Corticothérapie systémique & pneumopathies communautaires: facteur de risque ou traitement ?

GREPI, Chantilly, 26 novembre 2015

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Paul Cézanne (1839-1906), *la Montagne Sainte-Victoire* (1904-1906)
(collection privée)

Liens d' intérêt

- Versement associatif pour réalisation d' essais cliniques :
  - Kenta Biotech LTD
  - Orion Pharma
  - Eli Lilly
  - Takeda
  - Glaxo Smith Kline
  - Eisai Limited
  - Johnson & Johnson
  - Agennix
  - Astra-Zeneca
  - Chiron
  - Novartis
  - MedImmune
  - Fehring

- Contrats de recherche :
  - Air liquide
  - Aerogen / Nektar
  - Diffusion Technique Française

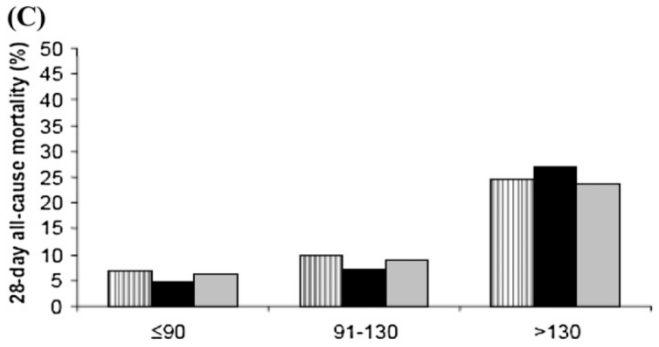
Mortalité des PAC hospitalisées (J30)

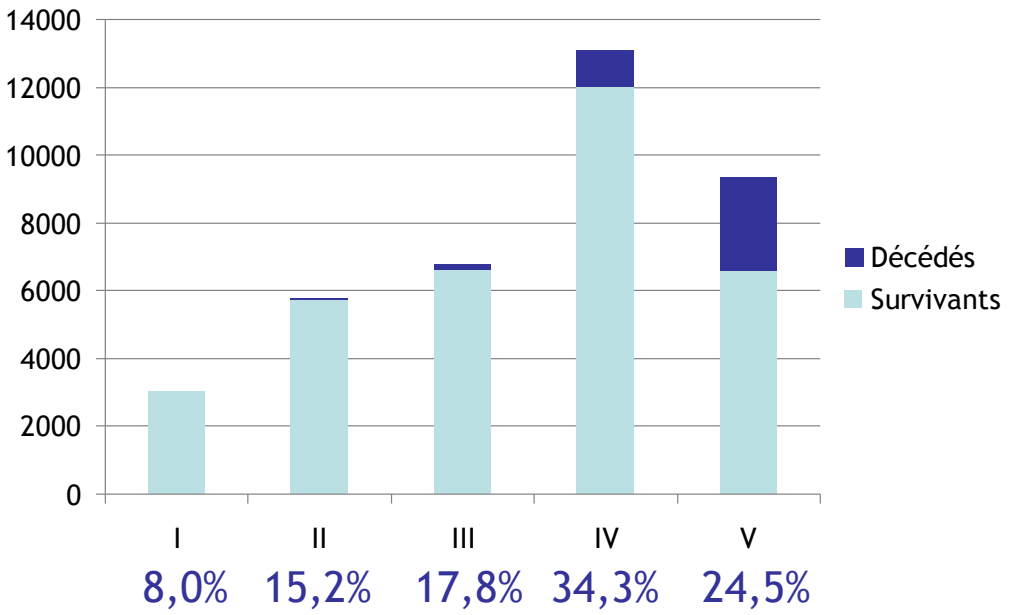
Table 4 Patient mortality from community-acquired pneumonia according to comorbidity.

Comorbidity	2005 deaths (%)	2006 deaths (%)	Total (%)
Malignancy (other than bronchial)	27.65	28.66	28.2
Lung cancer	25.07	25.33	25.21
Pulmonary diseases (other than COPD)	24.03	24.82	24.45
Dementia	21.93	22.76	22.36
Renal diseases	20.2	21.3	20.79
CNS disorders	19.27	19.54	19.41
Cardiac comorbidity	17.06	17.63	17.35
Diabetes mellitus	13.41	13.88	13.66
Liver diseases	12.26	13.6	12.93
COPD	9.85	10.37	10.12
Total	17.08	17.75	17.43
No comorbidity	12.5	13.35	12.95

COPD, chronic obstructive pulmonary disease.

d' après Ewig et al. Thorax 2009;64:1062-9.





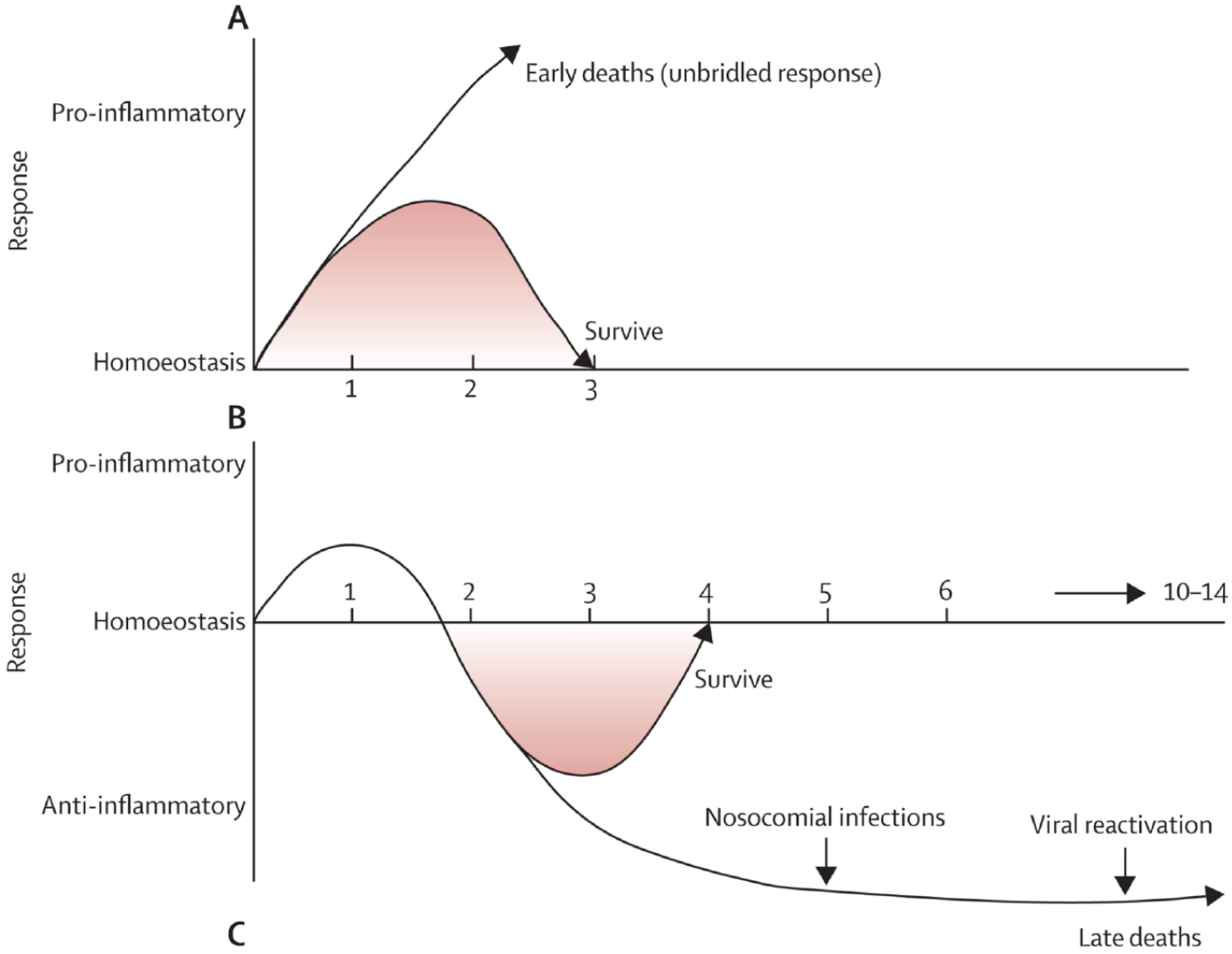
8,0% 15,2% 17,8% 34,3% 24,5%

d' après Fine et al. NEJM 1997;336:243-50.

Cohorte de validation MedisGroup,
n = 38 039 (1991).
Mortalité globale: 10,6%. Fine V: 29,2%.

CAPTIVATE, Wunderink AJRCCM 2011 ;183 :1561-8.

Sepsis: inflammation / immunosuppression



THE LANCET Infectious Diseases

Hotchkiss et al. 2013;13:260-8

Effets antiinflammatoires des corticostéroïdes

Main anti-inflammatory effects of glucocorticoids

Anti-inflammatory effect	Details
Proinflammatory cytokine production	Inhibition of IL-2, IL-3, IL-4(?), IL-5, IFN-γ, GM-CSF synthesis by T lymphocytes
	Inhibition of IL-1, TNF-α, IL-6, IL-8, IL-12, MIF synthesis by macrophages/monocytes
	Inhibition of IL-8 synthesis by neutrophils
Anti-inflammatory cytokine production	Increase in IL-10, TGF-β, IL-1 receptor antagonist synthesis
Inflammatory cell migration	Inhibition of chemokine production (MCP-1, IL-8, MIP-1α)
	Stimulation of MIF and lipocortine-1 production by macrophages
Inflammation mediator expression	Inhibition of soluble PLA_2, inducible COX-2 and inducible NOS synthesis
Cell membrane markers expression	Inhibition of CD14 expression on macrophages/monocytes
	Inhibition of adhesion molecule expression (ICAM-1, ECAM-1, LFA-1, CD2) on endothelial cells
Apoptosis	Activation of eosinophils and mature T lymphocyte apoptosis

COX, cylo-oxygenase; ECAM, endothelial cell adhesion molecule; GM-CSF, granulocyte–macrophage colony-stimulating factor; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; LFA, leucocyte function associated antigen; MCP, monocyte chemoattractant protein; MIF, migration inhibitory factor; MIP, macrophage inflammatory peptide; NOS, nitric oxide synthase; PL, phospholipase; TGF, transforming growth factor; TNF, tumour necrosis factor.

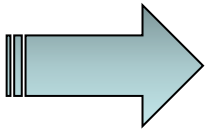
Clinical review: Corticotherapy in sepsis

Helene Prigent[1], Virginie Maxime[2] and Djillali Annane[3]

Critical Care 2004, **8**:122-129

Effets immunosuppresseurs des corticoïdes

Dysfonction lymphocytaire T



Infections bactériennes:
- Pyogènes
- L. Monocytogenes
- L. pneumophila
- Nocardioses
- Actinomycoses
- mycobactérioses atypiques

Tuberculose

Anguillulose maligne

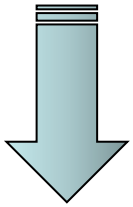
Viroses
- Herpèsvirus

Opportunistes
- pneumocystose
- aspergillose
- cryptococcose
- mucormycose

Risque à partir 10 mg/j x 6 mois

Mais…

Infection grave chez patient sous corticothérapie au long cours



Hydrocortisone 200 mg/j …

Pneumocystis: une vieille histoire

A CONTROLLED TRIAL OF EARLY ADJUNCTIVE TREATMENT WITH CORTICOSTEROIDS FOR *PNEUMOCYSTIS CARINII* PNEUMONIA IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME

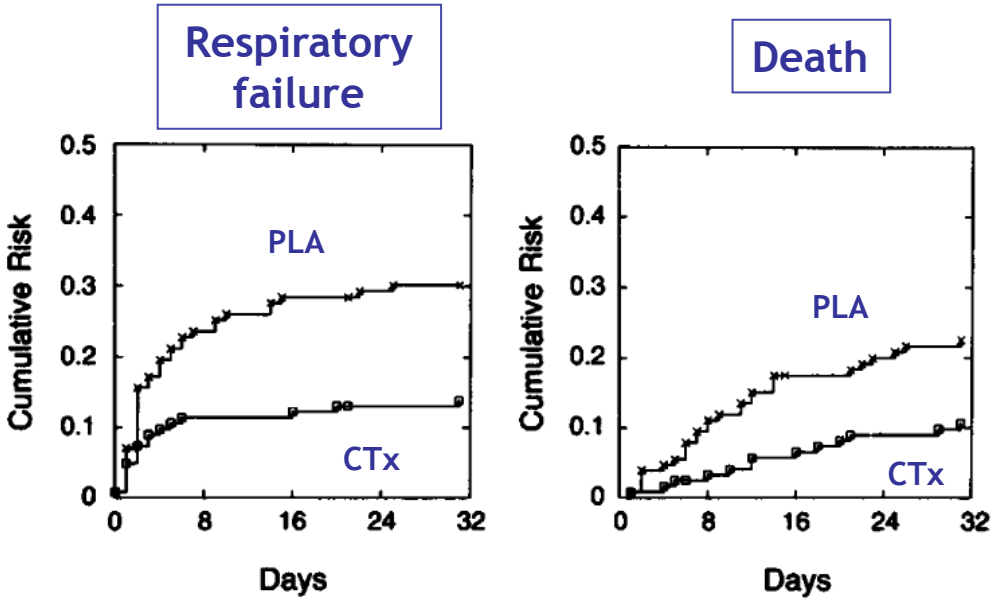


Figure 1. Cumulative Risk of an Unfavorable Outcome over a Period of 31 Days.

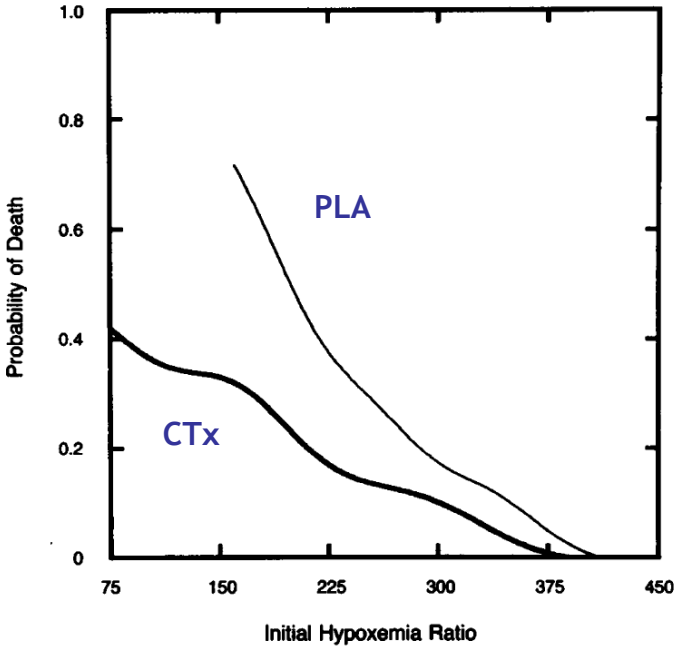


Figure 2. Probability of Death from Respiratory Causes, According to Initial Hypoxemia Ratio.

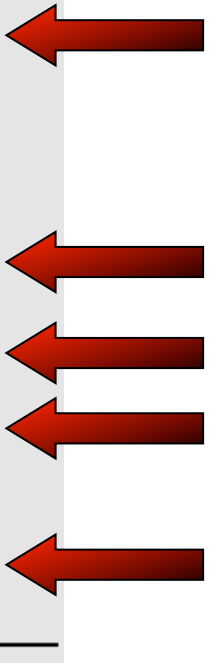
Bozette et al. NEJM 1990;323:1451-7

PAC: quels germes ?

Table 1 Prevalence of pathogens isolated in community-acquired pneumonia by treatment setting.

	Outpatients (%)	Hospitalised patients non-ICU (%)	ICU patients (%)
S. pneumoniae	38	27	28
M. pneumoniae	8	5	2
H. influenzae	13	6	7
C. pneumoniae	21	11	4
S. aureus	1.5	3	9
Enterobacteriaceae	0	4	9
P. aeruginosa	1	3	4
Legionella spp.	0	5	12
C. burnetii	1	4	7
Respiratory viruses	17	12	3
Unknown	50	41	45

ICU, intensive care unit



Adapté d' après Welte et al. Thorax 2012;67:71-9.

Corticostéroïdes & grippe

Do corticosteroids reduce the mortality of influenza A (H1N1) infection? A meta-analysis

CRITICAL CARE

Study or Subgroup	death Events	Total	survival Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chawla, 2013	9	10	29	67	1.9%	11.79 [1.41, 98.42]
Fernando, 2011	38	85	37	93	10.9%	1.22 [0.67, 2.22]
Hong, 2013	62	99	45	146	11.7%	3.76 [2.20, 6.44]
Jose, 2013	29	41	39	88	8.3%	3.04 [1.37, 6.71]
Jung, 2011	54	78	45	141	10.8%	4.80 [2.64, 8.72]
Kinikar, 2012	9	15	12	77	4.9%	8.13 [2.44, 27.05]
Li, 2012	47	58	436	1071	9.9%	6.22 [3.19, 12.13]
Perez-Padilla, 2009	3	7	2	11	1.9%	3.38 [0.40, 28.74]
Sertogullarindan, 2011	34	68	12	74	8.5%	5.17 [2.37, 11.27]
Silvio, 2012	4	9	3	11	2.4%	2.13 [0.33, 13.81]
Sun, 2010	7	7	5	11	1.0%	17.73 [0.81, 385.60]
Xi, 2010	17	27	35	128	7.5%	4.52 [1.89, 10.81]
Yu, 2011	14	18	40	110	5.0%	6.13 [1.89, 19.88]
Zhang, 2013	236	292	814	1858	15.4%	5.41 [3.98, 7.34]
Total (95% CI)		**814**		**3886**	**100.0%**	**4.22 [3.10, 5.76]**
Total events	563		1554			

Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 25.47$, df = 13 (P = 0.02); $I^2 = 49\%$

Test for overall effect: Z = 9.09 (P < 0.00001)

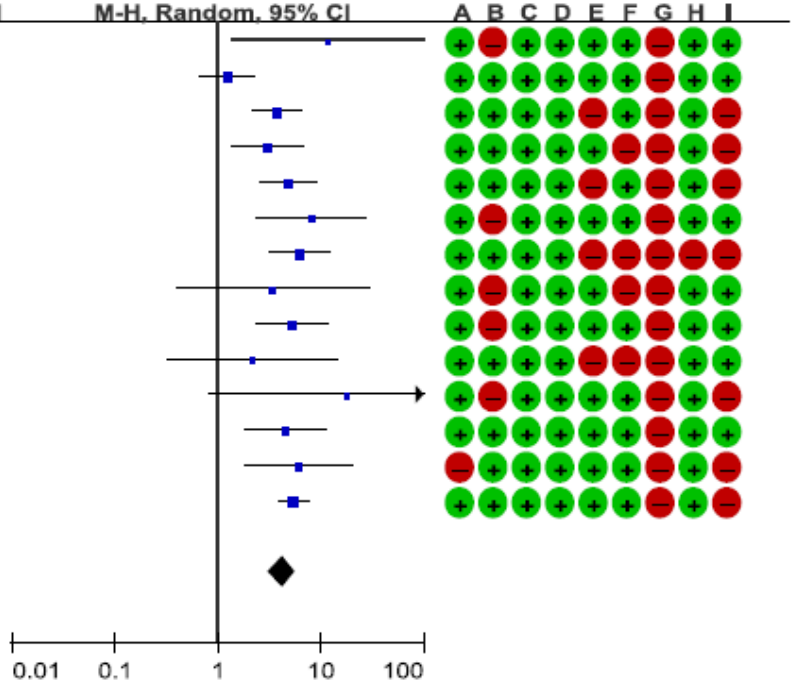


Figure 2 Effect of corticosteroids on influenza A (H1N1) cases from case–control studies. Diamond, overall estimate from the meta-analysis; square, point estimate of the result of each study; horizontal line that runs through the square and the width of the diamond represents the CI. Red dot, high risk of bias; green dot, low risk of bias; A to I, see Additional file 1. CI, confidence interval; M-H, Mantel-Haenszel.

(Etudes cas-témoin & cohortes)

Zhang *et al. Critical Care* (2015) 19:46

Author/ Year	Study Design	Location	No.	Mean Age (y)	Patient Selection	Steroids Used
Wagner 1956	Quasi-RCT	USA multi	113	N/A	Mild to severe	HC 560 mg, 5 d
McHardy 1972	Open-label RCT	UK single	126	60	Mild to severe	Prednisolone 20 mg/d, 7 d
Marik 1993	DB RCT	USA single	30	34	Severe	HC 10 mg/kg, 1 d
Confalonieri 2005	DB RCT	Italy multi	48	64	Severe	HC 240 mg, 7 d
Mikami 2007	Open-label RCT	Japan single	31	72	Mild to severe	Prednisolone 40 mg/d, 3 d
Snijders 2010	DB RCT	NL single	213	63	Mild to severe	Prednisolone 40 mg/d, 7 d
Meijvis 2011	DB RCT	NL multi	304	63	Mild to severe	DXM 5 mg/d, 4d
Sabry 2011	DB RCT	Egypt multi	80	62	Severe	HC 300 mg/d, 7 d
Fernandez 2011	DB RCT	Spain Single	56	63	Severe	MPD 620 mg/d, 9 d
Blum 2015	DB RCT	CH multi	785	73	Mild to severe	Prednisone 50 mg/d, 7d
Torres 2015	DB RCT	SP multi	120	65	Severe	MPD 1 mg/kg/d, 5d

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La dolce vita

Hydrocortisone Infusion for Severe Community-acquired Pneumonia

A Preliminary Randomized Study

AJRCCM 2005;171:242-8

Marco Confalonieri, Rosario Urbino, Alfredo Potena, Marco Piattella, Piercarlo Parigi, Giacomo Puccio, Rossana Della Porta, Carbone Giorgio, Francesco Blasi, Reba Umberger, and G. Umberto Meduri

- 48 patients avec pneumopathie communautaire
  - Dont 34 ventilés
- HSHC 200 mg puis 10 mg/h x 7 j vs. PLA

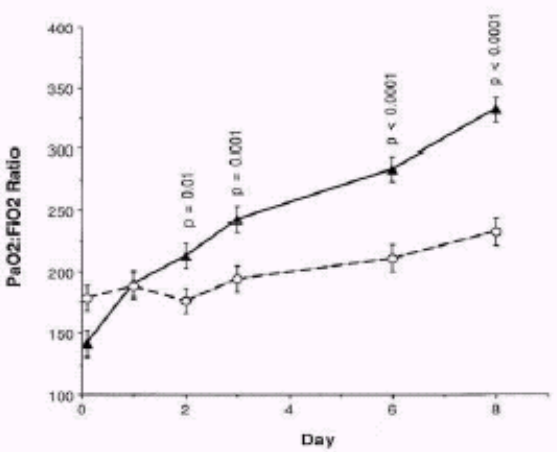

TABLE 4. OUTCOME

Outcome Variable	Placebo	Hydrocortisone	p Value
ICU mortality*	7 (30%)	0 (0%)	0.009
Hospital mortality*	7 (30%)	0 (0%)	0.009
60-d mortality*†	8 (38%)	0 (0%)	0.001
Length of ICU or RICU stay, d‡	18 (3–45)	10 (4–33)	0.01
Length of hospital stay, d‡	21 (3–72)	13 (10–53)	0.03
Duration of mechanical ventilation, d‡	10 (2–44)	4 (1–27)	0.007

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Un souffle du sud

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

A Randomized Clinical Trial

JAMA. 2015;313(7):677-686.

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

- 3 hôpitaux espagnols
- CAP avec CRP > 150 mg/L
- MPD 0,5 mg/kg x 2/j x 5j vs. PLA
- Début < 36 h post admission
- Critère jugement: échec thérapeutique (précoce ou tardif)

MAIN OUTCOMES AND MEASURES The primary outcome was treatment failure (composite outcome of early treatment failure defined as [1] clinical deterioration indicated by development of shock, [2] need for invasive mechanical ventilation not present at baseline, or [3] death within 72 hours of treatment; or composite outcome of late treatment failure defined as [1] radiographic progression, [2] persistence of severe respiratory failure, [3] development of shock, [4] need for invasive mechanical ventilation not present at baseline, or [5] death between 72 hours and 120 hours after treatment initiation; or both early and late treatment failure). In-hospital mortality was a secondary outcome and adverse events were assessed.

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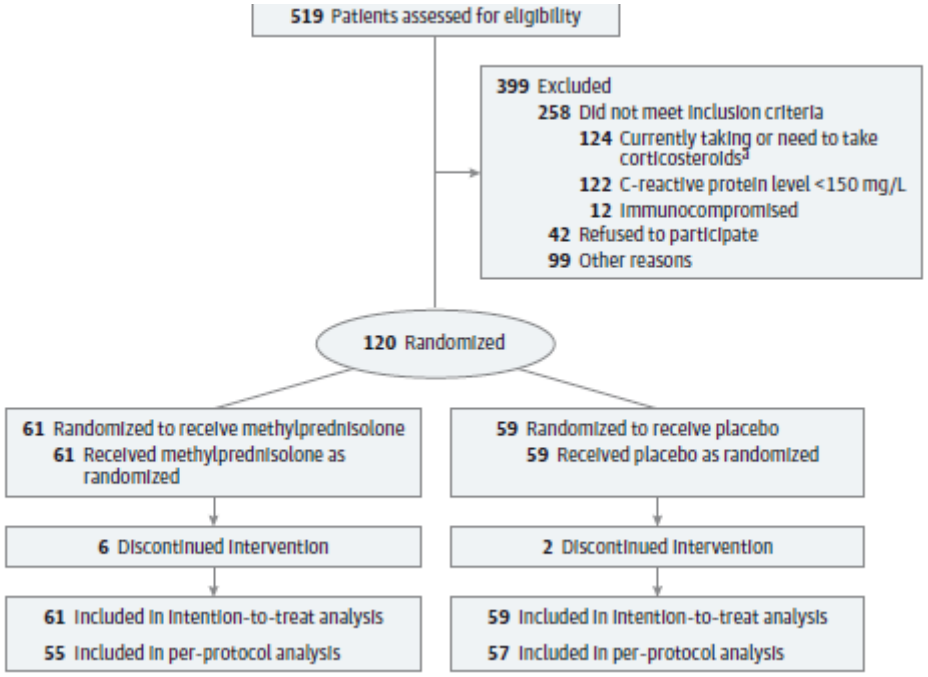
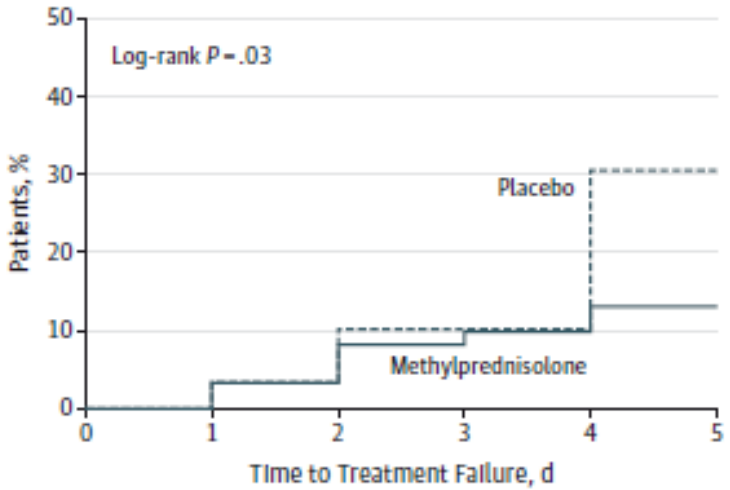


Figure 2. Kaplan-Meier Analysis of the Effect of Methylprednisolone on Time to Treatment Failure



No. at risk						
Placebo	59	57	53	53	41	41
Methylprednisolone	61	59	56	55	53	53

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STEP trial

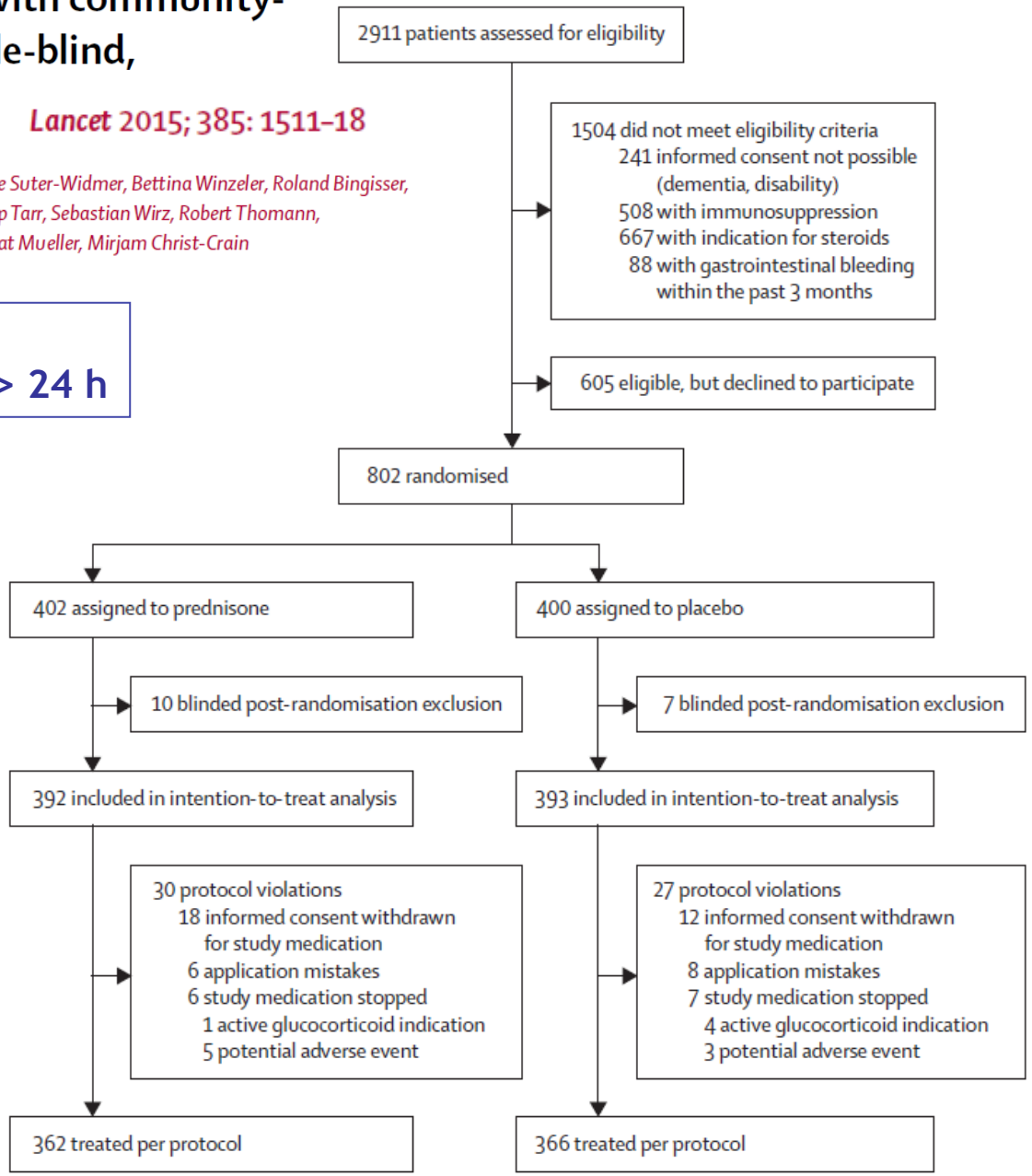
Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial

Lancet 2015; 385: 1511–18

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*

Critère de jugement
= durée (jours) ad stabilité clinique > 24 h

- T ≤ 37,8 °C
- FC ≤ 100/min
- FR ≤ 24/min
- Pas ≥ 90 mmHg
- Status mental idem baseline
- Alimentation possible
- PaO2 ≥ 60 T ou SpO2 ≥ 90%



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	Prednisone (n=392)	Placebo (n=393)	Regression analysis	
			HR, OR, or difference (95% CI)	p value
Primary endpoint				
Intention-to-treat: time to clinical stability, days	3·0 (2·5–3·4)	4·4 (4·0–5·0)	HR 1·33 (1·15 to 1·50)	<0·0001
Per-protocol: time to clinical stability, days	3·0 (2·5–3·2)	4·4 (4·0–5·0)	HR 1·35 (1·16 to 1·56)	<0·0001
Secondary endpoints				
Time to effective hospital discharge, days	6·0 (6·0–7·0)	7·0 (7·0–8·0)	HR 1·19 (1·04 to 1·38)	0·012

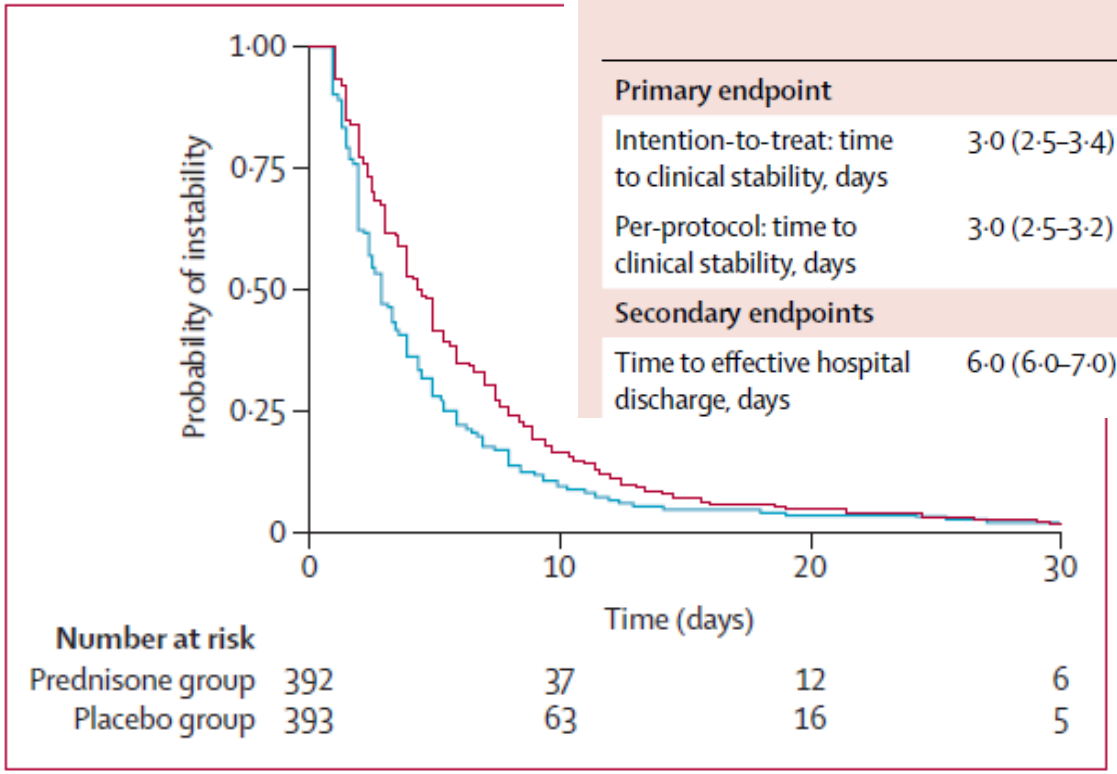


Figure 2: Kaplan-Meier-curve of time to clinical stability

Méta-analyses

Corticosteroids in the Treatment of Community-Acquired Pneumonia in Adults: A Meta-Analysis

October 2012 | Volume 7 | Issue 10

PLOS ONE

Efficacy and safety of glucocorticoids in the treatment of community-acquired pneumonia: A meta-analysis of randomized controlled trials

World J Emerg Med, Vol 6, No 3, 2015

Li-ping Chen[1], Jun-hui Chen[2], Ying Chen[1], Chao Wu[1], Xiao-hong Yang[1]

Corticosteroid Therapy for Severe Community-Acquired Pneumonia: A Meta-Analysis

RESPIRATORY CARE

Ming Cheng MD, Zhi-yong Pan MD, Jiong Yang PhD, and Ya-dong Gao PhD

RESPIRATORY CARE • APRIL 2014 VOL 59 No 4

Annals of Internal Medicine

REVIEW

Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia

A Systematic Review and Meta-analysis

Reed A.C. Siemieniuk, MD; Maureen O. Meade, MD; Pablo Alonso-Coello, MD, PhD; Matthias Briel, MD, MSc; Nathan Evaniew, MD; Manya Prasad, MBBS; Paul E. Alexander, MSc, PhD; Yutong Fei, MD, PhD; Per O. Vandvik, MD, PhD; Mark Loeb, MD, MSc; and Gordon H. Guyatt, MD, MSc

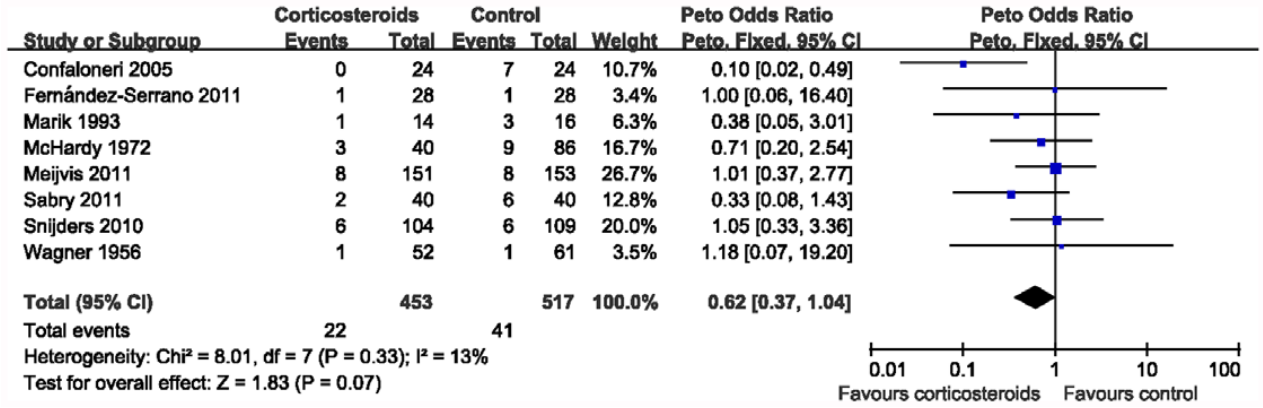
Adjunctive Systemic Corticosteroids for Hospitalized Community-Acquired Pneumonia: Systematic Review and Meta-Analysis 2015 Update

Nobuyuki Horita[1], Tatsuya Otsuka[2], Shusaku Haranaga[3], Ho Namkoong[4], Makoto Miki[5], Naoyuki Miyashita[6], Futoshi Higa[7], Hiroshi Takahashi[8], Masahiro Yoshida[9], Shigeru Kohno[10] & Takeshi Kaneko[1]

SCIENTIFIC REPORTS

5:14061 | DOI: 10.1038/srep14061

Pneumonies non sévères ou de sévérité variable

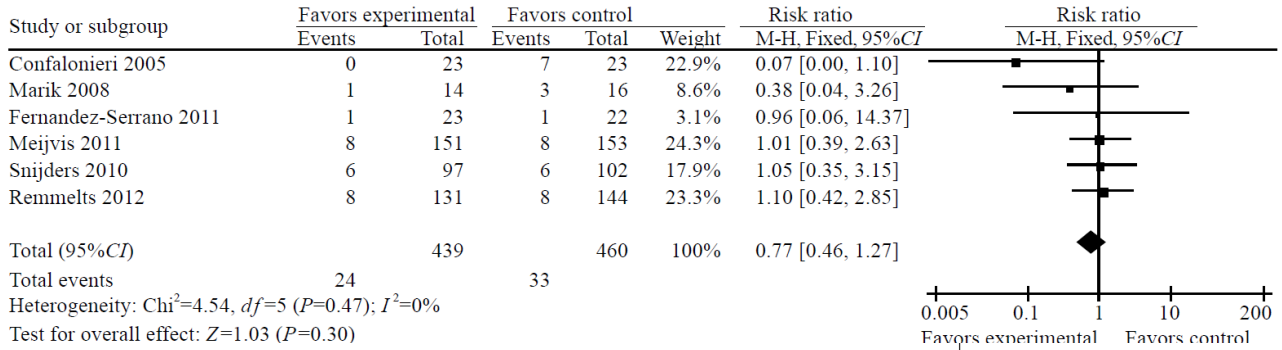


Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Confaloneri 2005	0	24	7	24	10.7%	0.10 [0.02, 0.49]
Fernández-Serrano 2011	1	28	1	28	3.4%	1.00 [0.06, 16.40]
Marik 1993	1	14	3	16	6.3%	0.38 [0.05, 3.01]
McHardy 1972	3	40	9	86	16.7%	0.71 [0.20, 2.54]
Meijvis 2011	8	151	8	153	26.7%	1.01 [0.37, 2.77]
Sabry 2011	2	40	6	40	12.8%	0.33 [0.08, 1.43]
Snijders 2010	6	104	6	109	20.0%	1.05 [0.33, 3.36]
Wagner 1956	1	52	1	61	3.5%	1.18 [0.07, 19.20]
Total (95% CI)		**453**		**517**	**100.0%**	**0.62 [0.37, 1.04]**
Total events	**22**		**41**			

Heterogeneity: Chi² = 8.01, df = 7 (P = 0.33); I² = 13%
Test for overall effect: Z = 1.83 (P = 0.07)

Peto Odds Ratio Peto, Fixed, 95% CI
0.01 0.1 1 10 100
Favours corticosteroids Favours control

PLOS ONE

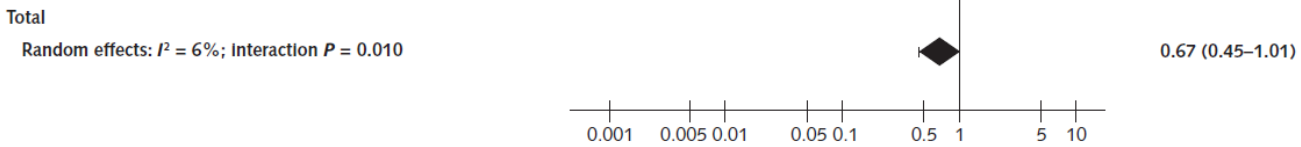


Study or subgroup	Favors experimental Events	Total	Favors control Events	Total	Weight	Risk ratio M-H, Fixed, 95%*CI*
Confalonieri 2005	0	23	7	23	22.9%	0.07 [0.00, 1.10]
Marik 2008	1	14	3	16	8.6%	0.38 [0.04, 3.26]
Fernandez-Serrano 2011	1	23	1	22	3.1%	0.96 [0.06, 14.37]
Meijvis 2011	8	151	8	153	24.3%	1.01 [0.39, 2.63]
Snijders 2010	6	97	6	102	17.9%	1.05 [0.35, 3.15]
Remmelts 2012	8	131	8	144	23.3%	1.10 [0.42, 2.85]
Total (95%*CI*)		439		460	100%	0.77 [0.46, 1.27]
Total events	24		33			

Heterogeneity: Chi²=4.54, *df*=5 (*P*=0.47); I^2=0%
Test for overall effect: *Z*=1.03 (*P*=0.30)

Risk ratio M-H, Fixed, 95%*CI*
0.005 0.1 1 10 200
Favors experimental Favors control

World J Emerg Med,



Total
Random effects: I^2 = 6%; Interaction *P* = 0.010
0.67 (0.45–1.01)
0.001 0.005 0.01 0.05 0.1 0.5 1 5 10

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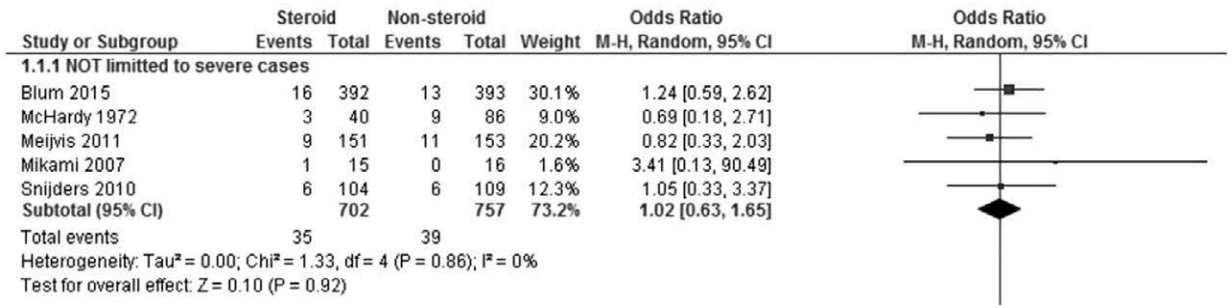


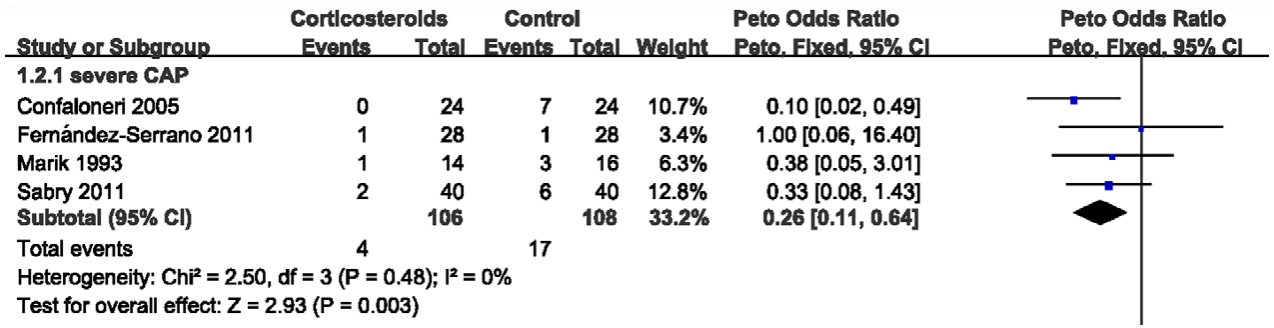
Study or Subgroup	Steroid Events	Total	Non-steroid Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 NOT limitted to severe cases						
Blum 2015	16	392	13	393	30.1%	1.24 [0.59, 2.62]
McHardy 1972	3	40	9	86	9.0%	0.69 [0.18, 2.71]
Meijvis 2011	9	151	11	153	20.2%	0.82 [0.33, 2.03]
Mikami 2007	1	15	0	16	1.6%	3.41 [0.13, 90.49]
Snijders 2010	6	104	6	109	12.3%	1.05 [0.33, 3.37]
Subtotal (95% CI)		**702**		**757**	**73.2%**	**1.02 [0.63, 1.65]**
Total events	35		39			

Heterogeneity: Tau² = 0.00; Chi² = 1.33, df = 4 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)

Odds Ratio M-H, Random, 95% CI

SCIENTIFIC REPORTS

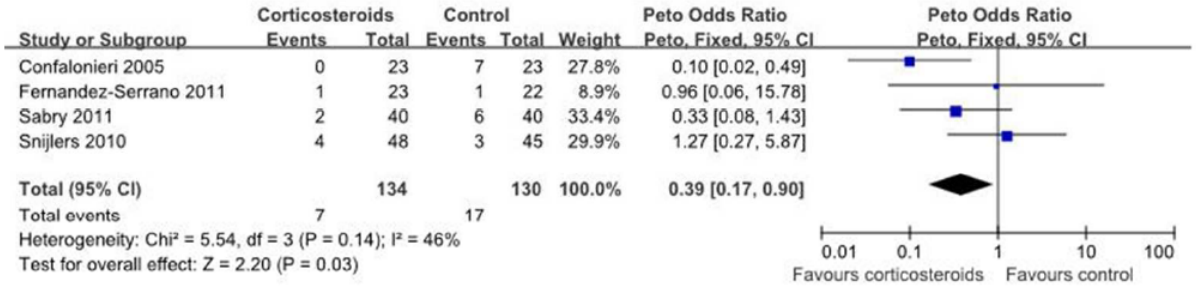
Pneumonies sévères



Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.2.1 severe CAP						
Confaloneri 2005	0	24	7	24	10.7%	0.10 [0.02, 0.49]
Fernández-Serrano 2011	1	28	1	28	3.4%	1.00 [0.06, 16.40]
Marik 1993	1	14	3	16	6.3%	0.38 [0.05, 3.01]
Sabry 2011	2	40	6	40	12.8%	0.33 [0.08, 1.43]
Subtotal (95% CI)		**106**		**108**	**33.2%**	**0.26 [0.11, 0.64]**
Total events	4		17			

Heterogeneity: Chi² = 2.50, df = 3 (P = 0.48); I² = 0%
Test for overall effect: Z = 2.93 (P = 0.003)

PLOS ONE

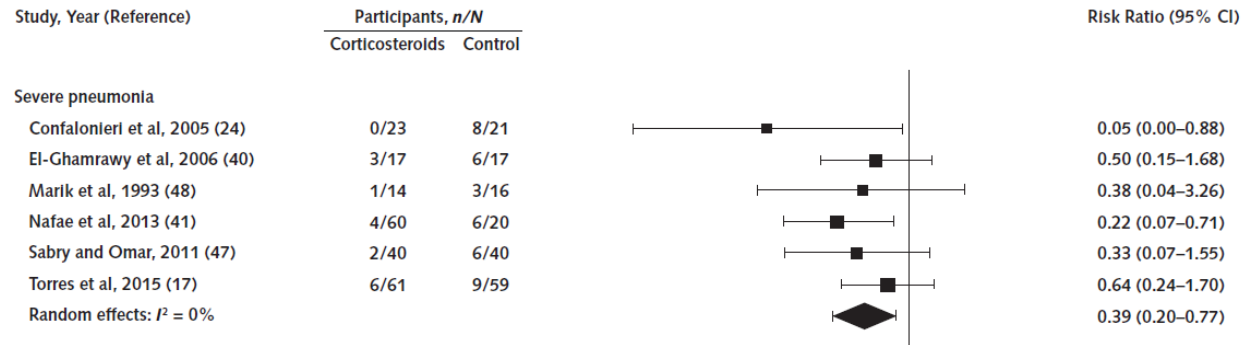


Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Confalonieri 2005	0	23	7	23	27.8%	0.10 [0.02, 0.49]
Fernandez-Serrano 2011	1	23	1	22	8.9%	0.96 [0.06, 15.78]
Sabry 2011	2	40	6	40	33.4%	0.33 [0.08, 1.43]
Snijlers 2010	4	48	3	45	29.9%	1.27 [0.27, 5.87]
Total (95% CI)		**134**		**130**	**100.0%**	**0.39 [0.17, 0.90]**
Total events	7		17			

Heterogeneity: Chi² = 5.54, df = 3 (P = 0.14); I² = 46%
Test for overall effect: Z = 2.20 (P = 0.03)

0.01 0.1 1 10 100
Favours corticosteroids Favours control

RESPIRATORY CARE



Study, Year (Reference)	Participants, *n/N* Corticosteroids	Control	Risk Ratio (95% CI)
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)

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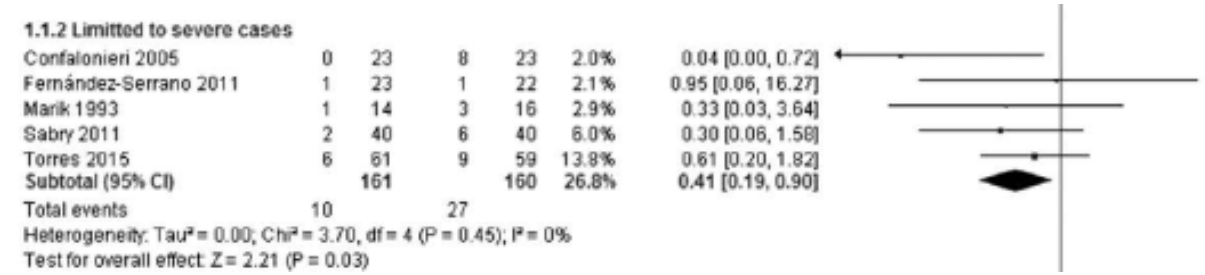
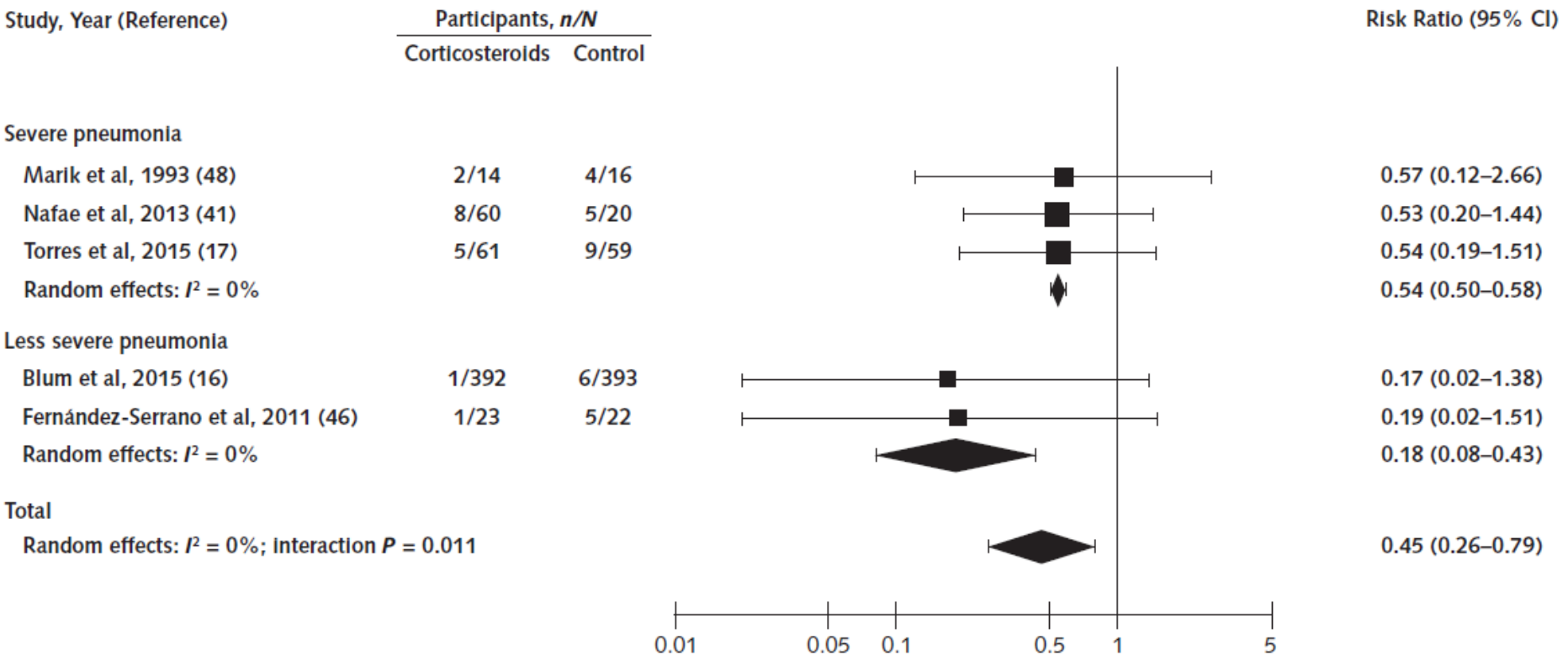


1.1.2 Limitted to severe cases						
Confalonieri 2005	0	23	8	23	2.0%	0.04 [0.00, 0.72]
Fernández-Serrano 2011	1	23	1	22	2.1%	0.95 [0.06, 16.27]
Marik 1993	1	14	3	16	2.9%	0.33 [0.03, 3.64]
Sabry 2011	2	40	6	40	6.0%	0.30 [0.06, 1.58]
Torres 2015	6	61	9	59	13.8%	0.61 [0.20, 1.82]
Subtotal (95% CI)		161		160	26.8%	0.41 [0.19, 0.90]
Total events	10		27			

Heterogeneity: Tau² = 0.00; Chi² = 3.70, df = 4 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.21 (P = 0.03)

SCIENTIFIC REPORTS

Recours à la ventilation mécanique



Annals of Internal Medicine REVIEW

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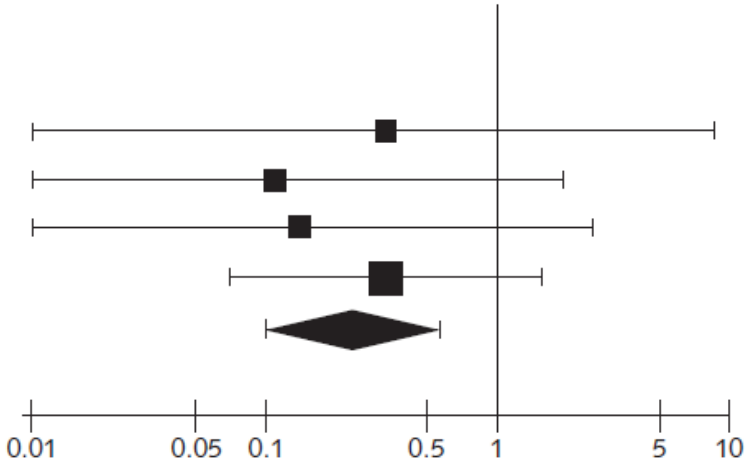
Ann Intern Med. 2015;163:519-528.

Développement d' un SDRA

Study, Year (Reference)	Participants, *n/N*		Risk Ratio (95% CI)
	Corticosteroids	Control	
Blum et al, 2015 (16)	0/392	1/393	0.33 (0.01–8.18)
Confalonieri et al, 2005 (24)	0/23	4/23	0.11 (0.01–1.95)
El-Ghamrawy et al, 2006 (40)	0/17	3/17	0.14 (0.01–2.57)
Sabry and Omar, 2011 (47)	2/40	6/40	0.33 (0.07–1.55)
Random effects: I^2 = 0%			0.24 (0.10–0.56)



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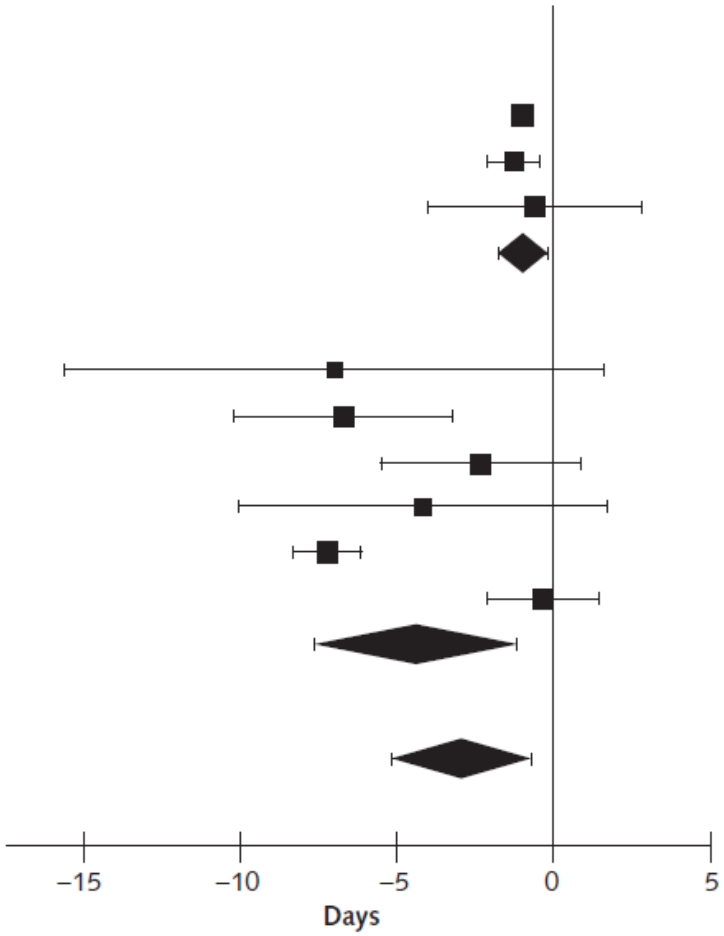
Ann Intern Med. 2015;163:519-528.

Durée d' hospitalisation



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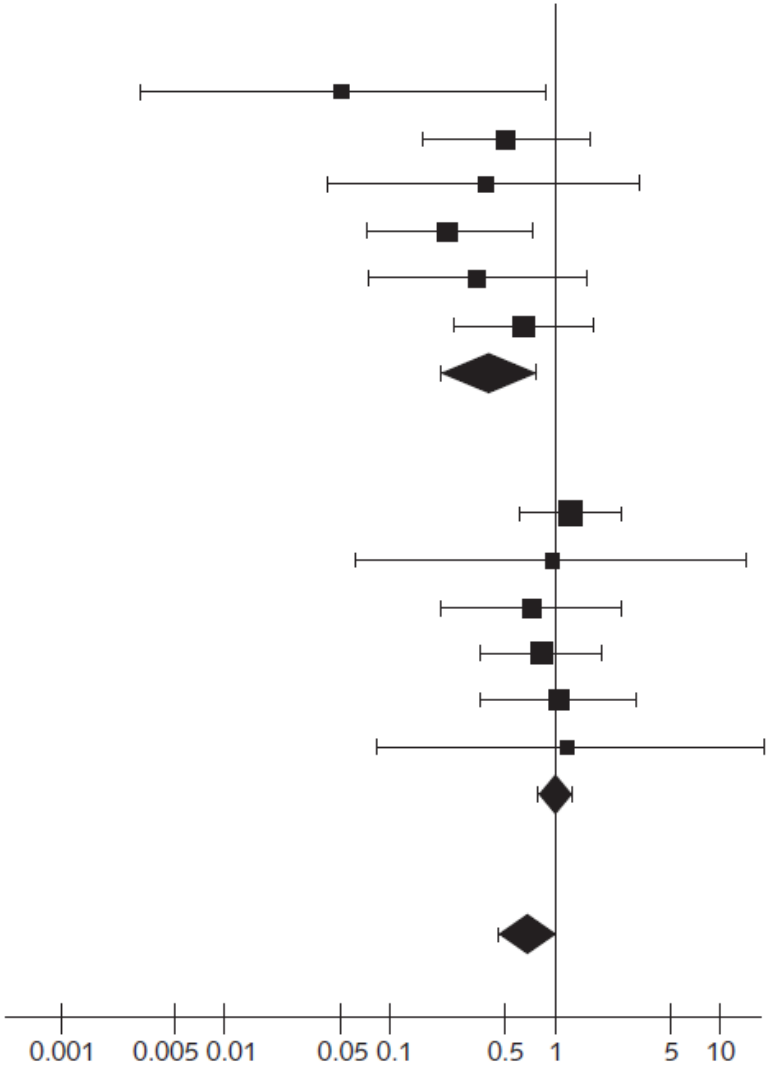
Ann Intern Med. 2015;163:519-528.

Mortalité

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)



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Ann Intern Med. 2015;163:519-528.

Synthèse des effets bénéfiques de la corticothérapie

- **PAC toutes sévérités**
  - Ventilation mécanique ↘
    - 5 essais, n=1060
    - RR 0,45 [0,26;0,79]
  - Délai stabilité clinique ↘
    - 5 essais, n=1180
    - MD -1,22j [-2,08;-0,35]
  - Durée d'hospitalisation ↘
    - 6 essais, n=1499
    - MD -1,0j [-1,79;-0,21]

- Mortalité
  - **PAC toutes sévérités**
    - 12 essais, n=1974
    - RR 0,67 [0,45;1,01]
    - NNT 38
  - **PAC sévères**
    - 6 essais, n=388
    - RR 0,39 [0,20;0,77]
    - NNT 7

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Effets secondaires: STEP trial

	Prednisone (n=392)	Placebo (n=393)	Regression analysis	
			OR (95% CI) or difference (95% CI)	p value
Incidence of adverse events compatible with corticosteroid use until day 30				
Weight change, kg	−1·0 (−3·0 to 1·0)	−1·0 (−3·0 to 0·4)	Difference 0·34 (−0·56 to 1·25),	0·46
Adverse events, any	96 (24%)	61 (16%)	1·77 (1·24 to 2·52)	0·0020
In-hospital hyperglycaemia needing new insulin treatment	76 (19%)	43 (11%)	1·96 (1·31 to 2·93)	0·0010
New insulin dependence at day 30	5 (1%)	1 (<1%)		
New hypertension at day 30	6 (2%)	2 (1%)		
Delirium	5 (1%)	2 (1%)		
Gastrointestinal bleeding	3 (1%)	4 (1%)		
Nosocomial infections	13 (3%)	14 (4%)		

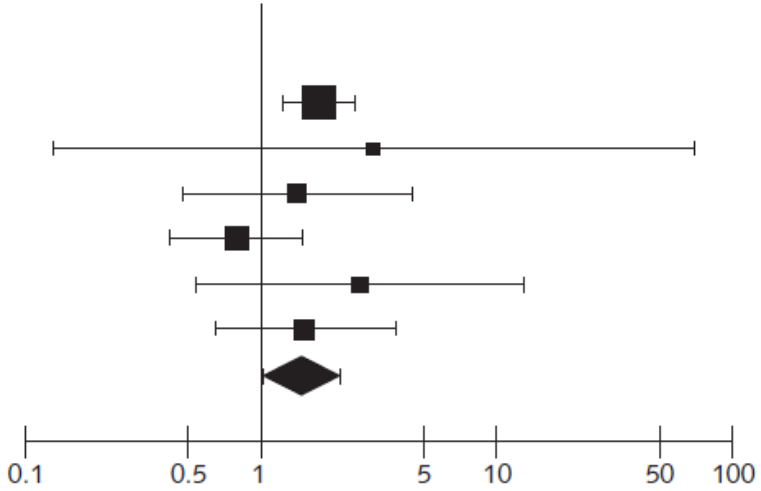
Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial

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*

Lancet 2015; 385: 1511–18

Hyperglycémie

Study, Year (Reference)	Participants, *n/N*		Risk Ratio (95% CI)
	Corticosteroids	Control	
Blum et al, 2015 (16)	76/392	43/393	1.77 (1.25–2.51)
Fernández-Serrano et al, 2011 (46)	1/23	0/23	3.00 (0.13–70.02)
Meijvis et al, 2011 (43)	7/151	5/153	1.42 (0.46–4.37)
Nafae et al, 2013 (41)	19/60	8/20	0.76 (0.41–1.52)
Snijders et al, 2010 (42)	5/97	2/102	2.63 (0.52–13.23)
Torres et al, 2015 (17)	11/61	7/59	1.52 (0.63–3.66)
Random effects: I^2 = 6%			1.49 (1.01–2.19)



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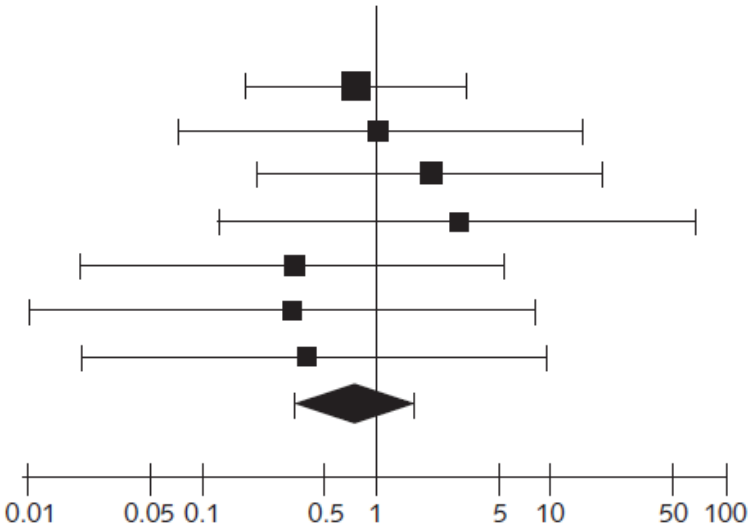
Ann Intern Med. 2015;163:519-528.

Hémorragies digestives

Study, Year (Reference)	Participants, *n/N*		Risk Ratio (95% CI)
	Corticosteroids	Control	
Blum et al, 2015 (16)	3/392	4/393	0.75 (0.17–3.34)
Confalonieri et al, 2005 (24)	1/23	1/23	1.00 (0.07–15.04)
El-Ghamrawy et al, 2006 (40)	1/17	1/17	2.00 (0.20–20.04)
Fernández-Serrano et al, 2011 (46)	1/23	1/22	2.88 (0.12–67.03)
Nafae et al, 2013 (41)	1/60	1/20	0.33 (0.02–5.09)
Torres et al, 2015 (17)	0/61	1/59	0.32 (0.01–7.76)
Wagner et al, 1956 (39)	0/52	1/61	0.39 (0.02–9.37)
Random effects: $I^2 = 0\%$			0.82 (0.33–1.62)



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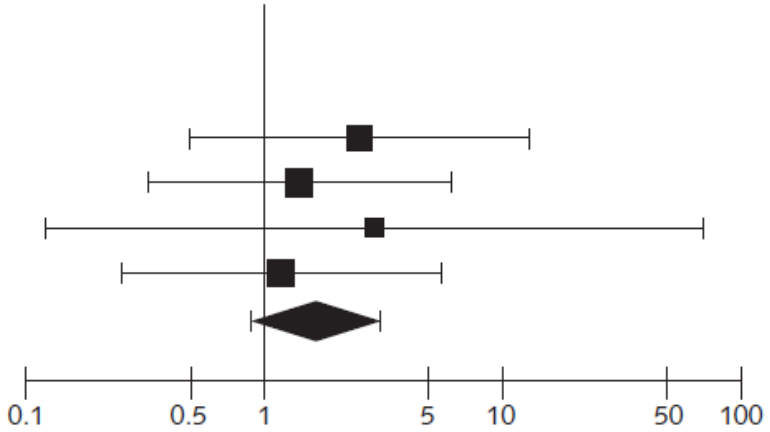
Ann Intern Med. 2015;163:519-528.

Complications neuropsychiatriques

Study, Year (Reference)	Participants, *n/N*		Risk Ratio (95% CI)
	Corticosteroids	Control	
Blum et al, 2015 (16)	5/392	2/393	2.51 (0.49–12.84)
Snijders et al, 2010 (42)	4/97	3/102	1.40 (0.32–6.10)
Torres et al, 2015 (17)	1/61	0/59	2.90 (0.12–69.87)
Wagner et al, 1956 (39)	1/52	3/61	1.17 (0.25–5.57)
Random effects: $I^2 = 0\%$			1.65 (0.88–3.08)



Severe neuropsychiatric complications include but are not limited to mania, psychosis, and delirium.

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Ann Intern Med. 2015;163:519-528.

Risque infectieux ?

Table 4. Adverse Events (Per-Protocol Population).*

Event	Hydrocortisone (N=234)	Placebo (N=232)	Relative Risk (95% CI)
	no. of patients (%)		
Superinfection	78 (33)	61 (26)	1.27 (0.96–1.68)
Catheter-related	3 (1)	3 (1)	0.99 (0.20–4.86)
Lung	34 (15)	30 (13)	1.12 (0.71–1.77)
Gastrointestinal	22 (9)	19 (8)	1.15 (0.64–2.06)
Urinary tract	11 (5)	10 (4)	1.09 (0.47–2.52)
Wound	9 (4)	7 (3)	1.27 (0.48–3.37)
Other	16 (7)	8 (3)	1.98 (0.87–4.54)
New sepsis	6 (3)	2 (1)	2.97 (0.61–14.59)
New septic shock	14 (6)	5 (2)	2.78 (1.02–7.58)

Hydrocortisone Therapy for Patients with Septic Shock

Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rui Moreno, M.D., Ph.D., Mervyn Singer, M.D., F.R.C.P., Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D., Julie Benbenishty, R.N., Armin Kalenka, M.D., Helmuth Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Briegel, M.D., Ph.D., for the CORTICUS Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2008;358:111-24.

October 6, 2015

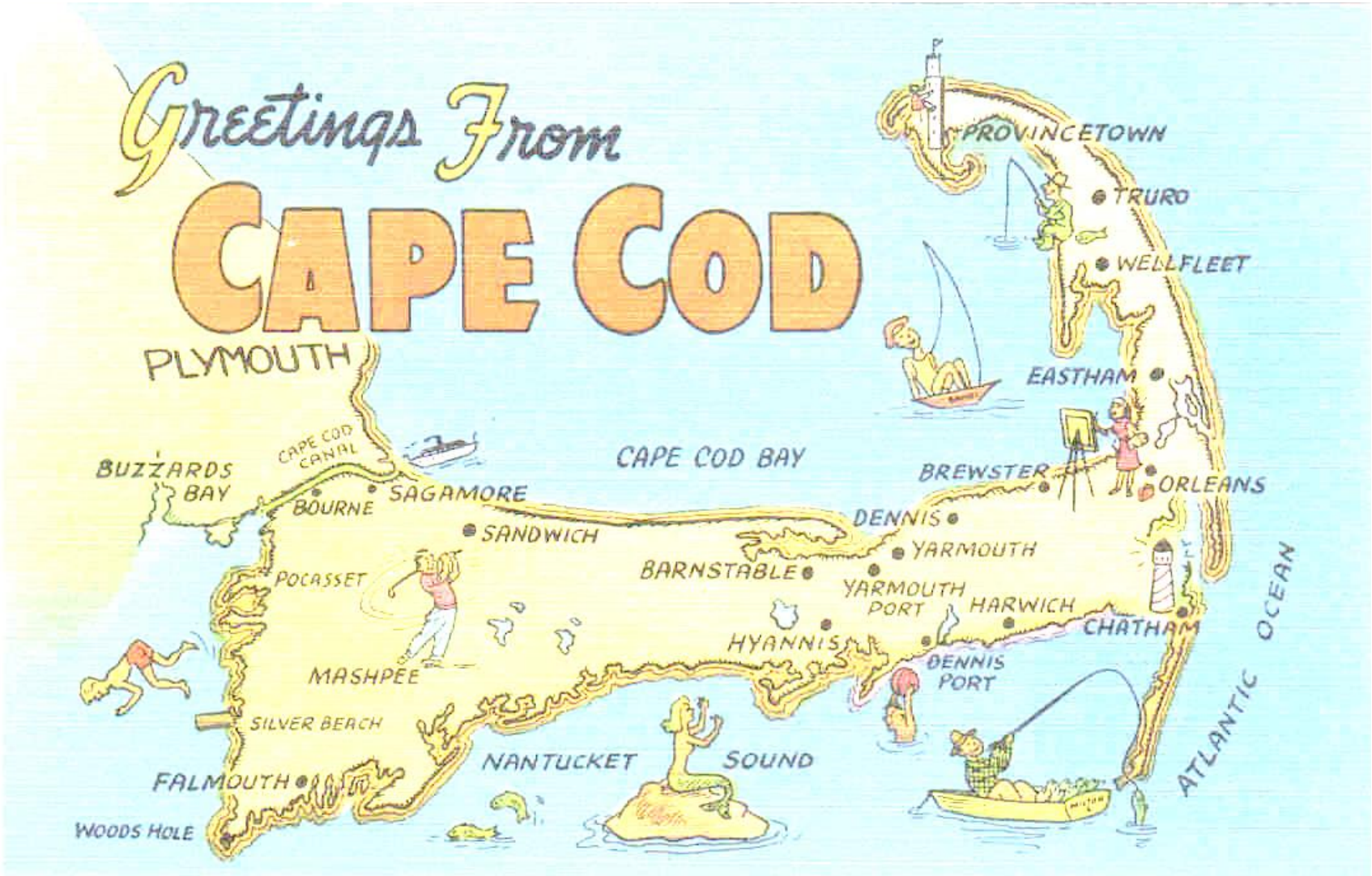
A Feather in the CAP: Steroids for Community-Acquired Pneumonia

Daniel D. Dressler, MD, MSc, SFHM, FACP reviewing *Siemieniuk RAC et al. Ann Intern Med 2015 Oct 6. Restrepo MI et al. Ann Intern Med 2015 Oct 6.*

In a meta-analysis of 13 randomized, placebo-controlled trials (>2000 hospitalized CAP patients), moderate systemic corticosteroids doses (20–60 mg of prednisone or equivalent total daily dose) significantly lowered incidences of in-hospital mortality (5.3% vs. 7.9%; number needed to treat [NNT], 38), acute respiratory distress syndrome (0.4% vs. 3.0%; NNT, 38), and mechanical ventilation (3.1% vs. 5.7%; NNT, 38) and shortened hospital length of stay (by 1.0 days). Mortality benefit seemed to occur only in the subgroup of patients with severe pneumonia (7.4% vs. 22.0%; NNT, 7), whereas steroids improved other outcomes regardless of disease severity. Hyperglycemia that required treatment was more common in the corticosteroid group.

COMMENT

This meta-analysis establishes corticosteroids as a valuable intervention in hospitalized CAP patients, especially those with severe pneumonia. A large randomized trial, scheduled to be completed in 2018, will help clarify dose and duration, but clinicians should consider a brief course (3–7 days) of daily moderate-dose (20–60 mg of prednisone or equivalent) systemic corticosteroids for hospitalized CAP patients.



Community-Acquired Pneumonia: Evaluation of COrticosteroiDs

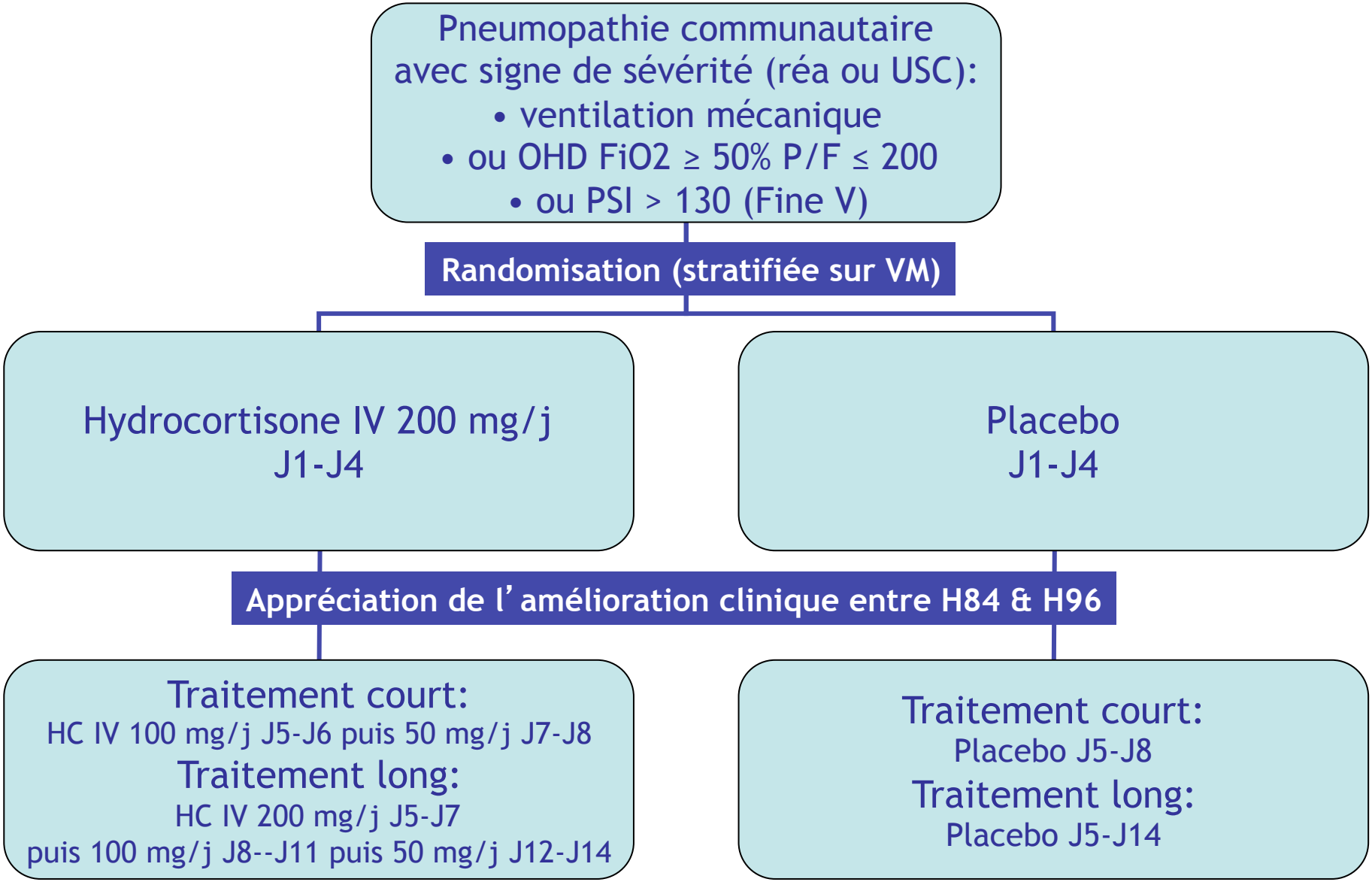
PHRN 2014 - Clinical Trial NCT02517489

CAPE COD: objectifs

- Principal:
  ↘ relative de 24% de la mortalité à J28

- Secondaires:
  - Intubation
  - VM
  - Catécholamines
  - Durée séjour
  - Survie J90
  - Biomarqueurs
  - P/F
  - SOFA
  - SF-36
  - Complications

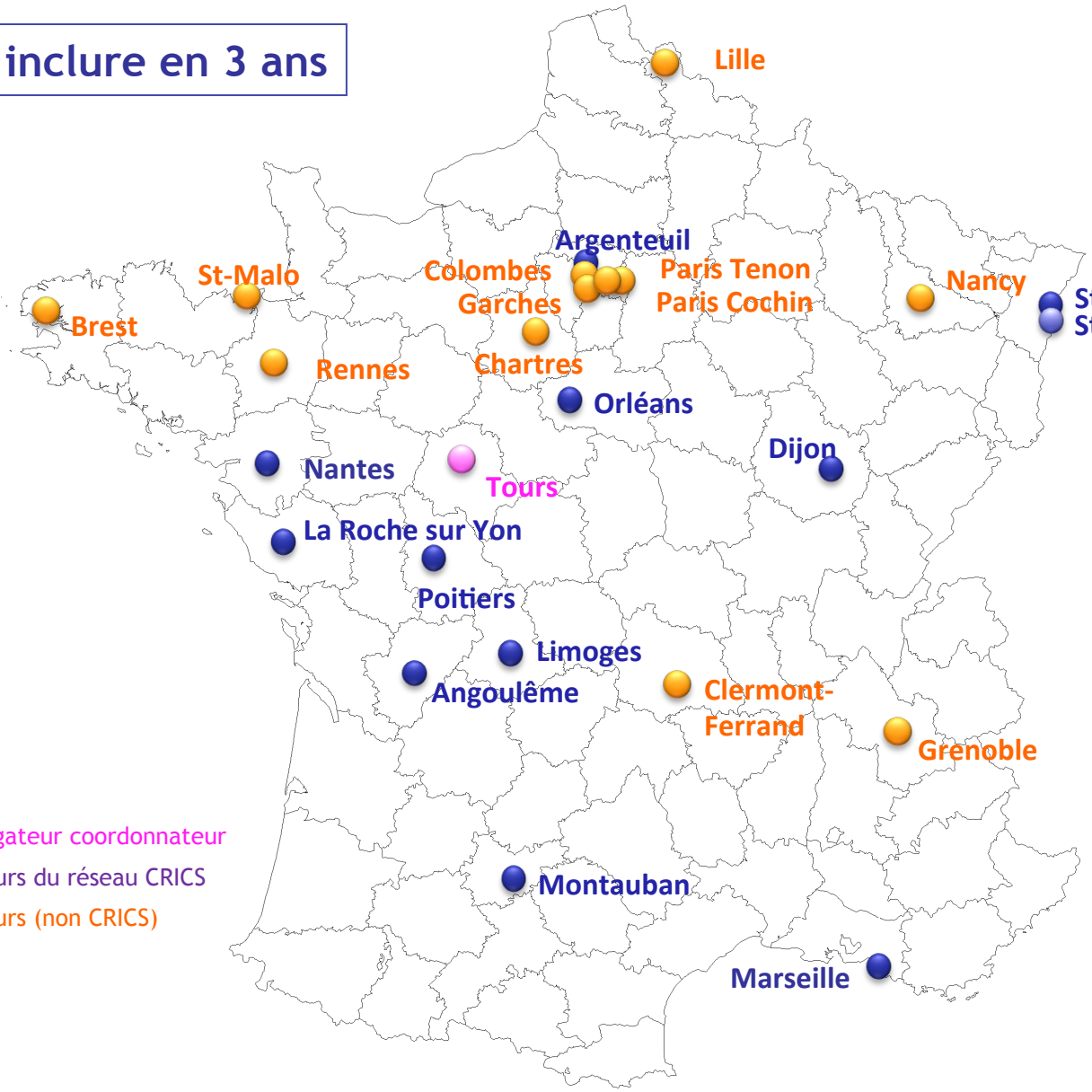
CAPE COD: design



CAPE COD: screening

- Inclusion:
  - Pneumopathie
    - 2 parmi toux, expectoration purulente, douleur thoracique, dyspnée
    - Infiltrat ou condensation
  - Communautaire
    - Dx dans les 48h post-admission
  - Sévère:
    - Ventilation
    - ou OHD FiO2 ≥ 50% P/F ≤ 200
    - ou(et) PIS > 130
  - Traitement débuté dans les 24h post-sévérité
- Non inclusion:
  - Items habituels
  - Inhalation, obstruction bronchique, …
  - Grippe !
  - Choc septique ! (catécholamines acceptées sous condition)
  - Indication à corticothérapie ouverte

1 200 patients à inclure en 3 ans



- Promoteur - Investigateur coordonnateur
- Centres investigateurs du réseau CRICS
- Centres investigateurs (non CRICS)