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New Insights in Hospital Acquired Legionnaires Disease: A Retrospective Multicentre Cohort Study

Marco Moretti*

Department of internal Medicine and Infectious disease, Universiteit Ziekenhuis Brussel, Laarbeeklaan, Belgium

***Corresponding author:** Marco Moretti, Department Of internal Medicine and Infectious Disease, Universiteit Ziekenhuis Brussel, Laarbeeklaan, Belgium, Tel: 32 474208736; E-mail: marco.moretti9@gmail.com

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Abstract

Background: Legionnaires' disease is a recognised cause of community acquired pneumonia, however legionella is an overlooked pathogen in hospital-acquired pneumonia. Death rate seems to be greater whenever hospital-acquired legionnaires' disease occurs, however factors related to the poor outcome and preferred treatment strategy are poorly known.

Aim: Investigate mortality in patients admitted for legionnaires' disease and its associated factors. Additionally, determinant factors of onset of hospital-acquired Legionnaires' disease were analysed.

Methods: Medical records of the last three years were retrospectively reviewed at three university hospitals (UZ Brussel, CHU Brugmann and CHU Saint Pierre). Hospital-acquired legionnaires' disease was defined as symptoms onset at ten days or more after admission. Univariate and propensity score adjusted multivariate logistic regressions analyses were performed.

Results: Fifty patients were included in the study, among them 13 (26%) were diagnosed with hospital acquired legionnaires' disease. Mortality was 22%, mainly driven by patients affected by hospital acquired legionnaires' disease, with a death rate of 61.54% in this group. Multivariate analysis for prediction of all cause mortality showed significant differences in Sepsis related Organ Failure Assessment (SOFA) score and treatment with respiratory fluoroquinolones based regimen. Complementary adjusted regression analyses for prediction of hospital acquired Legionnaires' disease pointed out significant differences in chronic respiratory disease and bilateral pulmonary involvement.

Conclusion: In the current cohort, hospital acquired legionnaires' disease represents a considerable burden as its mortality seems to be elevated. It may affect particularly chronic respiratory disease patients with bilateral lung injuries. SOFA score at diagnosis was associated with higher risk of mortality while use of respiratory fluoroquinolones based treatment was associated with lower mortality.

Keywords: Legionnaires' disease; Legionella; Hospital acquired pneumonia; SOFA score; Fluoroquinolones

Introduction

Legionella is a gram negative microorganism, which grows between 25°C-45°C man made backwater systems represent the preferred habitat for this type of bacteria. As hospitals are provided of complex water systems, they contribute to the proliferation of these bacteria, which may eventually infect hospitalized patients. Legionnaires' Disease (LD) is a major cause of both community acquired and hospital-acquired pneumonia, with Legionella pneumophila serogroup 1 (Lp1) being the most virulent and the most frequent cause of disease. Sample culture of low respiratory tract is considered the gold standard in the diagnosis of LD, however its sensitivity seems to be poor and its performance is technically demanding [1]. The introduction of Urinary Antigen detection testing (LUA) brought a major advance in LD diagnosis, with up to 95% of cases in Europe being diagnosed with this method. Despite the high sensitivity of LUA for Lp1, ranging from 80-90%, its negative predictive value is low in other serogroup than Lp1 and therefore, Legionella may be underestimated as an agent of pneumonia. Although no randomized clinical trial evidence supported one preferred antibiotic regimen, macrolides and respiratory fluoroquinolones seem to be the most effective treatment. Average death rate of LD in Europe reaches 10%, but its mortality is considered to be even higher in patients affected by Hospital-Acquired (HA) LD, ranging between 15% and 47%. Older age, smoking status and medical history of neoplasms are risk factors that may promote the disease and its mortality in community acquired cases [2]. However, the role of these factors in HA LD has not been established. We report the data obtained from a multicentre retrospective observational study conducted to investigate determinants of mortality and factors associated with hospital-acquired LD onset in a cohort of hospitalised LD patients [3].

Materials and Methods

A retrospective search of the medical records was conducted from 1st January 2016 up to 31th January 2019. Medical records of CHU Brugmann, CHU Saint Pierre and UZ Brussel were explored. The study protocol was approved by the institutional review boards of all three institutions. Due to the retrospective design of the study, waiver of informed consent was obtained. Clinicaltrial.gov was used as repository for registration (trial number: NCT04106037). All confirmed cases of LD, admitted in one of the three previously cited hospitals, were enrolled in the current study [4,5]. Identification of LD cases was made through microbiology laboratory database. The definition of LD diagnosis was met whenever positive respiratory samples cultures or Polymerase Chain Reaction (PCR) were detected, or positive LUA was observed. Duration of Legionella incubation is between two and ten days, mainly six or seven day. Therefore, nosocomial acquisition of LD was defined as symptoms onset at ten or more days from admission, as defined by the Centres for Disease Control and prevention (CDC). Epidemiological, clinical, biological, radiological data were collected from the medical records of enrolled patients at diagnosis. The variable "chronic respiratory disease" was defined as presence of asthma or Chronic Obstructive Pulmonary Disease (COPD). Furthermore, their comorbidities were classified using the Charlson Comorbidity Index (CCI), a validated tool to quantify the burden of comorbidities. A Sepsis related Organ Failure Assessment (SOFA) score has been calculated for every patient at the time of LD diagnoses in order to estimate the prognosis and the severity of the disease. SOFA score was chosen in the current study considering the absence of a validated model to estimate the severity of both community acquired and HA pneumonia [6]. Another variant that was used to estimate disease severity was the presence of severe respiratory insufficiency, defined as arterial oxygen partial pressure inferior to 60 mmHg. Chest X Ray (CXR) findings were collected at diagnosis and bilateral lung injury was defined as bilateral infiltrations, with or without pleural effusion presence [7,8]. Positive outcome was defined as all cause mortality in the first analyses models. Secondly, the variable "hospital acquired LD" was chosen as endpoint of the additional analyses. Mann-Whitney tests and Chi square or Fisher exact tests were performed on cohort base characteristics data respectively for the assessment of quantitative and qualitative data (Tables 1 and 2).

Parameters	Overall study population (n=50)	Deceased patients (n=11)	Patients alive (n=39)	P-value
Age, year	64 (52-74)	70 (54-79)	63 (50-73)	0.281
CCI, index	4 (2-7)	8 (6-10)	4 (1-6)	0.002
CRP, mg/L	310 (224-391)	346 (181-437)	310 (226-385)	0.623
WBC, (103/µL)	14.5 (9.0-18.5)	15.0 (4.0-18.0)	14.0 (9.0-20.0)	0.614
Creatinine, mg/dL	1 (1.0-2.25)	2.0 (1.0-3.0)	1.0 (1.0-2.0)	0.151
SOFA, index	3 (2-5)	7 (5-9)	2 (1-4)	<0.001
Days of antibiotics	12 (10-20)	14 (7-21)	12 (10-19)	0.649
Gender male (%)	36 (72%)	9 (81.8%)	27 (69.2%)	0.705
Active smoker, yes (%)	24 (48%)	2 (18.2%)	22 (56.4%)	0.04
Neoplasms, yes (%)	10 (20%)	5 (45.5%)	5 (12.8%)	0.03
Chronic respiratory disease, yes (%)	15 (30%)	5 (45.5%)	10 (25.6%)	0.269
Hospital acquired, yes (%)	13 (26%)	8 (72.7%)	5 (12.8%)	<0.001
Severe respiratory insufficiency, yes (%)	19 (38%)	8 (72.7%)	11 (28.2%)	0.013
Lactate elevation, yes (%)	12 (24%)	5 (45.5%)	7 (17.9%)	0.105
Bilateral lung consolidations, yes (%)	9 (18%)	4 (36.4%)	5 (12.8%)	0.093
ICU Admission, yes (%)	20 (40%)	10 (90.9%)	10 (25.6%)	<0.001
Non-respiratory fluoroquinolones, antibiotic, yes (%)	10 (20%)	6 (54.5%)	4 (10.3%)	0.004
Negative LUA, yes (%)	3 (6%)	1 (9.1%)	2 (5.1%)	0.534
All-cause mortality yes (%)	11 (22%)	-	-	-

Note: Baseline characteristics for primary endpoint all cause mortality; CCI: Charlson Comorbidity Index; CRP: C Reactive Protein; WBC: White Blood Cells; SOFA: Sepsis Related Organ Failure Assessment; ICU: Intensive Care Unit; LUA: Legionella Urinary Antigen test; '-' is used for 'no observation' or 'not applicable'; Data are expressed as median and interquartile range for continuous variable and numbers and proportions for categorical variables

Table 1: Baseline characteristics for primary endpoint all cause mortality.

Study characteristics considering hospital acquired LD as primary endpoint			
Parameters	**Hospital acquired LD (n=13)**	**Community acquired LD (n=37)**	**P-value**
Age, year	71(59-78)	63 (73-48)	0.141
CCI, index	7 (6-9)	4 (1-6)	0.003
CRP, mg/L	289 (160-367)	313 (251-403)	0.269
WBC, (103/μL)	15.0 (5.5-19.0)	14.0 (9.5-19.0)	0.485
Creatinine, mg/dL	2.0 (1.0-3.5)	1.0 (1.0-2.0)	0.669
SOFA, index	6 (4-8)	2 (1-4)	<0.001
Days of antibiotics	14 (10-21)	12 (10-19)	0.839
Gender (%)	10 (76.9%)	26 (70.3%)	0.734
Active smoker, yes (%)	3 (23.1%)	21 (56.8%)	0.054
Neoplasms, yes (%)	4 (30.8%)	6 (16.2%)	0.42
Chronic respiratory disease, yes (%)	8 (61.5%)	7 (18.9%)	0.011
Severe respiratory insufficiency, yes (%)	8 (61.5%)	11 (29.7%)	0.054
Lactate elevation, yes (%)	5 (38.5%)	7 (18.9%)	0.256
Bilateral lung consolidations, yes (%)	5 (38.5%)	4 (10.8%)	0.04
ICU Admission, yes (%)	11 (84.6%)	9 (24.3%)	<0.001
Non-respiratory fluoroquinolones, antibiotic, yes (%)	3 (23.1%)	7 (18.9%)	0.707
Negative LUA, yes (%)	2 (15.4%)	1 (2.7%)	0.162
All-cause mortality, yes (%)	8 (61.5%)	3 (8.1%)	<0.001
Note: Baseline Characteristics for primary endpoint hospital acquired Legionnaires' disease; CCI: Charlson comorbidity Index; CRP: C Reactive Protein; WBC: White Blood Cells; SOFA: Sepsis Related Organ Failure Assessment; ICU: Intensive Care Unit; LUA: Legionella Urinary Antigen test; '-' is used for 'no observation' or 'not applicable'; Data are expressed as median and interquartile range for continuous variable and numbers and proportions for categorical Variables.			

Table 2: Baseline characteristics for primary endpoint hospital acquired Legionnaires' disease.

Initial exploration of independent predictors of mortality and onset of LD in hospital setting was done using univariate logistic regression analyses. This was further assessed using two multivariate propensity score adjusted regression models encompassing different composite adjustment factors [9]. In the first model, the propensity score was derived from age and gender and the second one, previously defined adjustment factors were complemented by the comorbidities, expressed as CCI (Table 3).

Independent variables	**Univariate regression analysis**		**Propensity score adjusted regression analysis**			
			Model 1		**Model 2**	
	OR (95%CI)	**P-value**	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**
Age	1.02 (0.98-1.07)	0.287	-	-	-	-
Gender	2.0 (0.37-10.69)	0.418	-	-	-	-
CCI	1.45 (1.11-1.89)	0.006	-	-	-	-
Chronic respiratory disease	2.42 (0.60-9.68)	0.213	2.10 (0.51-8.66)	0.305	1.27 (0.25-6.35)	0.769

Neoplasm	5.67 (1.25-25-73)	0.025	5.96 (1.23-28.85)	0.026	2.01 (0.32-12.75)	0.457
Active smoker	0.17 (0.03-0.90)	0.037	0.21 (0.04-1.20)	0.079	0.27 (0.04-1.63)	0.154
CRP	1.00 (0.99-1.01)	0.745	1.00 (0.99-1.01)	0.395	1.00 (0.99-1.01)	0.708
WBC	1.00 (0.99-1.00)	0.633	1.00 (1.00-1.00)	0.571	1.00 (1.00-1.00)	0.631
Creatinine	1.07 (0.80-1.45)	0.634	1.03 (0.76-1.41)	0.83	0.81 (0.47-1.37)	0.422
SRI	6.79 (1.52-30.39)	0.012	5.79 (1.26-26.66)	0.024	4.49 (0.88-23.04)	0.071
Lactate elevation	3.81 (0.90-16.10)	0.069	3.83 (0.86-17.13)	0.079	3.15 (0.63-15.81)	0.163
Bilateral lung consolidations	3.89 (0.83-18.24)	0.085	3.70 (0.73-18.61)	0.113	8.75 (1.22-62.53)	0.031
SOFA score	2.70 (1.48-4.91)	0.001	2.61 (1.40-4.85)	0.002	2.35 (1.24-4.44)	0.008
Negative LUA	1.85 (0.15-22.54)	0.63	1.18 (0.09-15.25)	0.9	0.15 (0.01-4.51)	0.276
ICU admission	29.00 (3.29-255.94)	0.002	31.22 (3.30-295.42)	0.003	22.05 (2.24-217.07)	0.008
Non respiratory fluoroquinolones antibiotic regimen	10.50 (2.17-50.69)	0.003	9.49 (1.91-47.21)	0.006	7.51 (1.32-42.60)	0.023
Days of antibiotics	0.96 (0.86-1.09)	0.552	0.98 (0.87-1.10)	0.706	0.99 (0.87-1.12)	0.875
Hospital acquired LD	18.13 (3.57-92.13)	>0.001	15.96 (3.07-82.98)	0.001	11.46 (2.04-64.44)	0.006

Note: OR: Odds Ratio; CI: Confidence Interval; CCI: Charlson Comorbidity Index; CRP: Creactive Protein; WBC: White Blood Cells; SRI: Severe Respiratory Insufficiency; SOFA: Sepsis-Related Organ Failure Assessment; LUA: Legionella Urinary Antigen test; ICU: Intensive Care Unit; '-' is used for 'no observation' or 'not applicable'; Model 1: Adjusted for propensity score derived from age and Gender; Model 2: Adjusted for propensity score derived from age, Gender and Charlson comorbidity index.

Table 3: Logistic regression analysis for the prediction of all cause mortality.

Additional analyses were performed in order to predict the variable "hospital-acquired LD". Univariate logistic regression analyses and two different propensity score adjusted model were computed. Likewise the previous analyses, the first model was adjusted for propensity score derived from age and Gender and the second model for propensity score derived from age, Gender and CCI All the analyses were performed with Stata statistical software release 16.0. (Table 4).

Independent variables	**Univariate regression analysis**		**Propensity score adjusted regression analysis**			
			Model 1		**Model 2**	
	OR (95%CI)	**P-value**	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**
Age	1.03 (0.99-1.07)	0.184	-	-	-	-
Gender	1.41 (0.32-6.13)	0.647	-	-	-	-
CCI	1.38 (1.09-1.75)	0.007	-	-	-	-
Chronic respiratory disease	6.86 (1.71-27.46)	0.007	6.22 (1.52-25.40)	0.011	4.79 (1.09-21.04)	0.038
Neoplasm	2.30 (0.45-8.01)	0.376	2.07 (0.46-9.21)	0.34	0.56 (0.08-3.99)	0.567
Active smoker	0.23 (0.05-0.97)	0.045	0.29 (0.06-1.37)	0.118	0.41 (0.08-1.97)	0.265
CRP	1.00 (0.99-1.00)	0.238	1.00 (0.99-1.00)	0.413	1.00 (0.99-1.00)	0.214

WBC	1.00 (0.99-1.01)	0.859	1.00 (0.99-1.01)	0.866	1.00 (0.99-1.00)	0.783
Creatinine	0.98 (0.72-1.34)	0.904	0.95 (0.68-1.32)	0.767	0.70 (0.39-1.26)	0.237
SRI	3.78 (1.01-14.17)	0.048	3.13 (0.80-12.21)	0.101	2.28 (0.53-9.80)	0.267
Lactate elevation	2.68 (0.67-10.73)	0.164	2.58 (0.62-10.78)	0.192	2.04 (0.45-9.22)	0.354
Bilateral lung consolidations	5.16 (1.12-23.69)	0.035	4.69 (1.13-22.59)	0.044	9.37 (1.51-58.33)	0.016
Negative LUA	6.54 (0.54-79.23)	0.14	4.79 (0.38-60.34)	0.226	1.91 (0.10-34.92)	0.664

Note: OR Odds ratio; CI: Confidence Interval; NA: Not Applicable; CCI: Charlson Comorbidity Index; CRP: C Reactive Protein; WBC: White Blood Cells; SRI: Severe Respiratory Insufficiency; SOFA: Sepsis Related Organ Failure Assessment; LUA: Legionella Urinary Antigen test; ICU: Intensive Care>Unit; '-' is used for 'no observation' or 'not applicable'; Model 1: Adjusted for propensity score derived from age and Gender; Model 2: Adjusted for propensity score derived from age, Gender and Charlson comorbidity index.

Table 4: Logistic regression analysis for the prediction of hospital acquired LD.

Results and Discussion

Population characteristics

Fifty cases of LD were hospitalized in one of the involved centres. The median of age in the study population was 64 years and 36 (72%) were male. The prevalence of chronic respiratory disease was 15 (30%) within the current cohort, 24 (48%) of study patients were active smoker and 10 (20%) had medical history of neoplasm. Urinary antigen detection testing was demanded in all patients and resulted positive in 47 (94%) of cases. Eight cases (16%) were diagnosed with PCR performed on sputum in three cases and on broncho alveolar lavage fluid in the other five cases. Hospital acquired LD was diagnosed in 13 (26%) of the study participants. Even though LUA was the preferred diagnostic method, three HA LD patients were affected by a non serogroup Lp1 and the results of LUA did not matched molecular analyses. All patients except one received a validated antibiotic regimen for Legionella. The patient, who did not receive any effective antibiotics, was diagnosed with HA LD with a relevant delay and died before the beginning of therapy due to rapid degradation. Moxifloxacine 400 mg daily in monotherapy was the most frequently used treatment, which was chosen in 21 (42%) cases. The second preferred antibiotic was high dose levofloxacin, from 750 mg to 1 g daily, used in 18 (36%). None of the patients was treated with standard dose, 500 mg once a day. Less used antibiotic regimens were ciprofloxacin in six patients (12%) and clarithromycin in four patients (8%). The median length of treatment was 12 days (IQR: 10-20). The death rate within the cohort was 11 (22%) and the highest mortality rate was reported within the HA LD group 8 (61.54%). Base characteristics for primary endpoint all cause mortality and hospital acquired LD are represented respectively [10].

Mortality analysis

There was no association between gender and age with mortality in univariate logistic regression. However, meaningful differences were appreciated in comorbidities, expressed as CCI, specifically in medical history of neoplasms OR (95%CI): 5.67 (1.25-25.73, p=0.025) and active smoking OR (95%CI): 0.17 (0.33-0.901, p=0.037). No significant differences were found in biochemical, haematological and radiological independent variables. Significant discrepancies were appreciated in SOFA score at time point of diagnosis OR (95%CI): 2.70 (1.48-4.91, p=0.001) and in patient affected by HA LD OR (95%CI): 18.13 (3.60-92.13, p<0.001). If a SOFA score equal to five or more is chosen to predict mortality, the score showed a sensitivity of 82% and a specificity of 79% in the current cohort. Whether the same estimations are performed in the HA LD group, SOFA score had a higher sensitivity (87%), but a lower specificity (60%). Moreover, considerable differences were found in ICU admission and treatment with a non respiratory fluoroquinolones antibiotic regimen OR (95%CI): 10.5 (2.17-50.69, p=0.003). All the previous differences persisted after adjustment for propensity score derived from age and Gender, except for the variable active smoking (p=0.079). Considering the second model, adjusted for propensity score derived from age, Gender and CCI, only significant differences in SOFA score (p=0.008), HA LD (p=0.006), ICU admission and non-respiratory fluoroquinolones antibiotic regimen (p=0.023) persisted [11].

Risk factors for HA LD

Additional logistic regression for prediction of the variable hospital acquired LD reported significant differences in comorbidities (CCI) and particularly in chronic respiratory disease OR (95%CI): 6.86 (1.71-27.46, p=0.007), active smoking OR (95%CI) 0.23 (0.05-0.97, p=0.045) and bilateral pneumonia OR (95%CI) 5.16 (1.12-23.69, p=0.035). All the previous differences persisted after adjustment for propensity score derived from age, Gender and comorbidities, except active smoking (p=0.265). During a period of three years, 13 patients affected by HA LD and 37 patients by community acquired LD were hospitalized in one of the involved centres. It could be speculated that Legionella has been overlooked, as one of the hospitals reported a limited number of cases (6), which is fewer than 3 folds less compared to the other centres. Furthermore, only one centre systematically performed molecular methods to detect Legionella. However, three patients had negative LUA and positive PCR in the current cohort.

Comorbidities may be predictor of all cause mortality in LD and specifically medical history of neoplasms, as reported in this study and previously. No significant differences in age were found, however the limited number of the patients might have influenced these results. As expected, hospital acquired LD death rate was elevated. It could be speculated that different factors contributed to the poor outcomes. Diagnostic may be delayed as Legionella is not an expected HA pneumonia pathogen. Moreover, typical HA pneumonia infectious agents are the selected target of initial empiric antibiotics, which are mainly inactive in LD. One patient of the current cohort affected by

HA LD died without receiving effective antibiotics, as the correct diagnosis was significantly delayed and empirical treatment did not cover Legionella. SOFA score seems to be an appropriate tool to estimate the mortality at diagnosis. As observed in the current study a high SOFA score, major or equal to five, had similar good specificity and sensitivity to predict mortality. In HA LD, SOFA score had better sensitivity but insufficient specificity [12].

A previous large retrospective cohort suggested a possible improvement in mortality whenever standard dose Levofloxacin, 500 mg daily, is chosen for community acquired LD treatment in comparison with Azithromycine. As culture of Legionella is technically demanding and standard disc diffusion susceptibility is considered to be not appropriate, microbial sensitivity tests are hence rarely performed. It is theoretically assumed that both first line antibiotic classes, fluoroquinolones and macrolides, are always susceptible. However, some resistance mechanisms, as macrolides efflux pumps, may reduce sensitivity for first line antibiotics. Furthermore, a patient diagnosed with a ciprofloxacin resistant LD pneumonia was previously reported. Additional investigations suggested lower alveolar macrophages and bronchial secretions concentration of ciprofloxacin compared with respiratory fluoroquinolones and less favourable minimal inhibitory capacity/ minimal bactericidal capacity rapport. In the current cohort patients treated with high dose Levofloxacine (750 mg up to 1000 mg daily) and Moxifloxacine (400 mg daily) had significant lower mortality in comparison with patients who received other antibiotic regimens. In case of oxygen dependent LD patients or HA LD previous cited antibiotic regimen should be considered. Hospital acquired LD patients represents a non negligible part of the current cohort. The major disease predictor was medical history of asthma or COPD. Controversially, active smoking status resulted as a negative predictor. Longstanding respiratory disease patients receive profound smoking counselling and the rate of active smoker in advanced respiratory disease are lower. Moreover, this significant difference disappears after Gender and age adjustment and a previous article reported the same issue. Furthermore, although it is estimated that the main imaging finding is patchy unilobar infiltrate, bilateral consolidation, independently of pleural effusion presence, was a predictor of HA LD diagnosis in the current cohort.

Conclusion

The strengths of this study are the multicentre design and the rigorous structure. Strict definition of the variants was applied, particularly of HA LD which followed CDC definition. Furthermore, the current cohort accounts one of higher described number of hospital acquired LD patients. To the best of our knowledge, this study is the first that found predictors for HA LD. Finally, the current study enforces the evidence based antibiotic treatment in hospitalized patients affected by LD and HA LD. A potential limitation of this study is the retrospective design, which may not exclude confounding factors. Moreover, a relative low number of patients were included in the current study, which may undermine the power of this study. A randomized clinical trial should address the same questions. However, it seems not feasible considering the relative rarity of this condition. In summary, even though underreported and overlooked LD represents a considerable burden and its investigation should be systematic. Outcomes are particularly poor in HA LD and SOFA score at diagnosis may be good prognostic tool. Moxifloxacine or high dose Levofloxacine based treatment may increase such low outcomes. Finally, HA LD should be particularly researched in chronic respiratory disease patients with bilateral HA pneumonia.

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