Πνευμονία και κορτικοστεροειδή. Σε ποιους ασθενείς και πότε ?

ΛΙΑΠΙΚΟΥ ΑΔΑΜΑΝΤΙΑ
Επιμελήτρια Α, 6η Πνευμον. Κλινική
ΝΝΘΑ ΣΩΤΗΡΙΑ

ΔΗΛΩΣΗ ΣΥΓΚΡΟΥΣΗΣ ΣΥΜΦΕΡΟΝΤΩΝ

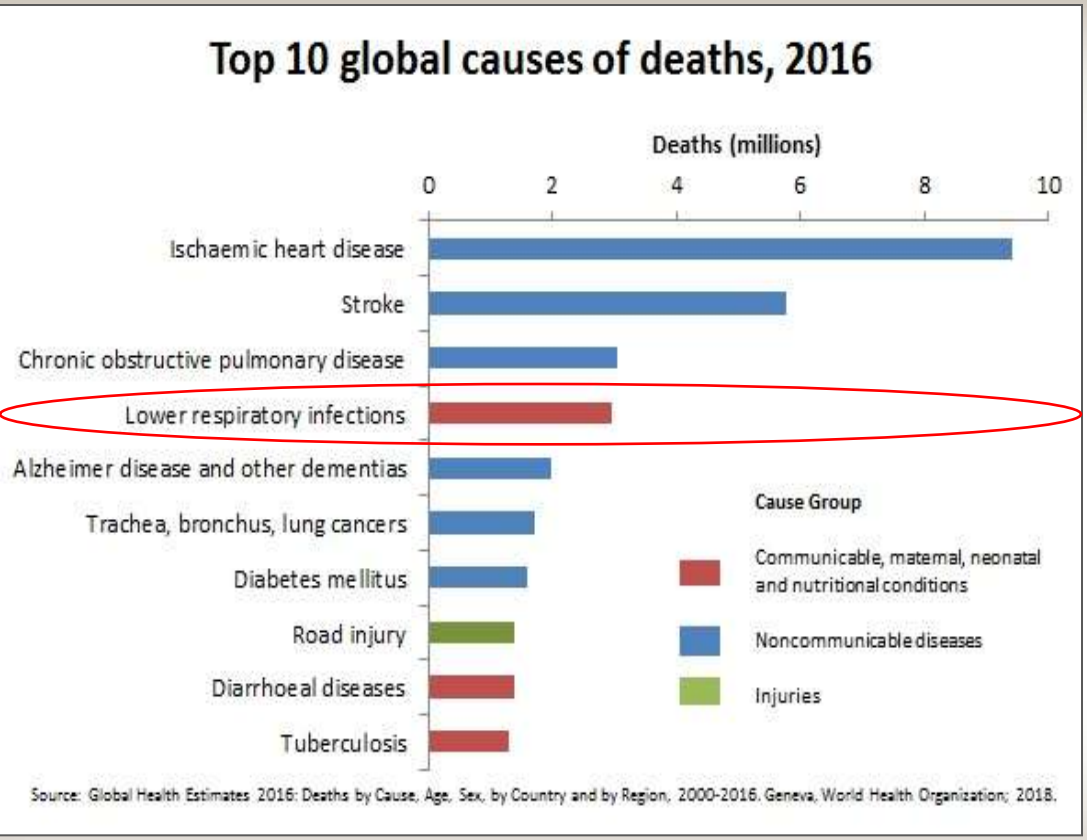
ΟΜΙΛΗΤΡΙΑ

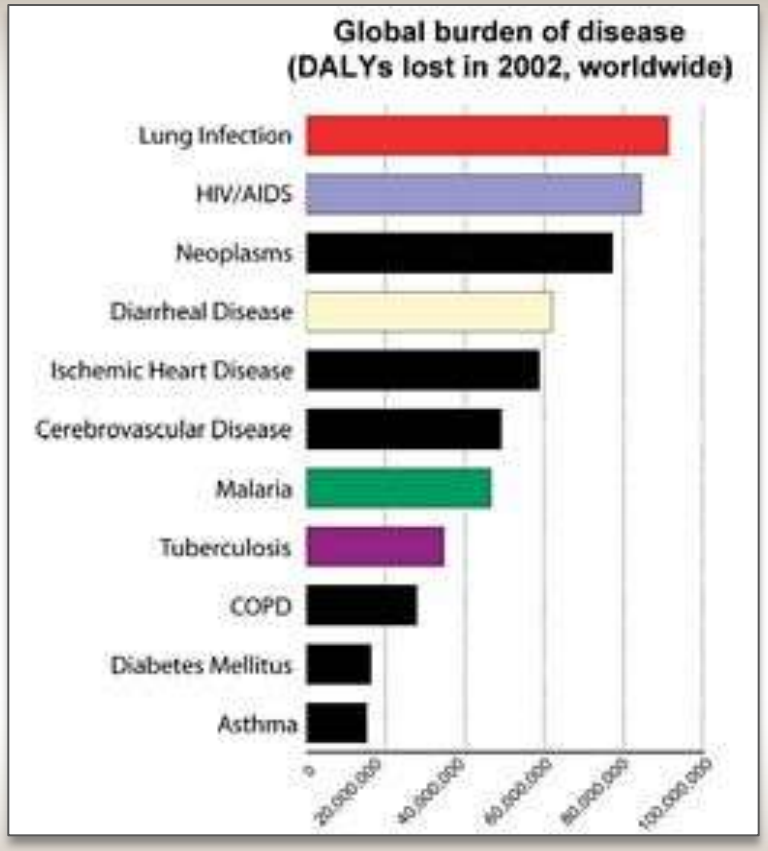
Pfizer, Astra, Elpen

ΜΕΛΕΤΕΣ

Angelini, Menarini, Eplen

ΘΝΗΤΟΤΗΤΑ ΠΝΕΥΜΟΝΙΑΣ





Risk factors for 30-day mortality in patients with pneumonia who receive appropriate initial antibiotics: an observational cohort study

Yuichiro Shindo, Ryota Ito, Daisuke Kobayashi, Masahiko Ando, Motoshi Ichikawa, Yasuhiro Goto, Yasutaka Fukui, Mai Iwaki, Junya Okumura, Ikuo Yamaguchi, Tetsuya Yagi, Yoshimasa Tanikawa, Yasuteru Sugino, Joe Shindoh, Tomohiko Ogasawara, Fumio Nomura, Hideo Saka, Masashi Yamamoto, Hiroyuki Taniguchi, Ryujiro Suzuki, Hiroshi Saito, Takashi Kawamura, Yoshinori Hasegawa, on behalf of the Central Japan Lung Study Group

- 1413 pts; 887 CAP, 526 HCAP
- 579 pts appropriate antibiotic therapy
- 168 inappropriate antb. therapy
- **30 day mortality:** 61/579(11%) & 29/168(17%)

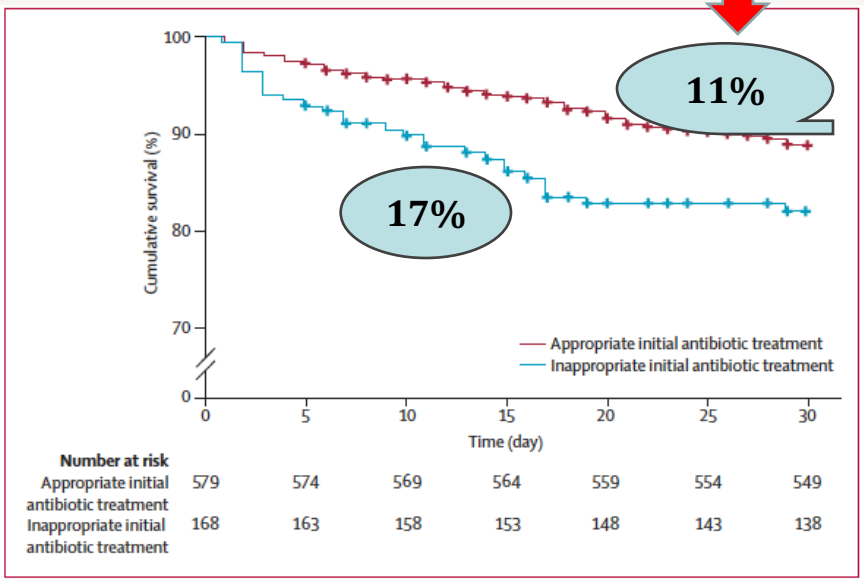
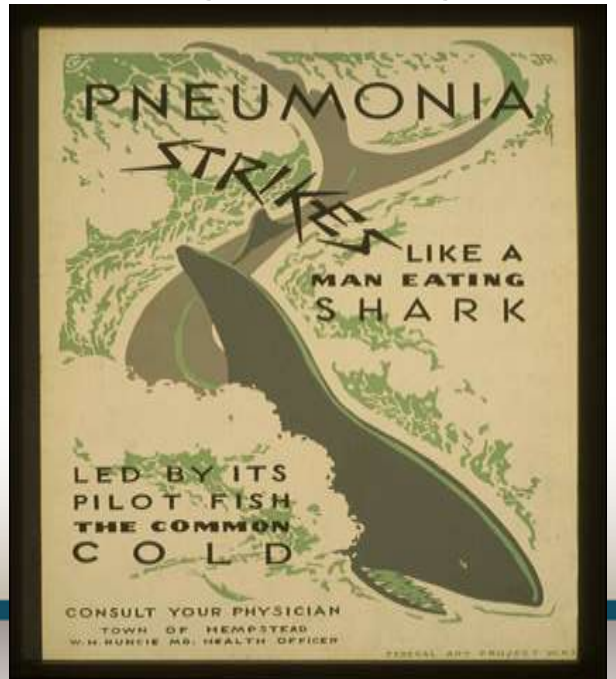


Figure 2: **30-day survival in the appropriate and inappropriate initial antibiotic treatment groups**
Patients without identified pathogens in whom appropriateness of initial antibiotics could not be assessed were not included in the analysis. Vertical lines indicate censoring of data.

Lancet , July 2015

Concept of <<excessive>> inflammation
Λογική για τη χρήση των κορτικοειδών

<<The inflammatory reaction is a stereotyped nonspecific reaction evoked by a wide range of bacteria. It is generally regarded as a defense reaction; but this must seem doubtful unless we are prepared to accept the paradox that, if the reaction be sufficiently severe, **the defense may destroy the host>>**



Breen GE,Talukdar PK.Lancet 1965
Annane & Meduri ,Crit Care 2008

Molecular Inflammatory Responses Measured in Blood of Patients with Severe Community-Acquired Pneumonia

Silvia Fernández-Serrano,[1] Jordi Dorca,[1*] Mercè Coromines,[2] Jordi Carratalà,[3] Francesc Gudiol,[3] and Frederic Manresa[1]

CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, Sept. 2003, p

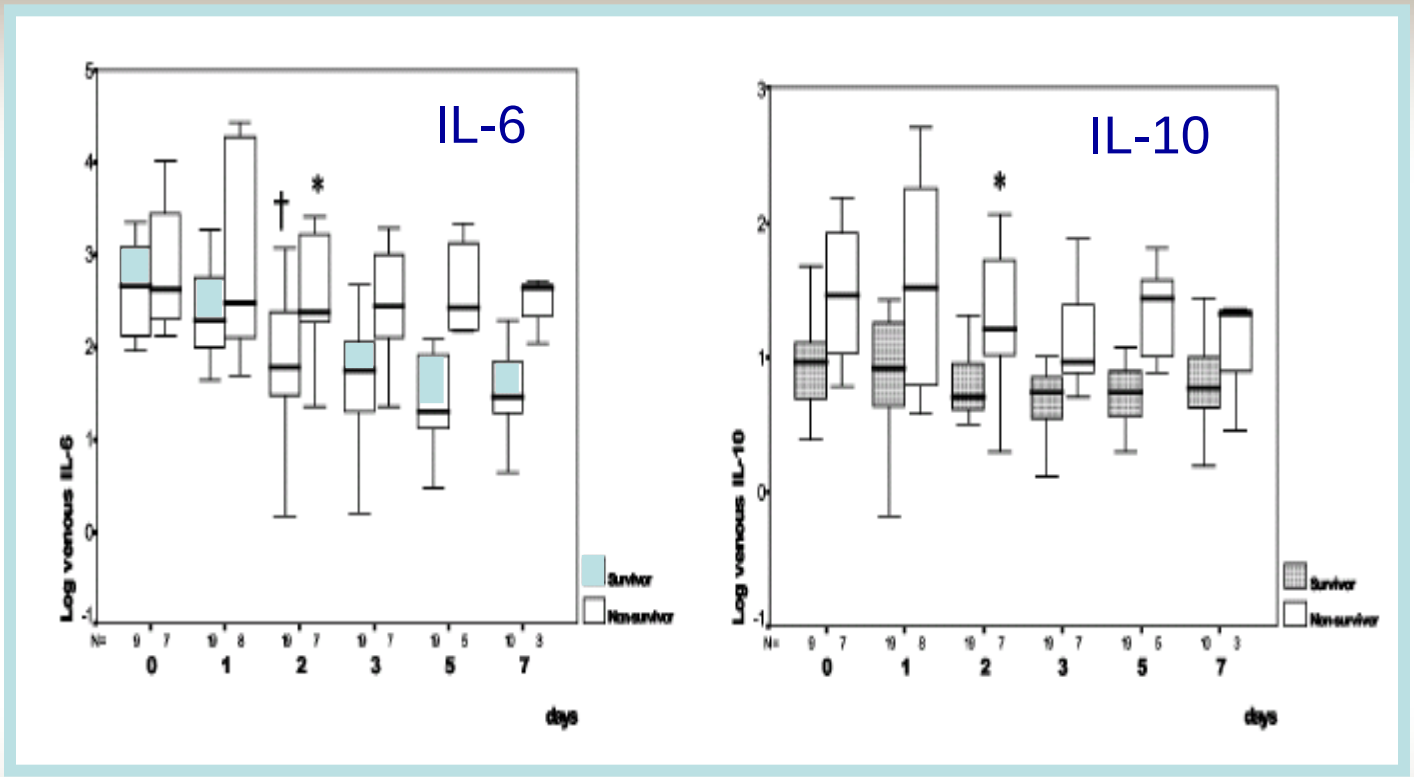


FIG. 3. Survivors and nonsurvivors. Daily changes as well as time course changes in plasma IL-6 and IL-10 concentrations are shown. A

ΦΛΕΓΜΟΝΩΔΗ ΑΝΤΙΔΡΑΣΗ ΤΟΥ ΞΕΝΙΣΤΗ ΣΤΗΝ ΠΝΕΥΜΟΝΙΑ

Anti-inflammatory cytokines

- ***sTNFrp55***
- ***sTNFrp75***
- ***IL-1 receptor antagonist***
- ***IL-10***

Proinflammatory cytokines

TNF-a
IL-1β
IL-6
IL-8

Based on their well-established inhibitory effects on the production of a variety of pro-inflammatory cytokines such as TNF-a, IL-1, IL-2, IL-6, and IL- 8, the use of glucocorticoids has been promoted as adjunctive therapy in severe pneumonia.

Bordon J, InterJournal of Infectious Dise2013

SHORT REPORT

Role of glucocorticoids on inflammatory response in nonimmunosuppressed patients with pneumonia: a pilot study

C. Montón*, S. Ewig‡, A. Torres*, M. El-Ebiary*, X. Filella+, A. Rañó*, A. Xaubet*

Eur Respir J 1999; 14: 218–220

- 20 MV ασθενείς -11 ασθενείς έλαβαν GC (mean.SD dose of i.v. methylprednisolone
- Θνητότητα σε ασθεν
συγκρινόμενη με 67%
- **GC επίσης μειώνει** 6 **στον ορό & BAL)** in
WBC στο BAL μειώθη

Table 1. – Cytokine expression in both study groups

	Not receiving GC (n=9)	Receiving GC (n=11)	p-value
Serum			
TNF-α pg·mL^{-1}	43±7	28±4	0.15
IL-1β pg·mL^{-1}	4±2	1±0.4	0.50
IL-6 pg·mL^{-1}	1089±342	630±385	0.03
CRP mg·dL^{-1}	34±5	19±5	0.03
Blood leukocyte count $\times 10^9$ cells·L^{-1}	13±2.4	15.6±2.1	0.60
BAL			
TNF-α pg·mL^{-1}	118±50	24±5	0.05
IL-1β pg·mL^{-1}	91±35	57±17	0.31
IL-6 pg·mL^{-1}	1569±965	889±432	0.49
Neutrophil count %	93±3	57±16	
($\times 10^9$ cells·L^{-1})	(2.4±1.1)	(1.9±1.8)	0.03

Effects of glucocorticoids in ventilated piglets with severe pneumonia

O. Sibila*,#, C.M. Luna¶, C. Agustí*,#, S. Baquero¶, S. Gando¶, J.R. Patrón¶, J.G. Morato+, R. Absi§, N. Bassi/ and A. Torres*,#

Eur Respir J 2008; 32: 1037–1046

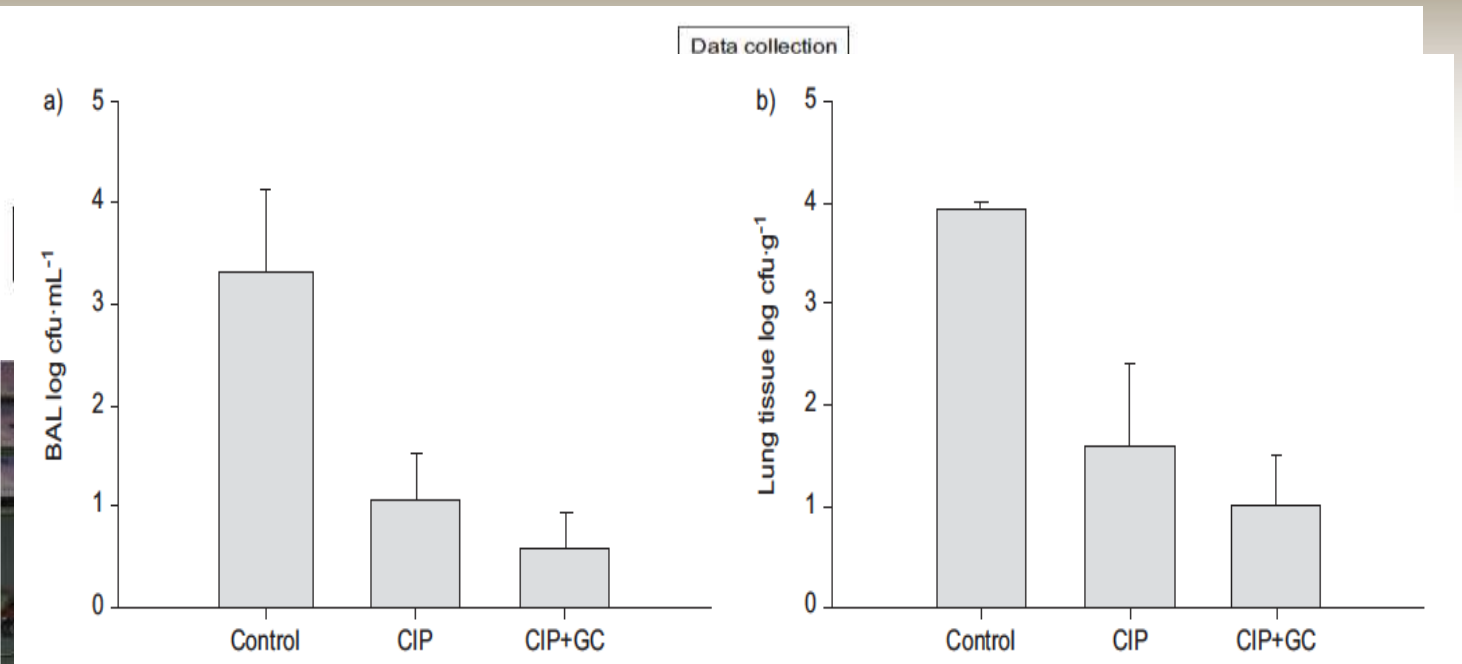
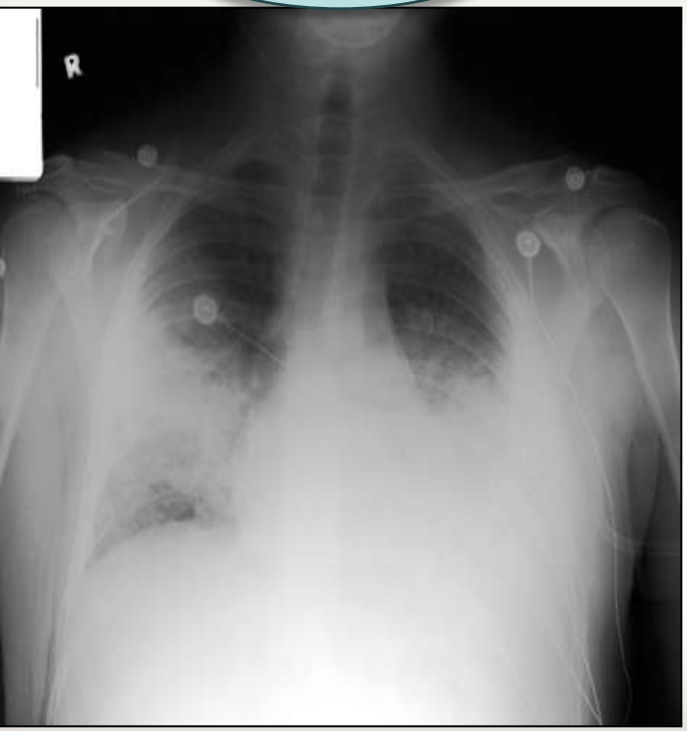


FIGURE 6. Global bacterial burden in the three groups of animals evaluated both in a) bronchoalveolar lavage (BAL; expressed as log colony forming units (cfu)·mL^{-1}) and b) in lung tissue (expressed as log cfu·g^{-1}). CIP: ciprofloxacin; GC: glucocorticoid. p-values were obtained using ANOVA test. a) p=0.03; b) p=0.01.

1.ΜΕΛΕΤΕΣ ΣΤΗΝ ΠΝΕΥΜΟΝΙΑ ΚΟΙΝΟΤΗΤΟΣ

+ GC

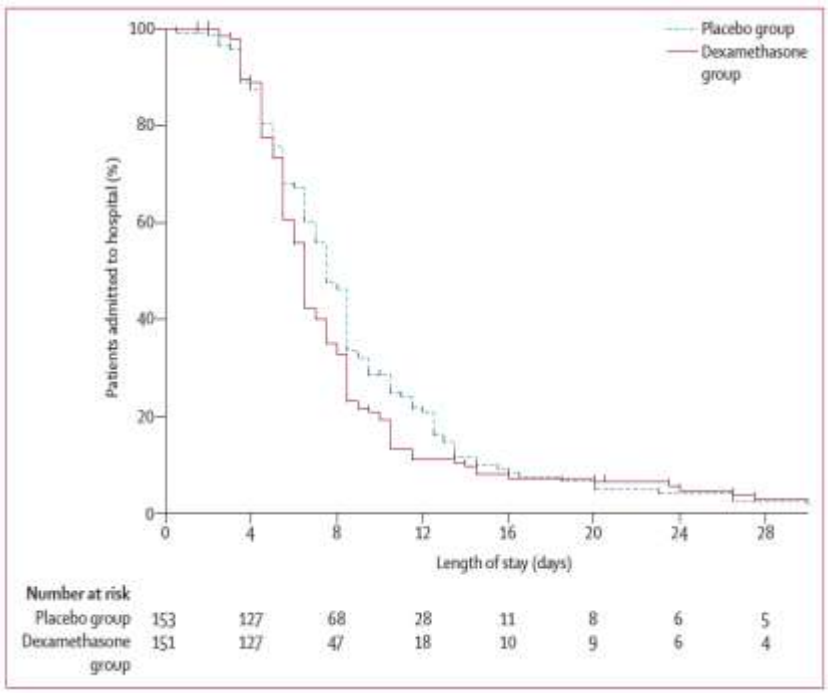


RCTs	Study Design & Population	Main Results	Adverse events
Confalonieri et al, 2005	Multicenter RCT Hydrocortisone vs placebo Patients with **severe CAP**	Improvement in PaO2/FiO2(p =.002), CXR score (p<.0001), reduction in CRP levels (p = .01), delayed septic shock (p= .001), **reduction in duration of hospital stay (p = .03) and mortality (p = .009**)	One digestive hemorrhage in each group.
Snijders et al, 2010	Single-center RCT in the Netherlands Prednisolone vs placebo Hospitalized patients with CAP	Clinical cure at days 7 was 81% in the prednisolone group and 85.3% in the placebo group (p =.38) **Clinical cure at days 30** was 66.3% in the prednisolone group and 77.1% in the placebo group (p =.08). **Late failure** (>72 h after admission) was more common in the prednisolone group than in the placebo group (19.2% vs 6.4%; p=.04 respectively)	Hyperglycemia in five(2.3%) pts in the prednisolone group and 2 (0.9%) pts in the placebo group (p =.27)
Fernandez-Serrano et al, 2011	Single-center RCT in Spain Methylprednisolone vs placebo in **Severe CAP**	Improvement in PaO2/FiO2 (p=.001) **and faster time to resolution** (median 5 d in MPN group vs 7 d in placebo group,<.05)	One patient with hyperglycemia and one digestive hemorrhage in the MPN group
Meijvis et al, 2011	Two-center RCT in Netherlands Dexamethasone(DXM) vs placebo Patients with CAP	**Decrease in duration of stay** in DXM group compared with the placebo (6.5 d vs 7.5 d; p = .048)	**Hyperglycemia** in 67 (44%) Of DXM group compared with 35(23%) of controls, p<.0001).
Torres et al, 2015	Multicenter RCT in Spain Methylprednisolone(MTP) vs Placebo. Patients with **severe CAP** and **high inflammatory response**	Corticosteroid treatment **reduced the risk of treatment failure** (OR, 0.34; p= .02) In-hospital mortality did not differ between the groups (10% in the MTP group vs 15% in the placebo group; p= .37)	Hyperglycemia occurred in 11 (18%) in the MTP group and in seven pts (12%) in the placebo group (p = .34).
Blum et al, 2015	Multicenter RCT in Switzerland Prednisone vs placebo Patients with CAP	**Reduction of time to clinical stability in** the prednisone group compared with the placebo group (3 d vs 4.4 d; p<.0001)	**Hyperglycemia** occurred in 76 (19%) in the prednisone group and in 43 pts (11%) in the placebo group (p=.001).

Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial

Sabine C A Meijvis, Hans Hardeman, Hilde H F Remmelts, Rik Heijligenberg, Ger T Rijkers, Heleen van Velzen-Blad, G Paul Voorn, Ewoudt M W van de Garde, Henrik Endeman, Jan C Grutters, Willem Jan W Bos, Douwe H Biesma

- RCT με 304 ασθενείς: 153 placebo & 151 δεξαμεθαζόνη (5mg για 4 μέρες). 3 χρόνια.
- **Αποτελέσματα: LOS =6.5 μέρες** (IQR 5.0–9.0) στην ομάδα δεξαμεθαζόνης vs 7.5 μέρες (5.3–11.5) στην ομάδα placebo (95% CI 0–2 days; p=0.0480)
- Θνητότητα και σοβαρές επιπλοκές ήταν σπάνια και παρόμοιας συχνότητας
- **Παρενέργειες**:67 (44%) από 151 ασθενείς στην ομάδα δεξαμεθαζόνης είχαν υπεργλυκαιμία συγκρινόμενοι με 35 (23%) από τους 153 controls (p<0.0001)

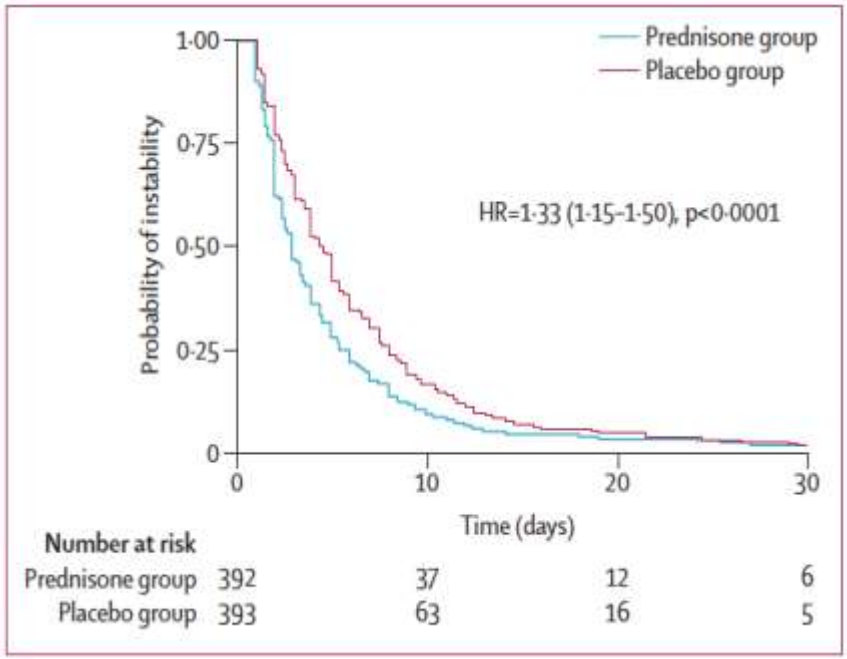


Lancet 2011; 377: 2023–30

Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial

Claudine Angela Blum*, Nicole Nigro*, Matthias Briel, Philipp Schuetz, Elke Ullmer, Isabelle Suter-Widmer, Bettina Winzeler, Roland Bingisser, Hanno Elsaesser, Daniel Drozdov, Birsen Arici, Sandrine Andrea Urwyler, Julie Refardt, Philip Tarr, Sebastian Wirz, Robert Thomann, Christine Baumgartner, Hervé Duplain, Dieter Burki, Werner Zimmerli, Nicolas Rodondi, Beat Mueller, Mirjam Christ-Crain

- RCT με 785 ασθενείς -> 392 με πρεδνιζόνη (50mg για 7d) vs. 393 με placebo. 5 χρόνια,7 νοσοκομεία.
- **Αποτελέσματα**: **Μέσος χρόνος κλινικής σταθερότητας** : 3.0 μέρες, IQR 2.5–3.4 vs. 4.4 μέρες, ([HR] 1.33, 95% CI 1.15–1.50, p<0.0001)
- Επιπλοκές πνευμονίας παρόμοιες
- Υψηλότερη **συχνότητα υπεργλυκαιμίας** θεραπευόμενη με ινσουλίνη στην ομάδα πρεδνιζόνης (76 [19%] vs 43 [11%]; OR 1.96, 95% CI 1.31–2.93, p=0.001)



Lancet 2015; 385: 1511–18

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients With Severe Community-Acquired Pneumonia and High Inflammatory Response

A Randomized Clinical Trial

Antoni Torres, MD, PhD; Oriol Sibila, MD, PhD; Miquel Ferrer, MD, PhD; Eva Polverino, MD, PhD; Rosario Menendez, MD, PhD; Josep Mensa, MD, PhD; Albert Gabarrús, MSc; Jacobo Sellarés, MD, PhD; Marcos I. Restrepo, MD, MSc; Antonio Anzueto, MD, PhD; Michael S. Niederman, MD; Carles Agustí, MD, PhD

- **Υπόθεση:** Τα κορτικοειδή modulate την απελευθέρωση κυτοκινών σ αυτούς τους ασθενείς. Μειώνοντας τη φλεγμονή ίσως προκαλούν μείωση της αποτυχίας θεραπείας σε νοσηλευόμενους με ΠΚ
- **Σκοπός ήταν να** ερευνήσει την επίδραση των κορτικοστεροειδών σε ασθενείς με σοβαρή **CAP και CRP>150 mg/l** σε μια πολυκεντρική RCT
- 3 Ισπανικά πανεπιστημιακά νοσοκομεία, από **Ιούνιο 2004-Φεβρ.2012**
- Οι ασθενείς έλαβαν είτε i.v. bolus of 0.5 mg/kg /12 h **methylprednisolone** (n = 61) ή placebo (n = 59) για 5 μέρες αρχίζοντας σε 36 ώρες από την εισαγωγή.

JAMA. 2015 Feb 17;313(7):677-86

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	Intention-to-Treat Population				Per-Protocol Population			
	Unadjusted OR or HR (95% CI)	P Value	Adjusted OR or HR (95% CI)[a]	P Value	Unadjusted OR or HR (95% CI)	P Value	Adjusted OR or HR (95% CI)[a]	P Value
Primary Clinical Outcome								
Treatment failure[b]	0.34 (0.14-0.87)	.02	0.33 (0.12-0.90)	.03	0.26 (0.09-0.76)	.01	0.26 (0.08-0.79)	.02
Early treatment failure (0-72 h)[c]	0.96 (0.29-3.18)	.95	1.14 (0.28-4.67)	.86	0.76 (0.16-3.58)	.73	0.93 (0.17-5.06)	.94
Early mechanical ventilation							9-6.46)	.81
Early septic shock							4-4.90)	.49
Death	0.97 (0.13-7.09)	.97	1.35 (0.04-40.84)	.86				
Late treatment failure (72-120 h)[c]	0.10 (0.02-0.46)	.003	0.09 (0.02-0.47)	.004	0.12 (0.03-0.54)	.006	0.11 (0.02-0.52)	.006
Radiographic pr							01-0.84)	.03
Respiratory failu							02-1.50)	.11
Late mechanical							02-2.10)	.19
Late septic shoc							-∞)[d]	>.99
Death								
Secondary Clinical Ou								
Time to clinical stability, d[e]	1.16 (0.78-1.73)	.46	1.11 (0.72-1.71)	.64	1.24 (0.83-1.87)	.29	1.20 (0.77-1.85)	.42
Length of stay, d								
Hospital	0.66 (0.23-1.85)	.43	0.61 (0.19-1.93)	.40	0.47 (0.12-1.81)	.27	0.40 (0.10-1.63)	.20
ICU[f]	0.18 (0.02-1.46)	.11	0.13 (0.01-1.44)	.10	0.02 (0-60.31)	.33	0 (0-∞)[d]	.29
In-hospital mortality	0.61 (0.20-1.82)	.37	0.57 (0.16-2.00)	.38	0.41 (0.10-1.68)	.22	0.38 (0.08-1.70)	.21

112 (93%) pts completed the study

Significant reduction in treatment failure of 18%. This was driven largely by a 14% reduction in radiographic progression.

JAMA. 2015 Feb 17;313(7):677-86

Χρειαζόμαστε άλλες RCTs?

- Η επίδραση των κορτικοστεροειδών στη θνητότητα δεν είναι καλά καθορισμένη **λόγω περιορισμών** στις μελέτες:

  1.Λίγοι ασθενείς σε μερικές μελέτες

  2. Επίπεδο φλεγμονής άγνωστο στις περισσότερες μελέτες

  3.Συμμετοχή και ήπιας-μέτριας βαρύτητας πνευμονίας σε κάποιες μελέτες

  4.Ετερογενής δόση κορτικοειδών

Meta-analyses about Corticosteroids in CAP

Author	N RCTs	N Patients	Mortality *	Mortality (SCAP) *	LOS †	TTCS †
Siempos,2008	8	189 SCAP	---	0.21 (0.05 to 0.83)	Reduced (NE)	---
Nie. 2012	9	1,001		0.26 (0.11 to 0.64)	---	---
Cheng,2014	4	264 SCAP	---	0.39 (0.17 to 0.90)	Decreased In ICU	---
Siemieniuk 2015	12	1,974	0.67 (0.45 to 1.01)	---	-1.00 (-1.79 to -0.21)	-1.22 (-2.08 to -0.35)
Horita, 2015	10	1,780	0.80 (0.53 to 1.21)	0.41 (0.19 to 0.90)	-0.98 (-1.26 to -0.71)	-1.16 (-1.73 to -0.58)
Marti,2015	14	2,077	0.84 (0.55-1.29)	0.47 (0.23 to 0.96)	0.89 ‡ (0.70 to 0.89)	0.89 ‡ (0.84 to 0.94)
Wan ,2016	9	1667	0.72 (0.43 to 1.21)	0.64 (0.32 to 1.29)	Reduced (NE)	Reduced (NE)
Bi,2016	8	538 SCAP	---	0.46 (0.28 to 0.77)	-4.76 (-8.13 to 1.40)	---
Wu, 2017	10	729 SCAP	---	0.49 (0.29 to 0.85)	-4.11 (-6.61 to 1.81)	---
Briel, 2017	6	1,506 (individual)	0.75 (0.46 to 1.21)	---	-1.15 (-1.75 to -0.55)	17

LOS: length of stay.
TTCS: time to clinical stability

Figure 1. Effect of corticosteroids on all-cause mortality in patients hospitalized with community-acquired pneumonia, by severity of pneumonia.

Study, Year (Reference)	Participants, *n/N*		Risk Ratio (95% CI)
	Corticosteroids	Control	
Severe pneumonia			
Confalonieri et al, 2005 (24)	0/23	8/21	0.05 (0.00–0.88)
El-Ghamrawy et al, 2006 (40)	3/17	6/17	0.50 (0.15–1.68)
Marik et al, 1993 (48)	1/14	3/16	0.38 (0.04–3.26)
Nafae et al, 2013 (41)	4/60	6/20	0.22 (0.07–0.71)
Sabry and Omar, 2011 (47)	2/40	6/40	0.33 (0.07–1.55)
Torres et al, 2015 (17)	6/61	9/59	0.64 (0.24–1.70)
Random effects: $I^2 = 0\%$			0.39 (0.20–0.77)
Less severe pneumonia			
Blum et al, 2015 (16)	16/392	13/393	1.23 (0.60–2.53)
Fernández-Serrano et al, 2011 (46)	1/23	1/22	0.96 (0.06–14.37)
McHardy and Schonell, 1972 (45)	3/40	9/86	0.72 (0.20–2.51)
Meijvis et al, 2011 (43)	9/151	11/153	0.83 (0.35–1.92)
Snijders et al, 2010 (42)	6/104	6/109	1.05 (0.35–3.15)
Wagner et al, 1956 (39)	1/52	1/61	1.17 (0.08–18.30)
Random effects: $I^2 = 0\%$			1.00 (0.79–1.26)
Total			
Random effects: $I^2 = 6\%$; interaction $P = 0.010$			0.67 (0.45–1.01)

Reed A.C. Siemieniuk, *Ann Intern Med.* 2015;163:519-528.

Corticosteroids for pneumonia (Review)

Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M

Cochrane Library
Cochrane Database of Systematic Reviews

17 RCTs, 4 for children

Corticosteroids significantly reduced mortality in adults with severe pneumonia (RR 0.58, 95% CI 0.40 to 0.84; moderate-quality evidence), but not in adults with non-severe pneumonia (RR 0.95, 95% CI 0.45 to 2.00). Early clinical failure rates (defined as death from any cause, radiographic progression, or clinical instability at day 5 to 8) were significantly reduced with corticosteroids in people with severe and non-severe pneumonia (RR 0.32, 95% CI 0.15 to 0.7; and RR 0.68, 95% CI 0.56 to 0.83, respectively; high-quality evidence). Corstocosteroids reduced time to clinical cure, length of hospital and intensive care unit stays, development of respiratory failure or shock not present at pneumonia onset, and rates of pneumonia complications.

Authors' conclusions

Corticosteroid therapy reduced mortality and morbidity in adults with severe CAP; the number needed to treat for an additional beneficial outcome was 18 patients (95% CI 12 to 49) to prevent one death. Corticosteroid therapy reduced morbidity, but not mortality, for adults and children with non-severe CAP. Corticosteroid therapy was associated with more adverse events, especially hyperglycaemia, but the harms did not seem to outweigh the benefits.

Cochrane Database Syst Rev. 2017 Dec 13;12:CD007720

Corticosteroids in Patients Hospitalized With Community-Acquired Pneumonia: Systematic Review and Individual Patient Data Metaanalysis

Matthias Briel,[1,2,a] Simone M. C. Spoorenberg,[3,a] Dominic Snijders,[4] Antoni Torres,[5] Silvia Fernandez-Serrano,[6] G. Umberto Meduri,[7,8] Albert Gabarrús,[5] Claudine A. Blum,[9,10] Marco Confalonieri,[7] Benjamin Kasenda,[1] Reed A.C. Siemieniuk,[2,11] Wim Boersma,[12] Willem Jan W. Bos,[3,a] Mirjam Christ-Crain,[9,a]; for the Ovidius Study Group, Capisce Study Group, and STEP Study Group[b]

Αναλύθηκαν 1506 ασθενείς σε 6 μελέτες

Table 1. Characteristics of Included Randomized, Placebo-Controlled Trials

Trial, Reference and year	Country	Patients, no.	Study Period	Median Age (Interquartile Range), y	Men, no. (%)	Patient Population	Corticosteroid, Dose, Route, and Duration	Follow-up for Mortality, months
Confalonieri, 2005	Italy	46	2000–2003	67.5 (51–76)	32 (70)	Patients with severe CAP according to 1993 ATS severity criteria	Hydrocortisone 200 mg IV bolus followed by 10 mg/h IV for 7 d	3
Snijders, 2010	The Netherlands	204	2005–2008	64.5 (71–80)	118 (58)	Adults hospitalized with CAP	Prednisolone 40 mg IV or orally for 7 d	84
Meijvis, 2011	The Netherlands	302	2007–2010	66.5 (51–79)	169 (56)	Adults with CAP but without need for intensive care	Dexamethasone 5 mg IV daily for 4 d	72
Fernandez-Serrano, 2011	Spain	52	2000–2002	62.5 (47–68.5)	16 (31)	Adults up to age 75 years with severe CAP (consolidation of ≥2 lobes and PO_2/FIO_2 <300)	Methylprednisolone 200 mg IV bolus followed by tapering infusion (3.3–0.8 mg/h IV) over 9 d	1
Blum, 2015	Switzerland	785	2009–2014	73 (61–83)	487 (62)	Adults hospitalised with CAP	Prednisone 50 mg oral daily for 7 d	6
Torres, 2015	Spain	120	2004–2012	69.5 (63–81)	74 (62)	Adults with severe CAP according to ATS or pneumonia severity index criteria and C-reactive protein >150 mg/L	Methylprednisolone 0.5 mg/kg IV twice daily for 5 d	1

Clinical Infectious Diseases® 2018;66(3):346–54

Corticosteroids in Patients Hospitalized With Community-Acquired Pneumonia: Systematic Review and Individual Patient Data Metaanalysis

Matthias Briel,[1,2,a] Simone M. C. Spoorenberg,[3,a] Dominic Snijders,[4] Antoni Torres,[5] Silvia Fernandez-Serrano,[6] G. Umberto Meduri,[7,8] Albert Gabarrús,[5] Claudine A. Blum,[9,10] Marco Confalonieri,[7] Benjamin Kasenda,[1] Reed A.C. Siemieniuk,[2,11] Wim Boersma,[12] Willem Jan W. Bos,[3,a] Mirjam Christ-Crain,[9,a]; for the Ovidius Study Group, Capisce Study Group, and STEP Study Group[b]

Table 3. Primary and Secondary Outcomes at 30 days After Randomization Using Random Intercepts for Included Trials

Outcome	Corticosteroid (n = 748)	Placebo (n = 758)	Intention-to-Treat Regression analysis, OR or Coefficient (95% Confidence Interval), *P* Value
Primary			
All-cause mortality, no. (%)	37 (5.0)	45 (5.9)	OR 0.75 (0.46 to 1.21), *P* = .24
Secondary			
Secondary intensive care unit admission, no. (%)[a]	38 (5.6)	43 (6.3)	OR 0.74 (0.45 to 1.21), *P* = .23
Length of hospital stay, days	7.0 (5.0–11.0)	8.0 (5.0–12.0)	–1.15 days (–1.75 to –0.55), *P* < .001
Time to clinical stability, days[b]	3.0 (2.0–5.4)	4.0 (2.5–7.0)	–1.03 days (–1.62 to –0.43), *P* = .001
Intravenous antibiotic treatment, days[c]	4.0 (3.0–6.0)	5.0 (3.0–7.0)	–0.62 days (–1.07 to –0.16), *P* = .01
Early (≤72 hours) treatment failure, no. (%)[d]	40 (5.7)	45 (6.4)	OR 0.84 (0.53 to 1.34), *P* = .47
Late (>72 hours) treatment failure, no. (%)[d]	67 (9.5)	66 (9.3)	OR 0.97 (0.67 to 1.40), *P* = .86
Community-acquired pneumonia–related rehospitalization, no. (%)[e]	33 (5.0)	18 (2.7)	OR 1.85 (1.03 to 3.32), *P* = .04
Nosocomial infections, no. (%)	33 (4.4)	25 (3.3)	OR 1.31 (0.77 to 2.24), *P* = .32
Hyperglycaemia requiring insulin, no. (%)[f]	160 (22.1)	88 (12.0)	OR 2.15 (1.60 to 2.90), *P* < .001
Empyema/complicated parapneumonic effusion, no. (%)	12 (1.6)	14 (1.9)	OR 0.90 (0.41 to 1.96), *P* = .79
Gastrointestinal bleeding, no. (%)	5 (0.7)	5 (0.7)	OR 0.95 (0.27 to 3.33), *P* = .93
Neuropsychiatric complications, no. (%)	6 (0.8)	2 (0.3)	OR 2.98 (0.60 to 14.9), *P* = .18

Clinical Infectious Diseases® 2018;66(3):346–54

ΠΑΡΕΝΕΡΓΕΙΕΣ

- <u>Υπεργλυκαιμία</u> → αύξηση
- ΓΕΣ αιμορραγία
- Επιλοιμώξεις
- Νευροψυχιατρικές επιπλοκές
- Μυική αδυναμία
- Επανεισαγωγή

Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study

Akbar K Waljee,[1,2,3,4] Mary A M Rogers,[2,4,5] Paul Lin,[2] Amit G Singal,[6] Joshua D Stein,[2,7,8] Rory M Marks,[9] John Z Ayanian,[2,5,8] Brahmajee K Nallamothu[1,2,4,10]

- 1.5 million US εισαγωγές σε νοσοκομείο
- 327,000(21%) ασθενείς έλαβαν μικρές δόσεις oral κορτικοστεροειδών(<30d)

Table 4 | Incidence rate ratios for adverse events associated with short term use of oral corticosteroids, by reason for medical visit

Adverse event	5-30 days* Incidence rate ratio† (95% CI)	P value	31-90 days* Incidence rate ratio† (95% CI)	P value
Sepsis:				
Respiratory conditions‡	3.77 (1.94 to 7.35)	<0.001	2.53 (1.25 to 5.10)	0.01
Musculoskeletal conditions§	12.91 (5.49 to 30.34)	<0.001	4.32 (1.87 to 9.97)	0.001
Venous thromboembolism:				
Respiratory conditions‡	3.11 (2.20 to 4.40)	<0.001	1.27 (0.88 to 1.82)	0.20
Musculoskeletal conditions§	4.70 (3.08 to 7.17)	<0.001	2.02 (1.31 to 3.11)	0.001
Fracture:				
Respiratory conditions‡	1.96 (1.63 to 2.37)	<0.001	1.33 (1.13 to 1.56)	<0.001
Musculoskeletal conditions§	2.46 (2.02 to 3.00)	<0.001	1.65 (1.37 to 1.99)	<0.001

the bmj | BMJ 2017;357:

Αντιβιοτικά ως ανοσοτροποποιητές

Macrolides

***Anti-inflammatory* benefits in pts with COPD/cysticfibrosis/asthma/bronchiectasis**

Support of immune system against "mucoidmbacteria" because of their anti-biofilm/quorum sensing abilities

Reports of a twice immunomodulatory effect in CAP, in the early and subsequent Phase of immune system response

ΚΑΛΥΤΕΡΗ ΔΡΑΣΤΙΚΟΤΗΤΑ ΣΕ ΑΣΘΕΝΕΙΣ ΠΟΥ ΛΑΜΒΑΝΟΥΝ ΜΑΚΡΟΛΙΔΕΣ?

Pathogen- and antibiotic-specific effects of prednisone in community-acquired pneumonia

Sebastian A. Wirz[1,7], Claudine A. Blum[2,3,7], Philipp Schuetz[3], Werner C. Albrich[4], Christoph Noppen[5], Beat Mueller[6], Mirjam Christ-Crain[2,7] and Philip E. Tarr[1,7] for the STEP Study Group[8]

Reduced TTCS with prednisone was seen in all microbiological, antibiotic, procalcitonin and afebrile patient subgroups. We found evidence for a different prednisone response in patients with pneumococcal pneumonia in whom intravenous antibiotic duration was not shorter (interaction p=0.01) with prednisone, as was observed in the remaining study population. ~~In patients without macrolide treatment, rehospitalisations were not lower with prednisone (interaction p=0.04)~~. After adjustment for multiple testing, these subgroup effects were no longer significant.

Eur Respir J 2016; 48: 1150–1159

Treatment with macrolides and glucocorticosteroids in severe community-acquired pneumonia: A post-hoc exploratory analysis of a randomized controlled trial

Adrian Ceccato[1,2], Catia Cilloniz[1], Otavio T. Ranzani[1,3], Rosario Menendez[4], Carles Agusti[1], Albert Gabarrus[1], Miquel Ferrer[1], Oriol Sibila[5], Michael S. Niederman[6], Antoni Torres[1]*

106 pts were classified into 4 groups according to antimicrobial therapy combination :1) β-lactam plus macrolide or 2) β-lactam plus fluoroquinolone and corticosteroid arm (placebo or corticosteroids).

The **primary outcome** was treatment failure (early and late)

Results: The **glucocorticosteroids and macrolides combination** had no statistically significant association with main clinical outcomes compared with other combinations in patients with severe CAP and a high inflammatory response after taking account potential confounders.

PLOS ONE June 15, 2017

Πνευμονιοκοκκική Πνευμονία & κορτικοστεροειδή

- <<In patients with pneumococcal pneumonia, the prednisone benefit on TTCS was somewhat smaller than in the other subgroups and prednisone was associated with **increased duration of intravenous antibiotics** and trends towards longer antibiotic treatment and longer hospital stay.>>

  Wirtz SA. ERJ2016

- << Patients with Pneumococcal pneumonia had a **lower cure rate and late failures** were more common in those treated with adjunct prednisolone than in those receiving placebo>>

  Snijders D.AJRCCM2010

2.ΙΟΓΕΝΕΙΣ ΠΝΕΥΜΟΝΙΕΣ

1.INFLUENZA?

Early Corticosteroids in Severe Influenza A/H1N1 Pneumonia and Acute Respiratory Distress Syndrome

Christian Brun-Buisson[1,2,3], Jean-Christophe M. Richard[4], Alain Mercat[5], Anne C. M. Thiébaut[3,6], and Laurent Brochard[1,2,7], for the REVA-SRLF A/H1N1v 2009 Registry Group*

- **Methods**: P ill patients with influen f fulfilling criteria for
- **Results**: O ed corticoster nt hydrocortis

  Steroid th rude analysis (33.7 vs. 16 **arly therapy**
- (< 3 d of m gly associated with morta ing steroids had more acquired pneumonia and a trend to a longer duration of ventilation

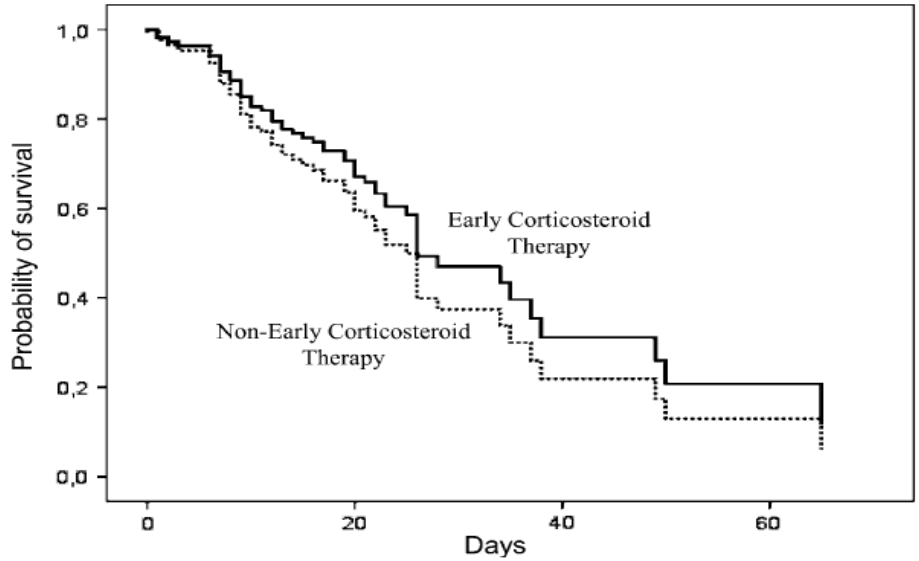


Fig. 1 Survival graph for patients with severe pandemic (H1N1)v influenza A infection with or without early corticosteroid therapy on ICU admission (censored at 60 days)

Am J Respir Crit Care Med Vol 183. pp 1200–1206, 2011

Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1)v influenza A infection

I. Martin-Loeches

Intensive Care Med (2011) 37:272–283

- **Methods**: Prospective, multicenter study from 23 June 2009-11 February 2010, reported in ESICM H1N1 registry.
- **Results**: 220 pts. 67 (30.5%) of the patients died in ICU and 75 (34.1%) whilst in hospital. 125 (57.3%) pts received corticosteroid on admission to ICU. These patients receiving corticosteroids had increased likelihood of **developing HAP**[26.2% vs. 13.8%, p=0.05; OR 2.2,). Patients who received corticosteroids had **significantly higher ICU mortality than patients who did not (46.0% versus 18.1%, p=0.01; OR 3.8, CI 2.1–7.2).**

Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study

Gerard Moreno[1], Alejandro Rodríguez[1*], Luis F. Reyes[2], Josep Gomez[1], Jordi Sole-Violan[3], Emili Díaz[4], María Bodí[1], Sandra Trefler[1], Juan Guardiola[5], Juan C. Yébenes[6], Alex Soriano[7], José Garnacho-Montero[8], Lorenzo Socias[9], María del Valle Ortíz[10], Eudald Correig[11], Judith Marín-Corral[12], Montserrat Vallverdú-Vidal[13], Marcos I. Restrepo[14], Antoni Torres[15], Ignacio Martín-Loeches[16] and on Behalf GETGAG Study Group

80 mg methylprednisolone (IQR 60–120) for of 7 days

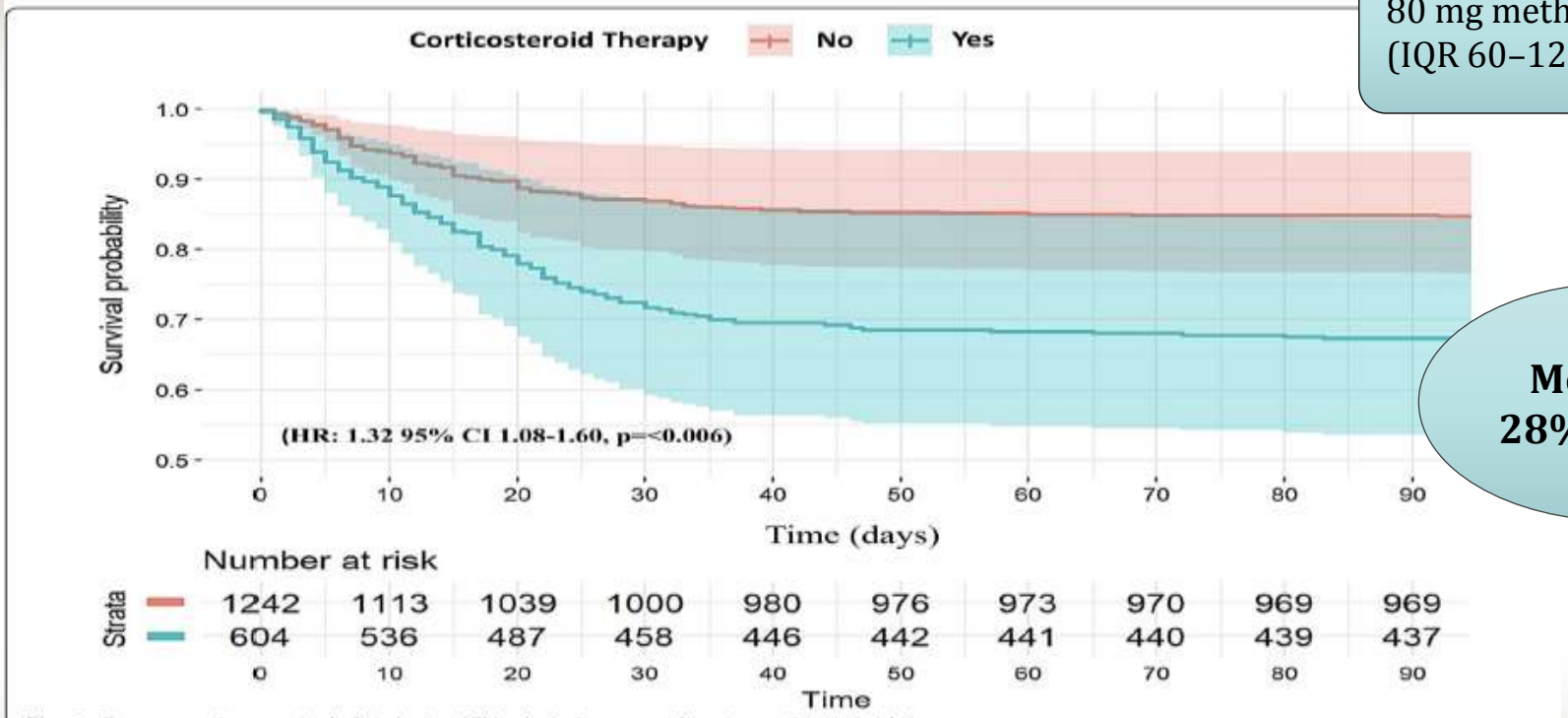


Fig. 3 Cox regression survival plot during ICU admission according to corticosteroid therapy

Mortality 28% vs.19%

Intensive Care Med. 2018 Sep

Effect of Corticosteroid Therapy on Influenza-Related Mortality: A Systematic Review and Meta-analysis

Chamira Rodrigo,[1] Jo Leonardi-Bee,[2] Jonathan S. Nguyen-Van-Tam,[2] and Wei Shen Lim[1]

16 studies, 1497 patients

Study, Year	Log[OR] ± SE	Weight, %	OR[a] (95% CI)
Unadjusted mortality			
Brun-Buisson et al [10]	0.9247 ± 0.3334	17.4	2.52 (1.31–4.85)
Diaz et al [9]	0.0688 ± 0.2802	19.6	1.07 (0.62–1.86)
Li et al [17]	1.6376 ± 1.1269	3.5	5.14 (0.56–46.82)
Mady et al [19]	1.0542 ± 0.4731	12.5	2.87 (1.14–7.25)
Sertogullarindan et al [20]	−1.674 ± 0.9789	4.4	0.19 (0.03–1.28)
Viasus et al [21]	1.0143 ± 0.7879	6.3	2.76 (0.59–12.92)
Subgroup findings		**63.8**	**1.74 (0.91–3.34)**
Heterogenity: $\tau^2 = 0.33$; $\chi^2 = 11.74$, df = 5 ($P = .04$); $I^2 = 57\%$			
Test for overall effect: $Z = 1.66$ ($P = .10$)			
Adjusted mortality			
Kim et al [16]	0.7885 ± 0.3872	15.3	2.20 (1.03–4.70)
Liem et al [18]	1.4134 ± 0.6543	8.3	4.11 (1.14–14.82)
Linko et al [11]	1.1939 ± 0.9628	4.5	3.30 (0.50–21.78)
Xi et al [22]	1.3002 ± 0.6685	8.0	3.67 (0.99–13.60)
Subgroup findings		**36.2**	**2.82 (1.61–4.92)**
Heterogenity: $\tau^2 = 0.00$; $\chi^2 = 0.92$, df = 3 ($P = .82$); $I^2 = 0\%$			
Test for overall effect: $Z = 3.63$ ($P = .0003$)			
Overall findings		**100.0**	**2.12 (1.36–3.29)**
Heterogenity: $\tau^2 = 0.18$; $\chi^2 = 15.08$, df = 9 ($P = .09$); $I^2 = 40\%$			
Test for overall effect: $Z = 3.35$ ($P = .0008$)			
Test for subgroup differences: $\chi^2 = 1.21$, df = 1 ($P = .27$); $I^2 = 17.6\%$			

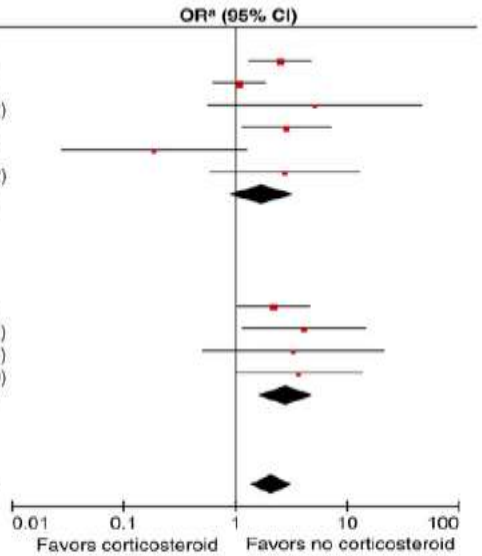


Figure 2. Meta-analysis of studies reporting mortality. [a]Odds ratios (ORs) were determined by random-effects modeling. Abbreviations: CI, confidence interval; SE, standard error.

The Journal of Infectious Diseases®

2015

2. ΠΝΕΥΜΟΝΙΑ ΑΠΌ ΑΝΕΜΟΒΛΟΓΙΑ

- Η πιο συχνή επιπλοκή:15-50%
- Θνητότητα:10-33%(MV & σε ανοσοανεπάρκεια)

Στεροειδή

- Βελτιώνουν P/F ratio
- Μικρότερη διάρκεια νοσηλείας ΜΕΘ
- Μικρότερη θνητότητα

MerChest1998;114

Adhami Resp 2006;11

3.Πνευμονία από Pn-jirovecii

- Κορτικοειδή δίνονται εάν η πνευμονία συνοδεύεται από σοβαρή υποξία, λόγω έντονης πνευμονίτιδας. Μαζί με την αντιβίωση δίνεται και πρεδνιζόνη 1-2mg/Kg/24h για 7-10 ημέρες και προοδευτική μείωση για άλλες 10-14 ημέρες

- *Ewald H, Raatz HCochrane Database Syst Rev. 2015*

4.ΣΗΠΤΙΚΟ ΣΟΚ?

The Rationale: Critical Illness-Related Corticosteroid Insufficiency (CIRCI)

- **2017 Definition:** State of **dysregulated** systemic inflammation resulting from inadequate intracellular glucocorticoid–mediated anti-inflammatory activity for the severity of the pt's critical illness.

3 major pathophysiologic events:

Dysregulation of HPA axis

Altered cortisol metabolism

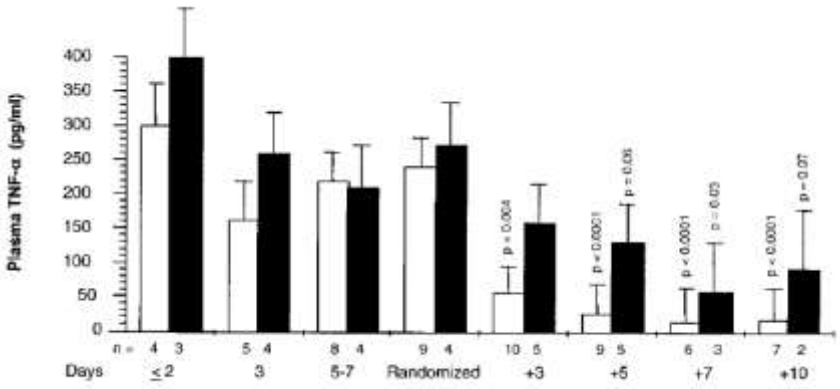
Tissue resistance to corticosteroids

Corticosteroid Use in Critical Illness: SCCM/ESICM Task Force 2017. Courtesy of Stephen M Pastores, MD

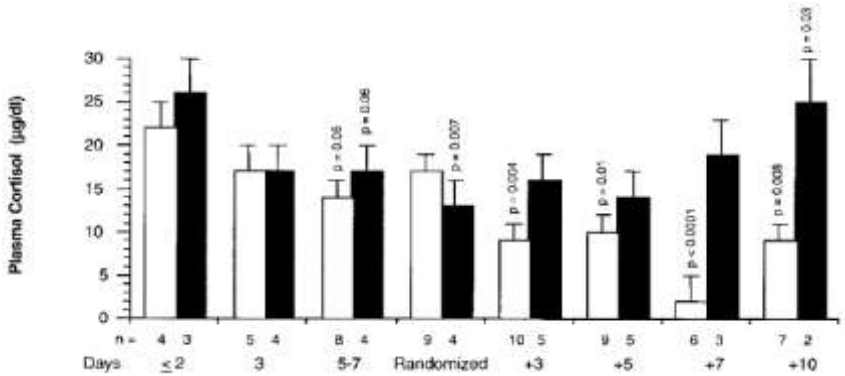
Prolonged Methylprednisolone Treatment Suppresses Systemic Inflammation in Patients with Unresolving Acute Respiratory Distress Syndrome

Evidence for Inadequate Endogenous Glucocorticoid Secretion and Inflammation-induced Immune Cell Resistance to Glucocorticoids

Prolonged methylprednisolone treatment suppresses systemic inflammation in patients with unresolving ARDS: evidence for inadequate glucocorticoid secretion and inflammation---induced immune cell resistance to glucocorticoids.



Patients treated with methylprednisolone had progressive and sustained reductions of TNF-, IL-1 , IL-6, ACTH, and cortisol concentrations



Meduri G,Am J Respir Crit Care Med 2002; 165: 983

RCTs για Σηπτικό Σοκ

CORTICUS 499 patients with septic shock hydrocortisone did not improve survival (28 days)or reversal of shock. There were more episodes of superinfection

2008

HYPRESS 380 patients, with severe sepsis, not septic shock, showed no difference in mortality or time to reversal of shock

2016

ADRENAL 3658 patients who had septic shock; no statistically significant difference in 90 day mortality between the hydrocortisone and placebo groups

2018

APROCCHSS 1241 patients who had septic shock; hydrocortisone plus fludrocortisone reduced 90 day mortality

2018

Comparison of Steroids in Sepsis Trials

Study	Year	Number of Pts	Overall Mortality	Treatment Start	Mortality Benefit	Shock Reversal
Annane et al	2002	299	57.9%	≤8 hrs	6.0%	2 Days
CORTICUS	2008	499	32.9%	≤72 hrs	NO DIFF	3.3 Days
HYPRESS	2016	380	8.5%	≤48 hrs	NO DIFF	NO DIFF
ADRENAL	2018	3800	28.4%	≤24 hrs	NO DIFF	1 Day
APROCCHSS	2018	1241	46.1%	≤24 hrs	6.1%	2 Days

Κορτικοστεροειδή στο σηπτικό σοκ: Guidelines ?

- **2013**

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012

We suggest not using intravenous hydrocortisone as a treatment of adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). If this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).

2016

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).

Κορτικοστεροειδή στο σηπτικό σοκ: Guidelines ?

Table 2 | Current recommendations for corticosteroid therapy in patients with sepsis

Society	Recommendation regarding corticosteroid use		
	In sepsis	In septic shock	Other situations
"Surviving Sepsis" for SCCM and ESICM, 2016[7]	Against	In favour for hypotension refractory to fluid resuscitation and vasopressor	History of adrenal insufficiency or corticosteroid use
CIRCI guidelines for SCCM and ESICM, 2018[12 13]	Against	In favour for shock not responsive to fluid and at least moderate dose vasopressor	Acute respiratory distress syndrome Community acquired pneumonia Bacterial meningitis History of adrenal insufficiency or corticosteroid use
CAEP, 2008[14]	Against	In favour for haemodynamically unstable patients not responsive to fluid resuscitation and vasopressor	
NICE, 2017[15]	Not mentioned	Not mentioned	Not mentioned
JSICM, 2018[16]	Against	In favour for shock not responsive to initial fluid resuscitation and vasoactive drugs	

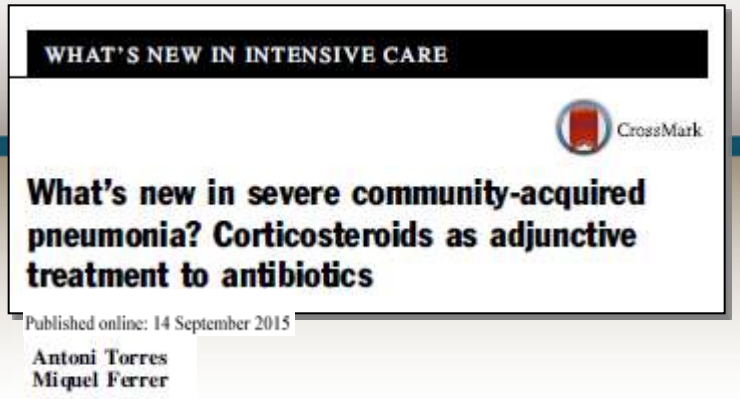
SCCM = Society of Critical Care Medicine. ESICM = European Society for Intensive Care Medicine. CIRCI = critical illness-related corticosteroid insufficiency. CAEP = Canadian Association of Emergency Physicians. NICE = National Institute for Health and Care Excellence (UK). JSICM = Japanese Society for Intensive Care Medicine.

Χρήση Κορτικοστεροειδών στη Σήψη και Σηπτικό Σόκ

1. Κορτικοστεροειδή πρέπει να δίνονται σε ασθενείς με σηπτικό shock που παραμένουν υποτασικοί παρόλη την επαρκή χορήγηση υγρών & υψηλής αγγειοσυσπαστικής θεραπείας
2. Συστήνεται IV hydrocortisone 200 mg/day
3. Σχετικός κίνδυνος επιλοίμωξης (1.02) και υπεργλυκαιμίας (1.11)

Corticosteroid Use in Critical Illness: SCCM/ESICM Task Force 2017 . Courtesy of Stephen M Pastores, MD

Select patients with criteria for severe CAP (IDSA/ATS guidelines)


WHAT'S NEW IN INTENSIVE CARE

CrossMark

What's new in severe community-acquired pneumonia? Corticosteroids as adjunctive treatment to antibiotics

Published online: 14 September 2015

Antoni Torres
Miquel Ferrer

- Discard Influenza A H1N1 pneumonia during influenza season
- Discard general contraindications for corticosteroid administration:
  - Diabetes mellitus needing insulin treatment
  - Major gastrointestinal bleeding within 3 months

Select patients with serum levels of C-reactive protein >15 mg/dL

Select the most appropriate empiric antibiotic therapy

Start corticosteroids as soon as possible

- 0.5 mg/kg/12 h Methylprednisolone or equivalent, for 5 days*

*We recommend 5 days of treatment although the meta-analysis of Nie *et al* recommends more than 5 days

ΕΡΩΤΗΜΑΤΑ

1. Ανακάλυ θενών με ανταπόκρ
2. Ομάδες α εγμονωδών βιοδεικτώ
3. Καθορισμός του τύπου του στεροειδούς, της δόσης, της διάρκειας
4. Μελέτες για συσχετίσεις με μακρολίδες ή άλλα αντιβιοτικά

ΝΕΕΣ ΜΕΛΕΤΕΣ?

CAPE-COD Trial (NCT02517489)
Santeon-CAP (NCT01743755)