

FIGHTING THE LEGION OF DOOM



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History

A 58 year-old man presents to the ER of the VAMC with fevers. It is the end of June.

The patient felt hot upon arriving home from work around 11 pm on the night prior to admission. Given the nature of his work, he initially attributed his symptoms to over-heating. He remained quite sweaty throughout the night and was able to sleep only intermittently.

On the next day, he measured his temperature as 104°F. He also noticed the recent onset of headaches and dry heaves. He has had diarrhea for the past 3 days. He has had a cough for the past 9 months. He denies neck stiffness, chest pain, shortness of breath, abdominal pain, urinary symptoms or rash.

Additional history

- **PMH:** HTN, hyperlipidemia, depression, ventral hernia repair
- **Medications:** atorvastatin, fenofibrate, fluoxetine
- **Social history:** He has smoked cigarettes for 40 pack-years. He'll drink a beer 1-2 times per month. He lives in Muscatine, Iowa and is monogamous with his common-law-wife. He works as an industrial painter (office furniture). In his spare time, he does odd jobs around his house. No other outdoor activities. No animal exposures. No recent travel.
- **Family history:** diabetes

Physical exam findings and laboratory results

T 102°F, P 112, BP 102/65, RR 18

General: alert and oriented, flushed appearance

HEENT: anicteric, no oral lesions

Neck: supple

Heart: tachycardic, no murmurs

Lungs: clear to auscultation bilaterally

Abdomen: obese, nontender

Ext: no peripheral edema

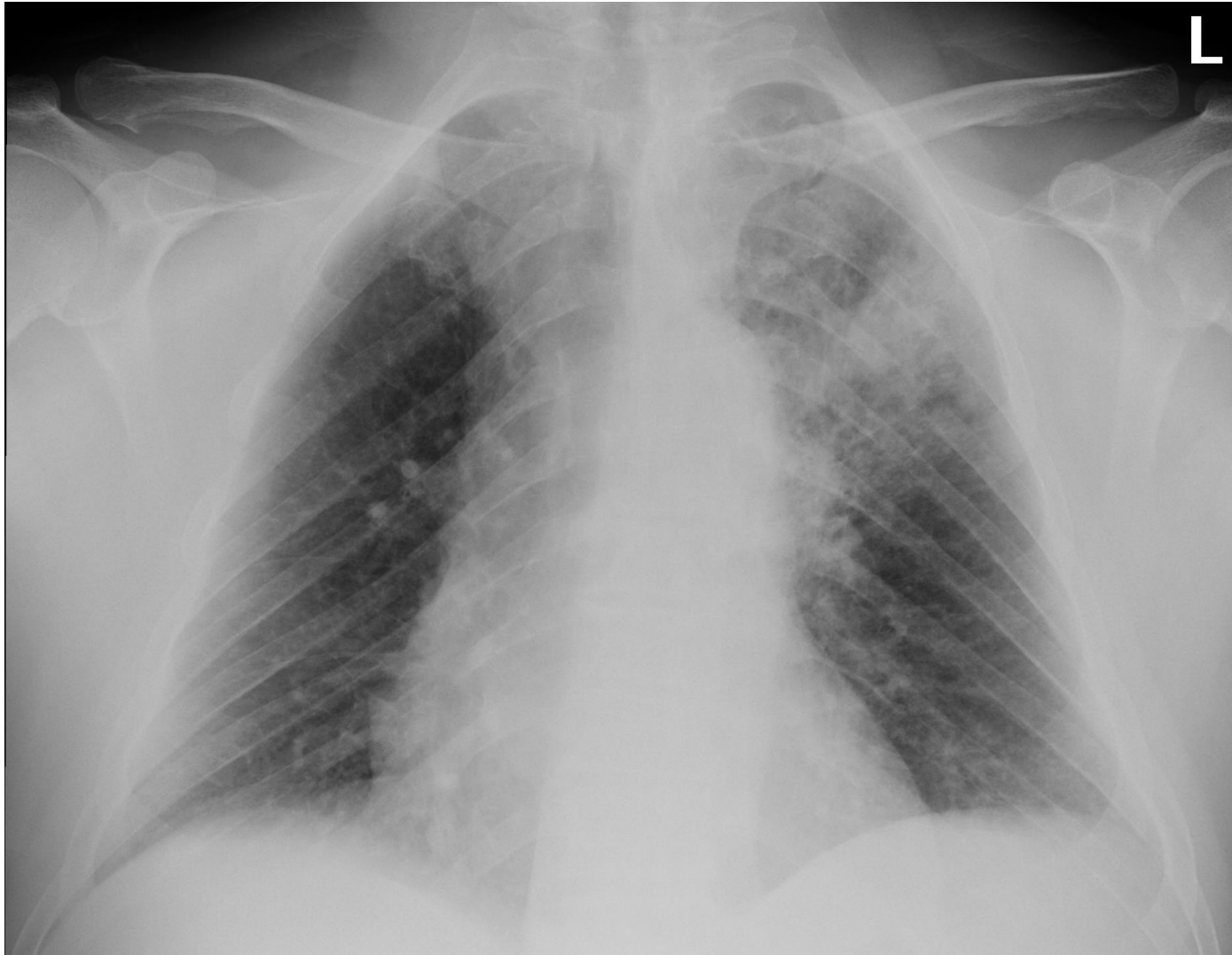
Skin: no rash

Neuro: normal gait, 5/5 strength in all muscle groups

WBC 16.9K (N 90%, L 4%)/Hgb 12.2/Plt 183

Na 130, K 4.9, Cl 93, CO₂ 20, Bun 34, Cr 2.0

Patient was admitted for “presumed heat stroke.” He was started on IV fluids and additional cooling measures were provided. Overnight, a chest x-ray showed.....



A diagnostic test was performed.

What is the diagnosis?

Hospital Course

- Hospital Day #1: Ampicillin-sulbactam and azithromycin were started. Patient remained intermittently febrile.
- Hospital Day #2: Patient developed respiratory distress and was transferred to the ICU for BiPAP. He remained on BiPAP for the next 48 hours.
- Hospital Day #4: Urine Legionella antigen came back positive. He no longer required BiPAP and finally defervesced.
- Hospital day #6: Discharged to complete a 10-day course of azithromycin.

Clinical pearls

- Respiratory symptoms may not be initially prominent in patients with Legionella pneumonia.
- The findings of Legionella pneumonia are varied and non-specific, which highlights the importance of clinical suspicion and diagnostic testing.
 - ▣ High fevers ($\geq 104^{\circ}\text{F}$) are more common in Legionella infection than in pneumonia due to other pathogens.
 - ▣ Hyponatremia occurs significantly more frequently in Legionella pneumonia than in pneumonia due to other pathogens.

Fang GD, et al. *Medicine (Baltimore)*. 1990;69(5):307-16.

Yu VL, et al. *Am J Med*. 1982;73(3):357-61.



Legionella pneumonia:

Treatment considerations

- Legionella replicates solely within the intracellular compartment.
- Therefore, antibiotics need to achieve intracellular concentrations higher than the MIC.
 - Fluoroquinolones
 - Macrolides
 - Tetracyclines
 - Rifampin

Antimicrobial Chemotherapy for Legionnaires Disease: Levofloxacin versus Macrolides

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Background. The community outbreak of legionnaires disease that occurred in Murcia, Spain, in July 2001—to our knowledge, the largest such outbreak ever reported—afforded an unusual opportunity to compare the clinical response of patients with *Legionella* pneumonia treated with levofloxacin with that of patients treated with macrolides and to determine the role of rifampicin combined with levofloxacin in treating severe legionellosis.

Methods. An observational, prospective, nonrandomized study was conducted involving 292 patients seen at our hospital (Hospital "J. M. Morales Meseguer"; Murcia, Spain) who received a diagnosis of *Legionella* pneumonia during the Murcia outbreak. To compare both antibiotic regimens (macrolides vs. levofloxacin), patients were stratified by the severity of pneumonia. Duration of fever, clinical outcome, complications, side effects, and length of hospital stay were recorded. To assess the potential effects of adjuvant therapy with rifampicin, 45 case patients treated with levofloxacin plus rifampicin were evaluated and compared with 45 control pairs who were treated with levofloxacin alone.

Results. With the exception of 2 patients who died, all patients were cured. There were no significant differences between treatment groups in clinical outcome for patients with mild-to-moderate pneumonia. Nevertheless, in patients with severe pneumonia, levofloxacin exerted superior activity; it was associated with fewer complications (3.4% of patients receiving levofloxacin experienced complications, compared with 27.2% of patients receiving macrolides; $P = .02$) and shorter mean hospital stays (5.5 vs. 11.3 days; $P = .04$). Addition of rifampicin to the treatment regimen for patients receiving levofloxacin for severe pneumonia provides no additional benefit.

Conclusions. Our findings strongly suggest that monotherapy with levofloxacin is a safe and effective treatment for legionnaires disease, including in patients with severe disease. In these patients, levofloxacin appears to be more effective than clarithromycin.

Legionnaires disease (LD) is an acute pneumonia caused by *Legionella* species, a rod-shaped, gram-negative bacillus that is ubiquitous in aquatic reservoirs. Twenty-eight years after it was first detected [1], large, focal outbreaks of LD continue to occur worldwide. Since the early 1990s, the treatment of choice has shifted from erythromycin to newer macrozolides or fluoroquinolones [2–13]. Nevertheless, clinical experience with these agents is still limited, and there are many

aspects of treatment with these agents that currently remain unknown. Such aspects include the optimal duration of therapy, the preferred route of administration, and the impact of combination therapy.

The community outbreak of LD that occurred in the city of Murcia, Spain, in 2001 [14] was, to our knowledge, the largest such outbreak ever reported, and it afforded an unusual opportunity to conduct an observational study of treatment outcomes that compared macrolide therapy with quinolone therapy. We also analyze the role of combination therapy with levofloxacin and rifampicin.

PATIENTS AND METHODS

Patients. In July 2001, an outbreak involving >800 suspected cases of *Legionella pneumophila* pneumonia occurred in Murcia, Spain; 449 of these cases were con-

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Clinical Outcomes for Hospitalized Patients with *Legionella* Pneumonia in the Antigenuria Era: The Influence of Levofloxacin Therapy

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Background. Although the reduction in case-fatality rate recently observed among patients with *Legionella* pneumonia has been largely attributed to the progressive utilization of urine antigen testing, other factors, such as changes in empirical antibiotic therapy, may also have contributed. We have analyzed more-recent outcomes of *Legionella* pneumonia in an institution where urine antigen testing was reflexly performed in cases of community-acquired pneumonia without an etiological diagnosis.

Methods. From a prospective series of 1934 consecutive cases of community-acquired pneumonia in non-immunocompromised adults, 139 cases of *Legionella pneumophila* pneumonia were selected for observational review. *Legionella* cases were analyzed for outcome with respect to antibiotic treatment, mortality, complications, length of stay, time to defervescence, and stability.

Results. The early case-fatality rate was 2.9% (4 of 139 patients), and the overall case-fatality rate was 5% (7 of 139 patients). One hundred twenty patients (86.3%) received an appropriate initial therapy, which included macrolides (i.e., erythromycin or clarithromycin) in 80 patients and levofloxacin in 40. Levofloxacin progressively replaced macrolides as the initial therapy during the study period. Compared with patients who received macrolides, patients who received levofloxacin had a faster time to defervescence (2.0 vs. 4.5 days; $P < .001$) and to clinical stability (3 vs. 5 days; $P = .002$). No differences were found regarding the development of complications (25% vs. 25%; $P = .906$) and case-fatality rate (2.5% vs. 5%; $P = .518$). The median length of hospital stay was 8 days in patients treated with levofloxacin and 10 days in those who received macrolides ($P = .014$).

Conclusions. *Legionella* pneumonia is still associated with significant complications in hospitalized patients, but recent mortality is substantially lower than that found in earlier series. Levofloxacin may produce a faster clinical response than older macrolides, allowing for shorter hospital stay.

Legionella pneumophila is a leading cause of community-acquired pneumonia [1–5]. It has been estimated that 8000–18,000 people are hospitalized with legionellosis annually in the United States [6]. Moreover, *Legionella* is particularly frequent among patients with community-acquired pneumonia who require admission to an intensive care unit [7, 8].

Classically, *L. pneumophila* has been classified as a high-risk pathogen in community-acquired pneumo-

nia, accounting for substantial morbidity and with case-fatality rates of 5%–25% among immunocompetent hosts [1, 9–12]. However, a recent surveillance study [13] showed a remarkable reduction in case-fatality rates during the past decade, suggesting that new models of management may have improved outcomes in patients with *Legionella* pneumonia. Although it is reasonable to suppose that early recognition of *Legionella* pneumonia by means of urine antigen testing may have contributed to decreasing mortality, the impact of other factors, including new antibiotic options, is less clear. Furthermore, to assess more adequately the role of these factors, outcome measures other than mortality should be considered [14].

In this study, we analyzed more recent clinical outcomes of *Legionella* pneumonia, including response to antibiotic therapy, time to clinical stability, develop-

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Levofloxacin vs. macrolides during a Spanish Legionella outbreak

- **Setting:** A 400-bed hospital in Spain during a large *Legionella pneumophila* outbreak (2001)
- **Case definition:** Symptoms + x-ray findings + a positive Legionella test (titers, culture, urine antigen)
- **Results:**
 - ▣ 292 cases (223 hospital, 69 outpatients)
 - ▣ Treatment: oral azithro (35), clarithro (32), levofloxacin (187)
 - ▣ Overall mortality 0.6%

Comparison of clinical outcomes in patients with *Legionella pneumonia*

	Macrolide (n=65)	Levofloxacin (n=143)	p-value
Duration of fever, days (mean)	4.6	4.4	0.5
Complications	3 (4.6%)	1 (0.6%)	0.08
Cure	65 (100%)	142 (99.3%)	0.4
Side effects	10 (15.3%)	15 (10.4%)	0.3
Hospital stay, days (mean)	7.2	4.4	0.03

- Respiratory failure: levofloxacin 27%, macrolides 12% ($p < 0.03$)
- Difference in length of stay was driven by differences among sickest patients (clarithromycin or levo)

Levofloxacin vs. macrolides in patients with non-outbreak Legionella CAP

- Setting: 900-bed university hospital in Spain during 1995-2003
- Methods: 1934 non-severely immunosuppressed patients with CAP were screened for Legionella on hospital admission
- Case definition: Legionella identified by urine antigen, culture, or antibody titers
- Results:
 - 139 cases (7.2%) of CAP due to Legionella
 - Levofloxacin (40), erythromycin (53), clarithromycin (27)

Clinical outcomes for 120 patients with community-acquired Legionella pneumonia

	Macrolide (n=80)	Levofloxacin (n=40)	p-value
Time to defervescence (mean)	6.1 days	2.5 days	<0.001
Time to resolution of cough (mean)	5.2 days	3.1 days	<0.001
Time to achieve clinical stability (mean)	6.6 days	3.6 days	0.002
In-hospital complications	25%	25%	0.906
Length of stay, mean	14.5 days	9.7 days	0.014
Mortality	5%	2.5%	0.518

Community-Acquired *Legionella pneumophila* Pneumonia

A Single-Center Experience With 214 Hospitalized Sporadic Cases Over 15 Years

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Abstract: *Legionella pneumophila* has been increasingly recognized as a cause of community-acquired pneumonia. In this study, we report on the experience of a single center with 214 hospitalized sporadic cases of Legionella pneumonia over 15 years. The study was associated with a trend towards shorter hospital admission, length of stay, and mortality (p=0.09).

- **215 patients with Legionella pneumonia at a single center (1995-2010)**
- **Compared to macrolides, levofloxacin was associated with...**
 - **A shorter time to clinical stability (3 vs. 5 days, p=0.09)**
 - **Shorter length of hospital stay (7 vs. 10 days, p<0.01)**
- **Only 1 patient received azithromycin**

Viasus D, et al. Medicine (Baltimore) 2013; 92: 51-60.

Limitations of old literature

- In older clinical studies and intracellular/animal models, fluoroquinolones have been superior to macrolides, BUT many of these studies used clarithromycin or erythromycin, not azithromycin
- Azithromycin may be superior to other macrolides
 - ▣ Intracellular models: Most active macrolide
 - ▣ Animal models: 100% survival
 - ▣ Intracellular growth inhibition is comparable to quinolones (high-throughput screening technology)

The Association of Antibiotic Treatment Regimen and Hospital Mortality in Patients Hospitalized With *Legionella* Pneumonia

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Background. Guidelines recommend azithromycin or a quinolone antibiotic for treatment of *Legionella* pneumonia. No clinical study has compared these strategies.

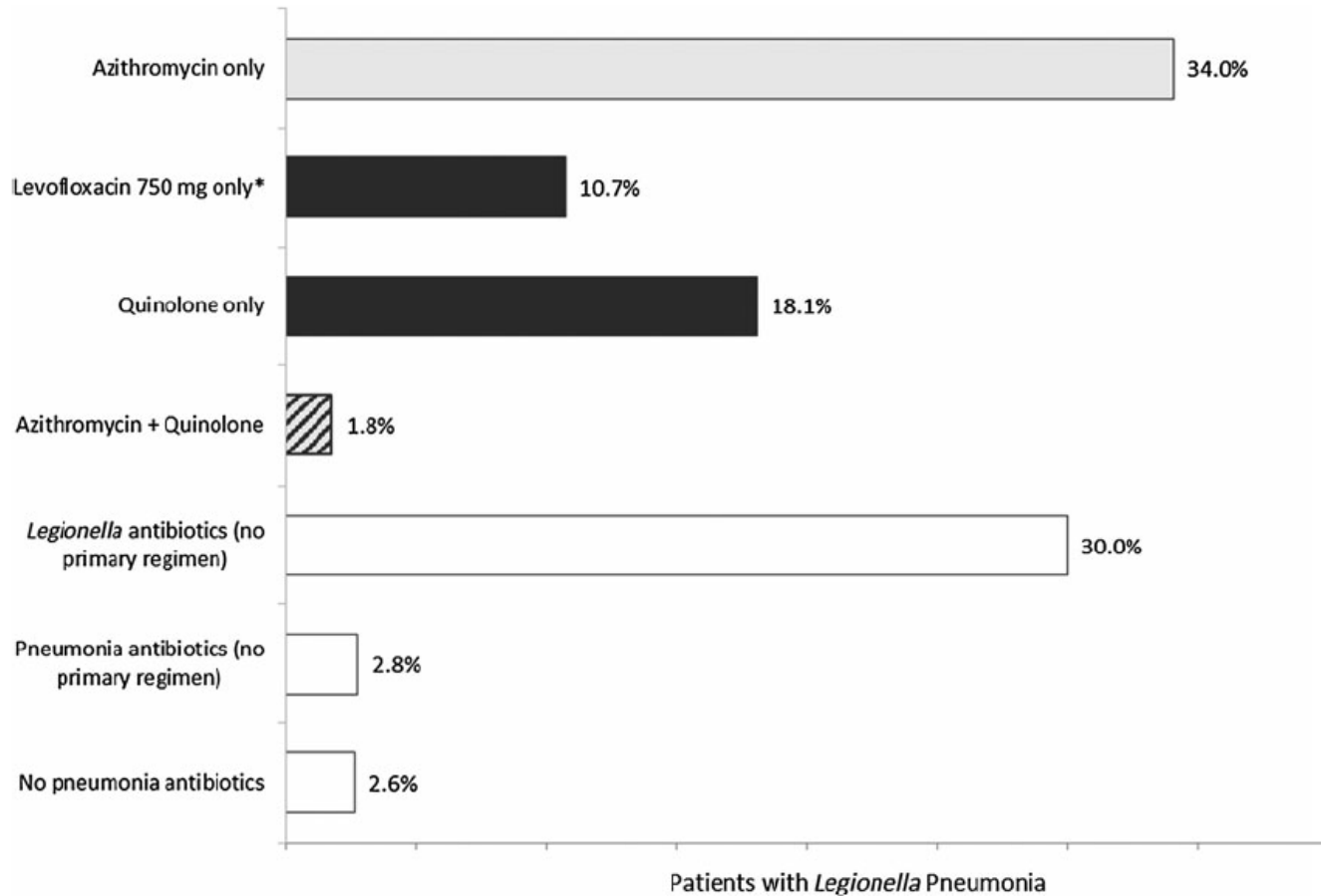
Methods. We performed a retrospective cohort analysis of adults hospitalized in the United States with a diagnosis of *Legionella* pneumonia in the Premier Perspectives database (1 July 2008–30 June 2013). Our primary outcome was hospital mortality; we additionally evaluated hospital length of stay, development of *Clostridium difficile* colitis, and total hospital cost. We used propensity-based matching to compare patients treated with azithromycin vs a quinolone. All analyses were repeated on a subgroup of more severely ill patients, defined as requiring intensive care unit admission or mechanical ventilation or having a predicted probability of hospital mortality in the top quartile for all patients.

Results. *Legionella* pneumonia was diagnosed in 3152 adults across 437 hospitals. Quinolones alone were used in 28.8%, azithromycin alone was used in 34.0%, and 1.8% received both. Crude hospital mortality was similar: 6.6% (95% confidence interval [CI], 5.0%–8.2%) for quinolones vs 6.4% (95% CI, 5.0%–7.9%) for azithromycin ($P = .87$); after propensity matching ($n = 813$ in each group), mortality remained similar (6.3% [95% CI, 4.6%–7.9%] vs 6.5% [95% CI, 4.8%–8.2%], $P = .84$ for the whole cohort, and 14.9% [95% CI, 10.0%–19.8%] vs 18.3% [95% CI, 13.0%–23.6%], $P = .36$ for the more severely ill). There was no difference in hospital length of stay, development of *C. difficile*, or total hospital cost.

Azithromycin versus quinolones

- Retrospective analysis of a large drug utilization database (2008-2013), which includes ~20% of all hospital discharges in the United States
- Primary cohort: adults with ICD-9 code for Legionnaires' disease
- Primary outcome: hospital mortality
- Primary antibiotic regimen
 - ▣ Antibiotic for first 2-days of appropriate therapy
 - ▣ At least 75% of total course

In-hospital treatment strategies used for 3152 patients with Legionnaire's disease



Comparison of outcomes of azithromycin-and quinolone-treated patients with Legionnaire's disease

Outcome	All patients who received primary azithro or FQ			Propensity-matched patients stratified by primary agent			Highest-severity propensity-matched stratified by agent		
	Azithro	FQ	p-value	Azithro	FQ	p-value	Azithro	FQ	p-value
Hospital mortality	6.4%	6.6%	0.87	6.5%	6.3%	0.84	18.3%	14.9%	0.36
Length of stay	9.3 days	10.2 days	0.046	9.5 days	10.0 days	0.34	13.4 days	13.4 days	0.97
C.difficile	2.1%	1.3%	0.21	2.1%	1.4%	0.25	3.8%	1.9%	0.24

Macrolides vs. fluoroquinolones: conclusions

- If Legionella pneumonia is suspected or proven, azithromycin or fluoroquinolones are appropriate therapy.



