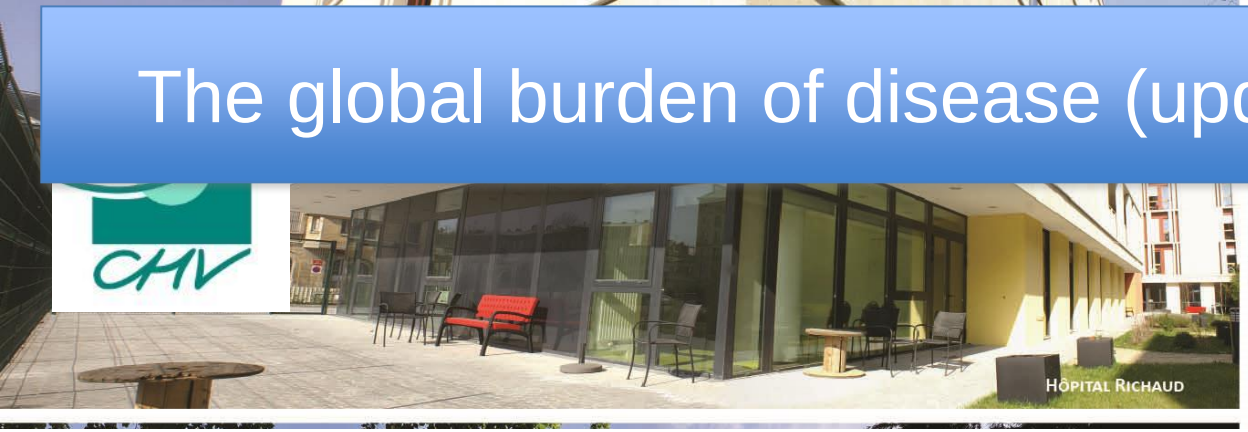
CENTRE HOSPITALIER DE VERSAILLES

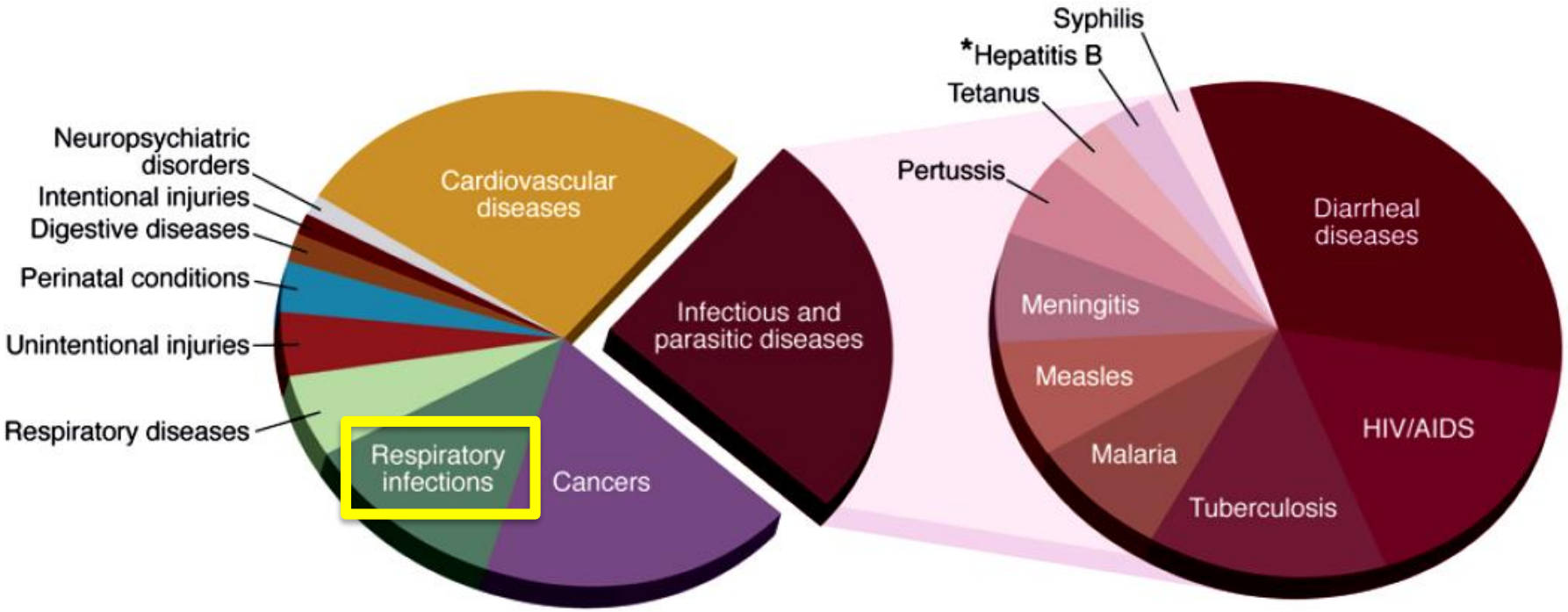
Pneumonies à pneumocoques

JP Bedos, Réanimation, Hôpital Mignot, CH Versailles

Journée de Claude Bernard 2019

The global burden of disease (update 2008 WHO)

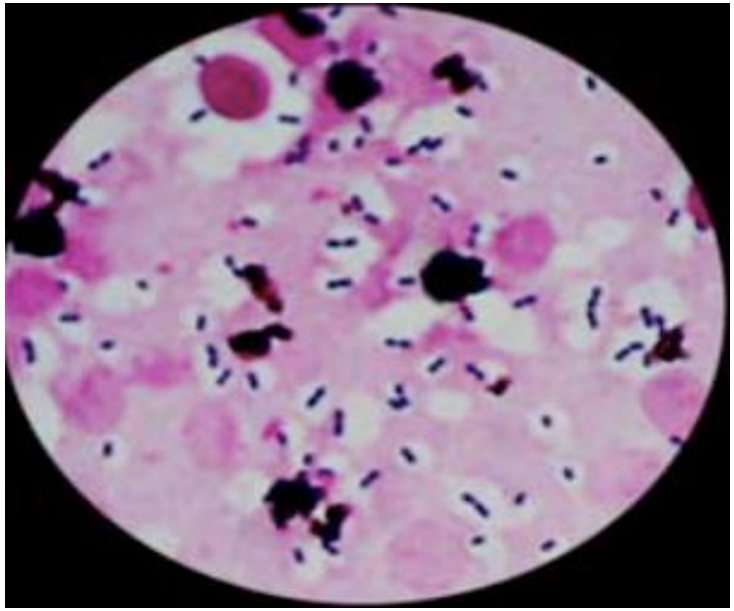


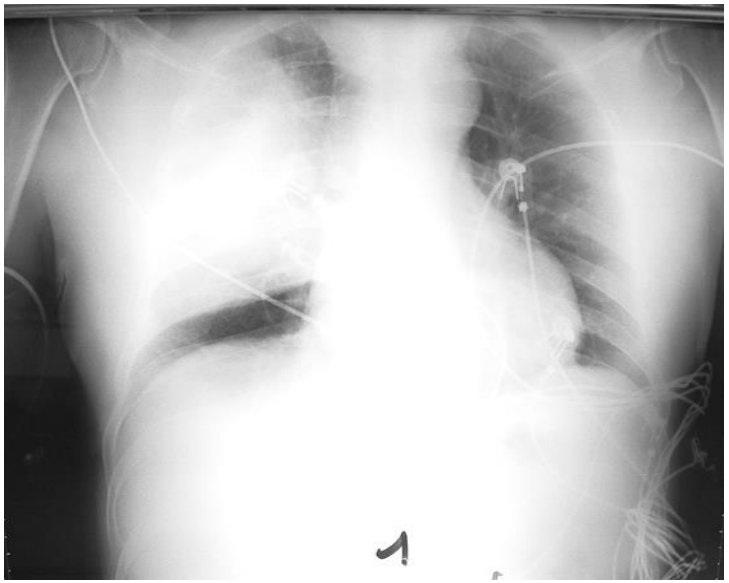


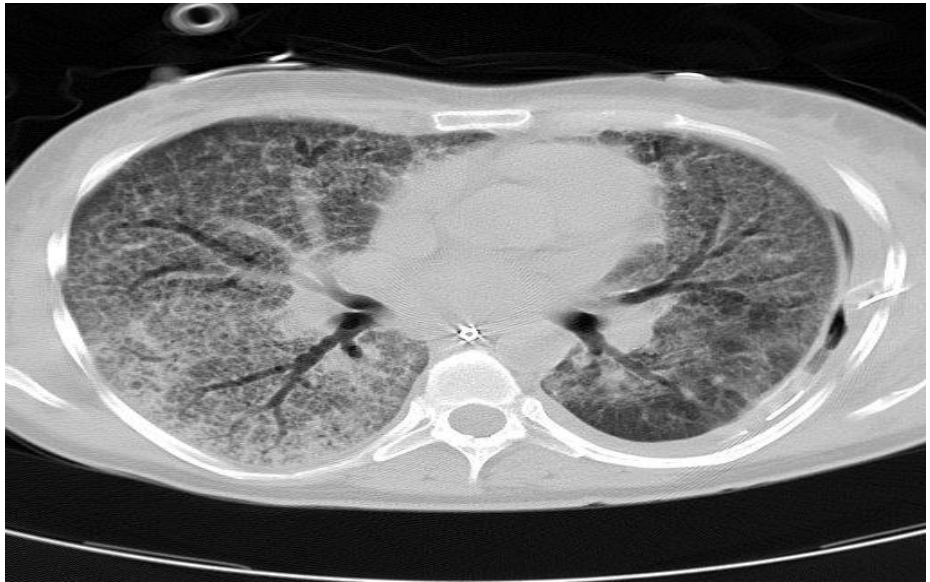
- 4ème position dans le TOP 10 !!!!

Honey K. J Clin Invest 2009; 119: 2452

Pneumocoque = diplocoque gram +





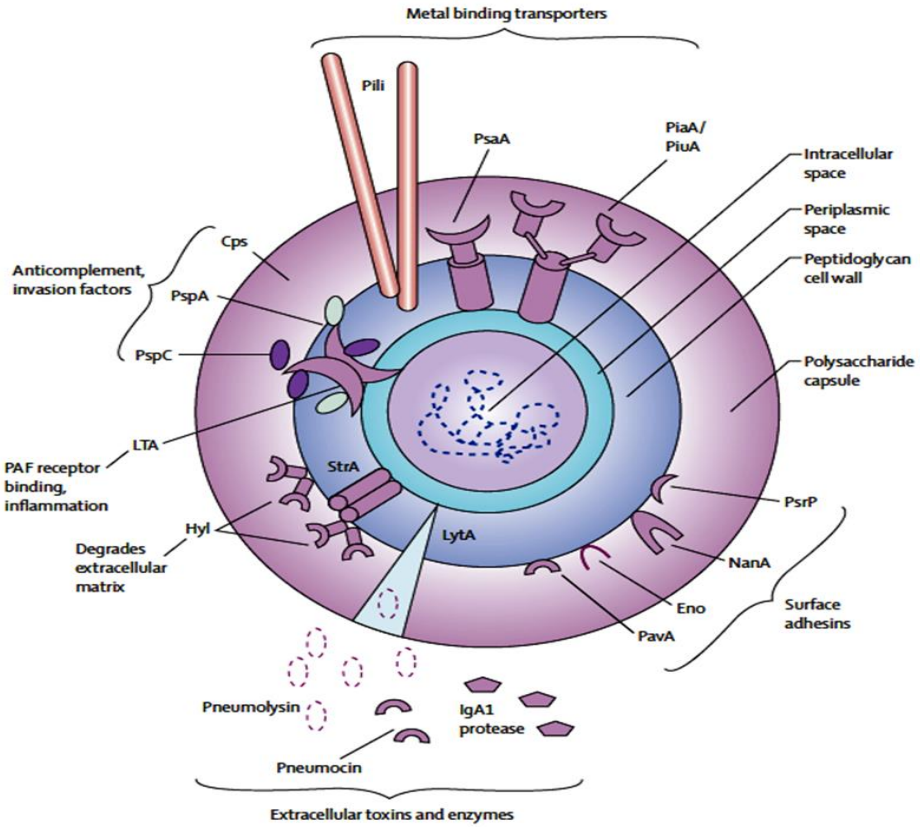


Qu’est ce que le pneumocoque (*Streptococcus pneumoniae*)?

Paradoxe « existentiel »

Commensal rhinoharynx …..et « tueur »

Souche de Sp TIGR 4 (Science 2001) → 2 millions de paires de bases → 2236 gènes



→ 64% rôle biologique

Lancet 2009; 374: 1543-56

- ≈ 300 gènes de virulence : facteurs de virulence « classiques »; des transporteurs, des facteurs de transcription; des voies métaboliques/énergétiques; fonctions inconnues…

- Expression variable de ces gènes de virulence dans le temps, selon l'inoculum et selon l'environnement tissulaire +++ → spécificité de site +++ et pouvoir d'adaptation
→ Plasticité et hétérogénéité génomique

- Polymorphismes de ces gènes de virulence …

→ 91 sérotypes de pneumocoques définis par leurs polyosides capsulaires → Vaccination +++

ICU-PACs : quels pathogènes ?

Outpatient	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* *Haemophilus influenzae* *Chlamydophila pneumoniae* Respiratory viruses[a]
Inpatient (non-ICU)	*S. pneumoniae* *M. pneumoniae* *C. pneumoniae* *H. influenzae* *Legionella* species Aspiration Respiratory viruses[a]
Inpatient (ICU)	*S. pneumoniae* →**25% à 40%** *Staphylococcus aureus* *Legionella* species Gram-negative bacilli *H. influenzae*

Coinfections bact possibles notamment Sp + Hi : PAC sur BPCO…

Bactéries « traditionnelles » et atypiques = rares ++ surtout si PAC grave

Virus isolé possible quand on le cherche (10% à 15%) *[Chest 2008;134:1141]*

Co-infections virus (influenzae et rhinovirus +++) – *S.pneumoniae* +++ *S.aureus* /Hi +

Qui fait une infection à pneumocoque?

Pathogenesis, treatment, and prevention of pneumococcal pneumonia

Tom van der Poll, Steven M Opal

Lancet 2009; 374: 1543–56

Panel: **Risk factors for pneumococcal pneumonia and invasive pneumococcal disease**

Definite risk factors* (high risk)

- Younger than 2 years or older than 65 years
- Asplenia or hyposplenia
- Alcoholism
- Diabetes mellitus
- Antecedent influenza
- Defects in humoral immunity (complement or immunoglobulin)
- HIV infection
- Recent acquisition of a new virulent strain

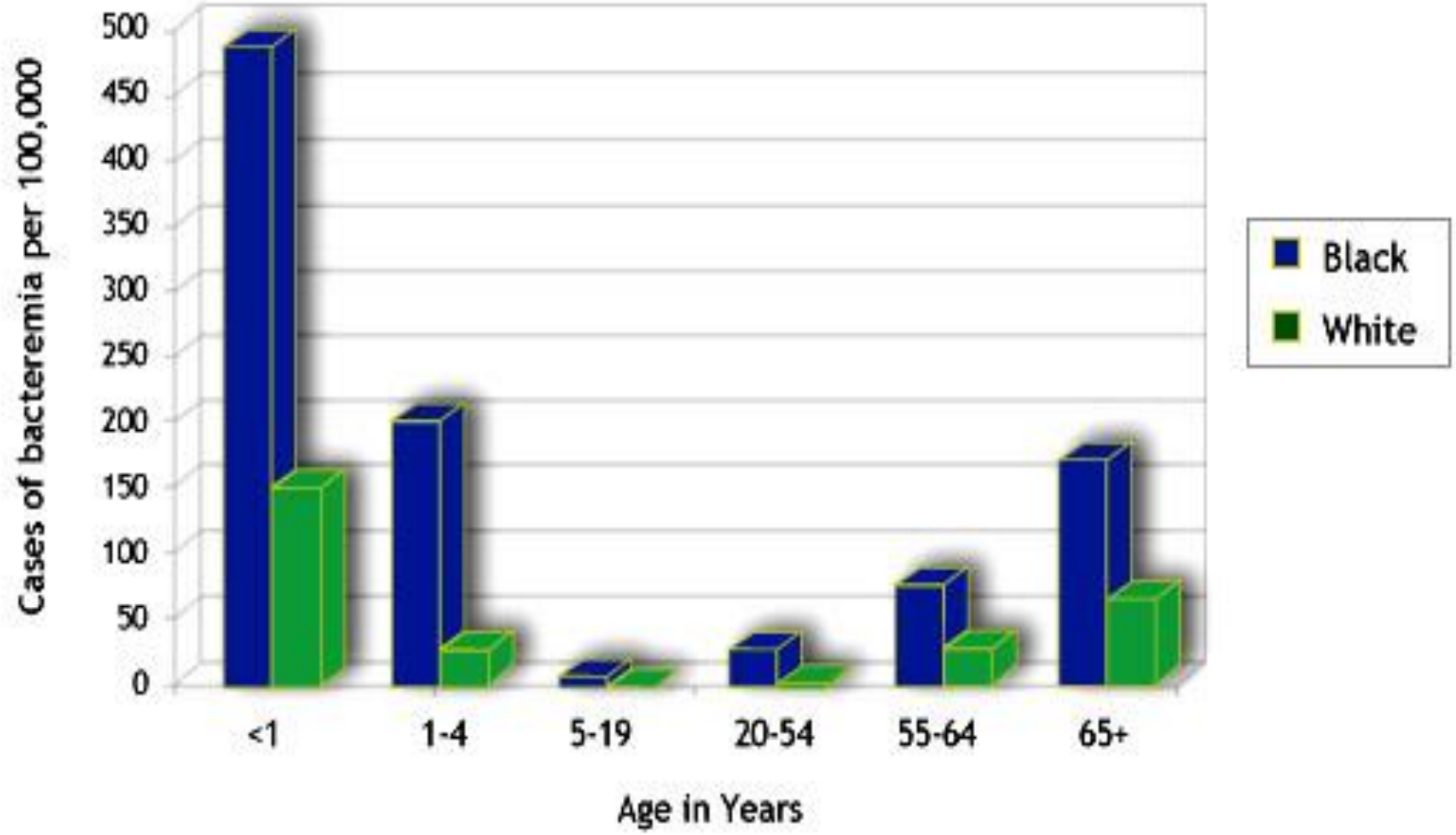
Probable risk factors† (moderate risk)

- Genetic polymorphisms (eg, complement, MBL, IRAK-4, Mal, MyD88)
- Isolated populations
- Poverty, crowding, low pneumococcal vaccine use
- Cigarette smoking
- Chronic lung disease
- Severe liver disease
- Other antecedent viral infections
- Poor mucociliary function

Possible risk factors‡ (low risk)

- Recent exposure to antibiotics
- Defects in cellular immunity and neutrophil defects
- Diminished cough reflex, aspiration pneumonitis
- Proton-pump inhibitors and other gastric-acid inhibitors
- Large organism burden in upper airways
- Childhood day care

Pneumococcal Bacteremia by Ethnie and Age

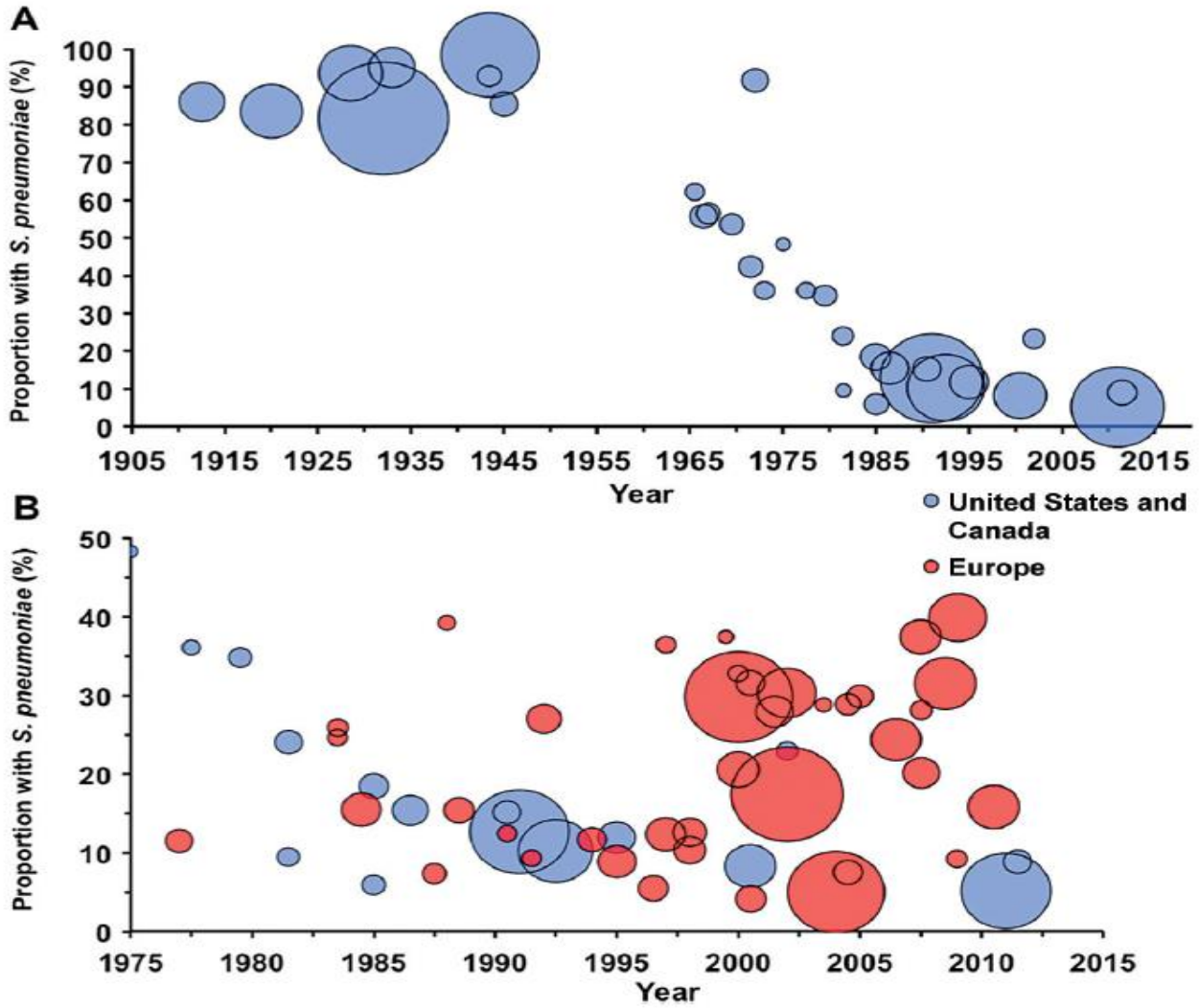


Monroe County, New York, 1985-1989

Bennet NM; Am J Public Health 1992;82:15

Evolving Understanding of the Causes of Pneumonia in Adults, With Special Attention to the Role of Pneumococcus

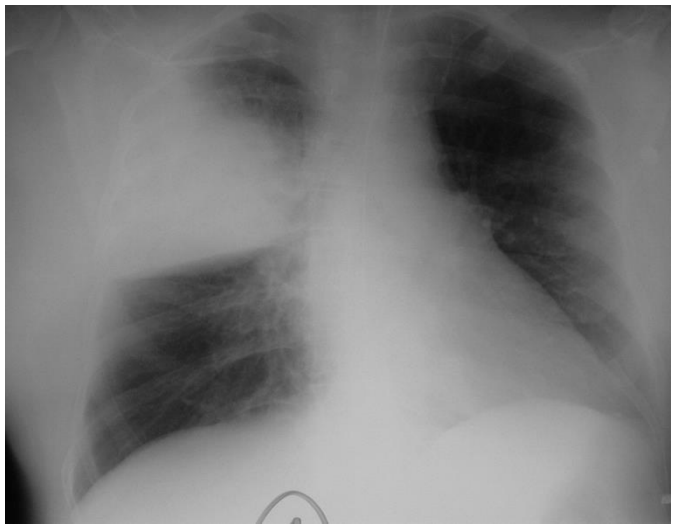
Daniel M. Musher,[1,2] Michael S. Abers,[3,4] and John G. Bartlett[5]

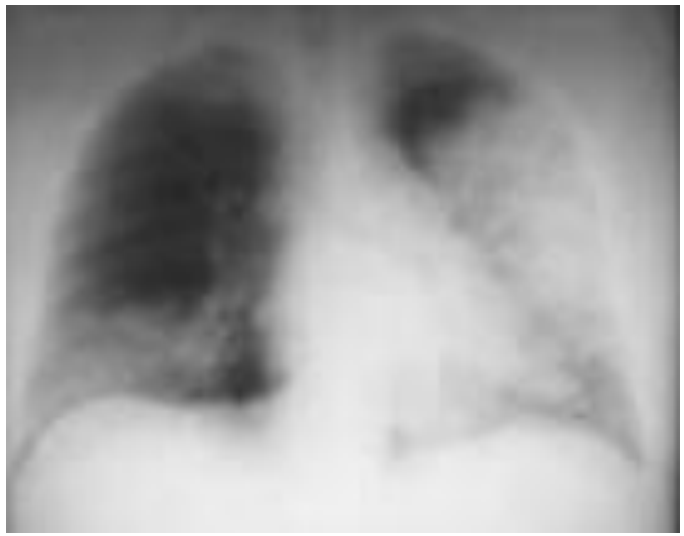


CID 2017

Peut on prédire une PAC a *S.pneumoniae* sur les données (cliniques, biologiques, radiologiques) de routine ?

- Certaines séries disent oui notamment légionnelle *versus* pneumocoque ***[BMC Pulm Med 2009;9:4] …***
- **Les méta-analyses disent NON**
- **Donc le traitement probabiliste DOIT « couvrir » au minimum Sp et Lp en cas de PAC grave**





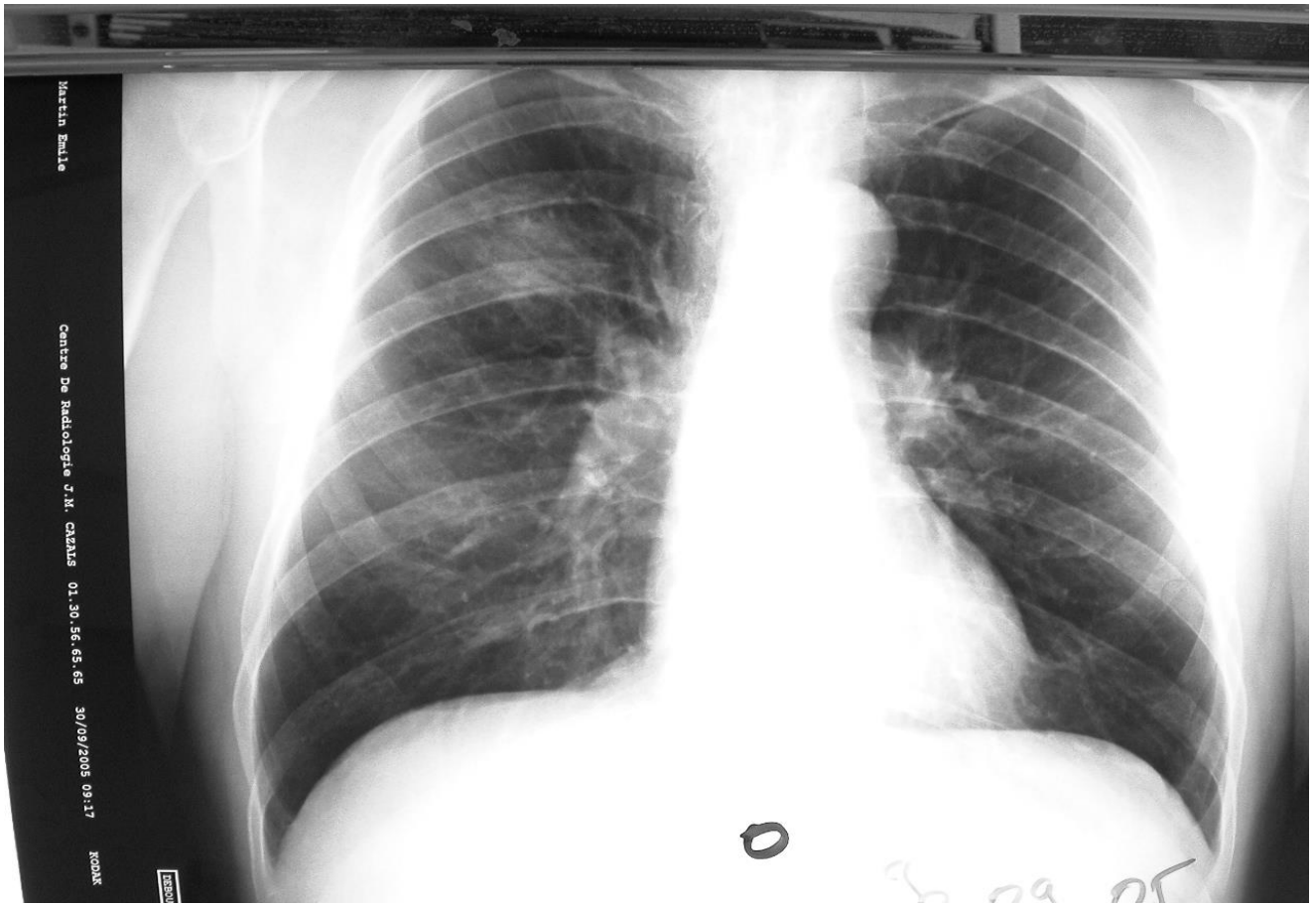
Quels éléments diagnostiques?

- Fièvre/frissons
- Toux sèche > productive
- Polypnée
- Douleur thoracique +++ (réaction pleurale)
- Infiltrats radiologique nouveau
- Personnes agées : apyrexie = 30%
- Obèse, chronic lung disease: peu ou pas d'images radio....
- TDM pulm >> radiologie pulm

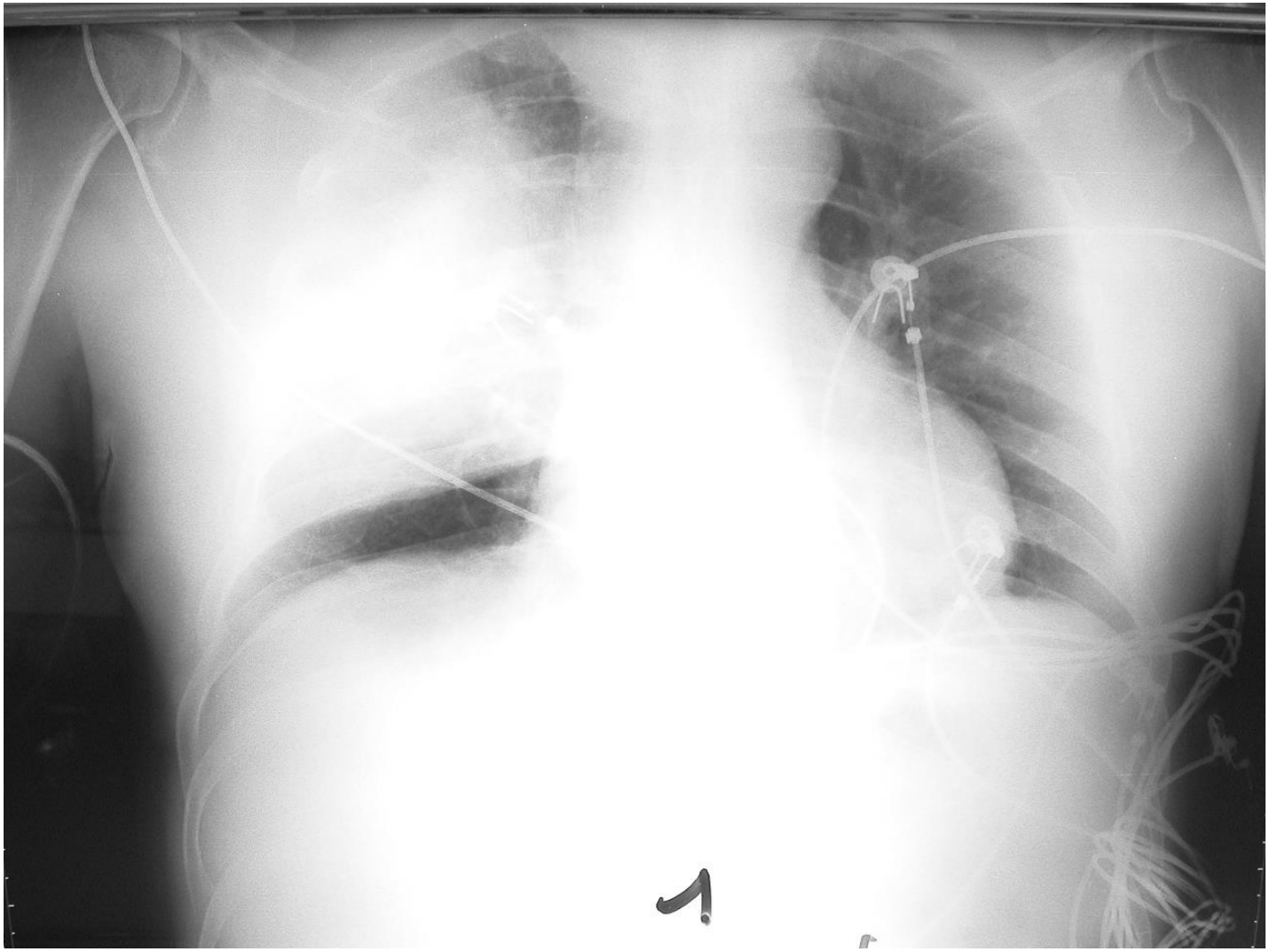
Favoring typical bacterial or legionella pneumonia

- Hyperacute presentation
- Presentation with septic shock
- Absence of upper respiratory symptoms
- Initial upper respiratory illness followed by acute deterioration (suggesting viral infection with bacterial superinfection)
- White-cell count, >15,000 or ≤6000 cells per cubic millimeter with increased band forms
- Dense segmental or lobar consolidation
- Procalcitonin level, ≥0.25 μg per liter

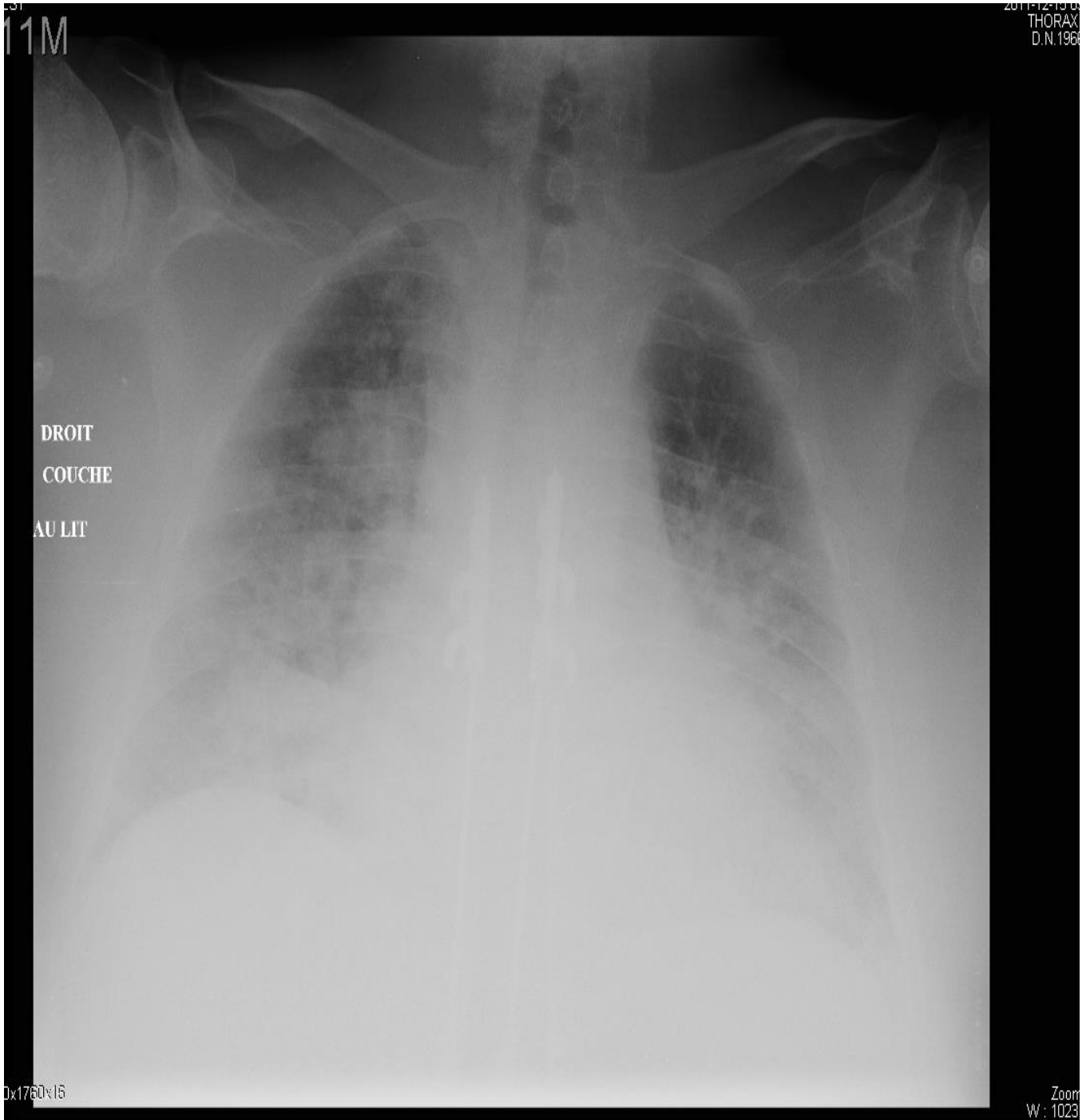
??????????????????.....


Martin Emile
Centre De Radiologie J.M. CAZAIS 01.30.56.65.65 30/09/2005 09:17
KODAK

H + 20h !!!!



→ **Dégradation très rapide possible (surveillance +++)**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THORAX
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COUCHE
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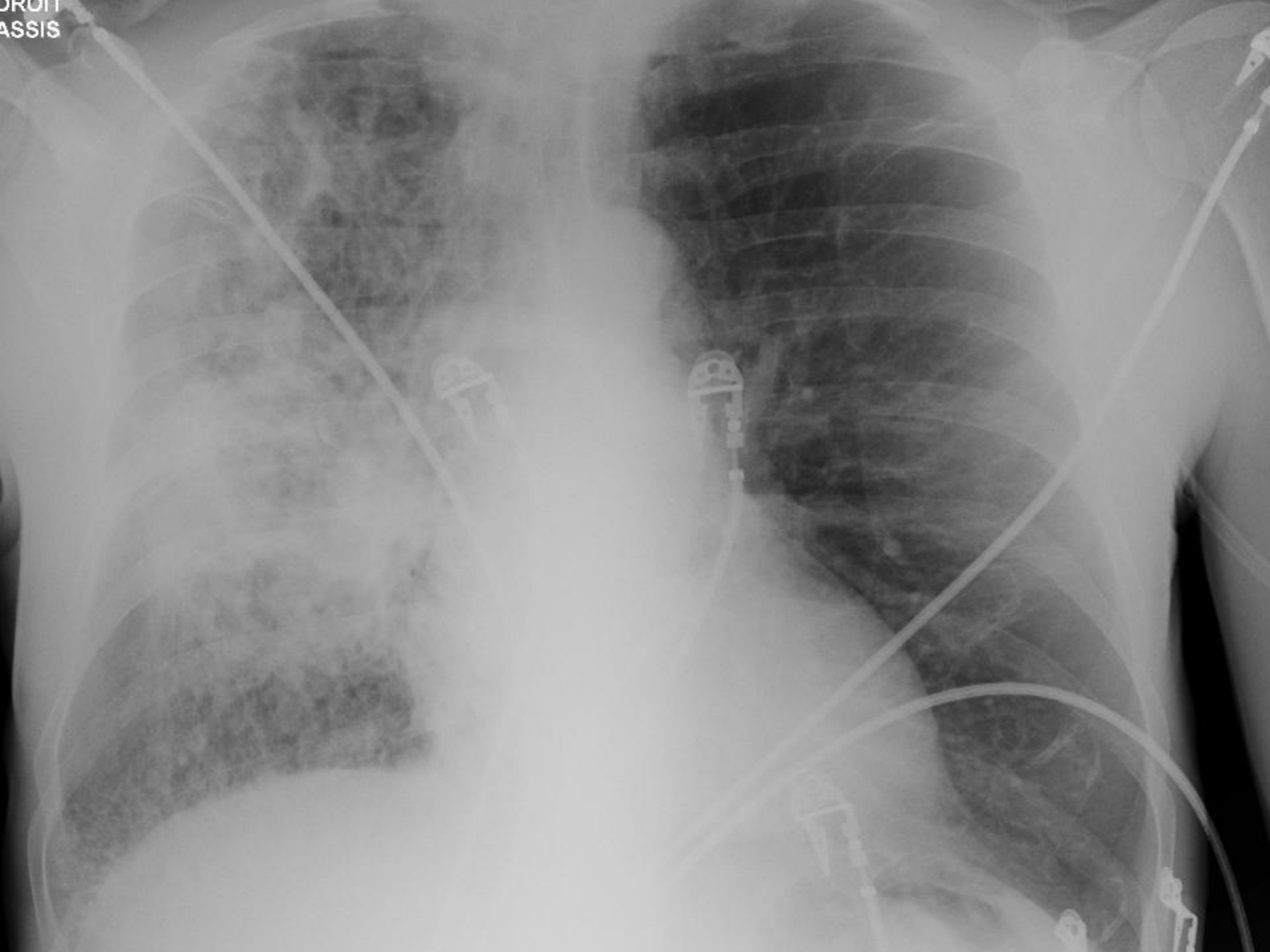
W : 1023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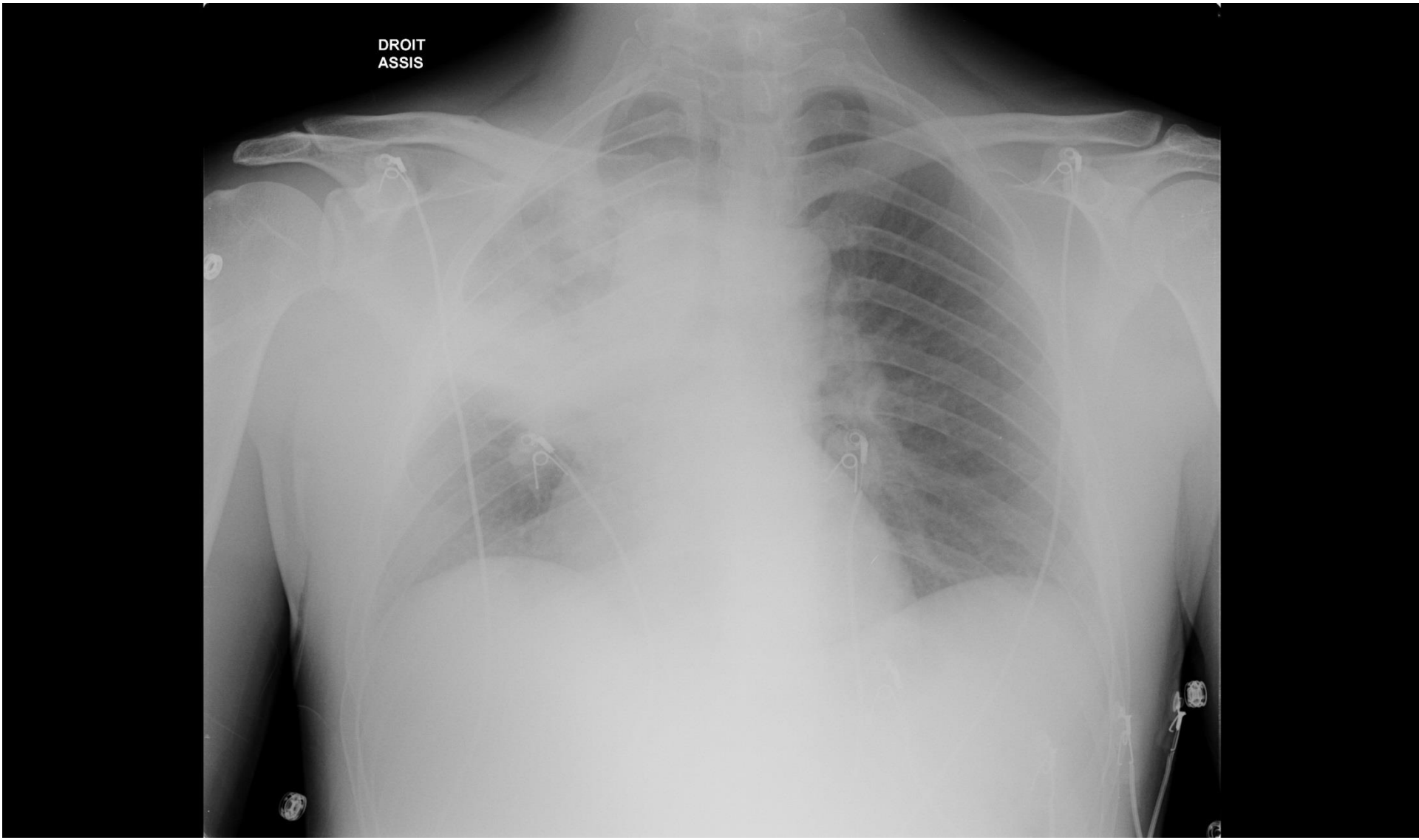

DROIT
ASSIS

PAC grave : diagnostic étiologique

- Hémocultures « **One shot** » : 1 prélèvement de 2 paires d'hémocultures avec 10 ml/flacon si possible avant ATB
  - Si pneumocoque = 30 à 50% de positivité

- **Si non IOT : ECBC**

- **Si IOT : prélèvement protégé: PDP, LBA, Brosse…**
- ***Au moindre signes neurologiques*:** **confusion/Tr de conscience/signes de localisation/convulsions/ TDM cérébral ET PL → Méningite associée ? (< 5%)**

Autres infos

- **Ag urinaire de pneumocoque (longue durée + 50% 6 sem….3mois)**
  - + à 80% si PAC bactériémique
  - + à 50% si PAC non bactériémique

►Quelles performances de l'Ag Ur *Sp* (20€/20 mn) ???

- *Streptogène study*: 26% Ag Ur *Sp* SEUL +
- Se: **85%** (SOFIA ®)
- **Sp: 88% (SOFIA®)**

- **Faux +**: PAC *Sp* récente ..6 mois/Vaccination anti-*Sp* < 15 jours/ Infection à *E.coli, K.pneumoniae, E.cloacae* et n'élimine pas une co-infection *Sp* et H.*influenzae* +++....!!!

Où mettre le patient dans l'hôpital?

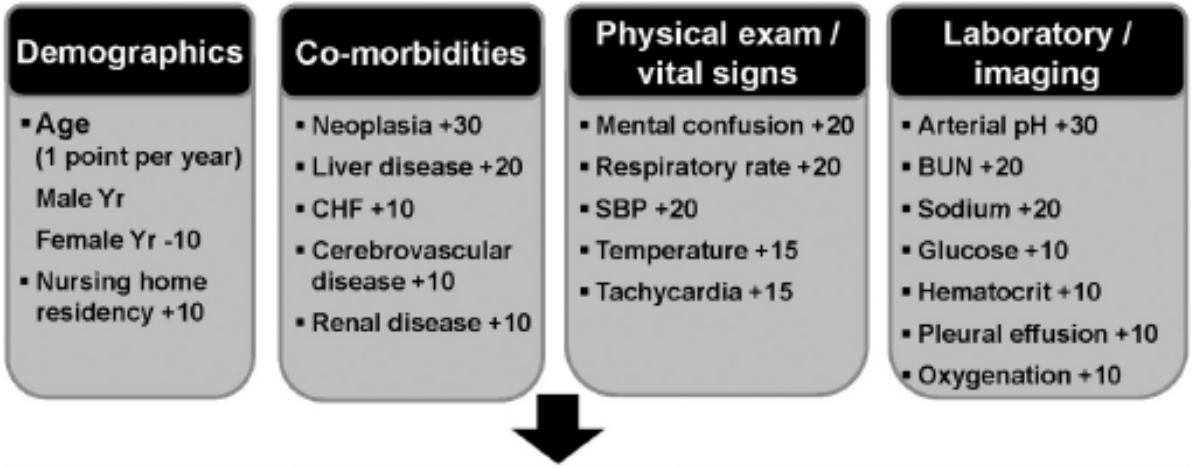
Association between timing of intensive care unit admission and outcomes for emergency department patients with community-acquired pneumonia*

CCM 2009 B Renaud

Late Admission to the ICU in Patients With Community-Acquired Pneumonia Is Associated With Higher Mortality

CHEST 2010 MI Restrepo

PSI : savoir qui traiter en ambulatoire, moins pertinent pour savoir qui hospitaliser en réanimation



Risk class (Points)	Mortality (%)	Recommended site of care
I (<50)	0.1	Outpatient
II (51–70)	0.6	Outpatient
III (71–90)	2.8	Outpatient or brief inpatient
IV (91–130)	8.2	Inpatient
V (>130)	29.2	Inpatient

Pneumonia Severity Index (PSI) as a site-of-care tool. BUN, blood urea nitrogen; CHF, chronic heart failure; SBP, systolic blood pressure.

CURB 65 : plus simple, plus pertinent pour décider d'une hospitalisation en réanimation

1 point given for each of:

- Confusion
- Urea (>7 mmol/L)
- Respiratory rate (≥30/min)
- BP (SBP <90 mmHg or DBP ≤60 mmHg)
- Age (≥65 years)

Risk class	Mortality (%)	Recommended site of care
0	0.7	Outpatient
1	2.1	Outpatient
2	9.2	Short hospital stay / supervised outpatient
3	14.5	Hospital, assess for ICU
4	40	Hospital, assess for ICU
5	57	Hospital, assess for ICU

CURB-65 as a site-of-care tool. CURB-65, Confusion, Urea, Respiratory rate, Blood pressure, age ≥65 years; DBP, diastolic blood pressure; ICU, intensive care unit; SBP, systolic blood pressure.

Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults

LA Mandell, CID 2007

Table 4. Criteria for severe community-acquired pneumonia.

Minor criteria[a]
Respiratory rate[b] ≥30 breaths/min
PaO_2/FiO_2 ratio[b] ≤250
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN level, ≥20 mg/dL)
Leukopenia[c] (WBC count, <4000 cells/mm^3)
Thrombocytopenia (platelet count, <100,000 cells/mm^3)
Hypothermia (core temperature, <36°C)
Hypotension requiring aggressive fluid resuscitation
Major criteria
Invasive mechanical ventilation
Septic shock with the need for vasopressors

Jugement clinique +++

≥ 3 Critères mineurs > PSI et CURB 65 pour prédire l'admission en REA et la mortalité..

Quel traitement ?

→ Les antibiotiques …

La **R** de *S.pneumoniae* à l'amoxicilline/céfotaxime
CMI > 2 mg/L est insignifiante : **< 1%**

→ Autres Ttrs « adjuvants » car mortalité ...

PAC sévère/REA = Bactéries « traditionnelles » (Sp +++) mais aussi «atypiques» (*L.pneumophila*)

➔ Association d'antibiotiques « incontournable » …en probabiliste…

➔ Bêta-lactamine + macrolide ou fluoroquinolone ....

Quelle bêtalactamine en **probabiliste = spectre « large » +++**

- Privilégier les Céphalosporines de 3éme génération à activité anti-pneumococcique: **Céfotaxime** ou **ceftriaxone** : Activité sur pneumocoque, *H. Influenzae*, Entérobactéries, *S. aureus* MS…

- Associé à un **macrolide** (Rovamycine®) ou une fluoroquinolone: levofloxacine (Tavanic)/ofloxacine (Oflocet)

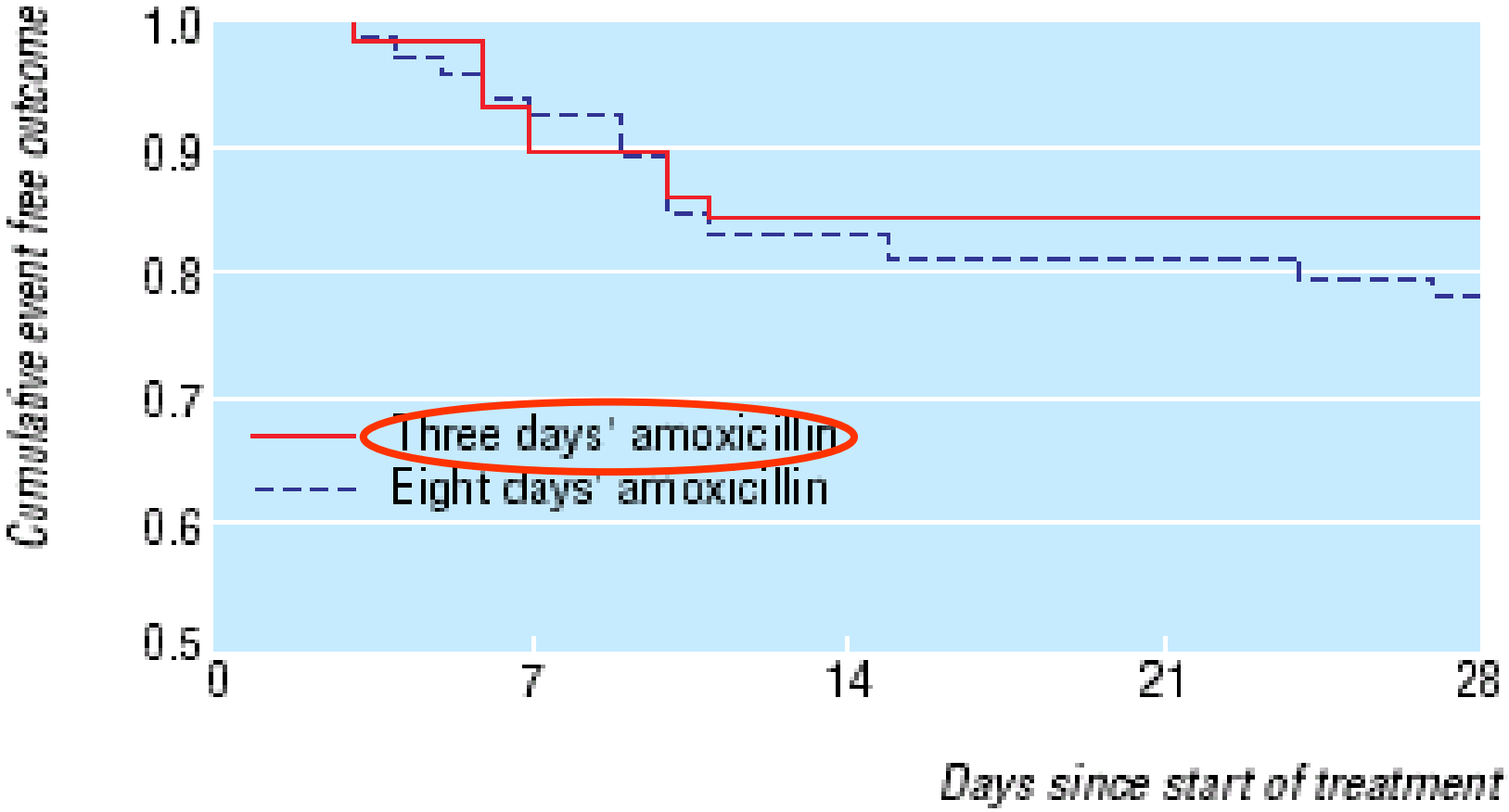
→ **REA Versailles**:

Cefotaxime 2g puis 1g x 6/j + rova 3M x 3 puis 1,5M x 3/j à J2

Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study

BMJ 2006

…**randomisation après amélioration à J3➔ placebo ou amoxicilline 5j de plus**



Effectiveness of three days of beta-lactam antibiotics for hospitalized community-acquired pneumonia: a randomized non-inferiority double-blind trial

A.Dinh[1], J. Ropers[1] B. Davido[1], C. Duran[1], L. Deconinck[1], M. Matt[1], O. Senard[1], A. Lagrange[2], V. De Lastours[3], F. Bouchand[4], V. Delcey[5], D. Benhamou[6], V. Vitrat[7], P. Rouselot, M.-C. Dombret[8], B. Renaud[9], Y.-E. Claessens[10], J. Labarère[11], J.-P. Bedos[12], Ph Aegerter[13], A.-C. Crémieux[14], The PTC Study group

[1]Infectious disease unit, R. Poincaré University Hospital, APHP, UVSQ, Garches, France; [2]Pneumology department, Pontoise Hospital, Pontoise, France; [3]Internal medecine department, Beaujon University Hospital, APHP, Clichy, France; [4]Pharmacy, R. Poincaré University Hospital, APHP, UVSQ, Garches, France; [5]Internal medecine department, Lariboisière hospital, APHP, Paris, France; [6]Pneumology department, Bois-Guillaume University Hospital, Rouen, France; [7]Internal medecine, Annecy Hospital, Annecy, France; [8]Pneumology department, Bichat University Hospital, APHP, Paris, France; [9]Emergency department, Cochin University hospital, APHP, Paris, France; [10]Emergency department, Princesse Grace Hospital, Monaco; [11]Epidemiology unit, Grenoble University Hospital, Grenoble, France; [12]ICU, André Mignot Hospital, Versailles, France; [13]Clinical research unit, A. Paré University Hospital, APHP, UVSQ, B.-Billancourt, France; [14]Infectious disease department, Saint-Louis University Hospital, APHP, Paris, France

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CHV

Outcome at Day 15

	3-day treatment group	8-day treatment group	95% CI
Intention-to-treat analysis, n	156	152	
Cure at Day 15	109 (69.9%)	93 (61.2%)	[-1.09%; 20.55%]
Per-protocol analysis, n	136	131	
Cure at Day 15	103 (75.7%)	90 (68.7%)	[-2.07%; 20.43%]

Non inferiority demonstrated !

3 days is not inferior to 8 days of treatment

Quelques éléments pronostiques….

Host–pathogen interactions and prognosis of critically ill immunocompetent patients with pneumococcal pneumonia: the nationwide prospective observational STREPTOGENE study

- 614 Pts / 51 REA / 45% choc septique / 44% Hc+ / VM 50%
- Diagnostic par Ag Ur Sp SEULE = 26%
- Résistance aux Bêta-lactamines (CMI>2 mg/l) = 0
- 36 sérotypes identifiés dont 7 regroupent 72% des sérotypes: 3, 7F; 19A, 12F, 1, 6C et 11A
- PREVENAR 13 couverture vaccinale: 64%
- Antibiothérapie appropriée = 100% des Pts / dans les 6h = 74% des Pts

Characteristic	All patients	Age category, years			ICU admission criteria[a]			Shock	
		18–50	51–65	> 65	Major	Minor	None	No	Yes
N of patients	614	143	194	277	480	124	10	336	278
Day-5 mortality, *n* (%)	37 (6.0)	6 (4.2)	8 (4.1)	23 (8.3)	37 (7.7)	0 (0)	0 (0)	6 (1.8)	31 (11.2)
Hospital mortality, *n* (%)	116 (18.9)	14 (9.8)	27 (13.9)	75 (27.1)	114 (23.8)	2 (1.6)	0 (0)	29 (8.6)	87 (31.3)

ICM 2018

Facteurs prédictifs de mortalité hospitalière

Variable	Pooled over imputed datasets	
	Crude OR (95% CI)	Adjusted OR (95% CI)
Age 51–65 vs. 18–50 ys	1.49 (0.75 to 2.96)	1.15 (0.57 to 2.32)
Age >65 vs. 18–50 ys	3.42 (1.86 to 6.31)	2.92 (1.49 to 5.74)
Male gender	1.84 (1.18 to 2.86)	2.23 (1.30 to 3.81)
BMI 25–30 vs <25	1.02 (0.62 to 1.69)	—
BMI >30 vs <25	0.94 (0.53 to 1.67)	—
HC vs. PS	1.04 (0.66 to 1.65)	—
UAg only vs. PS	0.54 (0.30 to 0.98)	—
McCabe > 2	2.27 (1.22 to 4.22)	4.63 (1.64 to 13.1)
SOFA (per unit)	1.29 (1.22 to 1.37)	—
SAPS II (per unit)	1.06 (1.05 to 1.08)	1.03 (1.02 to 1.05)
Charlson index 2 vs. ≤1	0.73 (0.27 to 2.01)	—
Charlson index 3 vs. ≤1	1.62 (0.70 to 3.76)	—
Charlson index ≥4 vs. ≤1	3.28 (1.63 to 6.61)	—
WBC <4 $\times 10^9$/L	1.77 (1.10 to 2.85)	—
Platelets ≤100 $\times 10^9$/L	2.66 (1.62 to 4.36)	7.69 (2.80 to 21.1)
Lactates 2–4 vs. <2 mmol/L	2.19 (1.17 to 4.11)	1.24 (0.67 to 2.27)
Lactates >4 vs. <2 mmol/L	6.10 (3.27 to 11.4)	2.39 (1.26 to 4.52)
Bilateral pulmonary infection	1.72 (1.15 to 2.59)	1.59 (1.02 to 2.47)
Time to antibiotics >6 h	1.60 (1.01 to 2.54)	—
Shock	4.82 (3.05 to 7.62)	2.23 (1.27 to 3.91)
Need for EER	5.63 (2.37 to 13.4)	—
Mechanical ventilation	5.05 (3.11 to 8.18)	1.78 (1.00 to 3.18)
Non-invasive ventilation	1.27 (0.82 to 1.97)	—

Host–pathogen interactions and prognosis of critically ill immunocompetent patients with pneumococcal pneumonia: the nationwide prospective observational STREPTOGENE study

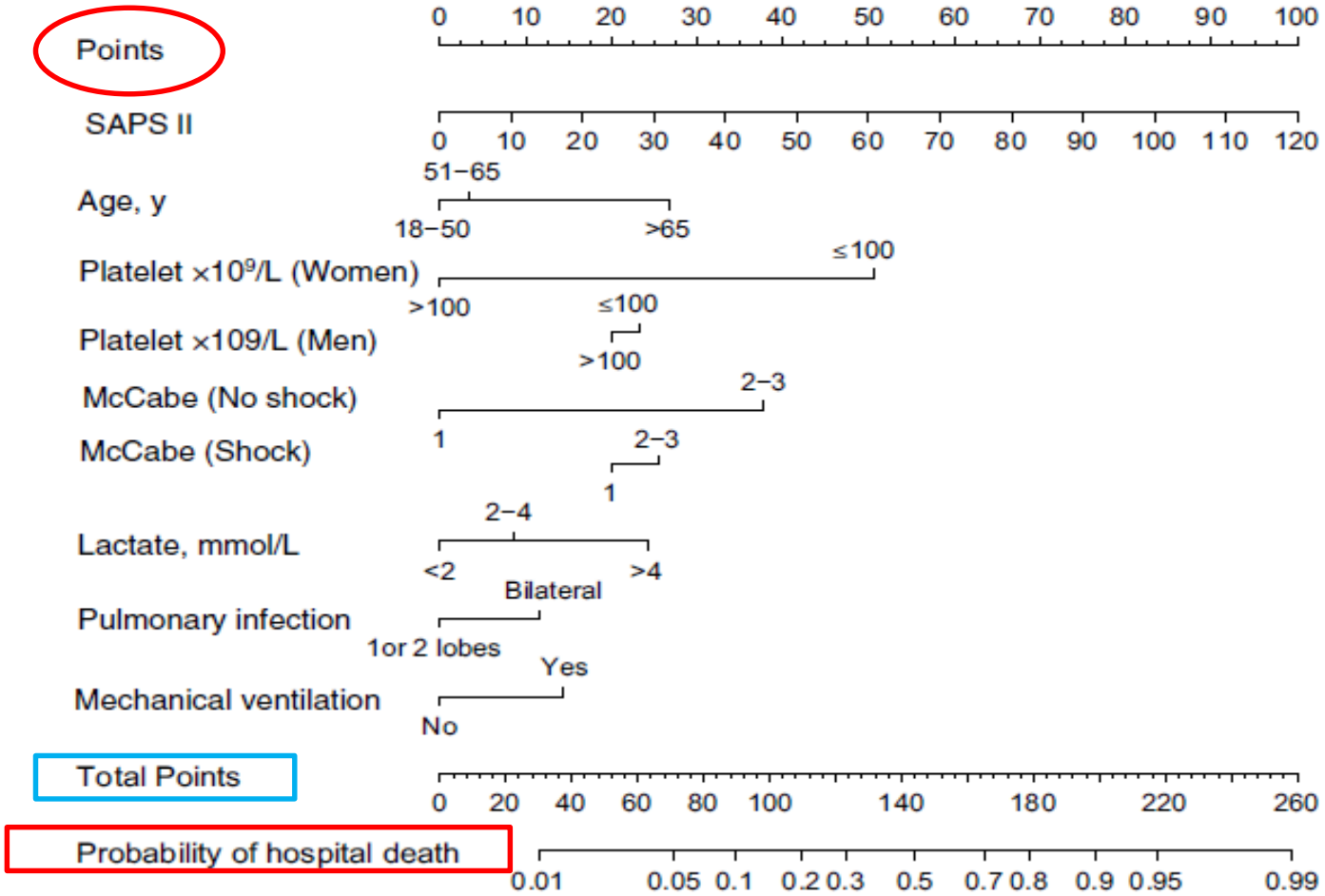


Fig. 2 Nomogram for predicting hospital death. The nomogram provides an estimate of the probability of death according to patient characteristics. For each characteristic listed, locate the relevant value on the horizontal line, and draw the vertical line from that value to the points line at the top of the figure. Sum the points for each characteristic and locate this number on the total points line at the bottom of the figure. Draw a straight line down from the number on the total points line to the probability of hospital death line just below it

Polymorphismes génétiques de l'hôte

Variable	N	N hospital deaths (%)	Unadjusted OR (95%CI)	*P*
TNF-308				
GG	426	73 (17)	1	
AA+GA	159	38 (24)	1.52 (0.98 to 2.37)	0.065
PAI-1				
4G/4G	159	40 (25)	1	
4G/5G+5G/5G	426	71 (17)	0.59 (0.38 to 0.92)	0.021

TNF2 associé à

- la mortalité des patients en choc septique (p = 0.03)

- la mortalité des patients bactériémiques (p= 0.025)

PAI-1 4G/4G associé

- la mortalité des patients en choc septique (p=0.042)

The Presence of Pneumococcal Bacteremia Does Not Influence Clinical Outcomes in Patients With Community-Acquired Pneumonia*

Results From the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study

Conclusions: Pneumococcal bacteremia does not increase the risk of poor outcomes in patients with CAP. Factors related to severity of disease are confounders of the association between pneumococcal bacteremia and poor outcomes. This study indicates that the presence of pneumococcal bacteremia by itself should not be a contraindication for deescalation of therapy in clinically stable hospitalized patients with CAP.

(CHEST 2008; 133:618–624)

PAC: Pronostic à long terme

- Long-term morbidity and mortality after hospitalization with CAP: a population-based study. *Medicine 2008; 87: 329-34*
- Long-term survival after hospitalization for CAP and helthcare associated pneumonia. *Respiration 2010; 79: 128-36.*
- Pneumonia: still the old man's friend? *Arch Intern Med 2003; 163: 317-23.*
- Prognosis after CAP in the elderly: a population-based 12 year follow-up study.: 39% vs 61% *Am J Med 199; 159:1550-55.*

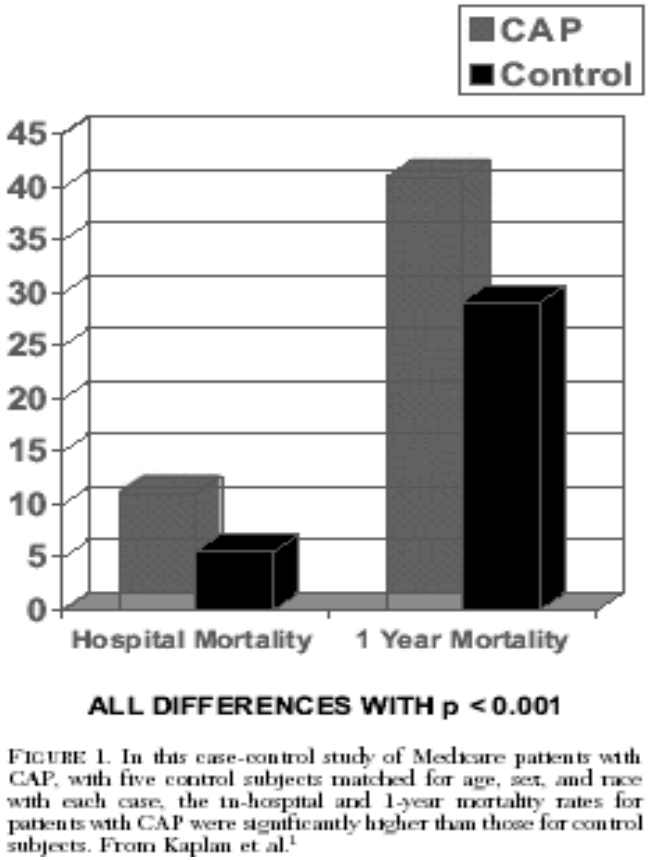
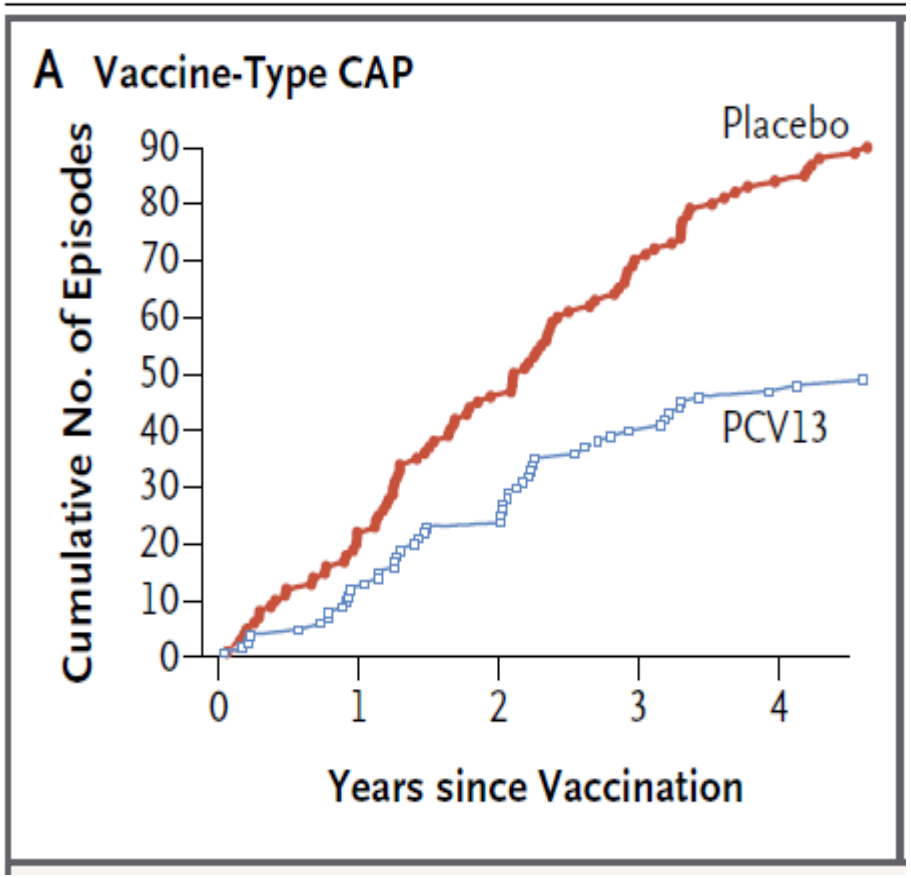


FIGURE 1. In this case-control study of Medicare patients with CAP, with five control subjects matched for age, sex, and race with each case, the in-hospital and 1-year mortality rates for patients with CAP were significantly higher than those for control subjects. From Kaplan et al.[1]

→Prévenir les PAC = vaccins Prevenar 13 puis S+8 Pneumo 23

Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults

In a randomized, double-blind, placebo-controlled trial involving 84,496 adults 65 years of age or older, we evaluated the efficacy of 13-valent polysaccharide conjugate



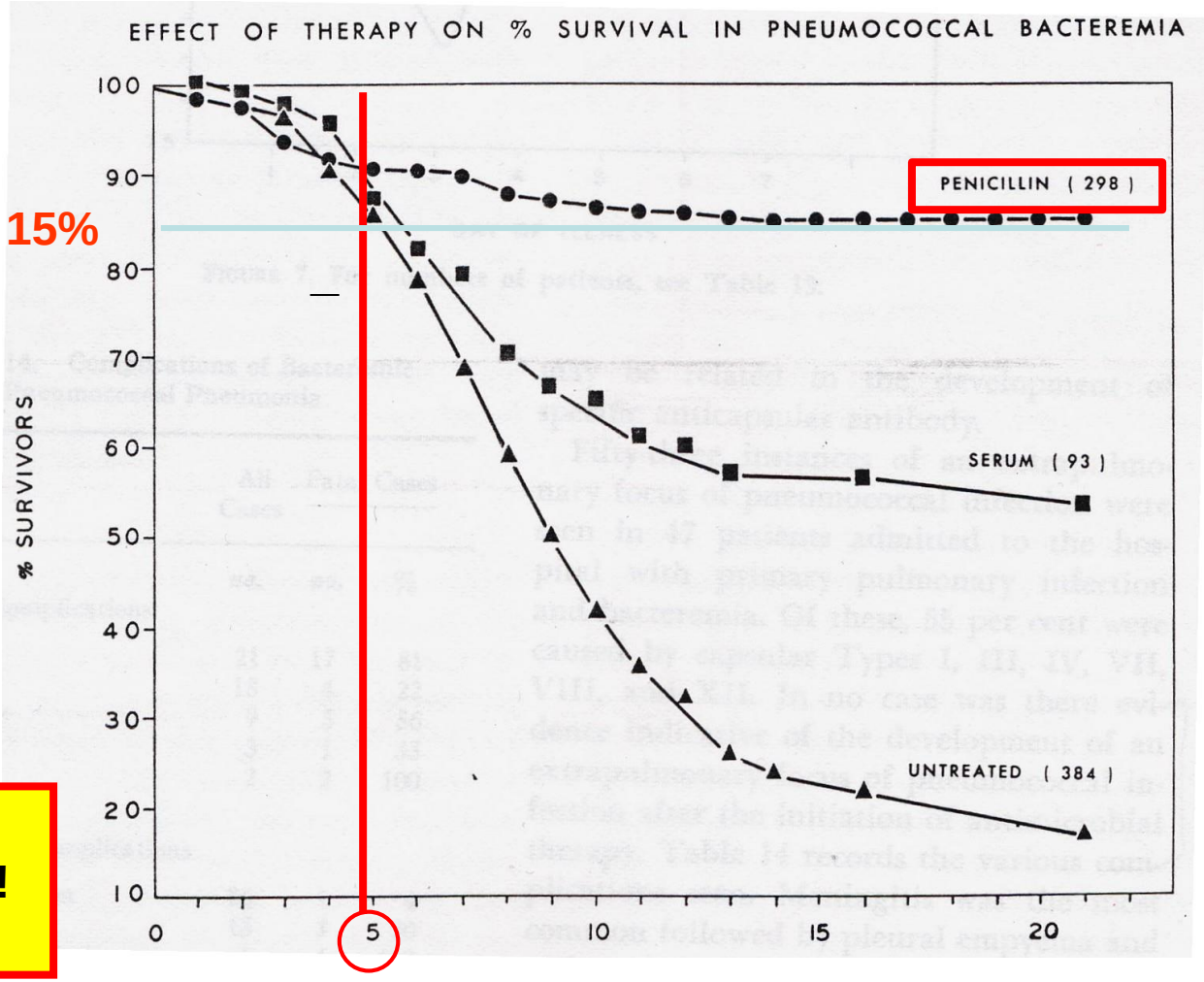
► Efficacité dans la prévention des PAC à *Sp* de sérotypes vaccinaux bactériémiques ou non

NEJM , Bonten et coll , 2015

Comment diminuer la mortalité des PAC à pneumocoques?

Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia.

R Austrian, J Gold, Annals of Internal Medicine, 1964, 60: 759-776.



- **Mortalité précoce**
- **Antibio-indépendante !!**

(= « inflammatoire » ?)...

Une ASSOCIATION antibiotique (macrolide) initiale diminue t'elle la mortalité des PAC sévères/bactériémiques à pneumocoque?

Beaucoup d'actions « immunomodulatrices » des macrolides HOTE et BACTERIE

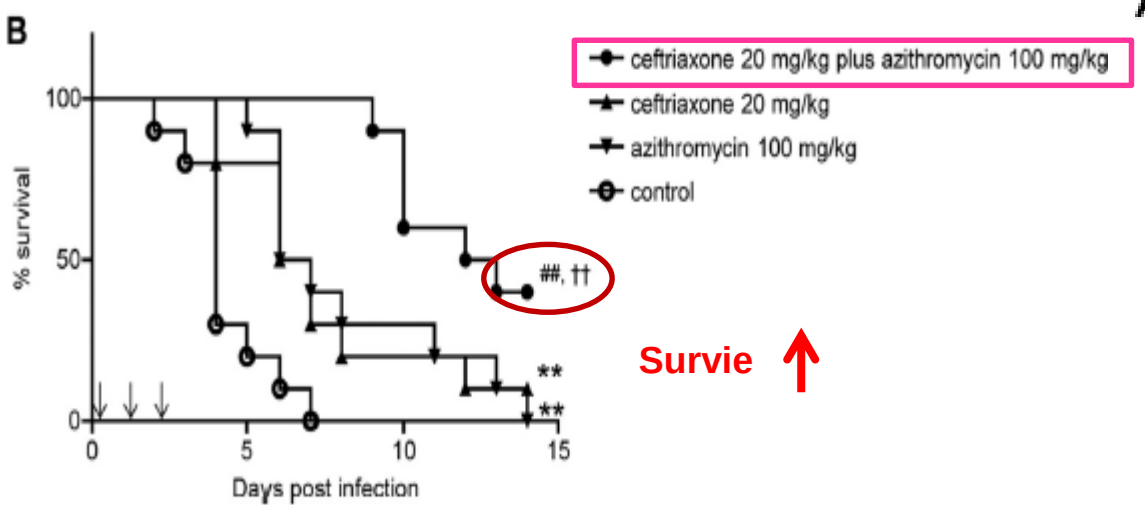
Effect	References
Attenuating the production of pro-inflammatory toxins, such as pneumolysin in *S. pneumoniae*	Witzenrath *et al.* [33]
	Anderson *et al.* [34]
	Fukuda *et al.* [35]
Inhibition neuthrophil mobilisation	Schultz *et al.* [36]
	Yamada *et al.* [38]
Affect NF-kB and ERK MAPK activation	Kanoh *et al.* [37]
Reduce the IgG mediated lung damage	Yamada *et al.* [38]
Decreased apoptosis of circulating lymphocytes	Koch *et al.* [39]
Reduce the production of:	Schultz *et al.* [36]
tumor necrosis factor (TNF), IL-6, IL-8, IL-1, IL-17, IL-10	Yamada *et al.* [38]
	Verleden *et al.* [40]
	Lin *et al.* [41]
	Zarogoulidis *et al.* [42]
	Kikuchi *et al.* [43]
	O'Dwyer *et al.* [44]
Inhibition of proinflammatory level of gene transcription and messenger RNA levels	Kikuchi *et al.* [43]
	O'Dwyer *et al.* [44]
Enhance polimorphonuclear activity against pneumococcus	Labro *et al.* [45]
Inhibit *P. aeruginosa* virulence factors	Giamarellos-Bourboulis *et al.* [52]
	Laserna *et al.* [54]
Reduce cystic fibrosis and COPD exacerbations	Giamarellos-Bourboulis *et al.* [52]
	Saiman *et al.* [53]

Lisboa T, Minerva Anestesiologica 2016

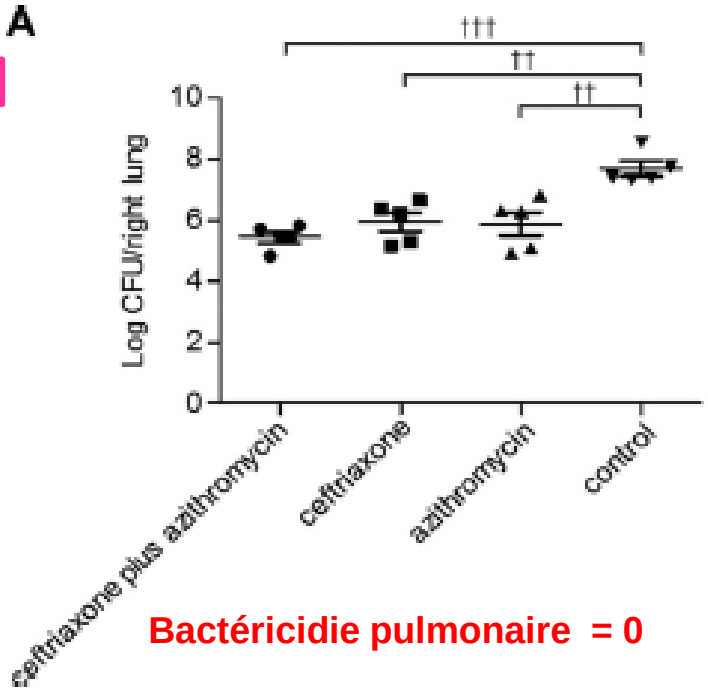
Quelle est la question posée?

L'addition d'un macrolide et de son « effet non antibiotique » à une bêta-lactamine anti-*Sp* améliore t'elle le pronostic (la mortalité?) des patients ayant une PAC à *Sp*?

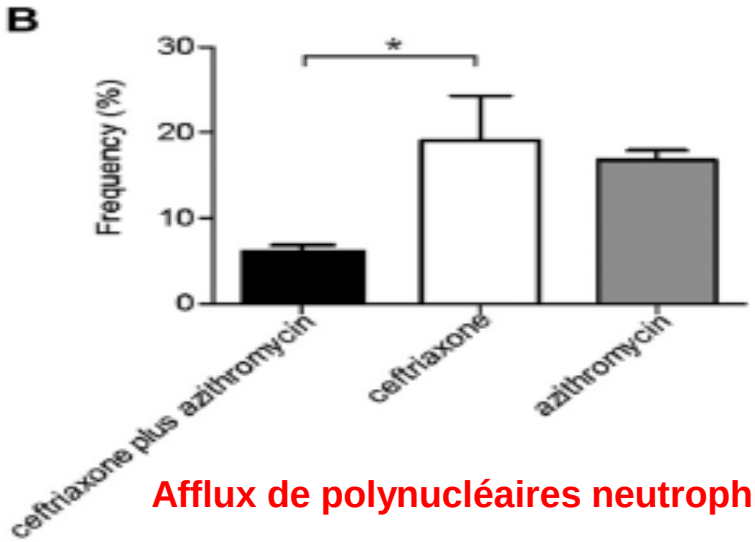
Efficacy of β-Lactam-plus-Macrolide Combination Therapy in a Mouse Model of Lethal Pneumococcal Pneumonia



Survie ↑



Bactéricidie pulmonaire = 0



Afflux de polynucléaires neutrophiles LBA ↓

→ Modulation du système inflammatoire de l'hôte et des facteurs de virulence de *S.pneumoniae*

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Yoshioka D oct 2016

En faveur de l'association Bêta-lactamine + macrolides…

Author	Year	Cohort	Site	Outcome	Study design
Gleason et al. [16]	1999	Patients aged ≥ 65 years with CAP	Ward	Lower 30-day mortality with β-lactam plus macrolide	Multicenter, retrospective
Dudas et al. [17]	2000	CAP	Ward	Lower mortality with β-lactam plus macrolide and reduced LOS	Multicenter, prospective
Waterer et al. [19]	2001	Pneumococcal bacteremia	Ward	Lower hospital mortality with combination	Multicenter, retrospective
Brown et al. [21]	2003	CAP	Ward	Lower 30-day mortality with β-lactam plus macrolide	Multicenter, retrospective
Martínez et al. [20]	2003	Pneumococcal bacteremia	Ward	Lower in-hospital mortality with β-lactam plus macrolide	Monocenter, retrospective
Baddour et al. [22]	2004	Pneumococcal bacteremia	Ward ICU	Lower 14-day mortality with combination	Multicenter, prospective
Weiss et al. [5]	2004	Pneumococcal bacteremia	Ward	Lower mortality with combination	Monocenter, retrospective
García-Vázquez et al. [23]	2005	CAP	Ward	Lower mortality with β-lactam plus macrolide	Multicenter, prospective
Mortensen et al. [24]	2006	CAP	Ward ICU	Lower 30-day mortality with β-lactam plus other than FQ	Multicenter, retrospective
Rodríguez et al. [25]	2007	CAP	ICU	Lower 28-day mortality with combination	Multicenter, retrospective
Metersky et al. [26]	2007	Pneumococcal bacteremia	Ward	Lower 30-day mortality with β-lactam plus macrolide	Multicenter, retrospective
Restrepo et al. [27]	2009	Severe sepsis pneumonia	Ward	Lower 30- and 90-day mortalities with combination plus macrolide	Multicenter, retrospective
Tessmer et al. [28]	2009	CAP	Ward	Lower 14- and 30-day mortalities with β-lactam plus macrolide	Multicenter, retrospective
Martín-Loeches et al. [29]	2010	Intubated CAP	ICU	Lower ICU mortality IDSA/ATS combination plus macrolide	Multicenter, prospective

►Méthodologie inadaptée…

Caballero J , Annals Intens Care 2011

Limitations ++++ de ces études concernant les PAC à Sp Hc+/-

- Analyse **rétrospective** post-hoc de cohortes prospectives ….
- **Pas d'ajustement** initial sur la sévérité…
- Pas d'ajustement sur les décès précoces…
- Antibiothérapie préalable?
- Timing de l'antibiothérapie?
- Choix AB subjectif par le médecin !
- **Qualité de la monothérapie?**
- Durée de la bitherapie?? Modifications de l'association??
- Polymorphismes génétiques des patients ??
- « Génomic bacterial load à Sp » des patients???
- Thérapeutiques adjuvantes (corticoides…)
- LATA….

► Aucune conclusion possible … trop de facteurs confondants = RCT

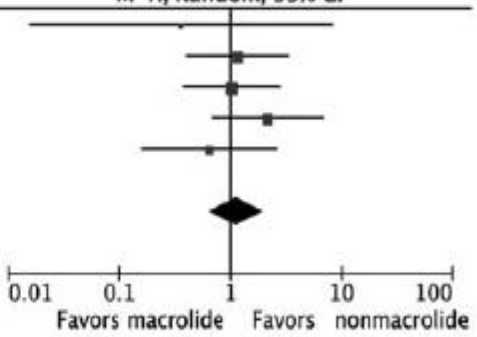
Macrolide-Based Regimens and Mortality in Hospitalized Patients With Community-Acquired Pneumonia: A Systematic Review and Meta-analysis

Asadi L, CID 2012

Study or Subgroup	Macrolide Events	Macrolide Total	Nonmacrolide Events	Nonmacrolide Total	Weight	Risk Ratio M-H, Random, 95% CI
Lin 2007 [25]	0	24	1	26	3.1%	0.36 (.02–8.43)
Portier 2005 [32]	7	175	6	174	27.3%	1.16 (.40–3.38)
Romanelli 2002 [35]	7	101	7	103	30.5%	1.02 (.37–2.80)
Welte 2005 [36]	5	77	6	200	23.3%	2.16 (.68–6.89)
Zervos 2004 [37]	3	102	5	110	15.8%	0.65 (.16–2.64)
Total (95% CI)		**479**		**613**	**100.0%**	**1.13 (.65–1.98)**
Total events	22		25			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.37$, df = 4 ($P = .67$); $I^2 = 0\%$

Test for overall effect: $Z = 0.44$ ($P = .66$)



► Etudes randomisées (n = 5) !!!! = RIEN !!

Conclusions. In hospitalized patients with CAP, macrolide-based regimens were associated with a significant 22% reduction in mortality compared with nonmacrolides; however, this benefit did not extend to patients studied in RCTs or patients that received guideline-concordant antibiotics. Our findings suggest guideline concordance is more important than choice of antibiotic when treating CAP.

Macrolides and Mortality in Critically Ill Patients With Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis

Sligl WI; CCM 2014

- 9850 Pts « critically ill » dans 27 études, aucune randomisée
- Mortalité globale (J 28/30): 22% → 21% macrolide + vs 24% macrolide - (p: 0;.02)
- Sous-groupes:
  - Exclusion macrolide monothérapie (25 études, 8872 pts): 21%/23% (p:0,05)
  - BLM vs BLF « crit ill pts » (19 études, 4241 pts): 20% vs 23% (p: 0,09)
  - Etudes prospectives (19 études, 2356 pts): 24% vs 23% (p: 0,32)
  - Patients avec VM (4 études, 71 pts): 27% vs 32% (p: 0,06)
  - Patients avec choc septique (4 études, 484 pts): 36% vs 42% (p: 0,45)
  - **PAC à *S.pneumoniae* (6 études, 499 pts): 32% vs 24% (p: 0,48)**

Diminution de 3% de mortalité absolue….
Effet non antibiotique des macrolides ???

PAC graves : Tt adjuvants ??

Mortality in ICU patients with bacterial community-acquired pneumonia: when antibiotics are not enough

Intensive Care Med (2009) 35:430–438

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*

The inflammatory response was attenuated in patients receiving GC, both systemically (IL-6 1,089±342 *versus* 630±385 pg·mL^{-1}, p=0.03; C-reactive protein 34±5 *versus* 19±5 mg·L^{-1}, p=0.04) and locally in BALF (TNF-α 118±50 *versus* 24±5 pg·mL^{-1}, p=0.05; neutrophil count: 2.4±1.1×10^{9} cells·L^{-1} (93±3%) *versus* 1.9±1.8×10^{9} cells·L^{-1} (57±16%), p=0.03). Four of the 11 (36%) patients receiving GC died compared to six (67%) who were not receiving GC (p=0.37).

The present pilot study suggests that glucocorticoids decrease systemic and lung inflammatory responses in mechanically ventilated patients with severe pneumonia receiving antimicrobial treatment.

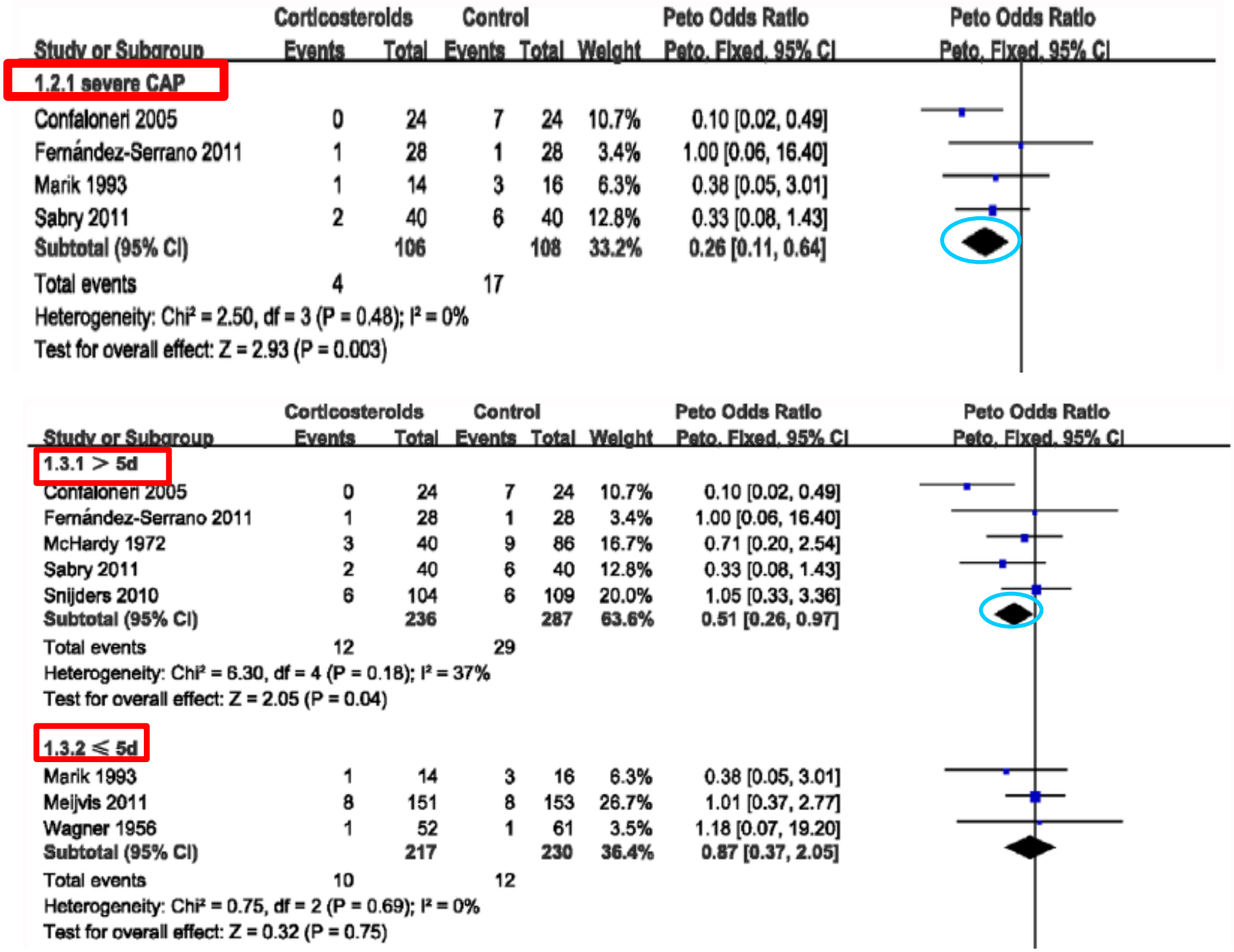
Eur Respir J 1999; 14: 218–220.

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

Plos One octobre 2012

Author/Year	Study Design	Location	No. Patients	Mean Age (y)	Patient Selection	Corticosteroids Used
Wagner [19]/1956	Quasi-RCT	USA	113	N/A	Mild to severe	Hydrocortisone, 560 mg, 5 d
		Multicenter				
McHardy [20]/1972	Open-label RCT	UK	126	60	Mild to severe	Prednisolone, 20 mg/d, 7 d
		Single center				
Marik [25]/1993	DB RCT	USA	30	34	Severe	Hydrocortisone, 10 mg/kg, 1 d
		Single center				
Confalonieri [8]/2005	DB RCT	Italy	48	64	Severe	Hydrocortisone, 240 mg/d, 7 d
		Multicenter				
Mikami [26]/2007	Open-label RCT	Japan	31	72	Mild to severe	Prednisolone, 40 mg/d, 3 d
		Single center				
Snijders [13]/2010	DB RCT	Netherlands	213	63	Mild to severe	Prednisolone, 40 mg/d, 7 d
		Single center				
Meijvis [12]/2011	DB RCT	Netherlands	304	63	Mild to severe	Dexamethasone, 5 mg/d, 4d
		Multicenter				
Sabry [14]/2011	DB RCT	Egypt	80	62	Severe	Hydrocortisone, 300 mg/d, 7d
		Multicenter				
Fernández-Serrano [11]/2011	DB RCT	Spain	56	63	Severe	Methyl-prednisolone, 620 mg, 9d
		Single center				

➔ 1001 Pts (9 études; mais 4 PAC sévère), petits effectifs, hétérogénéité, protoc CS #, durée ≠, effet hémodynamique *vs* effets anti-inflammatoires ?, safety …hyperglycémie…



► Etudes randomisées …

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. doi:10.1001/jama.2015.88

Annals of Internal Medicine

Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia

A Systematic Review and Meta-analysis

Ann Intern Med. doi:10.7326/M15-0715

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. doi:10.1001/jama.2015.88

	Intention-to-Treat Population				Per-Protocol Population			
	Methylprednisolone Group (n = 61)	Placebo Group, (n = 59)	*P* Value	Difference Between Groups, % (95% CI)	Methylprednisolone Group (n = 55)	Placebo Group (n = 57)	*P* Value	Difference Between Groups, % (95% CI)
Primary Clinical Outcome								
Treatment failure, No. (%)[a]	8 (13)	18 (31)	.02	18 (3 to 32)	5 (9)	16 (28)	.01	19 (5 to 33)
Early treatment failure (0-72 h), No. (%)[b]	6 (10)	6 (10)	.95	0 (−10 to 11)	3 (5)	4 (7)	>.99	2 (−7 to 11)
Early mechanical ventilation	4 (7)	5 (8)	.74	2 (−8 to 11)	2 (4)	3 (5)	>.99	2 (−6 to 9)
Early septic shock	2 (3)	3 (5)	.68	2 (−5 to 9)	1 (2)	2 (4)	>.99	2 (−4 to 8)
Death	2 (3)	2 (3)	>.99	0 (−6 to 7)	0	0		
Late treatment failure (72-120 h), No. (%)[b]	2 (3)	15 (25)	.001	22 (10 to 34)	2 (4)	14 (25)	.002	21 (9 to 33)
Radiographic progression	1 (2)	9 (15)	.007	14 (4 to 23)	1 (2)	8 (14)	.03	12 (3 to 22)
Respiratory failure	1 (2)	5 (8)	.11	7 (−1 to 15)	1 (2)	5 (9)	.21	7 (−1 to 15)
Late mechanical ventilation	1 (2)	4 (7)	.20	5 (−2 to 12)	1 (2)	4 (7)	.36	5 (−2 to 13)
Late septic shock	0	4 (7)	.06	7 (0 to 13)	0	4 (7)	.12	7 (0 to 14)
Death	0	0			0	0		
Secondary Clinical Outcomes								
Time to clinical stability, median (IQR), d[c]	4 (3 to 6)	5 (3 to 7)	.28	1 (−0.4 to 2.4)	4 (3 to 6)	5 (3 to 7)	.13	1 (0 to 2)
Length of stay, median (IQR), d								
Hospital	11 (7.5 to 14)	10.5 (8 to 15)	.83	−0.5 (−4.6 to 3.6)	11 (8 to 14)	11.5 (8 to 15)	.70	0.5 (−3.3 to 4.3)
ICU[d]	5 (3 to 8)	6 (4 to 8)	.63	1 (−0.4 to 2.4)	5 (3 to 8)	6 (4 to 8)	.38	1 (0 to 2)
In-hospital mortality, No. (%)	6 (10)	9 (15)	.37	5 (−6 to 17)	3 (5)	7 (12)	.21	7 (−4 to 17)

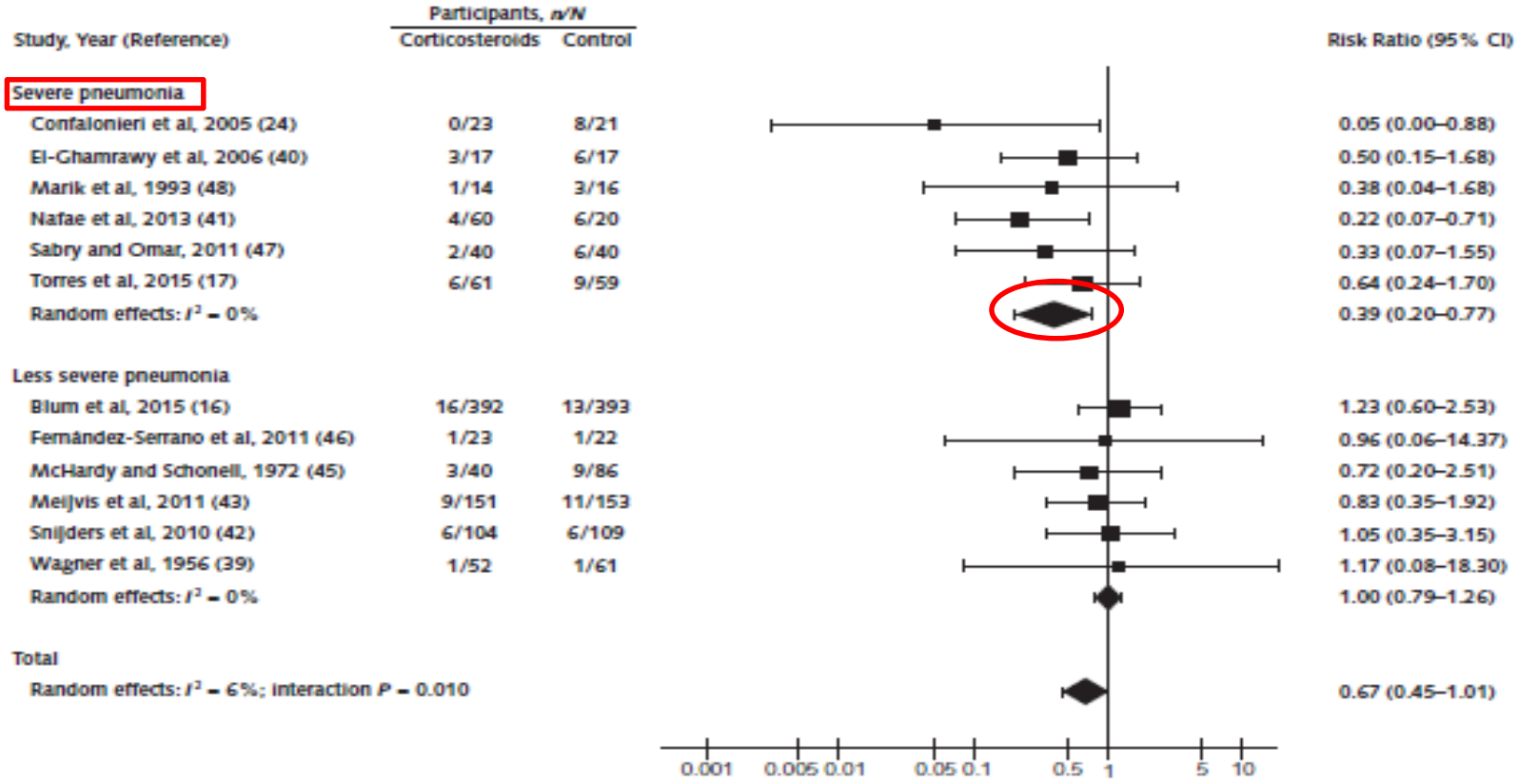
Annals of Internal Medicine

Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia

A Systematic Review and Meta-analysis

Ann Intern Med. doi:10.7326/M15-0715

- 13 études randomisées contrôlées = 2001 Pts
- 5 études incluent 70% de tout l'effectif



► Diminution de : Nécessité VM(5%); Evolution vers SDRA (6%); Durée d'hospitalisation (1j)...augmentation des hyperglycémies (3,5%)

Take home messages…

►Faire et respecter des procédures locales de prise charge des PAC sévères tirées des guidelines(Leroy et al, BMC Infect Dis 2013, 13: 196)

►Bien « trier » les patients avec des scores de sévérité ≠ du PSI et du CURB 65 (Marti C et al, Crit Care 2012, 16: R141) mais VPN >>VPP…

►Faire dans les 4h de l'admission une bithérapie initiale plutôt avec un macrolide vs une FQ et désescalader dés la documentation bactériologique (J2/3)

►La positivité des Hc à Sp ne change en rien la prise en charge thérapeutique, ni la durée du traitement

►La désescalade est double: arrêt du macrolide (ou FQ) et relais du CTX ou CRO par l'amoxicilline (1g x 3/6 IV)

Take home messages…

►La durée de traitement d'une PAC à Sp est de 8j maximum pouvant être diminuée avec l'aide de biomarqueurs (PCT) (Quenot JP et al, Annals of Intensive care 2013, 3:21)

► Corticoides →Etudes randomisées

→Revenir à la physiopathologie ++++ pour mieux comprendre l'interaction hôte-pathogène et avoir une intervention thérapeutique «personnalisée »

→Prévention des comorbidités +++

→Prévention vaccinale des PAC à Sp