



ΕΝΔΟΦΛΕΒΙΑ ΚΛΑΡΙΘΡΟΜΥΚΙΝΗ

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Δ΄ Παθολογική Κλινική

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Εθνικό & Καποδιστριακό Πανεπιστήμιο Αθηνών



SEVERITY GUIDES MACROLIDE PRESCRIPTION

META-ANALYSIS OF 16 OBSERVATIONAL STUDIES

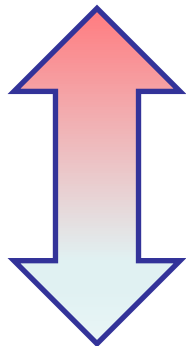
(Nie W, et al. *J Antimicrob Chemother* 2014; 69: 1441)

Characteristic	No of studies	OR (95%CI)	p
All studies	16	0.66 (0.61-0.77)	<0.0001
Severe	7	0.66 (0.58-0.76)	<0.0001
Pneumococcal	6	0.59 (0.37-0.95)	0.03

PARADOX PHENOMENON

Survival benefit

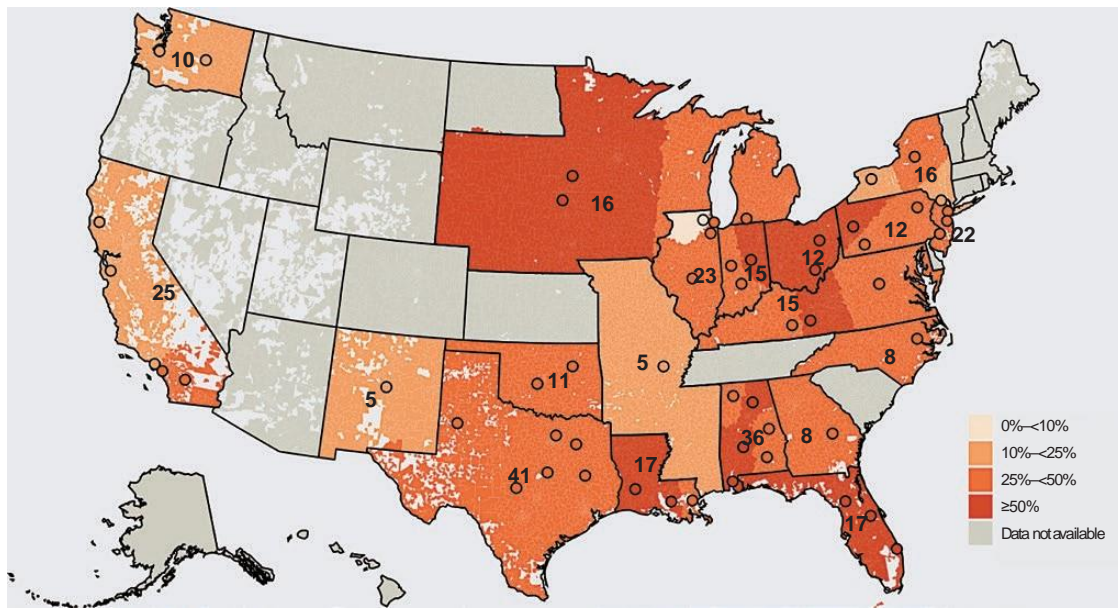
- Nie W, et al. *J Antimicrob Chemother* 2014; 69: 1441



↑↑ macrolide resistance

- 3626 *S.pneumoniae* isolates
- Blood= 43.9%; respiratory 56.1%

Gupta V, et al. *Open Forum Infect Dis* 2021; 8: ofab063



MACROLIDES AND TREATMENT FAILURE OF COMMUNITY-ACQUIRED PNEUMONIA

(Reiner-Benaim A, et al. *Eur J Clin Microbiol Infect Dis* 2022; 41: 99)

- Database of Maccabi Healthcare Services
- January 2010-April 2020
- Failure: incidence during the first 14 days from start of treatment of any of need for hospitalization; 2nd therapy; death

	Odds ratio (95% CI)*	p-value
Cephalosporins + atypical coverage**	0.77 (0.73-0.81)	<0.0001
Penicillins	1.25 (1.16-1.34)	<0.0001
Fluoroquinolones	1.10 (1.01-1.20)	0.056
Penicillins + atypical coverage**	0.85 (0.77-0.95)	0.0009
Fluoroquinolones + atypical coverage**	1.16 (0.94-1.42)	0.266
Macrolide intake	0.93 (0.88-0.98)	0.012

*reference: cephalosporins

**macrolide or tetracycline

CI: confidence interval

PUBLISHED STUDIES BETWEEN 2016 AND 2021 ON THE ADJUNCTIVE ROLE OF MACROLIDES FOR SEVERE CAP

Ref.	Design	Groups	Most common pathogens	Outcome measure*
1	Retrospective analysis from the CAPO database	<ul style="list-style-type: none"> No macrolide= 302 Macrolide= 247 	Streptococcus pneumoniae 75%	In-hospital 30-day mortality for severe CAP: <ul style="list-style-type: none"> No-macrolide 16.4% Macrolide 5.8%; p: 0.027
2	Retrospective analysis	<ul style="list-style-type: none"> β-lactam = 369 β-lactam plus macrolide= 225 	<i>S. pneumoniae</i> 17.9% vs 18.2% <i>K. pneumoniae</i> 15.4% vs 9.3%	30-day mortality: 13.8% vs 1.8% (p< 0.001)
3	Prospective cohort	<ul style="list-style-type: none"> β-lactam plus macrolide= 932; severe 57% Fluoroquinolone \pm β-lactam= 783 	<i>S. pneumoniae</i> 45% vs 44% Polymicrobial 16% vs 12%	30-day mortality <ul style="list-style-type: none"> Overall 5% vs 8% (p: 0.015) CRP >150 mg/l 3% vs 8% (p<0.001)
4	Open-label quasi-RCT	<ul style="list-style-type: none"> Ceftriaxone + clarithromycin (n=104) Ampicillin/sulbactam + clarithromycin (n=108) 	<i>S. pneumoniae</i> 33.6% vs 24.1% <i>M. pneumoniae</i> 36.5% vs 25.9%	Efficacy end-of-treatment: 57% vs 94% (p: 0.055)

1. Arnold FW, et al. *Resp Med* 2018; 140: 115
2. Okumura J, et al. *Respirology* 2018; 23: 526
3. Ceccato A, et al. *Chest* 2019; 155: 795
4. Hamao N, et al. *BMC Pulm Med* 2020; 20: 160

CAP: community-acquired pneumonia
 CRP: C-reactive protein

*p-values refer to comparisons with the β -lactam plus clarithromycin group



Patients with documented infection and ≥ 2 SIRS criteria= 6,213

Patients with CAP= 1,396

Excluded= 172

- Did not meet Sepsis-3 definitions= 216
- Lost to follow-up= 6

Patients with CAP and sepsis (Sepsis-3)= 1,174

Clarithromycin group= 136

- Excluded = 6 (no β -lactam intake= 6)

Analyzed= 130

Azithromycin group= 196

- Excluded = 16 (no β -lactam intake= 16)
- Matching for: APACHE II, SOFA, CCI, PSI, β -lactam

Analyzed= 130

β -lactam group= 529

- Intake of any macrolide=0
- Excluded= 79 (Intake of quinolones= 47; intake of ceftazidime= 32)
- Matching for: APACHE II, SOFA, CCI, PSI, β -lactam

Analyzed= 130

Respiratory

fluoroquinolone group= 162

- Excluded= 6 (Intake of macrolides=1; intake of antibiotics= 5)
- Matching for: APACHE II, SOFA, PSI, CCI

Analyzed= 130

MULTICENTER STUDY FROM GREECE

(Kyriazopoulou E, et al. *Intern J Antimicrob Agents* 2020; 55: 105836)

	Clarithromycin + β -lactam	Azithromycin + β -lactam	Fluoro- quinolone	β -lactam
Number	130	130	130	130
Male gender (n, %)	76 (58.5)	75 (57.7)	70 (60.8)	68 (52.3)
Age (years)	72.5 \pm 15.6	74.1 \pm 15.1	72.3 \pm 16.0	73.4 \pm 15.9
APACHE II	15.2 \pm 7.1	15.4 \pm 7.1	16.8 \pm 7.1	16.1 \pm 6.1
SOFA	5.21 \pm 3.65	4.76 \pm 3.12	5.01 \pm 3.18	5.69 \pm 3.04
CCI	4.35 \pm 2.56	4.35 \pm 2.48	4.23 \pm 2.62	4.48 \pm 2.25
PSI	155.7 \pm 46.4	149.9 \pm 45.5	158.9 \pm 47.3	156.7 \pm 40.1

APACHE: acute physiology and chronic health evaluation

CCI: Charlson's Comorbidity Index

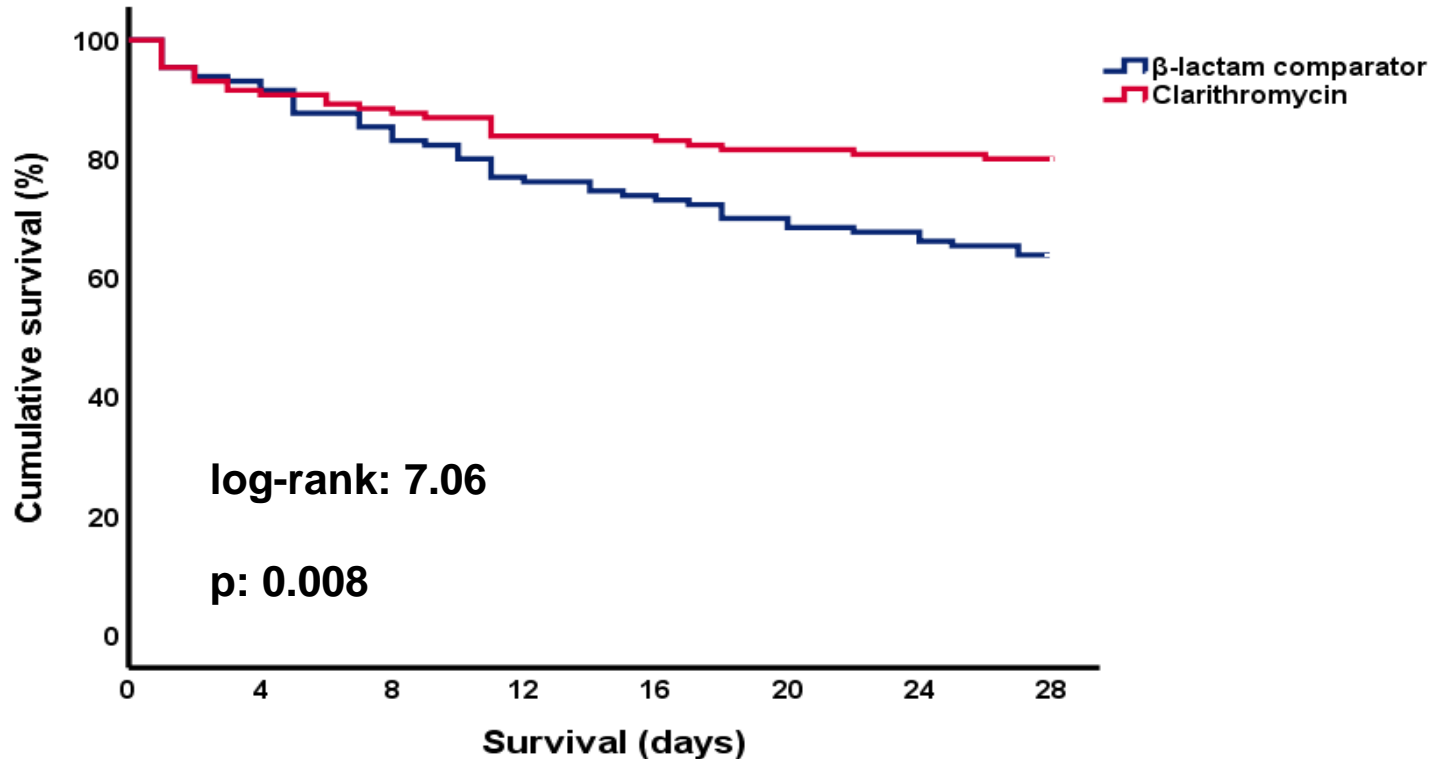
PSI: pneumonia severity index

SOFA: sequential organ failure assessment

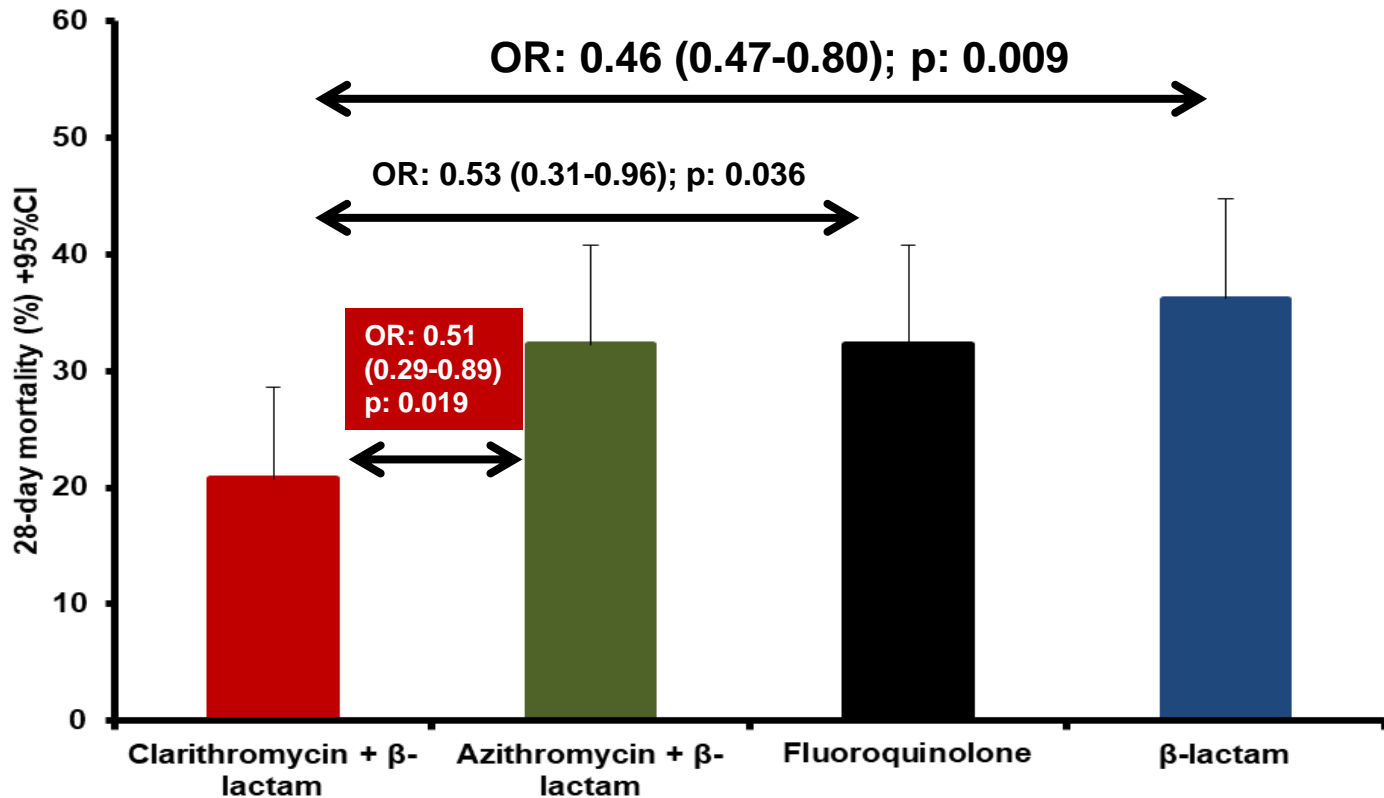
28-DAY MORTALITY

CLARITHROMYCIN + β -LACTAMS VS β -LACTAMS

(Kyriazopoulou E, et al. *Intern J Antimicrob Agents* 2020; 55: 105836)

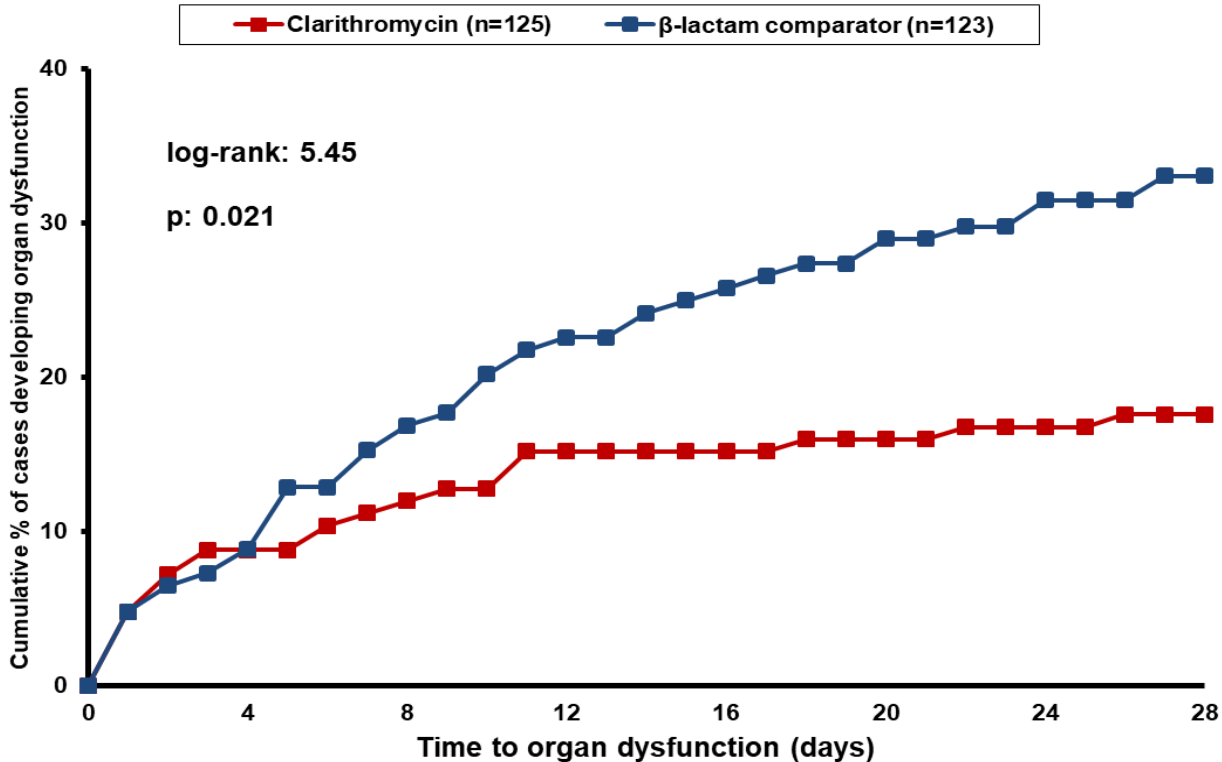


28-DAY MORTALITY: ALL GROUP COMPARISONS

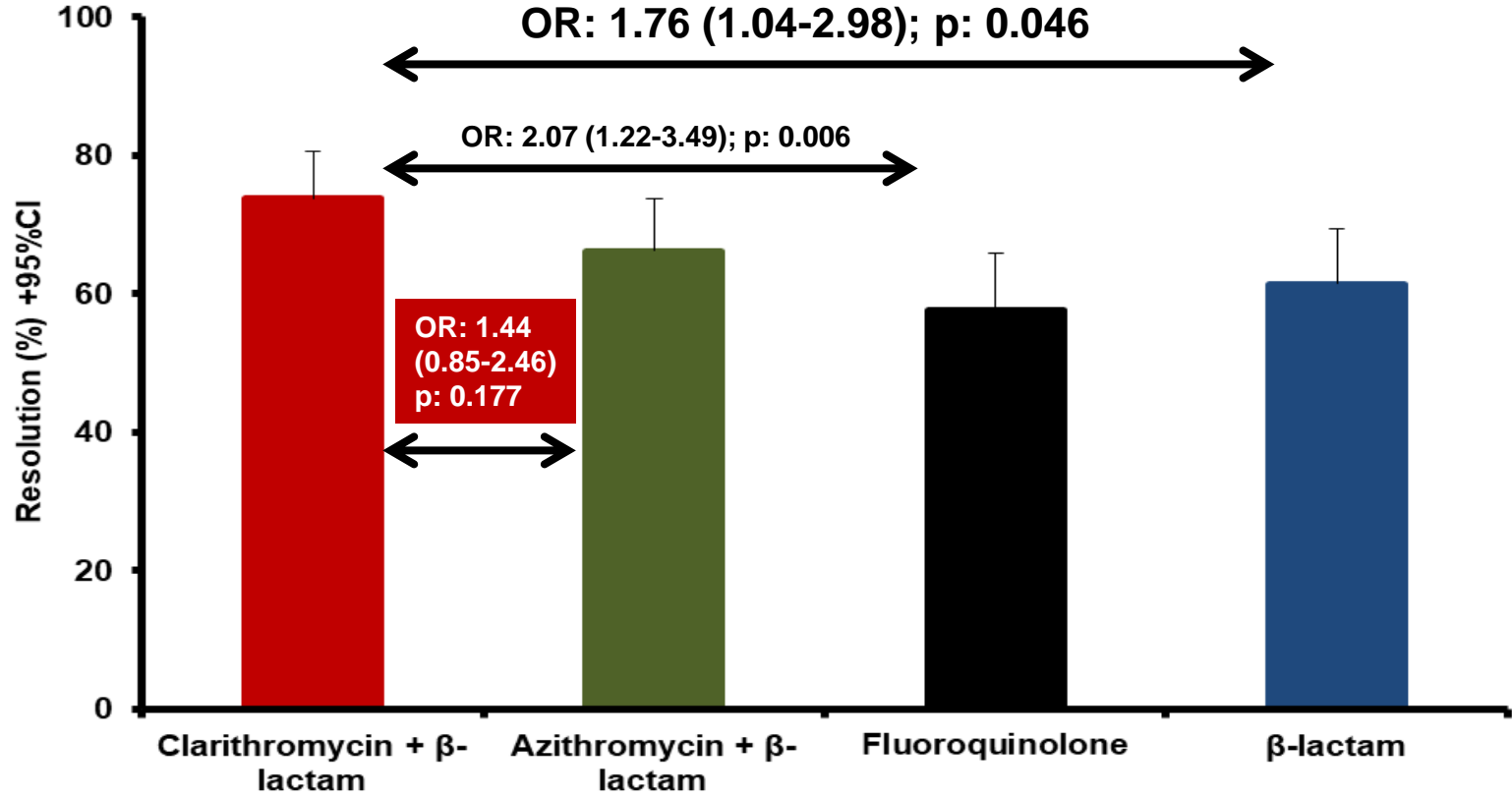


CI: confidence interval
OR: odds ratio

TIME TO DEVELOPMENT OF ORGAN DYSFUNCTION



EFFECT ON PNEUMONIA RESOLUTION

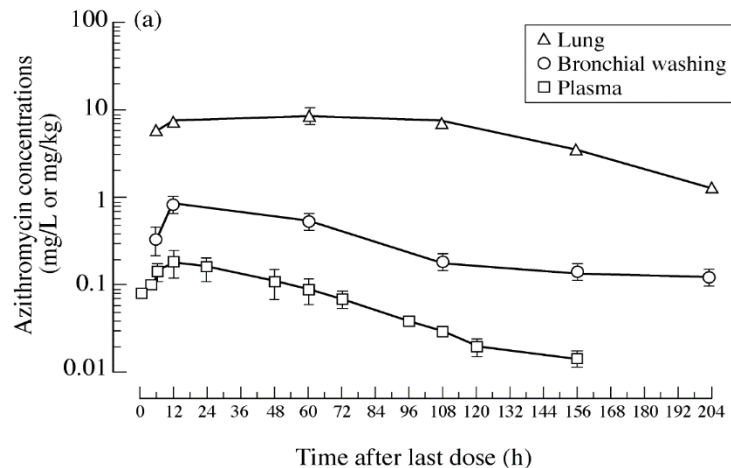
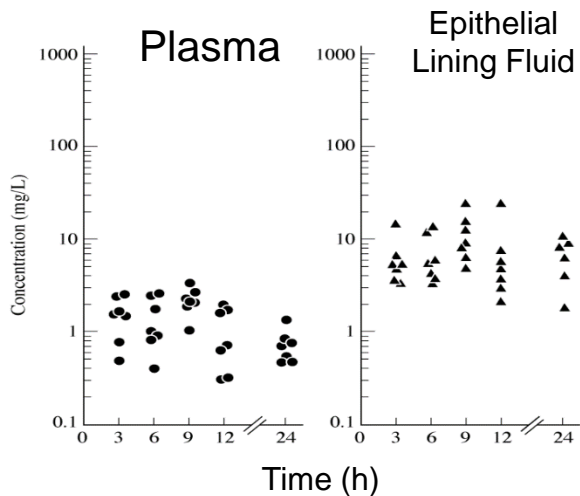


CI: confidence interval
OR: odds ratio

POSSIBLE EXPLANATION 1:

↑ penetration in the epithelial lining fluid (ELF)

Median Azithromycin ELF: $1.01 \mu\text{g/ml}$
Danesi R et al. *J Antimicrob Chemother* 2003; 51: 939



Median Clarithromycin ELF : $34.4 \mu\text{g/ml}$
Gotfried MH et al. *J Antimicrob Chemother* 2003; 52: 450

POSSIBLE EXPLANATION 2: MODULATION OF THE ACUTE INFLAMMATORY RESPONSE

HOW TO EVIDENCE IN A CLINICAL SETTING?

- Study a setting of high mortality
- Infections caused by Gram-negative isolates outside the macrolide antimicrobial spectrum

Two studies

- Gram-negative sepsis¹
- Ventilator-associated pneumonia²

1. Giamarellos-Bourboulis EJ, et al. *J Antimicrob Chemother* 2014; 69: 1111

2. Giamarellos-Bourboulis EJ, et al. *Clin Infect Dis* 2008; 46: 1157

Η ΒΑΡΥΤΗΤΑ ΤΗΣ ΠΝΕΥΜΟΝΙΑΣ ΠΟΥ ΣΥΝΔΕΕΤΑΙ ΜΕ ΤΟ ΜΗΧΑΝΙΚΟ ΑΕΡΙΣΜΟ

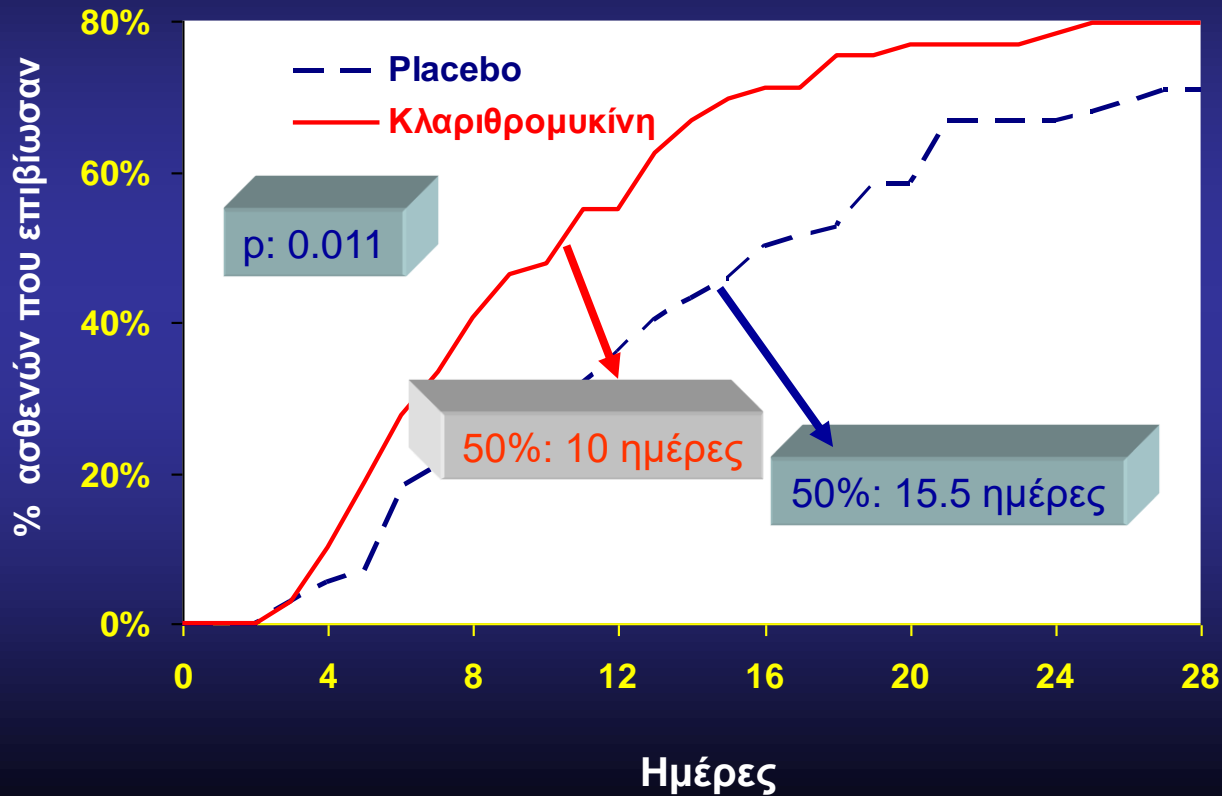
(Giamarellos-Bourboulis EJ, et al. *Clin Infect Dis* 2008, 46: 1157)

(N= 100) PLACEBO +
ANTIBIOTIKA

(100) ΚΛΑΡΙΘΡΟΜΥΚΙΝΗ + ANTIBIOTIKA
1000 mg ημερησίως ωριαία έγχυση x 3 ημέρες

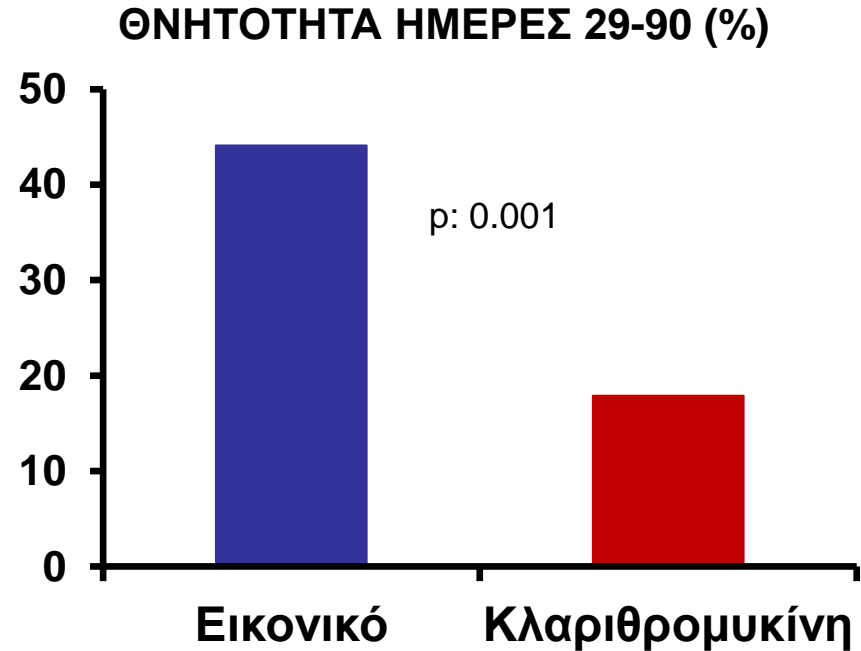
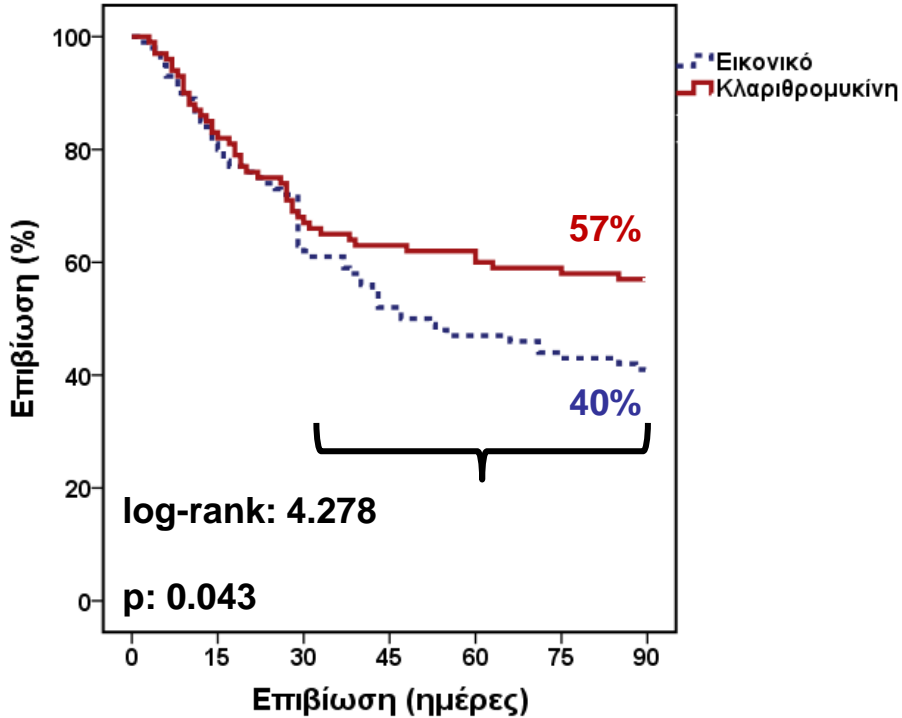
64% τεκμηρίωση παθογόνων
ΟΛΑ πολυανθεκτικά Gram-αρνητικά

ΕΠΙΔΡΑΣΗ ΣΤΗ ΛΥΣΗ ΤΗΣ ΝΑΡ



Η ΤΕΛΙΚΗ ΕΠΙΒΙΩΣΗ!!!

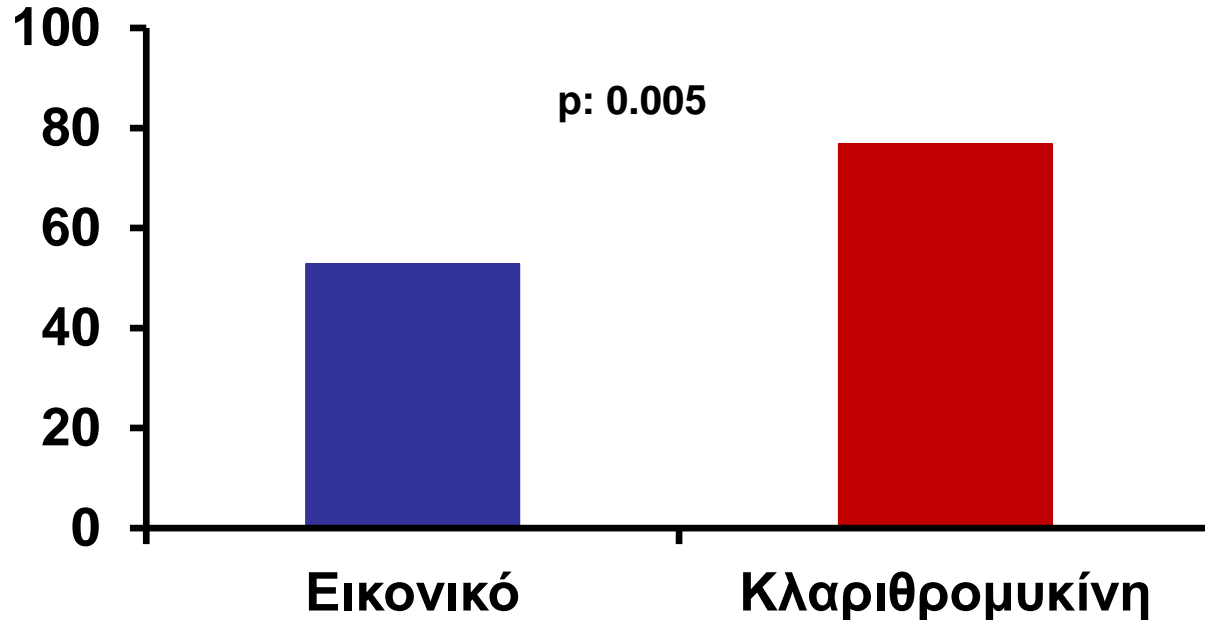
(Tsaganos T, et al. *Antimicrob Agents Chemother* 2016; E-pub Apr28)



ΤΙ ΣΥΜΒΑΙΝΕΙ ΜΕΤΑ ΤΗΝ ΗΜΕΡΑ 28;

(Tsaganos T, et al. *Antimicrob Agents Chemother* 2016; E-pub Apr28)

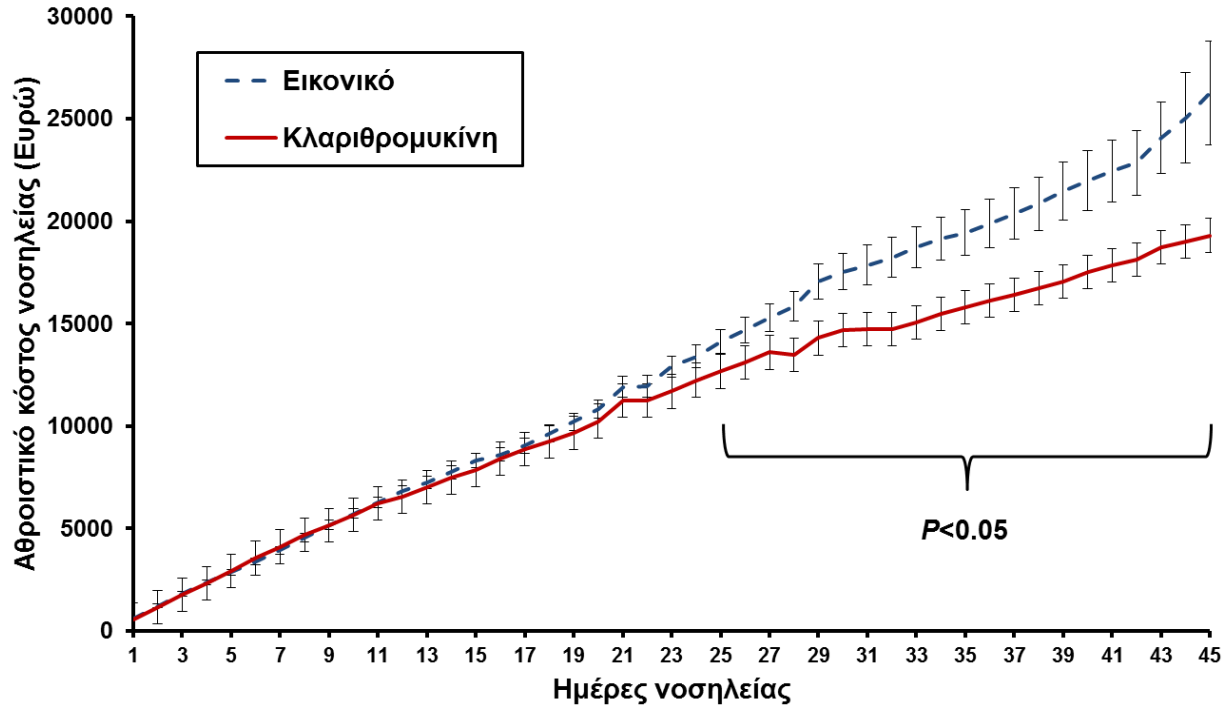
ΜΕΤΑΦΟΡΑ ΣΤΗΝ ΠΤΕΡΥΓΑ ΚΑΙ ΕΞΟΔΟΣ(%)



Ο ΑΠΑΝΘΡΩΠΟΣ ΠΡΟΒΛΗΜΑΤΙΣΜΟΣ: Η ΕΠΙΒΙΩΣΗ ΚΟΣΤΙΖΕΙ!!!

(Tsaganos T, et al. *Antimicrob Agents Chemother* 2016; E-pub Apr28)

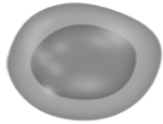
ΣΥΝΟΛΟ ΑΣΘΕΝΩΝ



ΟΡΟΣ

Καταπληξία/MODS
↓ IL-10/TNF α

ΜΟΝΟΚΥΤΤΑΡΑ



OXI MODS
↑ mCD86
↑ TNF α

OXI MODS
↑ TNF α

OXI MODS
↑ mTREM-1
↑ TNF α

Καταπληξία/MODS
↑ mTREM-1

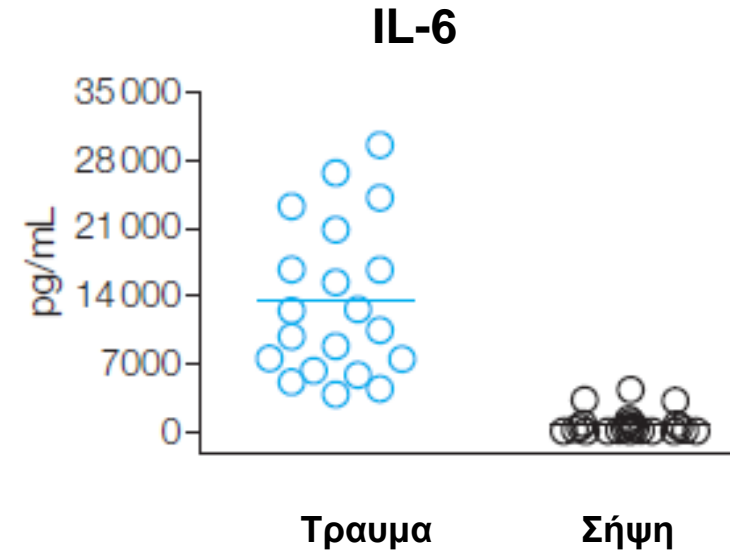
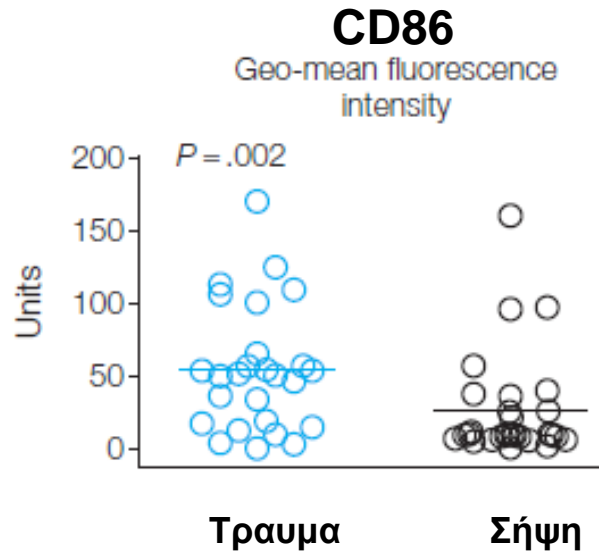
Καταπληξία/MODS
↑ Αποπτωση
↑ mCD86
↓ TNF α
↑ IL-6

Καταπληξία/MODS
↑ IL-6



Η ΣΗΨΗ ΧΑΡΑΚΤΗΡΙΖΕΤΑΙ ΑΠΟ ΑΝΟΣΟΠΑΡΑΛΥΣΗ

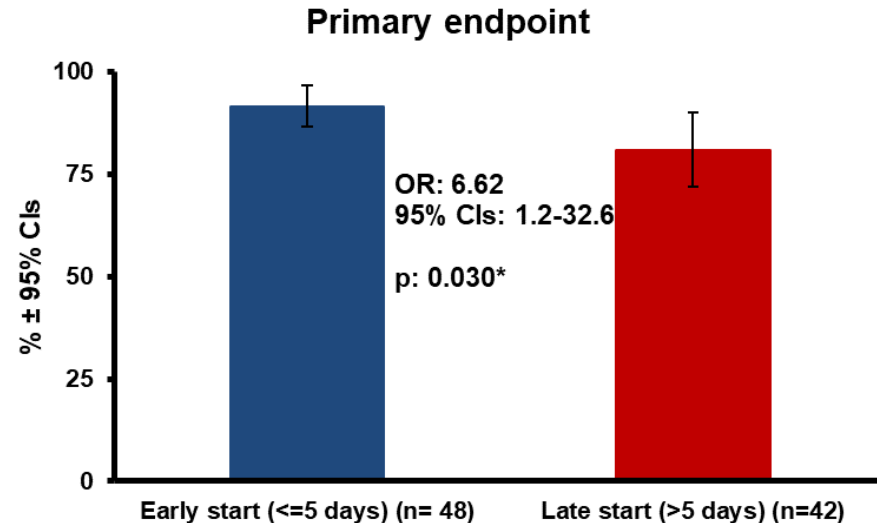
(Boomer JS, et al. *JAMA* 2011; 306: 2594-2605)



Anti-inflammatory Clarithromycin to Improve SARS-CoV 2 Infection Early: ACHIEVE trial

(Tsiakos K, et al. *Infect Dis Ther* 2021; 10: 2333)

- Open-label, single-arm, 90 hospitalized adults with COVID-19 pneumonia
- WHO-CPS 4 or 5
- Oral 500mg clarithromycin 500mg twice daily for 7 days
- Primary endpoint: patients recovered at the end of treatment



* After forward step-wise logistic regression analysis

CI: confidence interval

CPS: clinical progression scale

OR: odds ratio

WHO: World Health Organization

ΑΠΟΔΕΙΞΗ: ΛΟΙΜΩΞΕΙΣ ΑΠΟ ΠΑΘΟΓΟΝΑ ΕΚΤΟΣ ΤΟΥ ΦΑΣΜΑΤΟΣ ΤΩΝ ΜΑΚΡΟΛΙΔΩΝ

(Giamarellos-Bourboulis EJ, et al. *J Antimicrob Chemother* 2014, 69: 1111-118)

ΑΣΘΕΝΕΙΣ ΜΕ ΣΗΨΗ ΚΟΙΝΟΤΗΤΑΣ Ή ΝΟΣΟΚΟΜΕΙΑΚΗ ΣΗΨΗ (v= 654)

Πρωτοπαθής-δευτεροπαθής Gram-αρνητική βακτηριαιμία/Οξεία πυελονεφρίτιδα/Οξεία ενδοκοιλιακή λοίμωξη

ΑΠΟΚΛΕΙΣΘΗΚΑΝ (v= 54)

- Λήψη μακρολιδών (v= 53)
- Άρνηση συγκατάθεσης (v =1)

ΕΙΚΟΝΙΚΟ (v= 298) +
ΑΝΤΙΜΙΚΡΟΒΙΑΚΑ

- Πρόωρη διακοπή= 20
- Αναλύθηκαν= 298

IV ΚΛΑΡΙΘΡΟΜΥΚΙΝΗ (v= 302) +
ΑΝΤΙΜΙΚΡΟΒΙΑΚΑ

*1000 mg ημερησίως ωριαία έγχυση x 4
ημέρες*

- Πρόωρη διακοπή= 49
- Αναλύθηκαν= 302

ΚΑΤΑΛΗΚΤΙΚΑ ΣΗΜΕΙΑ

- **Πρωτογενές καταληκτικό σημείο**

Θνητότητα από σοβαρή σήψη/καταπληξία + MODS

- **Δευτερογενές καταληκτικό σημείο**

Χρόνος λύσης της εστίας σήψης

- **Διερευνητικό καταληκτικό σημείο**

Κόστος νοσηλείας

ΧΑΡΑΚΤΗΡΙΣΤΙΚΑ ΒΑΡΕΩΣ ΠΑΣΧΟΝΤΩΝ

	Εικονικό	Κλαριθρομυκίνη	p
APACHE II	12.8 ± 7.3	13.7 ± 7.6	0.116
WBCs (/mm ³)	15133.9 ± 11215.8	15291.2 ± 8587.6	0.851
Στάδιο σήψης			0.412
Απλή σήψη	189 (63.4%)	177 (58.6%)	
Σοβαρή Σήψη	65 (21.8%)	79 (26.2%)	
Σηπτική καταπληξία	44 (14.7%)	46 (15.2%)	

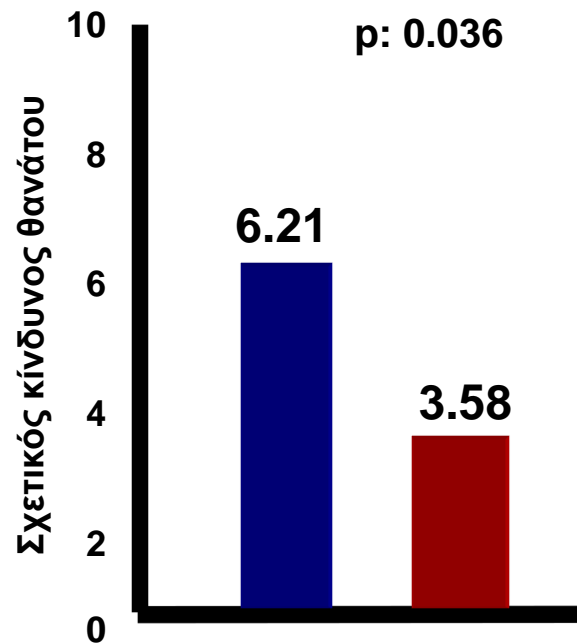
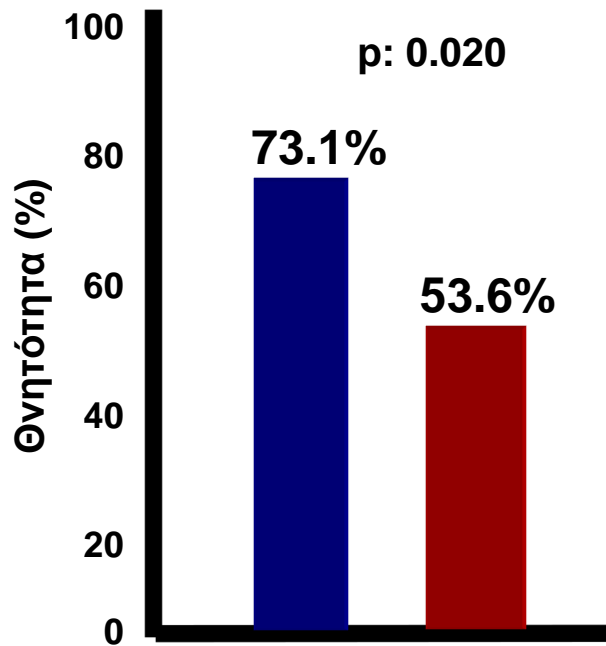
ΚΑΤΑΛΛΗΛΟΤΗΤΑ ΧΟΡΗΓΟΥΜΕΝΩΝ ΑΝΤΙΜΙΚΡΟΒΙΑΚΩΝ

	Εικονικό	Κλαριθρομυκίνη	p
Ευαισθησία παθογόνων ΑΙΜΑΤΟΣ στα χορηγούμενα αντιμικροβιακά	48 (78.7%)	59 (88.1%)	0.232

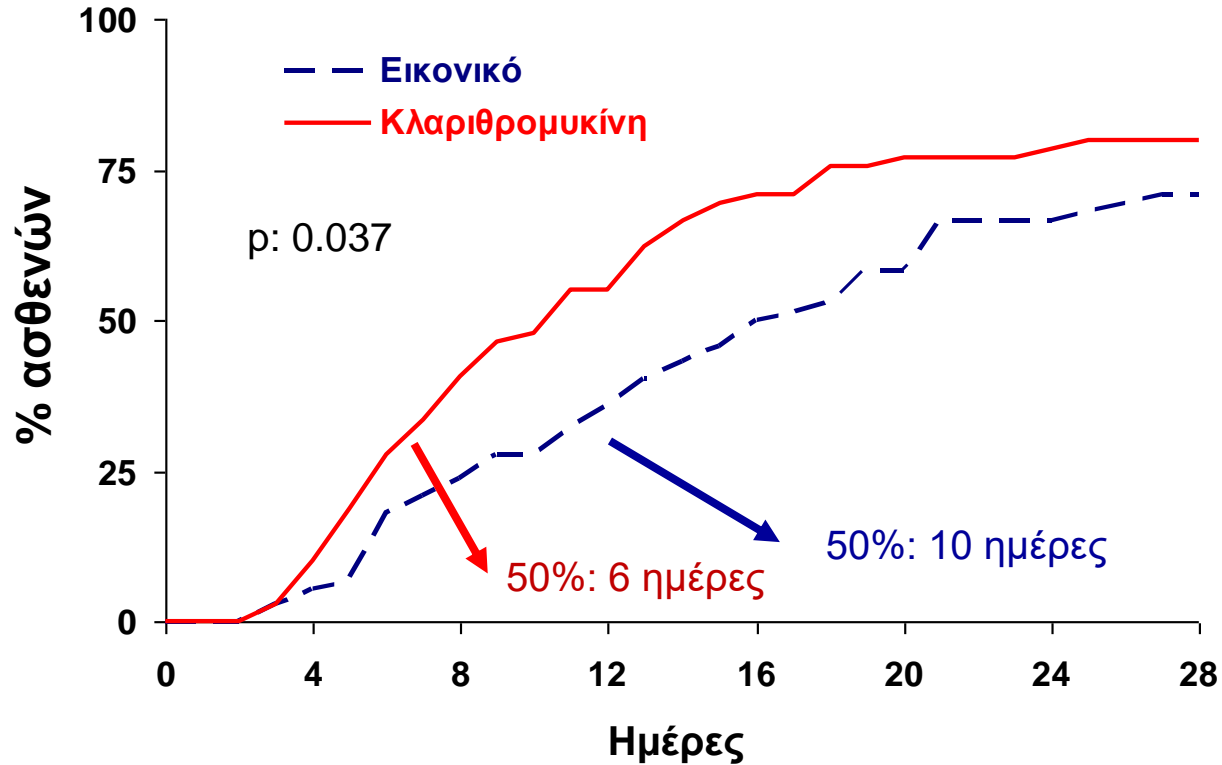
	Εικονικό	Κλαριθρομυκίνη	p
Ευαισθησία παθογόνων ΟΥΡΩΝ στα χορηγούμενα αντιμικροβιακά	63 (86.3%)	60 (93.8%)	0.170

ΘΝΗΤΟΤΗΤΑ ΑΠΟ ΣΗΠΤΙΚΗ ΚΑΤΑΠΛΗΞΙΑ + MODS

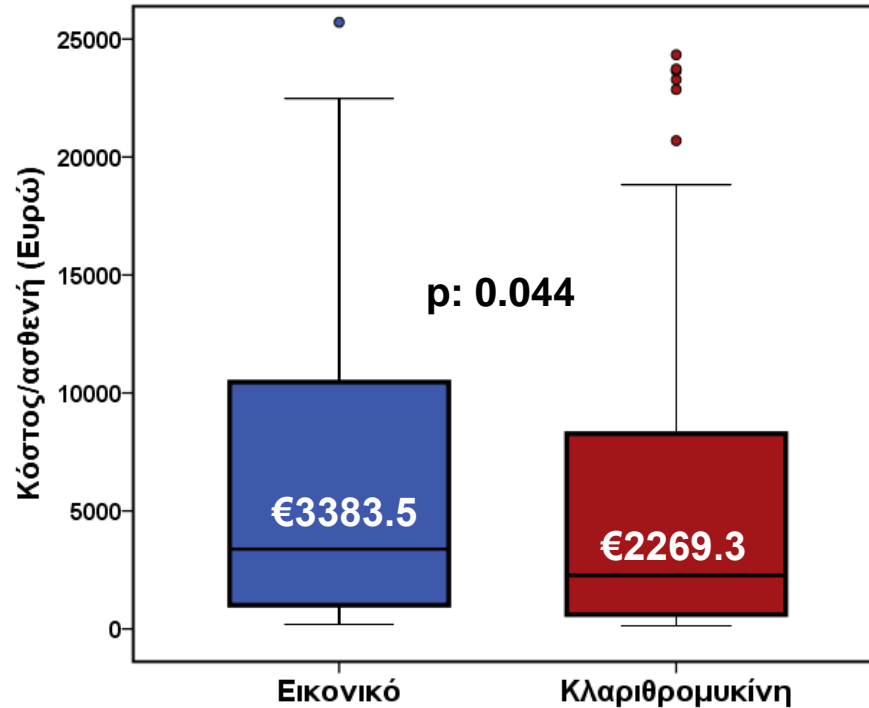
ΕΙΚΟΝΙΚΟ ΚΛΑΡΙΘΡΟΜΥΚΙΝΗ



ΕΠΙΔΡΑΣΗ ΣΤΗ ΛΥΣΗ ΤΗΣ ΣΗΠΤΙΚΗΣ ΕΣΤΙΑΣ

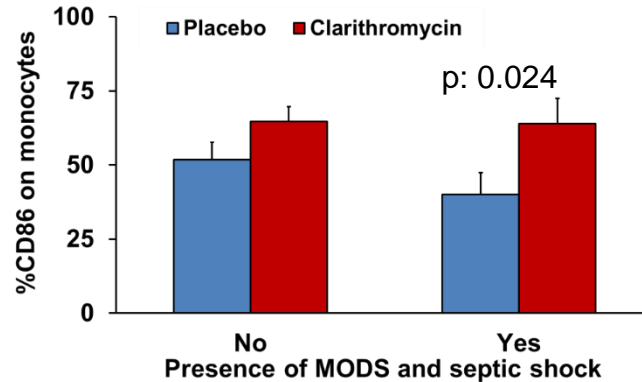
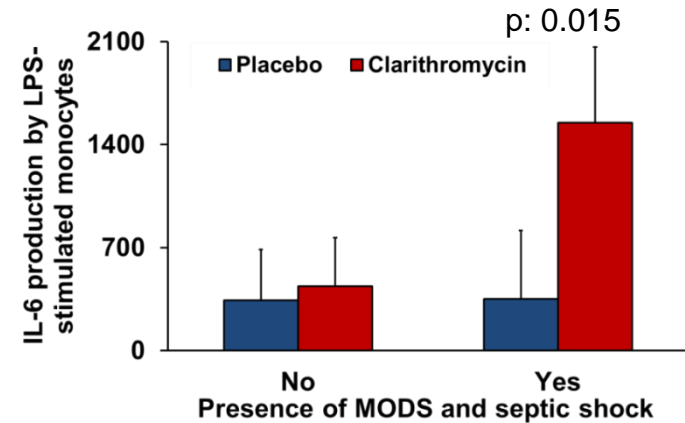
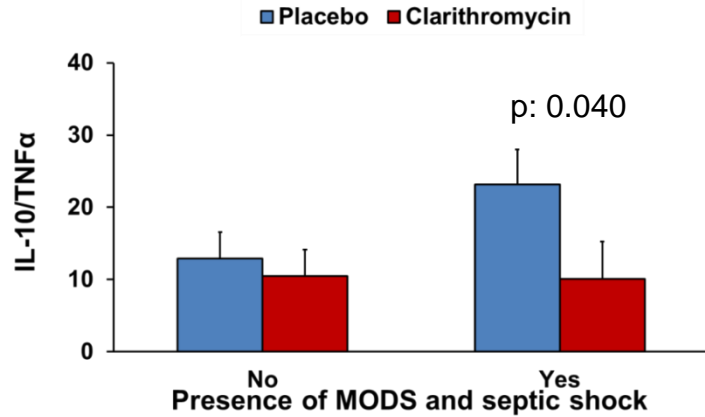


ΟΙΚΟΝΟΜΙΚΗ ΩΦΕΛΕΙΑ



REVERSAL OF IMMUNOPARALYSIS

(Spyridaki A, et al. *Antimicrob Agents Chemother* 2012; 56: 3819)

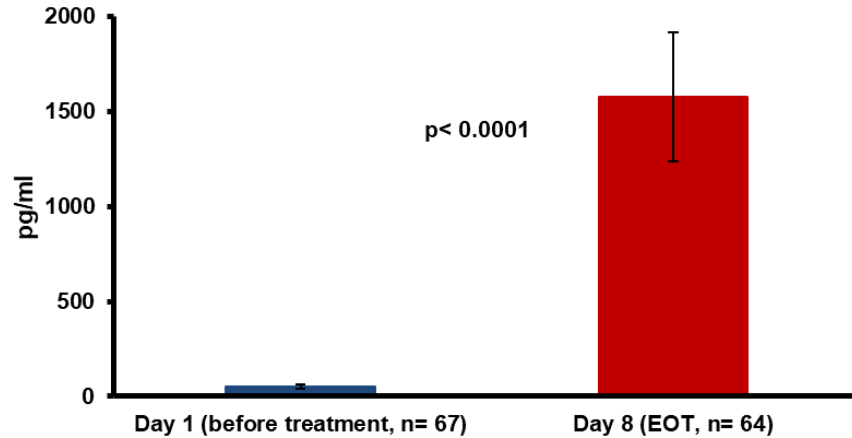


IL: interleukin
LPS: lipopolysaccharide
MODS: multiple organ dysfunction syndrome
TNFα: tumor necrosis factor-alpha

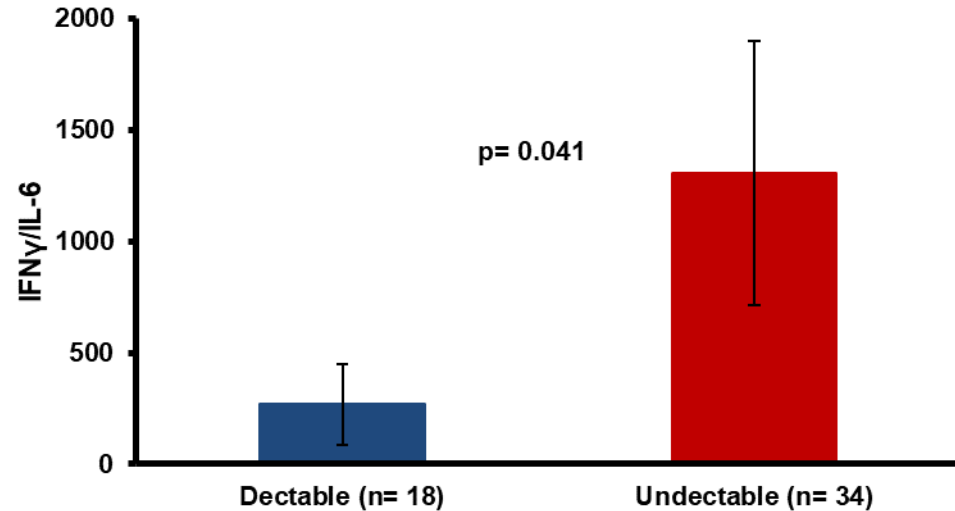
ACHIEVE: CYTOKINE STIMULATION TARGETING SARS-CoV-2

(Tsiakos K, et al. *Infect Dis Ther* 2021; 10: 2333)

IFN γ *C.albicans*-stimulation for 5 days



RdRp gene detection at EOT




EOT: end-of-treatment
IFN γ : interferon-gamma
IL: interleukin
n: number of patients



COMMENTARY

The Role of Macrolides for the Management of Community-Acquired Pneumonia and Pneumonia by the Novel Coronavirus SARS-CoV-2 (COVID-19): A Position Paper by Four Medical Societies from Greece

Evangelos J. Giamarellos-Bourboulis  · George L. Daikos ·
Panagiotis Gargalianos · Charalambos Gogos · Marios Lazanas ·
Periklis Panagopoulos · Garyphallia Poulakou · Helen Sambatakou ·
Michael Samarkos

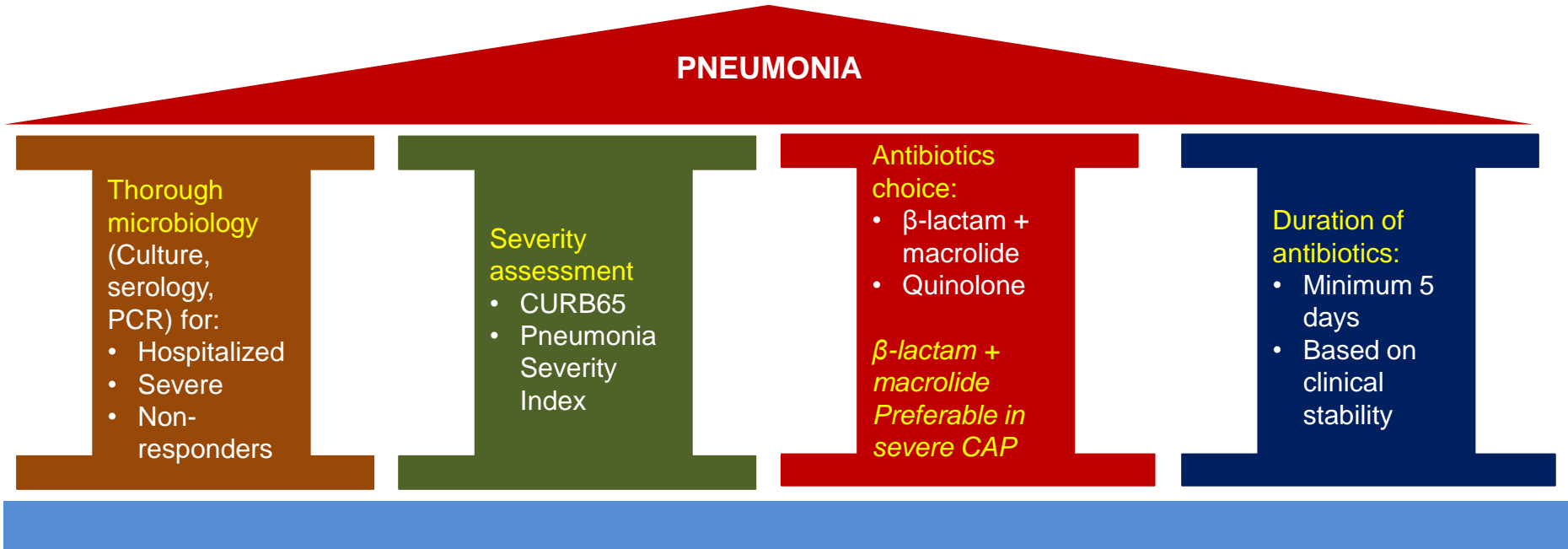
Received: March 13, 2021 / Accepted: May 26, 2021 / Published online: June 16, 2021
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- Hellenic Society for Infectious Diseases
- Hellenic Society for the Management of AIDS
- Hellenic Society for Chemotherapy
- Hellenic Sepsis Study Group



MAIN PILLARS OF PNEUMONIA MANAGEMENT

(Martin-Loeches & Torres. Curr Opin Pulm Med 2021; 27: 210)



CAP: community-acquired pneumonia

PCR: multiplex panels of polymerase chain reaction for syndromic testing