Treatment of Legionnaires' Disease

EPF Yzerman, MD, PhD
Regional Laboratory of Clinical Microbiology and Public Health
Dutch Reference Laboratory for Legionella

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Legionella

- Ubiquitous in freshwater environments
- Free-swimming as a resident of biofilms
- Parasite of protozoa and amoebae

Legionella Life Cycle

1. Planktonic transmissive form
    1. Motile
    2. Resistant to multiple environmental stresses
    3. Infectious to host cells

2. Replicative form
    1. Intracellular multiplication
    2. Resistant to acidic lysosomal components
    3. Can mature to a highly infectious cyst-like form

Human infection

- *Legionella* usually enters humans through breathing in of contaminated aerosols or droplet nuclei
- Once inhaled *Legionella* needs to reach the alveoli of the lungs to establish an infection
- In the alveoli it induces an immune response in order to draw macrophages

- The *mip*-gene facilitates opsonic-independent coiling phagocytosis
- The Icm/dot type IV secretion system prevents phago-lysozome fusion
- Turns phagosome into a replication vacuole

Cell-mediated adaptive immune response normally limits bacterial amplification

Risk Factors for Acquiring Legionnaires' Disease

- Immune suppressive therapy
- Cigarette smoking
- Alcohol intake
- Diabetes mellitus
- Cancer
- ESRD (end stage renal disease)

Clinical presentation of *Legionella* pneumonia

After an incubation time of 2 – 20 days:

- fever, fatigue, headaches, muscle aches, cough
- chest pain, diarrhoea, confusion, shaking chills
- shortness of breath
- full-blown pneumonia

Indistinguishable from other forms of bacterial pneumonia

No person-to-person spread

Legionella pneumonia

- Community acquired: ± 75%
- Hospital acquired: ± 25%

- Legionella species are overall responsible for 1-5% of cases of community-acquired pneumonia
- Mortality is still between 10 and 15%
- Cases can be sporadic or outbreak-related

Table 4. Most common aetiologies of community-acquired pneumonia in the United States and Europe (excluding the Netherlands)

	Study population		
	Outpatients	**Hospital**	**Intensive Care unit**
	8 studies[19-26]	Based on collective data from recent studies[5, 7, 27]	Based on collective data from recent studies[5, 7, 27]
S. pneumoniae	6 – 42 %	12 - 39 %	16 – 28 %
H. influenzae	0 – 14 %	5 – 10 %	2 – 8 %
Legionella spp	0 – 4 %	1 – 8 %	4 – 24 %
S. aureus	0 – 3 %	1 – 2 %	5 – 14 %
M. catharalis	0 – 1 %	0 – 2 %	0 – 6 %
Enterobacteriaceae	0 – 4 %	1 – 2 %	1 – 10 %
M. pneumoniae	0 – 16 %	7 – 32 %	1 – 6 %
Chlamydophila spp	0 – 13 %	2 – 9 %	0 – 5 %
C. burnetii	0 – 2 %	0 – 1 %	0 – 2 %
Viral (e.g Influenza)	15 – 29 %	1 – 23 %	1 – 15 %
Other	1 – 4 %	1 – 2 %	2 – 10 %
No pathogen identified	39 – 58 %	30 – 46 %	25 – 46 %

Data derived from most recent studies and categorized per patient type.

Nosocomial *Legionella* pneumonia

- Besides inhalation micro-aspiration as a mode of infection
- Mostly immunocompromised patients
- More diverse serotypes

Treatment considerations

- Intracellular concentrations in lysosomes have to be achieved
- Agent must have intrinsic activity against *Legionella*

Intrinsic activity

TABLE 1 MICs and MBCs of antibiotics against *L. pneumophila* strains

Antibiotics	MIC (mg/liter[a])		MBC (mg/liter[b])	
	50	90	50	90
Erythromycin	0.125	2	0.5	8
Azithromycin	0.0625	0.25	0.25	4
Ciprofloxacin	0.0156	0.125	0.0312	0.5
Ofloxacin	0.0312	0.125	0.0312	0.5
Levofloxacin	0.0156	0.125	0.0312	0.25
Doxycycline	1	4	8	32
Rifampin	0.00048	0.00097	0.00097	0.0156

[a] 50 and 90, MIC_{50} and MIC_{90}.
[b] 50 and 90, MBC_{50} and MBC_{90}.

Birteksöz et al

MIC_{50}, MIC_{90} and ECOFF values of 183 clinical isolates of L. pneumophila serogroup 1

Drug	*Range (mg/L)*	*MIC_{50} (mg/L)*	*MIC_{90} (mg/L)*	*ECOFF WT (mg/L)*
Ciprofloxacin	*0.25-2*	*0.50*	*0.50*	*1.0*
Levofloxacin	*0.064-1*	*0.25*	*0.25*	*0.5*
Moxifloxacin	*0.25-1*	*0.50*	*0.50*	*1.0*
Erythromycin	*0.032-2*	*0.125*	*0.25*	*1.0*
Azithromycin	*0.032*	*0.125*	*0.25*	*1.0*
Clarithromycin	*0.064-1*	*0.125*	*0.25*	*0.50*
Rifampicin	*0.004-0.032*	*0.016*	*0.032*	*0.032*
Cefotaxime	*0.008-1*	*0.125*	*0.50*	*1.0*
Tigecycline	*1-16*	*4*	*8*	*16*
Doxycycline	*1-8*	*4*	*8*	*8*

Bruin JP et al

Prediction of effective therapy

- *In vitro* models
- Animal models
- Clinical trials

In vitro models

- Human monocyte-derived macrophages, bone marrow macrophages, alveolar epithelial cells

- Guinea pig and mice alveolar macrophages

Results *in vitro* studies

Overall, from the quinolones levofloxacin and moxifloxacin are the most active in the intracellular infection models. Ciprofloxacin is slightly less active.

From the macrolides azithromycin is superior to clarithromycin and erythromycin.

Levofloxacin is as active as azithromycin.

Animal models

- Guinea pig model (PH Edelstein)
- Mouse model

  - intratracheal or intranasal inoculation of *Legionellae*
  - concentrations of 10^3 - 10^9 CFU are used

Results animal models

In general, in agreement with the *in vitro* results:

- azithromycin and levofloxacin have comparable activity

- both agents are superior to clarithromycin and erythromycin

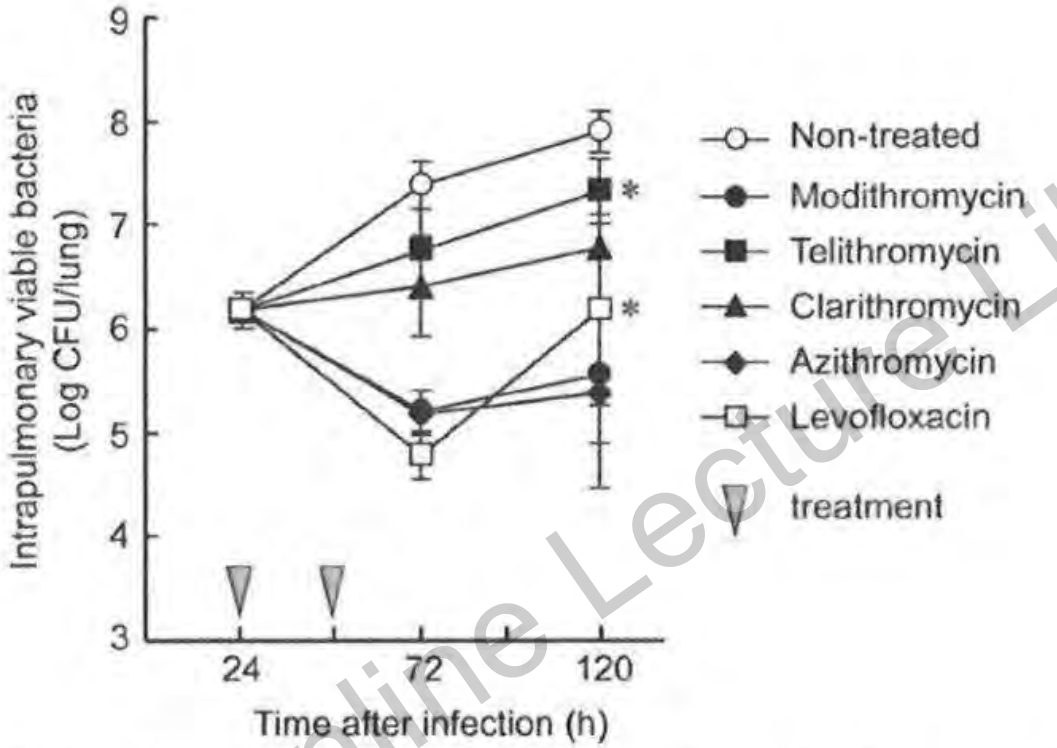

FIG. 3. *In vivo* efficacies of modithromycin and other antimicrobial agents with 2-day treatments against pulmonary infection with the *L. pneumophila* Suzuki strain in immunosuppressed A/J mice. The antimicrobial agents were orally administered at a dose of 30 mg/kg/day 24 and 48 h after infection ($n = 5$). *, the differences between the numbers of viable bacteria 72 and 120 h after infection in each antimicrobial agent were analyzed by Welch's t tests ($P < 0.05$).

Sato et al. AAC, 2011;1594-97

- Azithromycin accumulates in cells at high concentrations for longer periods

- Azithromycin leads to a reduction in lung inflammation that may be due to anti-inflammatory properties

Clinical trials

No adequately powered prospective comparative studies of the treatment of LD have been performed.

Observational studies

- Levofloxacin super to clarithromycin and erythromycin:
    - Shorter time to apyrexia
    - Less complications
    - Shorter hospital stay

- No data regarding *in vivo* activity of moxifloxacin
- No comparison of levofloxacin and azithromycin

Community-acquired Legionella Pneumonia in the intensive care unit: Impact on survival of combined antibiotic therapy

J. Rello, S. Gattarello, J. Souto, J. Sole-Violan, J. Valles, R. Peredo, R. Zaragoza, L. Vidaur, A. Parra, J. Roig, the Community-acquired Pneumonia in Unidad de Cuidados Intensivos 2 (CAPUCI 2) Study Investigators

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OBJECTIVES

To compare intensive care unit (ICU) mortality in patients with severe community-acquired pneumonia (SCAP) caused by *Legionella pneumophila* receiving combined therapy or monotherapy.

METHODS

A prospective multicenter study was made, including all patients with sporadic, community-acquired Legionnaires' disease (LD) admitted to the ICU. Admission data and information on the course of the disease were recorded. Antibiotic prescriptions were left to the discretion of the attending physician and were not standardized.

RESULTS

Twenty-five cases of SCAP due to *L. pneumophila* were included.

Seven patients (28%) out of 25 died after a median of 7 days of mechanical ventilation.

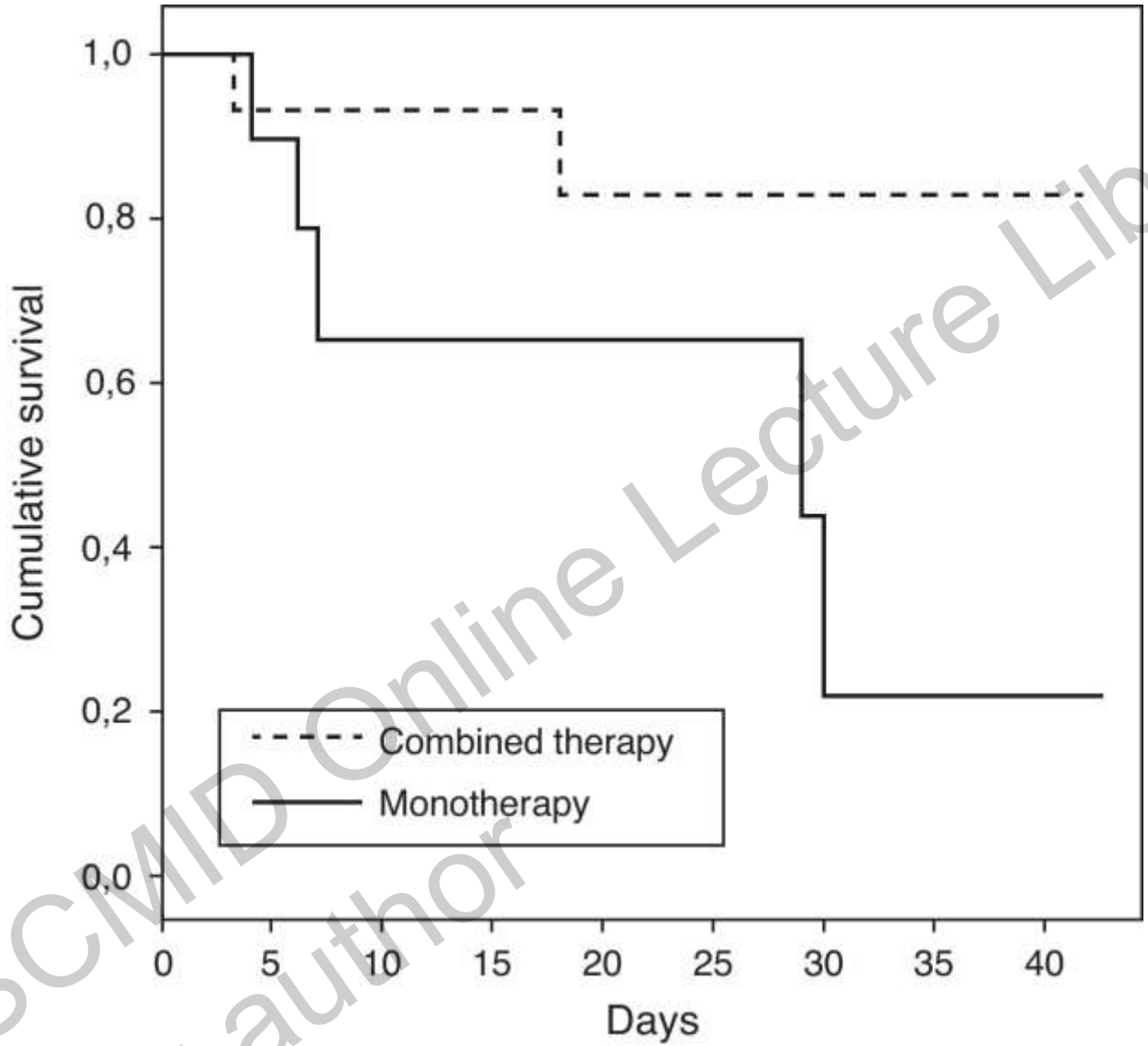
Fifteen patients (60%) presented with shock.

Levofloxacin and clarithromycin were the antibiotics most commonly used in monotherapy.

The most frequent combination was rifampicin plus clarithromycin.

Patients subjected to combination therapy presented a lower mortality rate (2/15) versus patients subjected to monotherapy (5/10) (odds ratio for death [OR] 0.15; 95% CI 0.02–1.04; ***P***=0.08).

In patients with shock, this association was stronger and proved statistically significant (OR for death 0.06; 95% CI 0.004–0.86; ***P***=0.04).



Kaplan–Meier survival curve for patients with shock receiving combination therapy versus monotherapy censored at 40 days (log rank test: ***P*** value=0.04).

Drawbacks

- Patient group is small
- Azithromycin is not used (no availability)
- Delay of treatment from onset of pneumonia is not recorded

Delay in therapy

- In 1999 large outbreak of LD in the Netherlands: 141 hospitalized patients
- Overall mortality 13%, ICU mortality 36%
- Starting adequate therapy within 24 hours after admission resulted in a higher ICU-free survival rate (p=0.005)

Lettinga et al. EID 2002;8:1448-54

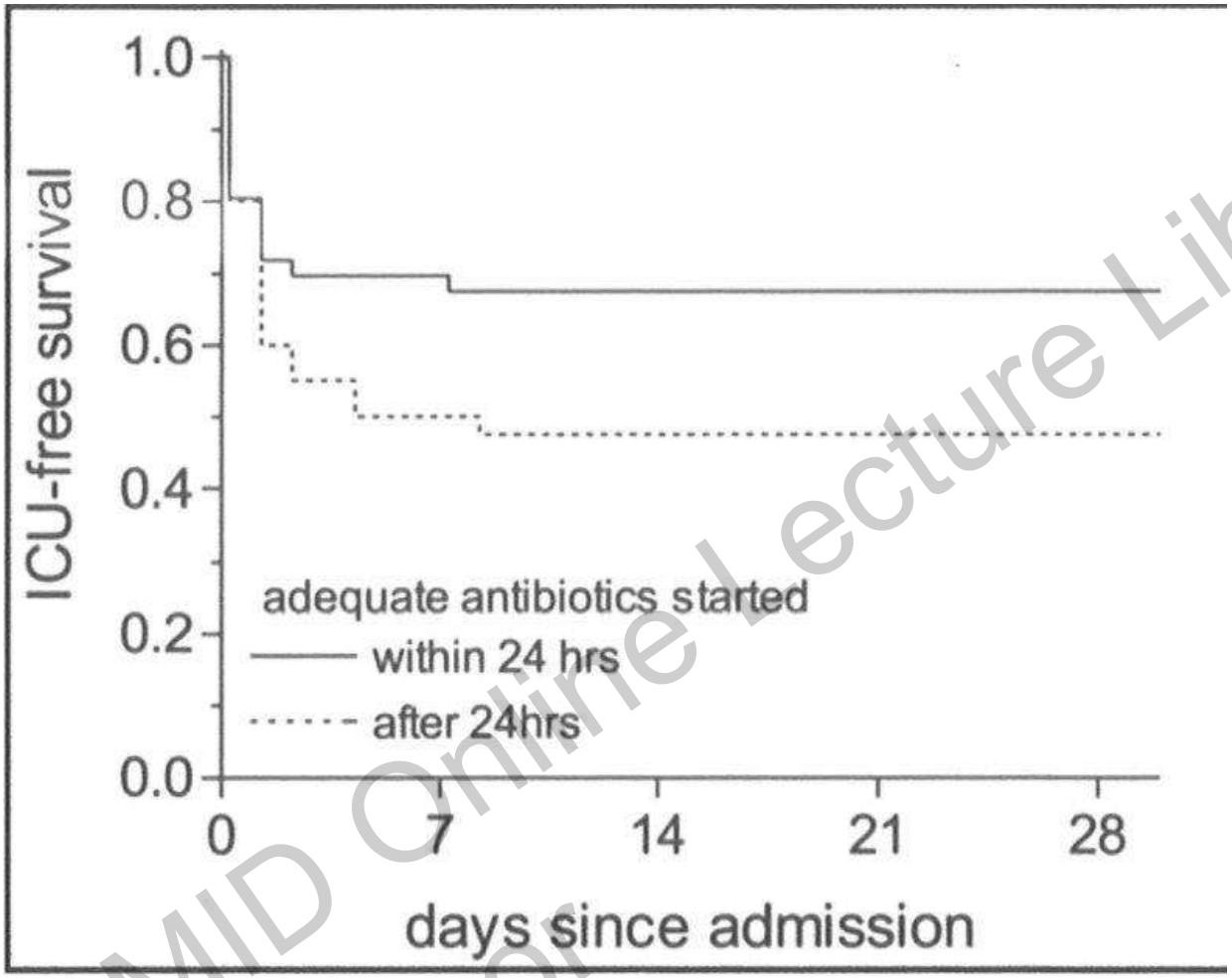


Figure 2. Kaplan-Meier curve for intensive care unit (ICU)–free survival ICU-free survival for patients treated with adequate antibiotics within and >24 h after admission.:___ adequate antibiotic therapy started within 24 h after admission (n=85); ----- adequate antibiotic therapy started >24 h after admission (n=56).

Lettinga et al. EID 2002;8:1448-54

Recommendations

- IDSA 2007 Guidelines for CAP
- Dutch SWAB/NVALT 2011 Guidelines for CAP
- Specific treatment for LD

Recommended empirical antibiotics for community-acquired pneumonia (IDSA 2007)

Outpatient treatment

1. Previously healthy and no use of antimicrobials within the previous 3 months:

   A macrolide (strong recommendation; level I evidence)

   Doxycyline (weak recommendation; level III evidence)

2. Presence of comorbidities:

   A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin (strong recommendation; level I evidence)

   A beta-lactam **plus** a macrolide (strong recommendation; level I evidence)

Inpatients, non-ICU treatment

A respiratory fluoroquinolone (strong recommendation; level I evidence)

A beta-lactam **plus** a macrolide (strong recommendation; level I evidence)

Inpatients, ICU treatment

A beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) **plus** either azithromycin (level II evidence) **or** a respiratory fluoroquinolone (level I evidence) (strong recommendation)

(for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)

Dutch Guidelines

Table 9. Guideline for the choice of initial therapy for community-acquired pneumonia

Severity	Antibiotic	Route	Dose	Freq.
Mild pneumonia				
1st choice	amoxicillin	oral	500-750 mg	q6h-q8h
2nd choice	doxycycline	oral	100 mg (first dose 200 mg)	q24h
Moderately severe pneumonia				
1st choice	penicillin	IV	1 ME	q6h
	amoxicillin	IV	1000 mg	q6h

SWAB/NVALT Guidelines Community-acquired Pneumonia 2011

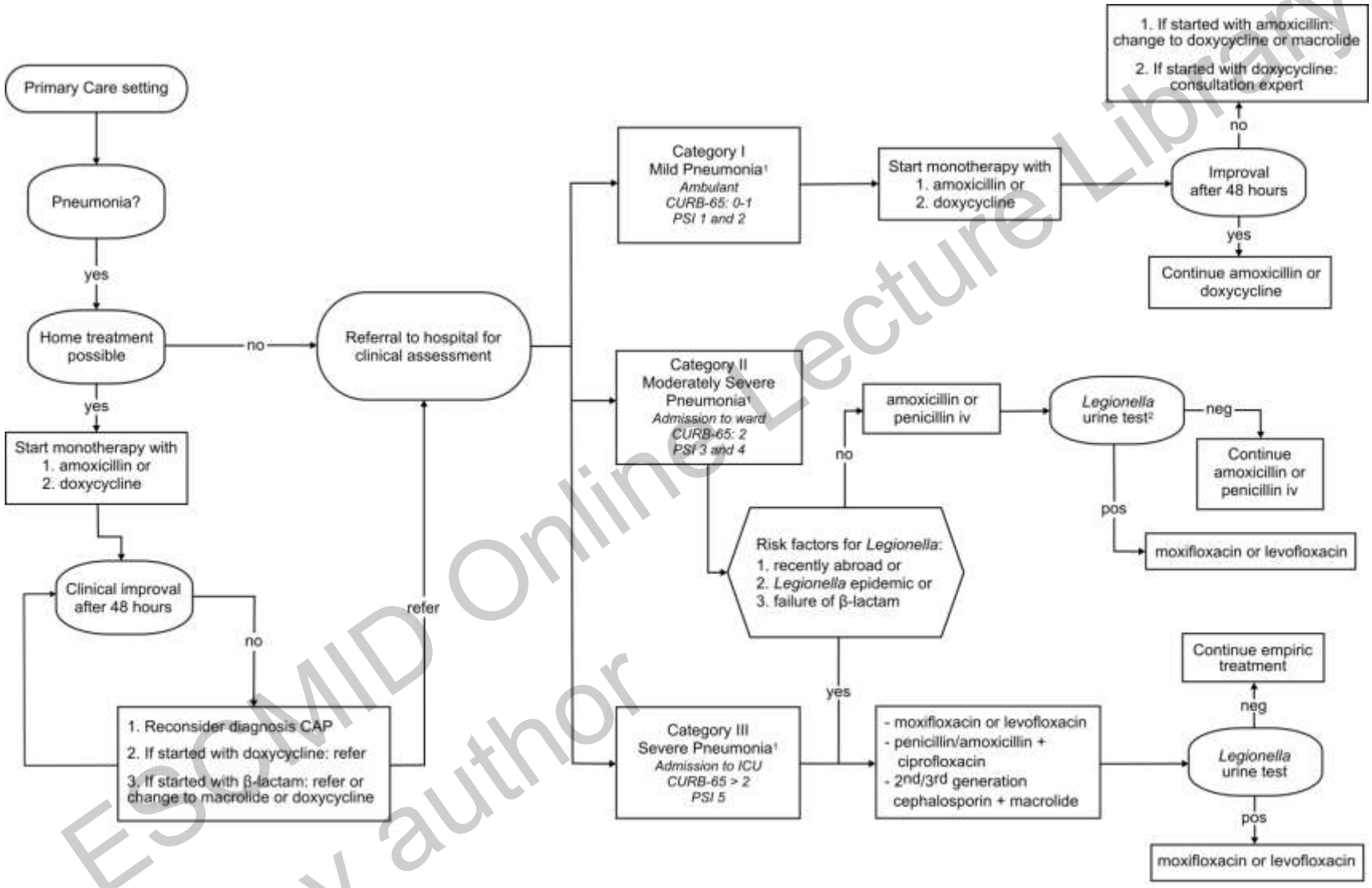
Severe pneumonia

Monotherapy	moxifloxacin *or* levofloxacin	IV / oral IV / oral	400 mg 500 mg	q24h q12h
Combination therapy	penicillin	IV	1 ME	q6h
	ciprofloxacin	IV / oral	400 mg (po 500 mg)	q12h
Combination therapy	cefuroxime *or* ceftriaxone *or* cefotaxime	IV IV IV	750-1500 mg 2000 mg 1000 mg	q8h q24h q6h
	erythromycin	IV	500-1000 mg	q6h

Recommended antimicrobial therapy for specific pathogens (IDSA 2007)

Legionella species

Preferred antimicrobials:	fluoroquinolone, azithromycin
Alternative antimicrobial:	doxycycline



[1] See legend

[2] Always perfrom a Legionella urine antigen test in patients with a PSI score 4 or presence of 2 CURB-65 criteria

Recommended therapy in LD

Antimicrobial agent	Dosage	Route
Macrolides		
Azithromycin	500 mg every 24 hours	IV, p.o.
Clarithromycin	500 mg every 12 hours	IV, p.o.
Erythromycin	1 g every 6 – 8 hours	IV, p.o.
Fluoroquinolones		
Levofloxacin	500–750 mg every 24 hours	IV, p.o.
Moxifloxacin	400 mg every 24 hours	IV, p.o.
Ciprofloxacin	400 mg every 8 – 12 hours	IV
	500-750 mg every 12 hours	p.o.
Tetracyclines		
Doxycycline	200 mg every 24 hours	IV, p.o.

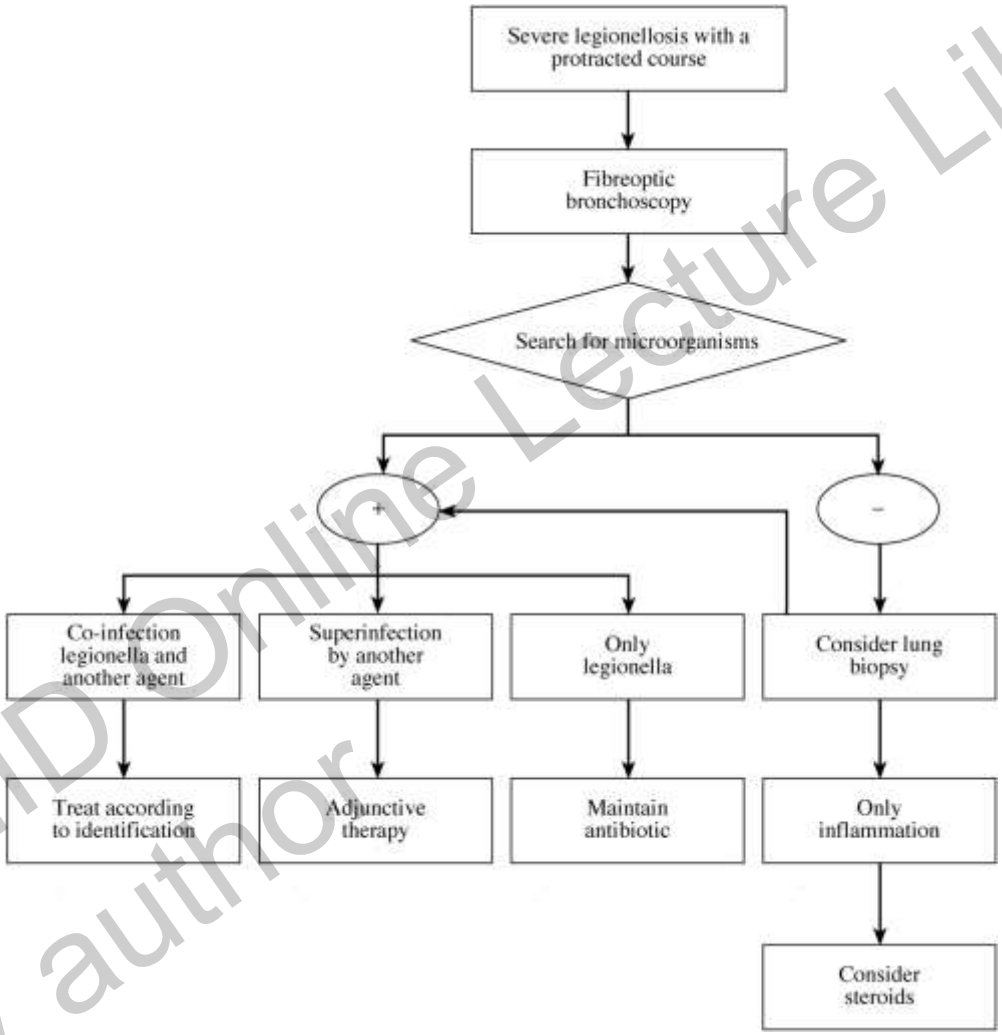
- Oral therapy is recommended only for outpatients

- Levofloxacin, moxifloxacin and azithromycin are recommended in severe cases

Prognostic factors for ICU or death

- Bilateral infiltrates on admission
- Smoking
- Acute renal failure
- Immunocompromised

Figure 1. Proposal for algorithmic approach to management of intubated patients with non-resolving legionellosis.



Roig J , and Rello J J. Antimicrob. Chemother. 2003;51:1119-1129

Journal of Antimicrobial Chemotherapy

Summary

- Legionellae are omnipresent in aqueous ecosystems
- Inhalation or aspiration of *Legionella* bacteria may lead to severe pneumonia
- Infection can be community-acquired as well as nosocomial
- No person-to-person spread (minimal risk of development of resistance)

- Quinolones and macrolides are still the cornerstones of antimicrobial treatment
- Insufficient evidence to recommend combination therapy
- Delay in adequate therapy is associated with a bad outcome
- In case of a protracted course search for other pathogens