Legionella pneumonia complicated with acquired Fanconi syndrome. *Intern Med* 2018;57:2975-80.
11. Watanabe S, Kono K, Fujii H, Nakai K, Goto S, Nishi S. Two

- cases of hypophosphatemia with increased renal phosphate excretion in legionella pneumonia. *Case Rep Nephrol Dial* 2016;6:40-5.
12. Fiumefreddo R, Zaborsky R, Haeuptle J, Christ-Crain M, Trampuz A, Steffen I, *et al.* Clinical predictors for Legionella in patients presenting with community-acquired pneumonia to the emergency department. *BMC Pulm Med* 2009;9:4.
 13. Miyashita N, Horita N, Higa F, Aoki Y, Kikuchi T, Seki M, *et al.* Validation of a diagnostic score model for the prediction of *Legionella pneumophila* pneumonia. *J Infect Chemother* 2019;25:407-12.
 14. Bolliger R, Neeser O, Merker M, Vukajlovic T, Felder L, Fiumefreddo R, *et al.* Validation of a prediction rule for legionella pneumonia in emergency department patients. *Open Forum Infect Dis* 2019;6:ofz268.
 15. Gupta SK, Imperiale TF, Sarosi GA. Evaluation of the Winthrop-University Hospital criteria to identify Legionella pneumonia. *Chest* 2001;120:1064-71.
 16. Löf E, Chereau F, Jureen P, Andersson S, Rizzardi K, Edquist P, *et al.* An outbreak investigation of Legionella non-pneumophila Legionnaires' disease in Sweden, April to August 2018: Gardening and use of commercial bagged soil associated with infections. *Euro Surveill* 2021;26:1900702. doi: 10.2807/1560-7917.ES.2021.26.7.1900702.
 17. Almeida DQ, Silva T, Rodrigues V, Ladeira R, Sousa F, Capucho R, *et al.* Outbreak of Legionnaires' disease in the Northern Portuguese coast during the COVID-19 pandemic. *Acta Med Port* 2021. doi: 10.20344/amp. 15823.
 18. Faccini M, Russo AG, Bonini M, Tunesi S, Murtas R, Sandrini M, *et al.* Large community-acquired Legionnaires' disease outbreak caused by *Legionella pneumophila* serogroup 1, Italy, July to August 2018. *Euro Surveill* 2020;25:1900523. doi: 10.2807/1560-7917.ES.2020.25.20.1900523.
 19. Nelson KN, Binney ZO, Chamberlain AT. Excess pneumonia mortality during a 2014-2015 Legionnaires' disease outbreak in Genesee county, Michigan. *Epidemiology* 2020;31:823-31.