Weill Cornell Medicine

What Have We Learned about Anti-Inflammatory Therapy in Severe Pneumonia?

- Michael S. Niederman , M.D.
  Lauder Family Professor in Pulmonary and Critical Care Medicine

  Professor of Clinical Medicine

  Weill Cornell Medical College

- Lead Academic and Patient Quality Officer
  Division, Pulmonary and Critical Care Medicine

  New York Presbyterian- Weill Cornell Medical Center

msn9004@med.cornell.edu

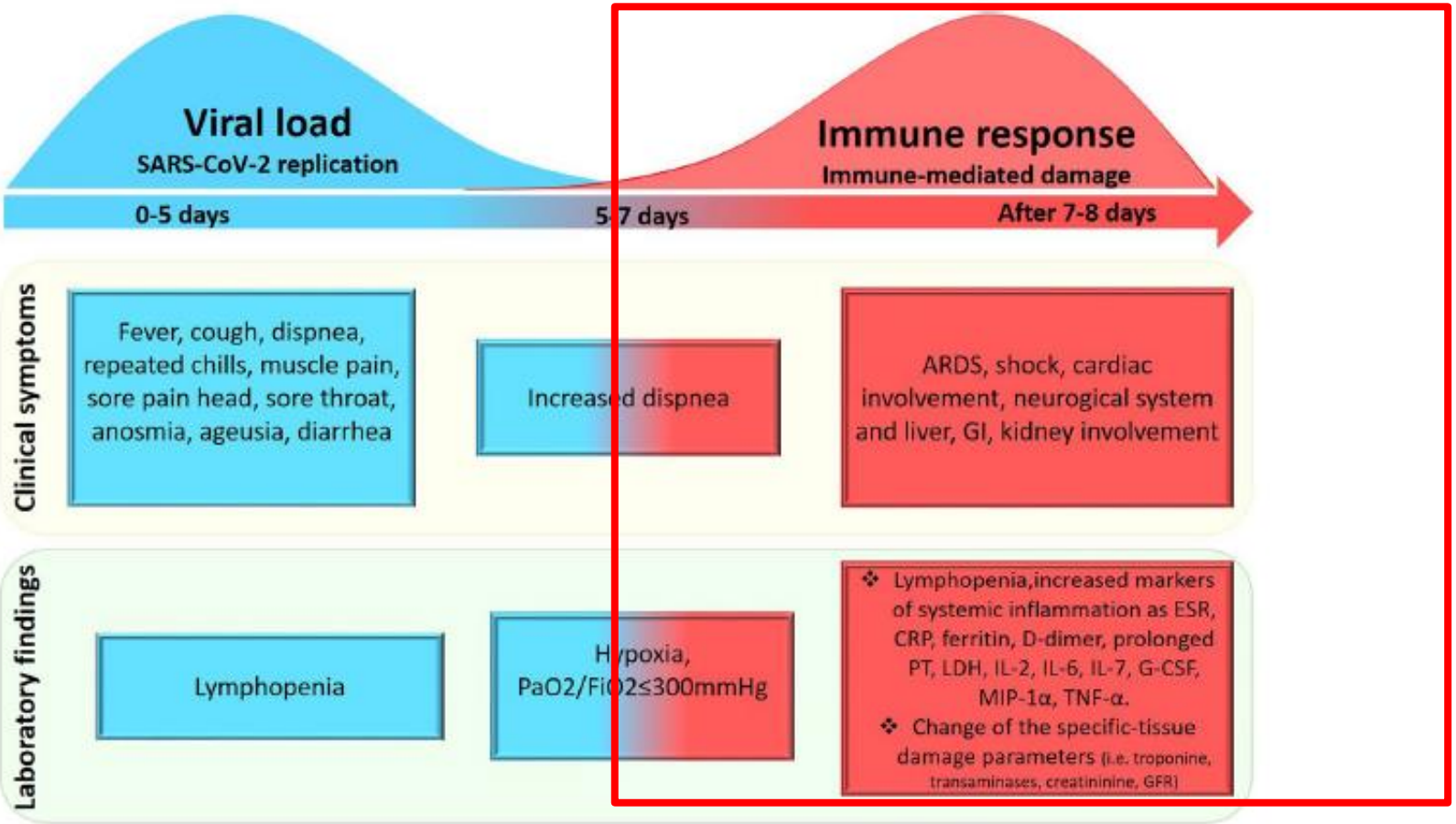
Aims and Objectives

- Discuss how an understanding of disease mechanisms can allow for PERSONALIZED use of anti-inflammatory therapy in severe pneumonia.
- Lessons learned and questions raised from the use of anti-inflammatory therapy in COVID-19 pneumonia
- Review the data about the efficacy of 2 anti-inflammatory therapies , commonly used for severe pneumonia
  - Macrolides
  - Systemic corticosteroids

Lessons Learned From The Use of Anti-inflammatory Therapy In COVID-19

- 4 anti-inflammatory therapies have had some success
  - Corticosteroids widely used
  - Tocilizumab (IL-6 antagonist, receptor binder) (BIIa). FDA approved.
  - Baricitinib (JAK inhibitor) (BIIa). FDA approved.
  - Anakinra (IL-1 receptor antagonist) .FDA EUA in COVID.
- Multiple other agents tested with limited success
- For success: need plausible pathogenesis mechanism, biomarker to identify those who may benefit
  - RCT may be more convincing than platform trial, but slower.
- Key issues of : timing, concomitant effective anti-viral therapy first , dosing, duration of therapy , combination therapy (maybe best eval with platform trials)

Timing is Everything!!



Cantini F, et al. Drugs 2020; 80:1929-46

Remdesivir + Dexamethasone vs. Dexamethasone Alone

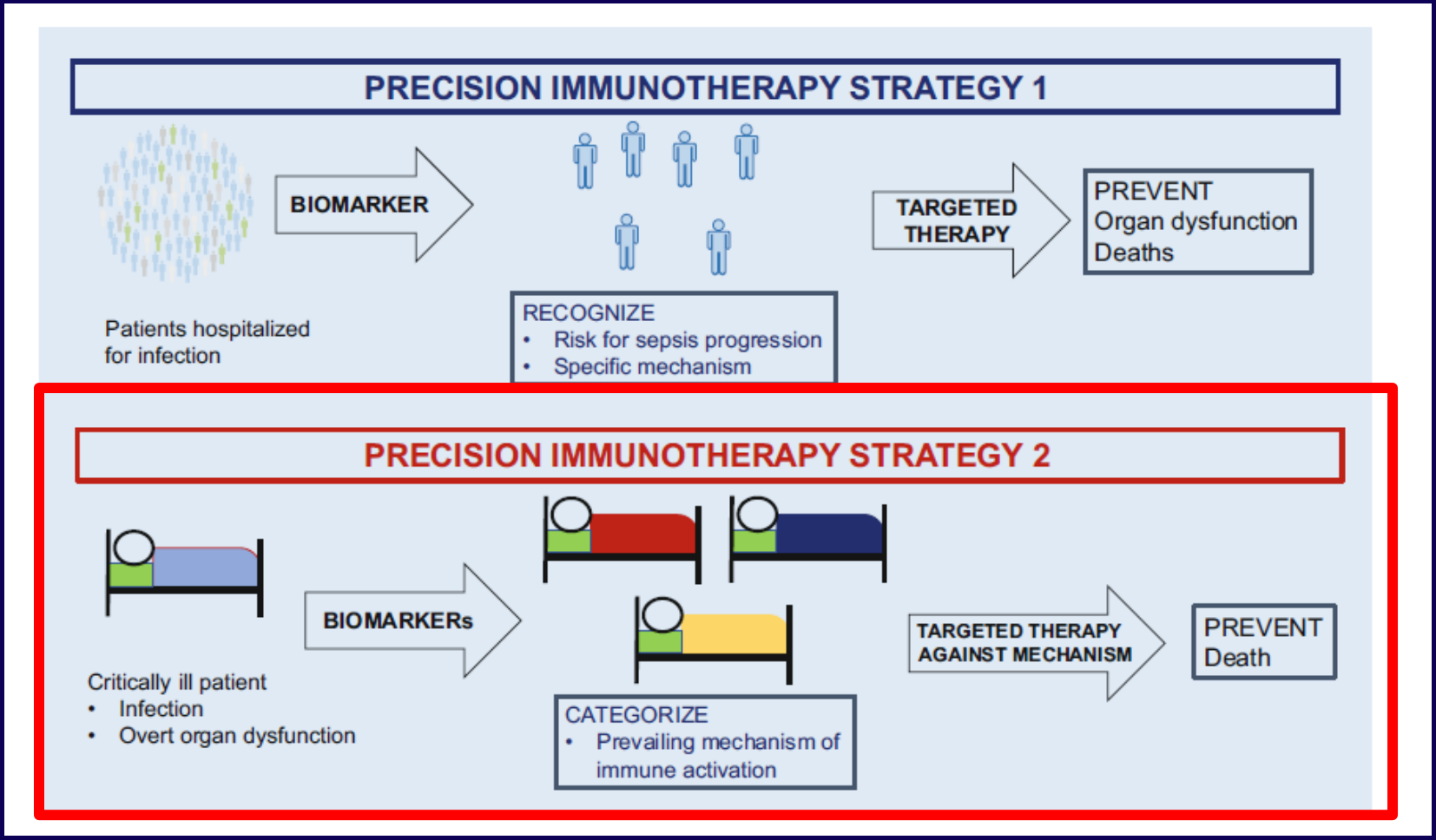
Table 2. Viral clearance, duration of the disease and mortality in the two groups of treatment.

Outcomes	Remdesivir + Dexamethasone	Dexamethasone	P <
Initial symptoms/discharge COVID free, median days, (IQR)	16 (15-20)	22 (19-26)	0.0001
Viral clearance from beginning of treatment, median days (IQR)	6 (6-8)	16 (13-19)	0.001
Hospitalization, median days, (IQR)	13 (10-15)	17 (12-19)	0.0001
30-days Mortality, n (%)	1 (1.3%)	12 (16%)	0.005

– Marrone A, et al. CID 2022; 75:e403-09

Is Precision Therapy Possible?

- Giamarellos-Bourboulis E. Med Klin IntensivmedNotfmed 2023 · 118 (Suppl 2):S80–S85



Choosing the Best Patients for Immunotherapy: Clinical Features vs Biomarker Levels?

- Steroids: hospitalization plus need for supplemental oxygen in COVID-19.
  - ? High level of inflammation in CAP
- Tocilizumab: mechanical ventilation or ECMO; elevated CRP and oxygen in RECOVERY
- Baricitinib: mechanical ventilaton or ECMO ; Ely W, et al: Lancet 2022
- Anakinra: suPAR (solubile urokinase plasminogen activator) > 6 ng/ml, ; PaO2/FiO2 ratio > 150 and 90% on supplemental oxygen; proposed to adjust dosing by ferritin levels Kyriazopoulou E. et al. Nature Med 2021; 27:1752-60

Intensive Care Med
https://doi.org/10.1007/s00134-023-07033-8

Question 3: When using initial empirical therapy for sCAP, should a macrolide or fluoroquinolone be used as part of combination therapy, to reduce mortality and adverse clinical outcomes?

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.

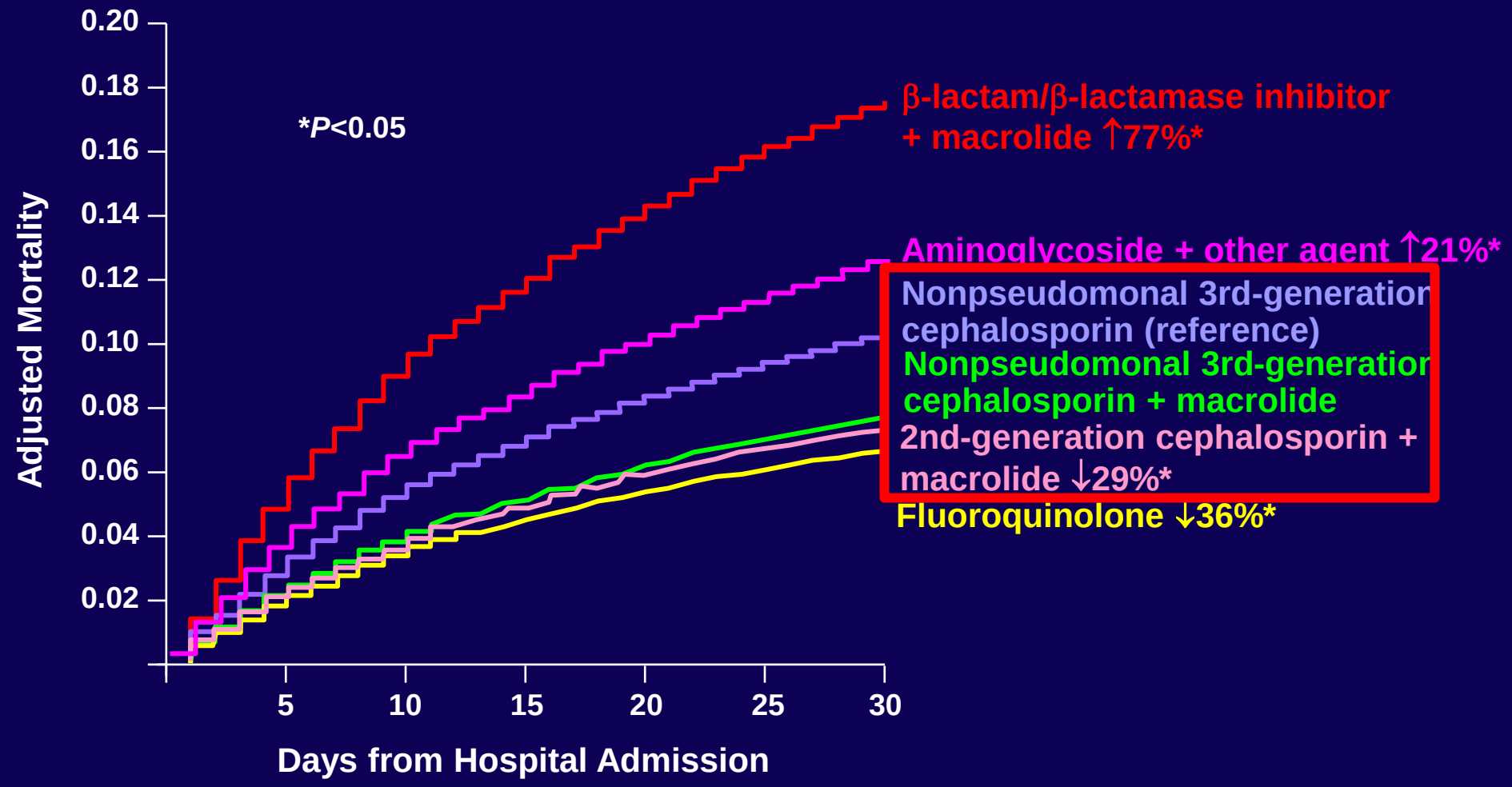
Check for updates

ne
red

elli[8],
ho-Montero[14],
19,

CAP: Decreased Mortality With Addition of a Macrolide to A Cephalosporin

Effect of Antimicrobials on 30-Day Mortality in Hospitalized Elderly Patients (n=12,945)



IS THE BENEFIT OF MACROLIDES IN CAP DUE TO ANTIMICROBIAL OR ANTI-INFLAMMATORY EFFECT?

The Benefit of Macrolides Varies Year to Year: Is this due to varying frequency of atypicals?

Empiric Antibiotic Therapy and Mortality Among Medicare Pneumonia Inpatients in 10 Western States*

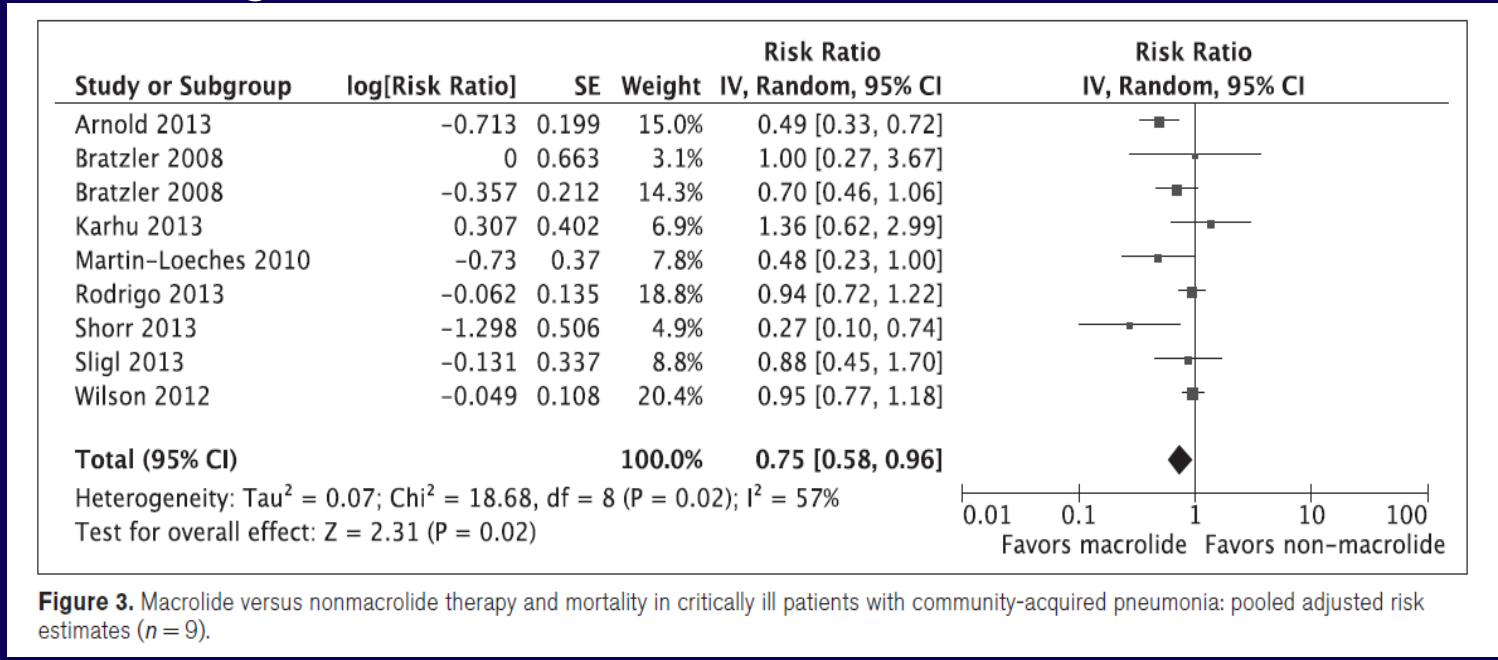
1993, 1995, and 1997

Peter M. Houck, MD; Richard F. MacLehose, MS; Michael S. Niederman, MD, FCCP; and Joseph K. Lowery, PhD

- 10,069 Medicare patients >age 65 years treated in Western states in 1993, 1995, 1997
  - 65%–70% in PSI risk groups III–V, 25%–28% in ICU
    - β-lactam monotherapy: 57% 1993, 56% 1995, 49% 1997
    - β-lactam/ macrolide: 10% 1993, 16% 1995, 24% 1997
    - Quinolone monotherapy: 1.5% all years
  - Macrolide plus β-lactam combination with OR <1.0 all years compared to β-lactam alone, but statistically significant (OR=0.42) only in 1993, but not 1995 or 1997
    - Not related to severity of illness: 60% getting macrolides in all years in 2 highest PSI classes.
- **Houck, et al. *Chest*. 2001;119:1420-1426**

Routine Macrolide Use In Severe CAP?

- Meta-analysis of macrolide use in severe CAP
- 28 studies, nearly 10,000 patients
- Mortality risk of 0.82 with macrolide (21% vs 24% (p=0.02)
- Higher benefit if risk adjusted
- Trend of BL/M being better than BL/F



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)

Figure 3. Macrolide versus nonmacrolide therapy and mortality in critically ill patients with community-acquired pneumonia: pooled adjusted risk estimates ($n = 9$).

Sligl W, et al. Crit Care Med 2014; 42:420-32

Combination Therapy in CAP: Macrolide vs. Quinolone: Are Differences due to anti-inflammatory effects?

- Prospective, observational, multicenter study of 218 intubated CAP patients in 27 ICU's
- 75.7% with severe sepsis and septic shock
- 46% got guideline-compliant therapy
- Macrolide, but not quinolone use associated with reduced mortality.
- Martin-Loeches, et al. Intens Care Med 2010; 36:612-620.

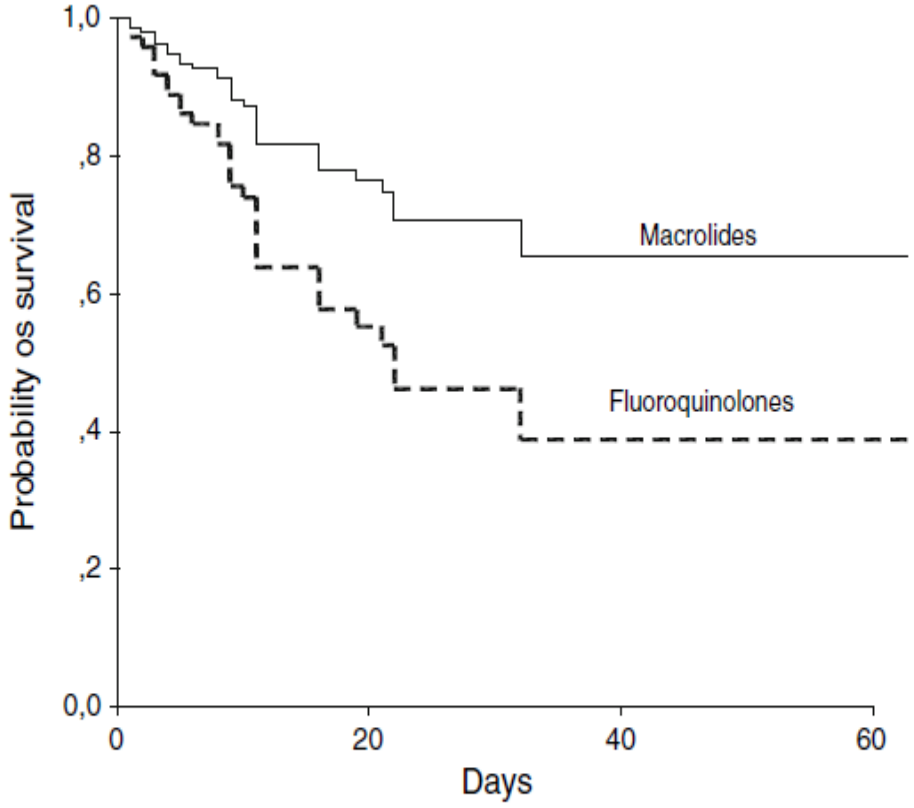
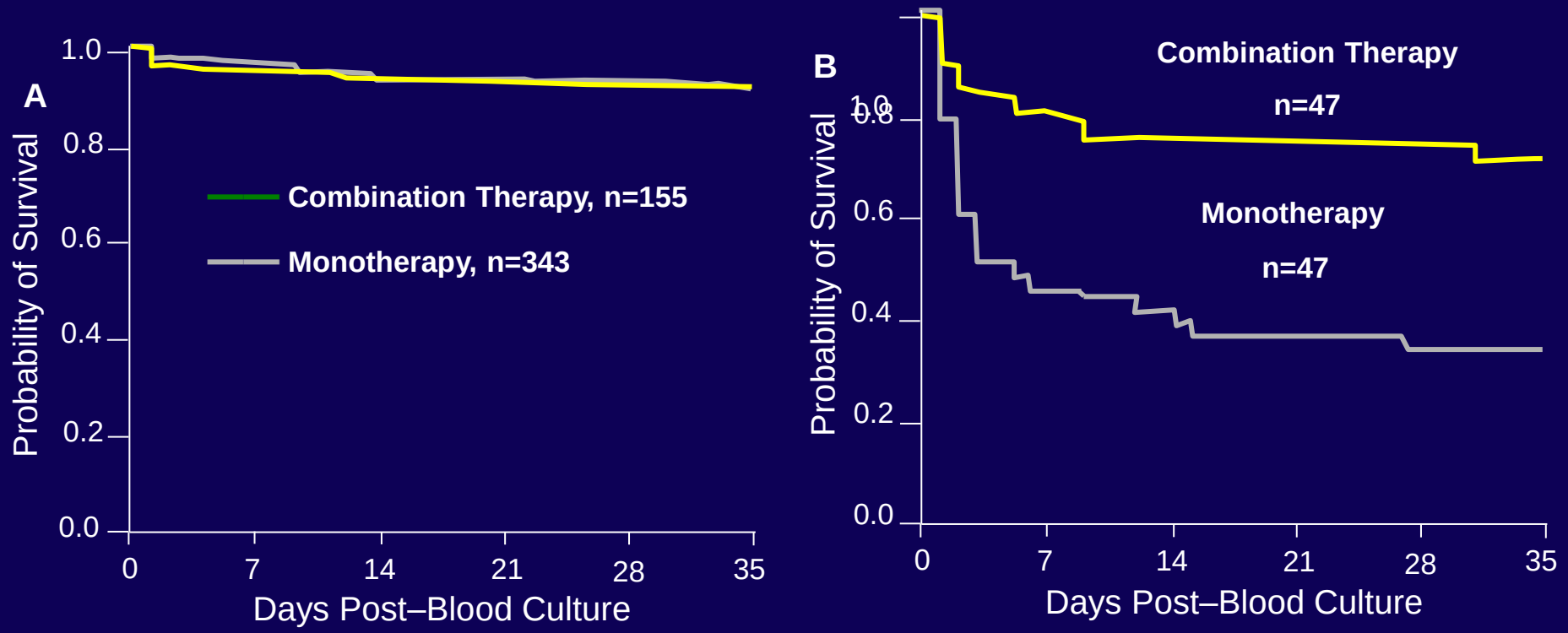


Fig. 3 Survival graph for severe sepsis/septic shock patients treated in accordance with IDSA/ATS guideline in combination with a macrolide or a quinolone (censored at 60 days)

Benefit of Dual Therapy of Pneumococcal Bacteremia : Specific Only To Critically Ill



Survival graphs stratified by severity of illness. (A) Kaplan-Meier survival plot for patients who were not critically ill as defined by the Pitt bacteremia score. (B) Kaplan-Meier survival plot for patients who were critically ill as defined by the Pitt bacteremia score. Combination therapy was superior to monotherapy among critically ill patients ($P<.008$, Mantel Cox).

Mechanism of benefit unclear: possibly atypical coverage, possible synergy, possibly anti-inflammatory effect

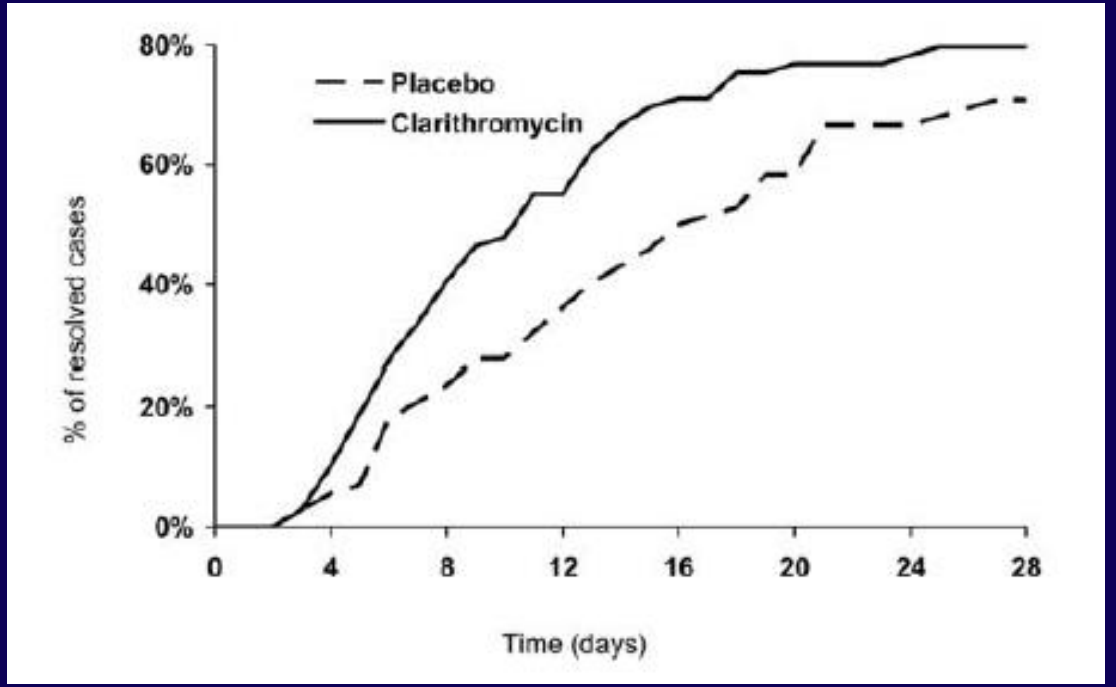
Baddour LM et al. *Am J Respir Crit Care Med.* 2004;170:440-444.

Benefit of Macrolides Even if Resistance Present: ? Immune effect

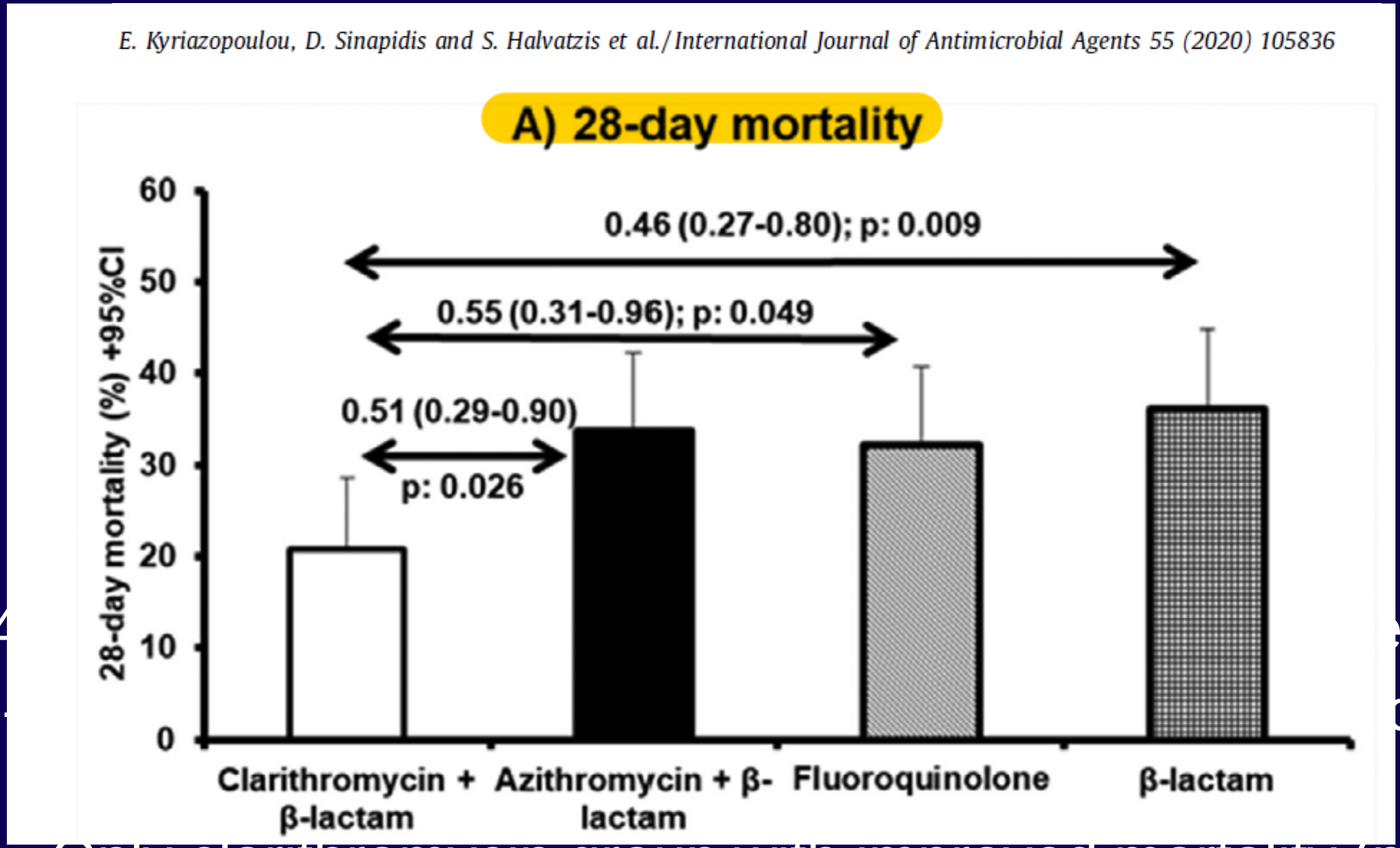
- VERDICT: 237 with CAP and sepsis.
  - 104 got macrolides within 48 hours
  - Macrolide use with reduced mortality in multivariate analysis
  - Applied even if macrolide resistant organism
    - Restrepo MI, et al. ERJ 2009; 33:153-159

Benefit of Clarithromycin in VAP and Gram-Negative Sepsis

- Double-blind , randomized trial of 200 patients with sepsis and VAP
- Clarithromycin 1 g QD x 3
- Most had gram-negatives (*P. aeruginosa or Acinetobacter*); no impact on pathogen eradication
- NO MORTALITY BENEFIT, BUT Macrolide with shorter time to resolution and weaning from vent among survivors
- Giamarellos-Bourboulis EJ, et al. Clin Infect Dis 2008; 46:1157-64.



Matched Comparator Study of Clarithromycin in Severe CAP : JAC 2020



- 4 epsis:
  ctam.
  – Only clarithromycin group with improved mortality (p<0.021)

Is The Macrolide Benefit In A Particular Subset of Patients? Those with a High Inflammatory Response

- 1715 CAP patients with a known cause
- 932 got BL+M vs. others getting FQ with or w/o BL
- BL+M with lower mortality than BL/FQ or FQ alone, BUT
- **After propensity score adjustment , BL+M had lower mortality only in those with high CRP and pneumococcal CAP**
  - Ceccato A, et al. Chest 2019; 155:795-804

TABLE 5] Significant Univariate and Multivariable Logistic Regression Analyses for 30-Day Mortality: Patients With High Inflammatory Response

	Univariate			Multivariable[a,b]		
Variable	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Interaction treatment and etiology			.062			.11
β-Lactam plus a macrolide and *Streptococcus pneumoniae*	0.27	0.09-0.80	**.019**	0.28	0.09-0.92	**.036**
β-Lactam plus a macrolide and Atypical bacterial	0.44	0.04-5.53	.52	0.59	0.04-7.83	.69

RCT of Adjunctive Macrolide Therapy in Severe CAP

Clarithromycin for early anti-inflammatory responses in community-acquired pneumonia in Greece (ACCESS): a randomised, double-blind, placebo-controlled trial

Evangelos J Giamarellos-Bourboulis, Athanasios Siampanos, Amalia Bolanou, Sarantia Doulou, Nikolaos Kakavoulis, Konstantinos Tsiakos, Sokratis Katopodis, Georgios Schinas, Lamprini Skorda, Zoi Alexiou, Konstantinos Armenis, Paraskevi Katsaounou, George Chrysos, Aikaterini Masgala, Garyphalia Poulakou, Nikolaos Antonakos, Asimina Safarika, Miltiades Kyprianou, Konstantina Dakou, Styliani Gerakari, Ilias C Papanikolaou, Haralampos Milionis, Markos Marangos, George N Dalekos, Vasiliki Tzavara, Karolina Akinosoglou, Eryfilli Hatziaggelaki, Styliani Sympardi, Theano Kontopoulou, Maria Mouktaroudi, Antonios Papadopoulos, Michael S Niederman

Summary

Background Addition of macrolide antibiotics to β-lactam antibiotics for the treatment of patients in hospital with community-acquired pneumonia is based on results from observational studies and meta-analyses rather than randomised clinical trials. We investigated if addition of the macrolide clarithromycin to treatment with a β-lactam antibiotic in this population could improve early clinical response—the new regulatory endpoint for community-acquired pneumonia—and explored the possible contribution of modulation of the inflammatory host response to that outcome.

Lancet Respir Med 2024

Published Online
January 3, 2024
https://doi.org/10.1016/S2213-2600(23)00412-5

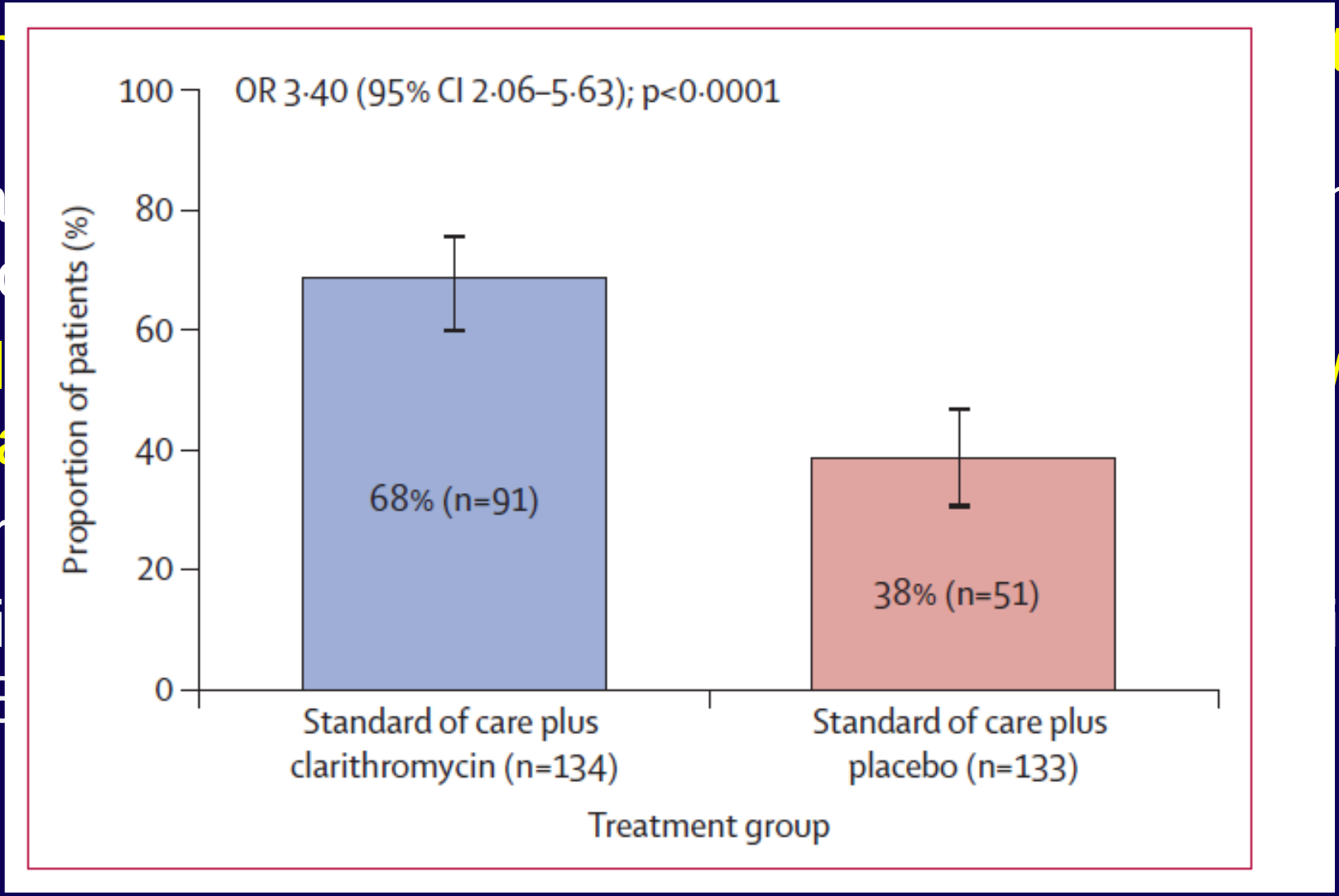
See Online/Comment
https://doi.org/10.1016/S2213-2600(23)00434-4

ACCESS Trial

- Double blind, placebo-controlled RCT of oral clarithromycin 500 mg bid x 7 days with IV beta-lactam rx (3rd gen ceph or BL/BLI) in 278 patients with severe CAP (SIRS + SOFA $\geq$ 2 + PCT > 0.25 ng/mL)
- For primary endpoint, composite of: 1) At least 50% decrease in resp sx score with no change in rx; 2) at least 30% decrease in SOFA or favorable PCT kinetics (at least 80% decrease in PCT), or both. Also other secondary clinical endpoints.
- Inflammatory endpoints: changes in serum tumour necrosis factor-a (TNFa), interleukin (IL)-6, IL-8, and IL-10 on visits 1, 4, 6, and 8; and production of TNFa, IL-10, and IL-17 on visits 1 and 4 by PBMCs
- None on MV or pressors at time of initial rx. 1 with clarithro and 3 with placebo had Legionella.

ACCESS Trial Results

- Com… …thromycin and … the same for a… …nd with or with…
  - Al… …wer in cl…
  - Tr…
  - Si… …ion by day 28…
  - M…



ACCESS Results: Inflammatory Markers

- More TNF alpha production by PMNCs at day 4, with clarithromycin than placebo.
- Higher percentage with decrease in IL-10 of at least 25%, or IL-10 below detection with clarithromycin (more with a decrease in early anti-inflammatory response)
- More with early proinflammatory response, LESS immune downregulation/immunoparalysis

Antibiotic and Non-antibiotic Macrolides

Zarogoulides et al. Eur J Clin Pharmacol 2012; 68:479-503. Macrolides inhibit protein synthesis at the RNA level .

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)		

Immune Modulating Effects of Macrolides

- Effect on Airway epithelium and mucus production
- Immune effects
  - Inhibit synthesis of pro-inflammatory cytokines and promote release of anti-inflammatory cytokines
  - Reduce T-cell mediated inflammation
- Host-pathogen interaction
  - Biofilm structure alteration: inhibit polysaccharide synthesis
  - Suppress quorum sensing
  - Decreased bacterial toxin production
    - Altenburg J, et al. Respiration 2011:81:67-74

Immunomodulatory Effects of Macrolides During Lung Infection. Reijnders TDY, et al. Lancet Resp Med 2020; 4: 619-30

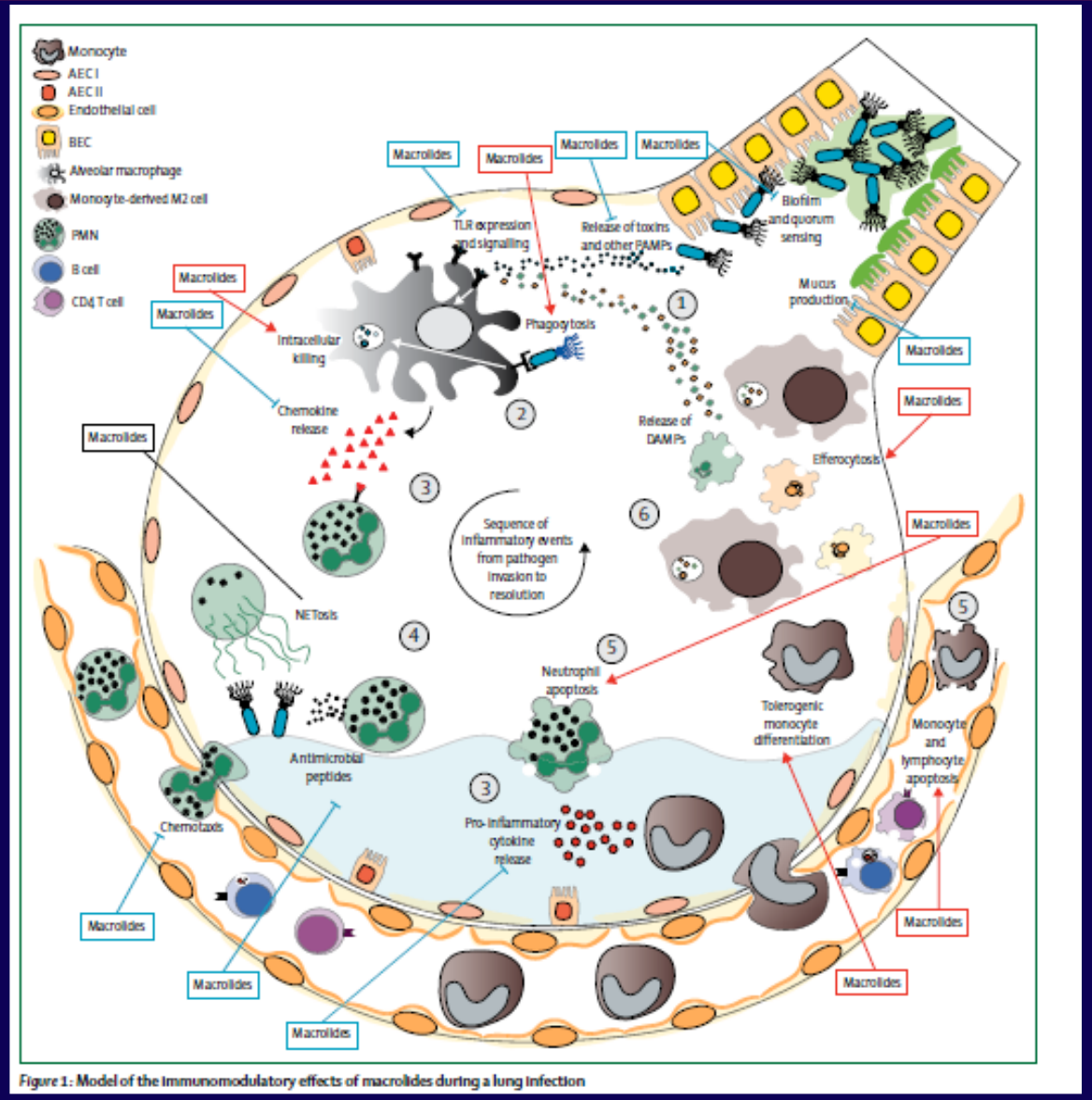


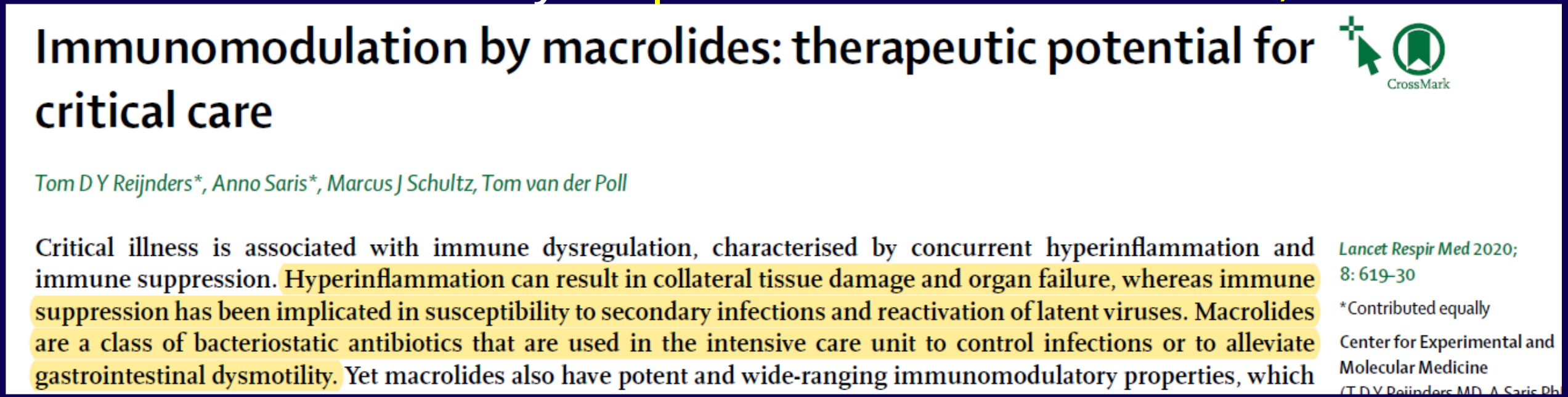
Figure 1: Model of the immunomodulatory effects of macrolides during a lung infection

Arguments for Immune Effect Rather than Anti-Bacterial effect of Macrolides in Severe CAP

- Benefit in bacteremia for macrolides , but not always quinolones
- No similar benefit with doxycycline
- Some benefit with gram-negative bacteremia
- Benefit in macrolide-resistant organisms : protects vs. mortality in breakthrough bacteremias
- Most benefit with severe illness
- Led to rapid resolution of septic shock in VAP with gram-negatives
  - Wunderink and Mandell. Semin Respir Crit Care Med 2012;33:311-318

Conclusions for Adding Macrolide Therapy in CAP

- Benefit for mortality in patients with severe CAP, even more



Immunomodulation by macrolides: therapeutic potential for critical care

Tom D Y Reijnders, Anno Saris*, Marcus J Schultz, Tom van der Poll*

Critical illness is associated with immune dysregulation, characterised by concurrent hyperinflammation and immune suppression. Hyperinflammation can result in collateral tissue damage and organ failure, whereas immune suppression has been implicated in susceptibility to secondary infections and reactivation of latent viruses. Macrolides are a class of bacteriostatic antibiotics that are used in the intensive care unit to control infections or to alleviate gastrointestinal dysmotility. Yet macrolides also have potent and wide-ranging immunomodulatory properties, which

Lancet Respir Med 2020; 8: 619–30

*Contributed equally

Center for Experimental and Molecular Medicine

(T D Y Reijnders MD, A Saris Ph

- Future: develop new macrolides with primarily anti-inflammatory properties, rather than anti-bacterial

Intensive Care Med
https://doi.org/10.1007/s00134-023-07033-8

GUID

ERS/
mar
pne

Ignacio M
Matteo B
Marin Ko
Marcos F
and Rich

2023 This is a

Question 6: Does the addition of steroids to antibiotic therapy in specific sCAP populations lead to better outcomes in comparison to when steroid therapy is not used?

:he
ired

nelli[8],
acho-Montero[14],
18,19]

Check for updates

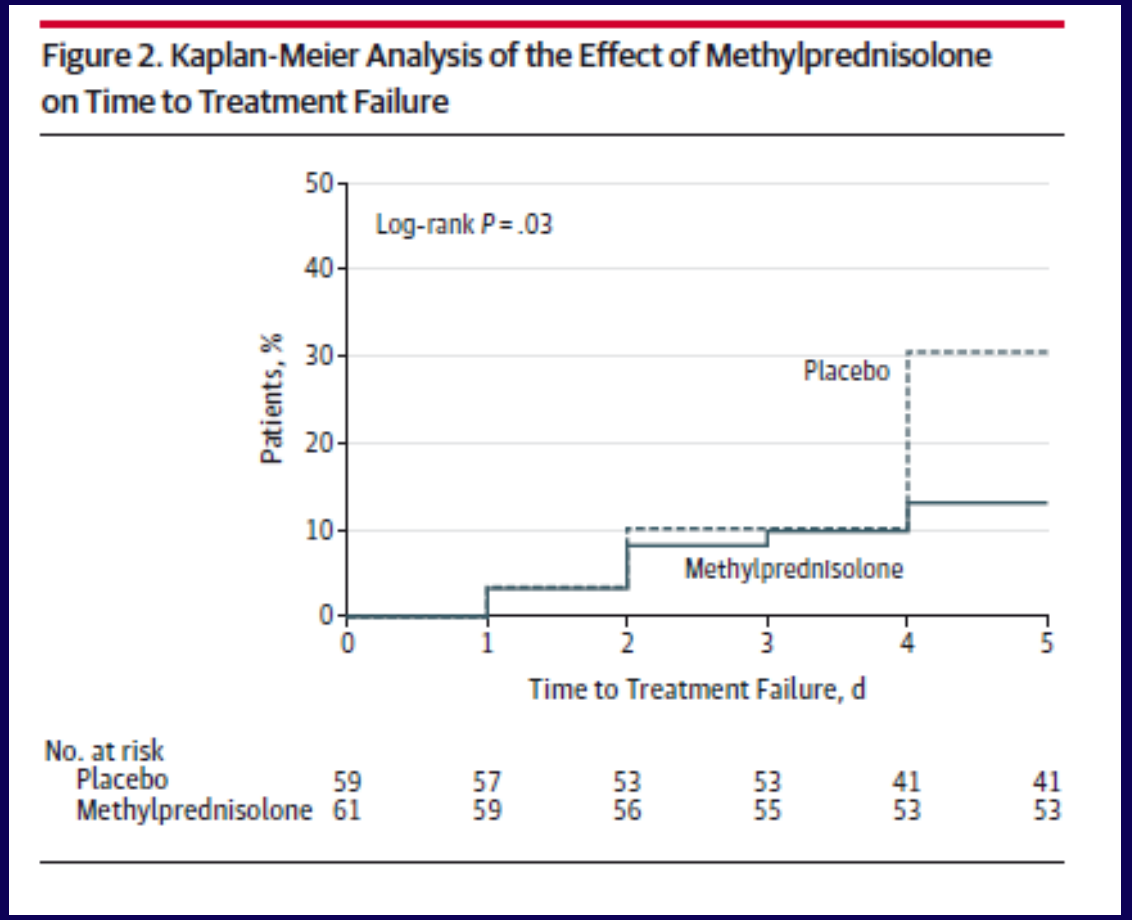
Recommendation

In patients with sCAP, we **suggest** the use of corticosteroids if shock is present.
Conditional recommendation, low quality of evidence.

Remarks: Based on common exclusion criteria from clinical trials, this recommendation does not apply to patients with viral sCAP (influenza, SARS, and MERS), uncontrolled diabetes and corticosteroid treatment for other reasons. When corticosteroid therapy is considered, methylprednisolone (0.5 $mg \cdot kg^{-1}$ every 12 h for 5 days) is a reasonable option.

Steroids in Severe CAP To Reduce Treatment Failure

- Multicenter randomized trial of 0.5mg/kg methylprednisolone q12h x 5 days (n=61) vs. placebo (n-59). Rx within 36 hours.
- Severe CAP (70-80% in ICU) + elevated CRP > 150 mg/L on admit
- Less treatment failure (esp late and with radiographic progression) in steroid group
  - No mortality difference.
- Torres et al. JAMA 2015; 313:677-86.



Do Macrolides Have Additive Benefit to Steroids in Severe CAP ?

JAMA 2015; 313:677-686

	Placebo plus macrolides (N=13)	Placebo plus ceftriaxone + fluoroquinolones (N=32)	MP plus macrolides (N=14)	Methylprednisolone plus ceftriaxone + fluoroquinolones (N=33)	P value
Late treatment failure (72-120h)[b]	4 (31%)	6 (19%)	**0 (0%)**	2 (6%)	0.045
Radiographic progression	2 (15%)	3 (9%)	**0 (0%)**	1 (3%)	0.29
Respiratory failure	2 (15%)	1 (3%)	**0 (0%)**	1 (3%)	0.20
Late mechanical ventilation	2 (15%)	1 (3%)	**0 (0%)**	1 (3%)	0.20
Late septic shock	1 (8%)	1 (3%)	**0 (0%)**	0 (0%)	0.39
ICU admission	7 (54%)	30 (94%)	**6 (43%)**	28 (85%)	<0.001

No impact after severity adjustment
Ceccato A, et al. PlosOne 2017

- No impact after severity adjustment
- Ceccato A, et al. PlosOne 2017

ORIGINAL ARTICLE

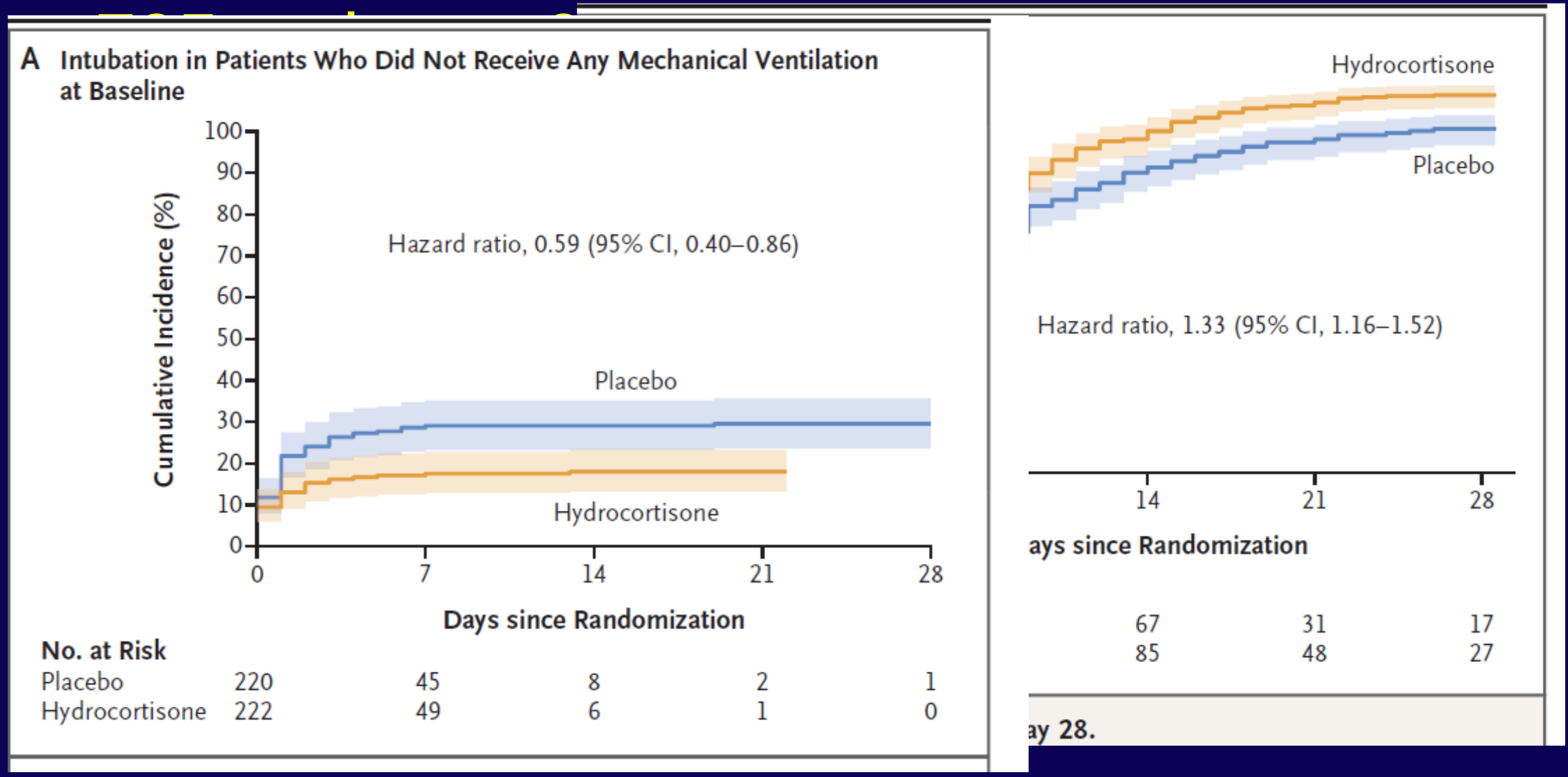
Hydrocortisone in Severe Community-Acquired Pneumonia

P.-F. Dequin, F. Meziani, J.-P. Quenot, T. Kamel, J.-D. Ricard, J. Badie, J. Reignier, N. Heming, G. Plantefève, B. Souweine, G. Voiriot, G. Colin, J.-P. Frat, J.-P. Mira, N. Barbarot, B. François, G. Louis, S. Gibot, C. Guitton, C. Giacardi, S. Hraiech, S. Vimeux, E. L'Her, H. Faure, J.-E. Herbrecht, C. Bouisse, A. Joret, N. Terzi, A. Gacouin, C. Quentin, M. Jourdain, M. Leclerc, C. Coffre, H. Bourgoin, C. Lengellé, C. Caille-Fénérol, B. Giraudeau, and A. Le Gouge, for the CRICS-TriGGERSep Network*

French CAPE COD Steroid trial

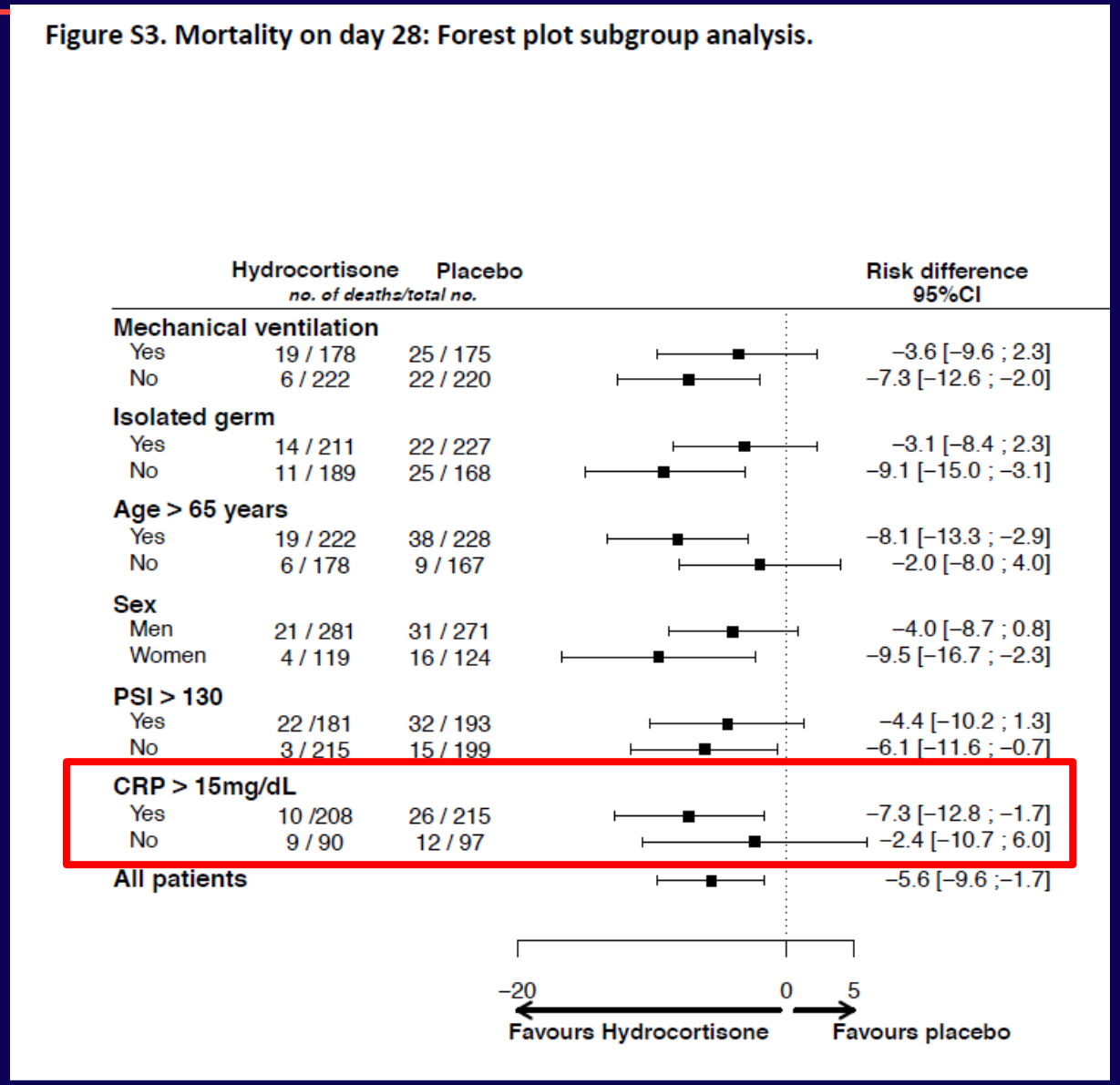
- Double blind RCT in ICU admitted severe CAP
- 200 mg hydrocortisone daily for 4-8 days, continuously, followed by taper for a total of 8-14 days, based on day 4 clinical response
  - 44% MV, only 22% invasive vent; 42% HFNC
- Exclude: septic shock, influenza, non-CAP
  - Dequin DF et al. NEJM 2023;

French CAPE COD Steroid trial



Who Benefits the Most and What Are the Open Questions?

- Male vs. female
- Prolonged infusion vs. bolus?
- Hydrocortisone vs. others?
- Ventilation and shock on admit?
- Duration of infusion?
- Preferentially if high level of inflammation? OR for mortality, NS if CRP <150
  - Approx 1/3 of all patients with low CRP



Hyper and Hypo Inflammatory Sepsis Phenotypes from Latent Class Analysis

- Hyperinflammatory phenotype with more inflammatory biomarkers and more bacteremia and mortality in patients with sepsis and ARDS
- Used whole blood transcriptional profile and plasma metagenomic sequencing of microbial DNA
- Prospective cohort from 2 hospitals of 76 with hyperinflammatory sepsis and 113 with hypoinflammatory profile
- Hyperinflammatory with elevated expression of innate immune response genes (esp for IL-8), and more *Enterobacteriaceae* while hypoinflammatory with elevated adaptive immune response genes , T cell phenotype and immunosuppression
- Steroids may have detrimental effect in sepsis with hypoinflammatory response in analysis of transcriptomic data from the VANISH sepsis data
- Leyton LPA, et al. Am J Respir Crit Care Med 2024; 209:805-15

Meta-analysis of Steroids for Influenza

- 21 observational studies on steroids in influenza and found OR for mortality of 3.9
  - No direct relationship of mortality risk to dosing , but most got at least 40 mg methylprednisolone
- 7 studies found OR of hospital-acquired infection (bacterial or fungal) to be 2.7
- Steroid use with higher mortality, rate of hospital-acquired infections (including VAP), longer LOS, more need for MV.
- Lansbury LE et al. Crit Care Med 2020; 48: e96-106

Corticosteroids Increase Risk for Invasive Fungal Infection in Influenza

- Up to 8.8% of patients with influenza A (H1N1) got invasive Aspergillosis
- Corticosteroid use is a risk factor for IPA (PR 1.6)
  - Martin-Loeches I and Torres A. ERR 2021; 30:200346
- Steroid use and mucor infection during Influenza
  - 10 reports of mucor during influenza, most given steroids and with diabetes.
  - Steroids may further add to uncontrolled diabetes and thus make mucor more likely
  - Ahmadikia A, et al. Mycoses 2021

Conclusions

- Anti-inflammatory therapy may have benefit in SELECTED patient subsets with severe pneumonia (COVID-19 and CAP)
  - Consider timing, dosing, duration
  - Select patients by biomarkers vs. clinical features
- Macrolides as adjunctive therapy with beta-lactams improve mortality in severe CAP, probably by multiple immune modulatory effects
  - Need to better define who benefits most
- Steroids have benefit in severe CAP, but probably not for everyone, and need to define subsets who benefit most (Personalized Medicine), probably based on inflammatory profiles