Pneumonie communautaire hypoxémiante: intérêt de la corticothérapie ?

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

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# Déclaration d'intérêts de 2014 à 2017

- Intérêts financiers: nihil
- Liens durables et permanents: nihil
- Interventions ponctuelles: nihil
- Intérêts indirects: investigateur coordonnateur essai CAPE COD

Bénéficiaire ▲	Type de bénéficiaires ⬍	Entreprise ⬍	Date ⬍	Nature ⬍	Montant ⬍	
DEQUIN PIERRE FRANCOIS	Médecin	SANOFI AVENTIS FRANCE	21/04/2015	Repas	40 €	Détail
Dequin Pierre-François	Médecin	PPD FRANCE SAS	18/12/2014	Platrau repas	28 €	Détail

www.transparence.sante

Mortalité des PAC hospitalisées (J30)

Comorbidity	Total (%)
Malignancy (other than bronchial)	28.2
Lung cancer	25.21
Pulmonary diseases (other than COPD)	24.45
Dementia	22.36
Renal diseases	20.79
CNS disorders	19.41
Cardiac comorbidity	17.35
Diabetes mellitus	13.66
Liver diseases	12.93
COPD	10.12
Total	17.43
No comorbidity	12.95

d'après Ewig et al.
Thorax 2009;64:1062-9.
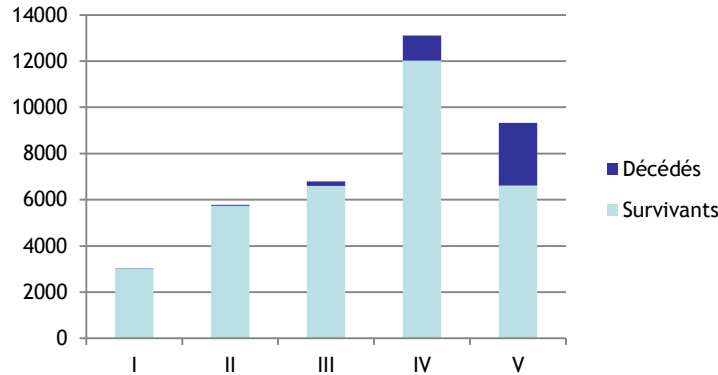
8,0%   15,2%   17,8%   34,3%   24,5%

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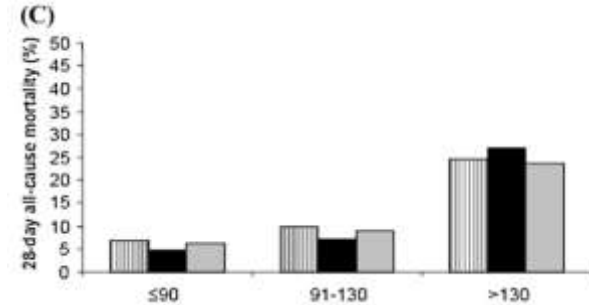
CAPTIVATE, Wunderink et al.
AJRCCM 2011 ;183 :1561-8.

432 PAC ventilées sur une période de 20 ans
Mortalité: 28,5%
Cilloniz et al., Eur Resp J 2018;51 pii:1702215

Comment ↘ la mortalité ?

- Antibiotiques □

- Place des virus ? (et des antiviraux ?)

- Vaccins... □ □

- Parcours de soins □ □

- Comorbidités

- Oxygénothérapie à haut débit □

- Ventilation mécanique 'protectrice' □

- Traitements adjuvants 🎯

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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Torres 2015	DB RCT	SP multi	120	65	Severe	MPD 1 mg/kg/d, 5d

La dolce vita

Hydrocortisone Infusion for Severe Community-acquired Pneumonia
A Preliminary Randomized Study

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
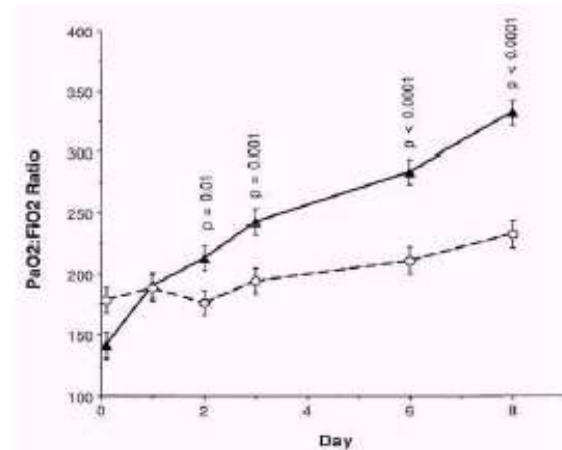- HSHC 200 mg puis 10 mg/h x 7 j vs. PLA

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

- 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 composite: échec thérapeutique
  - **Précoce** (72h) : choc, néo-recours à la VM, décès
  - et(ou) **tardif** (72-120h): progression radiologique, persistance IRA, choc, néo-recours à la VM, décès

Torres et al., JAMA 2015;313:677-86.

Un souffle du sud

Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients With Severe Community-Acquired Pneumonia and High Inflammatory Response
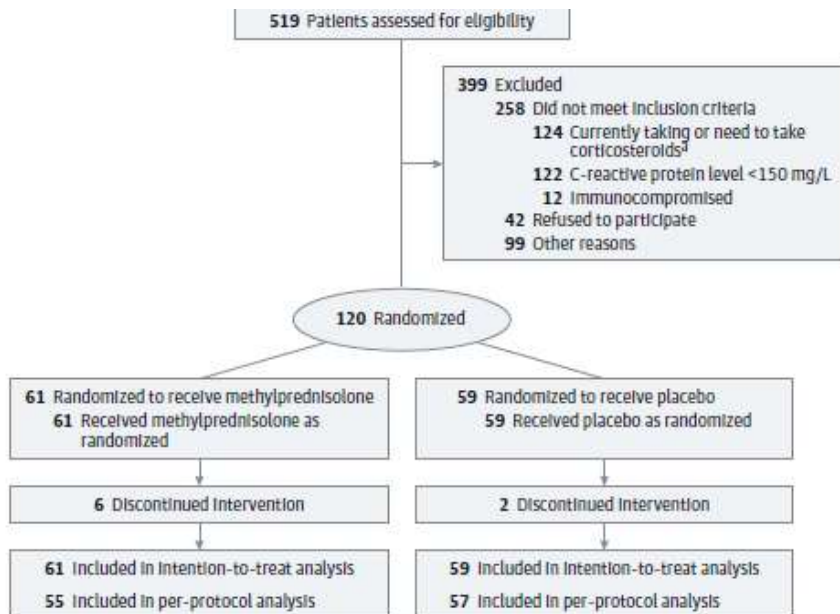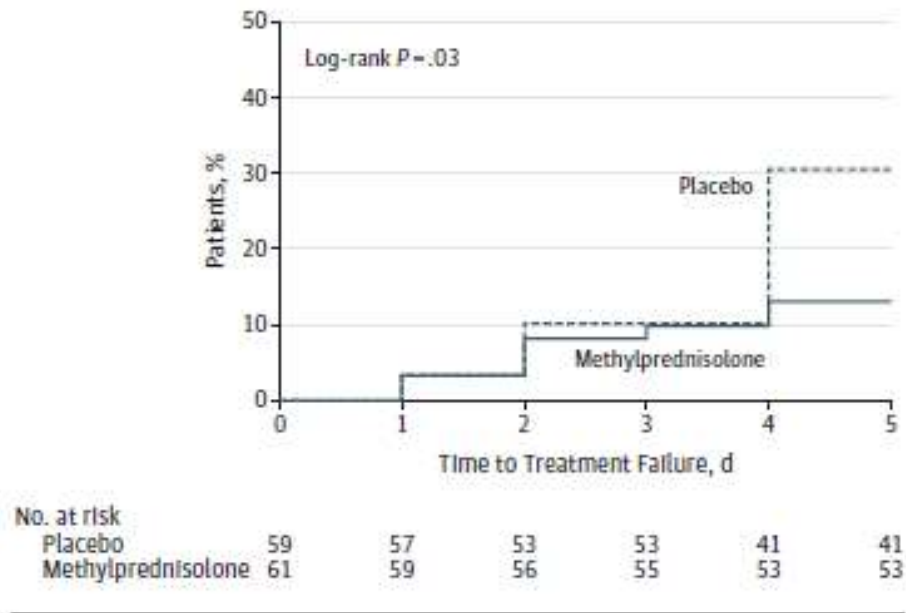### A Randomized Clinical Trial

519 Patients assessed for eligibility

399 Excluded
258 Did not meet inclusion criteria
124 Currently taking or need to take corticosteroids
122 C-reactive protein level <150 mg/L
12 Immunocompromised
42 Refused to participate
99 Other reasons

120 Randomized

61 Randomized to receive methylprednisolone
61 Received methylprednisolone as randomized

59 Randomized to receive placebo
59 Received placebo as randomized

6 Discontinued intervention

2 Discontinued intervention

61 Included in intention-to-treat analysis
55 Included in per-protocol analysis

59 Included in intention-to-treat analysis
57 Included in per-protocol analysis

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

Log-rank P = .03

Patients, %

Placebo

Methylprednisolone

Time to Treatment Failure, d

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

Torres et al., JAMA 2015;313:677-86.

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Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial
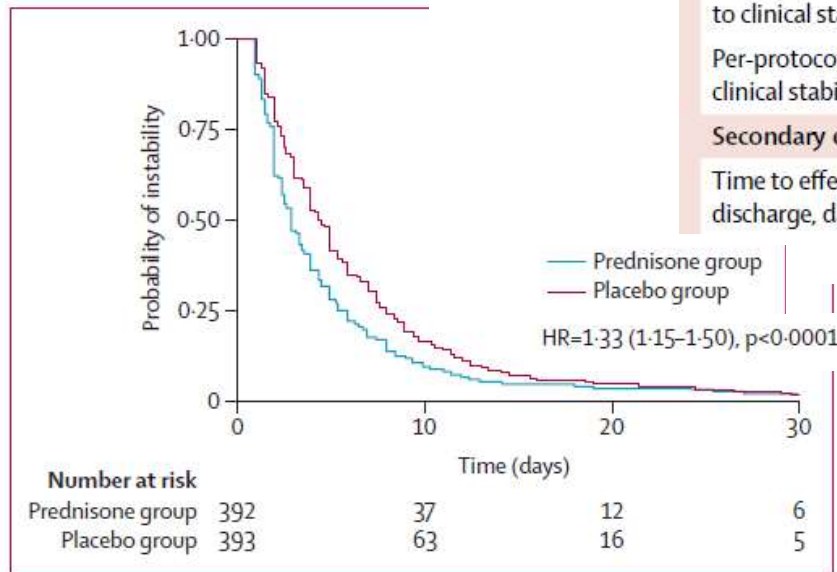
- 6 centres helvétiques, n=785
- CAP non sévères (ICU: 38)
- Prednisone 50 mg x 1/j x 7j vs. PLA
- Début < 24 h post admission
- Critère jugement : délai (j) avant stabilité clinique x 24h
  - T $\leq$ 37,8°C et FC $\leq$ 100/min et FR $\leq$ 24/min et Pas $\geq$ 90 mmHg et retour état mental antérieur et capacité d'ingesta oral et (PaO2 $\geq$ 60 mmHg ou SpO2 $\geq$ 90%)

2911 patients assessed for eligibility

1504 did not meet eligibility criteria
241 informed consent not possible (dementia, disability)
508 with immunosuppression
667 with indication for steroids
88 with gastrointestinal bleeding within the past 3 months

605 eligible, but declined to participate

802 randomised

402 assigned to prednisone

400 assigned to placebo

10 blinded post-randomisation exclusion

7 blinded post-randomisation exclusion

392 included in intention-to-treat analysis

393 included in intention-to-treat analysis

30 protocol violations
18 informed consent withdrawn for study medication
6 application mistakes
6 study medication stopped
1 active glucocorticoid indication
5 potential adverse event

27 protocol violations
12 informed consent withdrawn for study medication
8 application mistakes
7 study medication stopped
4 active glucocorticoid indication
3 potential adverse event

362 treated per protocol

366 treated per protocol

Blum et al., Lancet 2015;385:1511-8.

STEP trial

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

	Prednisone (n=392)	Placebo (n=393)	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

HR=1·33 (1·15–1·50), p<0·0001

Number at risk

Prednisone group	392	37	12	6
Placebo group	393	63	16	5

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

Blum et al., Lancet 2015;385:1511-8.

STEP trial

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

	Prednisone	Placebo
Pathogen identified		
Any community-acquired pneumonia pathogen	108 (29.8)	113 (31.0)
Any bacterial pathogen	78 (21.5)	87 (23.9)
Streptococcus pneumoniae	53 (14.6)	53 (14.6)
Other bacteria	25 (6.9)[#]	34 (9.3)[¶]
Influenza virus	11 (3.0)	13 (3.6)
Other respiratory viruses	29 (8.0)[+]	22 (6.0)[§]

- **Effets retrouvés quel que soit le germe (ou l'absence de germe):**
  – Délai avant stabilité clinique
  – Durée d'hospitalisation
- **Durée ABx IV idem dans les 2 bras pour le s/groupe des pneumocoques**

Wirz et al., ERJ 2016;48:1150-9.

Méta-analyses

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

October 2012 | Volume 7 | Issue 10

PLOS ONE

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

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

RESPIRATORY CARE

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

SCIENTIFIC REPORTS

5:14061 | DOI: 10.1038/srep14061

Nobuyuki Horita, Takuya Otsuka, Shunsuke Haranaga, Ho Namkoong, Makoto Miki,
Naoyuki Miyashita, Futoshi Higa, Hiroshi Takahashi, Masahiro Yoshida, Shigeru Kohno
& Takeshi Kaneko

Adjunctive Corticotherapy for Community Acquired Pneumonia: A Systematic Review and Meta-Analysis

PLOS ONE

Christophe Marti[1]*, Olivier Grosgurin[1], Stephan Harbarth[2], Christophe Combescure[3], Mohamed Abbas[2], Olivier Rutschmann[4], Arnaud Perrier[1], Nicolas Garin[1,5]

Clinical Infectious Diseases

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]

Efficacy and safety of glucocorticoids in the treatment of community-acquired pneumonia: A meta-analysis of randomized controlled trials
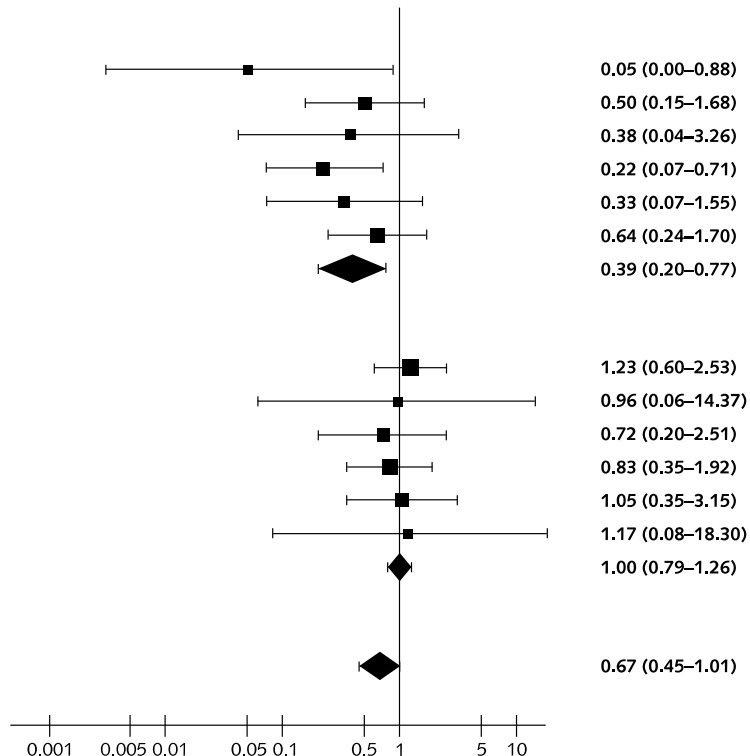
World J Emerg Med, Vol 6, No 3, 2015

Cochrane Library

Mortalité

Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia

A Systematic Review and Meta-analysis
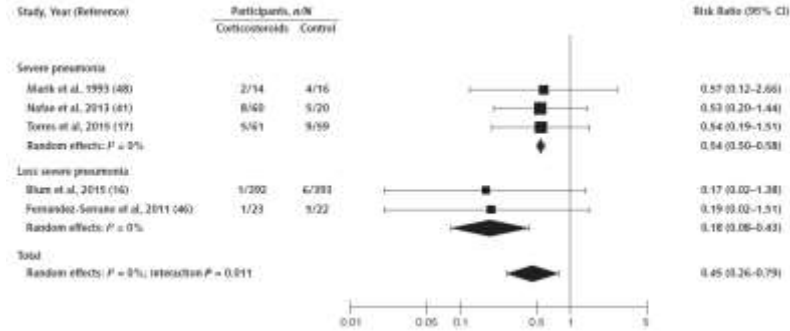
6 essais, n=388
RR 0,39 [0,20-0,77]
NNT = 7

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)

0.001 0.005 0.01 0.05 0.1 0.5 1 5 10

Siemieniuk et al., Ann Intern Med 2015;163:519-28.

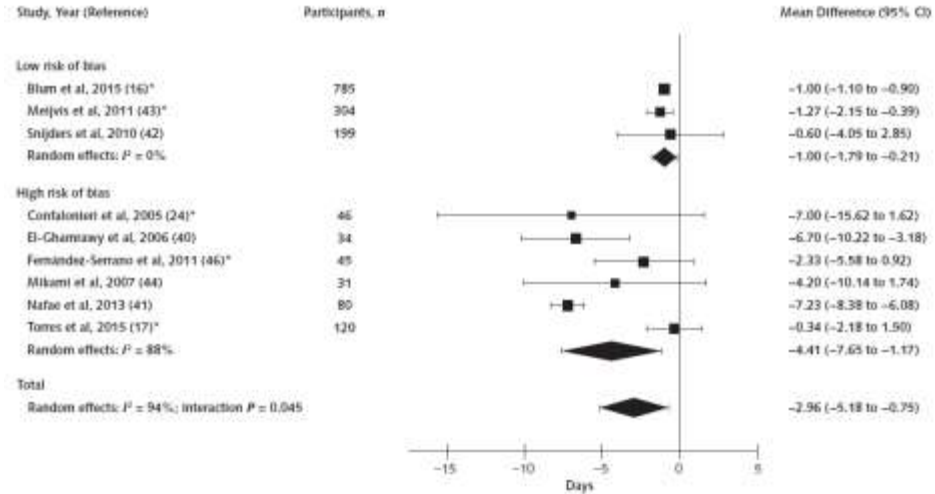# Autres critères

Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia

A Systematic Review and Meta-analysis

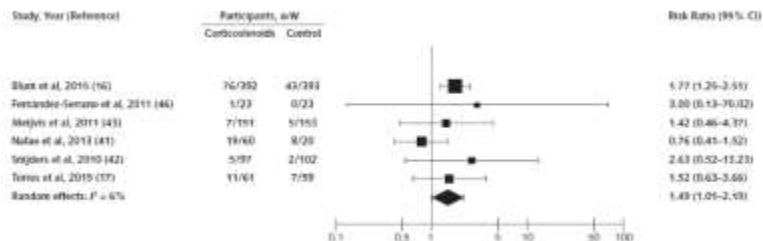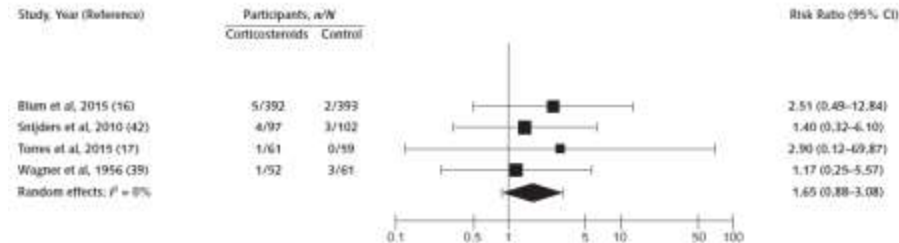**Recours à la VM**
5 essais, n=1060
RR 0,45 [0,26;0,79]

Evolution vers SDRA

Durée d'hospitalisation
6 essais, n=1499
MD -1,0j [-1,79; -0,21]

Siemieniuk et al., Ann Intern Med 2015;163:519-28.
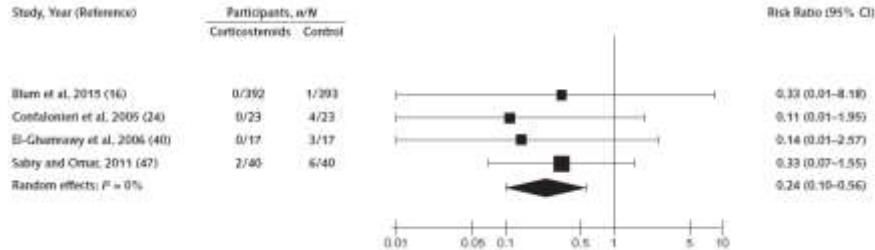
Effets secondaires

Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia

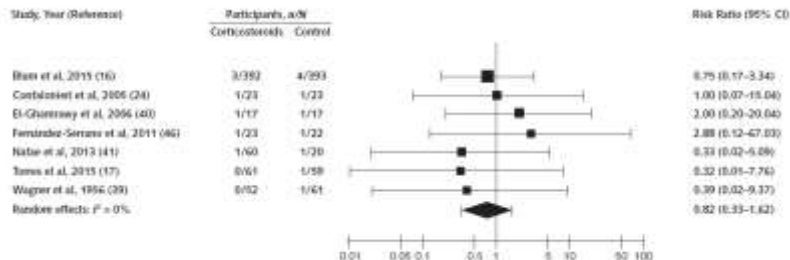**A Systematic Review and Meta-analysis**

Hyperglycémie RR [1,01-2,19]

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

Complications neuropsychiatriques RR [0,88-3,08]

Hémorragie digestive RR [0,33-1,62]

Infections secondaires?

Siemieniuk et al., Ann Intern Med 2015;163:519-28.

A ce jour (juin 2018):

- 'Les cortisoniques' (tous?)
  - Diminuent probablement la durée d'hospitalisation des PAC → essai SANTEON (NL)
  - Evitent sans doute des aggravations (VM, SDRA)
  - Améliorent peut-être la survie des PAC graves → essais ESCAPE (USA) & CAPE-COD (F)
  - Semblent bien tolérés (sauf hyperglycémie)... Infections ?
- Critères de jugement ?
  - Fièvre...
  - Durée d'hospitalisation: médecine vs. USI
  - Mortalité...
- Facteur confondant: choc
- Et la grippe ?
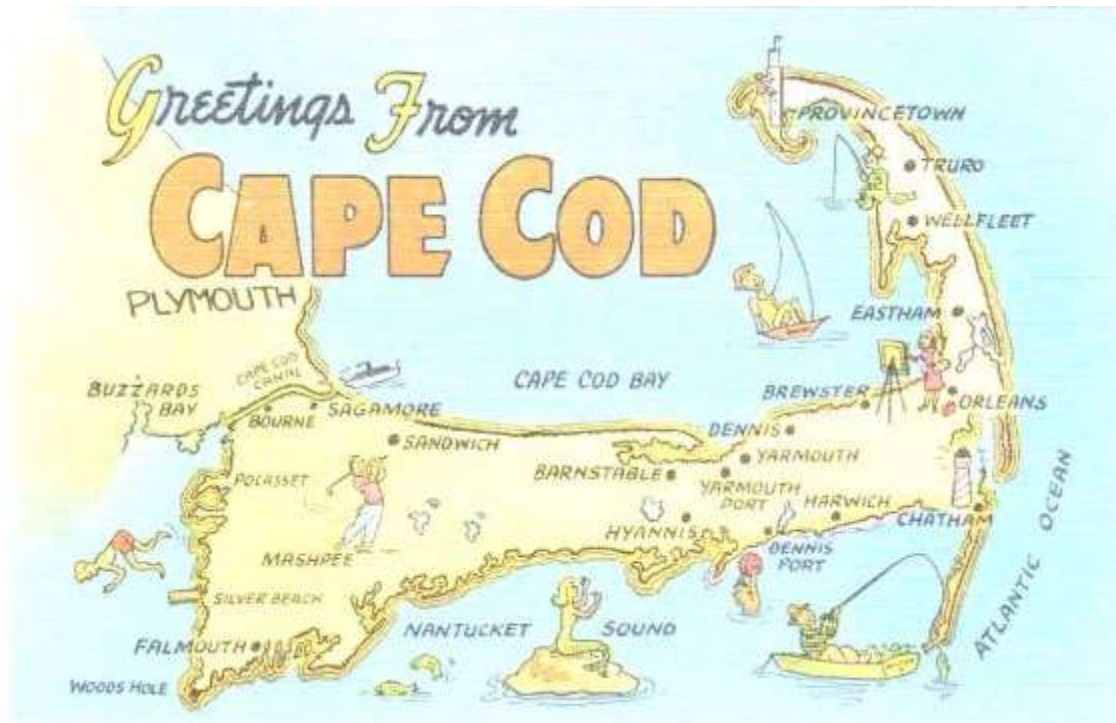
Community-**A**cquired **P**neumonia: **E**valuation of **CO**rticosteroi**D**s
PHRN 2014 - Clinical Trial NCT02517489
Réa, CAP avec critère sévérité < 24 h, HSHC x 8 à 14 j vs. PLA.
Exclusion: choc septique (à l'inclusion) & grippe.
Mortalité J28, n = 1 200.