Procalcitonine: une aide à la juste prescription des antibiotiques?

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Réanimation Médicale

C.H.U. Dijon

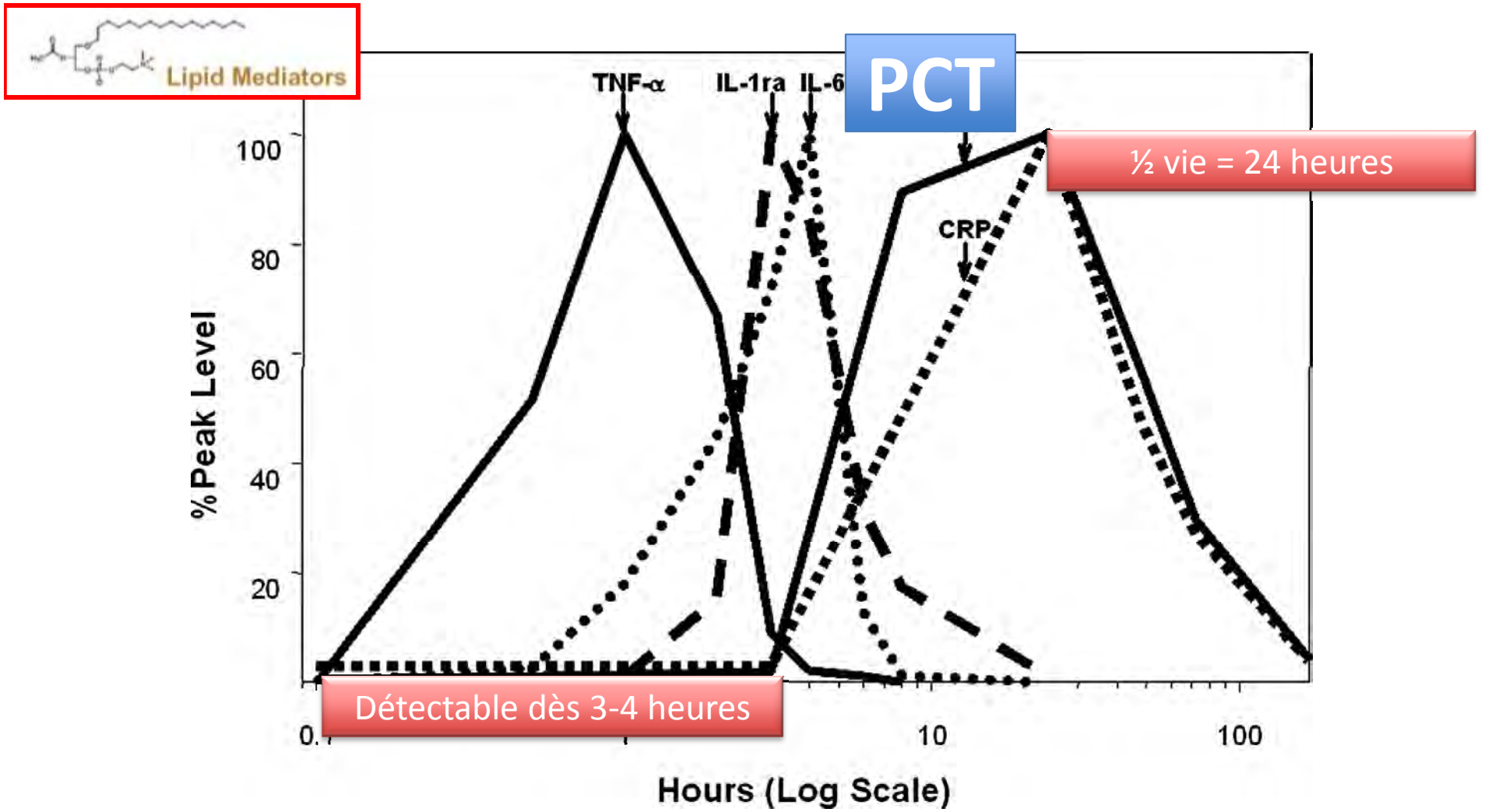
La juste prescription des antibiotiques?

- ATB seulement si **nécessaires**
- ATB seulement **le temps nécessaire**

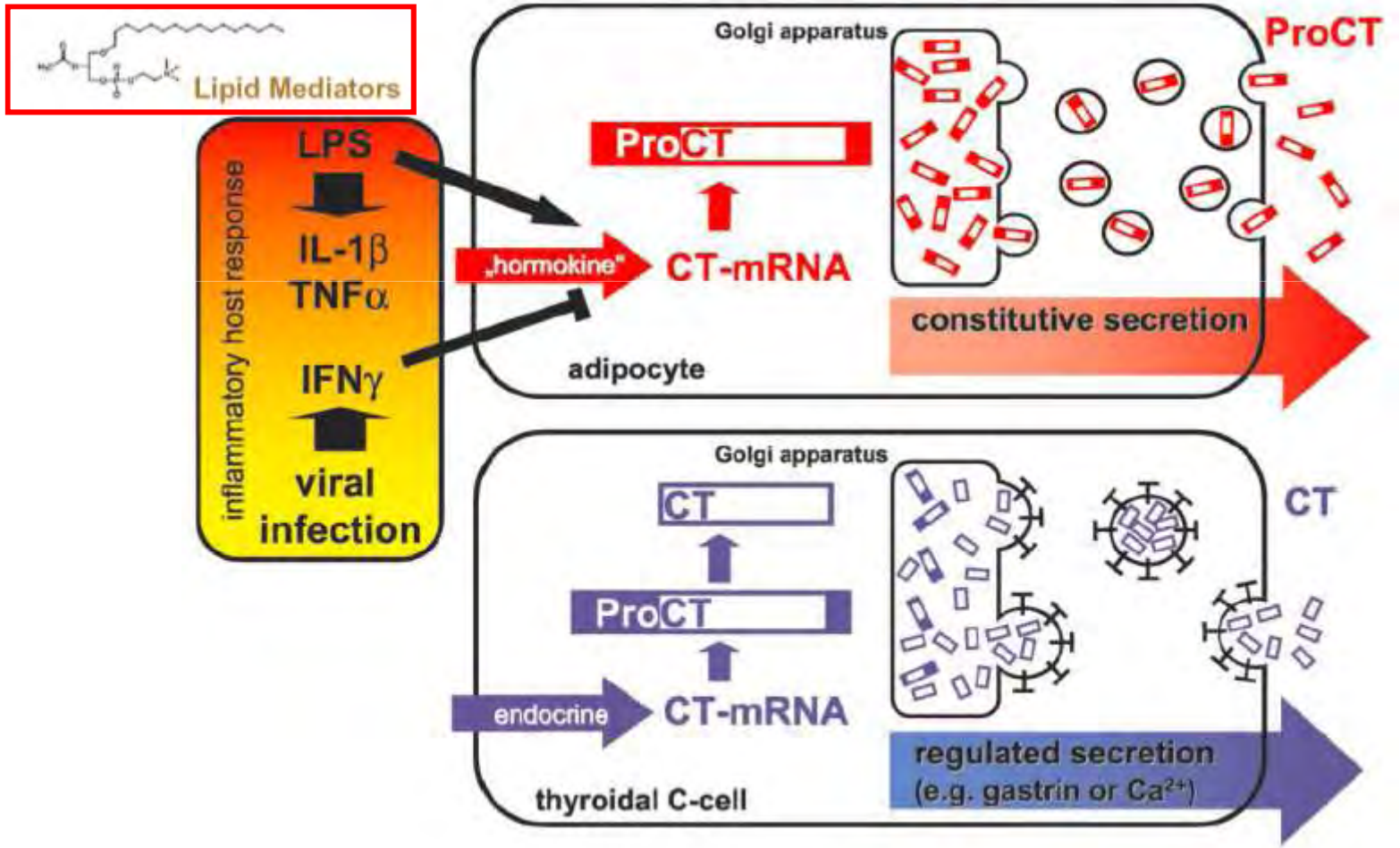
Procalcitonine: une aide à la juste prescription des antibiotiques?

PRÉAMBULE

Modèle **LPS**: inflammation **systémique**

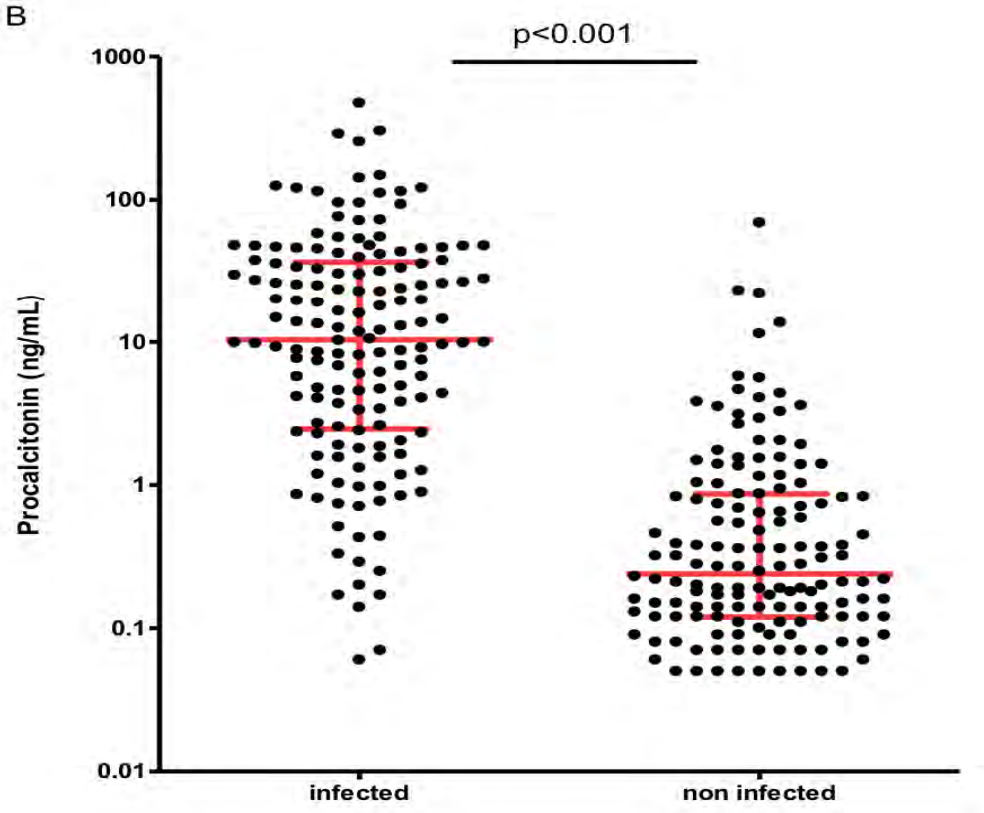


Modèle **LPS**: inflammation **systémique**



Linscheid *et al*. Endocrinology 2003

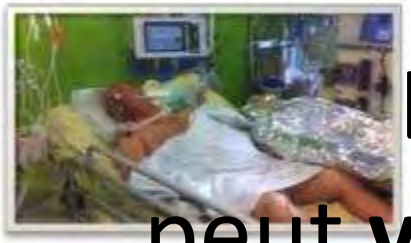
Diagnostic **précoce** de l'infection **grave**: **PCT** en **réanimation**



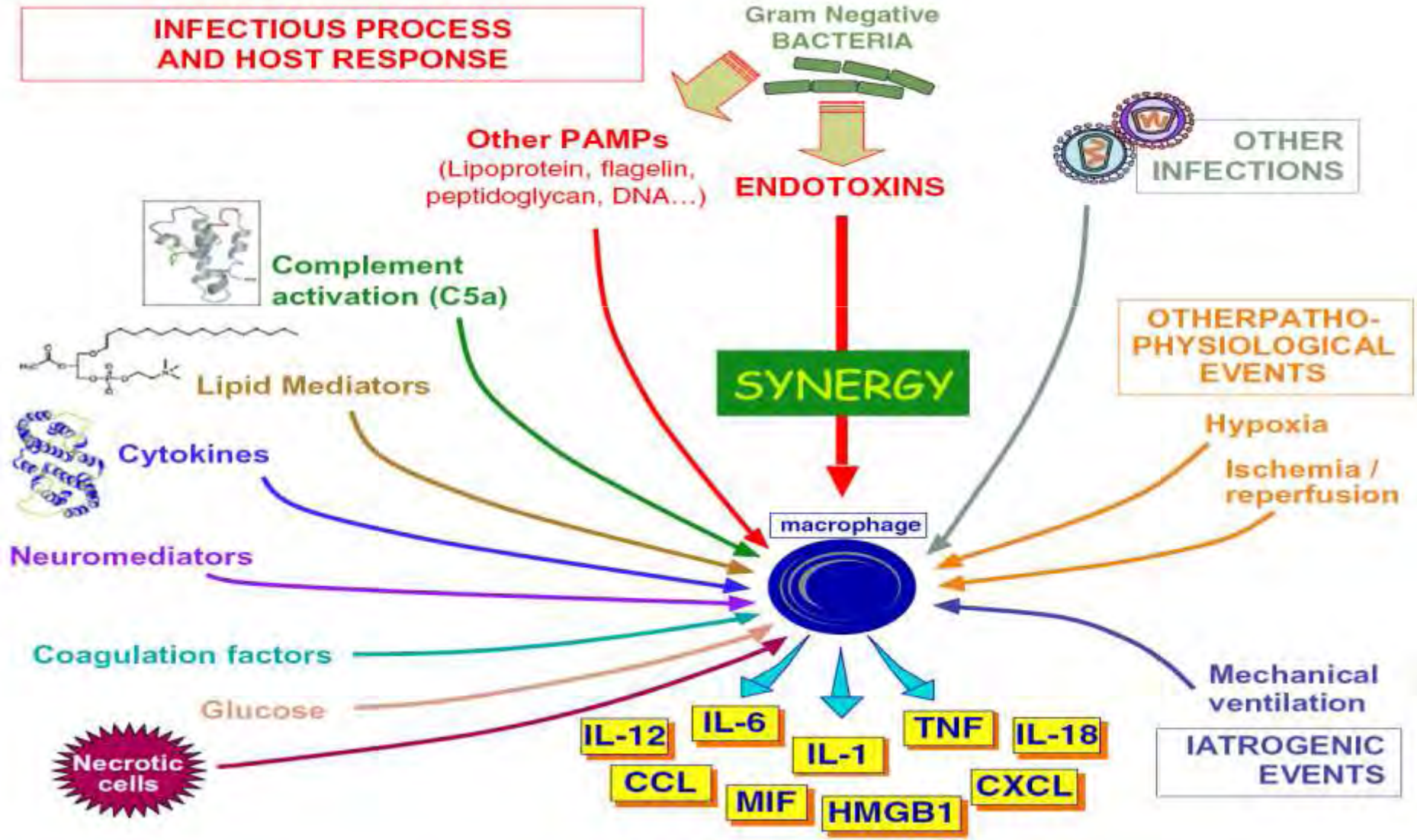
Threshold = 1.5 ng/mL

Se	Sp	PPV	NPV
83%	85%	85%	83%

Gibot, Charles *et al* Am J Respir Crit Care Med 2012



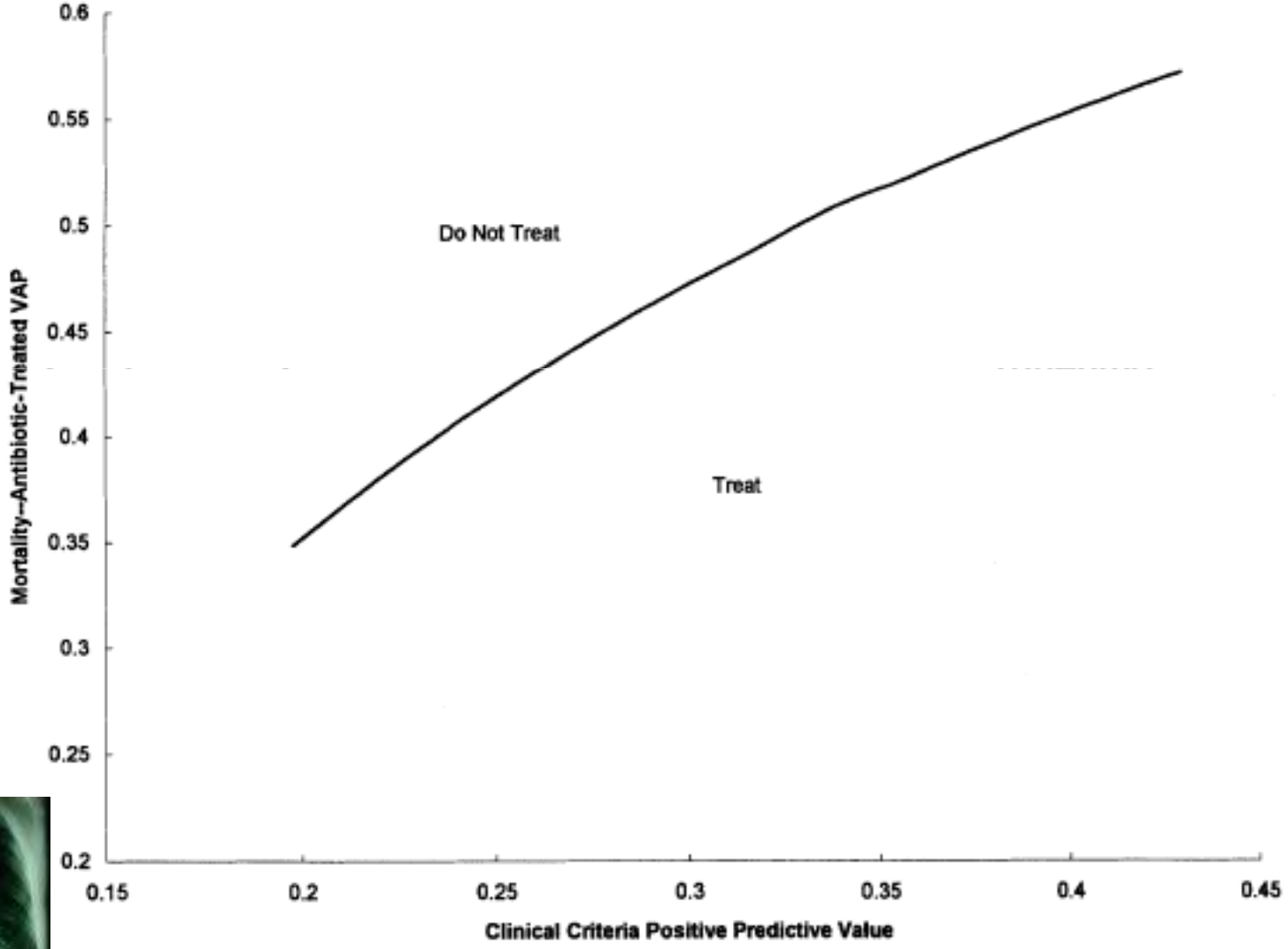
La réponse inflammatoire peut **varier** d'une **situation** à l'autre…

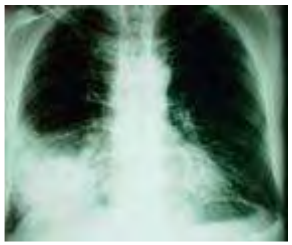


Procalcitonine: une aide à la juste prescription des antibiotiques?

ATB SEULEMENT SI NÉCESSAIRES

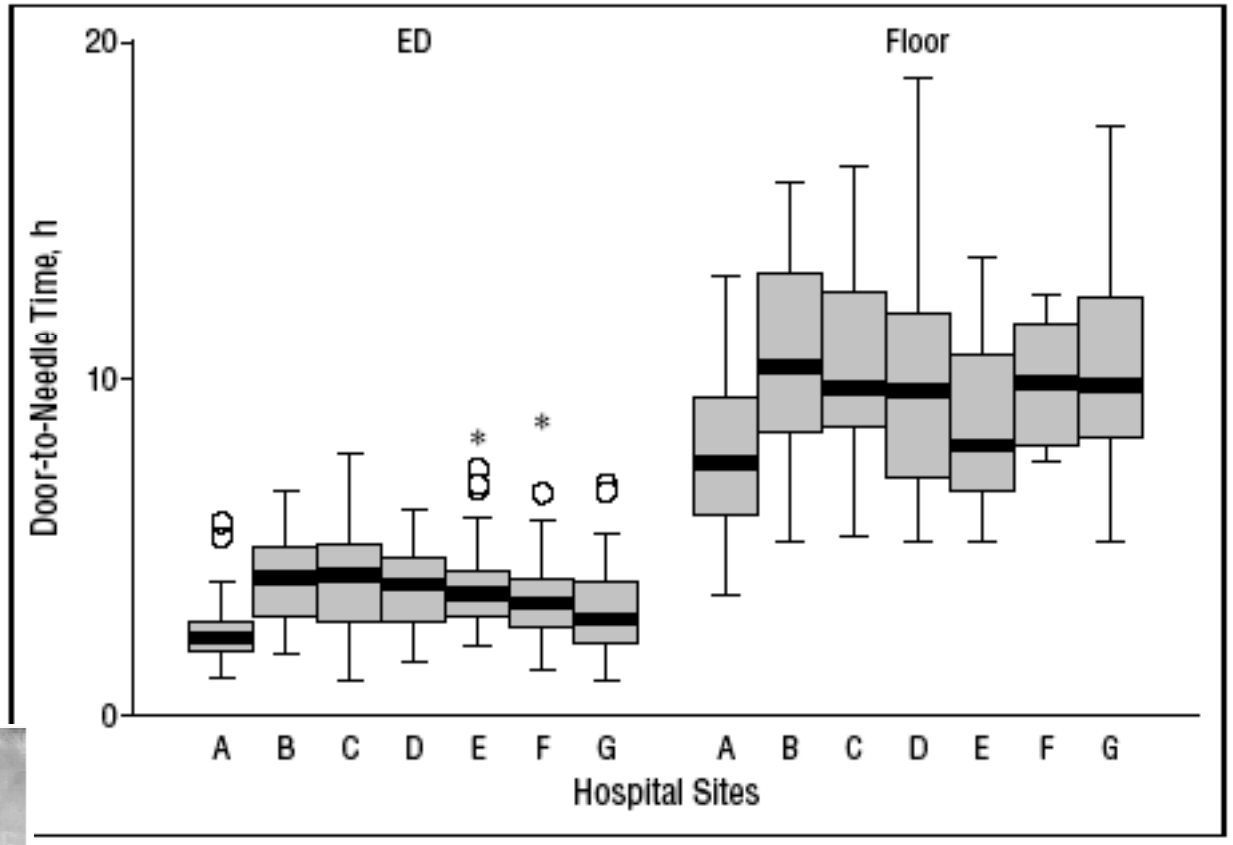
Antibiothérapie:
quel rapport bénéfices-risques?

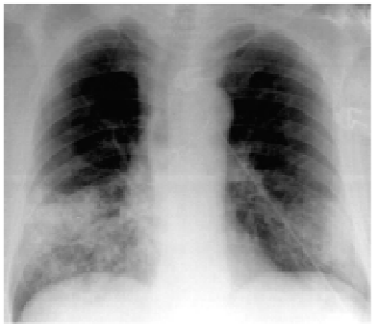




Sterling TR et al Chest 1996

Frapper *tôt*: dès les urgences!



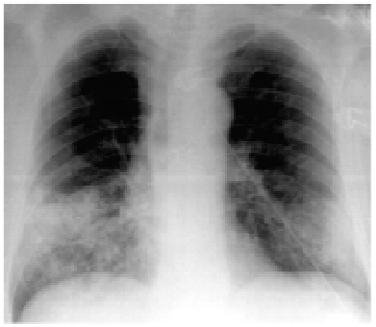


Battleman et al, Arch Intern Med 2002

Frapper *tôt*: dès les urgences!

Table 2. Associations of Demographic, Clinical, and Process Variables With Prolonged Length of Stay (pLOS)*

Variable	Patients With pLOS (n = 136)	Patients Without pLOS (n = 473)	Odds Ratio (95% Confidence Interval)	
			Univariate	Multivariate
Demographic				
Age, mean ± SD, y	74 ± 16.9	65 ± 19.4	1.28 (1.15-1.44)†‡	1.28 (1.12-1.46)†‡
Sex, % male	46	45	1.01 (0.69-1.48)	. . .
Ethnicity, % white	62	38	1.49 (1.02-2.19)§	1.39 (0.91-2.12)
Admit site, % SNF	21	15	1.51 (0.93-2.44)	. . .
Payer, % Medicaid/self-pay	52	49	1.19 (0.81-1.74)	0.75 (0.48-1.16)
Clinical				
COPD, %	31	25	1.38 (0.91-2.08)	0.69 (0.42-1.15)
Other comorbid illness, %	74	53	2.39 (1.57-3.65)†	2.64 (1.55-4.49)†
WBC at admission, mean ± SD, $\times 10^3/\mu L$	13 ± 6.5	12 ± 5.8	1.08 (0.93-1.26)‖	1.16 (0.98-1.38)‖
RR at admission, mean ± SD, beats/min	23 ± 5.7	26 ± 7.5	1.28 (1.11-1.48)‖¶	1.23 (1.04-1.45)‖¶
Positive CXR, %	93	91	1.29 (0.64-2.65)	. . .
Process				
Initial antibiotics, % ED	51	71	0.42 (0.28-0.61)†	0.31 (0.19-0.48)†
Appropriate antibiotic, %	55	57	0.94 (0.64-1.38)	0.55 (0.35-0.88)§



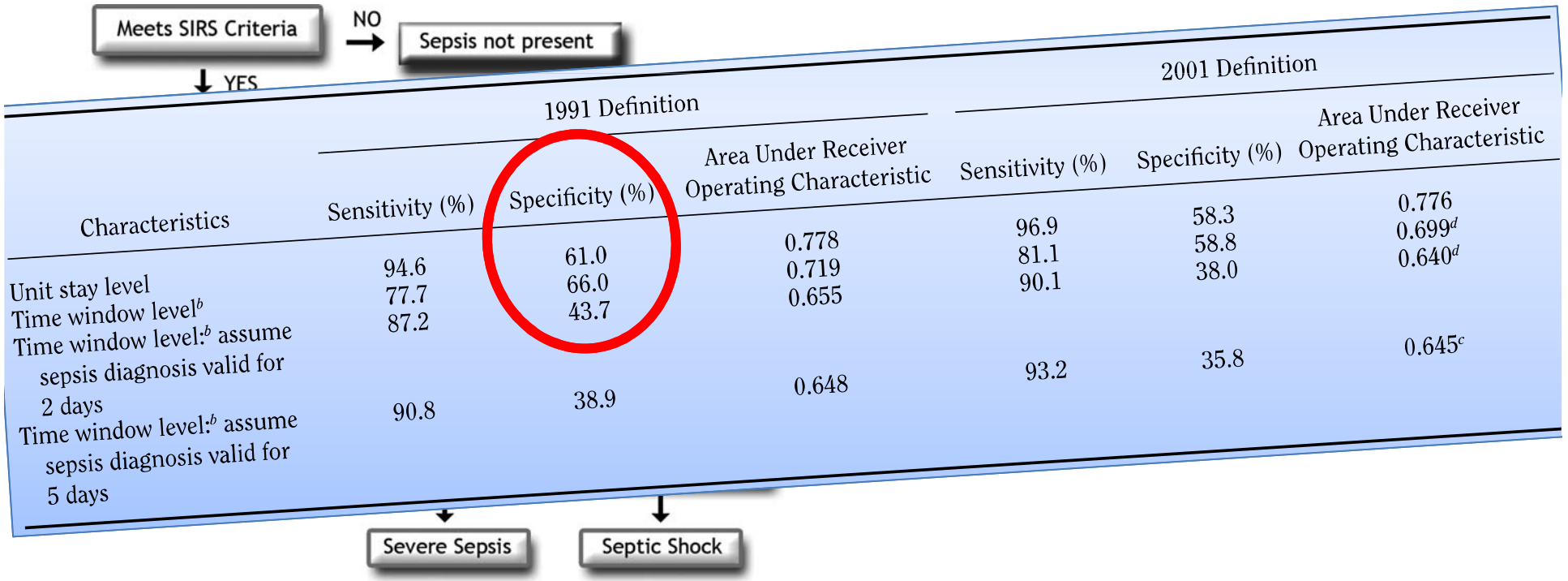
Battleman et al, Arch Intern Med 2002

Définitions du sepsis (1991 & 2001)

Variables	Définitions
Réponse inflammatoire systémique (au moins deux des critères suivants)	Température > 38,3°C ou < 36°C Pouls > 90 c/mn, *>2DS pour l'âge* Fréquence respiratoire > 20 c/mn, *>2DS pour l'âge* Glycémie > 7,7 mmol/L Leucocytes > 12 000/mm³ ou < 4 000/mm³ ou > 10 % de formes immatures Altération des fonctions supérieures Temps de recoloration capillaire >2 sec, *>5 sec* Lactatémie > 2 mmol/L
Sepsis	Réponse inflammatoire systémique + infection présumée ou identifiée

An evaluation of the diagnostic accuracy of the 1991 American College of Chest Physicians/Society of Critical Care Medicine and the 2001 Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians/American Thoracic Society/Surgical Infection Society sepsis definition*

Huifang Zhao, MD, PhD; Stephen O. Heard, MD; Marie T. Mullen, MD; Sybil Crawford, PhD; Robert J. Goldberg, PhD; Gyorgy Frendl, MD, PhD; Craig M. Lilly, MD



Characteristics	1991 Definition			2001 Definition		
	Sensitivity (%)	Specificity (%)	Area Under Receiver Operating Characteristic	Sensitivity (%)	Specificity (%)	Area Under Receiver Operating Characteristic
Unit stay level	94.6	61.0	0.778	96.9	58.3	0.776
Time window level[b]	77.7	66.0	0.719	81.1	58.8	0.699[d]
Time window level:[b] assume sepsis diagnosis valid for 2 days	87.2	43.7	0.655	90.1	38.0	0.640[d]
Time window level:[b] assume sepsis diagnosis valid for 5 days	90.8	38.9	0.648	93.2	35.8	0.645[c]

Zhao *et al*. Crit Care Med 2012

Prédiction du sepsis bactérien…

Test and cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
PCT				
≥0.1 µg/l	0.90 (0.85–0.94)	0.32 (0.22–0.43)	0.74 (0.68–0.80)	0.60 (0.47–0.74)
≥0.2 µg/l	0.77 (0.70–0.82)*	0.59 (0.48–0.70)	0.80 (0.74–0.86)	0.54 (0.43–0.64)*
≥0.5 µg/l	0.63 (0.55–0.70)	0.79 (0.68–0.87)	0.87 (0.80–0.92)	0.49 (0.40–0.58)
≥2 µg/l	0.36 (0.30–0.44)	0.93 (0.85–0.97)	0.92 (0.83–0.97)	0.40 (0.33–0.47)
≥5 µg/l	0.23 (0.17–0.30)	0.99 (0.93–1.00)	0.97 (0.87–0.99)	0.37 (0.30–0.44)
Emergency physician	0.85 (0.79–0.90)	0.57 (0.45–0.67)	0.81 (0.75–0.86)	0.63 (0.51–0.74)

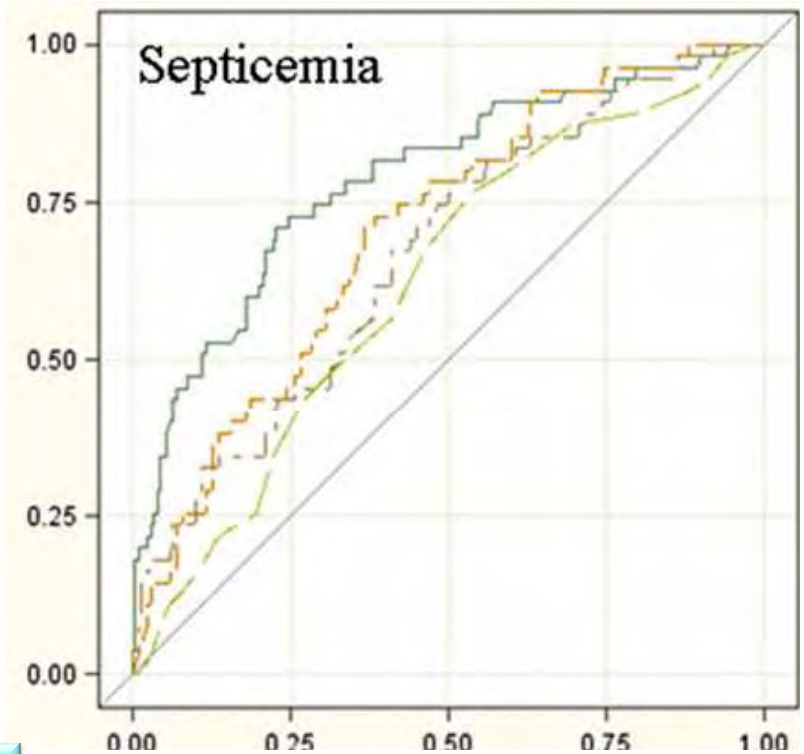
253 patients
Fièvre ≥ 38.5°C
Unicentrique (France)

Urgences

Gold standard = Expertise dossiers

Hausfater P *et al*. Crit Care 2007

Prédiction du sepsis bactérien…



Threshold = 0.5 ng/mL

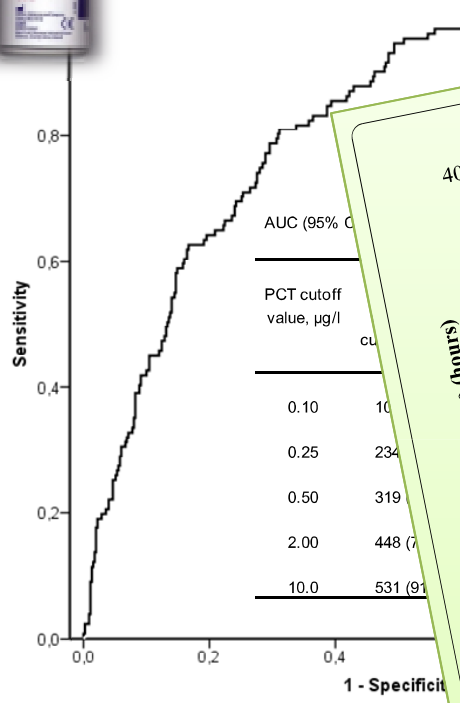
Se	Sp
72%	70%

335 patients
Suspicion clinique de sepsis
Bicentrique (U.S.A.)

Urgences

Gold standard = bactériémie

Prédiction du sepsis bactérien…



	Multivariate OR (95% CI)	*P*-value	R^2
			0.145
s	2.4 (1.5 to 3.8)	<0.001	
38.6°C	2.1 (1.3 to 3.3)	0.001	
status	1.8 (0.9 to 3.5)	0.093	
/minute	1.7 (1.1 to 2.7)	0.015	
s	1.6 (1.0 to 2.7)	0.063	
tment			
			0.252
18	39.5)	<0.001	

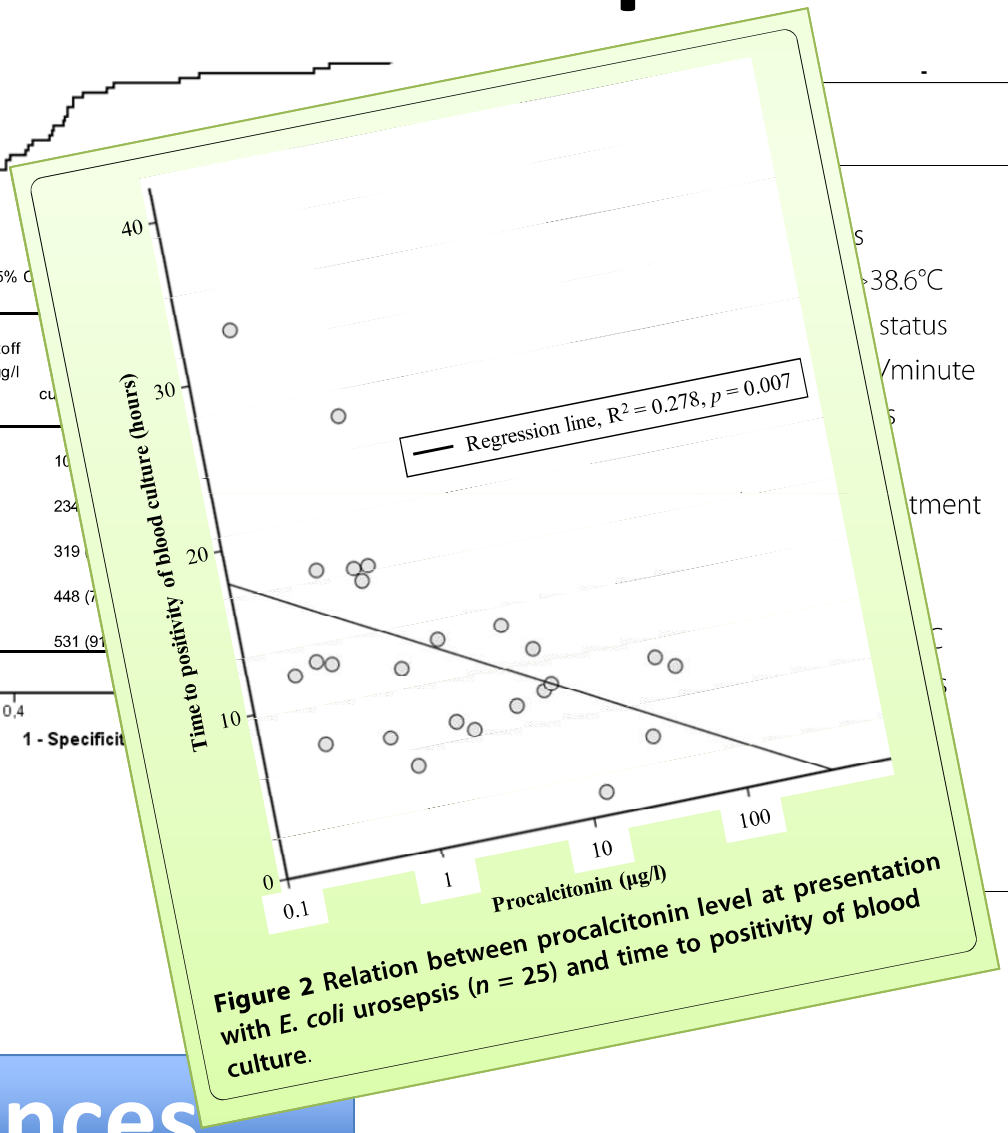


Figure 2 Relation between procalcitonin level at presentation with *E. coli* urosepsis (n = 25) and time to positivity of blood culture.

Threshold = 0.25 ng/mL

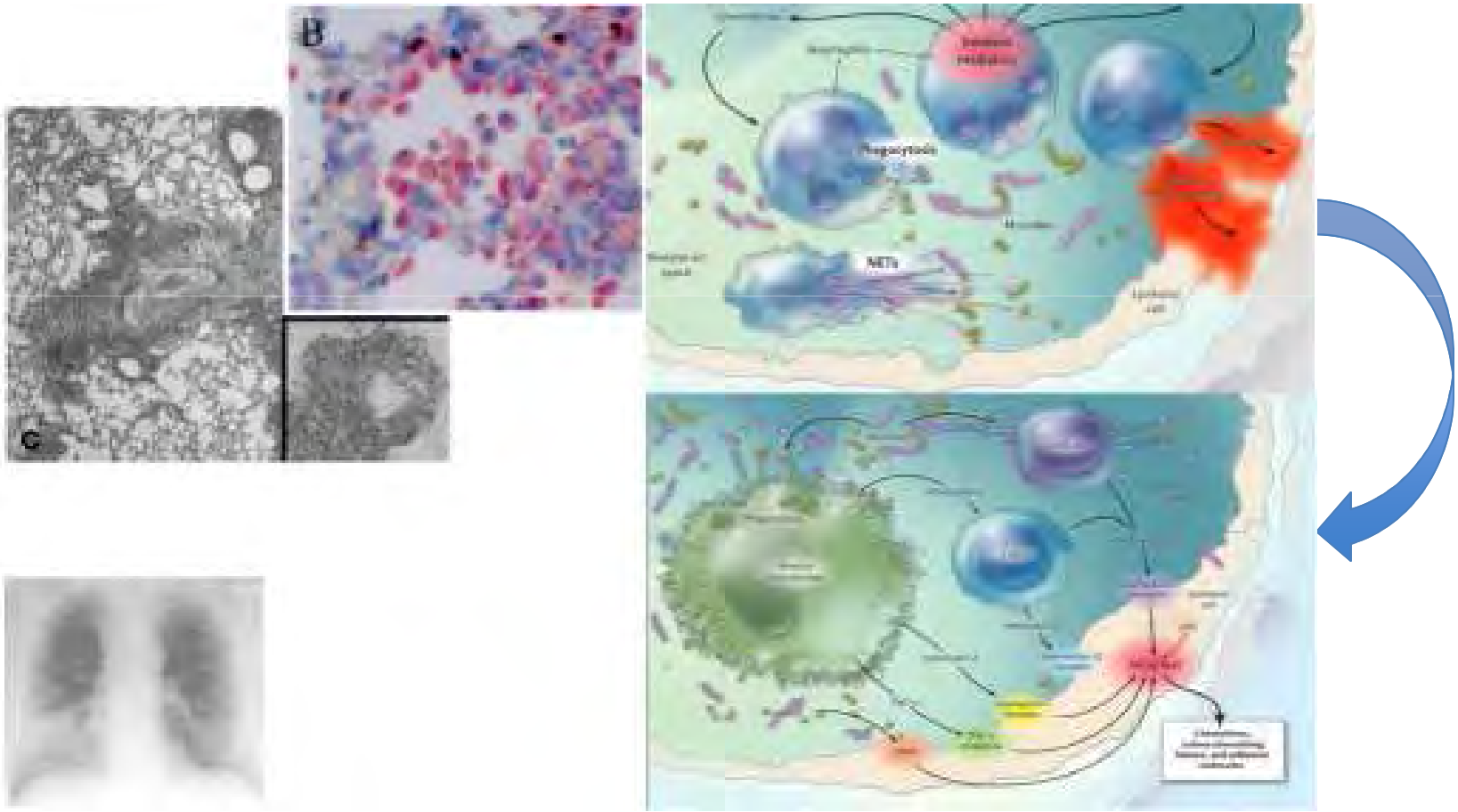
Se	Sp
98%	50%

Gold standard = bactériémie d'origine urinaire

Urgences

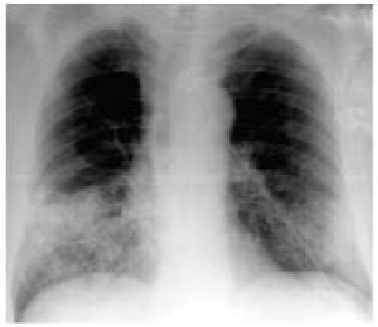
Claessens YE *et al*. Crit Care 2009

Infections respiratoires basses: prédire l'infection parenchymateuse & l'étiologie **bactérienne**…



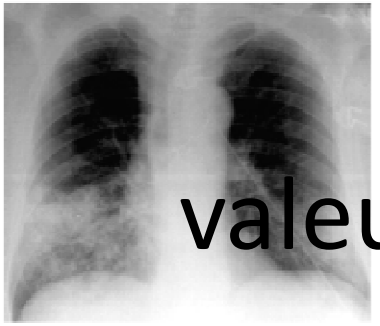
« **Signes** et **Symptômes** »: valeurs diagnostiques aux urgences…

	Sensitivity % x (y, z)	**Specificity %** x (y, z)	**PPV %** x (y, z)	**NPV %** x (y, z)
Cough	**94** (93, 94)	**6** (6, 7)	**27** (64, 13)	**71** (31, 88)
Sputum production	**75** (71, 71)	**34** (33, 31)	**29** (66, 14)	**76** (38, 88)
Discoloured sputum	**44** (45, 41)	**62** (61, 57)	**29** (67, 13)	**74** (38, 93)
Dyspnea	**66** (63, 69)	**27** (26, 33)	**25** (61, 14)	**68** (28, 88)
Crackles	**69** (43, 72)	**74** (76, 69)	**51** (76, 26)	**87** (42, 94)
Infiltrate	**97** (54, 100)	**86** (87, 70)	**73** (88, 34)	**99** (51, 100)
SaO_2 <90%	**19** (17, 18)	**91** (91, 87)	**43** (77, 18)	**75** (38, 88)



Gold standard = Expertise dossiers

Muller *et al*. BMC Infect Dis 2007



« **Signes** et **Symptômes** »: valeurs diagnostiques en méd. G[ale]…

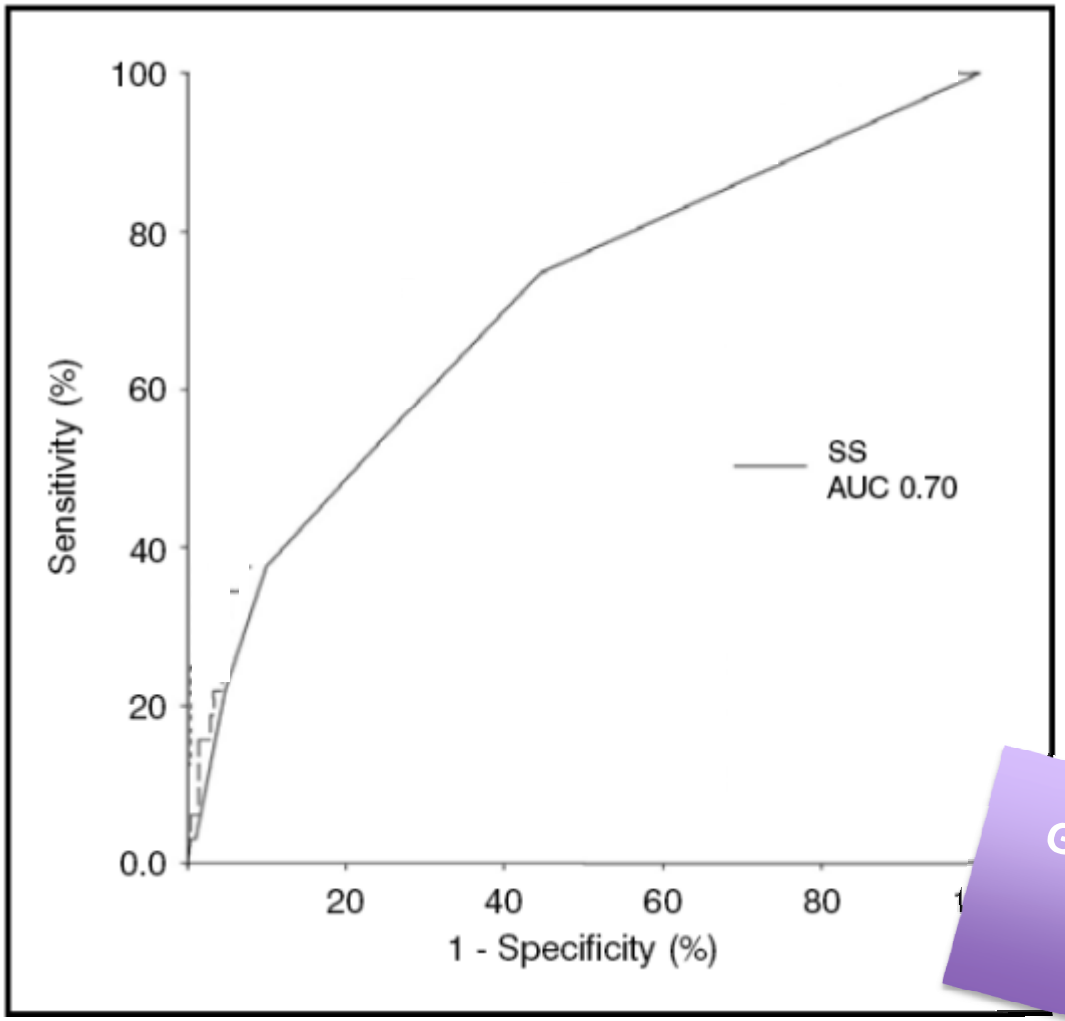
	Pneumonia (prior probability = 13.2%)				
	n	%	OR (95% CI)	PV+ (%)	PV- (%)
Symptoms					
Age 65 years or older	70	28.8	1.3 (0.6–3.0)	15.7	87.9
Recent cough ≤2 days	11	5.1	3.8 (1.0–13.8)[d]	36.4	86.9
Dry cough[a]	58	23.9	2.2 (1.0–4.7)[b]	20.7	89.2
Sputum purulence	133	54.7	1.2 (0.6–2.6)	14.3	88.2
Dyspnoea	188	77.4	0.7 (0.3–1.6)	12.2	83.6
Thoracic pain	145	59.7	1.3 (0.6–2.9)	14.5	88.8
Fever[c]	85	35.0	1.8 (0.8–3.8)	17.6	89.2
Chills[a]	122	50.2	2.4 (1.1–5.4)[d]	18.0	91.7
Confusion	8	3.3	4.3 (1.0–18.8)[b]	37.5	87.7
Nausea[a]	39	16.0	2.9 (1.2–6.6)[d]	25.6	89.2
Diarrhoea[a]	19	7.8	3.5 (1.2–10.0)[d]	31.6	88.4
Smoking	81	33.3	0.8 (0.3–1.7)	11.1	85.8
Smoking in the past	150	61.7	1.0 (0.5–2.2)	13.3	87.1
Co-morbidity					
Asthma	47	19.3	1.2 (0.5–3.0)	14.9	87.2
COPD	32	13.2	1.3 (0.4–3.6)	15.6	87.2
Physical signs					
General impression: moderate/severe illness[a]	65	26.7	2.8 (1.3–6.1)[d]	23.1	90.4
Respiration rate >20/min.	9	3.7	0.8 (0.1–6.8)	11.1	86.8
Percussion dullness	11	4.5	–		100
Auscultation abnormality	204	84.0	2.0 (0.6–6.9)		92.3
Bronchial breathing	64	26.3	1.4 (0.7–3.4)		
Crackles	50	20.6	1.5 (0.7–3.7)		
Temperature >38°C[a]	58	23.9	2.5 (1.2–5.5)[d]		
Clinical diagnosis of pneumonia	21	8.6	1.6 (0.5–5.2)		

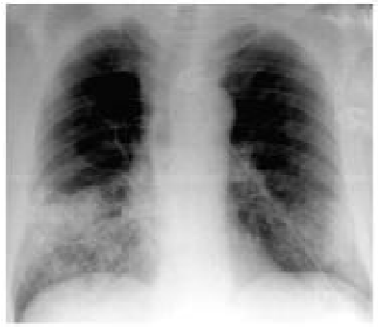
[a]Variable selected for multiple logistic regression analysis. [b]Number rounded to 1.0, but in reality less than 1
axillary temperature ≥38.5°C and measured less than 24 hours previously. [d]Statistically significant ($P<0.05$).

Gold standard = Opacité RxP

Hopstaken *et al*. Br J Gen Pract 2003

« **Signes** et **Symptômes** »: valeurs diagnostiques en méd. G^{ale}…





Gold standard = Opacité RxP

Hopstaken *et al*. Br J Gen Pract 2003

IRB: étiologies non bactériennes

[ ]											
Fransen and Wolontis [93]	78	8.0	3.0		3.0	3.0				20.0	12.0
Graffelman *et al.* [94]	145	6.2	9.0	2.1		9.0	1.3			39.0	30.3
Holm *et al.* [95]	364	6	4	1	<1	3		<1		24	10
Hopstaken *et al.* [96]	247	2.9	13.8	2.9							
Macfarlane *et al.* [97]	206	30.0	8.0	2	1.0	0.5			0.5	8.0	5.0
Macfarlane *et al.* [98]	316	17.1	9.8	2.2		7.3		17.4		19.3	7.3
Shaw and Fry [99]	40	16.0	14.0		10.0	5.0	3.0		0	11.0	11.0
Range		3–30	3–14	1–3	1–10	0.5–9	0–3		0–0.5	6–61	4–30

SP, *Streptococcus pneumoniae*; HI, *Haemophilus influenzae*; LP, *Legionella pneumophila*; MC, *Moraxella catarrhalis*; SA, *Staphylococcus aureus*; GNEB, *Gram-negative bacilli*; MP, *Mycoplasma pneumoniae*; CS, *Chlamydia species (all)*; CPne, *Chlamydophila pneumoniae*; CPsi, *Chlamydophila psittaci*; CB, *Coxiella burnetii*.

Woodhead *et al*. Clin Microbiol Infect 2011

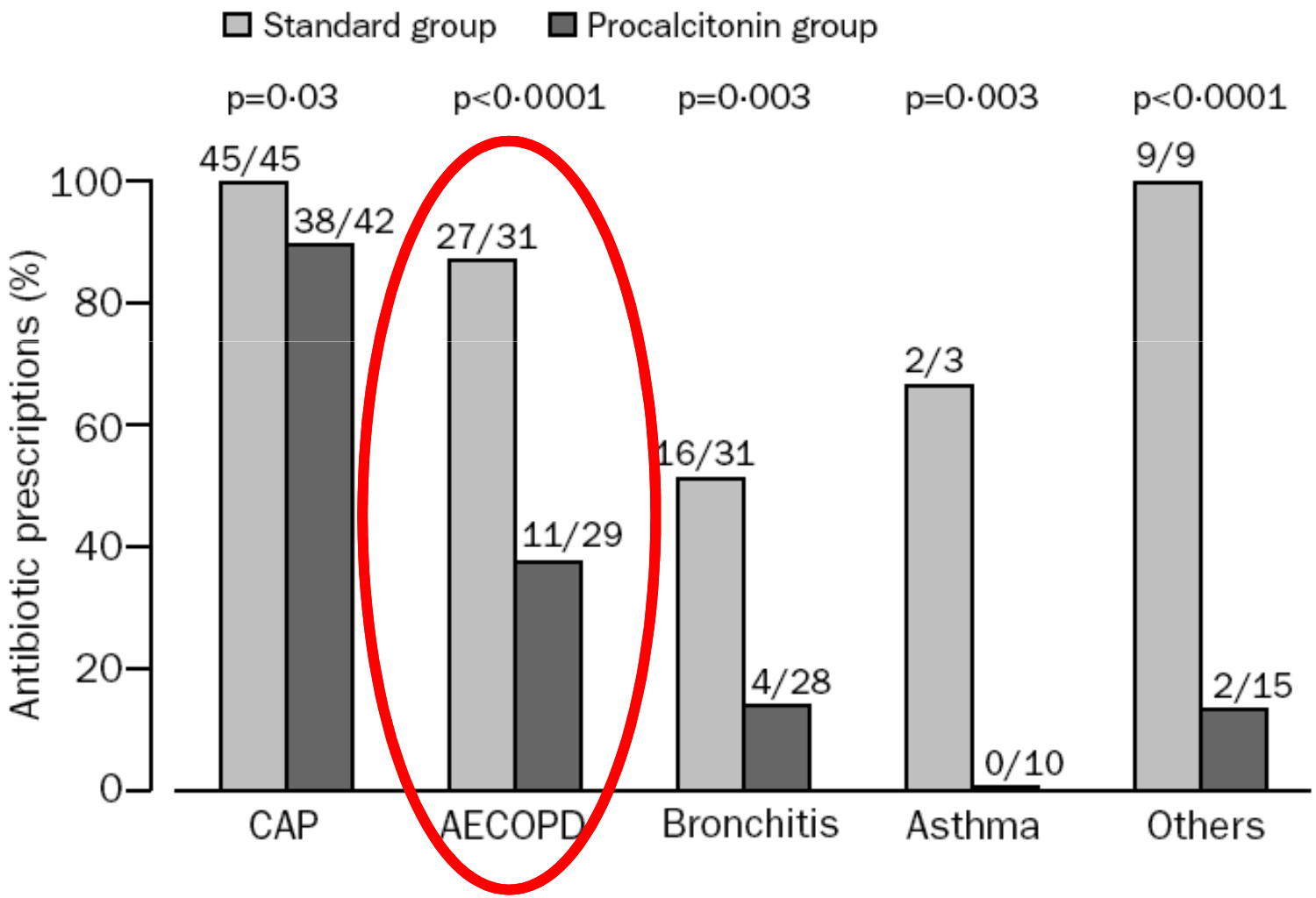
IRB: initiation ATB PCT-guidée…

Evaluation at time of admission

PCT result	**<0.10 µg/L**	**<0.25 µg/L**	**≥0.25 µg/L**	**>0.50 µg/L**
Recommendation regarding use of Abx	Strongly discouraged	Discouraged	Encouraged	Strongly encouraged
Overruling the algorithm	Consider use of antibiotics if patients are clinically unstable, have strong evidence of pneumonia, are at high risk (ie, COPD GOLD III-IV), or need hospitalization			
Follow-up/other comments	Follow-up only needed if no symptom resolution after 1 to 2 days; if clinical situation is not improving; consider Abx if PCT level increases to ≥0.25 µg/L		Clinical reevaluation as appropriate	

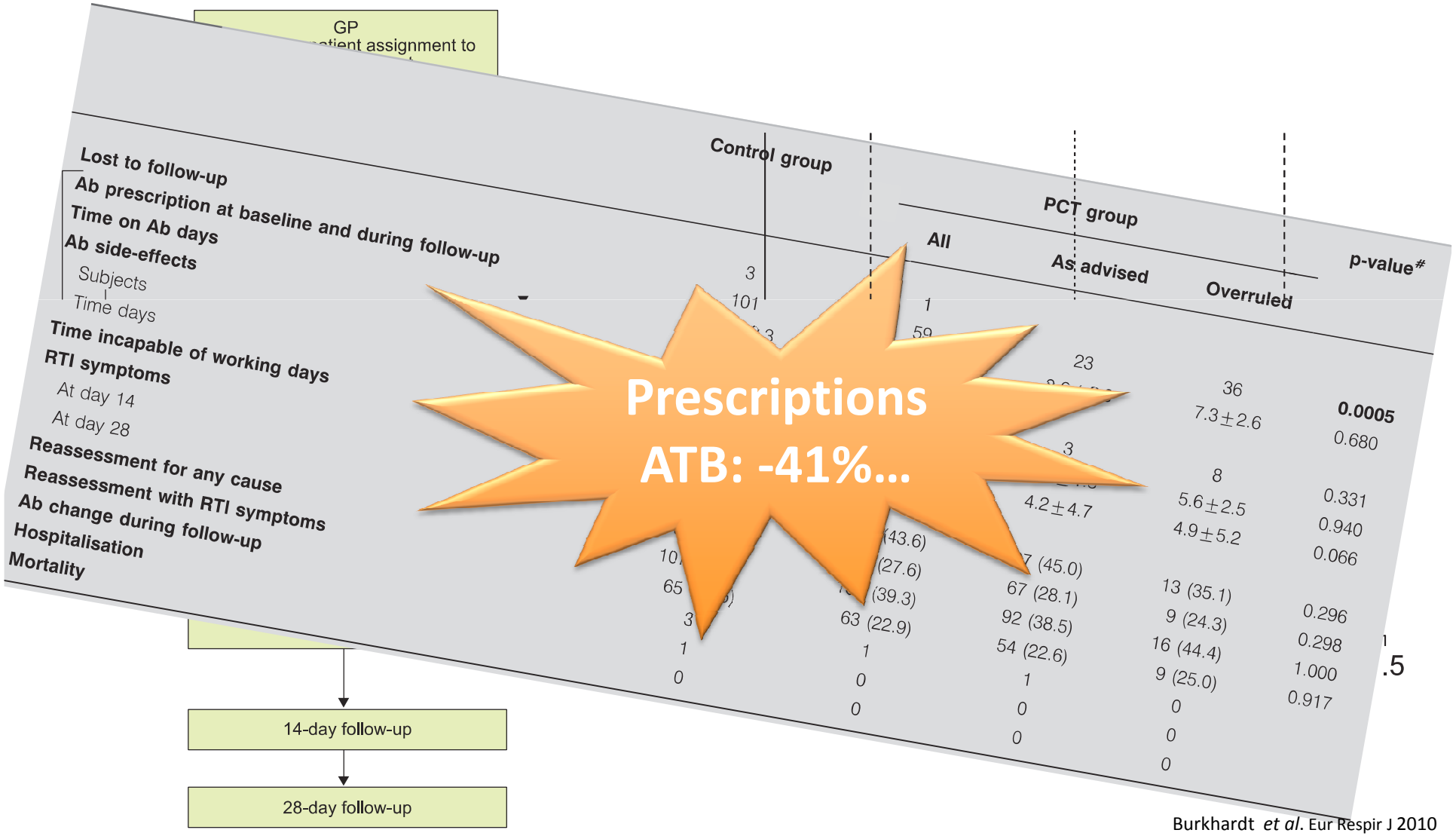
Christ-Crain M *et al*. Lancet 2004

IRB: initiation ATB
PCT-guidée aux urgences…



Christ-Crain M *et al*. Lancet 2004

IRB: initiation ATB
PCT-guidée en <u>méd. G^{ale}</u>…

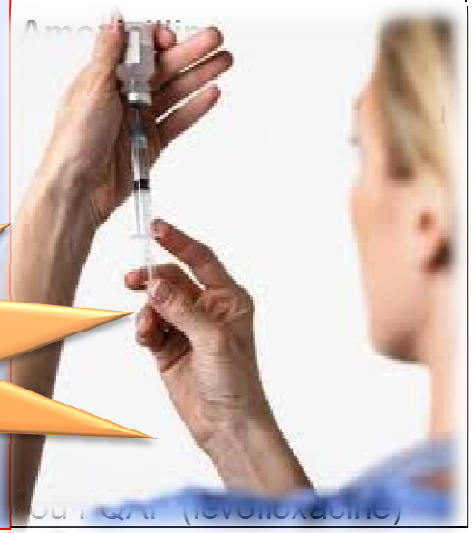


Burkhardt *et al.* Eur Respir J 2010

Exacerbation **BPCO**: **ATB?**

Tableau 9 *: Exacerbations de BPCO : Indications et choix de l'antibiothérapie*

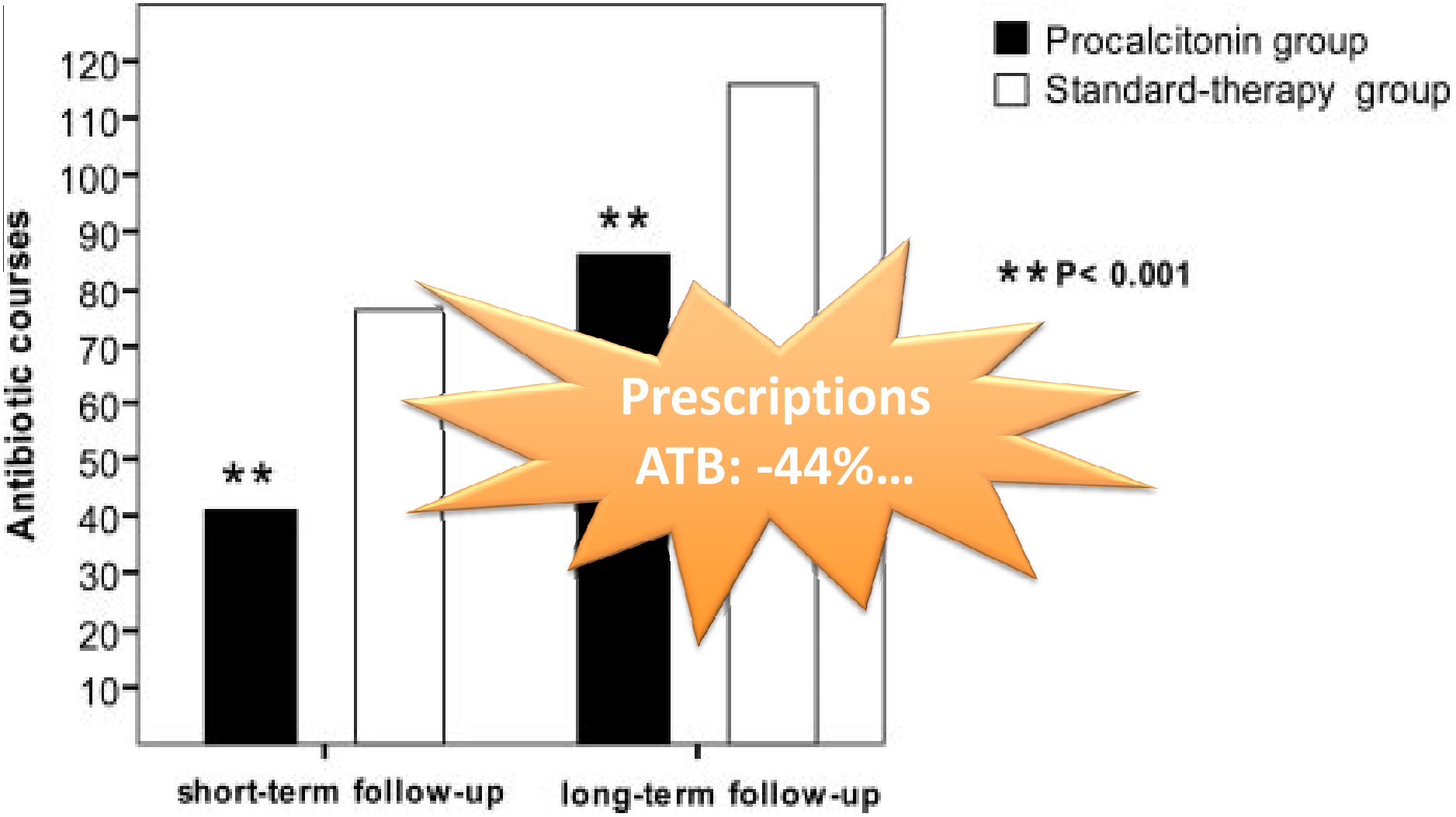
Stade clinique de gravité de la BPCO évalué en dehors de toute exacerbation		**Indications à l'antibiothérapie**	**Choix de l'antibiothérapie**
<u>En absence d'EFR connus</u>	<u>Résultats EFR connus</u>		
Absence de dyspnée	VEMS > 50%	Pas d'antibiotique	



Étude rétrospectives

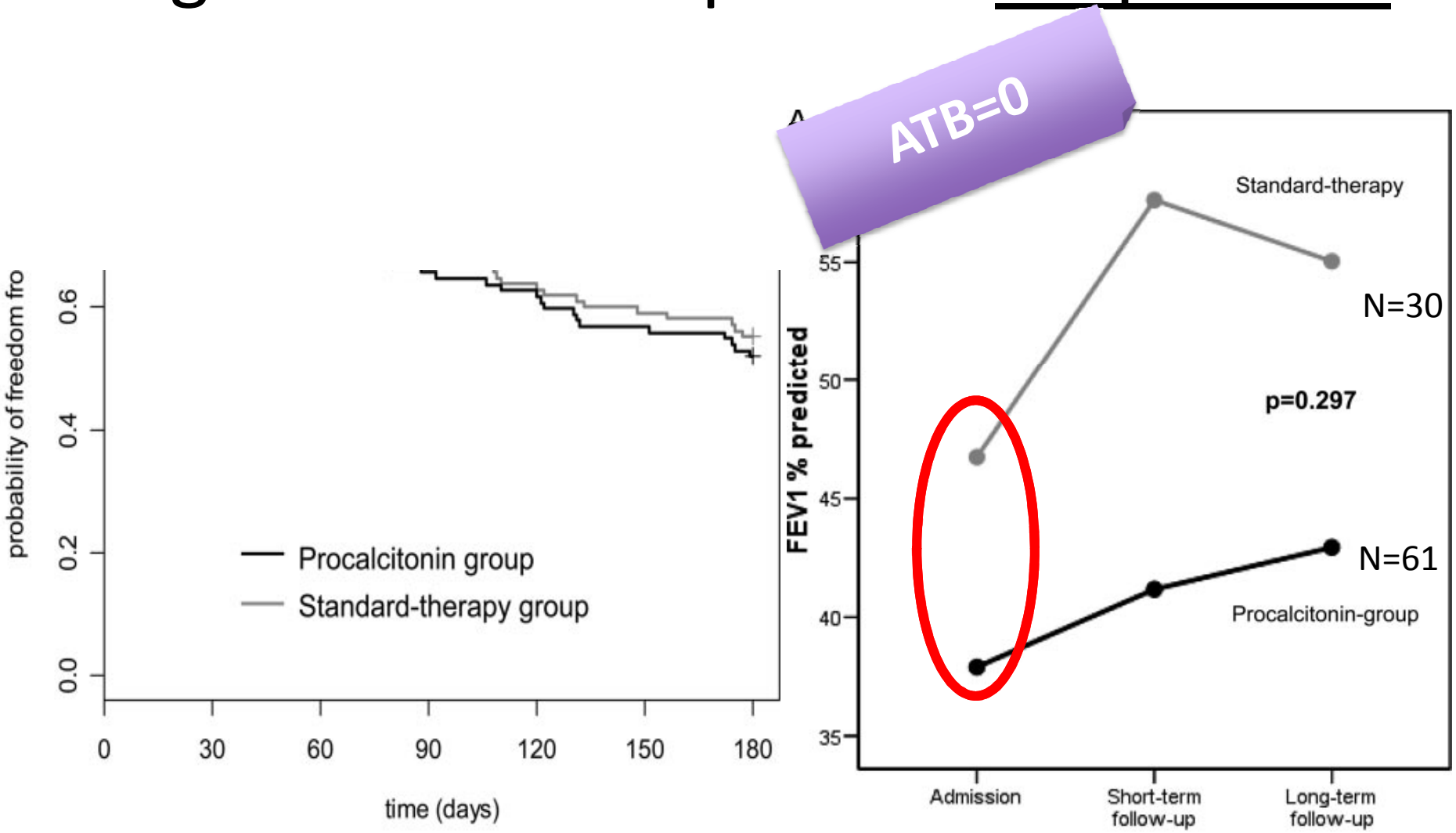
Mise au point 2010

IRB (EABPCO): initiation ATB PCT-guidée chez les patients <u>hospitalisés</u>…



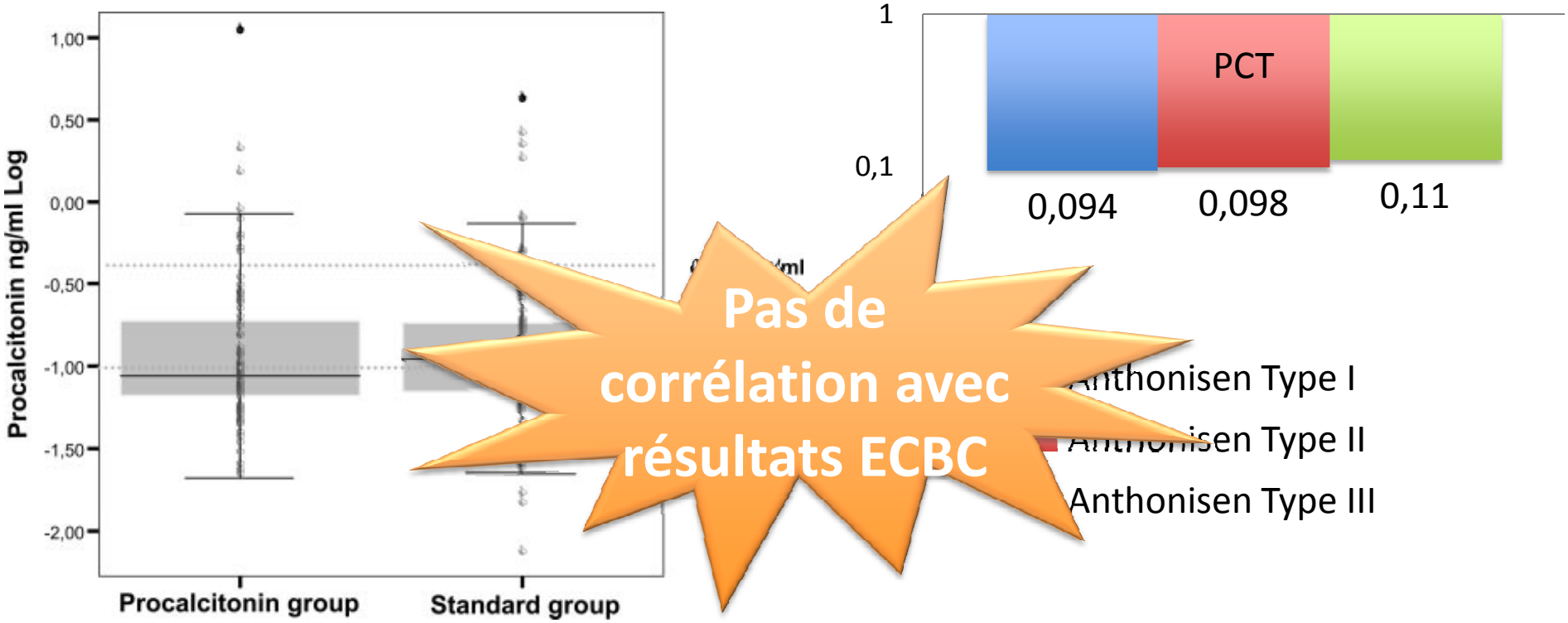
Stolz *et al*. Chest 2007

IRB (EABPCO): initiation ATB
PCT-guidée chez les patients <u>hospitalisés</u>…



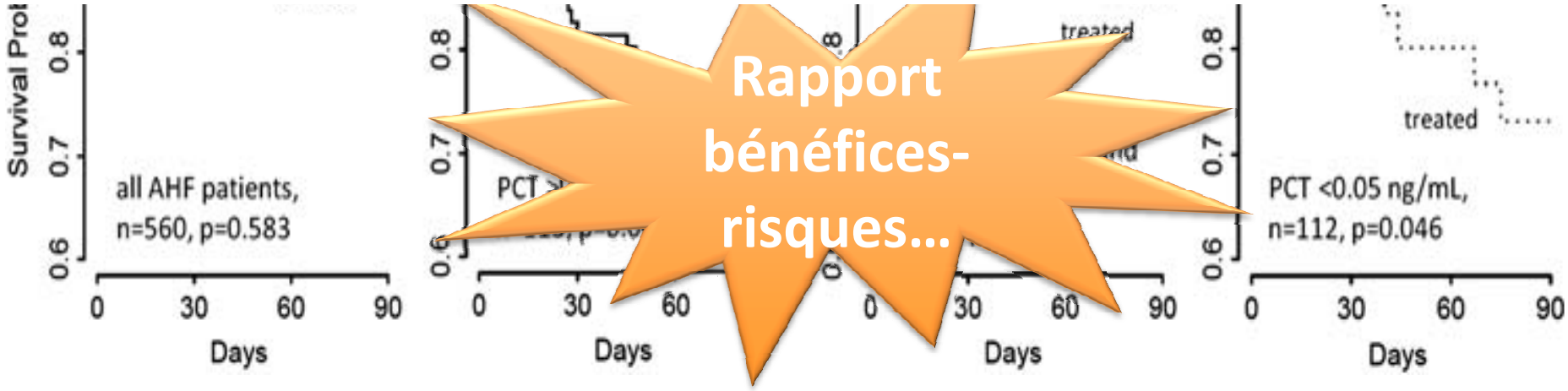
Stolz *et al*. Chest 2007

IRB (EABPCO): initiation ATB PCT-guidée chez les patients <u>hospitalisés</u>…



Stolz *et al*. Chest 2007

Impact **ATB** chez patients hospitalisés pour dyspnée Ä selon **PCT**



Urgences

Maisel *et al*. Eur J Heart Fail 2012

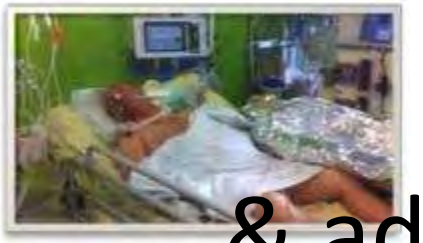
Initiation **ATB** & **PCT**: **conclusions**

- Détection **précoce** sepsis bactérien (Se)
- Valeurs **seuil**:
  - Basses (médecine G & urgences)
  - Détection **retentissement systémique**
  - Associé à une étiologie **bactérienne**
- **IRB**:
  - Approche **pragmatique** et **individuelle**
  - Inocuité démarche
  - **Réduction exposition aux ATB (**études d'impact)

Procalcitonine: une aide à la juste prescription des antibiotiques?

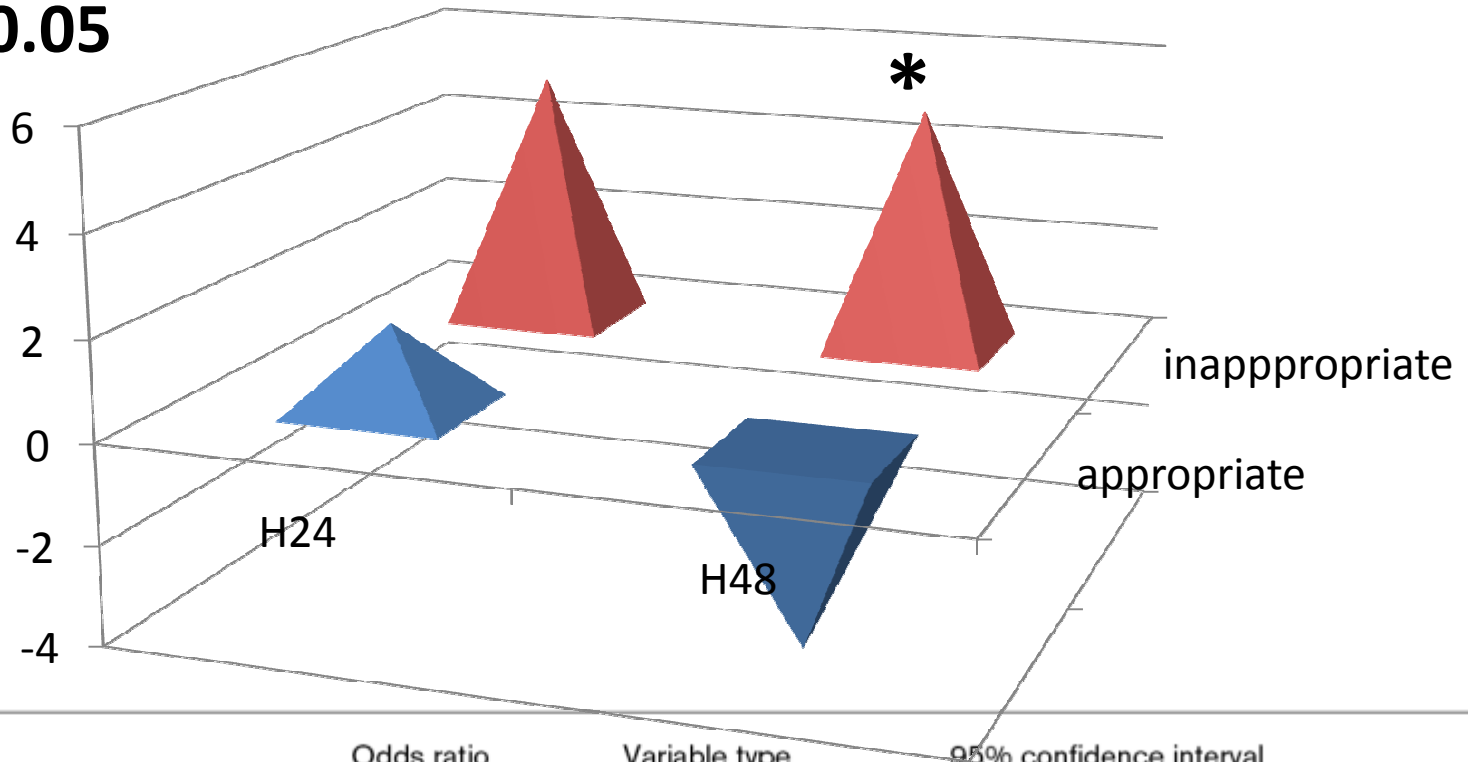
ATB SEULEMENT LE TEMPS NÉCESSAIRE


afssaps
7-14 jou
7-14 jours
Pénicillines A
Pénicillines M
Céphalosporines de troisième génération
Bêta-lactamines anti-Pseudomonas
Macrolides
Synergistine
Kétolide
Fluoroquinolone anti-pneumococcique
Oxazolidinone
Glycopeptides
Rifamycine
Lincosamides
Aminosides
Pneumonies Aiguës Communautaires
Amoxicilline PO/IV : 1 g x 3/j
Amoxicilline/acide clavulanique PO (rapport 8/1) /
(dose exprimée en amoxicilline)
Oxacilline ou cloxacilline IV : 8 à 12 g/j en 4 à 6
administrations par jour.
Ceftriaxone IV/IM/SC : 1 à 2 g x 1 /j
Céfotaxime IV : 1 à 2 g x 3 /j
Pipéracilline/tazobactam IV : 4 g / 500 mg x 3/j
Céfépime IV : 2 g x 2/j
Imipénème/cilastatine IV : 1 g / 1 g x 3/j
Méropénème IV : 1 à 2 g / 8 h
Doripénème IV : 500 mg / 8 h
Erythromycine IV : 1 g x 3 à 4 / jour ; PO : 1 g x 3/j
Clarithromycine PO (standard) : 500 mg x 2/j
Josamycine PO : 1 g x 2/j
Roxithromycine PO : 150 mg x 2/j
Spiramycine• IV : 3 MUI x 3/j ; PO : 9 MUI /j en 2 ou 3 prises
Pristinamycine PO : 3 g /j en 2 ou 3 prises; à prendre au
moment des repas
Télithromycine PO : 800 mg x 1/j
Lévofloxacine PO/IV : 500 mg x 1 à 2/j
Moxifloxacine PO/IV : 400 mg x 1/j
Linézolide PO/IV : 600 mg / 12 h
Vancomycine :
soit : 30 à 40 mg/kg/j en 2 à 4 administrations par jour.
soit : perfusion continue de 30 à 40 mg/kg/j, après
administration d'une dose de charge initiale de 15 mg/kg
Teicoplanine IV : 6 à 12 mg/kg/12 h pendant les 24-48
premières heures, puis 6 à 12 mg/kg/j en une injection
Rifampicine IV : 20 à 30 mg/kg/j en 2 perfusions
Clindamycine IV : 1800 à 2400 mg/j en 3 à 4 administrations
Amikacine IV, 15 à 20 mg/kg/j en dose unique journalie
pouvant être portée à 25 à 30 mg/kg/j, pour les
sévères ou pour les bactéries dont les
maximum 5 jours.
Tobramycine IV, 3 à 5 mg/kg
pouvant être portée à
sévères ou pour
maximum



Cinétique **PCT** & adéquation de l'antibiothérapie

* ***p*<0.05**

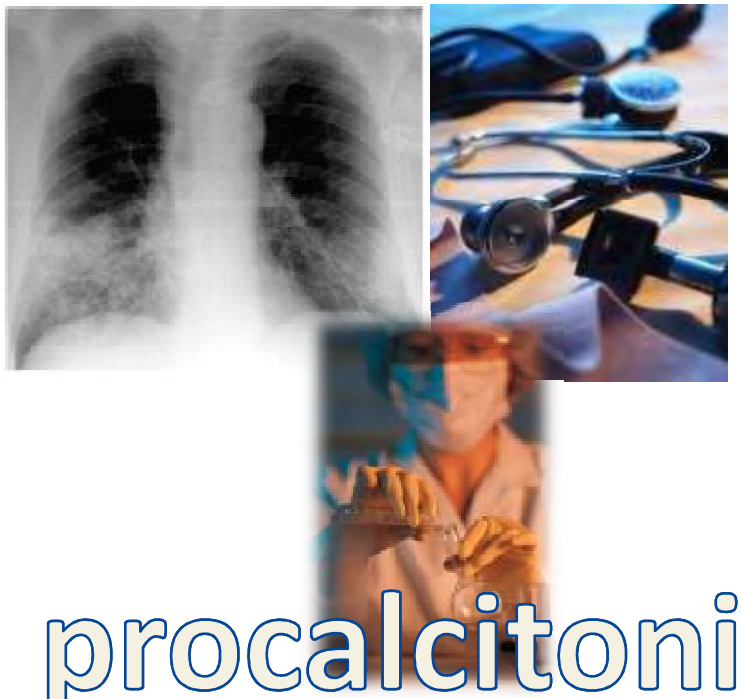


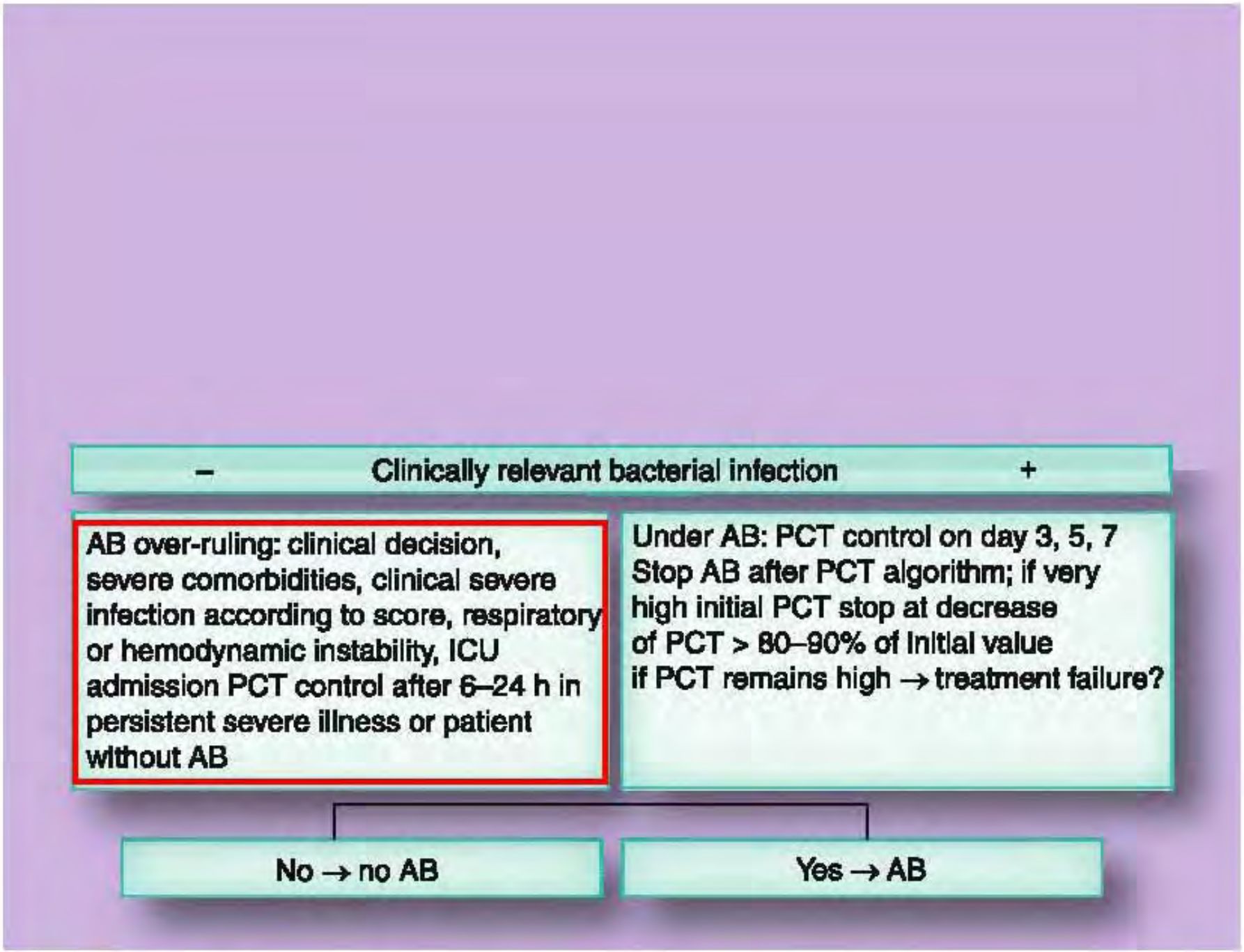
	Odds ratio	Variable type	95% confidence interval	*P* value
Gram staining (positive)	2.61	Dichotomous	1.13 to 6.03	0.02
ΔPCT D2–D3	10.29	Continuous	1.66 to 63.9	0.01

Charles *et al*. Crit Care 2009

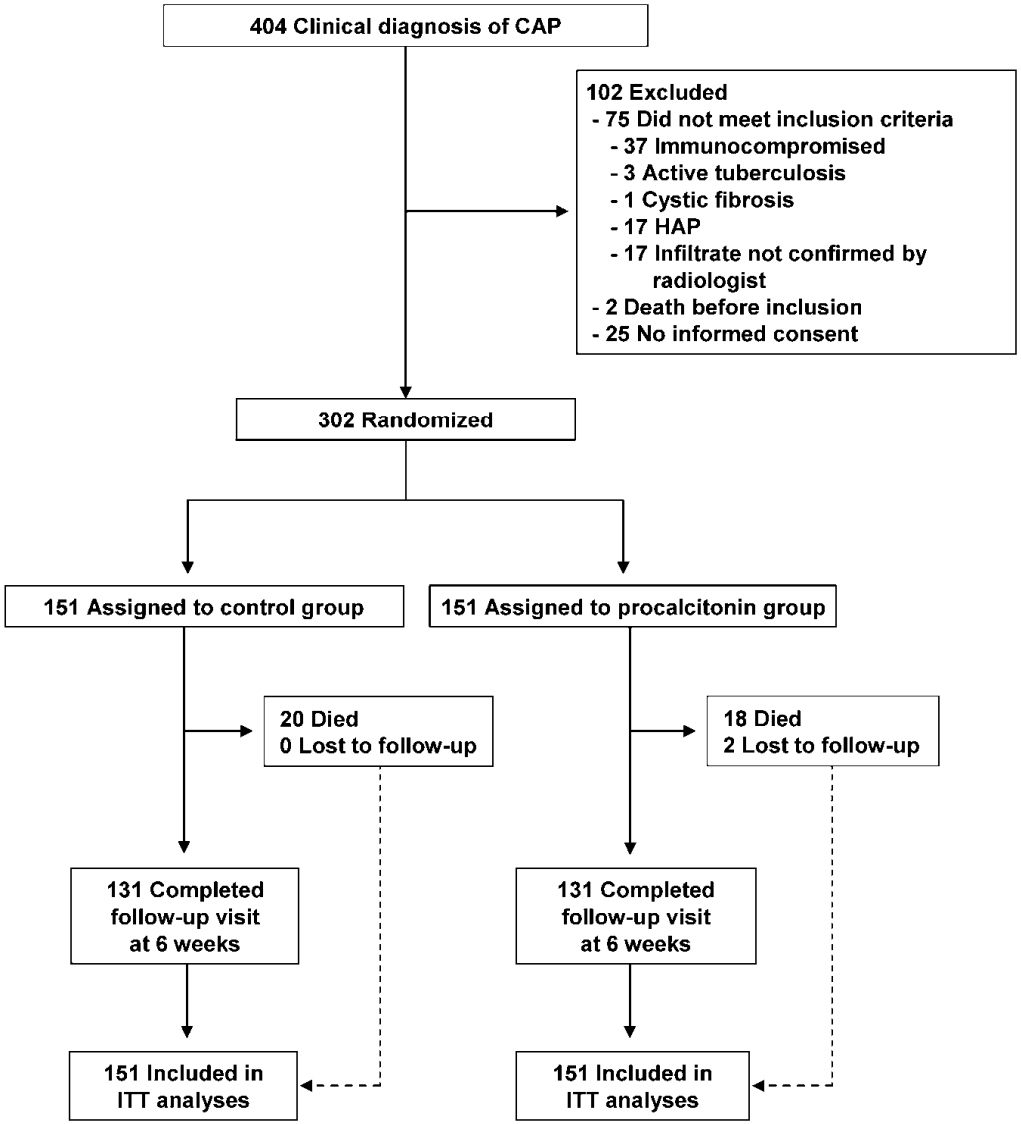
IRB (PAC): ATB PCT-guidée chez les patients hospitalisés…

vs.



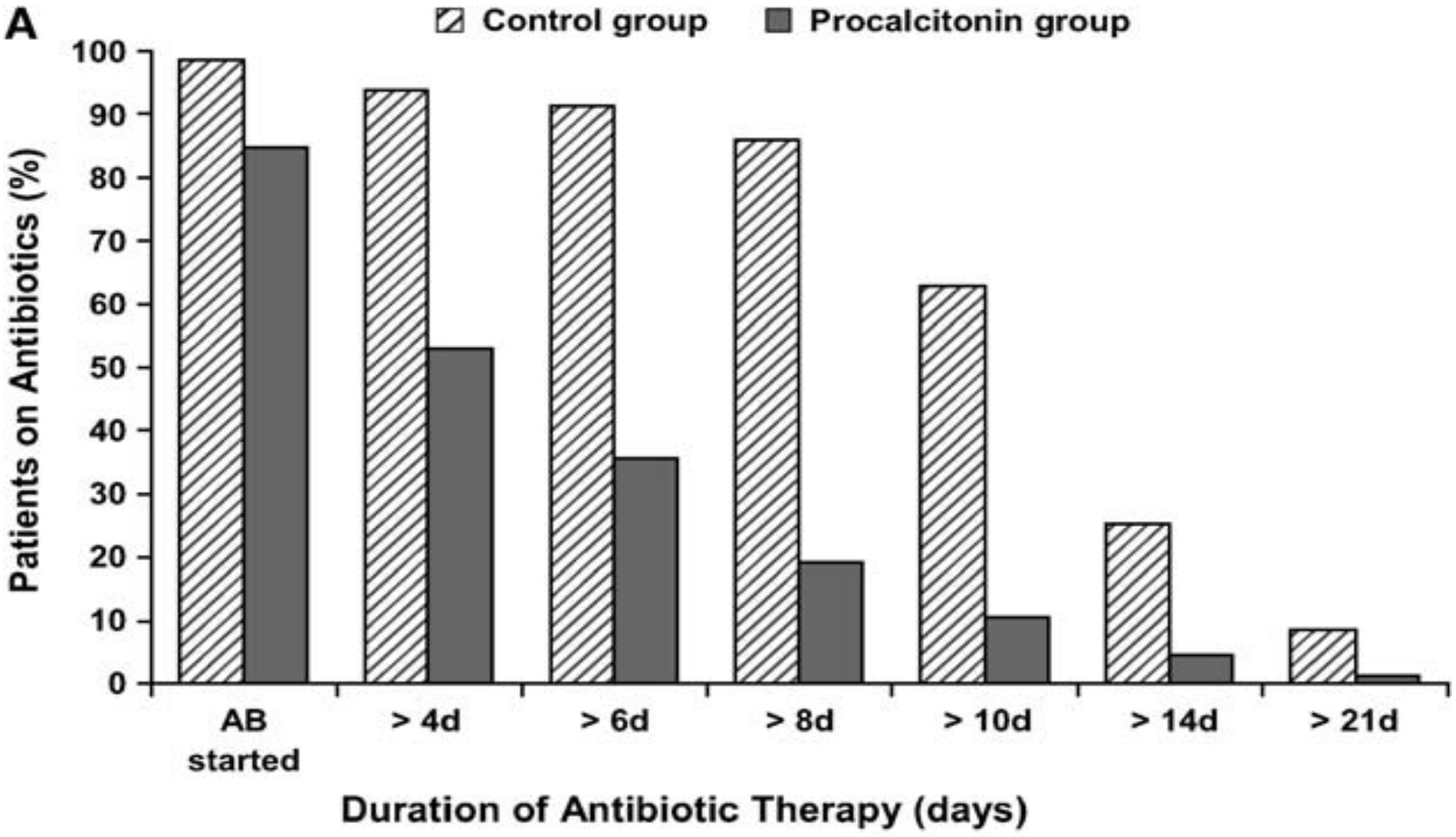

– Clinically relevant bacterial infection +
AB over-ruling: clinical decision, severe comorbidities, clinical severe infection according to score, respiratory or hemodynamic instability, ICU admission PCT control after 6–24 h in persistent severe illness or patient without AB
Under AB: PCT control on day 3, 5, 7
Stop AB after PCT algorithm; if very high initial PCT stop at decrease of PCT > 80–90% of Initial value
if PCT remains high → treatment failure?
No → no AB
Yes → AB

IRB (PAC): ATB PCT-guidée chez les patients hospitalisés…

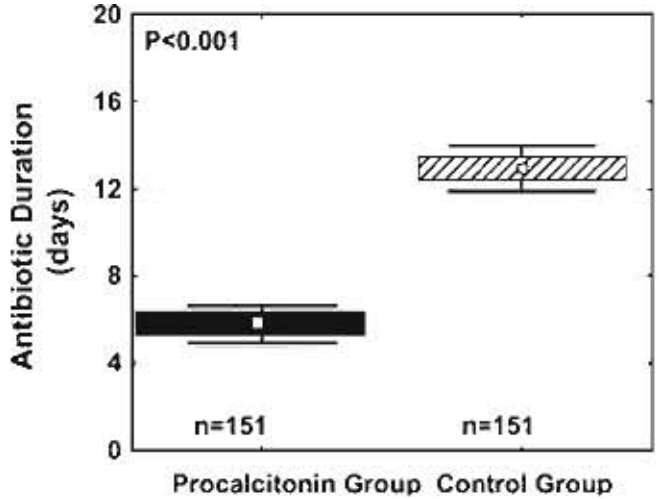


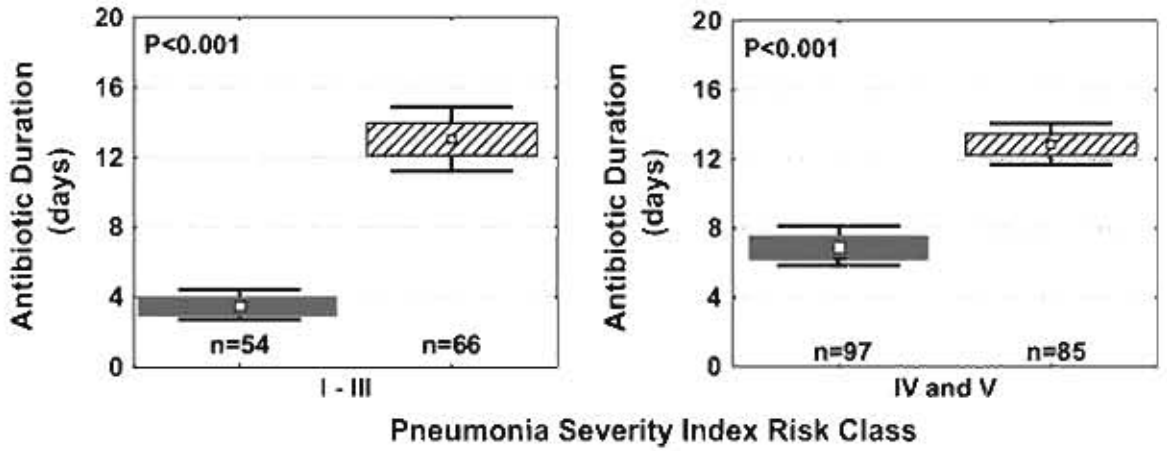
Christ-Crain *et al*. Am J Resir Crit Care Med 2006

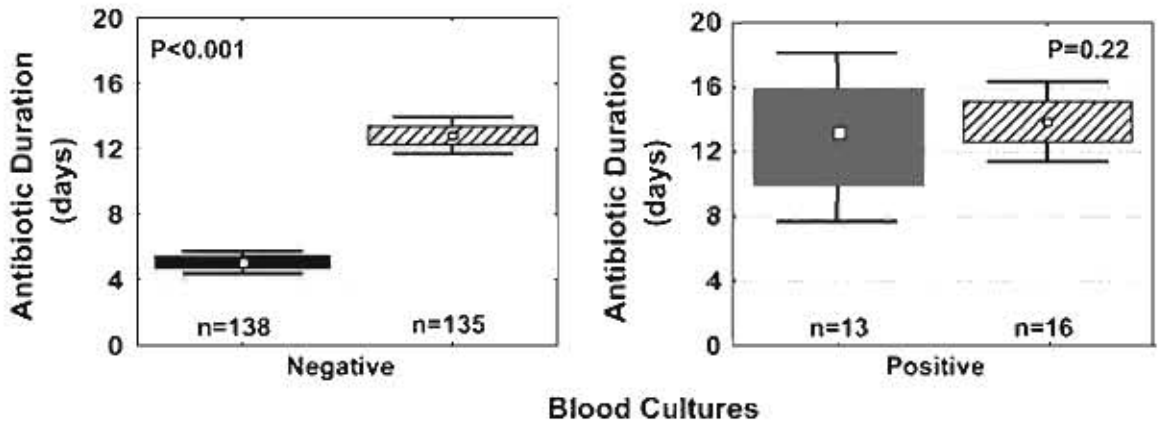
IRB (PAC): ATB PCT-guidée chez les patients hospitalisés…



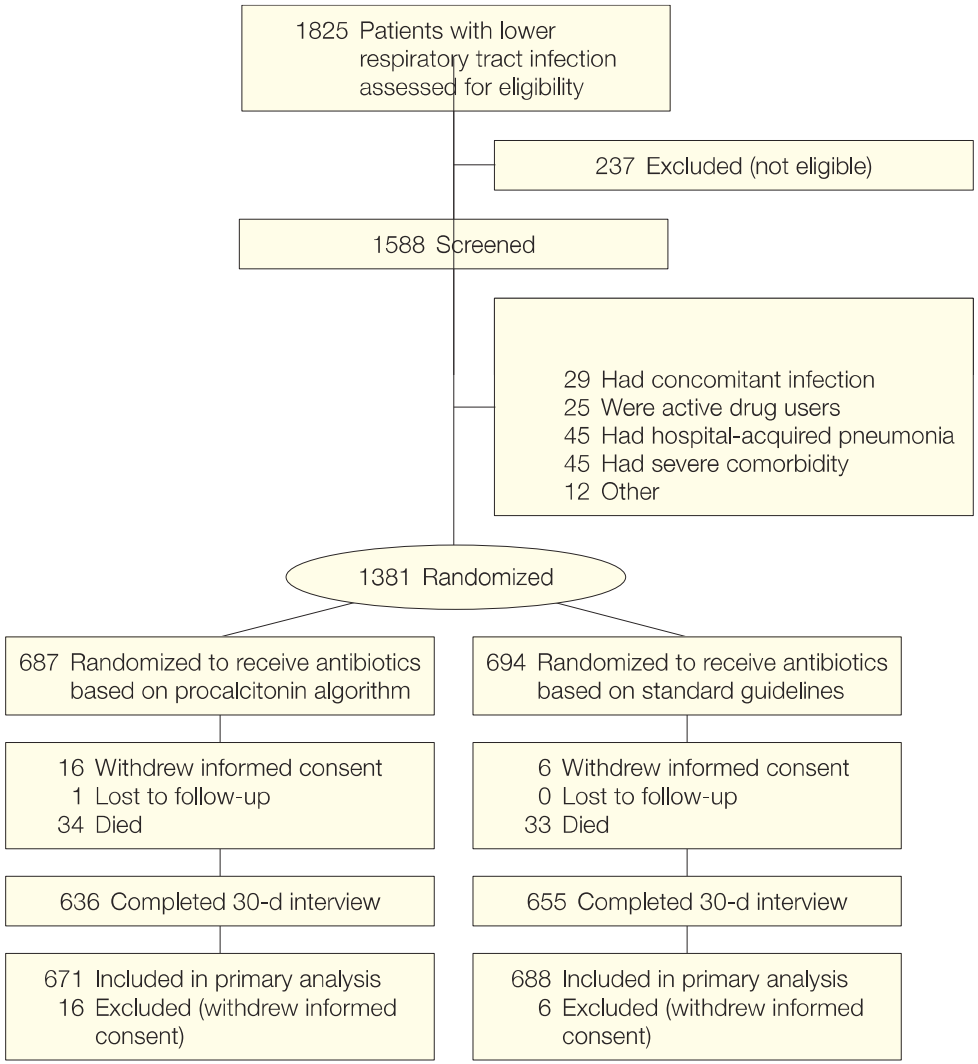
Christ-Crain *et al*. Am J Resir Crit Care Med 2006


P<0.001
Antibiotic Duration (days)
20
16
12
8
4
0
n=151
n=151
Procalcitonin Group
Control Group

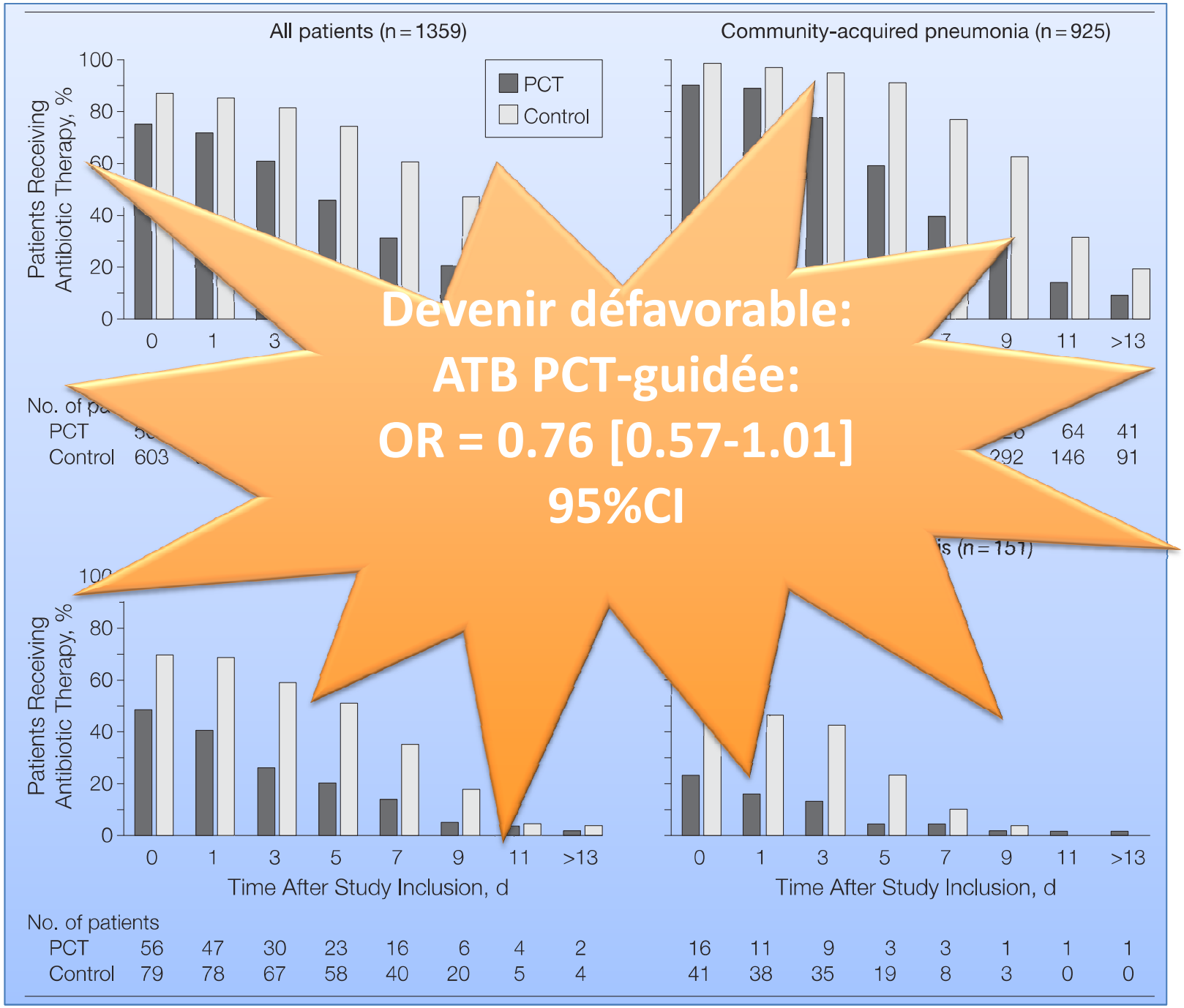

P<0.001
Antibiotic Duration (days)
n=54
n=66
I - III
P<0.001
Antibiotic Duration (days)
n=97
n=85
IV and V
Pneumonia Severity Index Risk Class


P<0.001
Antibiotic Duration (days)
n=138
n=135
Negative
P=0.22
Antibiotic Duration (days)
n=13
n=16
Positive
Blood Cultures

IRB (PAC): ATB PCT-guidée chez les patients hospitalisés…

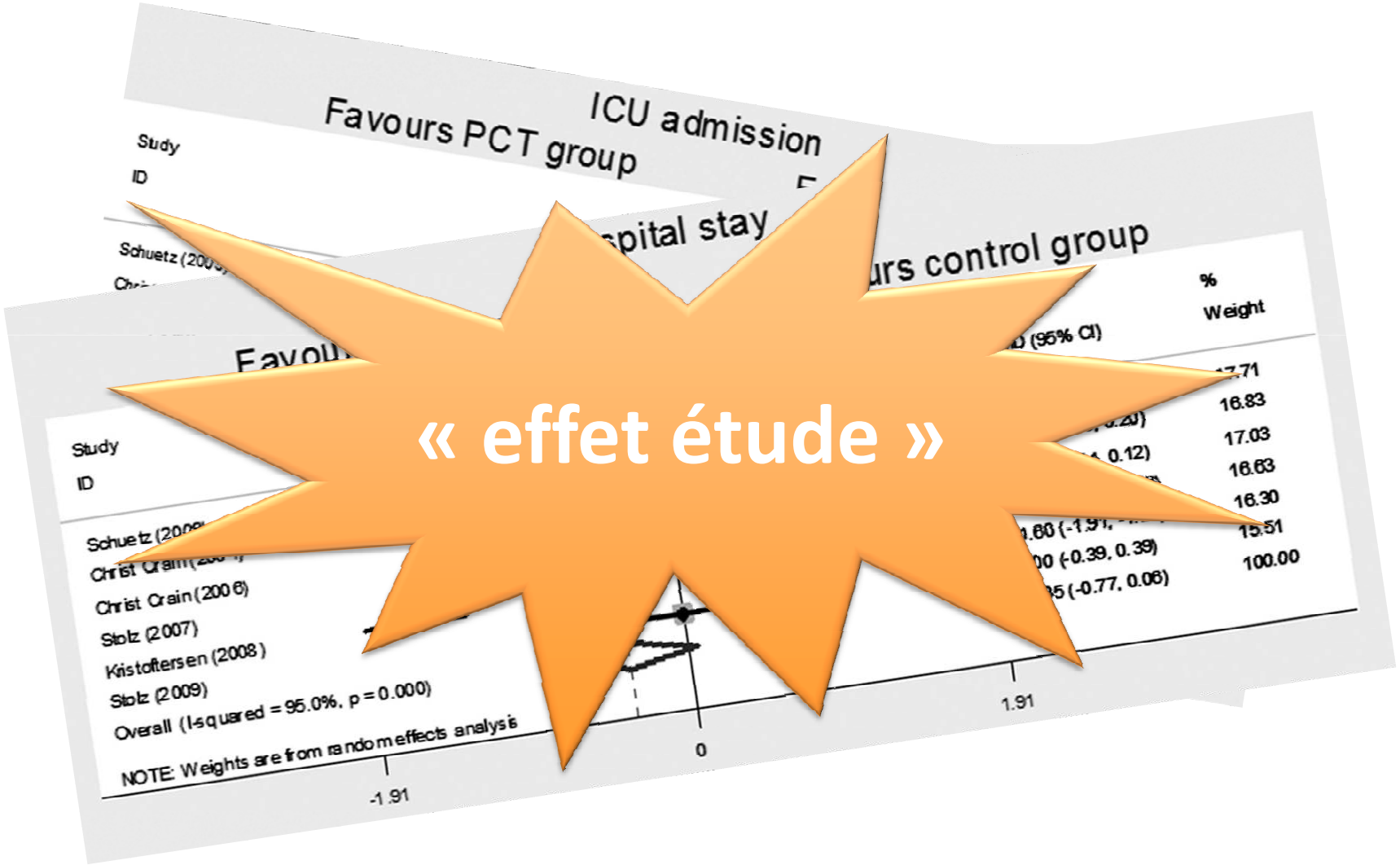


Schuetz *et al*. JAMA 2009



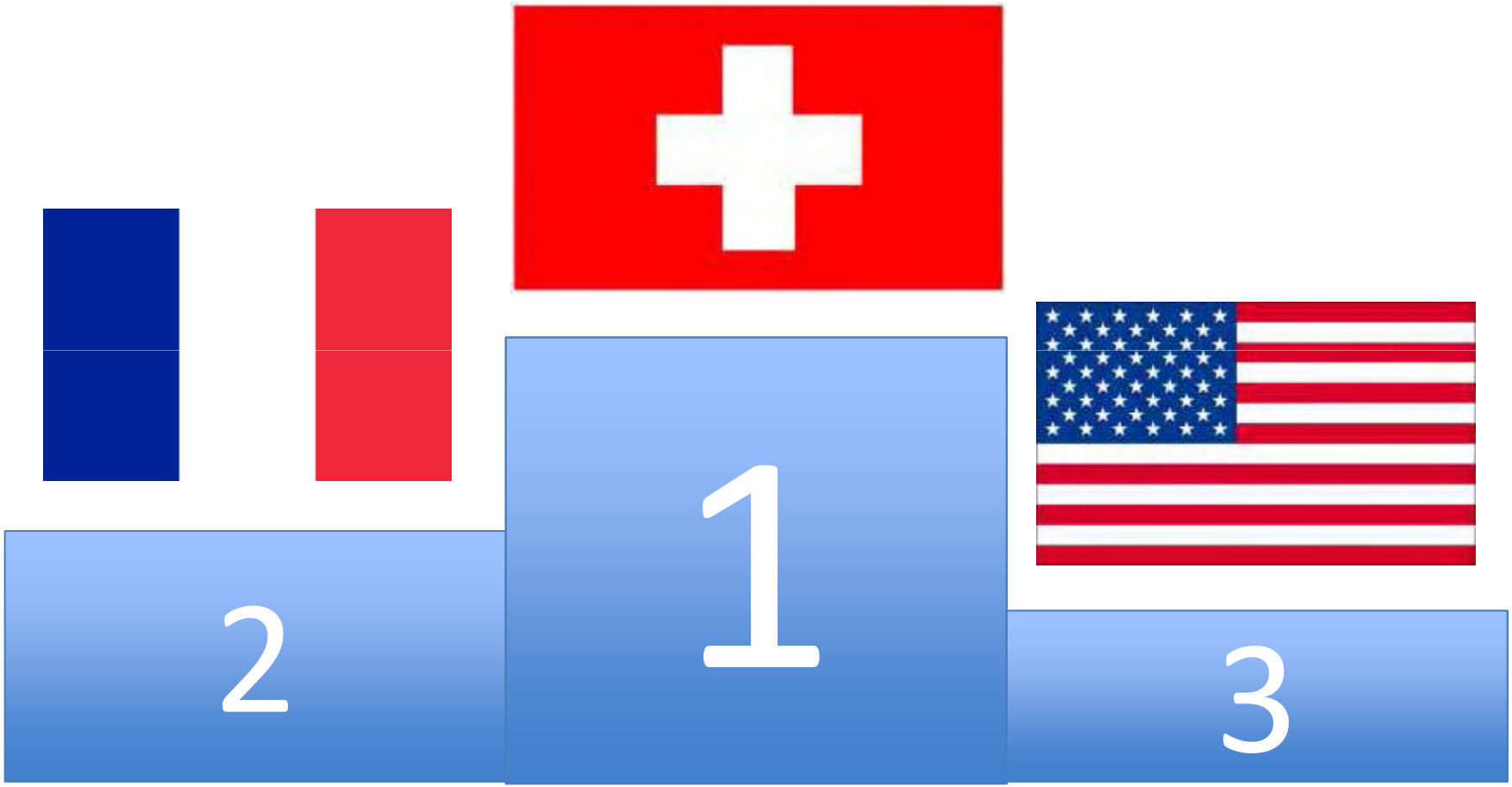
Schuetz *et al*. JAMA 2009

ATB PCT-guidée (IRB): **méta-analyse**



Li *et al* Antimicrobiol Agent Chemother 2011

ATB PCT-guidée (IRB):
dans la « vraie vie »…

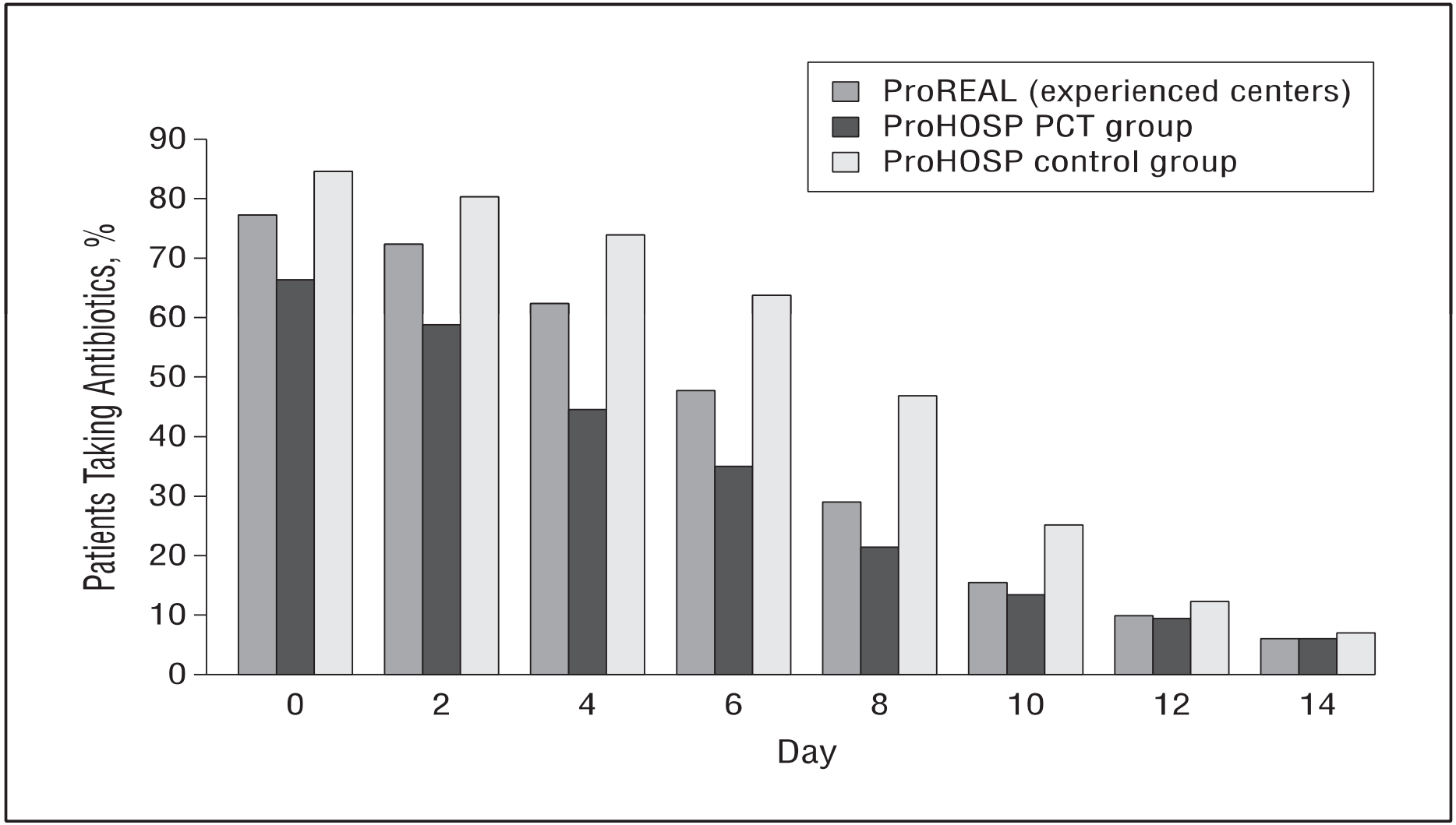


3 centres	10 centres	1 centre
(dont 0 « ProHosp »)	(dont 3 « ProHosp »)	(dont 0 « ProHosp »)

Albrich *et al* Arch Intern Med 2012

ATB PCT-guidée (IRB): **EFFICACITÉ**

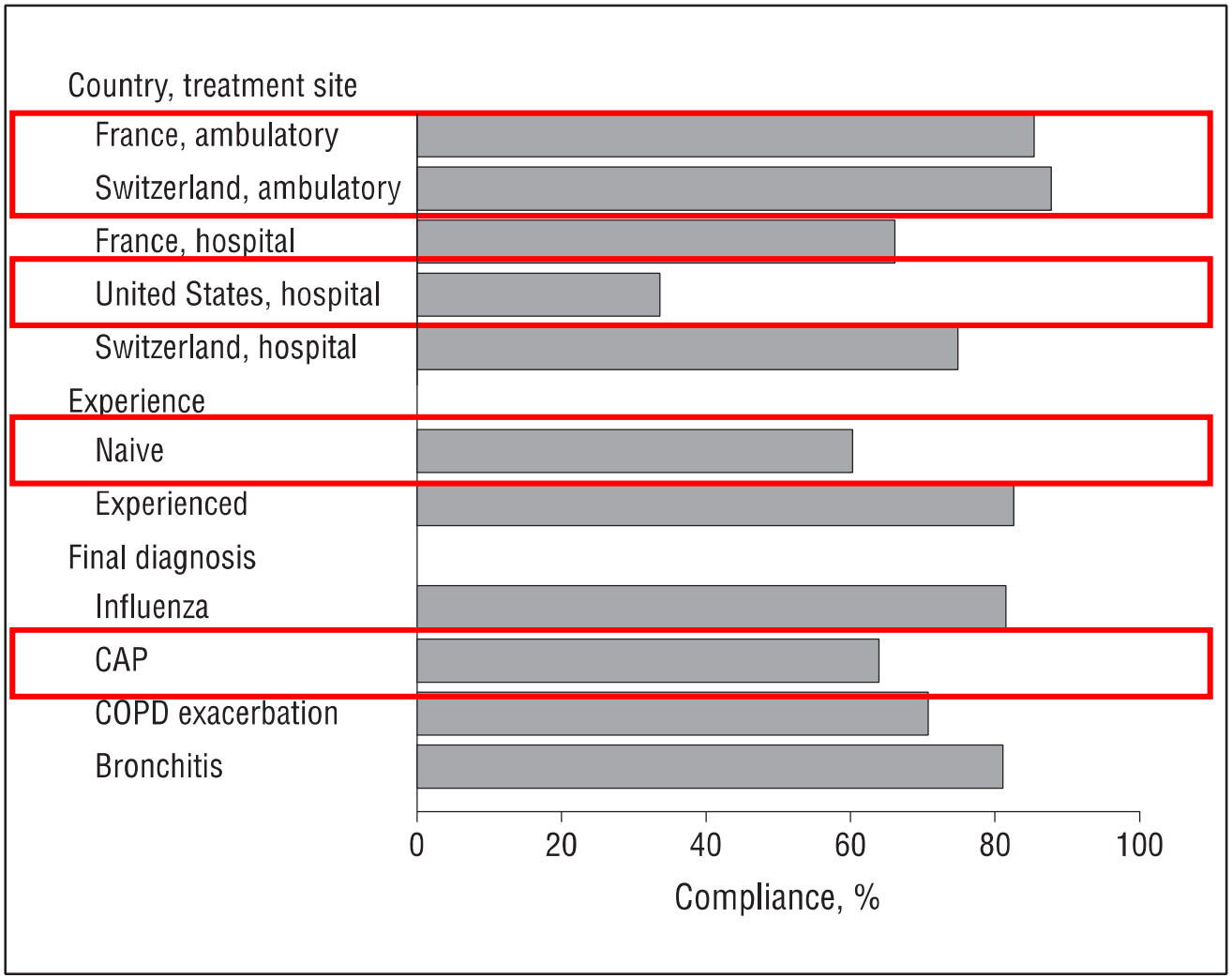
dans la « vraie vie »…



Albrich *et al* Arch Intern Med 2012

ATB PCT-guidée (IRB): **COMPLIANCE**

dans la « vraie vie »…



Albrich *et al* Arch Intern Med 2012

ATB PCT-guidée (IRB): **SURETÉ**

dans la « vraie vie »…

Mechanical ventilation	1.701 (0.372 to 7.786)	.49
Empyema	0.812 (0.040 to 16.457)	.89
30-d Mortality	1.044 (0.330 to 3.301)	.94
Recurrences	0.655 (0.246 to 1.748)	.40
Rehospitalization	0.045 (<0.001 to >0.999)	.98
Any 30-d complication[c]	0.830 (0.444 to 1.550)	.56
Antibiotic adverse effects[d]	0.232 (0.059 to 0.908)	.04

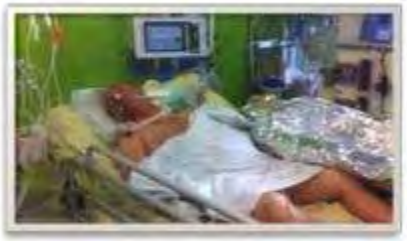
initiation

interruption

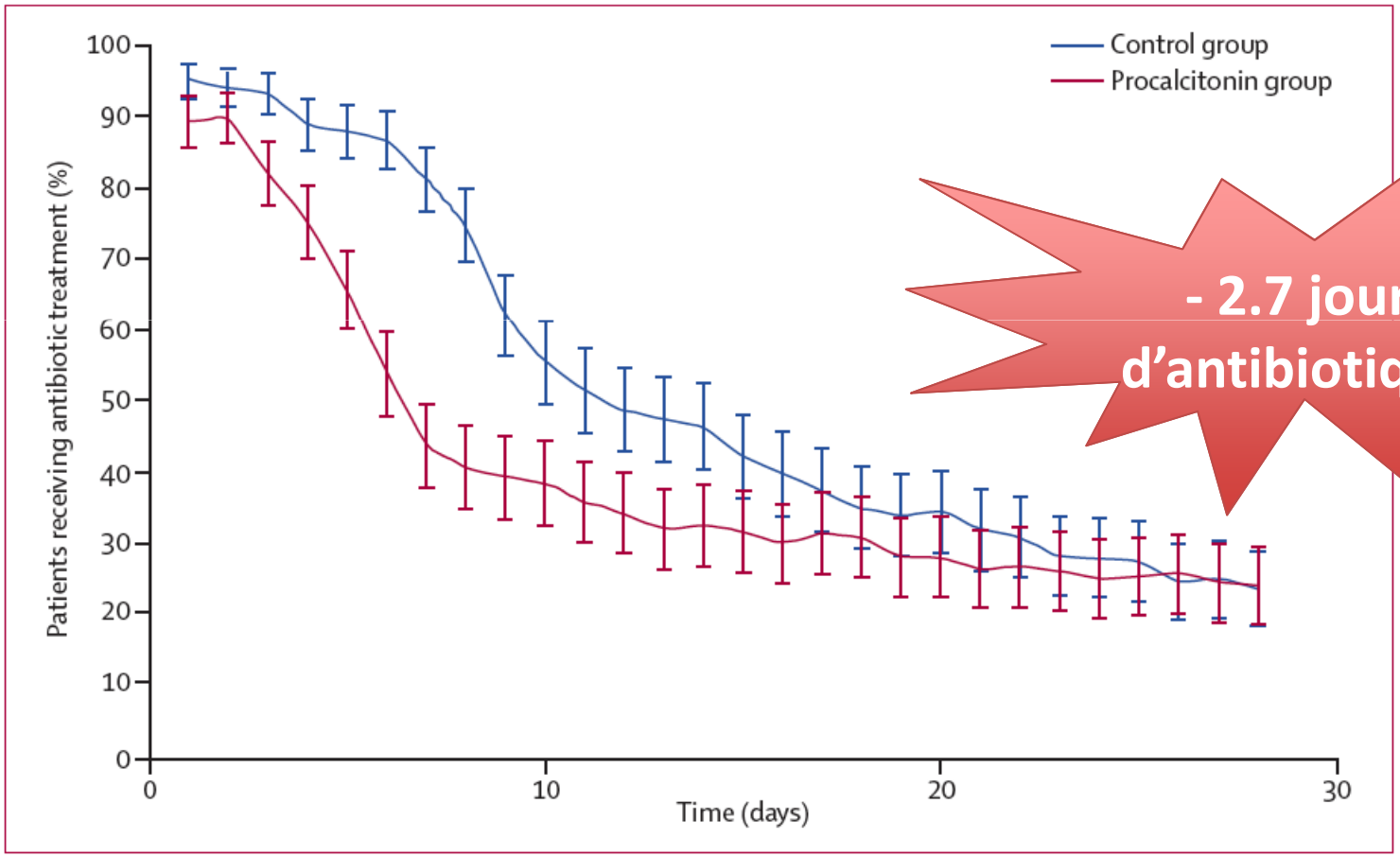
Table 4. Safety of Early Discontinuation of Antibiotic Therapy According to PCT Value After a Decrease in the PCT Value

Variable	Adjusted OR (95% CI)[a]	*P* Value
In-hospital complications[b]	1.095 (0.609 to 1.969)	.76
In-hospital mortality	1.498 (0.360 to 6.226)	.58
ICU admission	0.002 (<0.001 to >0.999)	.81
Mechanical ventilation	0.192 (<0.001 to >0.999)	.99
Empyema	<0.001 (<0.001 to >0.999)	.91
30-d mortality	0.771 (0.328 to 1.814)	.55
Recurrence	0.939 (0.483 to 1.824)	.85
Rehospitalization	0.758 (0.097 to 5.951)	.79
Any 30-d complication[c]	0.607 (0.355 to 1.038)	.07
Antibiotic adverse effects[d]	1.113 (0.560 to 2.212)	.76

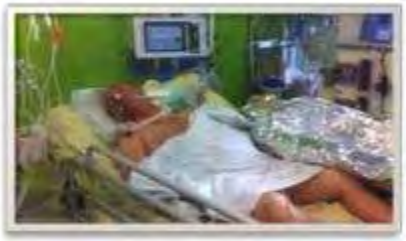
Albrich *et al* Arch Intern Med 2012



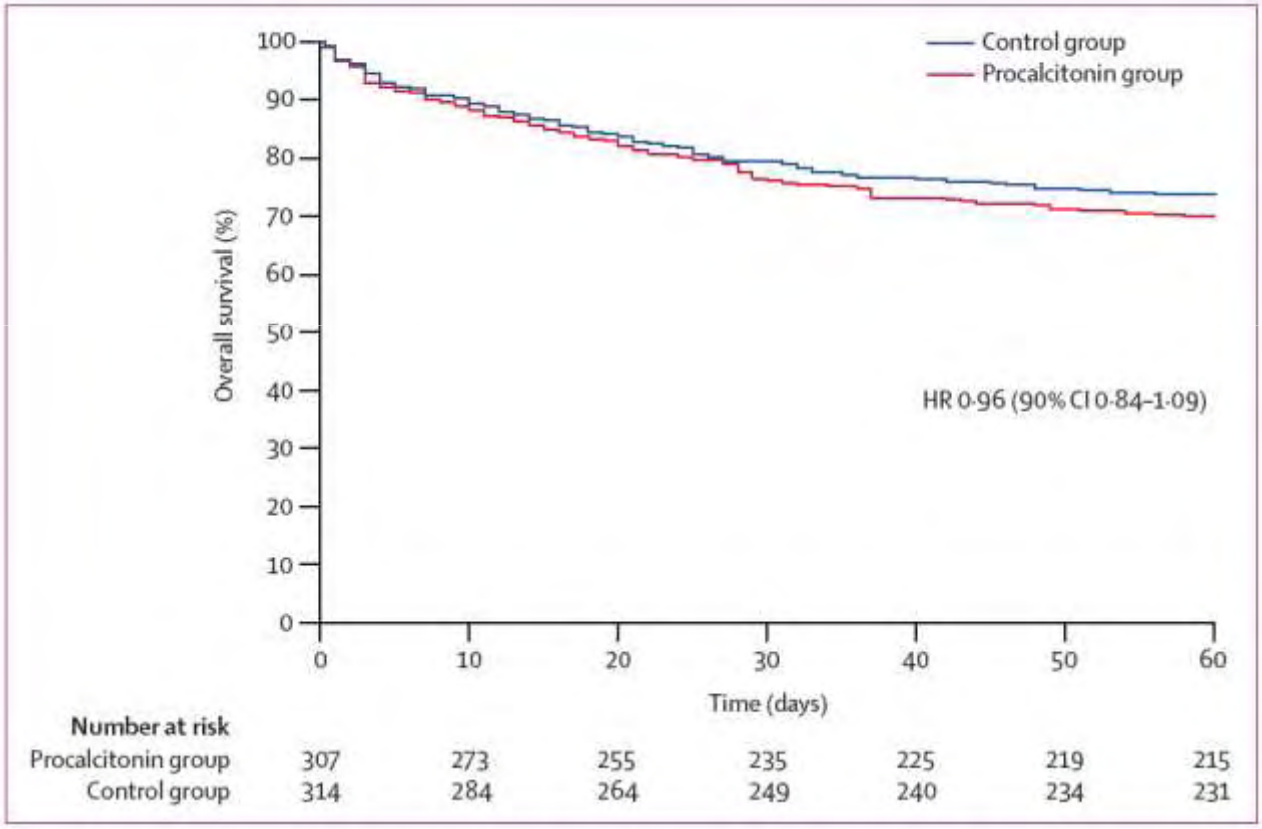
L'étude **PRORATA**
résultats



Bouadma *et al*. Lancet 2010



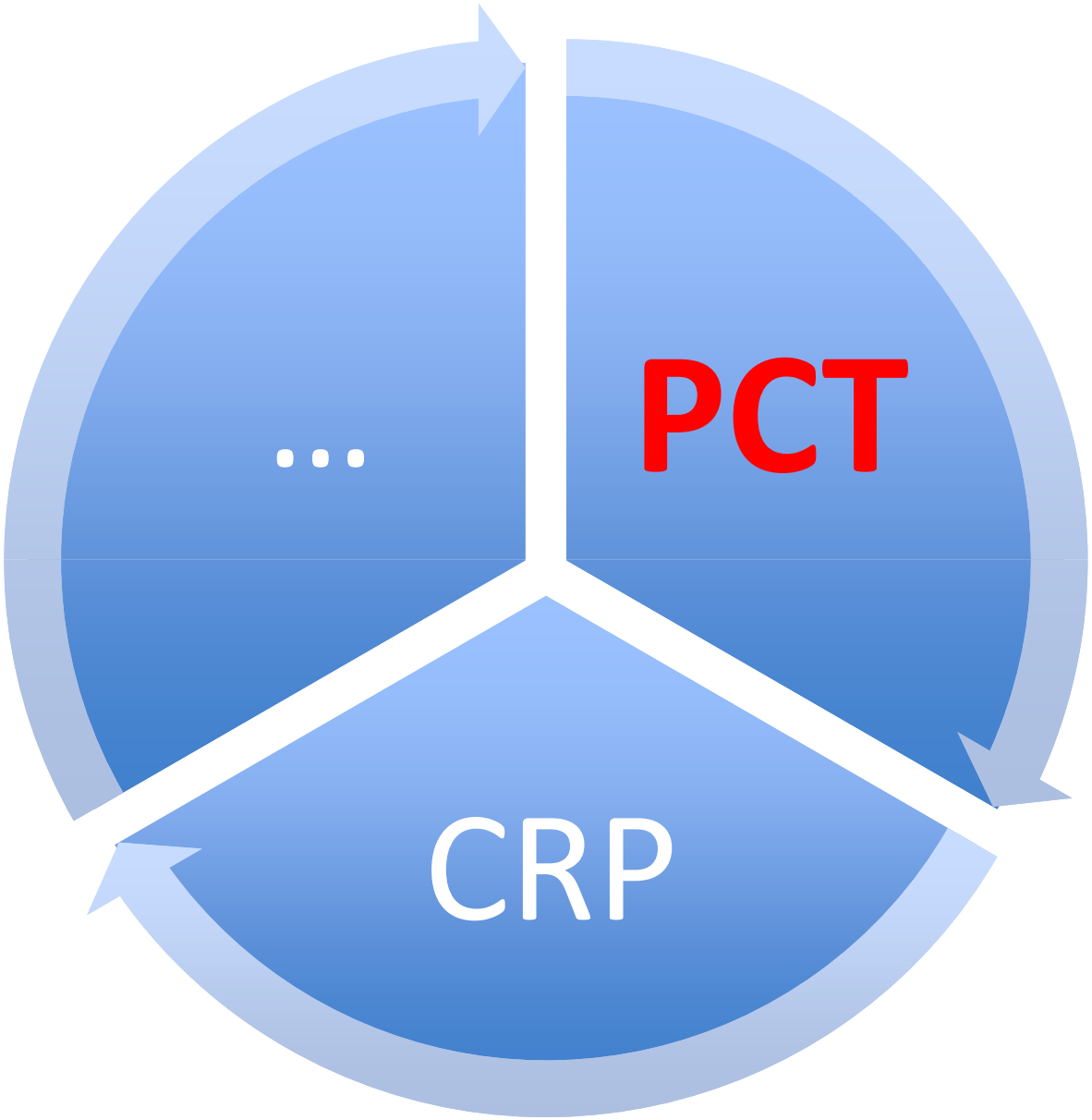
L'étude **PRORATA**
devenir des patients



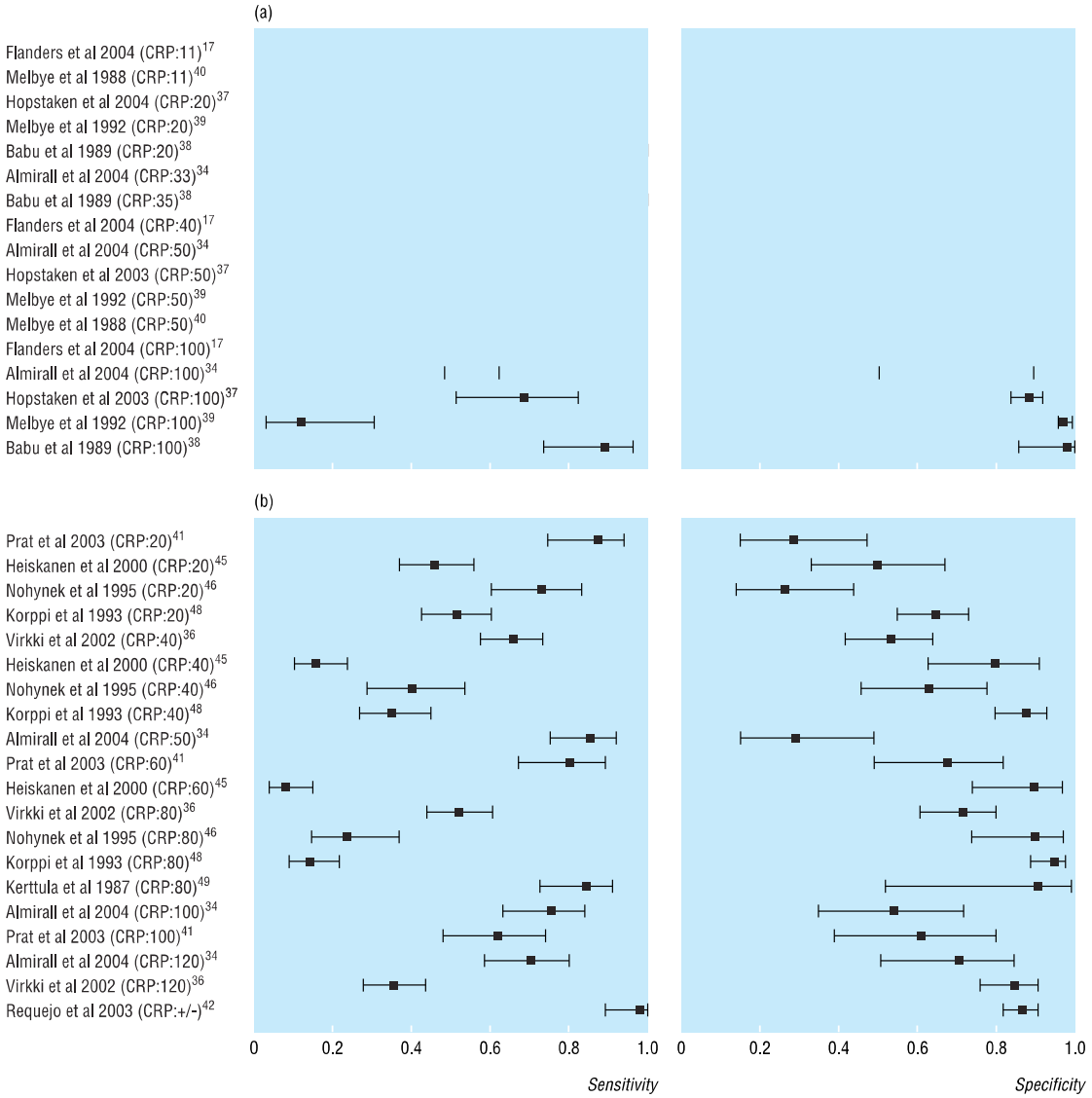
Bouadma *et al*. Lancet 2010

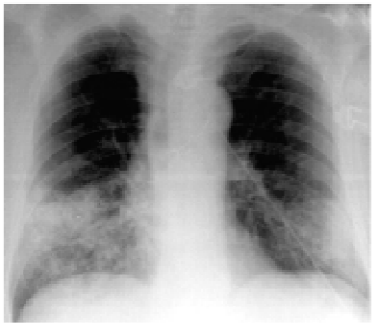
Durée **ATB** & **PCT**: **conclusions**

- Algorithme opérationnel dans les **IRB**
- Nombreuses données:
  - **RCT**
  - Nombreux patients inclus
  - Médecine générale & hospit.
- Etudes d'impact (IRB):
  - Approche **pragmatique** et **individuelle**
  - Inocuité & faisabilité
  - **Réduction exposition aux ATB**


...
PCT
CRP

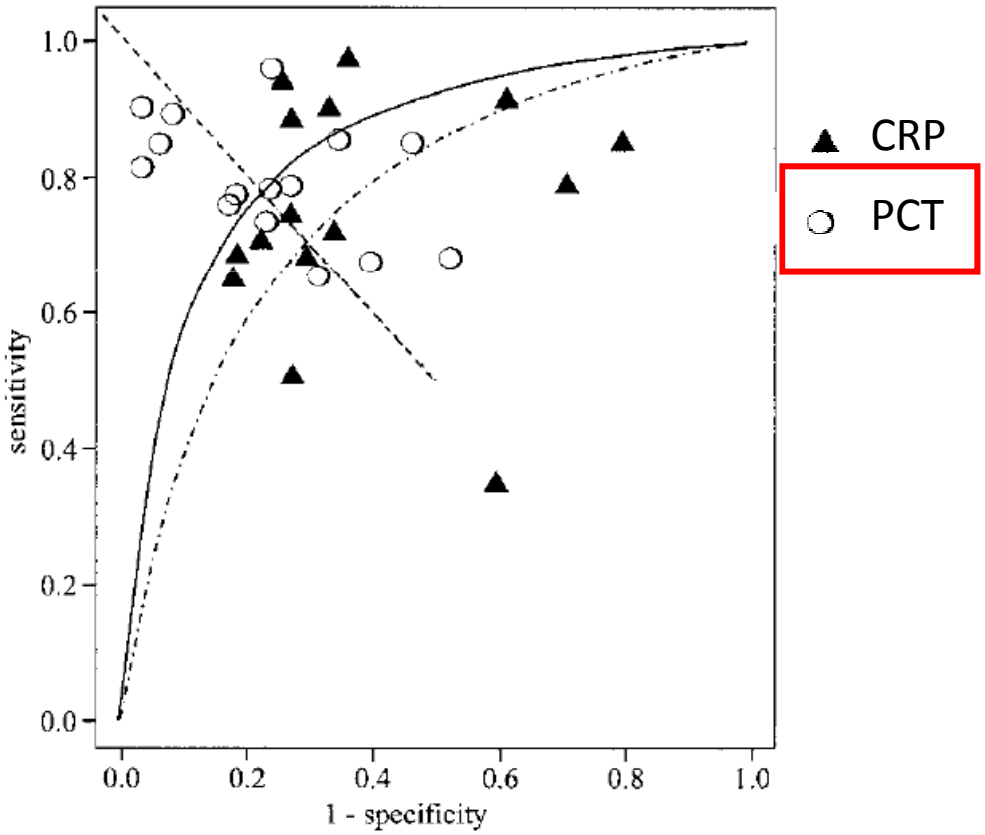
Diagnostic IRB: méta-analyse **CRP**

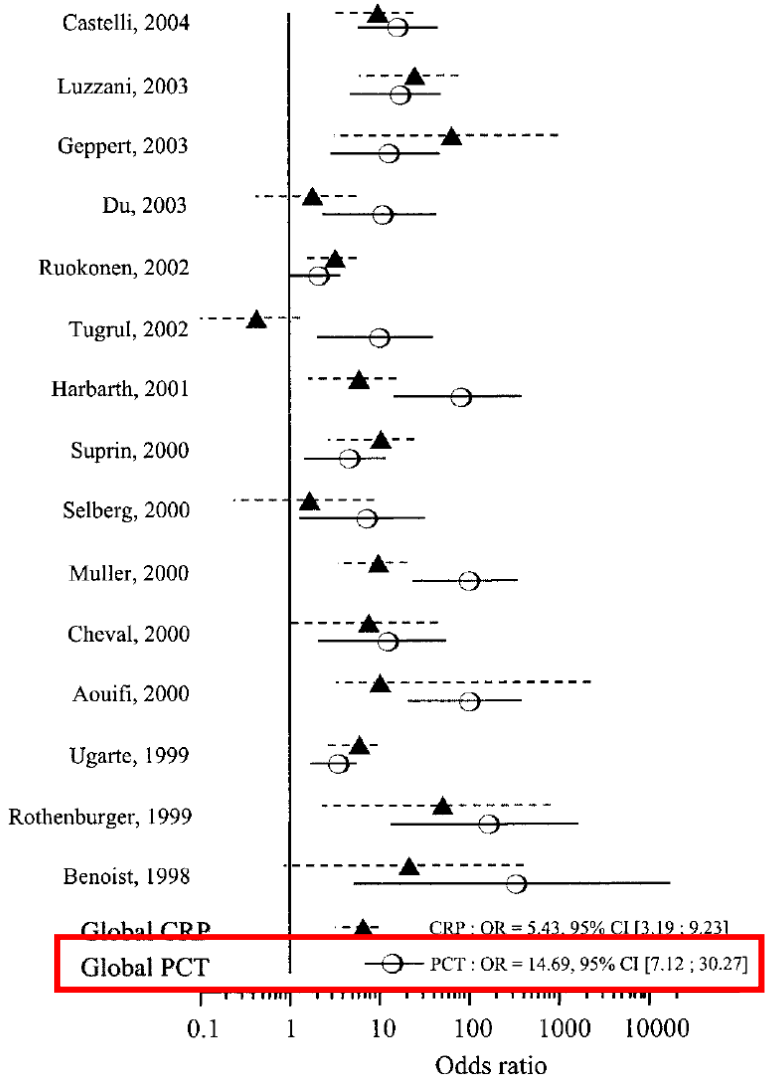




Van der Meer *et al*. Bri Med J 2005

PCT vs. **CRP** (patients hospitalisés)





Uzzan *et al*. Crit Care Med 2005

PCT vs. **CRP: Conclusions**

- Performances diagnostiques à **confirmer** (IRB)
- **Comparaison** à la PCT… variable selon population considérée
- **Cinétique** plus lente a priori
- Pas d'étude **d'impact**