Légionellose grave:
Macrolide ou Fluoroquinolone ?

J Dellamonica
Médecine Intensive - Réanimation

Liens d'intérêts

- GE prêt d'un ventilateur pour des études cliniques
- Medtronic
- Fisher Paykel
- MSD
- Getinge
- IMDsoft

Levcovich *et al. BMC Infectious Diseases* (2016) 16:75
DOI 10.1186/s12879-016-1374-9

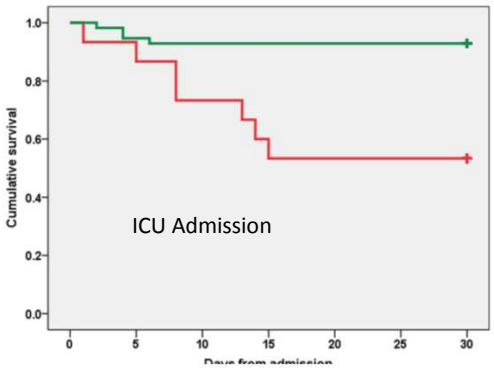
BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Complex clinical and microbiological effects on Legionnaires' disease outcone; A retrospective cohort study

72 legionelloses

Ariela Levcovich[1], Tsilia Lazarovitch[2], Jacob Moran-Gilad[3,4,5], Chava Peretz[6], Eugenia Yakunin[7], Lea Valinsky[7] and Miriam Weinberger[1,8*]



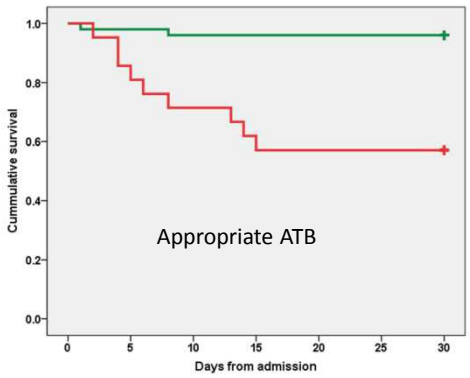


Table 2 Logistic regression, multivariate models of variables associated with all-cause 30-day in-hospital mortality

Parameter	OR	95 % CI	P-value
Multivariate model 1			
Mean age, years	1.05	0.98-1.13	0.18
Hospitalization within 30 days[a]	1.48	0.19-11.37	0.71
Charlson comorbidity index	1.20	0.81-1.79	0.36
Primary diagnosis by positive UAT[b]	0.18	0.03-0.98	0.05
Appropriate therapy on day +2[a]	0.16	0.03-0.90	0.04
Multivariate model 2			
Mean age, years	1.06	0.95-1.18	0.31
Hospitalization within 30 days[a]	1.93	0.19-19.28	0.58
Charlson comorbidity index	1.37	0.88-2.12	0.16
Primary diagnosis by positive UAT[b]	0.88	0.12-6.81	0.91
Appropriate therapy on day +2[a]	0.04	0.004-0.55	0.009
ICU admission[a]	55.54	2.94-1049.35	0. 007

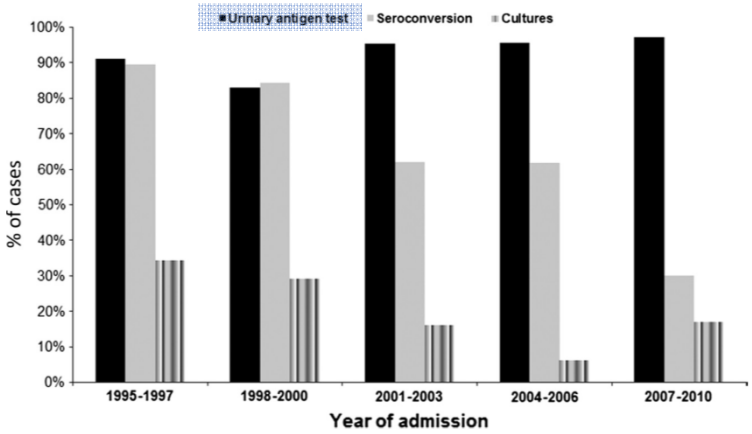
Apparié sur ICU admission

Community-Acquired *Legionella pneumophila* Pneumonia

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

Diego Viasus, MD, PhD, Silvana Di Yacovo, MD, Carolina Garcia-Vidal, MD, PhD, Ricard Verdaguer, MD, Frederic Manresa, MD, PhD, Jordi Dorca, MD, PhD, Francesc Gudiol, MD, PhD, and Jordi Carratalà, MD, PhD

Medicine • Volume 92, Number 1, January 2013



Présentation Clinique

Category, characteristic	*L. pneumophila* Pneumonia (n=214)*	*S. pneumoniae* Pneumonia (n=1346)*	P
Demographic data			
Age, mean (SD), yr	58.2 (13.8)	66.4 (16.9)	<0.001
Male sex			
Current/forr			0.67
Alcohol abu			0.001
Influenza vac			0.001
Pneumococ (5 yr)			0.001
Previous tra			0.45
Previous be therapy			0.001
Comorbid co			0.001
COPD	25 (11.7)	402 (29.9)	<0.001
Chronic heart disease	41 (19.2)	281 (20.9)	0.56
Diabetes mellitus	41 (19.2)	274 (20.4)	0.68
Chronic renal failure	9 (4.2)	86 (6.4)	0.21
Chronic liver failure	10 (4.7)	108 (8)	0.08
Chronic cognitive deficit	0 (0)	54 (4)	0.003
Clinical features			
Temperature, mean (SD), °C	38.5 (1.5)	37.8 (1)	<0.001
Tachycardia (≥100 beats·min^{-1})	107 (53.5)	684 (56.1)	0.49
Tachypnea (≥30 breaths·min^{-1})	91 (46.2)	604 (50.6)	0.24
Headache	87 (40.7)	187 (13.9)	<0.001
Arthralgia/myalgia	92 (43)	224 (16.7)	<0.001
Cough	141 (66.2)	1187 (88.5)	<0.001
ALT (≥40 UI)	134 (65.7)	344 (27.5)	<0.001
Hypoalbuminemia (albumin <30 g/L)	124 (61.4)	644 (52.9)	0.02
Hyponatremia (sodium <130 mEq/L)	55 (26.7)	119 (10.4)	<0.001
Multilobar pneumonia	87 (40.4)	447 (33.2)	0.03
Pleural effusion	31 (14.6)	278 (20.7)	0.03
High-risk PSI classes‡	100 (46.9)	856 (63.8)	<0.001

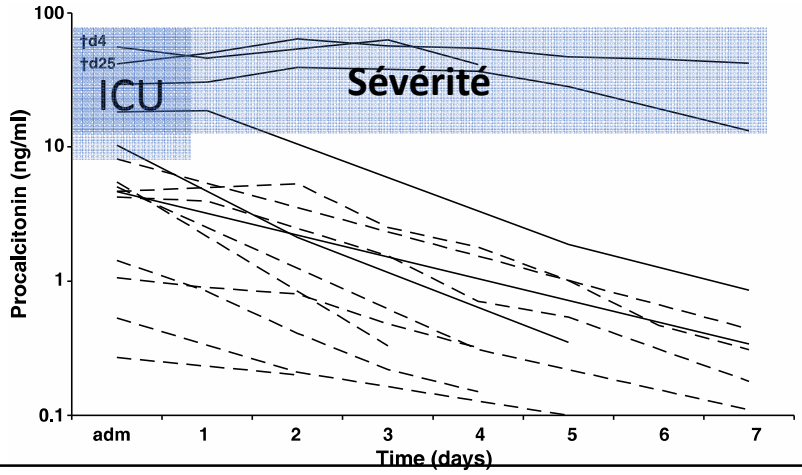
Des signes d'orientation mais rien d'absolu

ORIGINAL ARTICLE 10.1111/j.1469-0691.2009.02773.x

Procalcitonin kinetics in *Legionella pneumophila* pneumonia

C. P. C. de Jager[1], N. C. J. de Wit[2], G. Weers-Pothoff[3], T. van der Poll[4] and P. C. Wever[3]
1) Department of Emergency Medicine and Intensive Care, 2) Department of Clinical Chemistry & Haematology and 3) Department of Medical Microbiology and Infection Control, Jeroen Bosch Ziekenhuis, 's-Hertogenbosch and 4) Centre of Infection and Immunity Amsterdam and Centre of Experimental and Molecular Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

Clin Microbiol Infect 2009; **15:** 1020–1025



afssaps
Agence française de sécurité sanitaire des produits de santé

Traitement antibiotique de la légionellose chez l'adulte

Actualisation

Gravité de la légionellose / terrain sous-jacent	Choix antibiotique
Légionellose non grave : **Patient ambulatoire** **ou** **hospitalisé dans un service d'urgences** **ou en médecine**	**Monothérapie par Macrolide[1] :** Azithromycine[2] ou clarithromycine ou roxithromycine ou josamycine ou spiramycine ou érythromycine
Légionellose grave : **Patient hospitalisé dans un service de soins intensifs ou de réanimation,** **et/ou** **Patient immunodéprimé**	**Soit monothérapie par Fluoroquinolone[1] :** lévofloxacine ou ofloxacine ou ciprofloxacine
	Soit association[3] de 2 antibiotiques au sein des 3 familles d'antibiotiques suivantes : **- Macrolide disponible par voie IV[1] :** spiramycine ou érythromycine (en cas d'indisponibilité de la spiramycine) **- Fluoroquinolone[1,4] :** lévofloxacine ou ofloxacine ou ciprofloxacine **- Rifampicine**

Usage raisonné des Fluoroquinolones

Introduction

- Contexte : Les fluoroquinolones
  - Sont fréquemment prescrites
  - Participent à l'augmentation de la prévalence des bactéries multi-résistantes (BLSE, SARM, ….)
  - Sont associées à l'émergence de *C. difficile* (ribotype 027)
  - Sont associées à des effets indésirables
- Objectif de la mise au point : mieux les utiliser pour préserver leur efficacité

Mise au point Spilf 05/2015
http://www.infectiologie.com/fr/diaporamas-recommandations.html

Indication en premier choix
Après documentation et ATBgramme

- Infections ostéoarticulaires (ofloxacine-ciprofloxacine-levofloxacine)
- IU masculine (ofloxacine-ciprofloxacine-levofloxacine)
  - FQ à privilégier si active car diffusion prostatique
- Légionellose grave (levofloxacine)
- Typhoïde (ofloxacine-ciprofloxacine)
- Tuberculose multi-résistante (moxifloxacine)

Mise au point Spilf 05/2015
http://www.infectiologie.com/fr/diaporamas-recommandations.html

2. Quelles données microbiologiques et comment les utiliser pour un moindre usage des antibiotiques ?

- Dans la pneumonie aiguë communautaire de l'adulte :
  - ✓ Si l'antigénurie pneumocoque est positive, il faut stopper les antibiotiques prenant en compte les bactéries intracellulaires (*Accord faible*).
  - ✓ Si l'antigénurie légionelle est positive, il faut stopper la bêta-lactamine prescrite (*Accord faible*).
  - ✓ Si les deux sont négatives, il ne faut pas exclure le diagnostic de pneumopathie ni à pneumocoque (*Accord fort*) ni à légionelle (*Accord faible*).
- En cas d'hémoculture positive à cocci à Gram positif en amas, il faut utiliser des tests rapides permettant la détection de *S. aureus* et sa sensibilité à l'oxacilline (*Accord fort*).

Commentaire du comité des référentiels de la Spilf

- *Si hémocultures positives à BGN, il faut détecter les BLSE et les carbapénémases par des tests rapides.*

Macrolide ou quinolone ?

- Effet post antibiotique
- Très bonne diffusion pulmonaire
- Bonnes concentrations intracellulaires

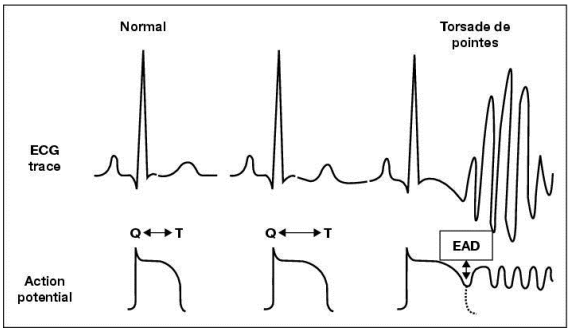
Pourquoi préférer les macrolides ?

- Choix historique…
- Biodisponibilité
- Nouveaux macrolides
  - Azithromycine (po en France)
  - Clarithromycine
  - Spiramycine IV et po
- Faible retentissement sur la flore digestive
- Coût 19 *vs* 27$

Mayaud JAC 1988

→ <0,1% du coût de l'hospitalisation

E.I. des macrolides



ansm
Agence nationale de sécurité du médicament et des produits de santé

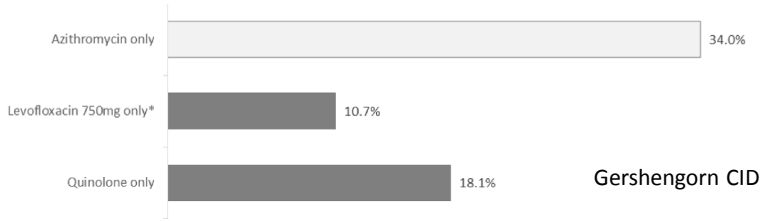
CYP	Principes actifs (substrats)	Inhibiteurs
3A4	• rivaroxaban, apixaban • inhibiteurs de la tyrosine kynase • pimozide • immunosuppresseurs* (ciclosporine, tacrolimus, sirolimus, everolimus, temsirolimus) • IPDE5 (sildénafil, tadalafil, vardénafil) • ergotamine, *dihydroergotamine* • amiodarone, disopyramide • midazolam, alprazolam, zolpidem, zopiclone • simvastatine, atorvastatine • vinca-alcaloïdes cytotoxiques, ifosfamide	• inhibiteurs de protéases boostés par ritonavir • cobicistat • antifongiques azolés (kétoconazole, itraconazole, fluconazole, posaconazole) • macrolides (érythromycine, clarithromycine, télithromycine, josamycine) • amiodarone • diltiazem, vérapamil • pamplemousse (jus ou fruit)

Pourquoi préférer les quinolones ?

- Moderne…
- Biodisponibilité IV / po
- Formes IV (levoflo oflo ciproflo)
- Peu d'EI (excepté Moxifloxacine)
- Large spectre

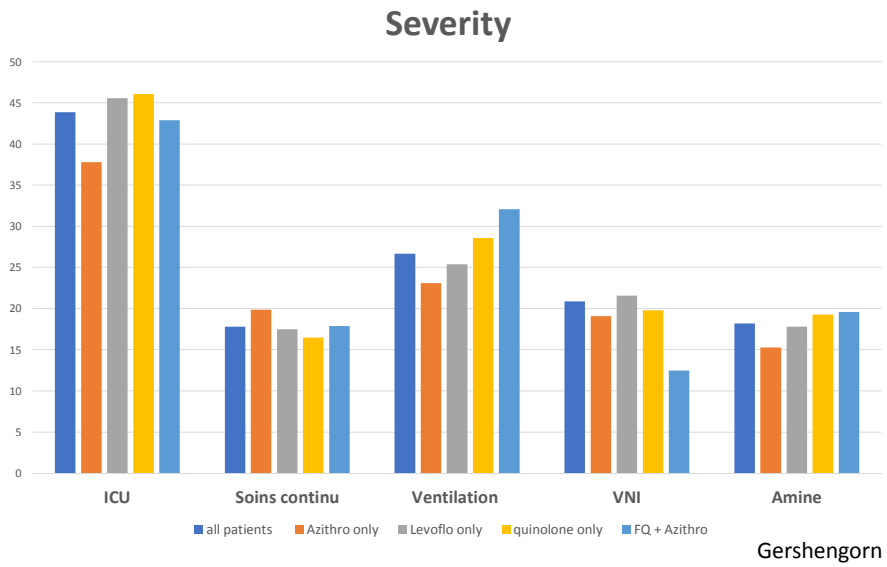
The Association of Antibiotic Treatment Regimen and Hospital Mortality in Patients Hospitalized with Legionella Pneumonia

- Analyse rétrospective de 3152 légionelloses (codage ICD)
  - Mortalité
  - Durée d'hospitalisation
  - Clostridium difficile
  - Coûts
- Analyse du sous-groupe les plus sévères (Réa, ventilation Mécanique, quartile de mortalité)



Gershengorn CID 2015

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



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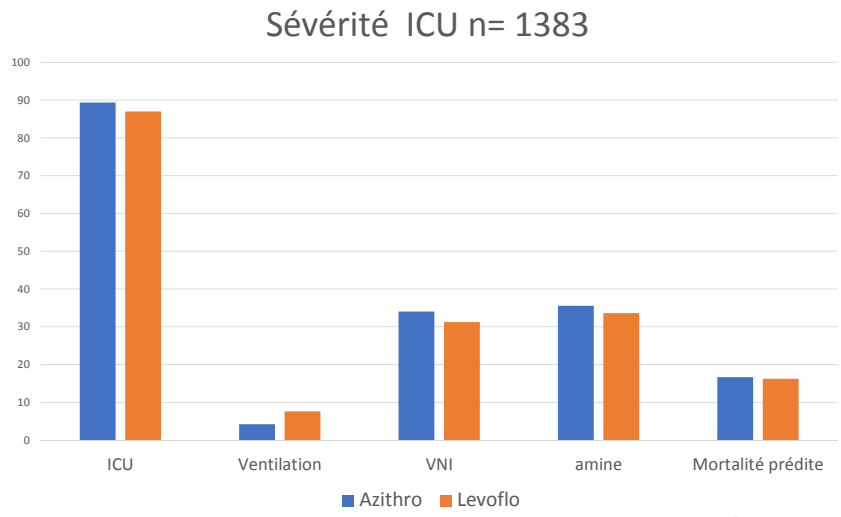

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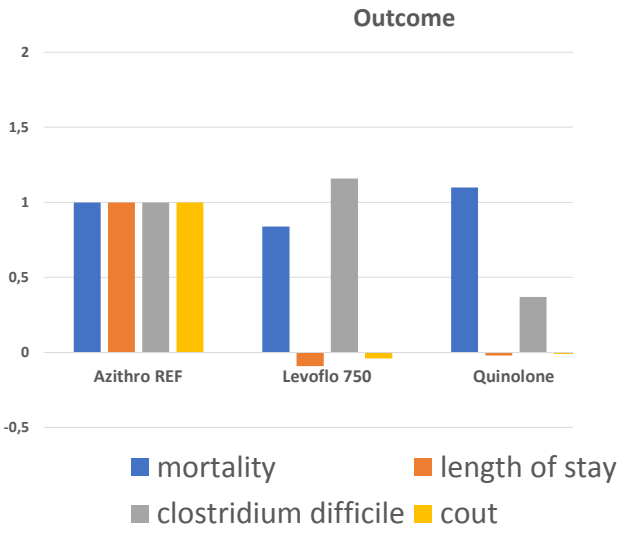

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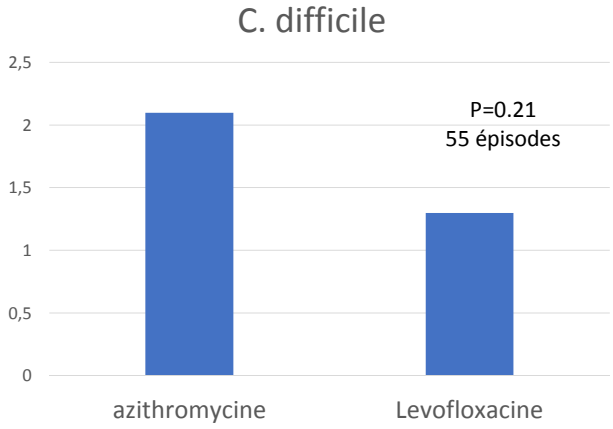
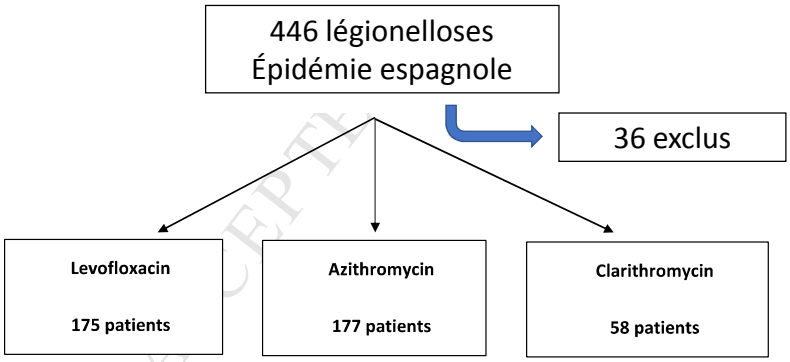


Gershengorn CID 2015

Levofloxacin versus azithromycin for treating legionella pneumonia: a propensity score analysis



Garcia-Vidal CMI 2017

	Levofloxacin (n=175) No. (%)	Azithromycin (n=177) No. (%)	*p*-value#	Clarithromycin (n=58) No. (%)	*p*-value*
				2000 à 2004	
Variable					
Male Sex	121 (69.1)	134 (75.7)	.168	41 (70.7)	.824
Age, mean (SD) years	59.8 (14.1)	63.3 (13.3)	**.019**	58.71 (14.4)	.598
Renal insufficiency	18 (10.3)	18 (10.2)	.971	13 (22.4)	**.018**
Respiratory failure	82 (59.9)	85 (48.0)	**.037**	23 (44.4)	**.013**
(PaO2/fiO2<300)ζ					
Multilobar pneumonia	59 (33.7)	25 (14.1)	**<.001**	12 (20.7)	.055
Pleural effusion	17 (9.7)	10 (5.7)	.152	2 (3.4)	.128
High-risk PSI classes&	77 (44)	63 (35.6)	.094	28 (48.3)	.641
Admission to the ICU	27 (15.4)	12 (6.8)	**.010**	8 (13.8)	.763

Garcia-Vidal CMI 2017

Analyse univariée

	Levofloxacin (n=175) No. (%)	Azithromycin (n=177) No. (%)	*p*-value#	Clarithromycin (n=58) No. (%)	*p*-value*
Time to defervescence (T≤37º), median days (IQR)	2 (1-4)	2 (1-3)	.453	2 (1-4)	.432
Time to achieve clinical stability, median days (IQR)	3 (2-5)	3 (2-5)	.486	4 (2-5)	.761
Length of iv antibiotic therapy	3 (2-5.25)	4 (3-6)	.058	5 (3-6.25)	**.002**
Length of hospital stay	7 (5-10)	6 (5-9)	.088	9 (7-14)	**.043**
Early mortality	1 (0.6)	2 (1.1)	.569	1 (1.7)	.410
Overall mortality (30 d)	4 (2.3)	9 (5.1)	.164	3 (5.17)	.264

Garcia-Vidal CMI 2017

Analyse de la mortalité

	Univariate analysis			Multivariate analysis			Multivariate analysis including treatment*		
	Unadjusted OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value	Adjusted OR	95% CI	*p*-value
Azithromycin versus Levofloxacin{	2.290	.692-7.580	.164	1.811	.526.6.234	.346	2.633	.409-16.97	.308

Analyse multivariée : seule l'**Immuno-dépression** est associée à la mortalité OR 10.2 p<0.0001

Garcia-Vidal CMI 2017

Levofloxacin versus azithromycin for treating legionella pneumonia: a propensity score analysis

In summary, no significant differences in time to defervescence, time to achieve clinical stability, length of intravenous therapy and length of hospital stay were found between patients treated with levofloxacin and those receiving azithromycin. The

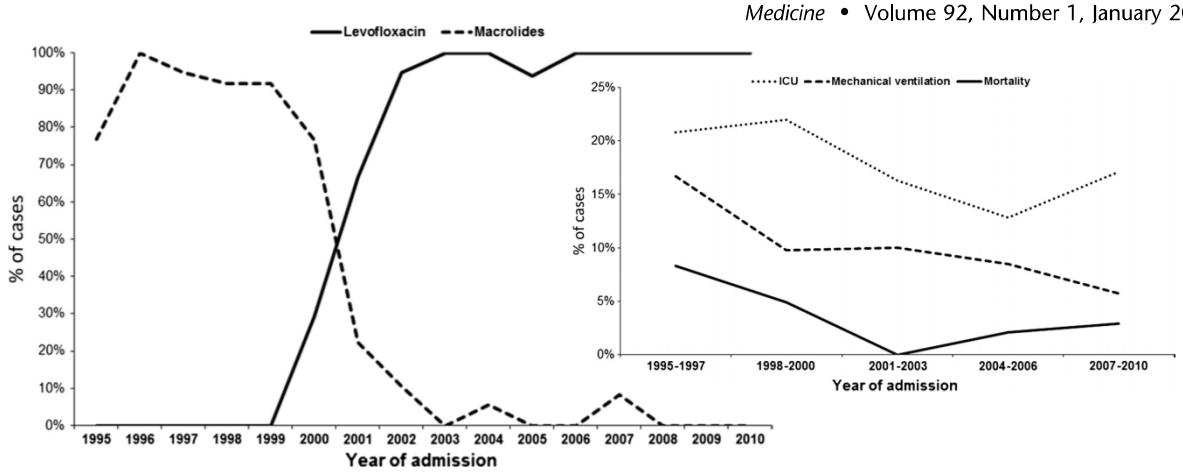
Garcia-Vidal CMI 2017

Community-Acquired *Legionella pneumophila* Pneumonia

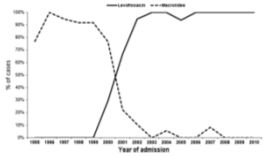
A Single-Center Experience With 214 Hospitalized Sporadic Cases Over 15 Years

Diego Viasus, MD, PhD, Silvana Di Yacovo, MD, Carolina Garcia-Vidal, MD, PhD, Ricard Verdaguer, MD, Frederic Manresa, MD, PhD, Jordi Dorca, MD, PhD, Francesc Gudiol, MD, PhD, and Jordi Carratalà, MD, PhD

Medicine • Volume 92, Number 1, January 2013



Characteristic	Nonsevere *L. pneumophila* Pneumonia (n=173)*	Severe *L. pneumophila* Pneumonia (n=41)*	P	OR (95% CI)
Age, mean ± SD, yr	58.6 (13.3)	56.3 (15.8)	0.33	0.47 (0.16–1.30)
Male sex	134 (77.5)	30 (73.2)	0.56	2.28 (0.88–5.88)
Current/former smoker	122 (70.5)	33 (82.5)	0.12	2.96 (1.01–8.62)
Alcohol abuse	65 (37.6)	19 (46.3)	0.30	0.82 (0.33–2.01)
Comorbid conditions	97 (56.1)	22 (53.7)	0.78	0.66 (0.27–1.61)
Tachypnea	58 (36.7)	33 (84.6)	<0.001	
Altered mental status	20 (11.6)	16 (39)	<0.001	
Septic shock at presentation	1 (0.6)	4 (9.8)	<0.001	
Multilobar pneumonia	62 (35.8)	25 (61)	0.003	
Respiratory failure	98 (56.6)	33 (80.5)	0.005	
Hyponatremia	43 (25.9)	12 (30)	0.59	
Hypoalbuminemia	94 (57.3)	30 (78.9)	0.01	
High-risk PSI classes†	68 (39.5)	32 (78)	<0.001	9.10 (3.52–23.4)
Macrolide use during admission	62 (35.8)	23 (56.1)	0.01	2.40 (1.03–5.56)
Levofloxacin use during admission	105 (60.7)	20 (48.8)	0.16	
Inappropriate antibiotic therapy	16 (9.2)	8 (19.5)	0.06	2.97 (1.01–8.74)



PAC + sévères avant 2000 ?

Viasus Medicine 2013

Intensive Care Med (2010) 36:612–620
DOI 10.1007/s00134-009-1730-y

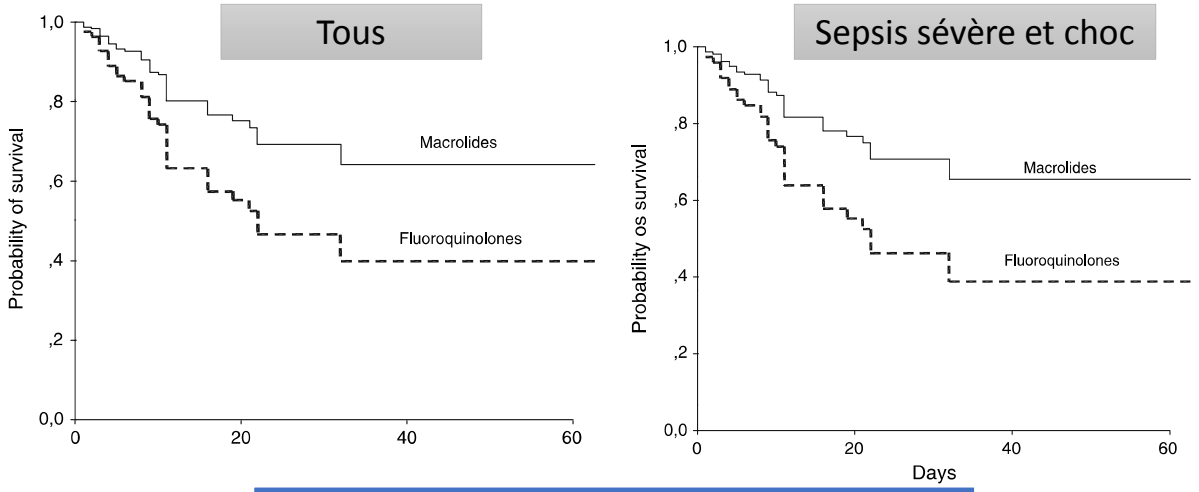
ORIGINAL

I. Martin-Loeches
T. Lisboa
A. Rodriguez
C. Putensen
D. Annane
J. Garnacho-Montero
M. I. Restrepo
J. Rello

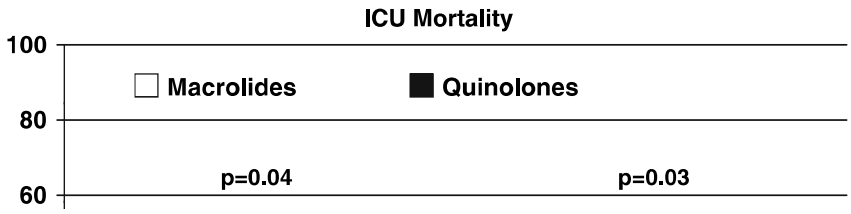
Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia

	Survivors (n = 137)	Non-survivors (n = 81)	P valu
Age mean years (SD)	58.6 (16.1)	63.4 (16.7)	0.03
Male gender, n (%)	97 (71.3%)	52 (63.4%)	0.22
Mean SAPS II score (SD)	45. 6 (15.5)	50.8 (17.5)	0.02
Mean SOFA score (SD)	7.4 (3.7)	8.3 (3.6)	0.16
Preexisting comorbid conditions			
COPD, n (%)	28 (20.6%)	12 (14.6%)	0.36
Diabetes, n (%)	17 (12.5%)	16 (19.5%)	0.17
Cardiomyopathy, n (%)	29 (21.3%)	24 (29.3%)	0.19
Cirrhosis, n (%)	5 (3.6%)	6 (7.4%)	0.33
Chronic renal failure, n (%)	8 (5.9%)	10 (12.%)	0.08
Alcohol, n (%)	22 (16.2%)	10 (12.2%)	0.55
Bacteremia, n (%)	12 (12.4%)	8 (13.3%)	0.99
IDSA/ATS compliant, n (%)	63 (46.3%)	37 (45.1%)	0.88
Macrolides, n (%)	34 (54.0%)	12 (32.4%)	0.05
Quinolones, n (%)	29 (46.0%)	25 (67.6%)	0.04

Martin-Loeches ICM 2009



Immuno-déprimés exclus



	Overall (n = 102)	Patients with sepsis (n = 17)	Patient with shock/severe sepsis (n = 85)	P value
S. pneumoniae	33 (32.3%)	2 (5.9%)	31 (16.8%)	0.12
S. aureus	24 (23.5%)[a]	5 (11.8%)[a]	19 (10.3%)	0.76
H. influenza/M. catarrhalis	12 (11.7%)	5 (11.8%)	7 (3.8%)	0.73
P. aeruginosa	11 (10.8%)	2 (5.9%)	9 (4.9%)	0.68
Enterobacteriacea	13 (12.7%)	2 (5.9%)	11 (6.0%)	0.99
L. pneumophila	3 (2.9%)	–	3 (1.6%)	1
Miscellaneous[b]	6 (5.8%)	1 (7.7%)	5 (5.1%)	0.33
Overall	102	17 (16.7%)	85 (83.3%)	0.71

First author	Cohort	Site	Outcome	Country	Study design
Gleason [29]	Elderly patients (≥65 years) with CAP	Ward	Lower 30-day mortality with β-lactam plus macrolide	USA	Multicentre retrospective
Waterer [22]	Pneumococcal bacteremia	Ward	Lower hospital mortality with combination	USA	Multicentre retrospective
Brown [28]	CAP	Ward	Lower 30-day mortality with β-lactam plus macrolide	USA	Multicentre retrospective
Martinez [21]	Pneumococcal bacteremia	Ward	Lower in-hospital mortality with β-lactam plus macrolide	Spain	Monocentre retrospective
Baddour [20]	Pneumococcal bacteremia	Ward and ICU	Lower 14-day mortality with combination	International	Multicentre prospective
Rodriguez [4]	CAP	ICU	Lower 28-day mortality with combination	Spain	Multicentre prospective
Mortensen [31]	CAP	Ward and ICU	Lower 30-day mortality with β-lactam plus other than FQ	USA	Multicentre retrospective
Metersky [30]	Pneumococcal bacteremia	Ward	Lower 30-day mortality with β-lactam plus macrolide	USA	Multicentre retrospective
Restrepo [6]	Severe sepsis pneumonia	Ward and ICU	Lower 30- and 90-day mortality with combination plus macrolide	USA	Multicentre retrospective
Tessmer [23]	CAP	Ward	Lower 14- and 30-day mortality with β-lactam plus macrolide	Germany	Multicentre prospective
Martín-Loeches	Intubated CAP	ICU	Lower ICU mortality IDSA/ATS combination with macrolide	Europe	Multicentre prospective

Que conclure … ?

Azithro et **Levoflox** →
Activités in vitro et intracellulaire comparables

Que conclure … ?

- Azithro et Levoflox → Activités in vitro et intracellulaire comparables
- ***British Thoracic society***
  - → **FQ** si sévère ou « life threatening »
  - IV jusqu'à réponse clinique
- ***IDSA***
  - « Dose importante »: Levoflo 750mg/j / Azithro 500mg/j
- **Durée**: Azithro 500mg/j 3-5 j - Levoflo 750mg 5-10j
- **Association:**
- Plus longtemps chez immuno-déprimé… combien ???
- **Transplanté** → interactions avec cyt P 450 **FQ, doxycycline, Azithro**

Résistance au traitement ?

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Advance Access publication 4 June 2014

Isolation of ciprofloxacin-resistant *Legionella pneumophila* in a patient with severe pneumonia

Jacob P. Bruin[1]*, Tetyana Koshkolda[2], Ed P. F. IJzerman[1], Christian Lück[2], Bram M. W. Diederen[1], Jeroen W. Den Boer[1] and Johan W. Mouton[3]

1. Echec de traitement par cefazoline + genta
2. Legionelle sur LBA après 4j de Ciprofloxacine
3. Amélioration clinique
4. **Puis** clarythromycine

70% des légionelloses guérissent sans traitement…

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Letter to the Editor

Imipenem therapy for Legionnaires' disease

To the Editor:

Nishzuka and colleagues report that imipenem therapy was successful for the treatment of *Legionella pneumophila* serogroup 12 pneumonia because the patient improved while being treated with doripenem and imipenem/cilastatin [1]. Their conclusion is not warranted. It is well established that the majority of patients recover from Legionnaires' disease without being given specific therapy, with at least 70% of such patients recovering completely [2,3]. Untreated immunosuppressed and elderly patients can have much higher fatality rates, as high as 70%, but this still leaves open the possibility that even in this group of patients cure without specific therapy can occur. Illness can be prolonged in those patients who are not treated specifically for the disease, with some patients recovering suddenly after several days of fever. Thus attributing successful therapy to imipenem/cilastain in this case is not warranted. Imipenem/cilastatin therapy is inactive in animal model studies of Legionnaires' disease, and in high quality studies of intracellular infection [4,5]. Simply showing that imipenem/cilastatin has good *in vitro* extracellular activity for *L. pneumophila* is irrelevant because many drugs with excellent *in vitro* activity against the bacterium have no clinical efficacy for the disease. Neither this drug, nor any beta-lactam drug, should ever be knowingly given as therapy for Legionnaires' disease.

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Agence française de sécurité sanitaire des produits de santé

Traitement antibiotique de la légionellose chez l'adulte

Actualisation

Gravité de la légionellose / terrain sous-jacent	Choix antibiotique
Légionellose non grave : **Patient ambulatoire** **ou** **hospitalisé dans un service d'urgences** **ou en médecine**	**Monothérapie par Macrolide[1] :** Azithromycine[2] ou clarithromycine ou roxithromycine ou josamycine ou spiramycine ou érythromycine
Légionellose grave : **Patient hospitalisé dans un service de soins intensifs ou de réanimation,** **et/ou** **Patient immunodéprimé**	**Soit monothérapie par Fluoroquinolone[1] :** lévofloxacine ou ofloxacine ou ciprofloxacine
	Soit association[3] de 2 antibiotiques au sein des 3 familles d'antibiotiques suivantes : **- Macrolide disponible par voie IV[1] :** spiramycine ~~ou érythromycine~~ (en cas d'indisponibilité de la spiramycine) **- Fluoroquinolone[1,4] :** lévofloxacine ou ofloxacine ou ciprofloxacine **- Rifampicine**

Niveau de preuve peu convaincant