Macrolides in patients with severe CAP

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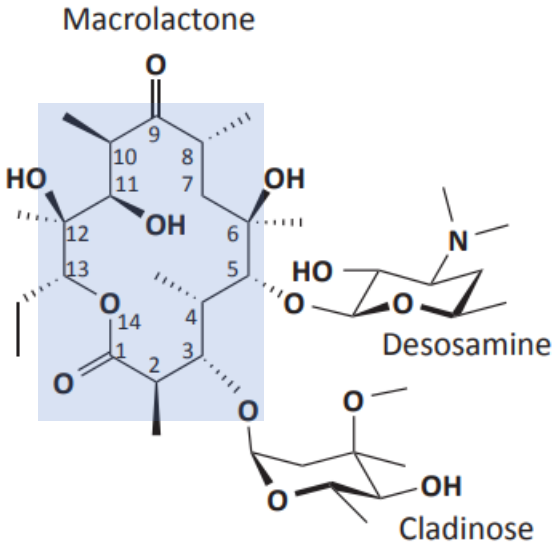
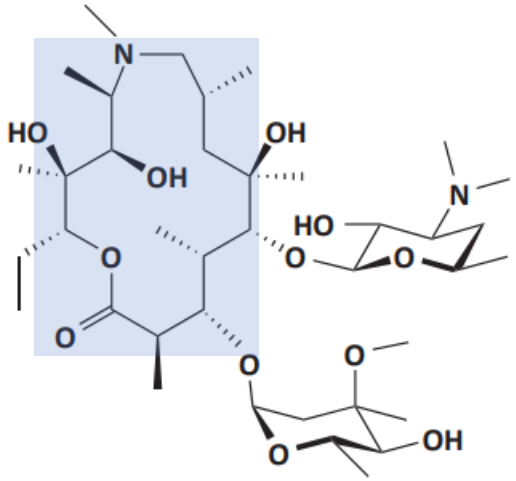
Contents

Macrolides

- Erythromycin A: isolated from *Streptomyces* in 1949, approved in 1952
- Macrolide: macrocyclic lactone ring ≥12 atoms



Erythromycin (ERY)



Azithromycin (AZI)

MACROLIDES

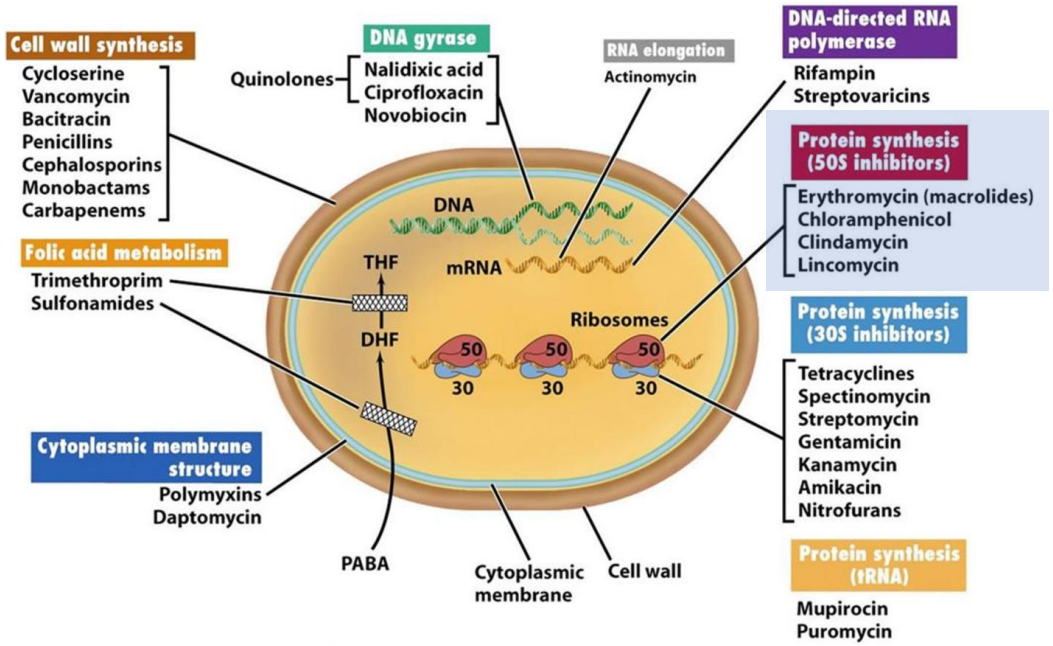
13-Membered Ring	14-Membered Ring		15-Membered Ring	16-Membered Ring	
semisynthetic	natural	semisynthetic	semisynthetic	natural	semisynthetic
Tulathromycin (10%)	Erythromycin Oleanthromycin	Clarithromycin Roxithromycin Dirithromycin Fluorithromycin	Azithromycin Tulathromycin (90%)	Spiramycin Tylamycin Josamycin Midecamycin	Tilmicosin Miokamycin Rokitamycin

Antibiotic Macrolides		Non Antibiotic Macrolides	Toxic Macrolides
US FDA-approved	Non US FDA-approved		
-Azithromycin	-Carbomycin A	-Tacrolimus	-Mycolactones
-Clarithromycin	-Josamycin	-Pimecrolimus	
-Dirithromycin	-Kitamycin	-Sirolimus	
-Erythromycin	-Midecamycin/		
-Roxithromycin	midecamycin acetate		
-Telithromycin	-Oleandomycin		
	-Solithromycin		
	-Spiramycin (approved in Europe and other countries)		
	-Troleandomycin (used in Italy and Turkey)		
	-Tylosin/Tylocine (used in animals)		

Trends Biochem Sci. 2018 Sep;43(9):668-684.
Eur J Clin Pharmacol. 2012 May;68(5):479-503.

Mechanism of macrolide antibiotic action

- Macrolide antibiotic
  - inhibit bacterial protein synthesis by binding to the 50S subunit
  - against gram (+) bacteria, *S. pneumoniae* and *H. influenzae,* atypical pathogens

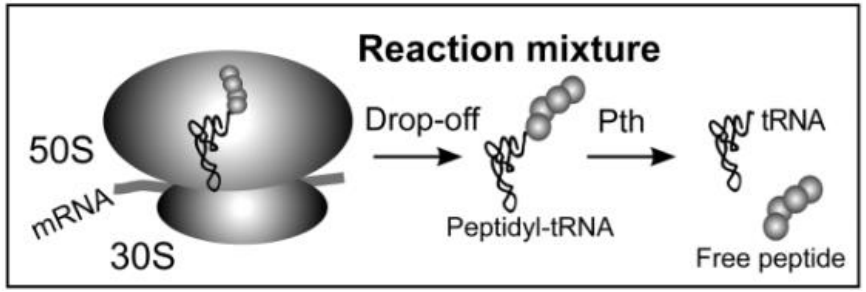


Subunits of ribosome: small (30S), large (50S)

- 30S: decoding the genetic information encoded in mRNAs
- **50S: polymerizing amino acids into proteins**

Macrolide binds to the 50S

- 1. preventing peptidyl-transferase from adding the peptidyl attached to tRNA to the next amino acid or **inhibiting ribosomal translocation**
- 2. premature dissociation of the peptidyl-tRNA from ribosomes

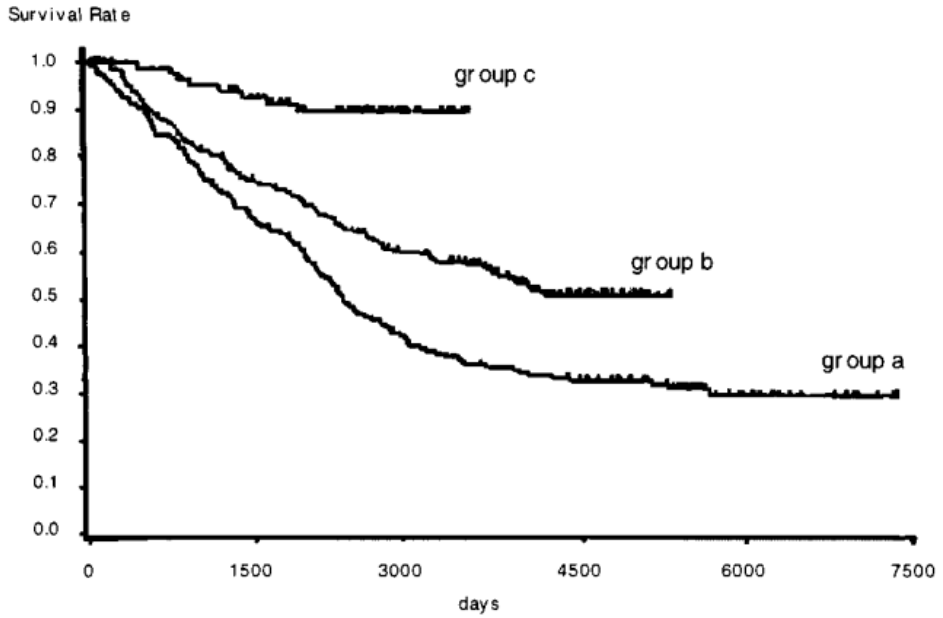


J. Mol. Biol. (2003) 330, 1005–1014

Immunomodulatory effects of macrolide

- in 1987 when Kudoh et al.
  - in patients with DPB, erythromycin decrease symptoms and an increase in life expectancy
- increase in 10-year survival: <40% in 1970s → >90%

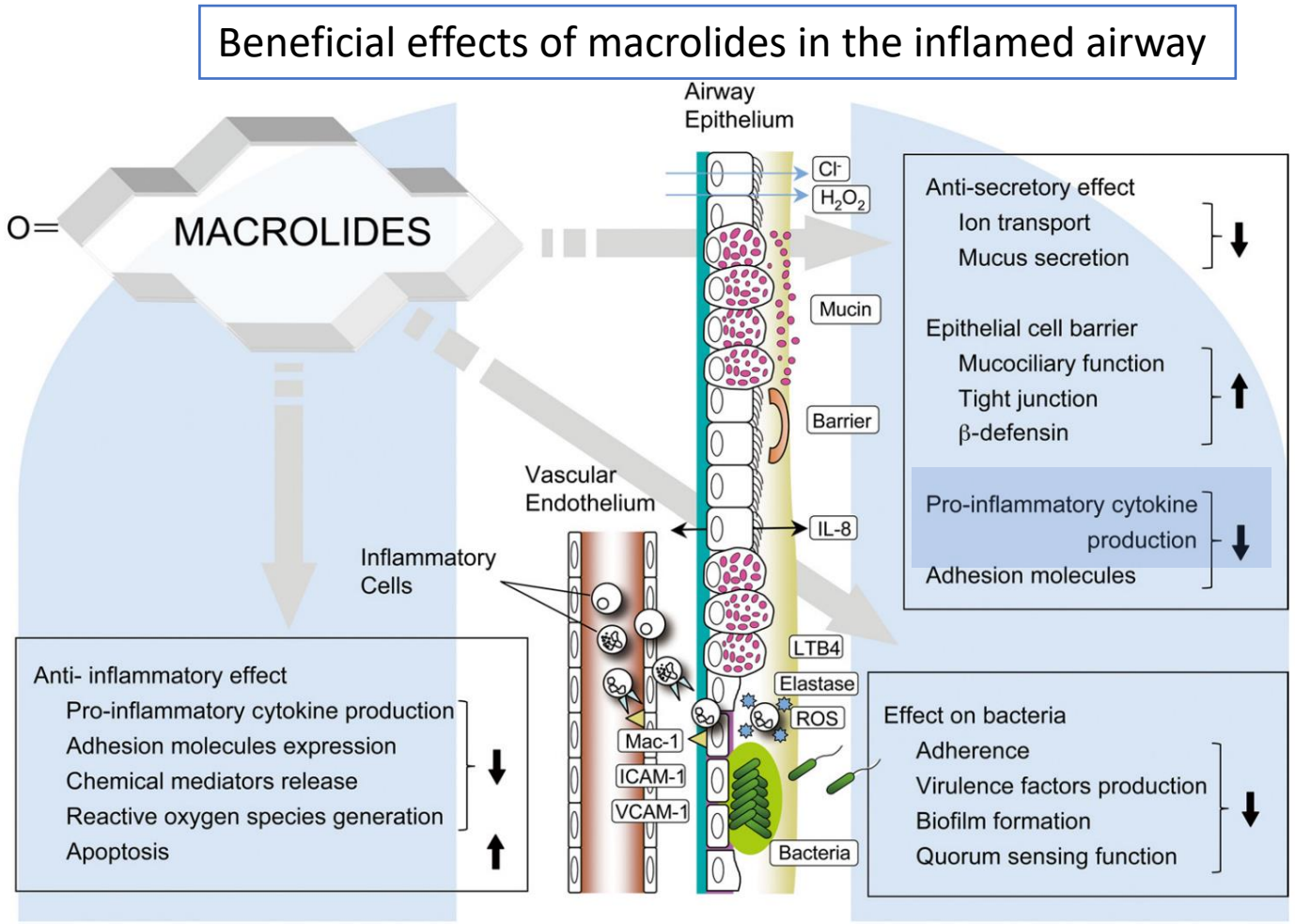
- DPB (n=498)
  - Group a (n=190): 1970–1979
  - Group b (n=221): 1980–1984, Quinolone
  - Group c (n=87): 1985–1990, Quinolone + EM



Unknown anti-inflammatory effect of erythromycin?
1. serum levels of erythromycin in DPB patients were well below MIC for the detected pathogens
2. lack of susceptibility of most Gram-negative organisms to erythromycin

Am J Respir Crit Care Med. 1998 Jun;157(6 Pt 1):1829-32

Effects of macrolide

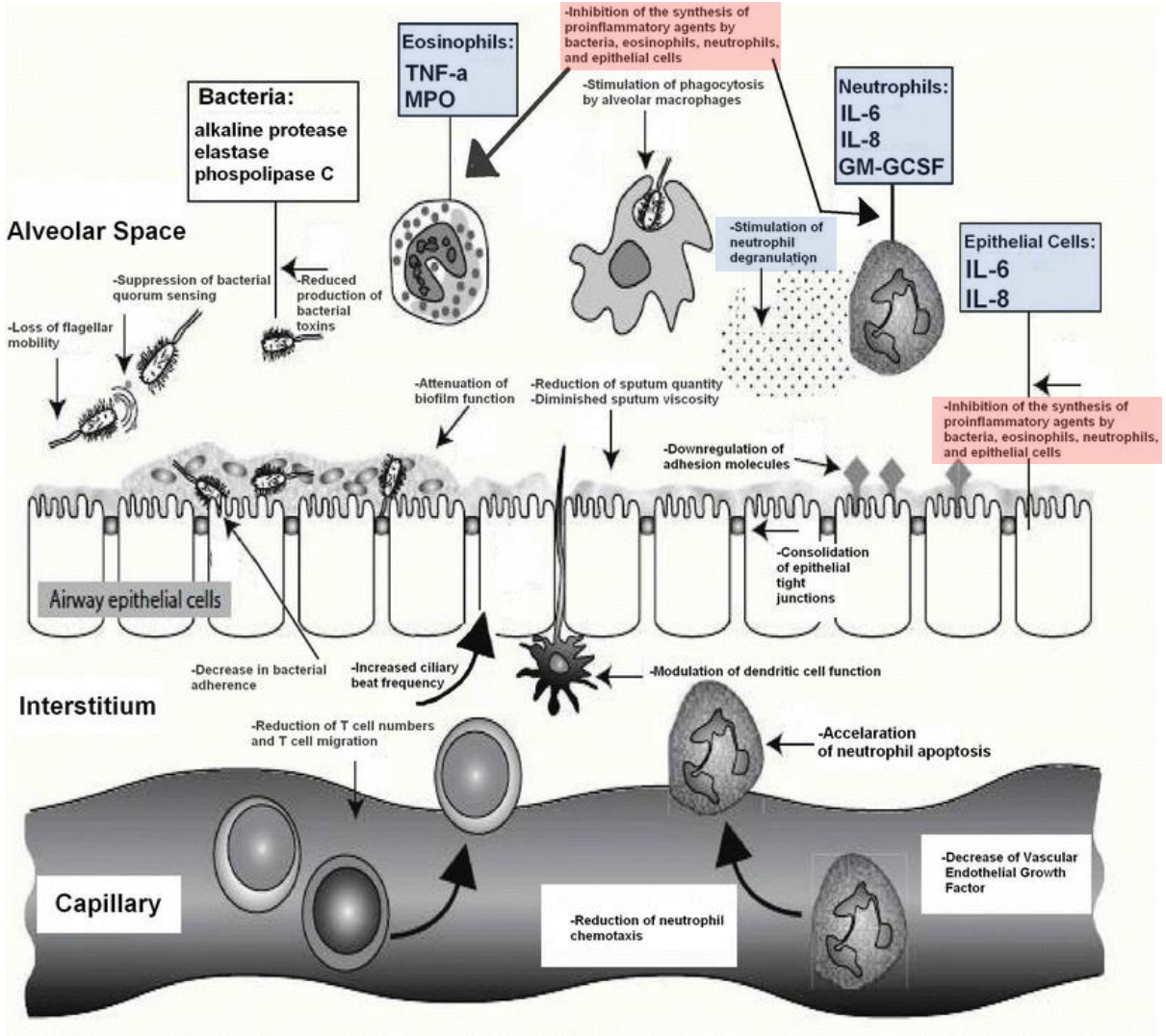


- Chronically inflamed airway
  - epithelial cell damage
  - infiltration of inflammatory cells
  - goblet cell hyperplasia
  - Hypersecretion
  - mucociliary dysfunction
  - recurrent airway infection

- Macrolides: inflammation and cellular damage↓

Clin Microbiol Rev. 2010 Jul;23(3):590-615.

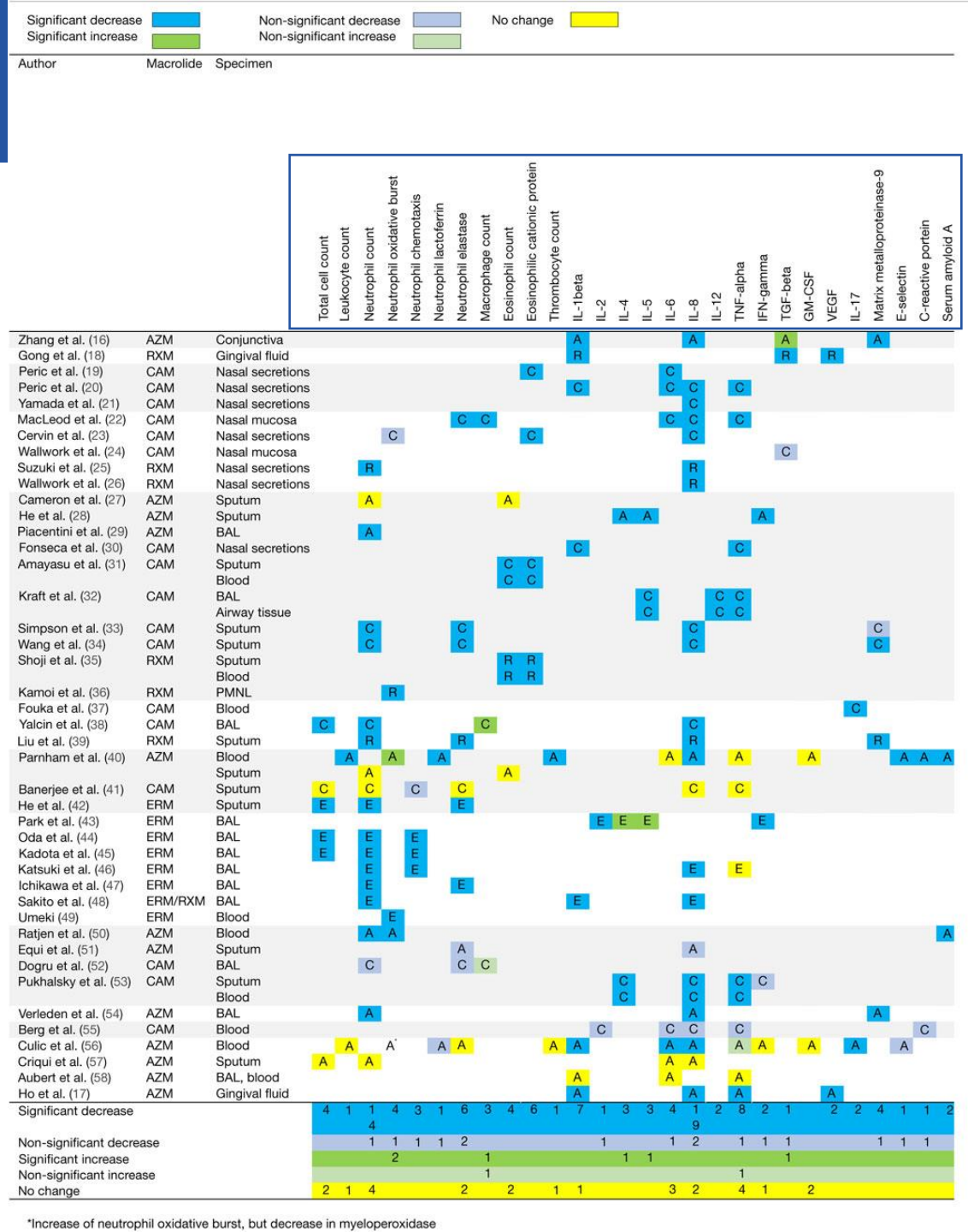
Immunomodulatory and antibacterial effect



Target	Effects
Mucus production and rheological properties	Decrease volume/secretion; increase mucociliary clearance, elasticity and ciliary motility
Bronchial hyper-responsiveness	Decreased bronchial hyper-responsiveness/endothelin-1; inhibition of bronchial muscle contraction
Epithelial damage and bioactive phospholipids	Protection against reactive oxygen species; protection of the respiratory ciliated epithelium
Adhesion	
Molecules	Reduction of the expression of ICAM-1, sICAM-1, e-selectin, β-2-integrins (CD11b/CD18), VCAM-1, LFA3, Mac-1, beta-2-integrins (CD11b/CD18)
Bacterial	Decrease in bacterial adhesion to the epithelium
Cytokines/chemokines	Suppression of IL-1b/NTF in monocytes; suppression of IL-1b,IL-4, IL-5, IL-6, IL-8, IFN-γ, PGF1a, PGE2, NTFa, GM-CSF in mast cells; no changes in IL-2 and LTB4; suppression of IL-8, ENA78, MIP-1 in macrophages and leucocytes; inhibition of eotaxin and GM-CSF; decrease in CCL-2 and CX
T cells	Dose-dependent inhibition of the production of IL-4, IL-5, IL-10, IL-13
Production of oxidising species	Increase/decrease of NO release via cNOS/iNOS; decrease in NADPH oxidase and nitroso-synthase
Polymorphonuclear cells	Inhibition of neutrophil elastase/anions; stabilisation of cell degranulation; accelerated neutrophil apoptosis due to increased cAMP
Signal protein	Decrease in VEGF; increase in EGF
Enzymes	Reduction in glutathione S-transferase (GST) activity
Effects on *Pseudomonas aeruginosa*	Reduction in bacterial adhesion to the epithelium; altered virulence factors: decreased biofilm production and reduced mobility; altered quorum sensing system: reduced transcription of implicated genes (Iasl and rhlR); decreased expression of stress proteins (Gro-ELK)
Plasma antibodies	No effects in BPI-Anca
Cell junctions	Increased expression of molecules for tight junctions, claudins, occludins, JAM
Membrane transporters	Increased expression of MPR1 and MDR1
Intracellular signaling metabolic pathways	Altered protein kinase pathway (MAPK): JNK
Nuclear transcription factors and gene regulation pathways	Changes in NF-I-B and AP-1 DNA junctions and promoters for proinflammatory cytokine genes; inhibition of the expression of genes coding for mucoid proteins via ERK

Respiration 2011;81:67–74

Immunologic markers



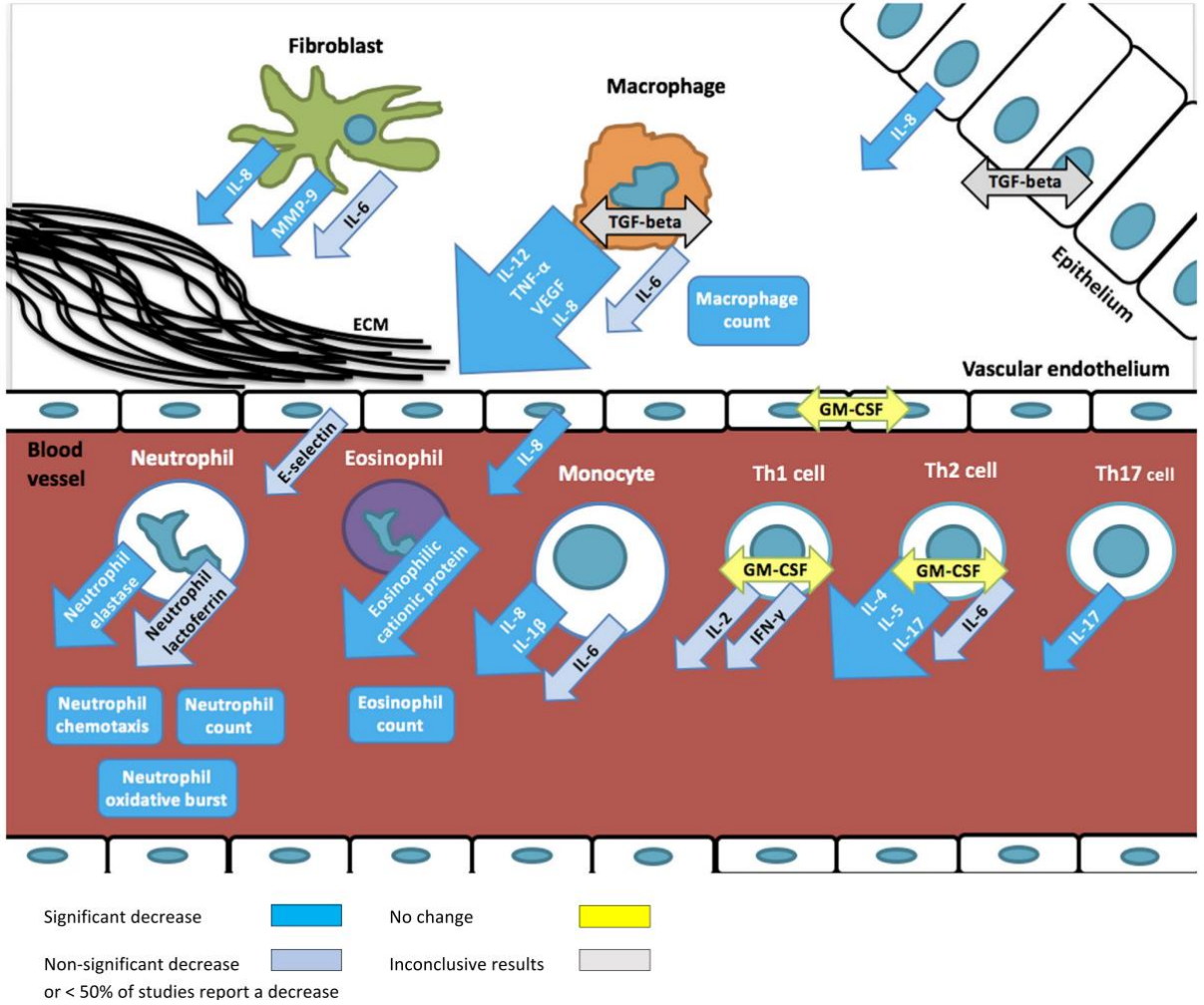
*Increase of neutrophil oxidative burst, but decrease in myeloperoxidase

- A systematic review
- 1946 to 2016, 45 studies in humans
- macrolides and immunological markers
- 47 immunological markers, 186 measurements

- Decrease in
  - **IL-8 (n = 21)**
  - neutrophil count (n = 15)
  - TNF-alpha (n = 9)
  - neutrophil elastase (n = 8)
  - IL-1 beta (n = 7)
  - eosinophilic cationic protein (ECP, n = 6)
  - **IL-6 (n = 5)**
  - matrix metalloproteinase 9 (MMP-9) (n= 5)
  - oxidative burst activity (n = 5)

Front Immunol. 2018 Mar 13;9:302.

Immunomodulatory effects of macrolides



- Cytokine and Chemokine Response
  - Proinflammatory cytokines
    - IL-1, IL-2, IL-4, **IL-6**, IFN-r, TNF-a, GM-CSF, chemokines (**IL-8** and RANTES)
  - Anti-inflammatory cytokines
    - **IL-10**, prostaglandins, TGF-b

- Macrolides
  - proinflammatory cytokines↓
  - antiinflammatory cytokines ↑

Front Immunol. 2018 Mar 13;9:302.

Immunomodulatory effects of macrolides

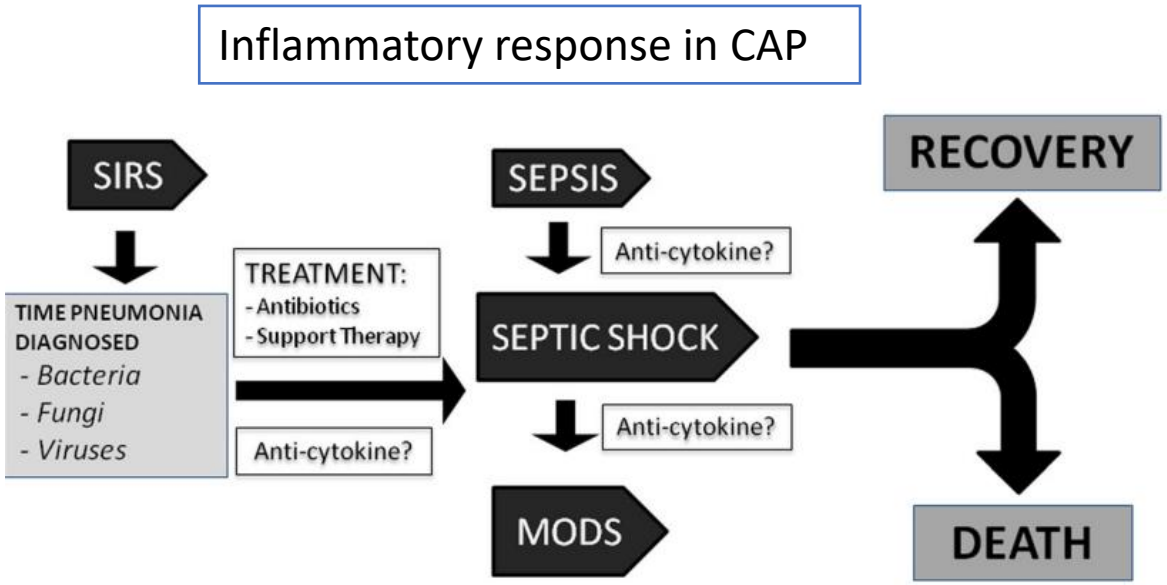
TABLE 4 | Number of measurements and changes in immunological markers for each macrolide.

	Decrease/ non-significant decrease	Increase/ non-significant increase	No change	Total
AZM	33/4	10/1	21	69
CAM	52/12	1/2	6	73
ERM	21/0	4/1	1	27
RXM	17/0	0/0	0	17
Total	123/16	15/4	28	186

AZM: compared to any of the other macrolides, no influence on the immunological markers investigated ↑

Front Immunol. 2018 Mar 13;9:302.

Inflammatory response in CAP



Etiology of CAP	Relevant cytokines and biomarkers	Potential anti-cytokine treatment
Bacterial CAP	IL-6, TNF-α, IL-10, ProADM, TREM-1, NGAL, MMP's	Systemic corticosteroids Macrolides
Viral CAP	IL-6, IL-8, IL-17, TGF-β, RAGE, IFN-β, IgM, NF-κB, GM-CSF	Macrolides/linezolid Statins NF-κB inhibitor acetylsalicylic acid (mice) Anti-IL-17 antibodies (mice)

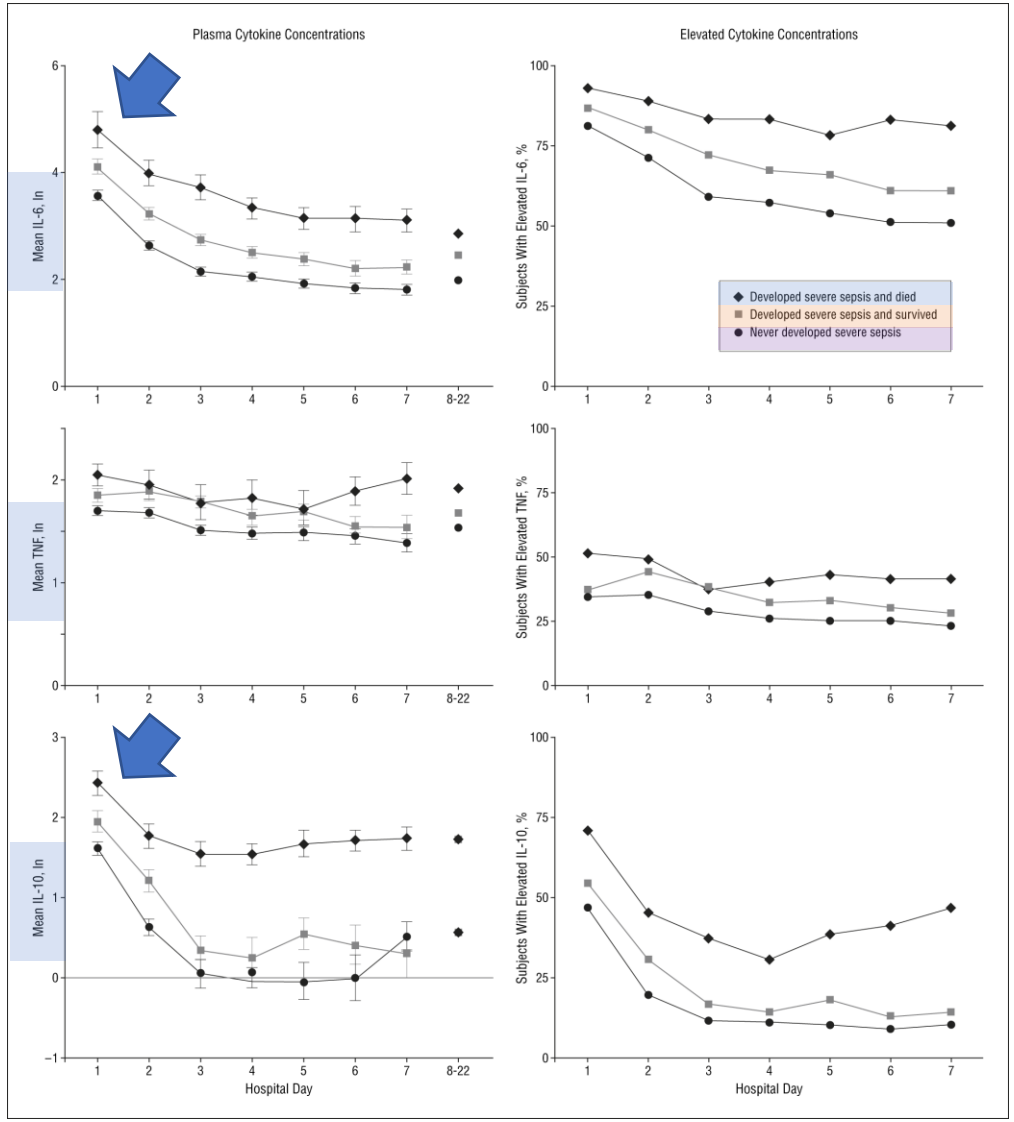
Macrolides
↓proinflammatory cytokines (TNF-α, IL-1, IL-6, IL-8, TGF-β)
↑anti-inflammatory cytokines (IL-10)

Curr Infect Dis Rep. 2016 Mar;18(3):10.

Cytokine levels during CAP

- hospitalized CAP via ED (n=1886)
- severe sepsis: SOFA≥3, n=583 (31%)
- plasma TNF, IL-6, IL-10 levels
  - daily for the first week and weekly thereafter

- In the ED, cytokine concentrations had already peaked
- high levels of both proinflammatory and anti-inflammatory cytokines → risk of severe sepsis and death↑



Arch Intern Med. 2007 Aug 13-27;167(15):1655-63.

Effects of macrolides on cytokine secretion *in vivo*

- A literature review: Effects of macrolides on cytokine production during CAP
- ~August 2011, 27 studies

Pathogen/stimulation	Model	Macrolide	Influence on cytokine secretion	No influence on cytokine secretion
S. pneumoniae	murine	HMR 3004	↓ IL-6	—
S. pneumoniae, macrolide resistant	murine	RXM	↓ KC, ↑ MCP-1	IL-1β, TNF-α
S. pneumoniae, killed	murine	HMR 3004	↓ IL-1β, IL-6	TNF-α
M. pneumoniae	murine	CLR	↓ IL-6, TNF-α, IFN-γ, KC, MCP-1, MIP-1α	IL-10
M. pneumoniae	murine	CLR	↓ IL-12 p40, KC, MCP-1, RANTES	IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-12 p70, IL-13, IL-17, TNF-α, IFN-γ, MIP-1α, MIP-1β, G-CSF, GM-CSF, PDGF, VEGF, eotaxin
M. pneumoniae	murine	AZM	↓ IL-12, TNF-α, KC, MCP-1, MIP-1α	IL-1β, IL-2, IL-4, IL-6, IL-10, IFN-γ, GM-CSF
M. pneumoniae	murine	CET	↓ IL-1β, IL-12, TNF-α, IFN-γ, KC, MCP-1, MIP-1α	IL-2, IL-4, GM-CSF
M. pneumoniae, killed	murine	CLR	↑ IL-6	IL-10, TNF-α, IFN-γ, KC, MCP-1, MIP-1α
Mycoplasma extract	murine	CLR	↑ IL-6, TNF-α, MCP-1, MIP-1α RANTES	IL-17, IL-23, KC
H. influenzae, macrolide resistant	murine	CLR	↓ IL-1β, MIP-2	—
LPS	murine	TEL	↓ TNF-α, MIP-2	—
Unknown	human	CLR	↓ IL-6, ↑ IL-10, IFN-γ	—

Macrolides can modulate cytokine production during CAP
Macrolides have immunomodulatory activities independent of their direct antibacterial effects

J Antimicrob Chemother. 2012 Mar;67(3):530-40.

1993 ATS Guidelines

HOSPITALIZED PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA*†

Organisms
- *S. pneumoniae*
- *H. influenzae*
- Polymicrobial (including anaerobic bacteria)
- Aerobic gram-negative bacilli
- *Legionella* sp.
- *S. aureus*
- *C. pneumoniae*
- Respiratory viruses
- Miscellaneous
  - *M. pneumoniae*, *Moraxella catarrhalis*, *M. tuberculosis*, endemic fungi

Therapy
- Second- or third-generation cephalosporin‡

OR
- Beta-lactam/beta-lactamase inhibitor

±
- Macrolide§

SEVERE HOSPITALIZED COMMUNITY-ACQUIRED PNEUMONIA*†

Organisms
- *S. pneumoniae*
- *Legionella* sp.
- Aerobic gram-negative bacilli
- *M. pneumoniae*
- Respiratory viruses
- Miscellaneous
  - *H. influenzae*, *M. tuberculosis*
  - Endemic fungi

Therapy
- Macrolide‡

PLUS
- Third-generation cephalosporin with anti-*Pseudomonas* activity§

OR
- Other antipseudomonal agents such as imipenem/cilastatin, ciprofloxacin

Although there is not a universally accepted definition of severe community-acquired pneumonia, the presence of at least one of the following conditions justifies defining the pneumonia as severe:

1. Respiratory frequency > 30 breaths min at admission.
2. Severe respiratory failure defined by a Pa_{O_2}/FI_{O_2} ratio < 250 mm Hg.
3. Requirement for mechanical ventilation.
4. Chest radiograph showing bilateral involvement or involvement of multiple lobes. In addition, an increase in the size of the opacity by 50% or greater within 48 h of admission is indicative of severe pneumonia.
5. Shock (systolic blood pressure below 90 mm Hg or diastolic blood pressure below 60 mm Hg) (35).
6. Requirement for vasopressors for more than 4 h.
7. Urine output lower than 20 ml/h, or total urine output lower than 80 ml in 4 h, unless another explanation is available (39), or acute renal failure requiring dialysis.

If severe pneumonia is identified, expectant admission to the intensive care unit should be considered.

Am Rev Respir Dis. 1993 Nov;148(5):1418-26.

Severe CAP

- October 1996 ~ December 1997
- hospitalized CAP (n=395)
- severe CAP (n=64): ICU admission

OVERVIEW OF 10 SEVERITY CRITERIA FOR THE ASSESSMENT OF SEVERE CAP

Baseline ("minor") criteria assessed at admission

1. Respiratory rate > 30/min
2. Severe respiratory failure (Pa_{O_2}/FI_{O_2} < 250)
3. Bilateral involvement in chest radiograph
4. Involvement of > 2 lobes in chest radiograph (multilobar involvement)
5. Systolic blood pressure < 90 mm Hg
6. Diastolic blood pressure < 60 mm Hg

"Major" criteria assessed at admission or during clinical course

1. Requirement for mechanical ventilation
2. Increase in the size of infiltrates by ⩾ 50% in the presence of clinical nonresponse to treatment or deterioration (progressive infiltrates)
3. Requirement of vasopressors > 4 h (septic shock)
4. Serum creatinine ⩾ 2 mg/dl or increase of ⩾ 2 mg/dl in a patient with previous renal disease or acute renal failure requiring dialysis (renal failure)

PROGNOSTIC IMPLICATIONS OF SEVERITY CRITERIA FOR CAP AS DEFINED BY THE ATS

Criteria	RR	95% CI	p Value	PPV (%)
Respiratory rate > 30/min	2.7	1.01–7.6	< 0.05	7
Pa_{O_2}/FI_{O_2} < 250	1.3	0.6–3.2	0.52	6
Bilateral involvement in chest radiograph	2.5	1.03–6.2	< 0.05	10
Multilobar involvement in chest radiograph	5.1	2.2–12.2	< 0.0001	14
Systolic blood pressure < 90 mm Hg	12.0	4.9–29.3	< 0.001	44
Diastolic blood pressure < 60 mm Hg	7.6	3.1–18.4	< 0.001	25
Requirement for mechanical ventilation	82.2	19.8–342.2	< 0.0001	46
Progressive infiltrates	4.5	1.9–10.9	< 0.001	16
Septic shock	33.5	13.9–80.3	< 0.0001	54
Renal failure	5.4	2.2–13.3	< 0.01	19

Am J Respir Crit Care Med. 1998 Oct;158(4):1102-8.

2001 ATS Guidelines

- In the ICU-admitted patient, current data **do not support the use of an antipneumococcal fluoroquinolone alone**, and therapy **should be with a β-lactam plus either a macrolide or quinolone**, using a regimen with two antipseudomonal agents in appropriate, at risk, patients

TABLE 5. GROUP IV: ICU-ADMITTED PATIENTS*,†

Organisms	Therapy‖,‡
a. No Risks for *Pseudomonas aeruginosa*	
Streptococcus pneumoniae (including DRSP) *Legionella* spp. *Hemophilus influenzae* Enteric gram-negative bacilli *Staphylococcus aureus* *Mycoplasma pneumoniae* Respiratory viruses Miscellaneous *Chlamydia pneumoniae*, *Mycobacterium tuberculosis*, endemic fungi	Intravenous β-lactam (cefotaxime, ceftriaxone)§ *plus either* Intravenous macrolide (azithromycin) *or* Intravenous fluoroquinolone

Severe CAP: ICU admission

- One of two major criteria
  - mechanical ventilation, septic shock
- or two of three minor criteria
  - SBP≤90 mm Hg, multilobar disease, PaO2/FIO2 ratio<250
- or two of four BTS criteria
  - RR≥30/min, DBP≤60 mm Hg, BUN>19.1 mg/dl, confusion

Am J Respir Crit Care Med. 2001 Jun;163(7):1730-54.

2007 ATS/IDSA Guidelines

Inpatients, non-ICU treatment

A respiratory fluoroquinolone (strong recommendation; level I evidence)

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

Inpatients, ICU treatment

A β-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)

Inpatient (ICU)	*S. pneumoniae*
	Staphylococcus aureus
	Legionella species
	Gram-negative bacilli
	H. influenzae

Table 4. Criteria for severe community-acquired pneumonia.

Minor criteria[a]
Respiratory rate[b] ⩾30 breaths/min
PaO_2/FiO_2 ratio[b] ⩽250
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN level, ⩾20 mg/dL)
Leukopenia[c] (WBC count, <4000 cells/mm^3)
Thrombocytopenia (platelet count, <100,000 cells/mm^3)
Hypothermia (core temperature, <36°C)
Hypotension requiring aggressive fluid resuscitation
Major criteria
Invasive mechanical ventilation
Septic shock with the need for vasopressors

NOTE. BUN, blood urea nitrogen; PaO_2/FiO_2, arterial oxygen pressure/fraction of inspired oxygen; WBC, white blood cell.

[a] Other criteria to consider include hypoglycemia (in nondiabetic patients), acute alcoholism/alcoholic withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia.

[b] A need for noninvasive ventilation can substitute for a respiratory rate >30 breaths/min or a PaO_2/FiO_2 ratio <250.

[c] As a result of infection alone.

Clin Infect Dis. 2007 Mar 1;44 Suppl 2(Suppl 2):S27-72.

2019 ATS/IDSA Guidelines

Table 4. Initial Treatment Strategies for Inpatients with Community-acquired Pneumonia by Level of Severity and Risk for Drug Resistance

	Standard Regimen	Prior Respiratory Isolation of MRSA	Prior Respiratory Isolation of *Pseudomonas aeruginosa*	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for MRSA	Recent Hospitalization and Parenteral Antibiotics and Locally Validated Risk Factors for *P. aeruginosa*
Nonsevere inpatient pneumonia*	β-Lactam + macrolide† or respiratory fluroquinolone‡	Add MRSA coverage§ and obtain cultures/nasal PCR to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*‖ and obtain cultures to allow deescalation or confirmation of need for continued therapy	Obtain cultures but withhold MRSA coverage unless culture results are positive. If rapid nasal PCR is available, withhold additional empiric therapy against MRSA if rapid testing is negative or add coverage if PCR is positive and obtain cultures	Obtain cultures but initiate coverage for *P. aeruginosa* only if culture results are positive
Severe inpatient pneumonia*	β-Lactam + macrolide† or β-lactam + fluroquinolone‡	Add MRSA coverage§ and obtain cultures/nasal PCR to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*‖ and obtain cultures to allow deescalation or confirmation of need for continued therapy	Add MRSA coverage§ and obtain nasal PCR and cultures to allow deescalation or confirmation of need for continued therapy	Add coverage for *P. aeruginosa*‖ and obtain cultures to allow deescalation or confirmation of need for continued therapy

Severe CAP definition 2007

Validated definition includes either one major criterion or three or more minor criteria

Minor criteria

- Respiratory rate ⩾ 30 breaths/min
- Pa_{O2}/F_{IO2} ratio ⩽ 250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (blood urea nitrogen level ⩾ 20 mg/dl)
- Leukopenia* (white blood cell count < 4,000 cells/μl)
- Thrombocytopenia (platelet count < 100,000/μl)
- Hypothermia (core temperature < 36°C)
- Hypotension requiring aggressive fluid resuscitation

Major criteria

- Septic shock with need for vasopressors
- Respiratory failure requiring mechanical ventilation

Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45-e67.

2019 ATS/IDSA Guidelines

Table 2. Differences between the 2019 and 2007 American Thoracic Society/Infectious Diseases Society of America Community-acquired Pneumonia Guidelines

Recommendation	2007 ATS/IDSA Guideline	2019 ATS/IDSA Guideline
Sputum culture	Primarily recommended in patients with severe disease	Now recommended in patients with severe disease as well as in all inpatients empirically treated for MRSA or *Pseudomonas aeruginosa*
Blood culture	Primarily recommended in patients with severe disease	Now recommended in patients with severe disease as well as in all inpatients empirically treated for MRSA or *P. aeruginosa*
Macrolide monotherapy	Strong recommendation for outpatients	Conditional recommendation for outpatients based on resistance levels
Use of procalcitonin	Not covered	Not recommended to determine need for initial antibacterial therapy
Use of corticosteroids	Not covered	Recommended not to use. May be considered in patients with refractory septic shock
Use of healthcare-associated pneumonia category	Accepted as introduced in the 2005 ATS/IDSA hospital-acquired and ventilator-associated pneumonia guidelines	Recommend abandoning this categorization. Emphasis on local epidemiology and validated risk factors to determine need for MRSA or *P. aeruginosa* coverage. Increased emphasis on deescalation of treatment if cultures are negative
Standard empiric therapy for severe CAP	β-Lactam/macrolide and β-lactam/fluoroquinolone combinations given equal weighting	Both accepted but stronger evidence in favor of β-lactam/macrolide combination
Routine use of follow-up chest imaging	Not addressed	Recommended not to obtain. Patients may be eligible for lung cancer screening, which should be performed as clinically indicated

BL-M vs BL-FQ?

Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45-e67.

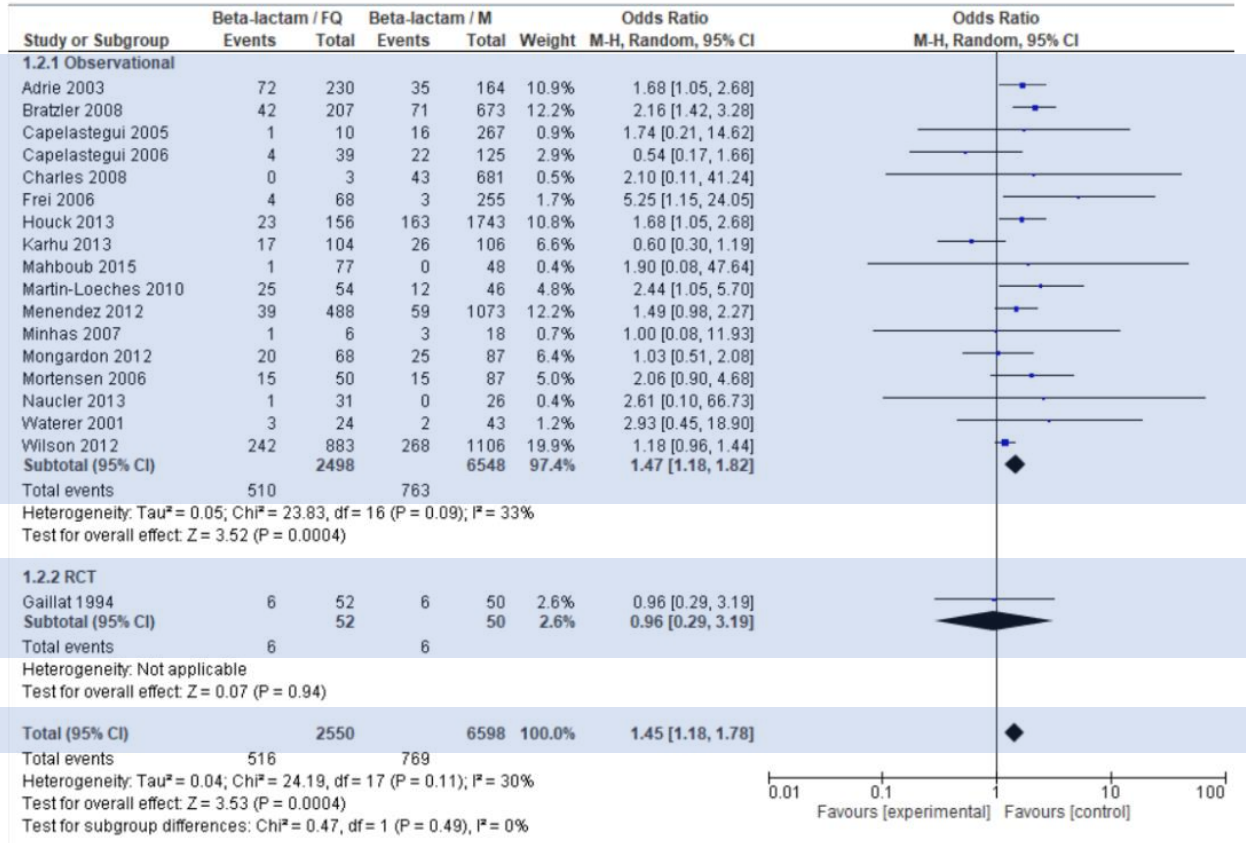
2023 ERS/ESICM/ESCMID/ALAT guidelines

Recommendation
We **suggest** the **addition of macrolides, not fluoroquinolones**, **to beta-lactams** as empirical antibiotic therapy in hospitalised patients with sCAP. Conditional recommendation, very low quality of evidence.
Remark: The task force also considered the duration of treatment of **macrolides being between 3 and 5 days**. This would be a reasonable timing especially in the context of de-escalation therapy.

Intensive Care Med. 2023 Jun;49(6):615-632.

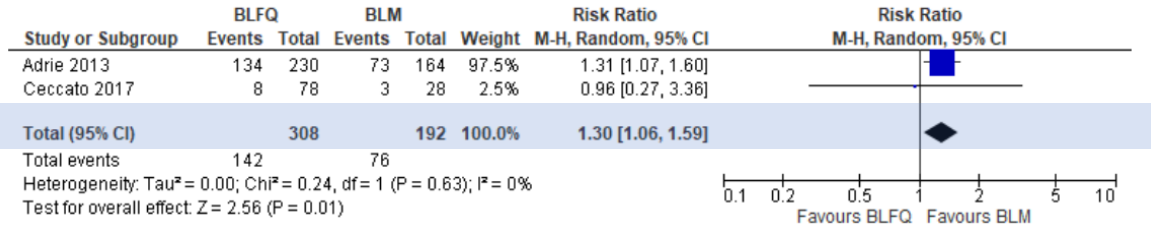
2023 ERS/ESICM/ESCMID/ALAT guidelines

Mortality – all studies



Mechanical Ventilation (invasive)

Severe CAP



Intensive Care Med. 2023 Jun;49(6):615-632.

Clarithromycin in VAP and sepsis

- Double-blind, RCT (n=200)
- Patients: MV (≥48 h) + VAP + sepsis
- June 2004 ~ November 2005
- IV Clarithromycin 1 g for 3 days vs placebo

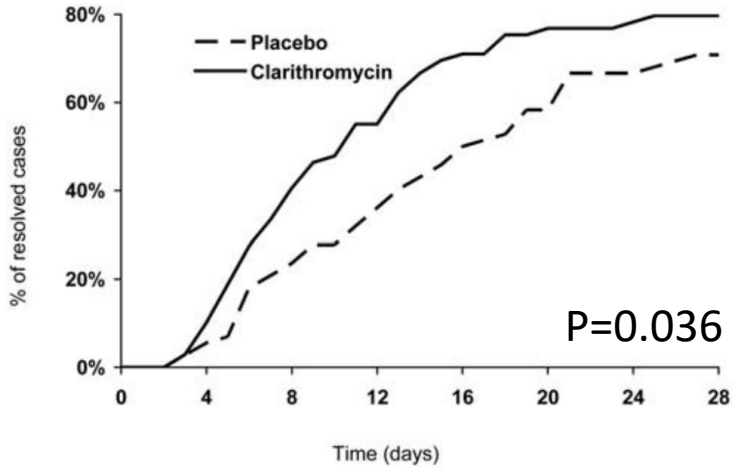
- VAP
  - new or persistent consolidation
  - purulent secretions
  - clinical pulmonary infection score (CPIS) >6
- Sepsis: SIRS≥2
- Severe sepsis: sepsis+ ≥ 1 organ failure
- Septic shock: SBP<90 mm Hg+ vasopressors for >1 h

Variable	Treatment with Placebo (n = 100)	Treatment with Clarithromycin (n = 100)	P
Age, mean years ± SD	58.40 ± 17.41	58.41 ± 20.74	.89
Age ⩾65 years, no. (%)	50 (50)	55 (55)	.48
Sex, M/F	73/27	74/26	1
Critical illness, no. (%) of patients			.95
Sepsis	26 (26)	25 (25)	
Severe sepsis	31 (31)	33 (33)	
Septic shock	43 (43)	42 (42)	
⩾10^6 CFU/mL in TBS, no. (%)	68 (68)	66 (66)	.88
Type of pathogen, no. (%) of patients			.28
Pseudomonas aeruginosa	12 (17.6)	17 (25.8)	
Acinetobacter baumannii	43 (63.2)	36 (54.5)	
Klebsiella pneumoniae	6 (8.8)	5 (7.6)	
Enterobacter species	2 (2.9)	4 (6.1)	
Stenotrophomonas maltophilia	2 (2.9)	0 (0)	
Providentia stuartii	0 (0)	1 (1.5)	
Other(s)	3 (4.4)	3 (4.5)	
Incidence of bacteremia by the same isolate, no. (%) of patients	21 (21)	26 (26)	.37
Type of administered antimicrobial agent, no. (%) of patients			.11
Piperacillin-tazobactam	9 (9)	12 (12)	
Carbapenem and vancomycin-linezolid	38 (38)	34 (34)	
Carbapenem, colistin, and vancomycin-linezolid	27 (27)	31 (31)	
Carbapenem monotherapy	8 (8)	4 (4)	
Third-generation cephalosporins and clindamycin	16 (16)	16 (16)	

Clin Infect Dis. 2008 Apr 15;46(8):1157-64.

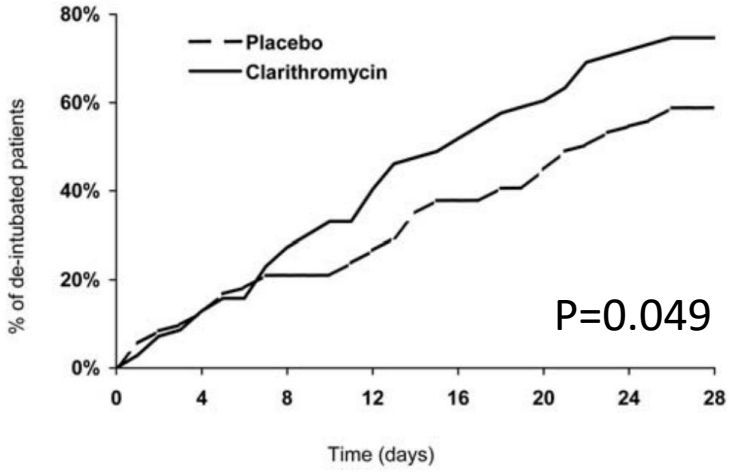
Clarithromycin in VAP and sepsis

Resolution of VAP

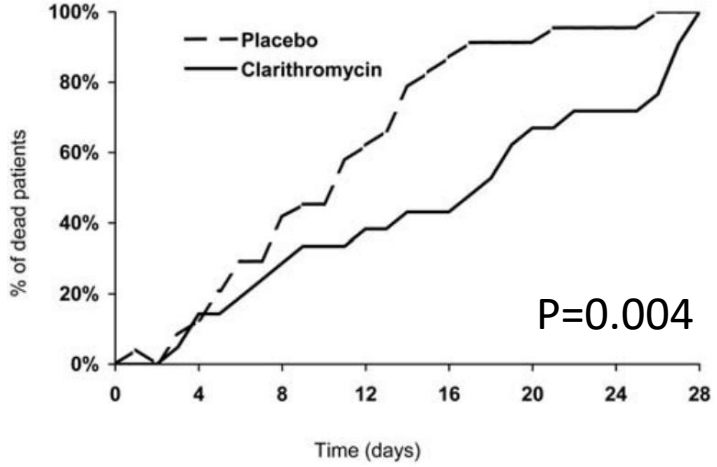


Resolution of VAP: all of the following
(1) absence of purulent material in TBSs
(2) improvement of the infiltrate on the lung radiography
(3) increase of the ratio of PaO2/FiO2
(4) resolution of the signs of sepsis that led to study enrollment

Time to weaning from MV



Time to death from sepsis



Clin Infect Dis. 2008 Apr 15;46(8):1157-64.

Clarithromycin in VAP and sepsis

Table 2. Primary study outcomes as assessed in the registry of the trial.

Outcomes	Treatment with		*P*
	Placebo (n = 100)	Clarithromycin (n = 100)	
Crude mortality for any reason	28	31	.76
Mortality at 7 days	8	6	.78
Sepsis-related mortality at 28 days, no. of patients/total patients, excluding those who died of other causes (%)	24/96 (25.0)	21/90 (23.3)	.86
Progression to MODS among the total enrolled patients	8	14	.26
Time until progression to MODS, mean days ± SD	3.38 ± 1.06	5.78 ± 3.52	.047
Time until resolution of VAP, median days (IQR)	11.5 (2 to >28)	7.0 (2–24)	.006
Time in ICU after diagnosis of VAP for patients who survived, mean days ± SD	21.58 ± 8.22	23.36 ± 7.05	.17

Clarithromycin in patients with VAP and sepsis

- **earlier resolution of VAP**
- **earlier weaning from MV**
- **later death in those who died of sepsis**
- **prolongation of the time of progression to MODS**
- **overall mortality: not different**

Clin Infect Dis. 2008 Apr 15;46(8):1157-64.

Clarithromycin in Gram negative sepsis

- Double-blind, RCT (n=600)
- July 2007 ~ April 2011
- placebo or IV clarithromycin 1g for 4 days
- Patients: Gram-negative sepsis
  - SIRS ≥2
  - Infections: Gram (-) bacteremia, APN, intra-abdominal infection

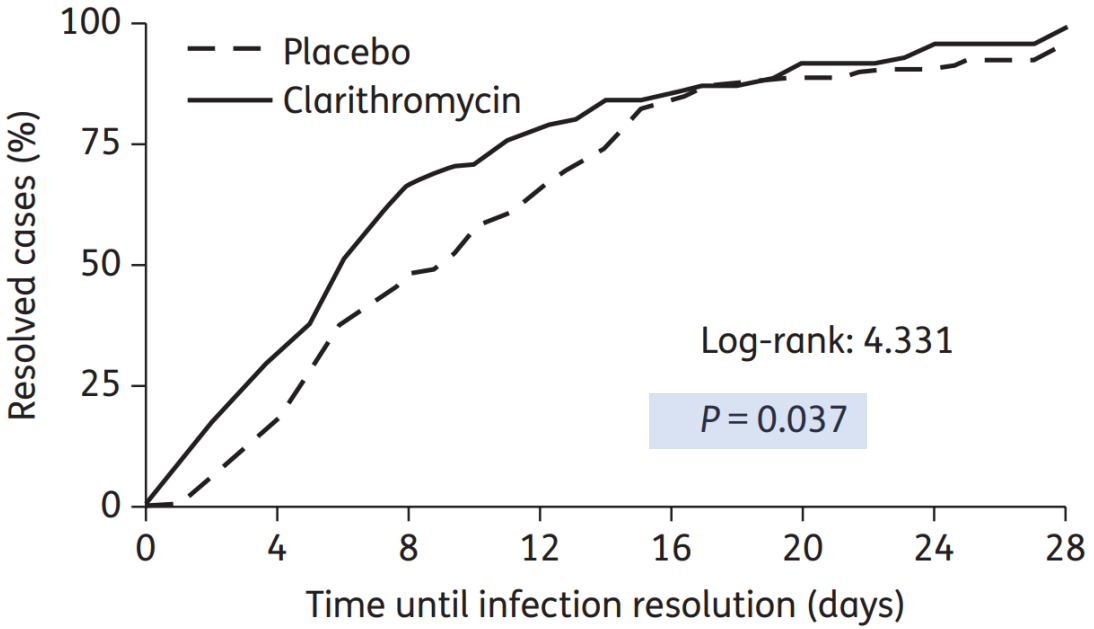
	Placebo ($n=298$)	Clarithromycin ($n=302$)	P value
Administered antimicrobials (n, %)			
β-lactam/β-lactamase inhibitors	31 (10.4)	25 (8.3)	
piperacillin/tazobactam	75 (25.2)	84 (27.8)	
3rd generation cephalosporin ± aminoglycoside	71 (23.8)	69 (22.8)	
3rd generation cephalosporin ± metronidazole	23 (7.7)	21 (7.0)	0.519
ciprofloxacin ± metronidazole	18 (6.0)	33 (10.6)	
carbapenem + glycopeptide/linezolid	37 (12.4)	35 (11.6)	
other	43 (14.4)	35 (11.6)	

- **Overall 28-day mortality (P=0.671)**
  - clarithromycin group: 18.5%
  - placebo group: 17.1%
- **Septic shock and MODS (n=54, P=0.020)**
  - clarithromycin group: 53.6%
  - placebo group: 73.1%

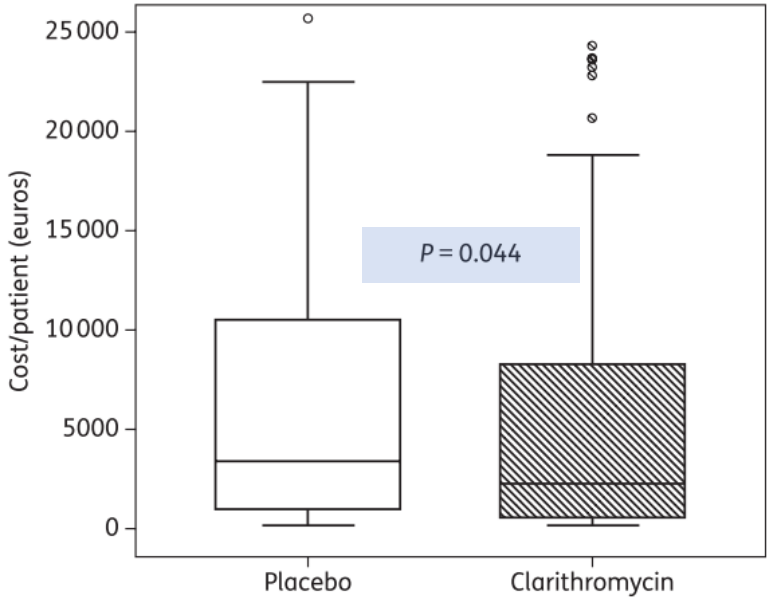
J Antimicrob Chemother. 2014 Apr;69(4):1111-8.

Clarithromycin in Gram negative sepsis

Survivors with severe sepsis/shock



Comparative cost of hospitalization



- Clarithromycin
  - **overall mortality: not different**
  - decrease of mortality due to septic shock and MODS
  - **shortened the time until infection resolution** among the more severely ill patients
  - cost of hospitalization was lower

J Antimicrob Chemother. 2014 Apr;69(4):1111-8.

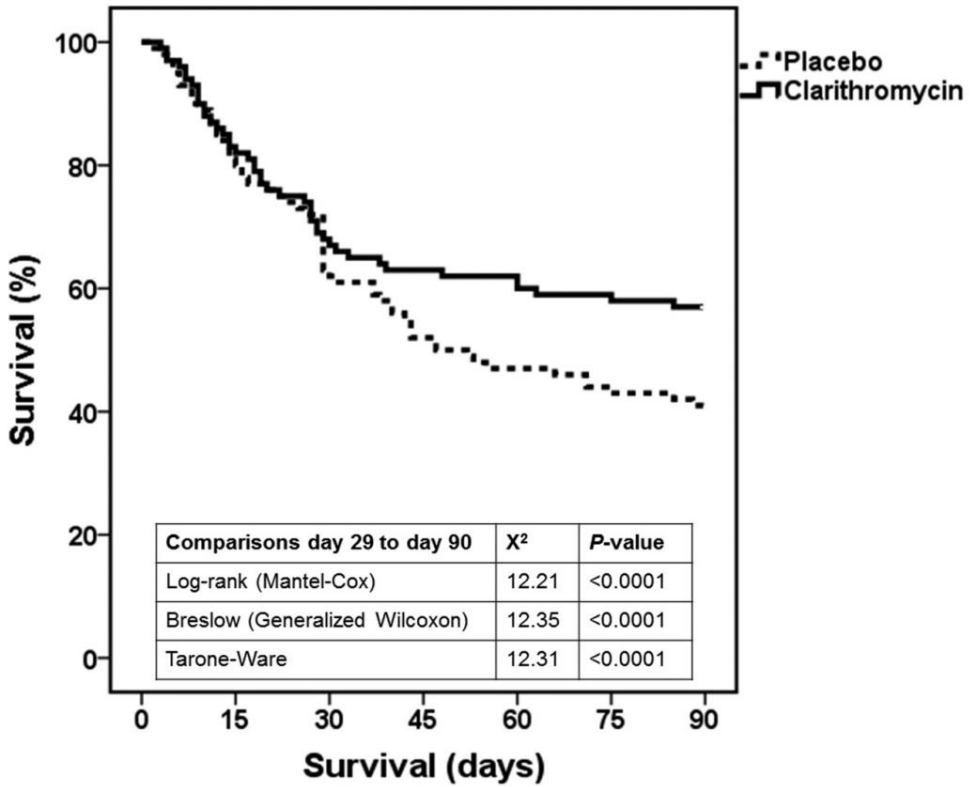
Clarithromycin in VAP and sepsis: long-term survival

- Double-blind, RCT (n=200)

→ retrospective analysis, clarithromycin on the 90-day mortality

- 28-day mortality
  - 28% in the placebo arm
  - 31% in the clarithromycin arm

- 90-day mortality (P=0.023)
  - Placebo: 60%
  - Clarithromycin: 43%
- OR for 90-day death: 0.50 (95% CIs, 0.28-0.58; P=0.024)



Comparisons day 29 to day 90	X^2	*P*-value
Log-rank (Mantel-Cox)	12.21	<0.0001
Breslow (Generalized Wilcoxon)	12.35	<0.0001
Tarone-Ware	12.31	<0.0001

Patients alive	Day 28	Day 30	Day 45	Day 60	Day 75	Day 90
Placebo	72	61	51	46	42	40
Clarithromycin	69	66	62	60	58	57

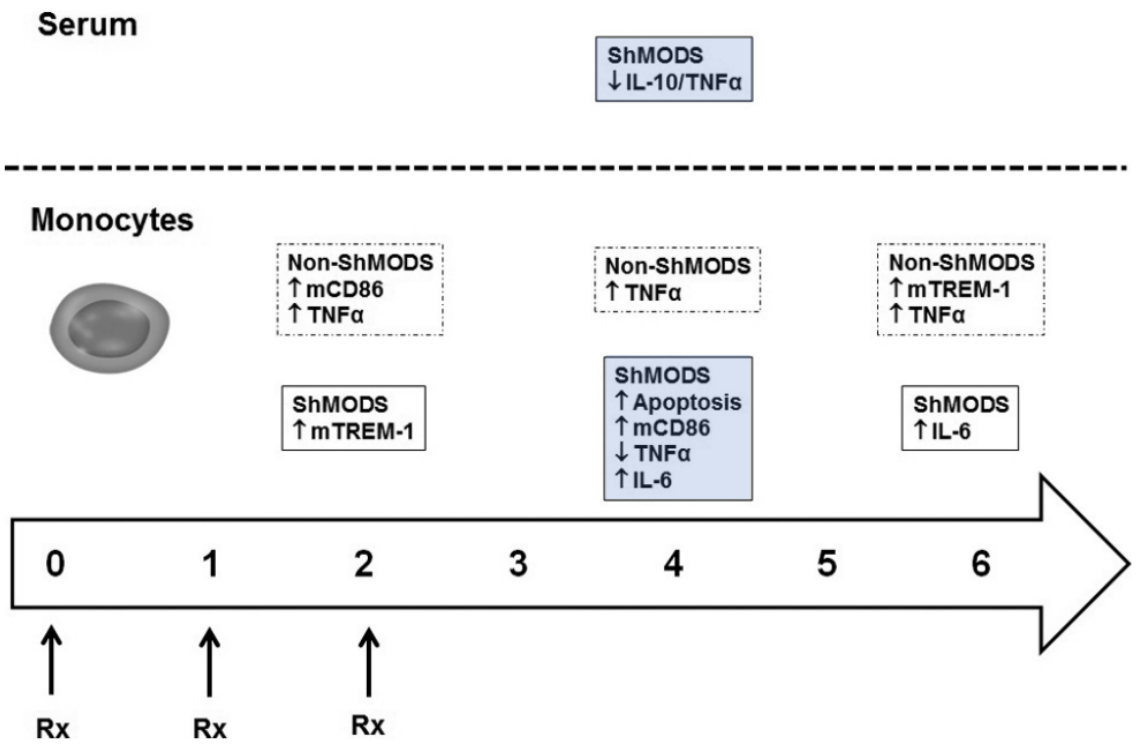
Antimicrob Agents Chemother. 2016 May 23;60(6):3640-6.

Clarithromycin in VAP and sepsis: inflammatory markers

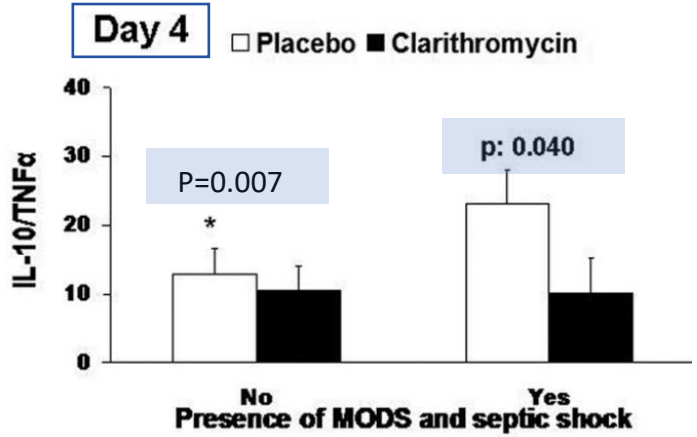
- Double-blind, RCT (n=200)

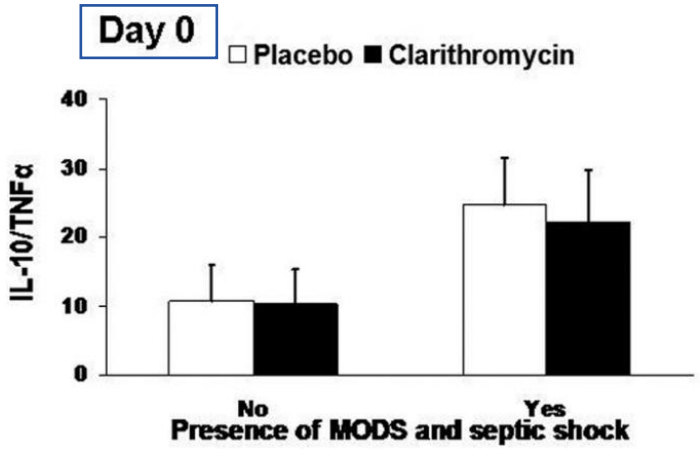
→ septic shock and MODS (n=69): 36 placebo and 33 clarithromycin

- Inflammatory markers, six consecutive days



serum IL-10/TNF- ratio↓





Clarithromycin: restore the balance between pro- vs anti-inflammatory mediators in patients with sepsis

Antimicrob Agents Chemother. 2012 Jul;56(7):3819-25.

BL vs. BLM or BLFQ in bacteremic pneumococcal pneumonia

- Single center, retrospective **propensity** analysis
- 2000 ~ 2015
- Patients: CAP + *S. pneumoniae* bacteremia
- 3rd cephalosporin + macrolide or fluoroquinolone (n=314)
- 3rd cephalosporin monotherapy (n=69)

Characteristics of patients according to the empirical treatment received.

Variables	Monotherapy (n = 69)	Combination therapy (n = 314)	P
Age ≥65 years, n (%)	39 (56.5)	137 (43.8)	0.054
Male sex, n (%)	38 (55.1)	196 (62.4)	0.257
Without comorbidities, n (%)	17 (24.6)	92 (29.3)	0.437
Non-fatal prognosis[a], n (%)	47 (68.1)	248 (79.0)	0.052
Chronic liver disease, n (%)	10 (14.5)	17 (5.4)	0.008
Diabetes mellitus, n (%)	10 (14.5)	51 (16.2)	0.719
Chronic obstructive pulmonary disease, n (%)	12 (17.4)	70 (22.3)	0.369
Kidney chronic disease, n (%)	2 (2.9)	14 (4.5)	0.747
Chronic alcohol intake	2 (2.9)	12 (3.8)	>0.999
Cardiovascular disease, n (%)	10 (14.5)	27 (8.6)	0.133
HIV infection, n (%)	14 (20.3)	56 (17.8)	0.633
Haematological neoplasia, n (%)	6 (8.7)	31 (9.9)	0.764
Solid neoplasm, n (%)	4 (5.8)	13 (4.1)	0.522
Neutropenia, n (%)	0	2 (0.6)	>0.999
Splenectomy, n (%)	1 (1.4)	3 (1.0)	0.550
Corticosteroid treatment, n (%)	6 (8.7)	22 (7.0)	0.625
Penicillin resistance[b], n (%)	3 (4.3)	32 (10.3)	0.166
Erythromycin resistance[c], n (%)	14 (20.3)	46 (14.8)	0.257
Fluid refractory hypotension, n (%)	6 (8.7)	42 (13.4)	0.288
30-day mortality, n (%)	8 (11.6)	11 (3.5)	0.005
7-day mortality, n (%)	6 (8.7)	8 (2.5)	0.014

J Infect. 2018 Apr;76(4):342-347.

BL vs. BLM or BLFQ in bacteremic pneumococcal pneumonia

Main characteristics of patients with bacteraemic pneumococcal pneumonia according to empirical treatment received after matching by propensity score.

Variables	Matched 1:1 sample			Matched 1:2 sample		
	Empirical treatment, n (%)		SD[a]	Empirical treatment, n (%)		SD[a]
	Monotherapy (N = 65)	Combined therapy (N = 65)		Monotherapy (N = 65)	Combined therapy (N = 129)	
Male sex	36 (55,4)	36 (55,4)	0,0	36 (55,4)	75 (58,1)	3,9
Age ≥65 years	35 (53,8)	35 (53,8)	0,0	35 (53,8)	77 (59,7)	8,3
Cardiovascular disease	9 (13,8)	9 (13,8)	0,0	9 (13,8)	23 (17,8)	6,6
Chronic obstructive pulmonary disease	12 (18,5)	13 (20,0)	2,4	12 (18,5)	27 (20,9)	3,9
Diabetes mellitus	10 (15,4)	9 (13,8)	2,6	10 (15,4)	23 (17,8)	4,0
Chronic kidney disease	2 (3,1)	1 (1,5)	4,0	2 (3,1)	3 (2,3)	1,9
Solid neoplasm	3 (4,6)	2 (3,1)	3,5	3 (4,6)	11 (8,5)	7,9
Haematological neoplasia	6 (9,2)	4 (6,2)	6,0	6 (9,2)	10 (7,8)	2,8
Chronic liver disease	7 (10,8)	8 (12,3)	2,7	7 (10,8)	8 (6,2)	8,7
HIV infection	14 (21,5)	10 (15,4)	9,9	14 (21,5)	22 (17,1)	7,1
Chronic alcohol intake	2 (3,1)	3 (4,6)	3,5	2 (3,1)	4 (3,1)	0,1
Splenectomy	1 (1,5)	0 (0)	6,2	1 (1,5)	1 (0,8)	2,3
Intravenous drug abuser	0 (0)	0 (0)		0 (0)	0 (0)	
Non-fatal prognosis	47 (72,3)	50 (76,9)	7,0	47 (72,3)	95 (73,6)	2,0
Neutropenia	0 (0)	0 (0)		0 (0)	0 (0)	
Corticosteroid treatment	4 (6,2)	5 (7,7)	3,0	4 (6,2)	9 (7,0)	1,6
Fluid refractory hypotension	6 (9,2)	7 (10,8)	2,8	6 (9,2)	10 (7,8)	2,8
7-day mortality	5 (7,7)	1 (1,5)	13,9	5 (7,7)	3 (2,3)	11,7
30-day mortality	7 (10,8)	1 (1,5)	19,8	7 (10,8)	5 (3,9)	13,7

Relationship among empirical monotherapy, combination therapy[a] and mortality matched by propensity score.

	OR (95% CI)[b]	P Wald[b]
1:1 matched sample		
7-day mortality	5.00 (0.58–42.80)	0.142
30-day mortality	7.00 (0.86–56.90)	0.069
1:2 matched sample		
7-day mortality	3.33 (0.80–13.95)	0.099
30-day mortality	3.50 (1.03–11.96)	0.046

[a] Combination therapy as reference and monotherapy as intervention.
[b] Data were obtained by conditional logistic regression analysis.

Relationship between empirical monotherapy or combination therapy[a] and mortality considering the whole cohort.

	OR (95% CI)[b]	P Wald[b]
7-day mortality		
Unadjusted	3.64 (1.22–10.86)	0.02
Adjusted by PS	3.23 (1.03–10.11)	0.04
30-day mortality		
Unadjusted	3.61 (1.40–9.35)	0.008
Adjusted by PS	2.89 (1.07–7.84)	0.04

[a] Combined treatment as reference and monotherapy as intervention.
[b] Data were obtained by logistic regression analysis.
PS = propensity score.

3rd cephalosporin + macrolide or fluoroquinolone

- lower mortality rate than monotherapy

J Infect. 2018 Apr;76(4):342-347.

BL vs BLM in hospitalized moderately severe CAP

- Randomized **noninferiority** trial (n=580)
- 2009 ~ 2013
- Patients: hospitalized CAP
- **Exclusion: severe pneumonia or PSI V**
- β-lactam vs β-lactam + macrolide (clarithromycin 500 mg twice a day)
- Recommended duration of treatment: 5-10 days

- Primary outcome: clinical stability at day 7
  - HR<100/min, SBP>90 mm Hg, BT<38.0°C, RR<24/min, SPO2>90% (RA)

Table 1. Patient Characteristics at Baseline[a]

Characteristic	Monotherapy (n = 291)	Combination Therapy (n = 289)
Age, median (IQR), y	76 (63-84)	76 (64-83)
Male sex	162 (55.7)	171 (59.2)
Comorbidities, median (IQR)	1 (0-2)	1 (0-2)
Chronic heart failure	64 (22.0)	52 (18.0)
Chronic obstructive pulmonary disease	61 (21.0)	61 (21.1)
Diabetes mellitus	44 (15.1)	52 (18.0)
Chronic renal failure	47 (16.2)	41 (14.2)
PSI score, mean (SD)	84.5 (25.8)	84.2 (24.1)
PSI category		
I	31 (10.7)	23 (8.0)
II	50 (17.2)	55 (19.0)
III	83 (28.5)	98 (33.9)
IV	127 (43.6)	113 (39.1)
CURB-65 score ≥2	155 (53.3)	156 (54.0)
Heart rate, mean (SD), /min	100 (21)	97 (18)
Respiratory rate, mean (SD), /min	24.5 (6.2)	23.6 (5.8)
Temperature, mean (SD), °C	37.9 (1.0)	37.9 (1.0)
Hypoxemia[b]	206 (70.8)	219 (75.8)
Pleural effusion	46 (15.8)	51 (17.6)
White blood cells, mean (SD), /μL	13 400 (6300)	13 600 (6500)

JAMA Intern Med. 2014 Dec;174(12):1894-901.

BL vs BLM in hospitalized moderately severe CAP

- Primary outcome (clinical stability at day 7): not significant

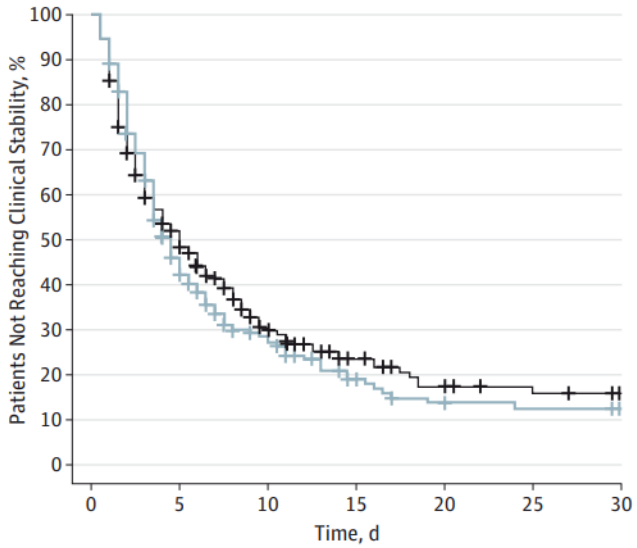
Table 2. Primary and Secondary End Points[a]

End Point	Monotherapy (n = 291)	Combination Therapy (n = 289)	*P* Value
Primary end point			
Patients not reaching clinical stability at day 7[b]	120 (41.2)	97 (33.6)	.07
Secondary end points			
Intensive care unit admission	12 (4.1)	14 (4.8)	.68
Complicated pleural effusion[c]	8 (2.7)	14 (4.8)	.19
Length of stay, median (IQR), d	8 (6-13)	8 (6-12)	.65
Any change in the initial antibiotic treatment	39 (13.4)	46 (15.8)	.39
In-hospital death	8 (2.7)	7 (2.4)	.80
30-Day death	14 (4.8)	10 (3.4)	.42
90-Day death	24 (8.2)	20 (6.9)	.54
30-Day readmission	23 (7.9)	9 (3.1)	.01
90-Day readmission	47 (16.2)	37 (12.7)	.25
New pneumonia within 30 days[d]	10 (3.4)	6 (2.1)	.31

Median time to clinical stability

- monotherapy arm: 5.0 days (IQR, 3.8-6.2 days)
- combination arm: 4.5 days (IQR, 3.9-5.1 days)

Figure 2. Proportions of Patients Not Reaching Clinical Stability



Black line indicates monotherapy arm; blue line, combination arm. *P* = .44 (log-rank test).

JAMA Intern Med. 2014 Dec;174(12):1894-901.

BL vs BLM in hospitalized moderately severe CAP

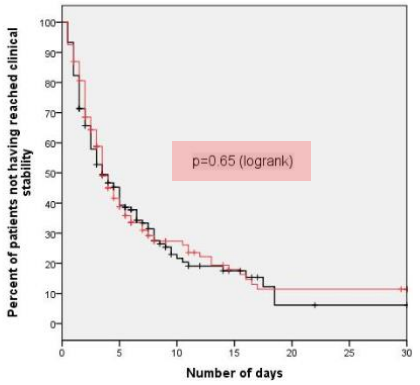
Table 3. Hazard Ratios for Clinical Stability in the Monotherapy Arm vs Combination Arm

Variable	No. of Patients	Hazard Ratio[a] (95% CI)	*P* Value
Unadjusted		0.93 (0.76-1.13)	.46
Adjusted for age and PSI category		0.92 (0.76-1.12)	.41
Stratified			
Atypical	31	0.33 (0.13-0.85)	.02
Nonatypical	549	0.99 (0.80-1.22)	.93
P value for interaction			.03
PSI category IV	240	0.81 (0.59-1.10)	.18
PSI category I-III	340	1.06 (0.82-1.36)	.66
P value for interaction			.18
CURB-65 category 2-5	311	0.80 (0.61-1.06)	.12
CURB-65 category 0-1	269	1.13 (0.85-1.50)	.40
P value for interaction			.09
Age, y			
<65	150	1.09 (0.75-1.59)	.65
≥65	430	0.87 (0.70-1.10)	.25
P value for interaction			.32

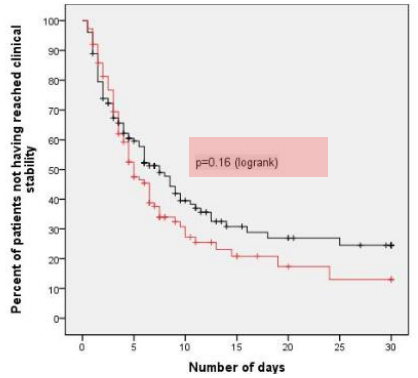
Combination therapy: +++++

Monotherapy: +++++

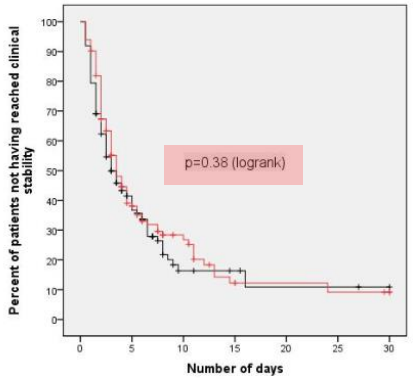
a. PSI category I-III



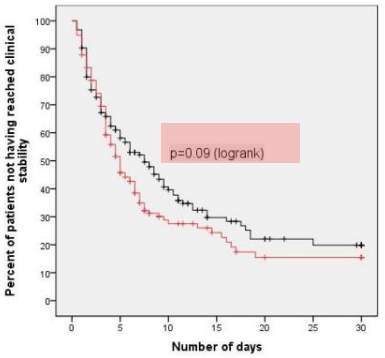
b. PSI category IV



c. CURB-65 category 0-1



d. CURB-65 category 2 or more



nonsignificant trend toward superiority of combination therapy

Combination therapy

- superior for patients with atypical pathogens
- less readmissions within 30 days
- trend toward better outcome for patients with more severe pneumonia

JAMA Intern Med. 2014 Dec;174(12):1894-901.

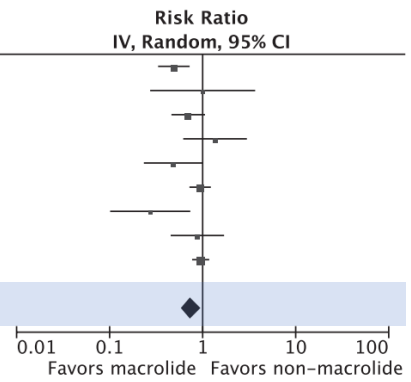
Macrolide combination in severe CAP

- A Systematic Review and Meta-Analysis
- **27 observational studies (n=9,850)**
- Inclusion
  - Population: critically ill patients with CAP (**admitted to an ICU**)
  - Exposure: macrolide
  - Comparison: nonmacrolide
  - Outcome: in-hospital, ICU, 28- or 30-d mortality

Pooled adjusted risk estimates (n = 9)

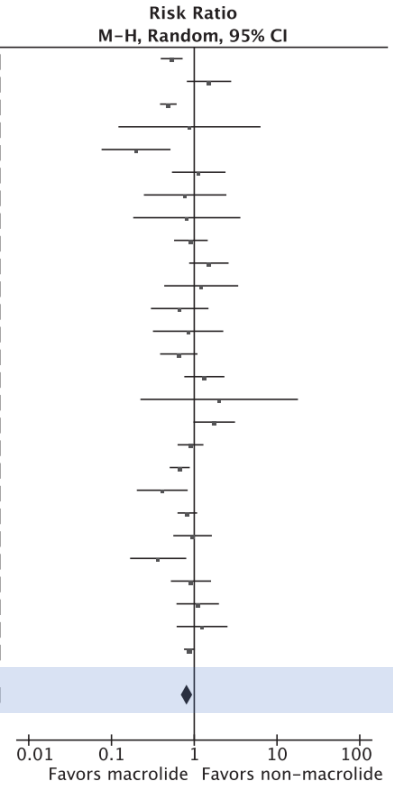
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Arnold 2013	-0.713	0.199	15.0%	0.49 [0.33, 0.72]
Bratzler 2008	0	0.663	3.1%	1.00 [0.27, 3.67]
Bratzler 2008	-0.357	0.212	14.3%	0.70 [0.46, 1.06]
Karhu 2013	0.307	0.402	6.9%	1.36 [0.62, 2.99]
Martin-Loeches 2010	-0.73	0.37	7.8%	0.48 [0.23, 1.00]
Rodrigo 2013	-0.062	0.135	18.8%	0.94 [0.72, 1.22]
Shorr 2013	-1.298	0.506	4.9%	0.27 [0.10, 0.74]
Sligl 2013	-0.131	0.337	8.8%	0.88 [0.45, 1.70]
Wilson 2012	-0.049	0.108	20.4%	0.95 [0.77, 1.18]
Total (95% CI)			**100.0%**	**0.75 [0.58, 0.96]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 18.68$, df = 8 (P = 0.02); $I^2 = 57\%$
Test for overall effect: Z = 2.31 (P = 0.02)



Study or Subgroup	Macrolide Events	Total	Non-macrolide Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Arnold 2013	51	346	99	358	6.2%	0.53 [0.39, 0.72]
Aspa 2006	28	78	10	42	3.7%	1.51 [0.81, 2.79]
Bratzler 2008	74	736	458	2214	6.8%	0.49 [0.39, 0.61]
Capelastegui 2006	1	8	6	42	0.6%	0.88 [0.12, 6.32]
Charles 2008	12	91	2	3	2.1%	0.20 [0.08, 0.52]
Cilloniz 2011	8	72	27	275	2.9%	1.13 [0.54, 2.38]
Dambrava 2008	5	40	5	31	1.6%	0.78 [0.25, 2.44]
Frei 2006	2	16	6	39	1.0%	0.81 [0.18, 3.61]
Grenier 2011	18	103	72	375	4.7%	0.91 [0.57, 1.45]
Karhu 2013	26	106	17	104	4.1%	1.50 [0.87, 2.60]
Kontou 2009	4	11	6	20	1.9%	1.21 [0.43, 3.39]
Le Bris-Tomczak 2012	10	30	5	10	2.7%	0.67 [0.30, 1.48]
Marras 2004	5	23	8	31	2.0%	0.84 [0.32, 2.24]
Martin-Loeches 2010	12	46	69	172	4.3%	0.65 [0.39, 1.09]
Menendez 2012	15	80	32	226	4.1%	1.32 [0.76, 2.31]
Minhas 2007	1	2	1	4	0.5%	2.00 [0.22, 17.89]
Mongardon 2012	53	163	11	59	3.9%	1.74 [0.98, 3.11]
Pascual 2000	29	67	37	77	5.7%	0.90 [0.63, 1.29]
Rello 2002	73	292	63	168	6.4%	0.67 [0.50, 0.88]
Restrepo 2009	8	47	22	53	3.1%	0.41 [0.20, 0.83]
Rodriguez 2007	74	290	74	239	6.4%	0.82 [0.63, 1.08]
Roson 2004	19	56	16	45	4.2%	0.95 [0.56, 1.63]
Shorr 2013	7	52	18	49	2.8%	0.37 [0.17, 0.80]
Sligl 2013	14	91	40	237	4.0%	0.91 [0.52, 1.59]
Song 2008	8	15	16	33	3.8%	1.10 [0.61, 1.98]
Wilson 2005	24	69	7	25	3.1%	1.24 [0.61, 2.52]
Wilson 2012	265	1106	242	883	7.4%	0.87 [0.75, 1.02]
Total (95% CI)		**4036**		**5814**	**100.0%**	**0.82 [0.70, 0.97]**
Total events	846		1369			

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 69.35$, df = 26 (P < 0.00001); $I^2 = 63\%$
Test for overall effect: Z = 2.38 (P = 0.02)



Macrolide use
- lower risk of mortality
- 21% vs 24% (RR, 0.82; 95% CI, 0.70–0.97; p = 0.02)

Crit Care Med. 2014 Feb;42(2):420-32.

BL vs BLM or BLFQ in severe CAP

- Prospective observational cohort study (n=956)
- Patients: CAP admitted to ICU
- 1997 ~ 2010

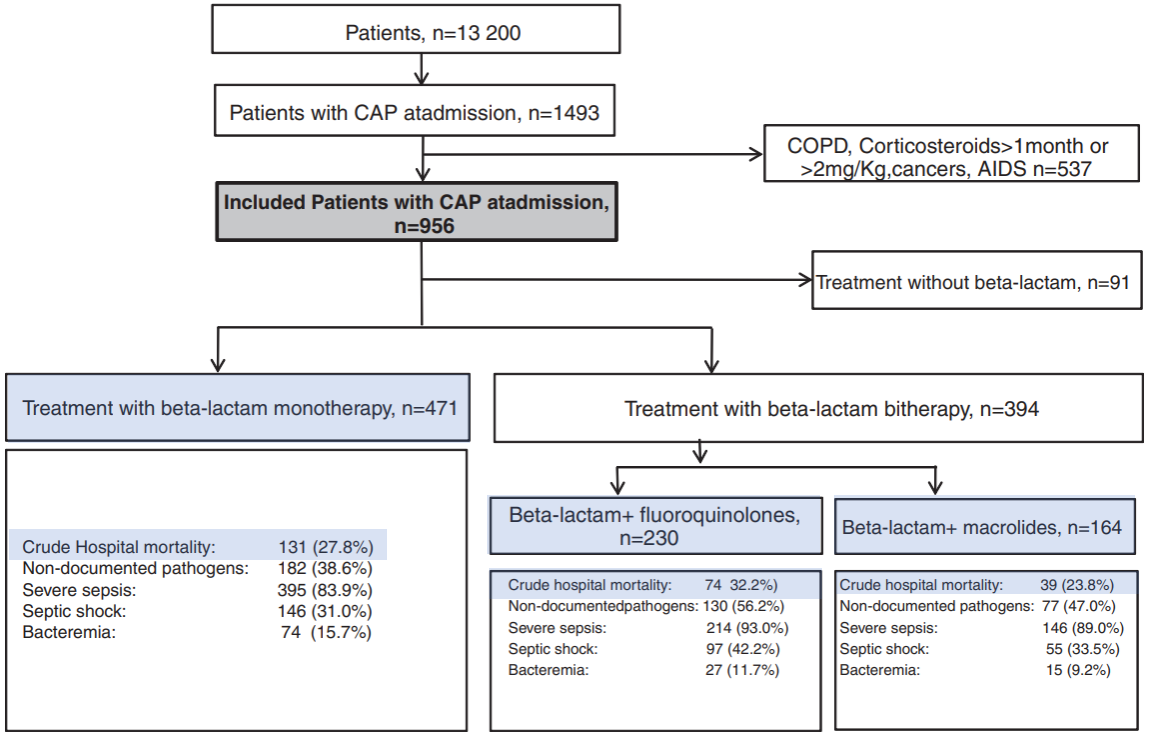


Figure 1 Flow diagram of the patients with community-acquired pneumonia (CAP).

Comparison of the monotherapy and dual therapy groups

	Monotherapy	Dual therapy		
Parameters	Total population (n = 471)	Total population (n = 394)	β-lactam + Macrolide (n = 164)	β-lactam + Fluoroquino-lone (n = 230)
Variables at admission				
Male, n (%)	301 (63.9)	274 (69.5)	110 (67.1)	164 (71.3)
Age in years	60 [45; 75]	64 [48; 77]	64 [49; 79]	64 [47; 76]
Scores, n (%)				
SAPSII*£	47 [34; 60]	39.5 [28; 57]	37 [28.5; 51]	43[28; 63]
SOFA score£	6 [4; 9]	6 [3; 9]	5 [3; 8]	7 [4; 10]
LOD score*£	5 [3; 7]	4 [2; 7]	3 [2; 5.5]	4 [2; 8]
Coma Glasgow Scale*£	8 [4; 15]	15 [8.5; 15]	15 [11;15]	14 [7; 15]
CURB-65,* n (%)				
0	3 (0.6)	7 (1.8)	1 (0.6)	6 (2.6)
1	20 (4.2)	38 (9.6)	15 (9.1)	23 (10.0)
2	88 (18.7)	71 (18.0)	34 (20.7)	37 (16.1)
3	157 (33.3)	107 (27.2)	42 (25.6)	65 (28.3)
4	122 (25.9)	107 (27.2)	46 (28.0)	61 (26.5)
5	81 (17.2)	64 (16.2)	26 (15.9)	38 (16.5)
Sepsis, n (%)	458 (97.2)	383 (97.2)	158 (96.3)	225 (97.8)
Severe sepsis, n (%) *	395 (83.9)	360 (91.4)	146 (89)	214 (93.0)
Septic shock, n (%)*	146 (31.0)	152(38.6)	55 (33.5)	97(42.2)
Treatments, n (%) unless otherwise stated				
Invasive ventilation*£	340 (72.2)	207 (52.5)	73 (44.5)	134 (58.3)
vasoactive agents*£	189 (40.1)	191 (48.5)	67 (40.9)	124 (53.9)
Corticosteroids*	69 (14.6)	96 (24.4)	40 (24.4)	56 (24.3)
Hemodialysis	23 (4.9)	31 (7.9)	11 (6.37)	20 (8.7)

Crit Care. 2013 Nov 7;17(6):R265

BL vs BLM or BLFQ in severe CAP

Comparison of the monotherapy and dual therapy groups

	Monotherapy (β-lactam)	Dual therapy		
Parameters	Total population (n = 471)	Total population (n = 394)	β-lactam + Macrolide (n = 164)	β-lactam + Fluoroquino-lone (n = 230)
Organisms, n (%)				
Streptococcus pneumoniae*£	125 (26.5)	69 (17.5)	42 (25.6)	27 (11.7)
Staphylococcus aureus*£	65 (13.8)	25 (6.3)	5 (3.0)	20 (8.7)
Streptococcus spp.	22 (4.7)	9 (2.3)	2 (1.2)	7 (3.0)
Enterococococcus spp.	3 (0.6)	0 (0)	0 (0)	0 (0)
Hemophilus influenzae*	57 (12.1)	29 (7.4)	15 (9.1)	14 (6.1)
Klebsiella pneumoniae	16 (3.4)	8 (2.0)	3 (1.8)	5 (2.2)
Escherichia coli	23 (4.9)	10 (2.5)	2 (1.2)	8 (3.5)
Enterobacteriaceae spp.*	11 (2.3)	2 (0.5)	1 (0.6)	1 (0.4)
Serratia marescens	3 (0.6)	1 (0.3)	0 (0)	1 (0.4)
Proteus mirabilis	7 (1.5)	1 (0.3)	0 (0)	1 (0.4)
Pseudomonas aeruginosa	13 (2.8)	14 (3.6)	5 (3.0)	9 (3.9)
Legionella pneumophila*	1 (0.2)	9 (2.3)	5 (3.0)	4 (1.7)
Mycoplasma pneumoniae	0 (0)	0 (0)	0 (0)	0 (0)
Chlamydia pneumoniae	0 (0))	2 (0.5)	0 (0)	2 (0.9)
Mycobacterium tuberculosis£	3 (0.6)	6 (1.5)	5 (3.0)	1 (0.4)
Aspergillus fumigatus	0 (0)	3 (0.8)	2 (1.2)	1 (0.4)
Viruses*	6 (1.3)	15 (3.8)	7 (4.3)	8 (3.5)
Other	6 (1.3)	6 (1.5)	1 (06)	5 (2.2)
Multiple organisms*	62 (13.2)	22 (5.6)	8 (4.9)	14 (6.1)
None identified*	182 (38.6)	207 (52.5)	77 (47.0)	130 (56.5)
Bacteremia*	74 (15.7)	42 (10.7)	15 (9.1)	27 (11.7)
ICU stay in days, median [IQR]	6 [3; 15]	7 [3; 16]	7 [3.5; 15.5]	8 [3; 17]
Hospital stay in days, median [IQR]	15 [8; 33]	18 [10; 31]	17.5 [10.5; 35]	18 [9; 30]
Patients who died within 60 days, £ n (%)	123 (26.1)	107 (27.2)	35 (21.3)	72 (31.3)

BLFQ group
- greater disease severity
- higher crude 60-day mortality

Crit Care. 2013 Nov 7;17(6):R265

BL vs BLM or BLFQ in severe CAP

Table 2 Factors independently associated with 60-day mortality between initially and secondarily adequate antibiotic therapy groups

Multivariate analysis (n = 898)	sHR (95% CI)	*P*-value
Inadequate antibiotic therapy (reference)	0.63 (0.42 to 0.94)	**0.02**
Initial adequate antibiotic therapy		
Secondary adequate antibiotic therapy	0.69 (0.37 to 1.27)	0.23
SAPSII per 10 points	1.65 (1.53 to 1.77)	<.0001
Female gender	0.70 (0.52 to 0.94)	0.02
At least one co-morbidity	1.49 (1.13 to 1.97)	0.005
Adequate antibiotic therapy on day 2 versus day 1	1.33 (0.92 to 1.93)	0.13
Adequate antibiotic therapy on day 3 versus day 1	1.29 (0.76 to 2.20)	0.35
Corticosteroids	0.98 (0.72 to 1.32)	0.87

Table 4 Factors associated with 60-day mortality in the groups given monotherapy or dual therapy

Multivariate analysis	sHR	95% CI	*P*-value
Dual therapy versus monotherapy	1.14	0.86 to 1.50	0.37
SAPSII (per 10 points)	1.66	1.54 to 1.79	<.0001
Female gender	0.72	0.53 to 0.96	0.03
≥One co-morbidity	1.43	1.07 to 1.91	0.01
Antibiotic therapy on Day 2 versus Day 1	1.38	0.98 to 1.93	0.07
Antibiotic therapy on Day 3 versus Day 1	1.28	0.75 to 2.19	0.36
Steroids	0.97	0.71 to 1.32	0.83
Multivariate sensitivity analysis*	**sHR**	**(95% CI)**	***P*-value**
Restricted to *Streptococcus pneumoniae* infection	1.42	0.73 to 2.77	0.31
Restricted to documented infection	1.29	0.89 to 1.89	0.18
Restricted to patients with septic shock	1.11	0.75 to 1.64	0.59

*Adjusted on SAPSII, female gender, at least one co-morbidity, day of antibiotic therapy initiation and use of steroids.

initial adequate antibiotic therapy is important

No difference in mortality between a combination vs monotherapy in severe CAP

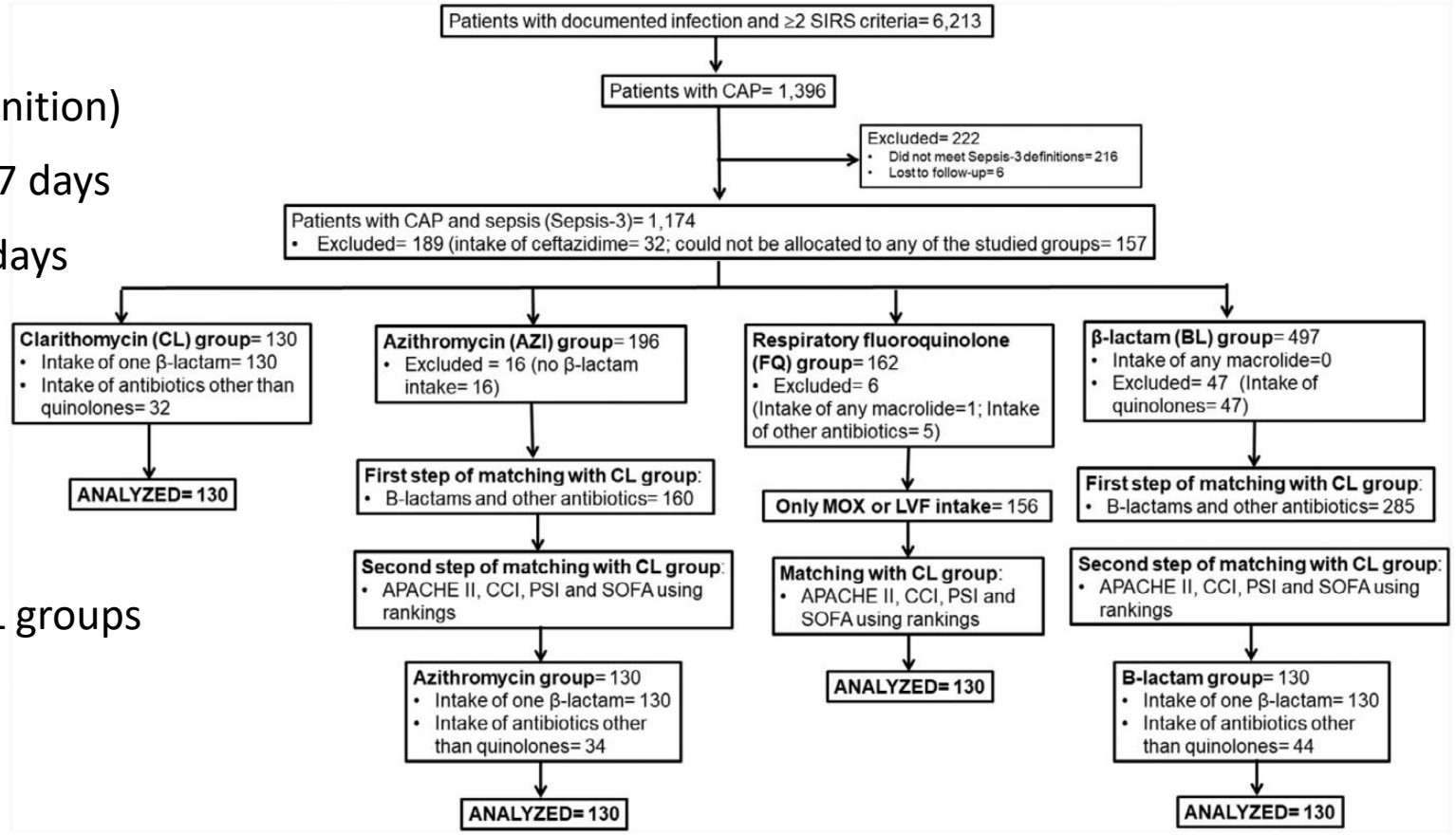
Crit Care. 2013 Nov 7;17(6):R265

Clarithromycin in CAP with sepsis

- Retrospective analysis of prospectively collected data
- matched comparator study
- Patients: CAP and sepsis (by sepsis-3 definition)
- IV Clarithromycin 500 mg twice daily for 7 days
- IV azithromycin 500 mg once daily for 7 days

- Primary endpoint
  - 28-day mortality between CL and BL groups

Matching process to define the β-lactam and fluoroquinolone groups



Int J Antimicrob Agents. 2020 Jan;55(1):105836.

Clarithromycin in CAP with sepsis

Comparative demographics of cases selected after the matching process.

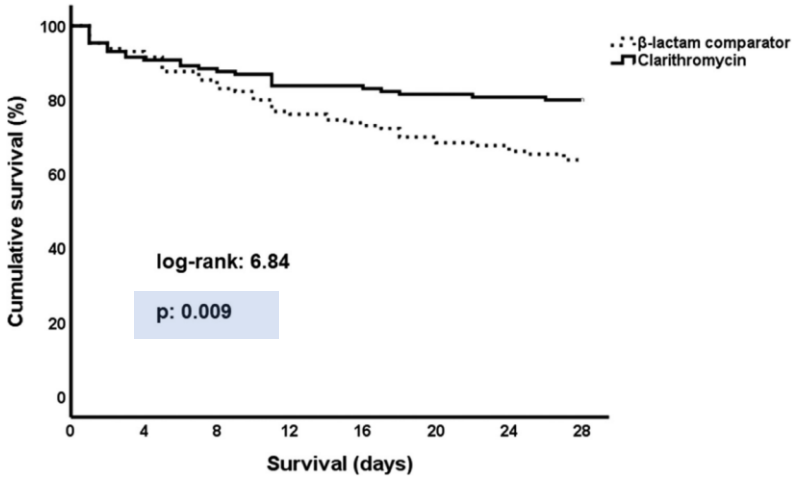
	CL	AZI	FQ	β-lactams	*P*-value CL vs AZI	*P*-value CL vs FQ	*P*-value CL vs β-lactams
Number	130	130	130	130			
Male gender (*n*, %)	76 (58.5)	75 (57.7)	70 (60.8)	68 (52.3)	1.00[a]	0.801[a]	0.383[a]
Age (years, mean ± SD)	72.5 ± 15.6	74.1 ± 15.1	72.3 ± 16.0	73.4 ± 15.9	0.418[b]	0.896[b]	0.652[b]
APACHE II score (mean ± SD)	15.2 ± 7.1	15.4 ± 7.1	16.8 ± 7.1	16.1 ± 6.1	0.807[b]	0.100[b]	0.235[b]
SOFA score (mean ± SD)	5.21 ± 3.65	4.76 ± 3.12	5.01 ± 3.18	5.69 ± 3.04	0.291[b]	0.635[b]	0.416[b]
CCI (mean ± SD)	4.35 ± 2.56	4.35 ± 2.48	4.23 ± 2.62	4.48 ± 2.25	0.980[b]	0.739[b]	0.626[b]
PSI (mean ± SD)	155.7 ± 46.4	149.9 ± 45.5	158.9 ± 47.3	156.7 ± 40.1	0.309[b]	0.586[b]	0.858[b]
White blood cells (/mm^3, mean ± SE)	13,392.7 ± 6582.0	12,789.8 ± 5465.4	15,557.9 ± 9236.1	14,180.1 ± 6927.2	0.422[b]	0.030[b]	0.349[b]
pO_2:FiO_2 (mmHg, mean ± SD)	236.5 ± 95.5	234.6 ± 115.3	235.4 ± 96.5	265.1 ± 128.7	0.891[b]	0.931[b]	0.048[b]

Forward conditional stepwise Cox regression analysis of variables associated with 28-day mortality among 520 analysed patients.

Variable	Hazard ratio	95% confidence interval	*P*-value
Acute respiratory distress syndrome	1.53	1.09–2.13	0.012
Septic shock	3.76	2.68–5.28	<0.0001
APACHE II score >12	2.73	1.55–4.80	0.001
SOFA score >3	2.55	1.44–4.50	0.001
Treatment with vancomycin or teicoplanin	2.38	1.64–3.44	<0.0001
Treatment with clarithromycin + β-lactam	0.59	0.39–0.90	0.014

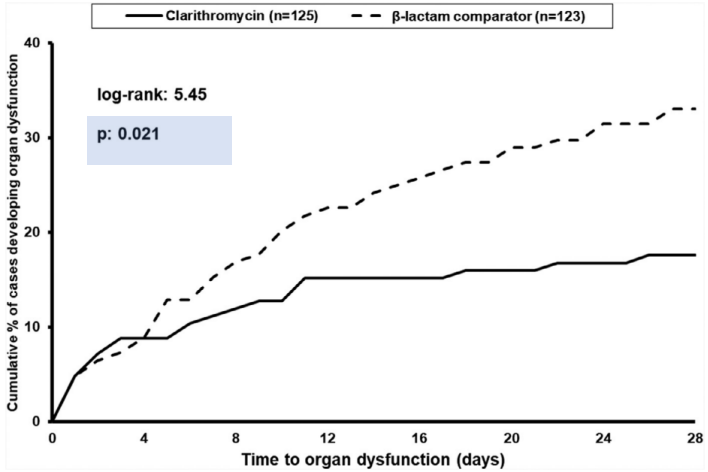
Int J Antimicrob Agents. 2020 Jan;55(1):105836.

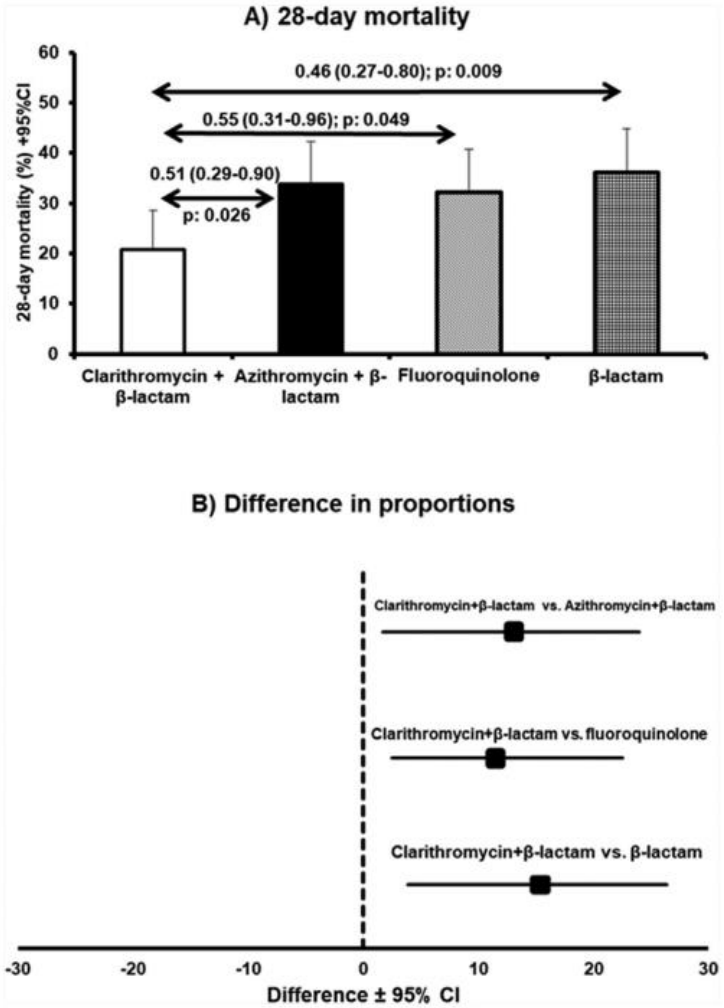
Clarithromycin in CAP with sepsis



28-day mortality (P=0.009)

- β-lactam group: 36.2%
- Clarithromycin group: 20.8%





28-day mortality

- azithromycin group : 33.8%
- fluoroquinolone group: 32.3%

In severe CAP (CAP with sepsis)

- **CL+BL is superior to AZI+BL, FQ, BL**
- survival benefit is due to the CL not AZI

Int J Antimicrob Agents. 2020 Jan;55(1):105836.

BL vs BLM in CAP with sepsis (ACCESS trial)

- ACCESS trial: clarithromycin for early anti-inflammatory responses in CAP
- Phase 3 prospective, double-blind RCT (n=278)
- Patients: **CAP, SIRS ≥ 2, SOFA score≥ 2, procalcitonin ≥0.25 ng/mL**
- Jan 25, 2021 ~April 11, 2023
- Antibiotics
  - IV ceftriaxone 2 g once daily or β-lactam/β-lactamase inhibitor
  - + oral placebo or **oral clarithromycin 500 mg twice daily for 7 days**
- *Legionella* spp or atypical pathogens: treatment switched to once-daily IV moxifloxacin (400 mg)
- Blood sample: cytokine measurements, isolation of peripheral blood mononuclear cells (PBMCs) for cytokine stimulation

- Primary composite endpoint at day 4
  - (1) early clinical response: respiratory symptom severity score ≥ of 50% ↓

  AND
  - (2) early inflammatory response
    - SOFA score ≥ 30% ↓
    - or favorable procalcitonin kinetics: from baseline ≥80% ↓
    - or procalcitonin <0.25 ng/mL

Lancet Respir Med. 2024 Apr;12(4):294-304.

ACCESS trial

	Standard of care plus clarithromycin (n=134)	Standard of care plus placebo (n=133)
Age, years	81·5 (73·0–87·0)	81·0 (71·0–88·0)
Sex		
Male	85 (63%)	78 (59%)
Female	49 (37%)	55 (41%)
Race		
White	134 (100%)	133 (100%)
Charlson Comorbidity Index	5 (4–7)	6 (4–7)
Pneumonia severity index	122 (101–138)	121 (94–141)
APACHE II score	12 (9–16)	13 (9–17)
SOFA score	3 (2–5)	4 (3–5)
Respiratory symptom severity score	5 (4–7)	6 (4–6)
Procalcitonin, ng/mL	0·91 (0·43–2·72)	1·21 (0·46–3·88)
Ferritin, ng/mL	330·0 (139·0–595·1)	245·4 (120·5–632·5)
CURB-65 score	2 (2–3)	2 (2–3)
Presence of pleural effusion	38 (28%)	37 (28%)
Active smoking	38 (28%)	32 (24%)
Laboratory findings		
PaO_2:FiO_2	244·71 (85·55)	233·36 (89·30)
White blood cell count, cells per µL	11170·9 (4711·7)	12031·9 (4773·6)
C-reactive protein, mg/L	133·3 (72·5–204·0)	154·5 (64·3–257·3)
At least one isolated pathogen	74 (55%)	71 (53%)
Most common pathogens		
Staphylococcus aureus	32 (24%)	22 (17%)
Streptococcus pneumoniae	8 (6%)	8 (6%)
Haemophilus influenzae	16 (12%)	23 (17%)
Klebsiella pneumoniae	8 (6%)	10 (8%)
Legionella pneumophila	1 (1%)	3 (2%)
Most common comorbidities		
Diabetes mellitus type 1 or 2	39 (29%)	48 (36%)
Chronic heart failure	21 (16%)	28 (21%)
Chronic kidney disease	18 (13%)	21 (16%)
Coronary heart disease	27 (20%)	22 (17%)
Dyslipidaemia	39 (29%)	37 (28%)
Hypertension	79 (59%)	72 (54%)
Atrial fibrillation	35 (26%)	33 (25%)
Chronic obstructive pulmonary disease	26 (19%)	29 (22%)
Most common administered antimicrobials as standard of care*		
Third-generation cephalosporins	54 (40%)	42 (32%)
β-lactam plus β-lactamase combination	78 (58%)	84 (63%)

	Standard of care plus clarithromycin (n= 134)	Standard of care plus placebo (n=133)	Difference, % (95% CI)	Odds ratio (95% CI)	p value
Primary study endpoint					
Composite* primary endpoint met by day 4	91 (68%; 60 to 75)	51 (38%; 31 to 47)	29·6% (17·7 to 40·3)	3·40 (2·06 to 5·63)	<0·0001
Secondary study endpoints					
≥50% decrease in respiratory symptom severity score at day 4	97 (72%; 64 to 79)	64 (48%; 40 to 57)	24·3% (12·6 to 35·1)	2·83 (1·70 to 4·70)	<0·0001
≥30% decrease in SOFA score at day 4	91 (68%; 60 to 75)	54 (41%; 33 to 49)	27·3% (15·4 to 38·1)	3·10 (1·88 to 5·11)	<0·0001
Favourable procalcitonin kinetics† at day 4	92 (69%; 60 to 79)	72 (54%; 46 to 62)	14·5% (2·8 to 25·7)	1·86 (1·12 to 3·06)	0·017
Favourable procalcitonin kinetics† at end-of-treatment visit (day 8)	104 (78%; 70 to 84)	88 (66%; 58 to 74)	11·5% (0·6 to 21·9)	1·77 (1·03 to 3·05)	0·042
≥50% decrease in SOFA score at end-of-treatment visit (day 8)	84 (63%; 54 to 70)	66 (50%; 41 to 58)	13·1% (1·2 to 24·5)	1·70 (1·05 to 2·78)	0·036
Clinical success at end-of-treatment visit (day 8)	43 (32%; 25 to 40)	23 (17%; 12 to 25)	14·8% (4·5 to 24·8)	2·26 (1·27 to 4·03)	0·0067
Clinical success at test-of-cure visit (day 14)	92 (69%; 60 to 76)	71 (53%; 45 to 62)	15·3% (3·6 to 26·4)	1·91 (1·16 to 3·15)	0·012
Clinical success at day 28	83 (62%; 54 to 70)	66 (50%; 41 to 58)	12·3% (0·4 to 49·6)	1·65 (1·02 to 2·69)	0·049
Progression to organ dysfunction by day 28‡	8 (6%; 3 to 11)	23 (17%; 12 to 25)	11·3% (3·7 to 19·2)	0·30 (0·13 to 0·71)	0·0041
Development of new sepsis by day 28‡	18 (13%; 9 to 20)	32 (24%; 18 to 32)	10·6% (1·2 to 19·8)	0·49 (0·26 to 0·93)	0·029
Discharge alive by day 90	106 (79%; 72 to 85)	83 (62%; 54 to 70)	16·7% (5·8 to 27·1)	2·28 (1·32 to 3·93)	0·031
Mortality by day 28§	27 (20%; 14 to 28)	35 (26%; 20 to 34)	6·2% (–3·9 to 16·2)	0·70 (0·39 to 1·25)	0·25
Mortality by day 90§	46 (34%; 27 to 43)	50 (38%; 30 to 46)	3·3% (–8·2 to 14·6)	0·87 (0·52 to 1·43)	0·61
Hospital readmission by day 90	11 (8%; 5 to 14)	20 (15%; 10 to 22)	6·8% (–0·9 to 14·7)	0·51 (0·23 to 1·10)	0·089

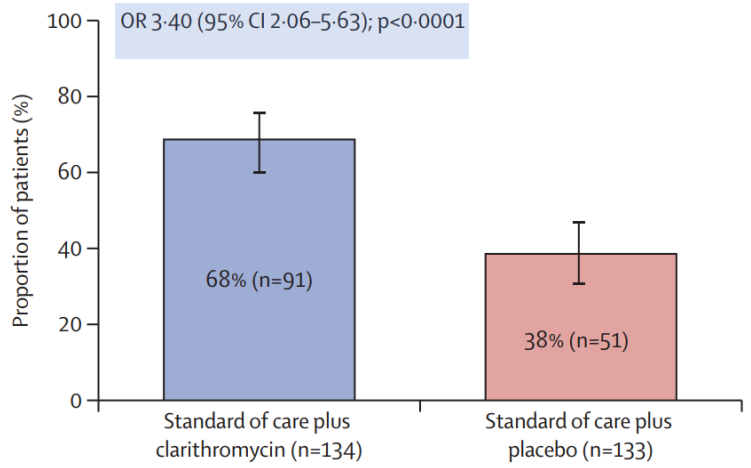
Data are n (%; 95% CI) unless otherwise stated. SOFA=Sequential Organ Failure Assessment. *Composite primary endpoint was (1) a 50% or more decrease in respiratory symptom severity score compared with visit 1; and (2) a 30% or more decrease in SOFA score compared with visit 1 or favourable change in procalcitonin kinetics (defined as ≥80% decrease in procalcitonin compared with visit 1 or blood procalcitonin <0·25 ng/mL), or both. †For definition of favourable procalcitonin kinetics, see previous footnote. ‡According to the protocol, this endpoint was scheduled at day 90. However, data were censored at day 28 because no new events occurred after day 28. §Includes patients dying early.

Table 2: **Primary and secondary study endpoints**

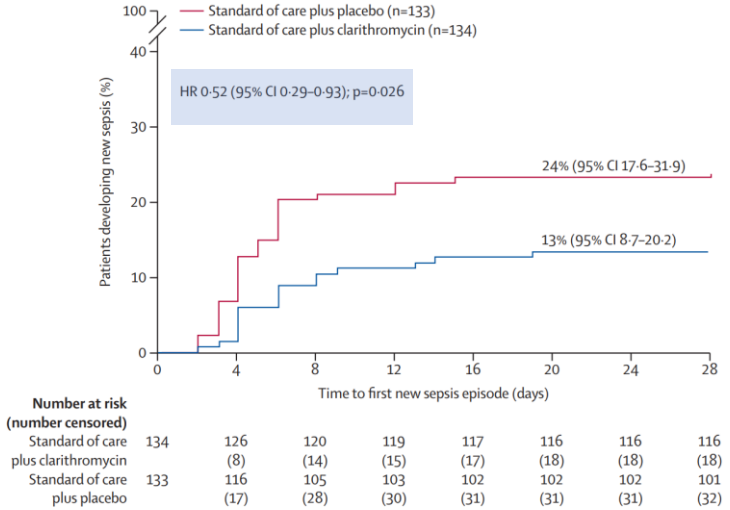
Lancet Respir Med. 2024 Apr;12(4):294-304.

ACCESS trial

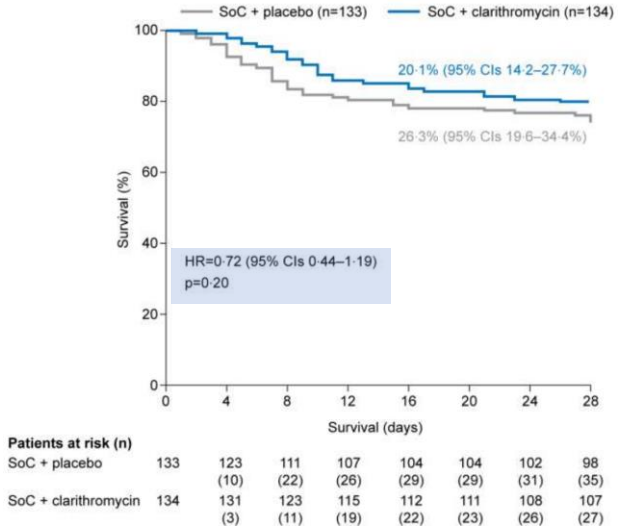
Primary endpoint at day 4



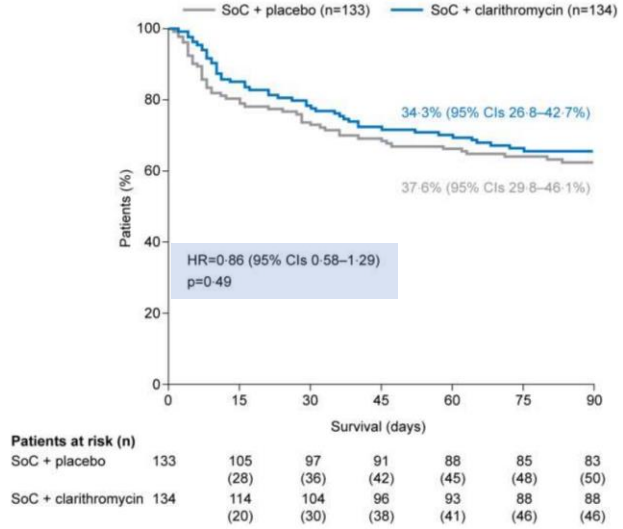
Development of new sepsis episode



28-day mortality



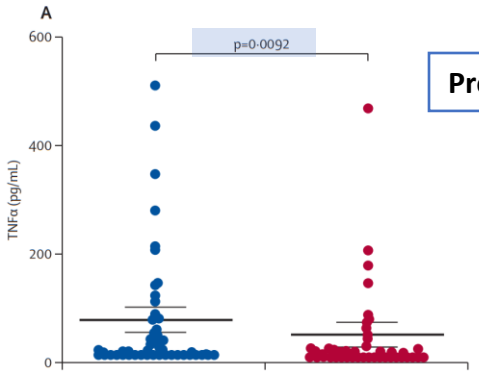
90-day mortality



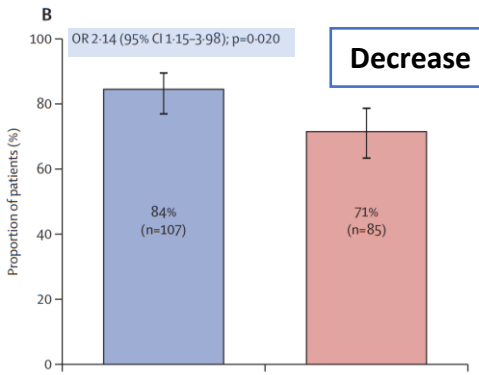
Lancet Respir Med. 2024 Apr;12(4):294-304.

ACCESS trial

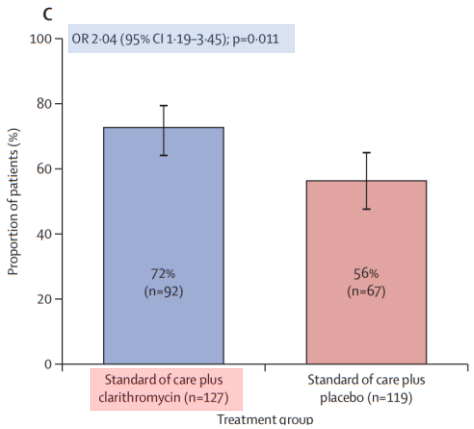
Effect of clarithromycin treatment on cytokine kinetics on day 4



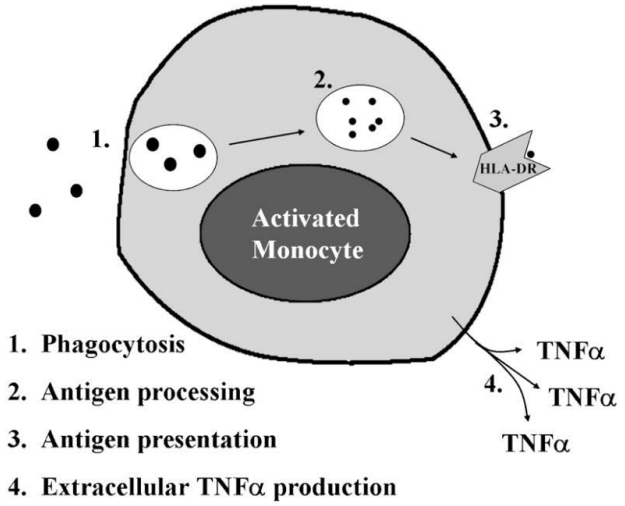
Production of TNFα by circulating PBMCs

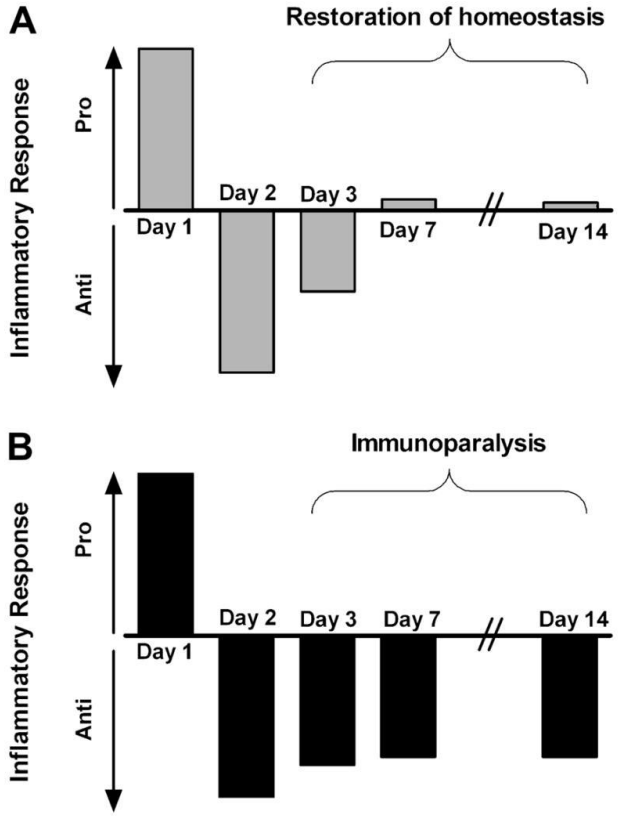


Decrease in IL-10 (≥25% baseline or <lower limit)



Decrease in IL-8/IL-10 (15%≤baseline)





Immunoparalysis: persistence of a marked compensatory anti-inflammatory innate immune response following an insult such as sepsis or trauma

- proinflammatory(IL-8)/anti-inflammatory (IL-10) ↓
- production of TNFα by circulating PBMCs ↓

Pediatr Clin North Am. 2008 Jun; 55(3): 647–xi.

ACCESS trial

Addition of clarithromycin in CAP with sepsis

- early clinical response↑
- inflammatory burden of the host↓
- progression to organ dysfunction↓
- development of new sepsis↓
- hospital stay↓

- 6.2% reduction in 28-day mortality: *not significant, but might be underpowered*
- Serious treatment-emergent adverse events by day 90: OR 0.67 [95% CI 0.42 to 1.11] (p=0.14)

- Clinical benefit may be reverse the immunoparalysis
  - TNFα from circulating PBMCs↑
  - Circulating IL-10↓

Lancet Respir Med. 2024 Apr;12(4):294-304.

BLM vs BLFQ in intubated severe CAP with sepsis

- Multicentre prospective study (n=2,436), 6-months, MV≥48h
- Patients (n=218): intubated severe CAP + (Sepsis, severe sepsis and septic shock)
- Combination therapy (n=175) → in accordance with the 2007 IDSA/ATS guidelines: 100 patients

Table 5 Comparison of demographic and clinical characteristics among 100 patients with CAP that received initial macrolide versus quinolones therapy in accordance with the 2007 IDSA/ATS guidelines

	Overall				Severe sepsis and septic shock			
	IDSA/ATS concordant ($n = 100$)	Macrolides ($n = 46$)	Quinolones ($n = 54$)	*P* value	IDSA/ATS concordant ($n = 92$)	Macrolides ($n = 40$)	Quinolones ($n = 52$)	*P* value
Age mean years (SD)	57.6 (16.2)	58.2 (16.4)	57.1 (16.2)	0.73	57.8 (16.1)	58.9 (16.3)	57.04 (16.1)	0.58
Male gender, *n* (%)	61 (61.0%)	25 (54.3%)	36 (66.7%)	0.22	58 (63.0%)	22 (55.0%)	36 (69.2%)	0.19
Mean SAPS II score (SD)	46.9 (15.6)	44.3 (15.5)	49.2 (15.5)	0.11	46.6 (15.6)	44.1 (16.1)	48.6 (15.2)	0.18
Mean SOFA score (SD)	7.68 (3.9)	7.18 (3.9)	8.14 (3.9)	0.26	7.85 (3.9)	7.33 (4.0)	8.29 (3.8)	0.29
Preexisting comorbid conditions								
COPD, *n* (%)	14 (14.0%)	7 (15.2%)	7 (13.0%)	0.77	14 (15.2%)	7 (17.5%)	7 (13.5%)	0.77
Diabetes, *n* (%)	18 (18.0%)	7 (15.2%)	11 (20.4%)	0.61	16 (17.4%)	6 (15.0%)	10 (19.2%)	0.78
Cardiomyopathy, *n* (%)	23 (23.0%)	10 (21.7%)	13 (24.1%)	0.81	22 (23.9%)	9 (22.5%)	13 (25.0%)	0.81
Chronic renal failure, *n* (%)	11 (11.0%)	3 (6.5%)	8 (14.8%)	0.21	11 (12.0%)	3 (7.5%)	8 (15.4%)	0.33
Alcohol, *n* (%)	14 (14.0%)	4 (8.7%)	10 (18.5%)	0.24	13 (14.1%)	4 (10.0%)	9 (17.3%)	0.37
Bacteremia, *n* (%)	10 (10.0%)	6 (13.0%)	4 (7.4%)	0.73	9 (12.7%)	5 (14.7%)	4 (10.8%)	0.73

Intensive Care Med. 2010 Apr;36(4):612-20.

BLM vs BLFQ in intubated severe CAP with sepsis

Lower ICU mortality in macrolide group

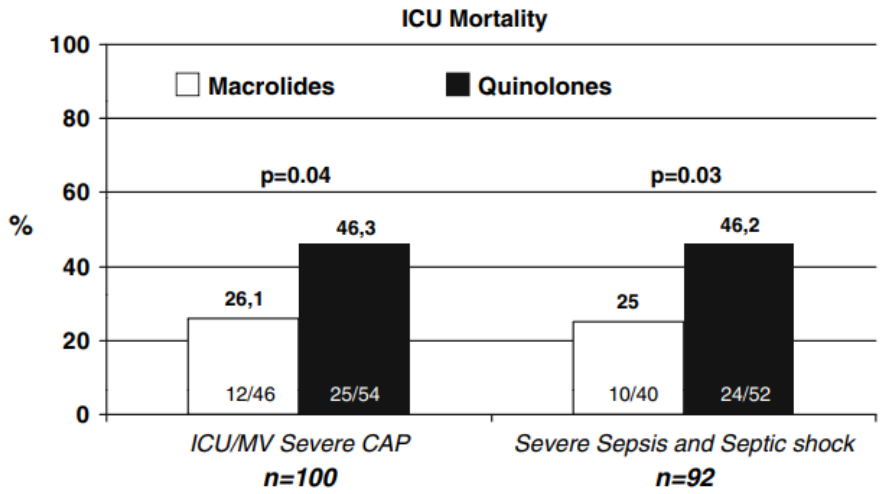


Fig. 1 Intensive care unit mortality among IDSA/ATS guideline-adherent patients according to the treatment in combination with a macrolide or a quinolone

60-day mortality

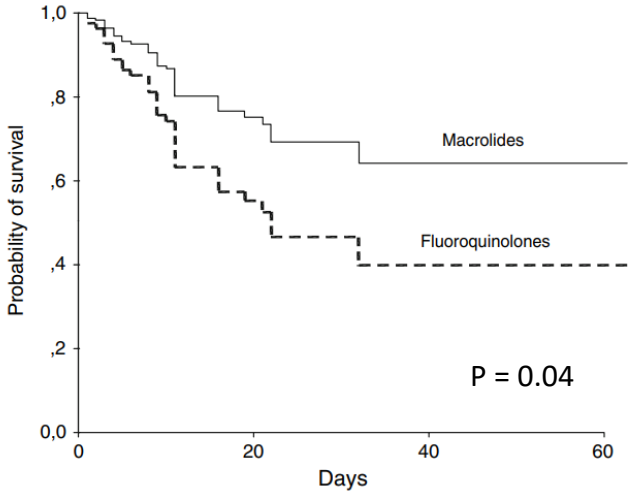


Fig. 2 Survival graph for patients treated in accordance with IDSA/ATS guideline in combination with a macrolide or a quinolone (censored at 60 days)

60-day mortality in severe sepsis/ septic shock

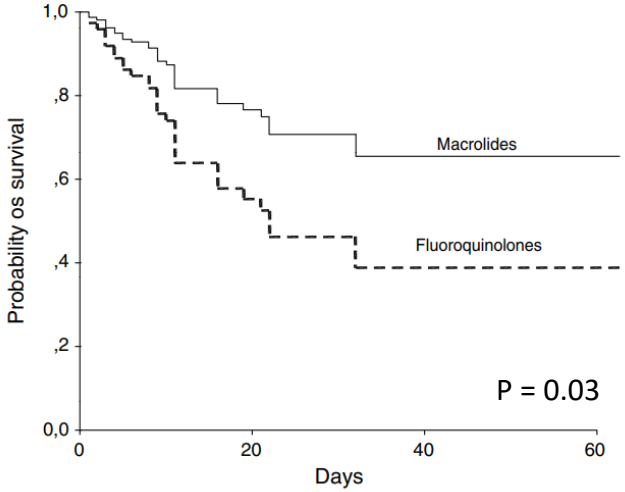


Fig. 3 Survival graph for severe sepsis/septic shock patients treated in accordance with IDSA/ATS guideline in combination with a macrolide or a quinolone (censored at 60 days)

HR of macrolide for ICU mortality compared to quinolone: 0.48 (95% CI 0.23–0.97)

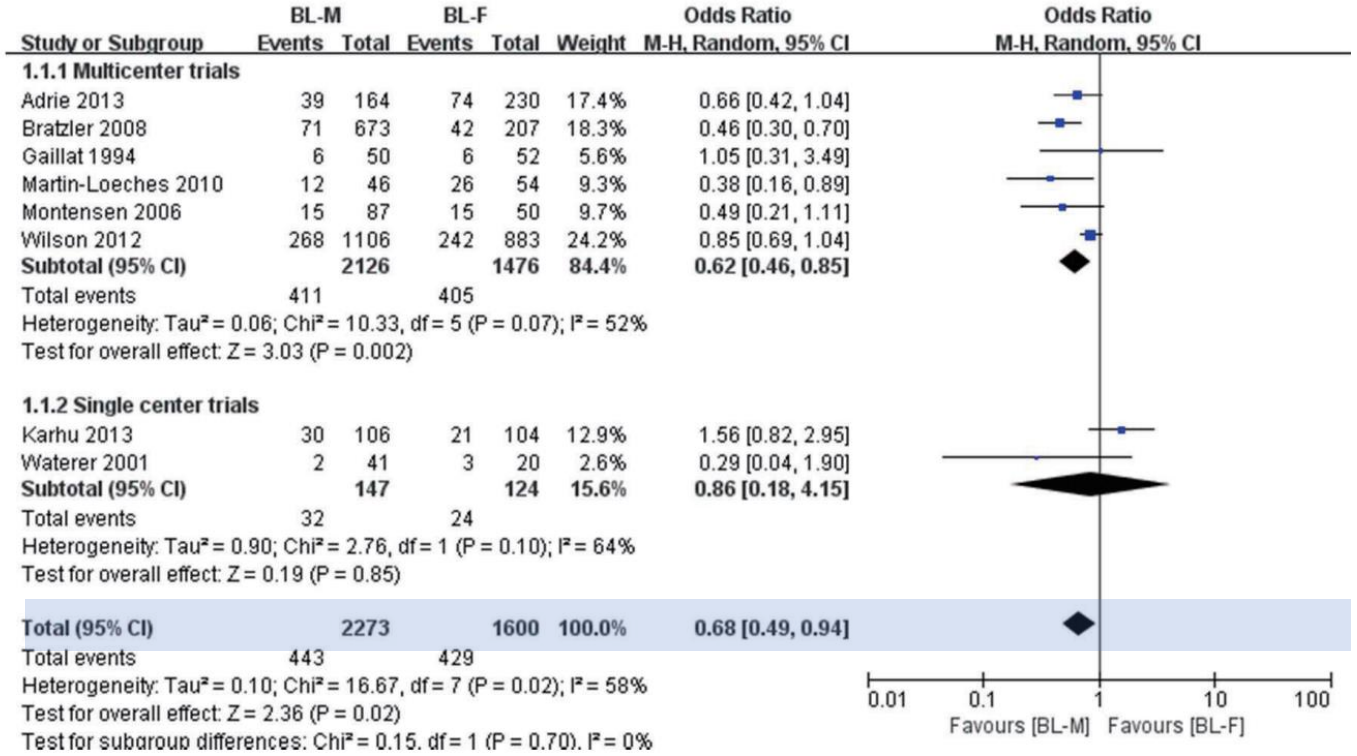
Macrolide in combination therapy improves survival when compared to fluoroquinolones

Intensive Care Med. 2010 Apr;36(4):612-20.

BLM vs BLFQ in severe CAP

- a Systemic Review and Meta-Analysis (8 studies, 3,873 patients)
- ~December 2015
- Inclusion: severe CAP, exposure to BL-M or BL-F combination
- Exclusion: outpatients, non-severe CAP, HCAP, HAP, VAP

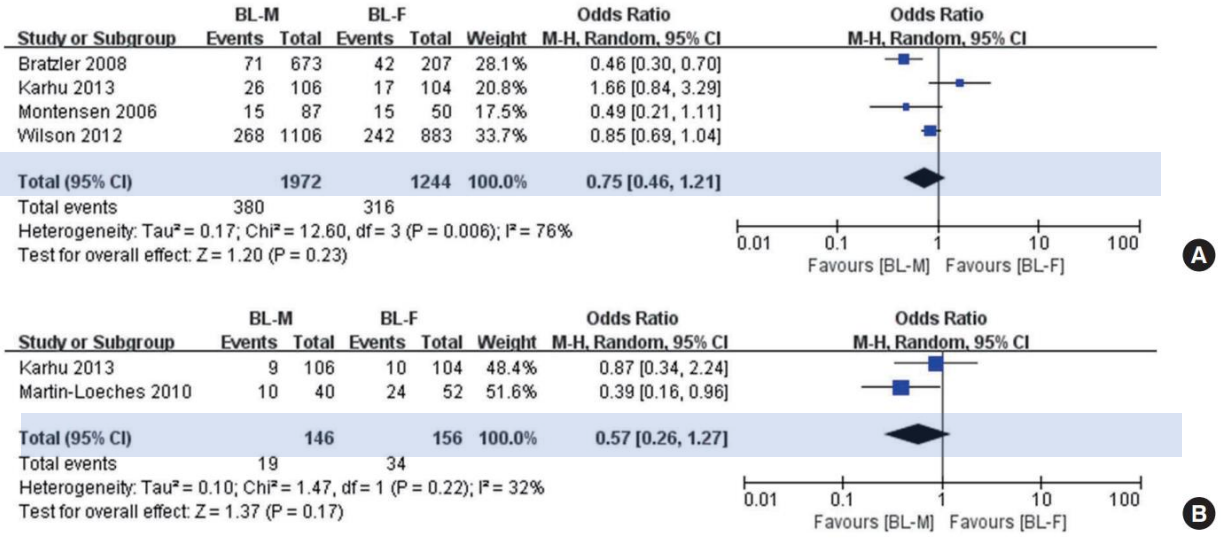
- Mortality
  - BL-M group: 19.4%
  - BL-F group: 26.8%
- OR 0.68; 95% CI 0.49 to 0.94 (P = 0.02)



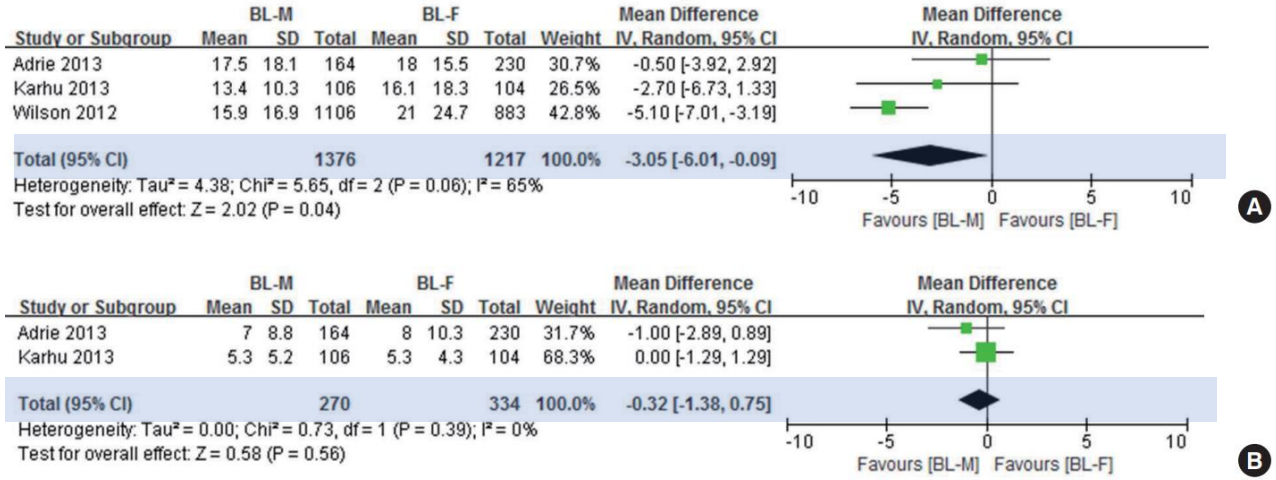
J Korean Med Sci. 2017 Jan;32(1):77-84.

BLM vs BLFQ in severe CAP

(A) Thirty-days mortality (B) ICU mortality



(A) Length of hospital stay (B) Length of ICU stay



BL-M compared to BL-F for severe CAP: may be more effective in reducing overall mortality and length of hospital stay

J Korean Med Sci. 2017 Jan;32(1):77-84.

Take home message

- Biphasic effect of macrolides: antibacterial and **anti-inflammatory effects**
- Current guidelines suggest the addition of macrolides, not fluoroquinolones, to beta-lactams as empirical antibiotic therapy in patients with severe CAP.
- Clinical benefit of macrolide may be reverse the immunoparalysis in patients with CAP with sepsis
- ACCESS study suggested that the best candidates for oral clarithromycin treatment are patients with **moderate or severe CAP in the early stages of sepsis**