Procalcitonine et infections graves: quelle utilité ?

M. Wolff

Hôpital Bichat-Claude Bernard,

EA 3964

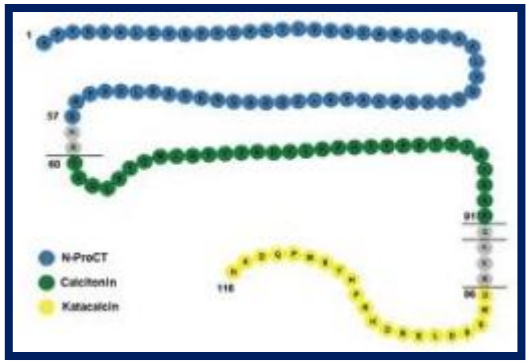
JNI, Tours, 2012

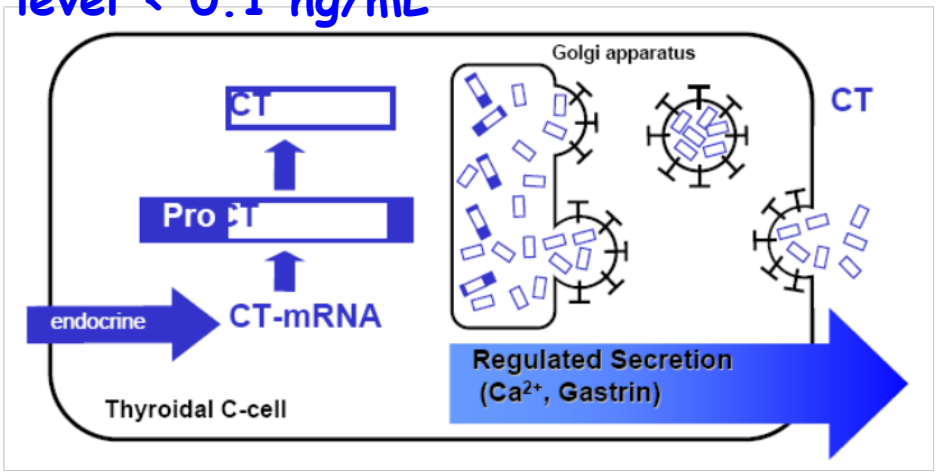
Conflicts of interest

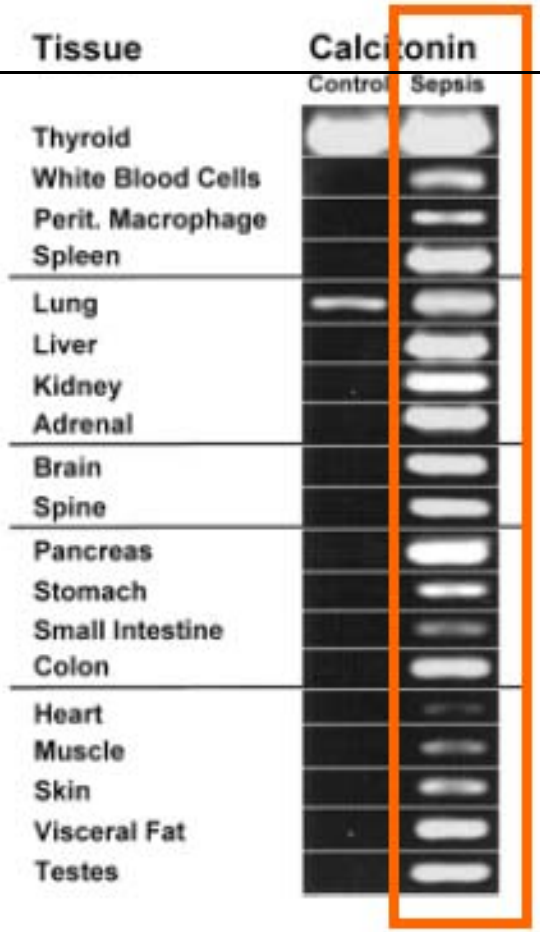
Board, lectures and fees from

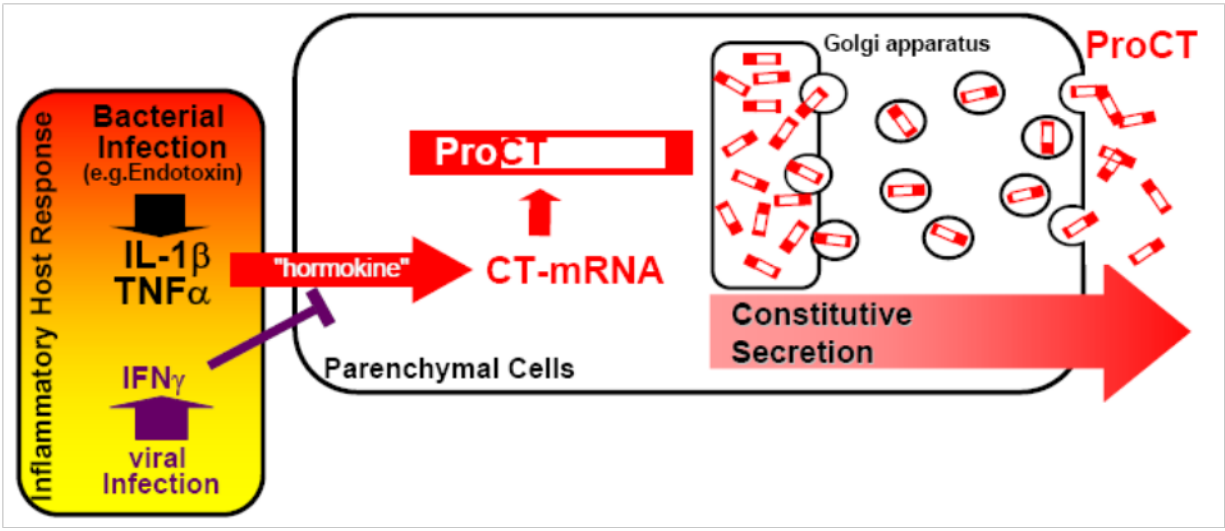
- Astellas
- AstraZeneca
- Cubist
- MSD
- Gilead
- Novartis
- Roche
- Teravance

Normal physiologic conditions: PCT level < 0.1 ng/mL









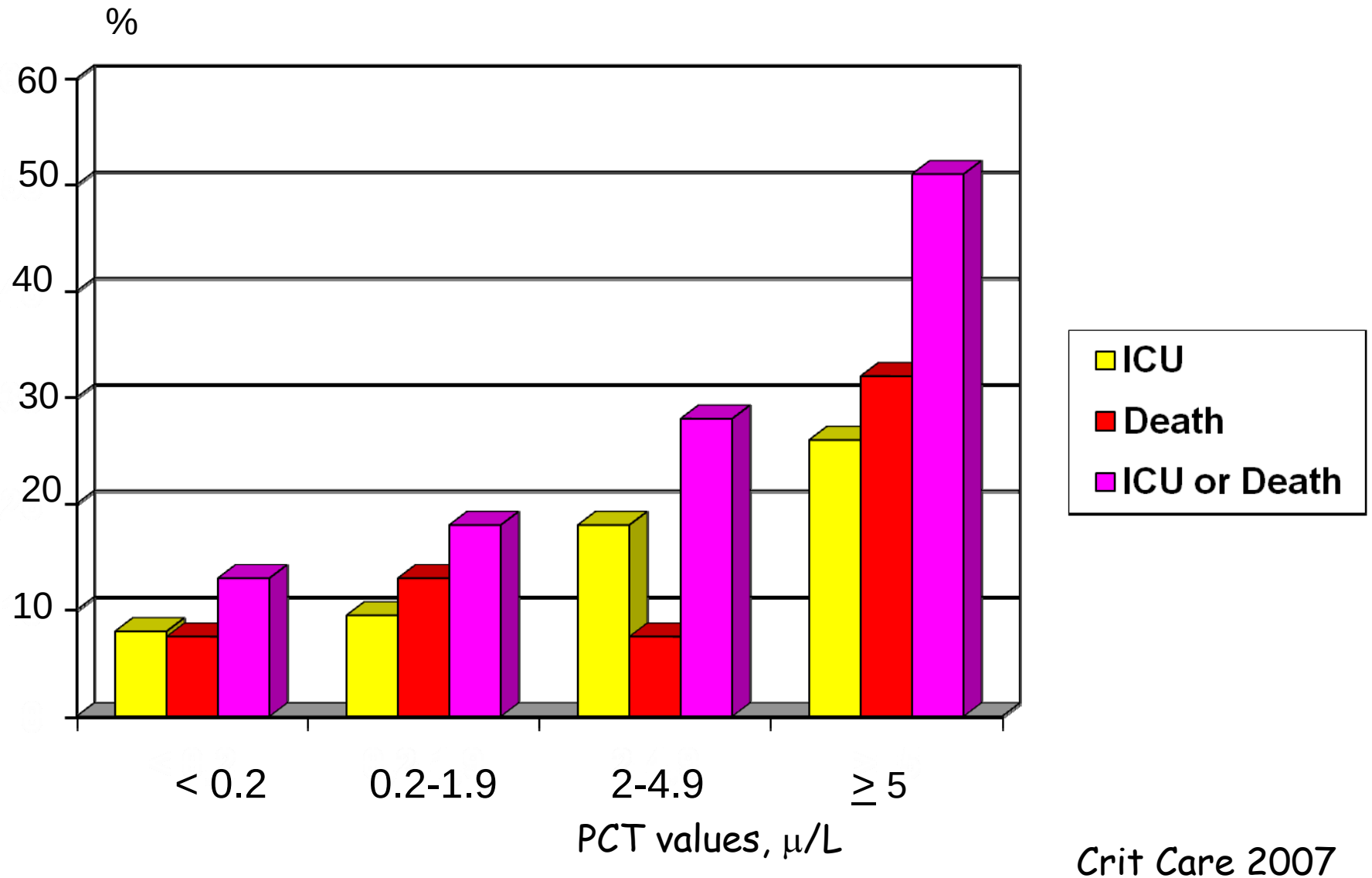
SEPSIS

Procalcitonine en réanimation : pour aider à

1. Evaluer la gravité et le pronostic
2. Discriminer entre infection bactérienne ou non et donc à débuter ou pas l'antibiothérapie
3. Réduire la durée de l'antibiothérapie au cours d'une infection bactérienne grave

Serum procalcitonin measurement as diagnostic and prognostic marker in febrile adult patients presenting to the emergency department

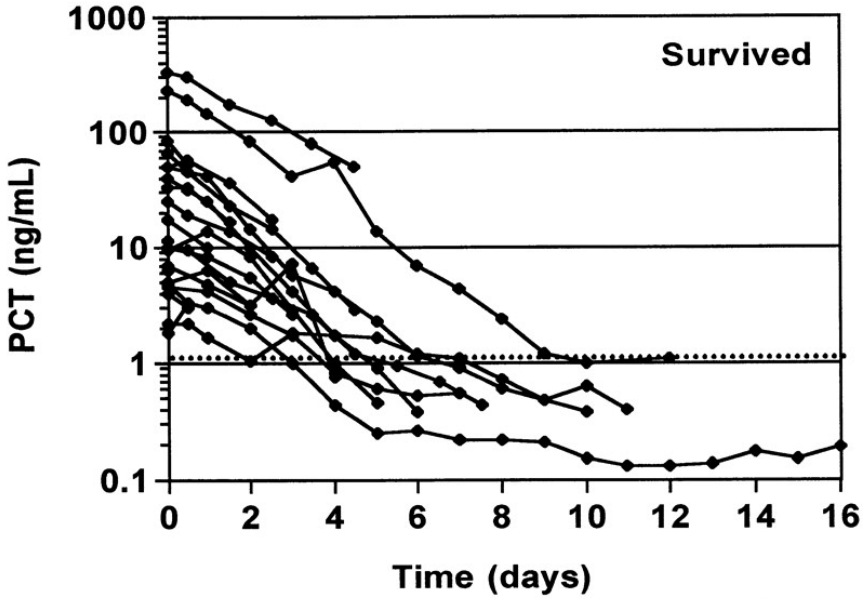
Pierre Hausfater[1], Gaëlle Juillien[1], Beatrice Madonna-Py[1], Julien Haroche[2], Maguy Bernard[3] and Bruno Riou[1]



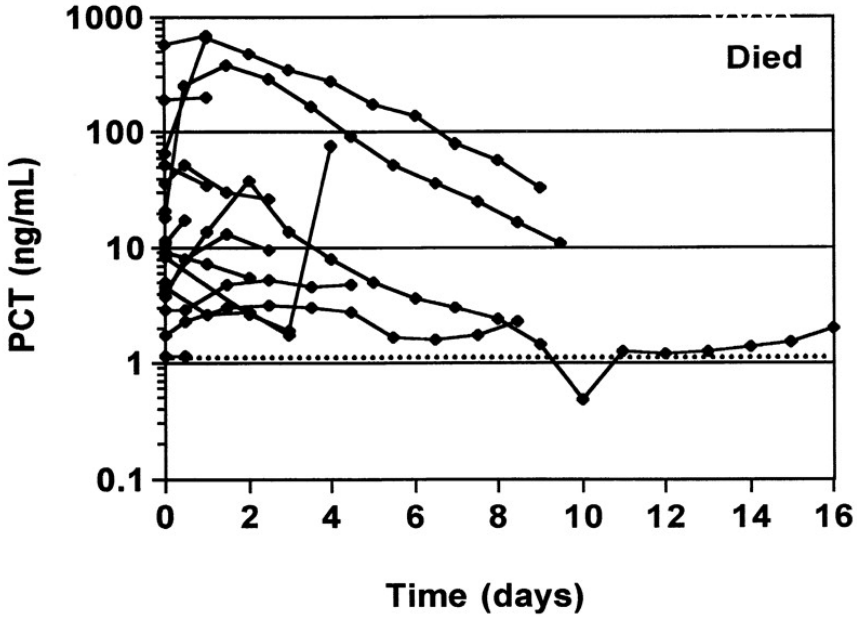
Crit Care 2007

Diagnostic Value of Procalcitonin, Interleukin-6, and Interleukin-8 in Critically Ill Patients Admitted with Suspected Sepsis

STEPHAN HARBARTH, KATARINA HOLECKOVA, CÉLINE FROIDEVAUX, DIDIER PITTET, BARA RICOU, GEORGES E. GRAU, LASZLO VADAS, JÉRÔME PUGIN, and the Geneva Sepsis Network



SIRS n = 18 | Sepsis n = 14 | Severe sepsis n = 21 | Septic shock n = 25



SIRS n = 18 | Sepsis n = 14 | Severe sepsis n = 21 | Septic shock n = 25

PCT and CRP :prognostic markers ?

Table 3. PCT and CRP plasma concentrations in the SOFA score groups

SOFA Score	PCT Median (Interquartile Range)	CRP Median (Interquartile Range)
1–6	3.1 (1.2–4.9)	135.9 (85.8–178.9)
7–12	3.9 (1.8–7.3)[a]	82.9 (59.4–149.2)[a]
13–18	31.0 (4.8–62.1)[a]	113.5 (107.9–222.9)[a]

Luzzani et al., Crit Care Med 2003

PCT: prognostic marker

Table 3. Prognostic value of procalcitonin (ng/mL) in septic shock

	Patients Who Died	Patients Who Survived	*p* Value
D1	16 (0.15–767)	6 (0.2–123)	.045
D3	14 (0.2–300)	3 (0.2–52)	.03
D7	15 (0.9–197)	1.1 (0.14–49)	.003
D10	6.5 (0.3–135)	1.05 (0.11–53)	.02

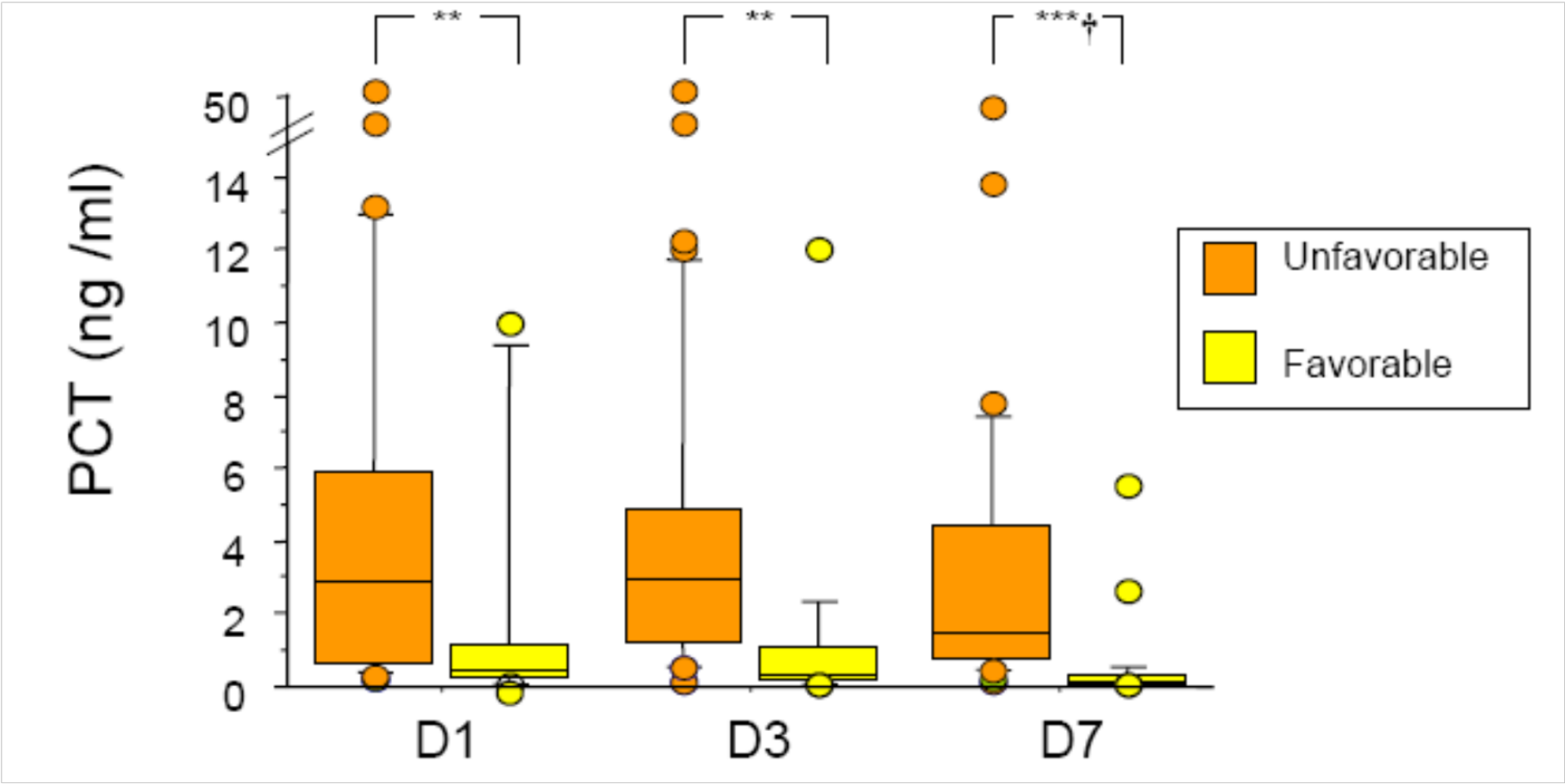
Table 4. Prognostic value of procalcitonin (ng/mL) in cardiogenic shock

	Patients Who Died	Patients Who Survived	*p* Value
D1	2 (0.15–36)	1 (0.2–9)	NS
D3	4 (0.4–23)	0.25 (0.2–32)	NS
D7	3 (2.2–5.6)	0.17 (0.14–0.26)	NS
D10	4.5 (1.1–6.4)	0.13 (0.11–0.15)	NS

Clec 'h et al., Crit Care Med 2004

Procalcitonin Kinetics as a Prognostic Marker of Ventilator-associated Pneumonia

Charles-Edouard Luyt, Valérie Guérin, Alain Combes, Jean-Louis Trouillet, Said Ben Ayed, Maguy Bernard, Claude Gibert, and Jean Chastre



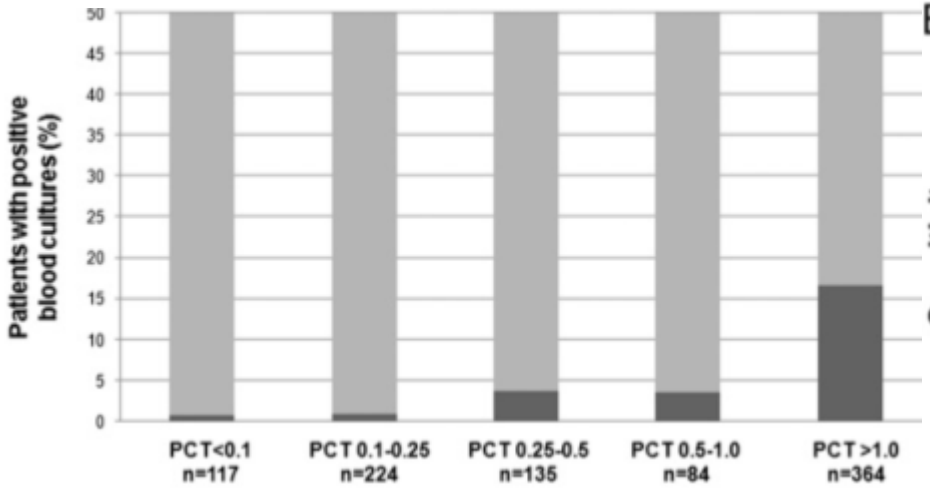
CHEST

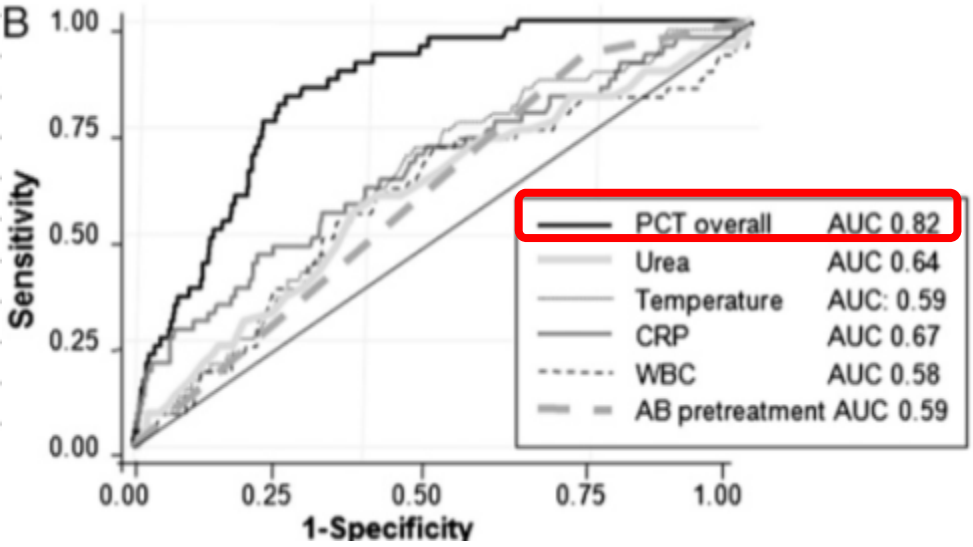
Original Research

COMMUNITY-ACQUIRED PNEUMONIA

Procalcitonin Levels Predict Bacteremia in Patients With Community-Acquired Pneumonia

A Prospective Cohort Trial





Müller F et al. CHEST 2010; 138:121-129

CRITICAL CARE

RESEARCH Open Access

Procalcitonin reflects bacteremia and bacterial load in urosepsis syndrome: a prospective observational study

Cees van Nieuwkoop[1*], Tobias N Bonten[1], Jan W van't Wout[1,2], Ed J Kuijper[3], Geert H Groeneveld[4], Martin J Becker[5], Ted Koster[6], G Hanke Wattel-Louis[7], Nathalie M Delfos[8], Hans C Ablij[9], Eliane MS Leyten[4], Jaap T van Dissel[1]

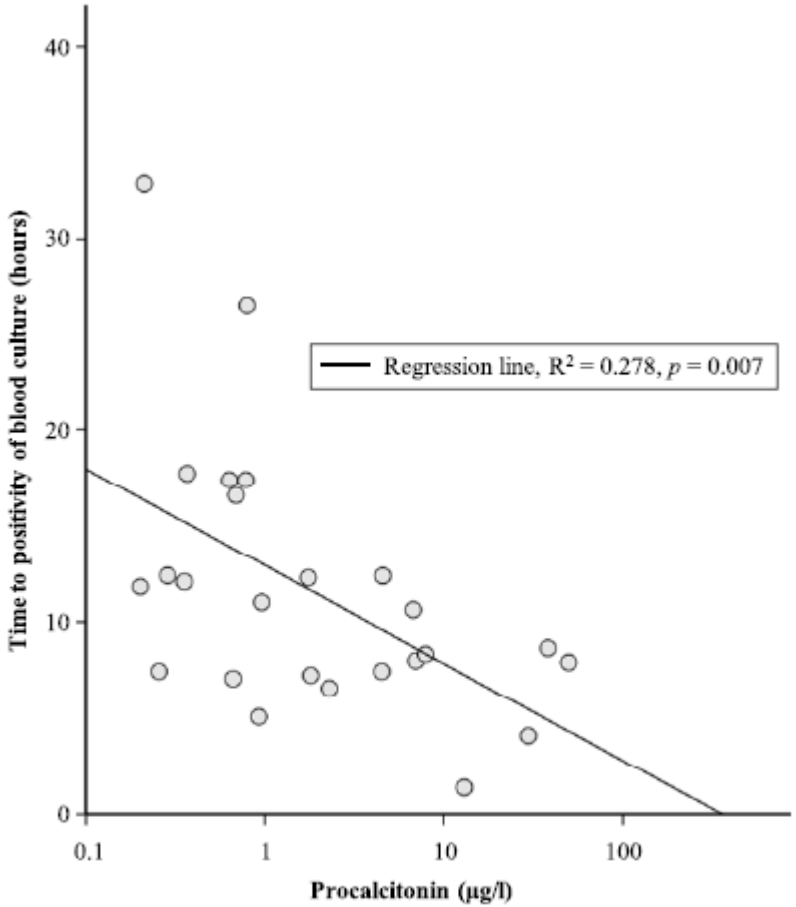
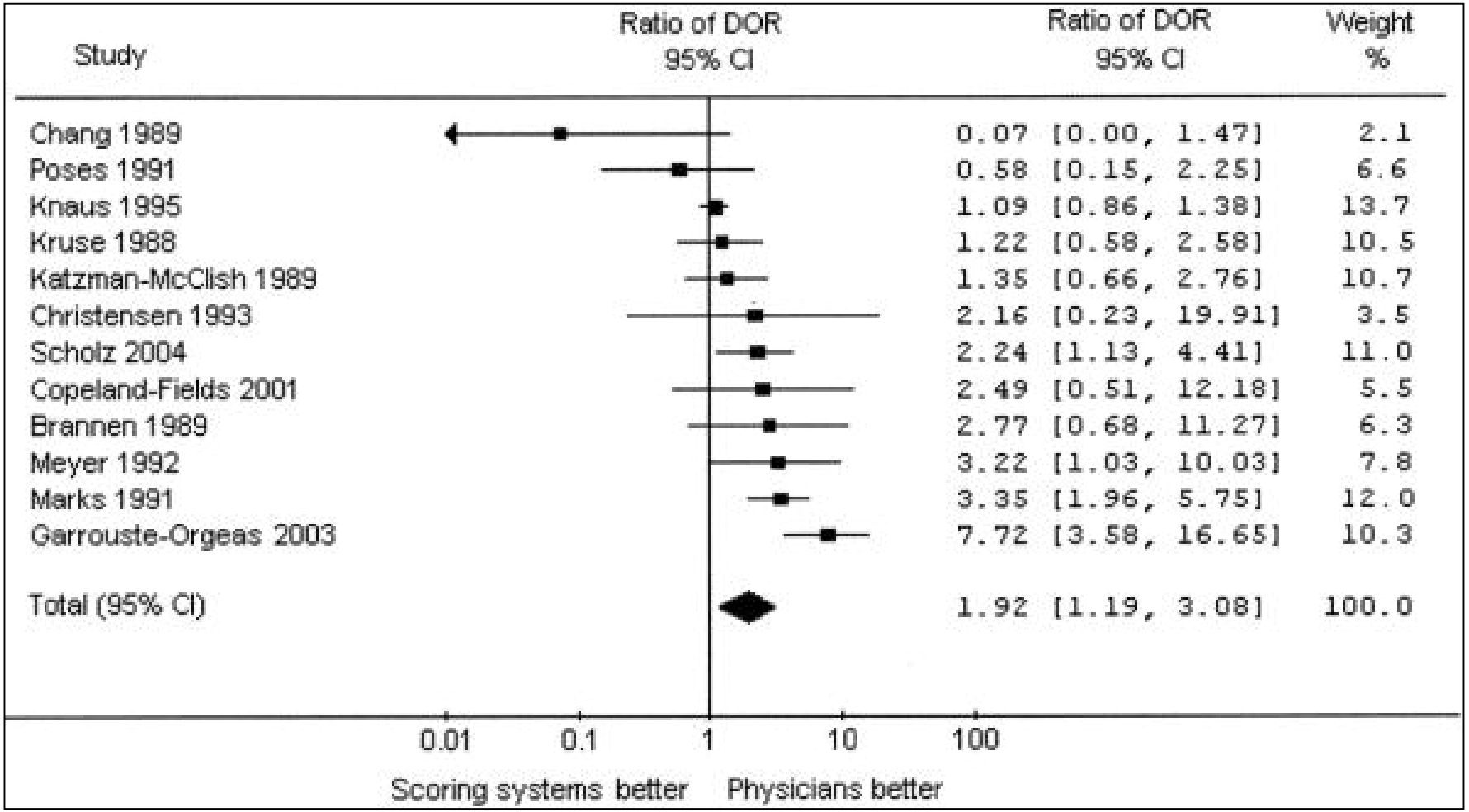


Figure 2 Relation between procalcitonin level at presentation with *E. coli* urosepsis (n = 25) and time to positivity of blood culture.

LE BON SENS CLINIQUE/SCORES



Sinuff T et al. Crit Care Med 2006

Procalcitonine en réanimation : pour aider à

1. Evaluer la gravité et le pronostic
    - Aide éventuelle pour le triage
    - Prédiction de la positivité des hémocultures
    - Donnée supplémentaire pour apprécier la gravité
    - Mais d'abord la clinique et le bon sens!

Procalcitonine en réanimation : pour aider à

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2. Discriminer entre infection bactérienne ou non et donc à débuter ou pas l'antibiothérapie
3. Réduire la durée de l'antibiothérapie au cours d'une infection bactérienne grave

BMC Infectious Diseases

BioMed Central

BioMed Central
The Open Access Publisher

Research article

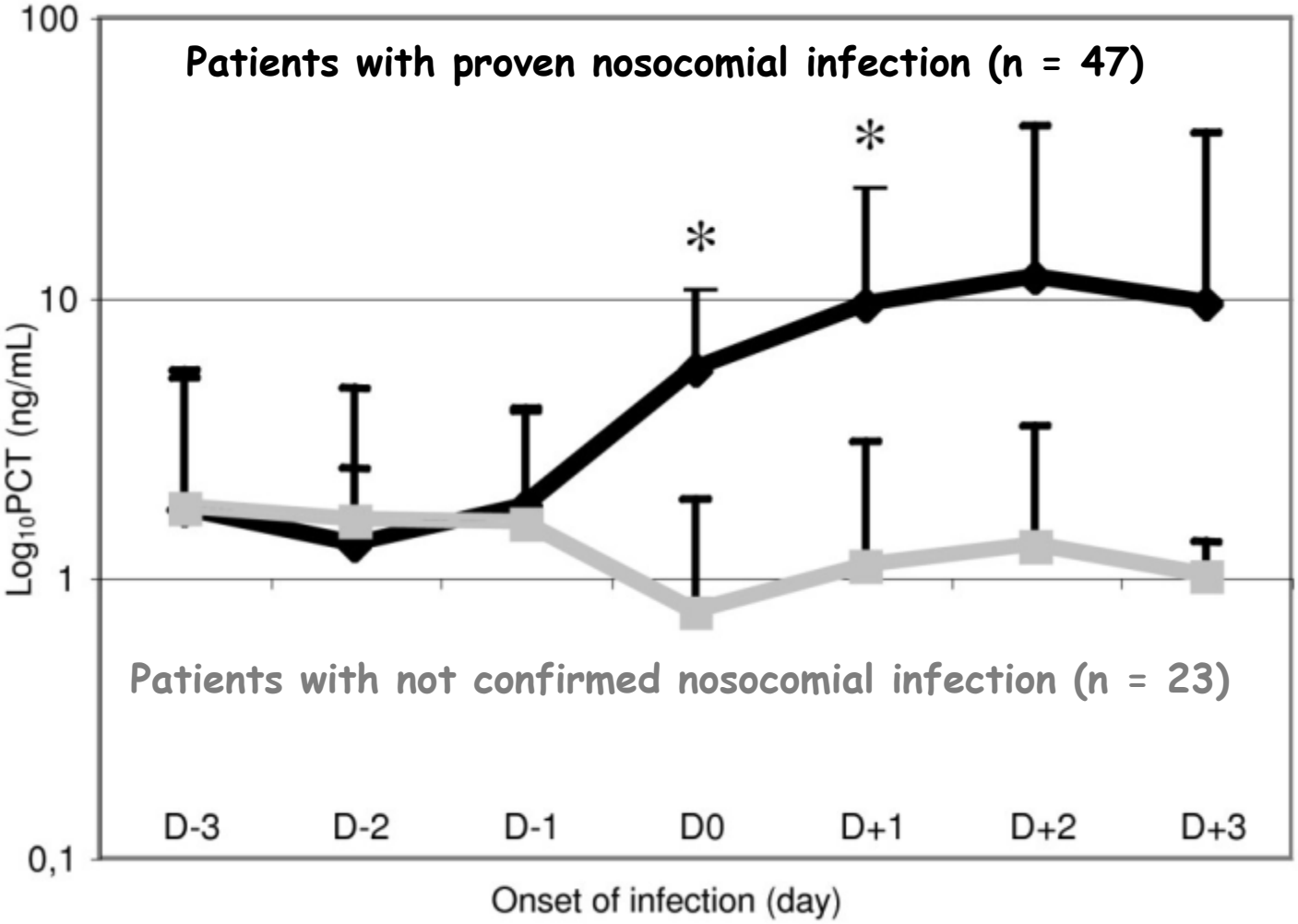
Open Access

Open Access

2009

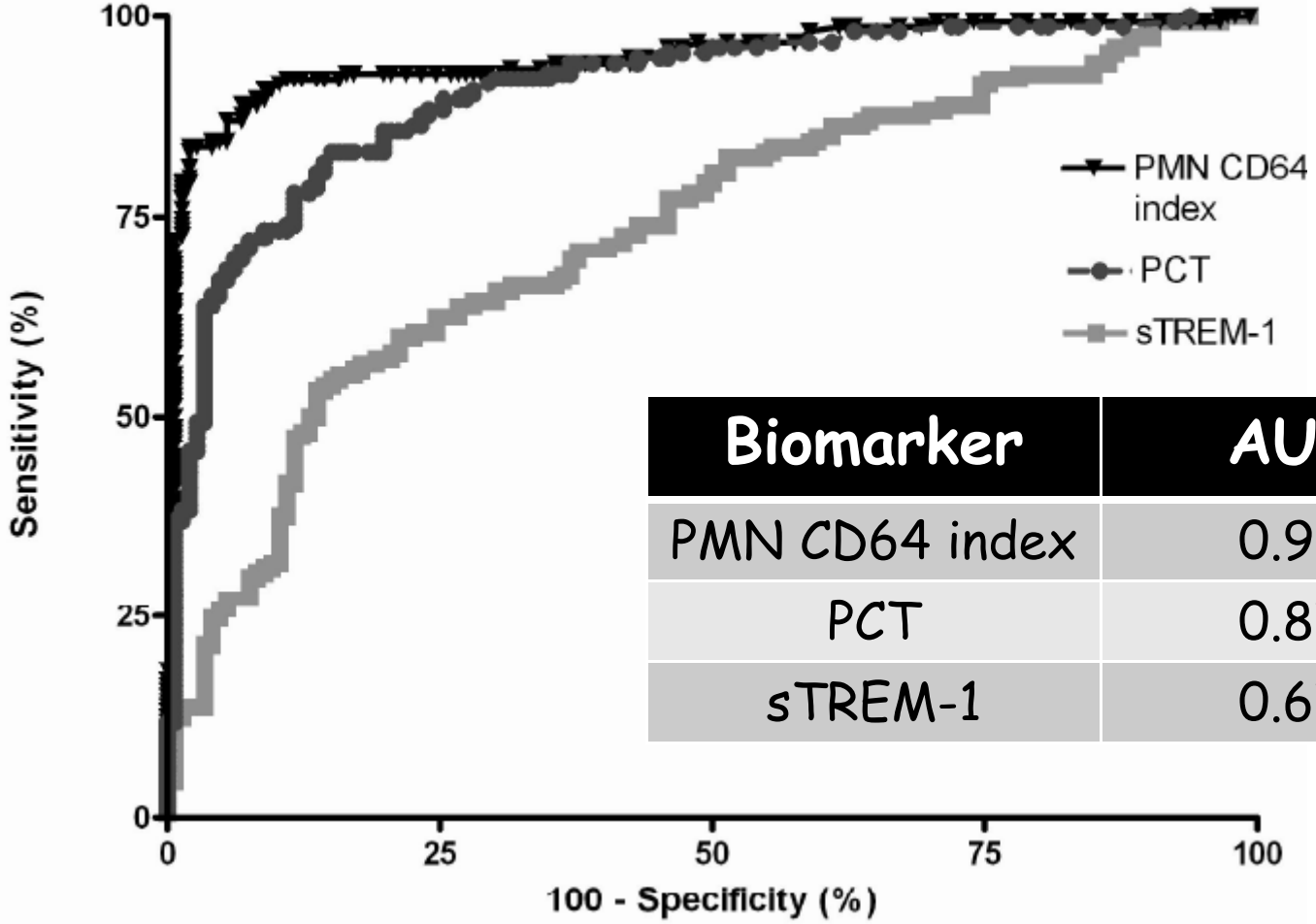
Serum procalcitonin for the early recognition of nosocomial infection in the critically ill patients: a preliminary report

Pierre Emmanuel Charles*[1], Emmanuel Kus[1], Serge AHO[2], Sébastien Prin[1], Jean-Marc Doise[1], Nils-Olivier Olsson[3], Bernard Blettery[1] and Jean-Pierre Quenot[1]



Biomarkers to diagnose sepsis

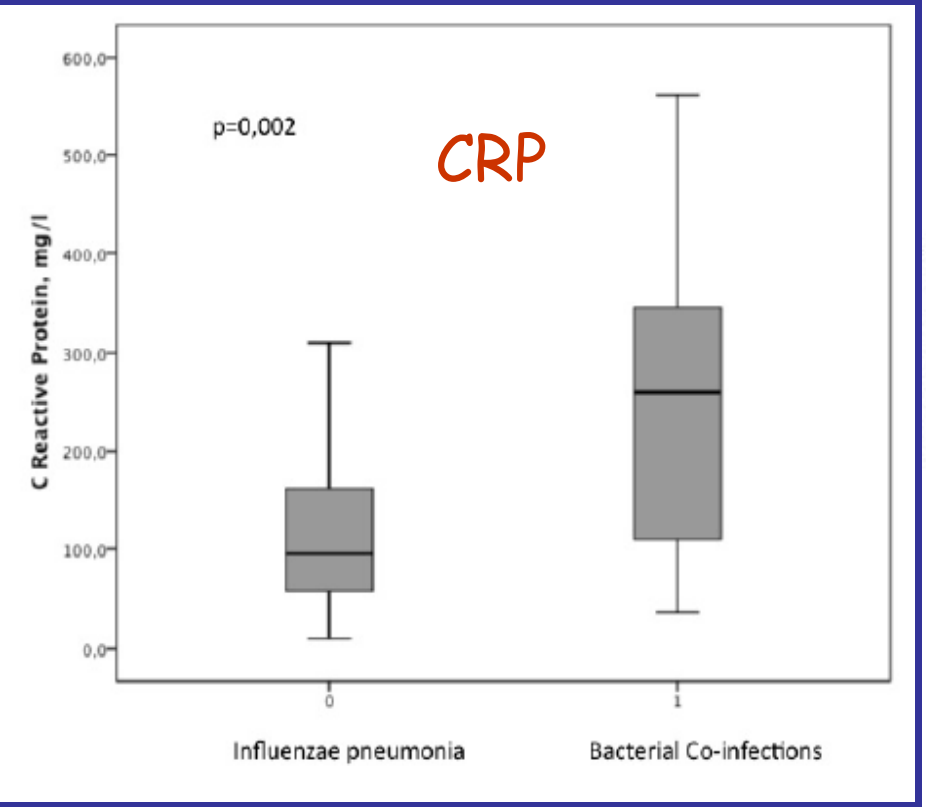
300 patients

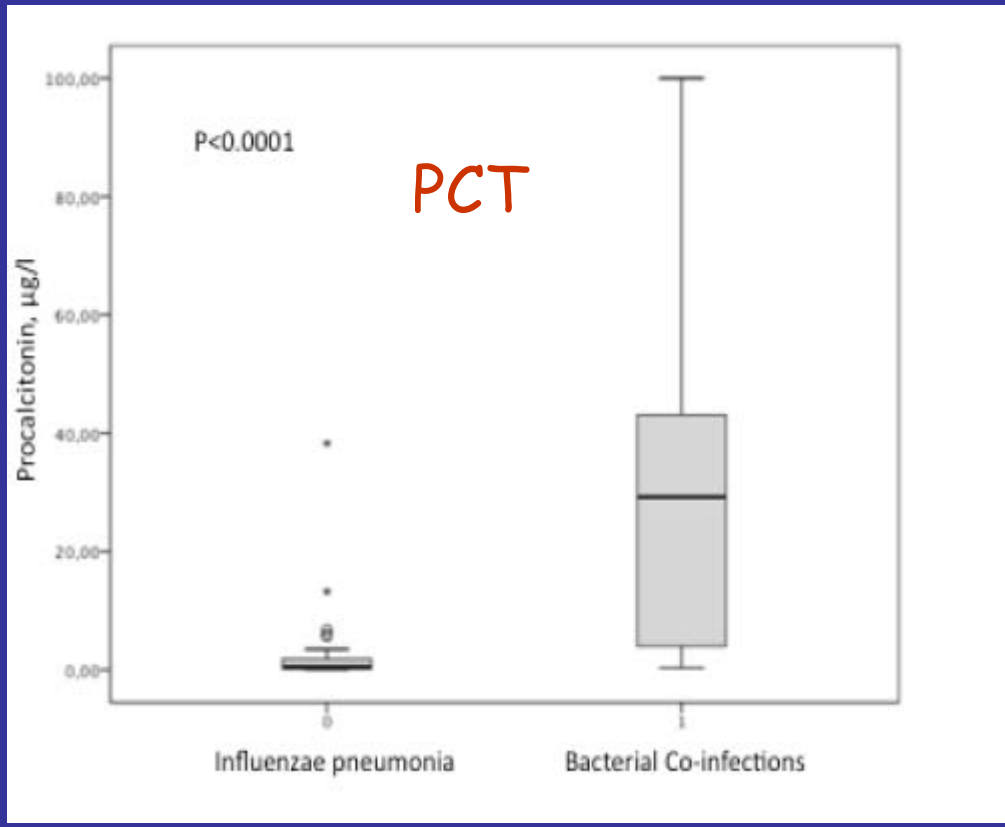


Biomarker	AUC
PMN CD64 index	0.95
PCT	0.87
sTREM-1	0.67

Gibot S et al. AJRCCM 2012

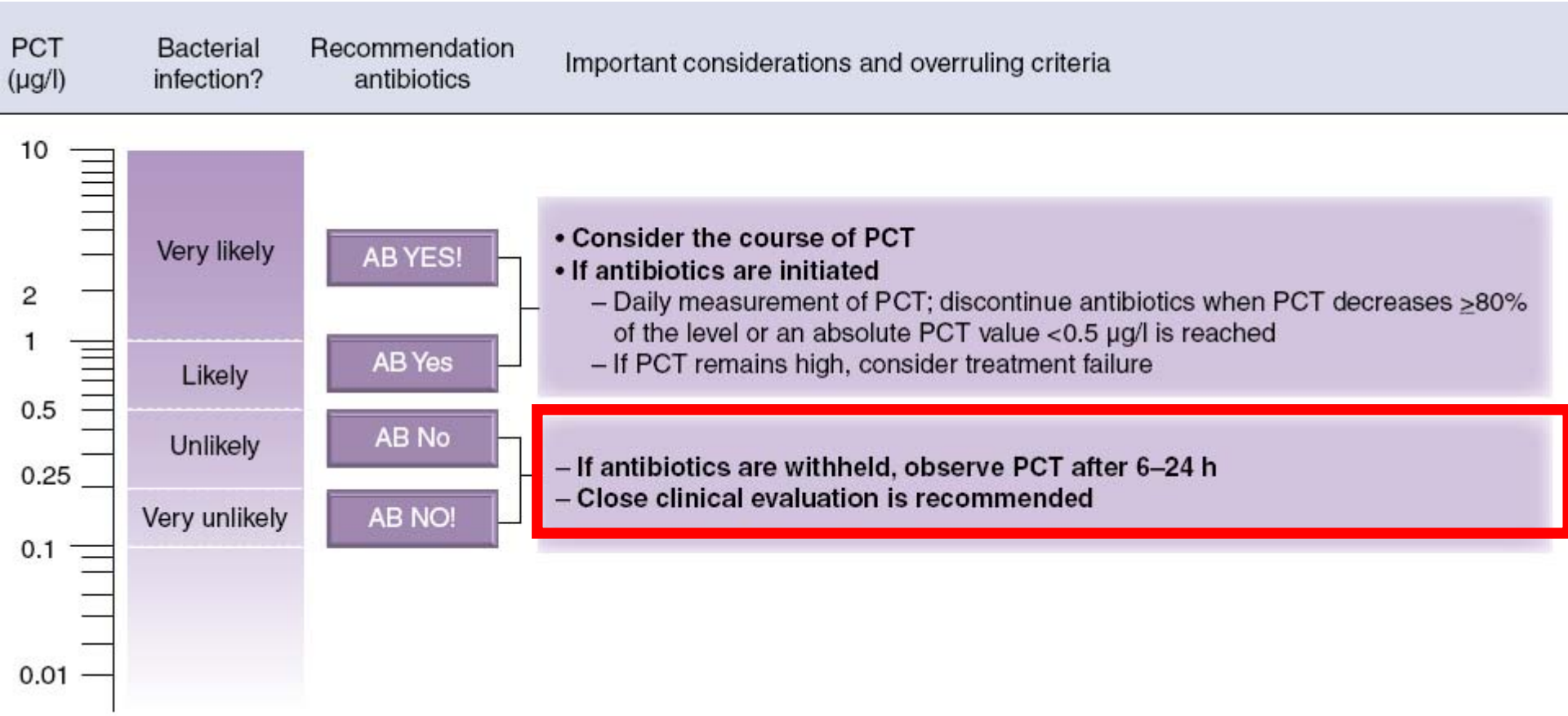
PCT and H1N1v: associated bacterial infection ?





Cuquemelle E et al. ICM 2011:37:796

Algorithm for sepsis in the ICU



Schuetz P et al. Expert Rev Antiinfect Ther 2010;8:575

Exposure to antibiotics in the ICU

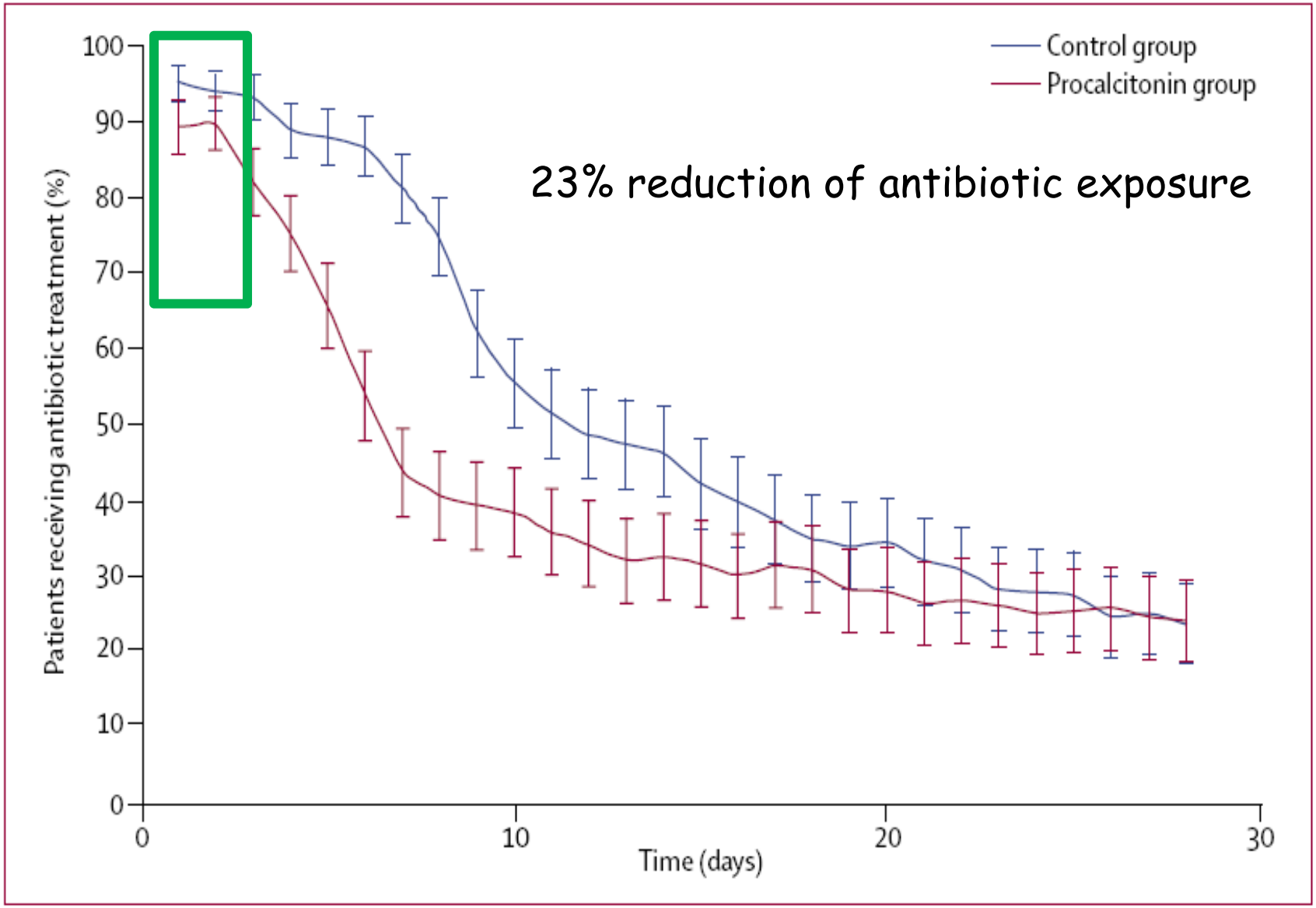


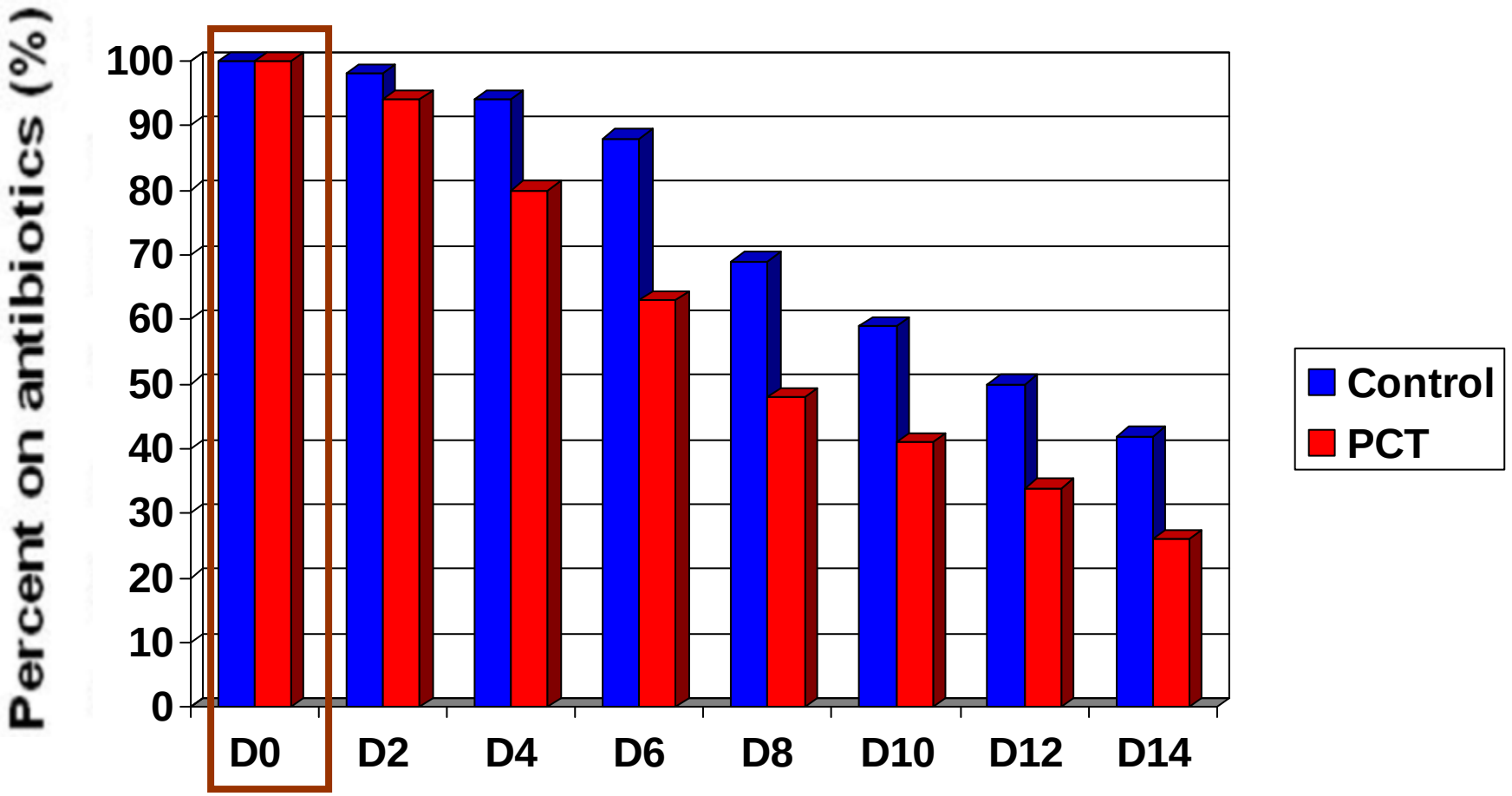
Figure 4: Patients receiving antibiotics for days 1–28

Bouadma L et al. Lancet 2010;375:463

PCT: peu utile pour initiation del'antibiothérapie en réanimation: pourquoi ?

Raisons potentielles	Commentaires
Beaucoup de patients ont une infection	Pas besoin de PCT
Les réanimateurs ont du mal à ne pas débuter les ATB	Diagnostic clinique > biomarqueur
PCT : pas un biomarqueur parfait	Performance ?

PCT and acute respiratory infections: ICU patients (n=598)



Schuetz P. et al Clin Infect Dis 2012

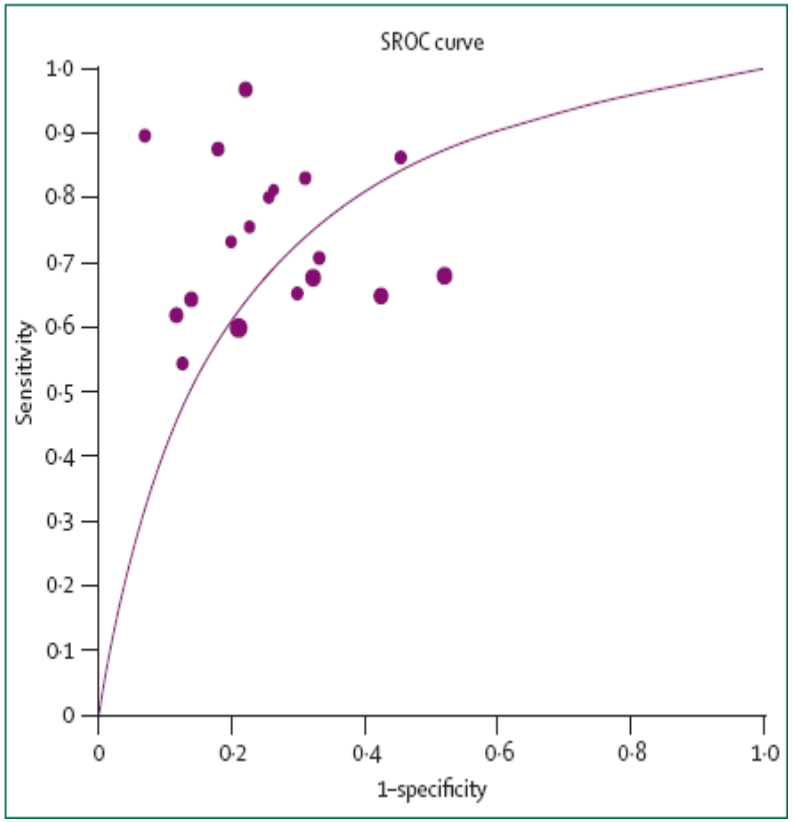
Procalcitonin: some problems

- False positive:
  - Heat stroke
  - Post-op SIRS
  - Cardiac surgery
  - Cardiac arrest
  - Pancreatitis
  - Trauma
  - Burns
  - Acute GVH
  - Paraneoplasic syndrome
  - Autoimmune disease
- False negative: infection
  - Localized (VAP?)
  - Early in the course
  - Previous ATB therapy

Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis

Benjamin M P Tang, Guy D Eslick, Jonathan C Craig, Anthony S McLean

Lancet Infect Dis 2007; 7: 210–17

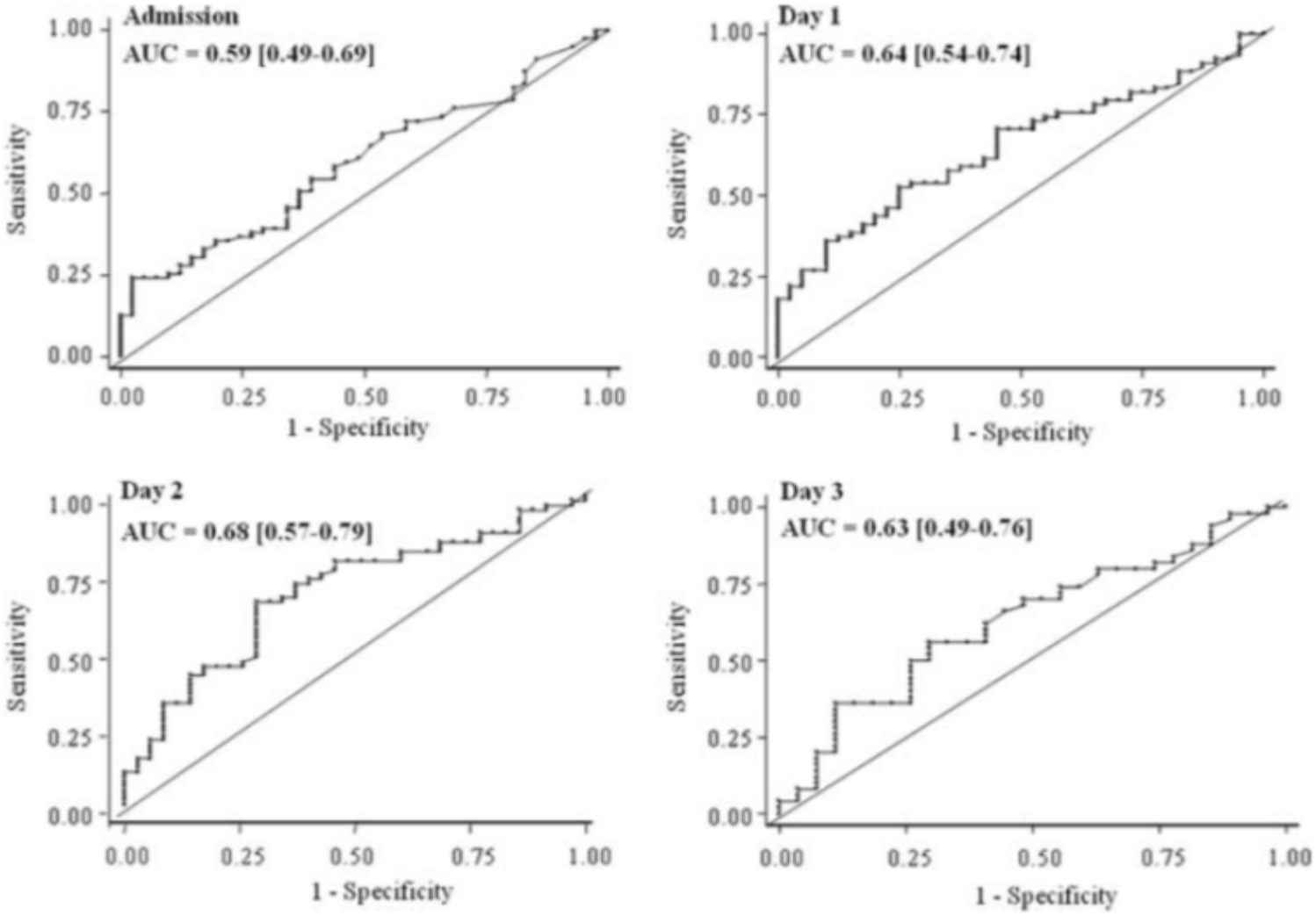


AUC: 0.78

Is it enough for ICU patients ?

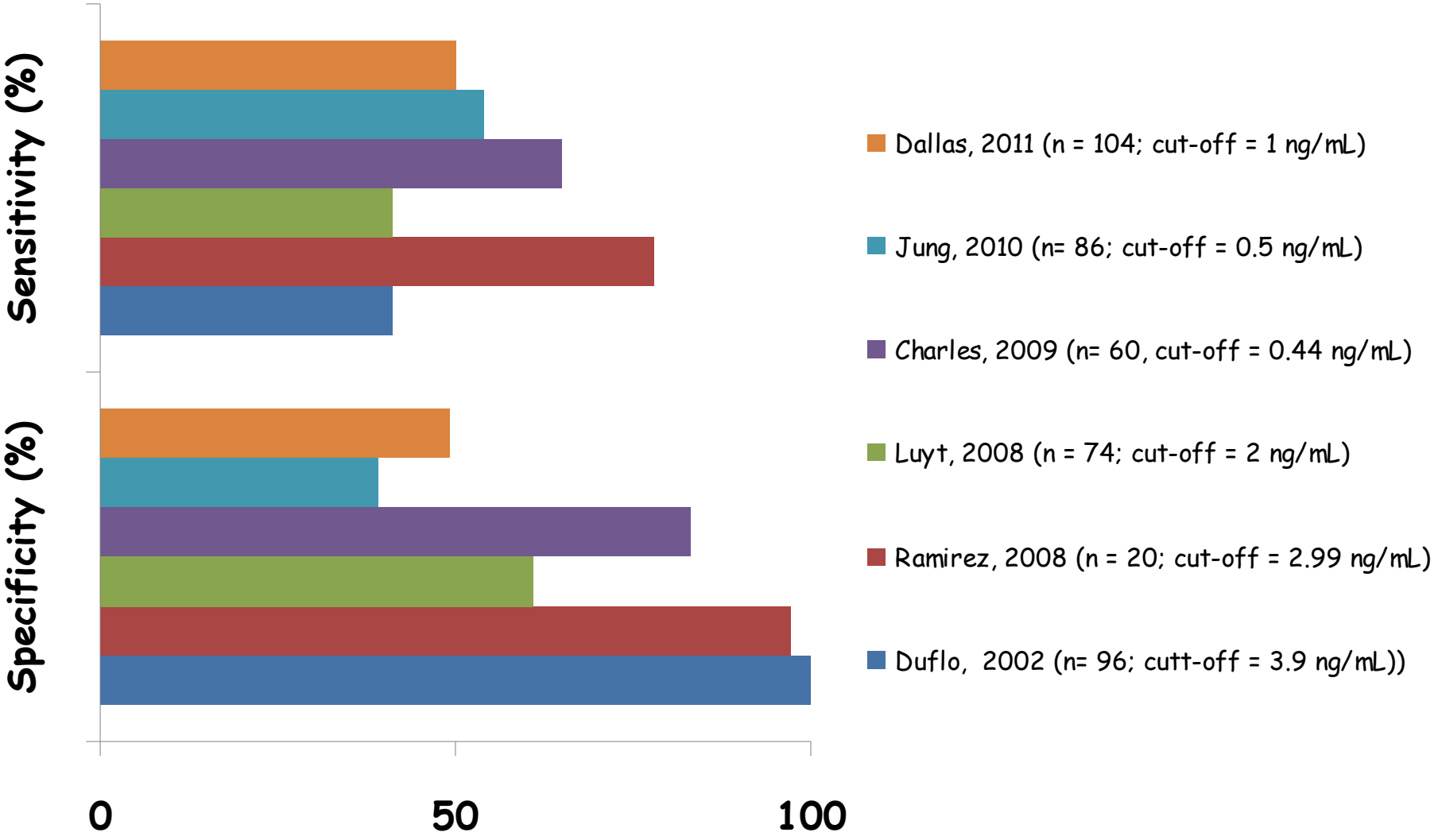
Procalcitonin cannot reliably differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome in critically ill adult patients. The findings from this study do not lend support to the widespread use of the procalcitonin test in critical care settings.

Value of procalcitonin for diagnosis of early onset pneumonia in hypothermia-treated cardiac arrest patients



Mongardon N et al. ICM 2010:36:92

Procalcitonin as a diagnostic marker of ventilator-associated pneumonia



Procalcitonine en réanimation : pour aider à

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More resistant pathogens, less new antibiotics

Highly resistant bugs

- AMPc
- ESBL
- CPE

] Enterobacteriaceae

- Pan R *P. aeruginosa*
- VRE
- *C. difficile*
- MRSA ⟹ VRSA ?

HEALTH SYSTEMS PERSPECTIVES

Stoking the antibiotic pipeline

C. Morel & E. Mossialos BMJ 2010

Acquisition of Multidrug-Resistant *Pseudomonas aeruginosa* in Patients in Intensive Care Units: Role of Antibiotics with Antipseudomonal Activity

Clin Infect Dis 2004

Elisabeth Paramythiotou[1,a], Jean-Christophe Lucet,[2] Jean-François Timsit,[3,6] Dominique Vanjak,[1] Catherine Paugam-Burtz,[4] Jean-Louis Trouillet,[5] Stéphanie Belloc,[1] Najiby Kassis,[1] Andreas Karabinis,[7] and Antoine Andremont[1]

Table 3. Multivariate analysis of risk factors associated with infection or colonization with multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) among patients hospitalized in intensive care units.

	OR (95% CI)	
Variable	Initial model	Final model
Receipt of hemodiafiltration or hemodialysis	3.05 (1.03–10.4)	…
Receipt of piperacillin or ticarcillin	4.13 (0.78–21.8)	…
Receipt of imipenem for duration longer than the median[a]	4.05 (1.26–13.1)	3.17 (0.92–10.9)
Receipt of ciprofloxacin for duration longer than the median[a]	53.7 (2.94–114)	11.0 (1.27–32.9)
Receipt of metronidazole	3.56 (1.01–12.7)	…

Durées d'antibiothérapie plus courtes en réanimation

Benefices moins de

- Resistance
- Effets secondaires
- Coûts

Risques: plus

- De rechutes
- D'échecs

International Journal of Antimicrobial Agents 38 (2011) 480–485

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Antibiotic treatment duration for bloodstream infections in critically ill patients: a national survey of Canadian infectious diseases and critical care specialists

Nick Daneman[a,b,c,*], Kevin Shore[a], Ruxandra Pinto[c], Rob Fowler[a,c,d]

[a] University of Toronto, Department of Medicine, Toronto, ON, Canada
[b] Sunnybrook Health Sciences Centre, Division of Infectious Diseases, Toronto, ON, Canada
[c] Sunnybrook Research Institute, Trauma Emergency and Critical Care Program, Toronto, ON, Canada
[d] Sunnybrook Health Sciences Centre, Department of Critical Care Medicine, Toronto, ON, Canada

Table 1
Mean recommended antibiotic treatment durations (days) for bacteraemic patients according to Canadian infectious diseases (ID) and critical care physicians.

Bacteraemic syndrome	ID physicians (n = 103)	Critical care physicians (n = 67)	P-value*
CVC-BSI	11.3 ± 3.3	8.3 ± 3.4	<0.001
Bacteraemic pneumonia	10.9 ± 2.9	9.5 ± 2.6	0.002
Bacteraemic UTI	12.3 ± 3.4	8.7 ± 3.3	<0.001
Bacteraemic IAI	11.5 ± 4.3	10.1 ± 3.6	0.068
Bacteraemic SSTI	12.3 ± 2.9	11.1 ± 3.5	0.014

CVC-BSI, central vascular catheter-related bloodstream infection; UTI, urinary tract infection; IAI, intra-abdominal infection; SSTI, skin and soft-tissue infection.
* Wilcoxon rank-sum test.

Strategies for reduction in duration of antibiotic use

Strategies	RCT	Comments
ATB stewardship (ATB discontinuation)	Very few	Considerable human and computer-assisted ressources
Application of results of RT	Relatively few	Not for all infections Inclusion/exclusion criteria « Rigid » duration
Customization (clinical parameters *and* PCT)	Several	Most studies: RTI

Impact of an Antimicrobial Stewardship Intervention on Shortening the Duration of Therapy for Community-Acquired Pneumonia

Clin Infect Dis 2012;54:1581

Edina Avdic,[1] Lisa A. Cushinotto,[4] Andrew H. Hughes,[2] Amanda R. Hansen,[5] Leigh E. Efird,[1] John G. Bartlett,[2,3] and Sara E. Cosgrove[2,3]

Variable	Preintervention (2008) (n = 56)[a]	Intervention (2010) (n = 63)[a]	*P*
Length of stay, median, days	4 days	5 days	
Duration of antibiotic therapy, median (IQR), days	10 (8–13)	7 (7–8)	<.001
Duration of antibiotic therapy, No.			
≤5 days	1	8	<.001
6–7 days	7	28	
8–10 days	24	18	
11–14 days	15	9	
>14 days	9	0	
Excess antibiotic days, total, days	241	93	
Excess antibiotic days, median (IQR), days	4 (2–6)	1 (0–3)	<.001
30-day readmissions, No. (%)[b]	9 (14.5)[c]	5 (7.7)[d]	.22
Clostridium difficile infections, No. (%)[e]	3 (4.8)[c]	1 (1.5)[d]	.28

The PCT-assisted strategy: the paradigm

Optimal duration of ATB may differ acording to

- Comorbidities
- Immune status
- The pathogen (virulence, resistance)
- Source control
- Complications of infection

Clearance rate of the infectious process not the same for all

THE LANCET

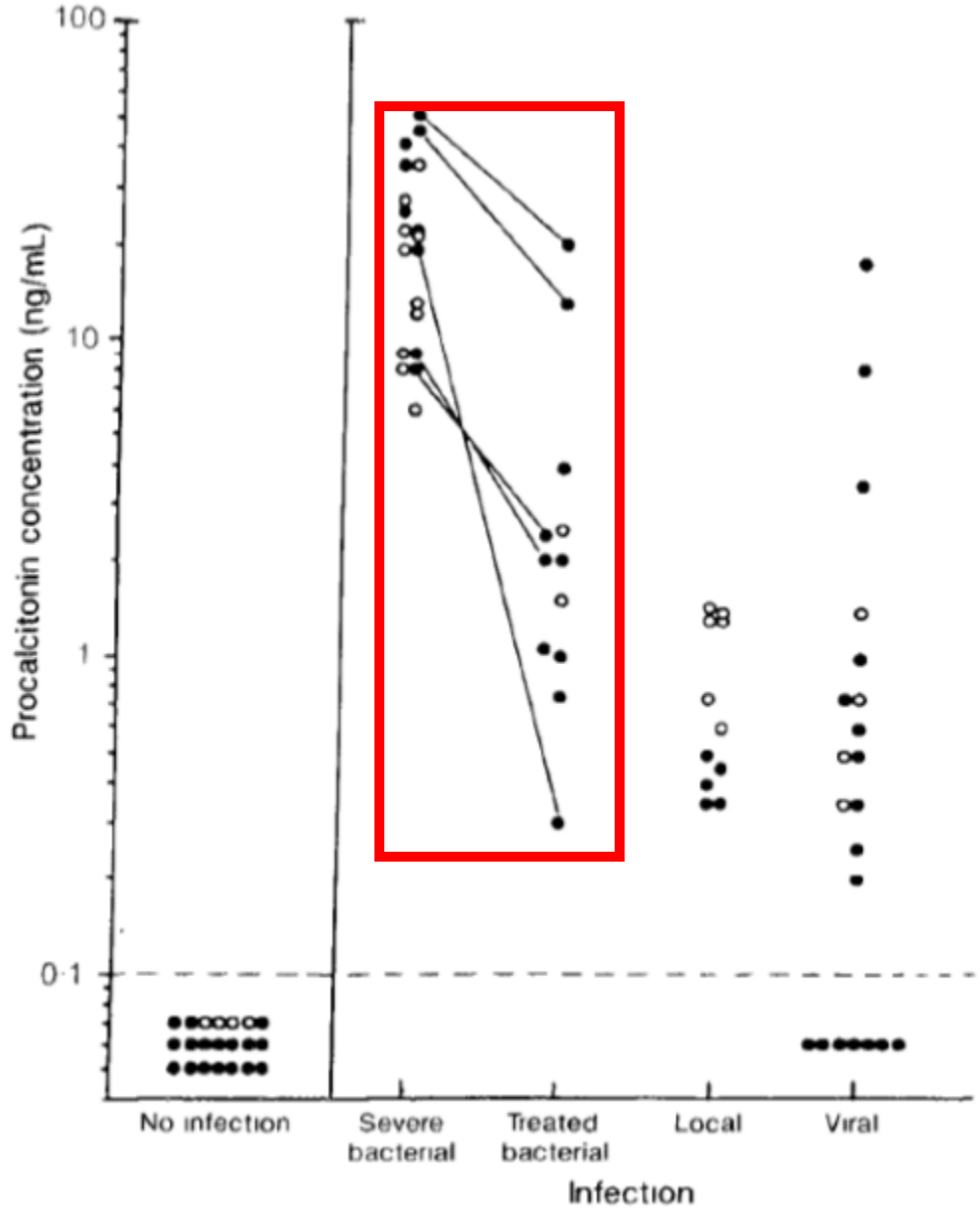
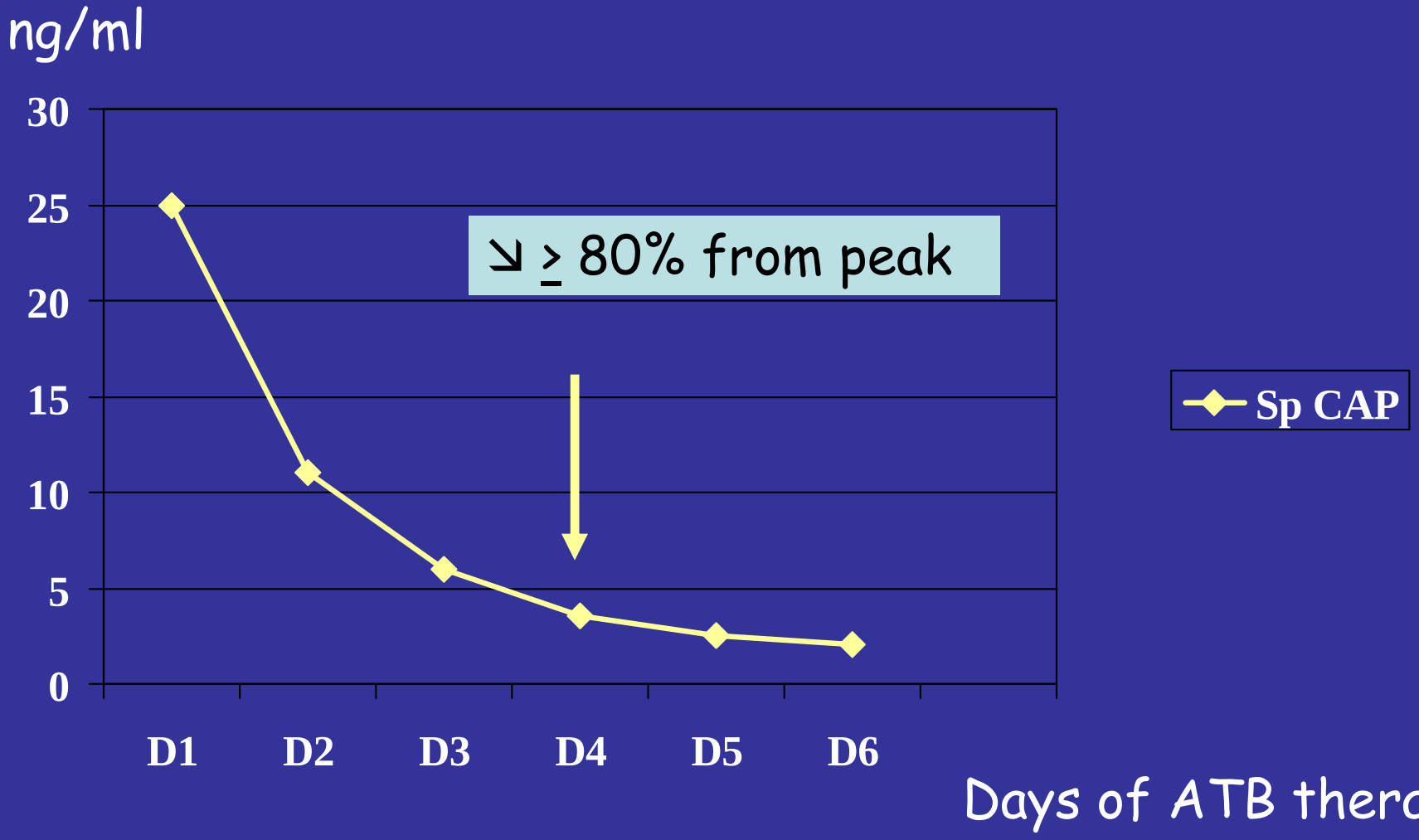


Fig 2—Serum procalcitonin concentrations in newborn infants (○) and older infants and children (●).

Assicot M et al. Lancet 1993: 341:515

Kinetics of PCT *S. pneumoniae* CAP



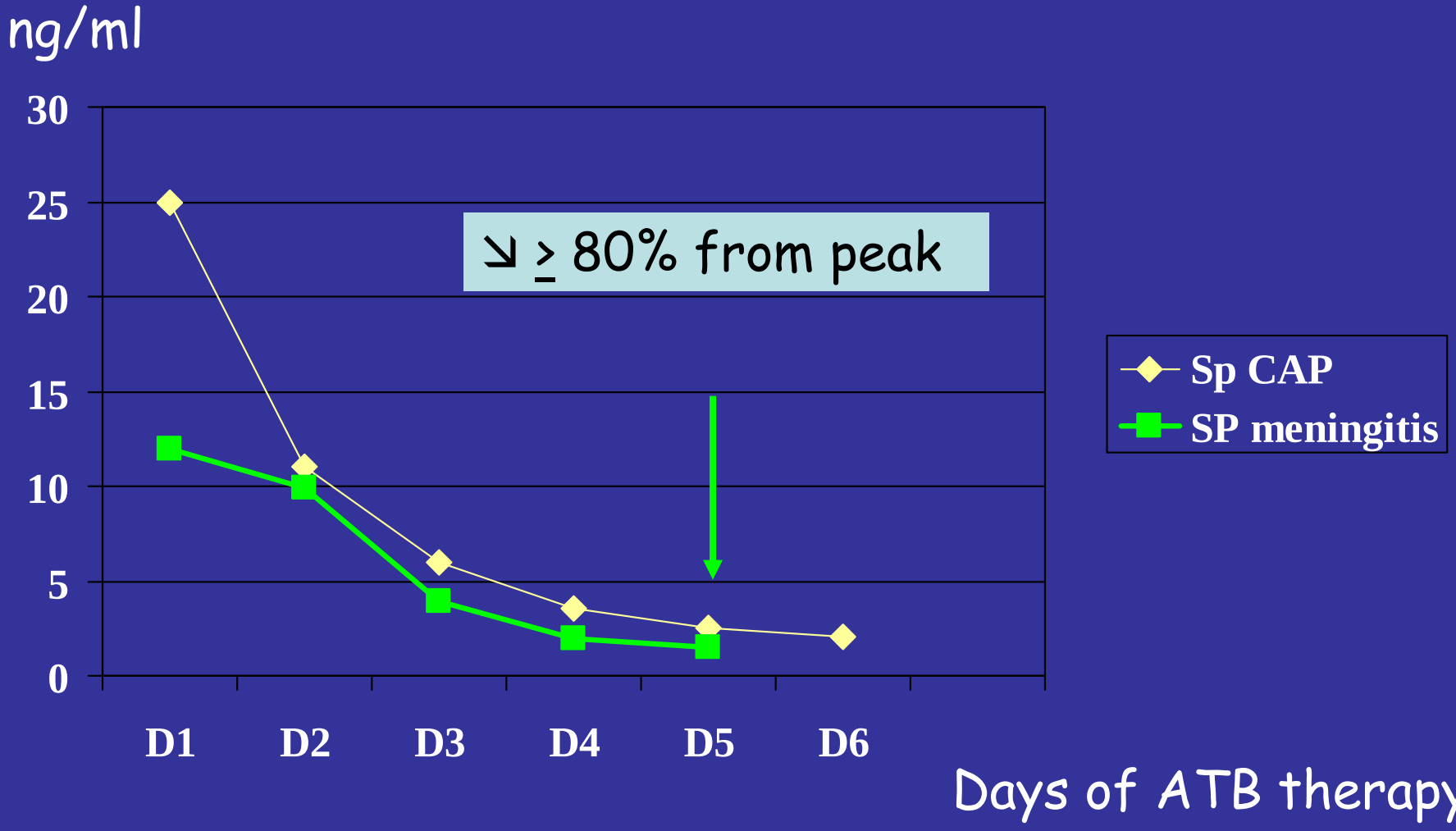
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2007, p. 208–214 Vol. 51, No. 1
0066-4804/07/$08.00+0 doi:10.1128/AAC.00004-06

Amoxicillin Is Effective against Penicillin-Resistant *Streptococcus pneumoniae* Strains in a Mouse Pneumonia Model Simulating Human Pharmacokinetics▽

Pierre Abgueguen,* Esther Azoulay-Dupuis, Violaine Noel, Pierre Moine, Veronique Rieux, Bruno Fantin, and Jean-Pierre Bedos

	4h	8h	24h	84h
MIC: 0.03 mg/L				
Controls	5.4±0.4	6.5±0.1	7.9±1	
Amoxicillin	3±0.1	< 2	< 2	
MIC: 2 mg/L				
Controls		6.2±0.4	7.9±0.1	
Amoxicillin		5.0±0.1	4.3±0.1	< 2

Kinetics of PCT
S. pneumoniae meningitis



5 versus 10 days of treatment with ceftriaxone for bacterial meningitis in children: a double-blind randomised equivalence study

The Lancet, 2011: 377

*Elizabeth Molyneux, Shaikh Qamaruddin Nizami, Samir Saha, Khanh Truong Huu, Matloob Azam, Zulfiqar Ahmad Bhutta, Ramadan Zaki, Martin Willi Weber, Shamim Ahmad Qazi, for the CSF 5 Study Group**

	5-day treatment group (n=496)	10-day treatment group (n=508)	Total	Risk difference (%; 95% CI)
Overall outcomes for all children				
Therapy successfully completed (10 days)	469 (95%)	485 (96%)	954	−0·92 (−3·6 to 1·8)
Antibiotic therapy modified after random assignment or therapy failure	17 (3%)	16 (3%)	33	0·3 (−1·9 to 2·5)
Changed diagnosis (to tuberculous meningitis)	2 (0%)	2 (0%)	4	0·009 (−0·7 to 0·7)
Adverse events to the study drug	0	0	0	..
Bacteriological failures	0	0	0	..
Another episode of meningitis	8 (2%)	13 (3%)	21	−0·95 (−2·7 to 8·2)
Relapse of meningitis	2	0	2	−0·4 (−0·15 to 0·96)
Deaths related to meningitis only*	9 (2%)	6 (1%)	15	0·63 (−0·87 to 2·1)
Deaths due to any reason after cure (until follow-up at 6 months after enrolment)	22 (4%)	19 (4%)	41†	0·69 (−1·8 to 3·1)

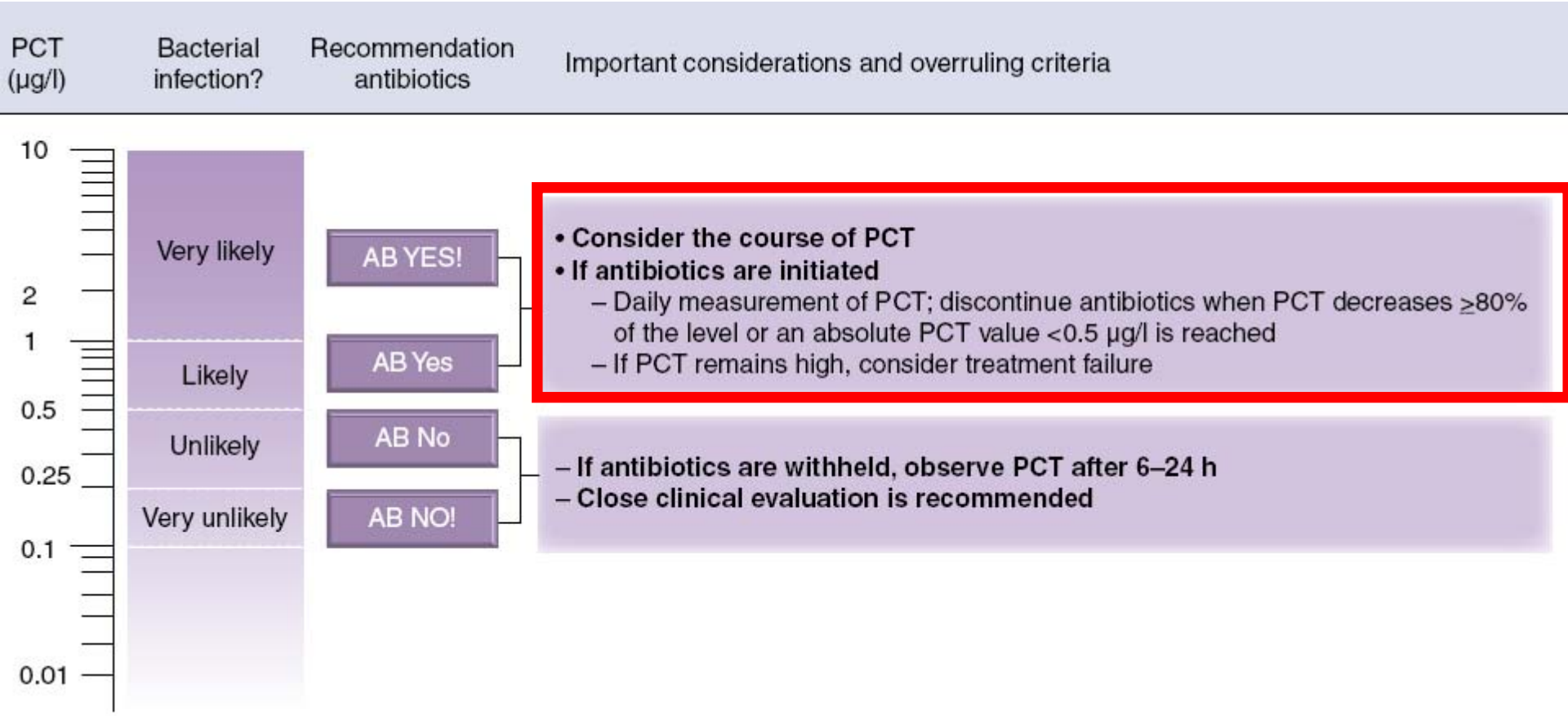
Le pré requis pour durée plus courte

Diminution rapide de l'inoculum bactérien

1. Antibiothérapie précoce et appropriée
2. Doses initiales élevées (PK-PD en réanimation)
3. Contrôle de la source (chirurgie, drainage…)

Si oui, une durée courte peut être discutée

Algorithm for sepsis in the ICU



Schuetz P et al. Expert Rev Antiinfect Ther 2010;8:575

Intensive Care Med
DOI 10.1007/s00134-012-2563-7

SYSTEMATIC REVIEW

Dimitrios K. Matthaiou
Georgia Ntani
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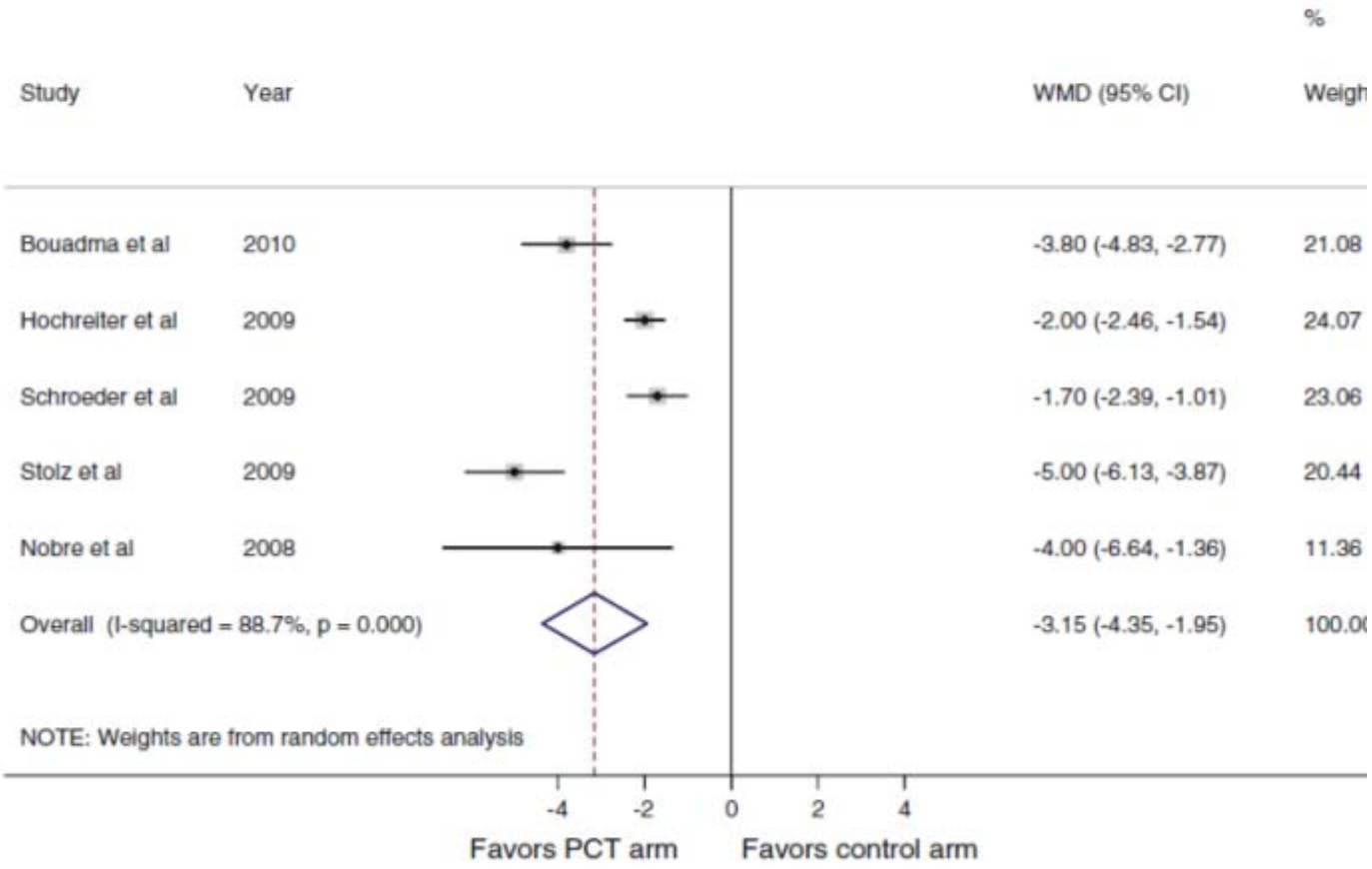
George Dimopoulos

An ESICM systematic review and meta-analysis of procalcitonin-guided antibiotic therapy algorithms in adult critically ill patients

Duration of antibiotic therapy for the first episode of infection



Exposure to antibiotics in the ICU

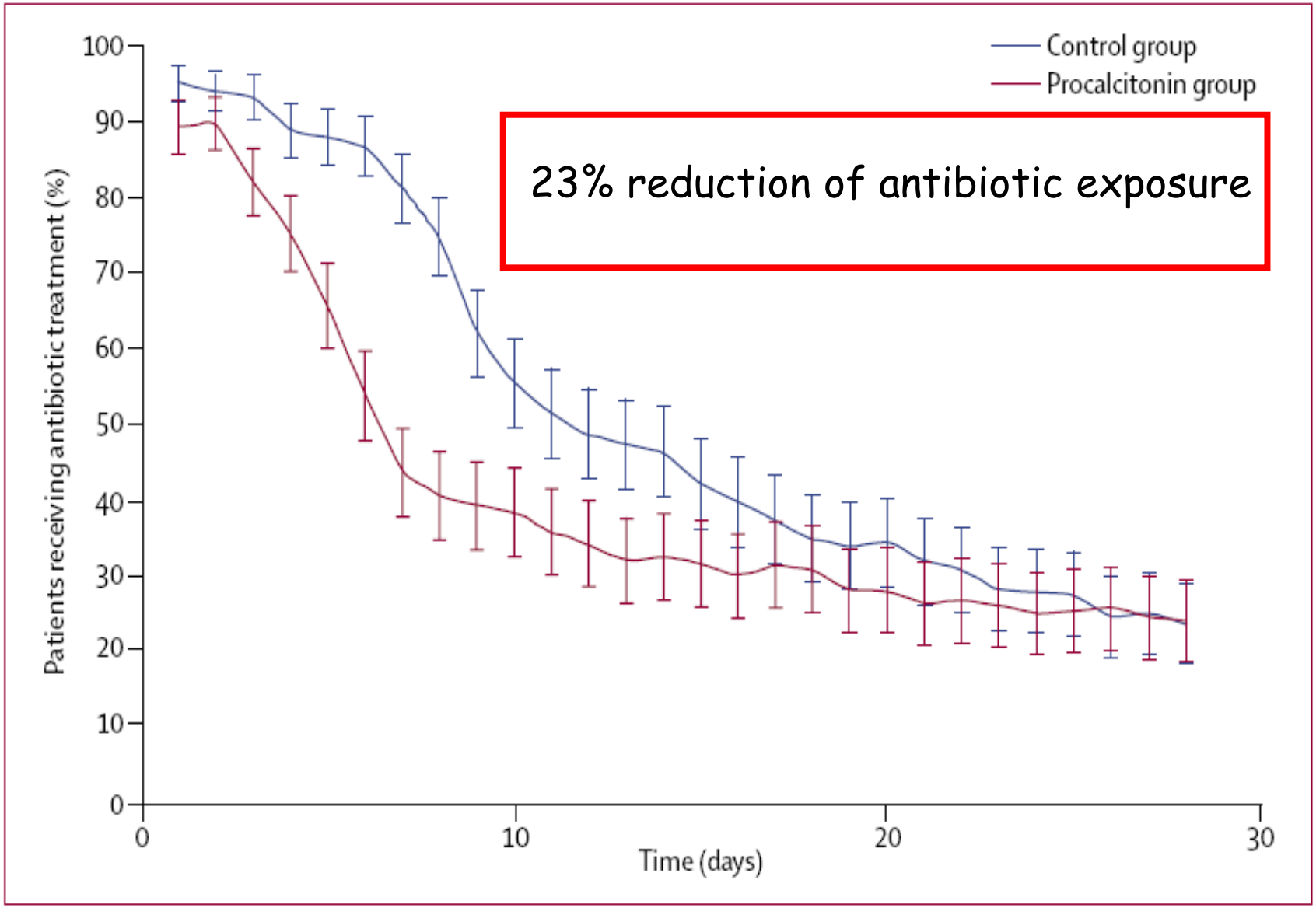
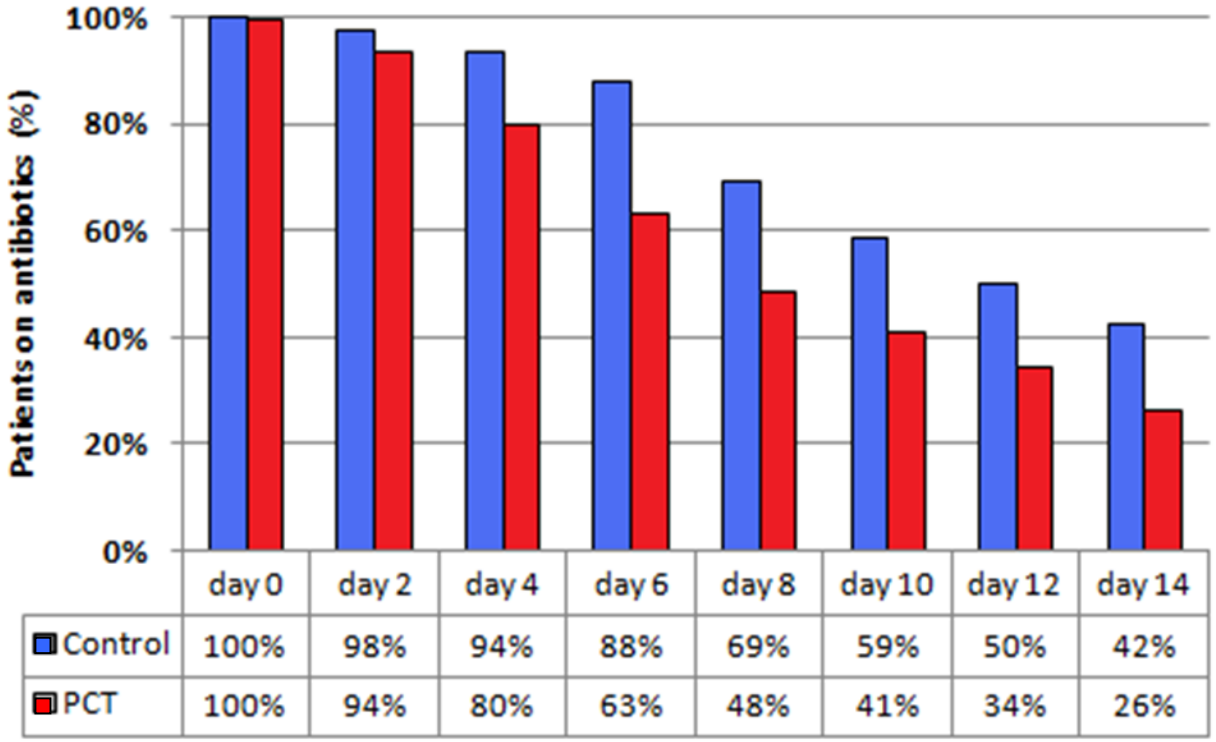
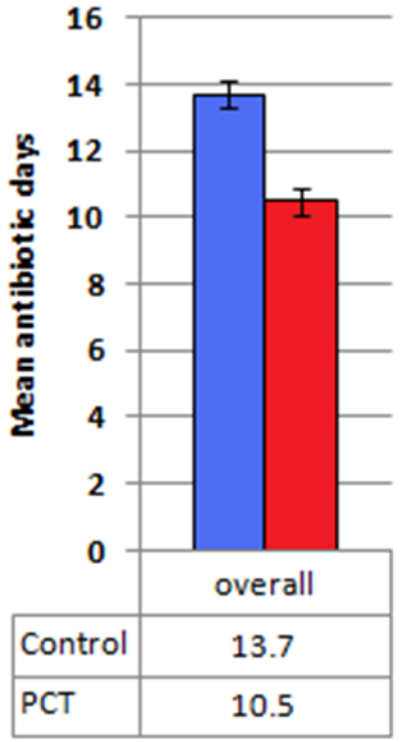


Figure 4: Patients receiving antibiotics for days 1–28 Bouadma L et al. Lancet 2010;375:463

PCT and acute respiratory infections: ICU patients (n=598)



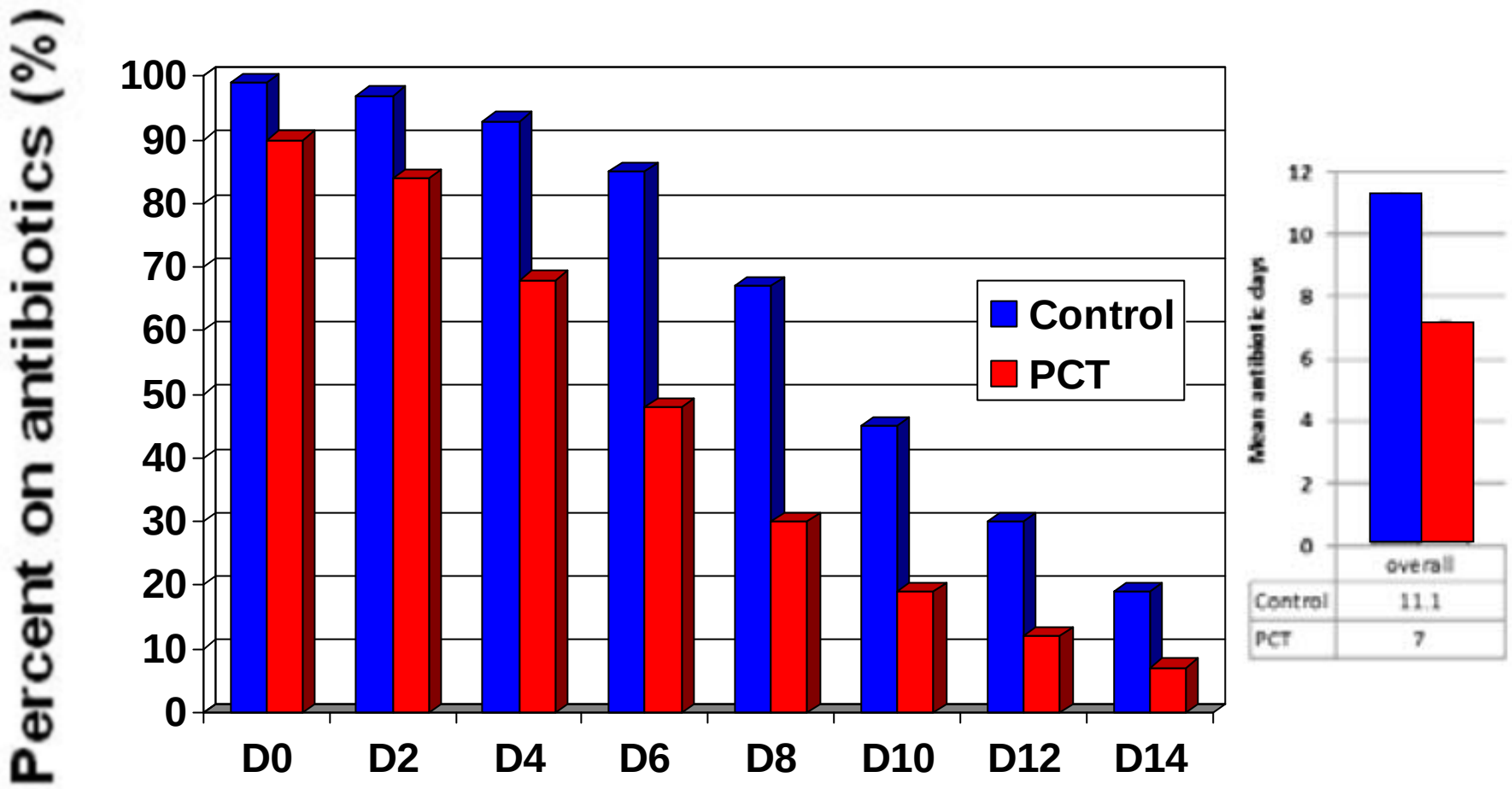
	day 0	day 2	day 4	day 6	day 8	day 10	day 12	day 14
Control	100%	98%	94%	88%	69%	59%	50%	42%
PCT	100%	94%	80%	63%	48%	41%	34%	26%



	overall
Control	13.7
PCT	10.5

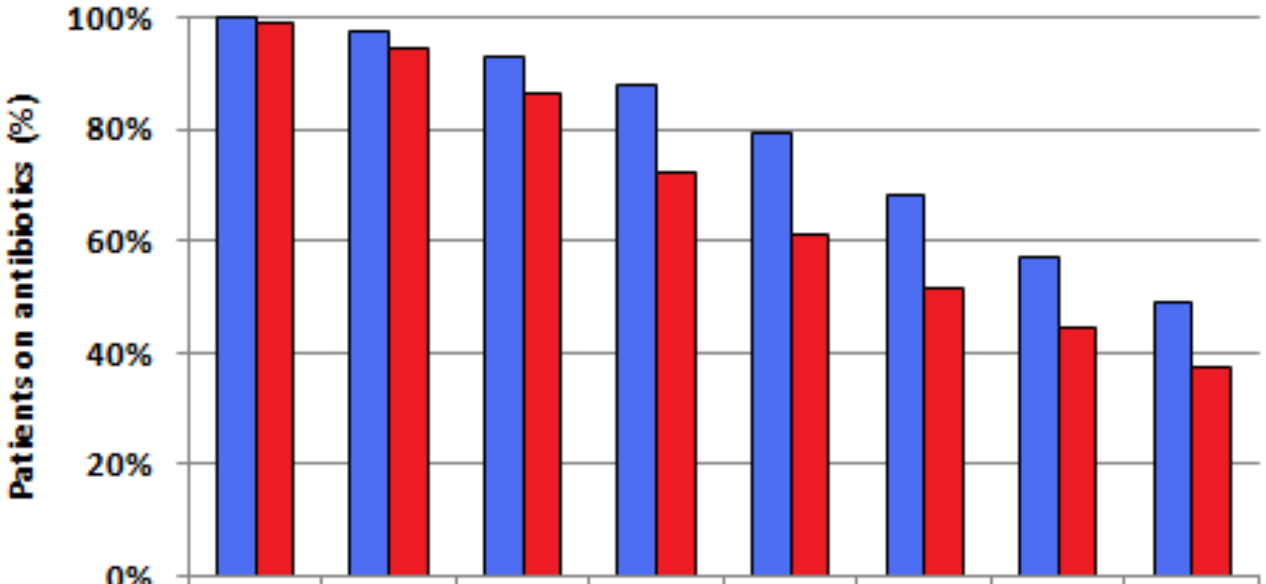
Schuetz P et al. Clin Infect Dis 2012

PCTand CAP (n=2027)

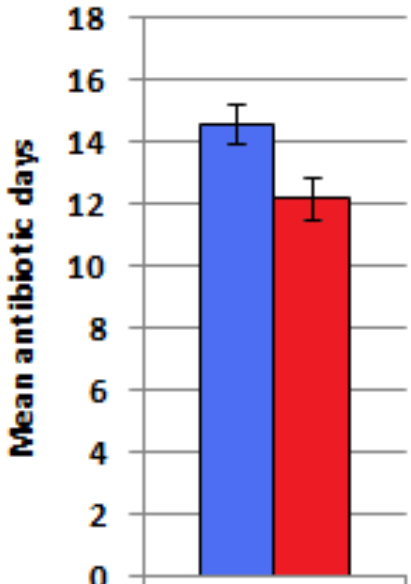


Schuetz P et al. Clin Infect Dis 2012

PCT and VAP (n=242)



	day 0	day 2	day 4	day 6	day 8	day 10	day 12	day 14
Control	100%	97%	93%	88%	79%	68%	57%	49%
PCT	99%	94%	87%	72%	61%	52%	44%	37%



	overall
Control	14.6
PCT	12.2

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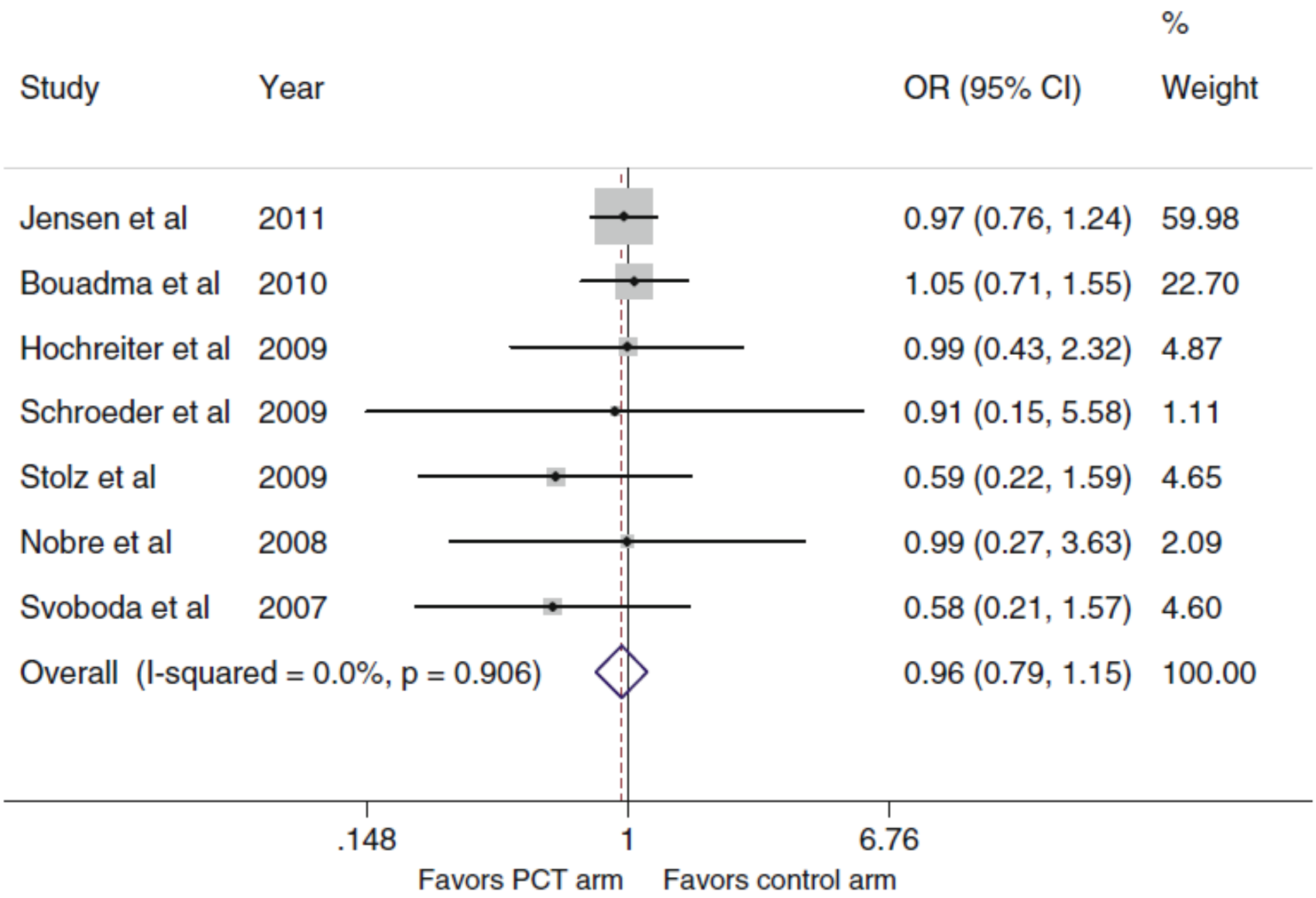
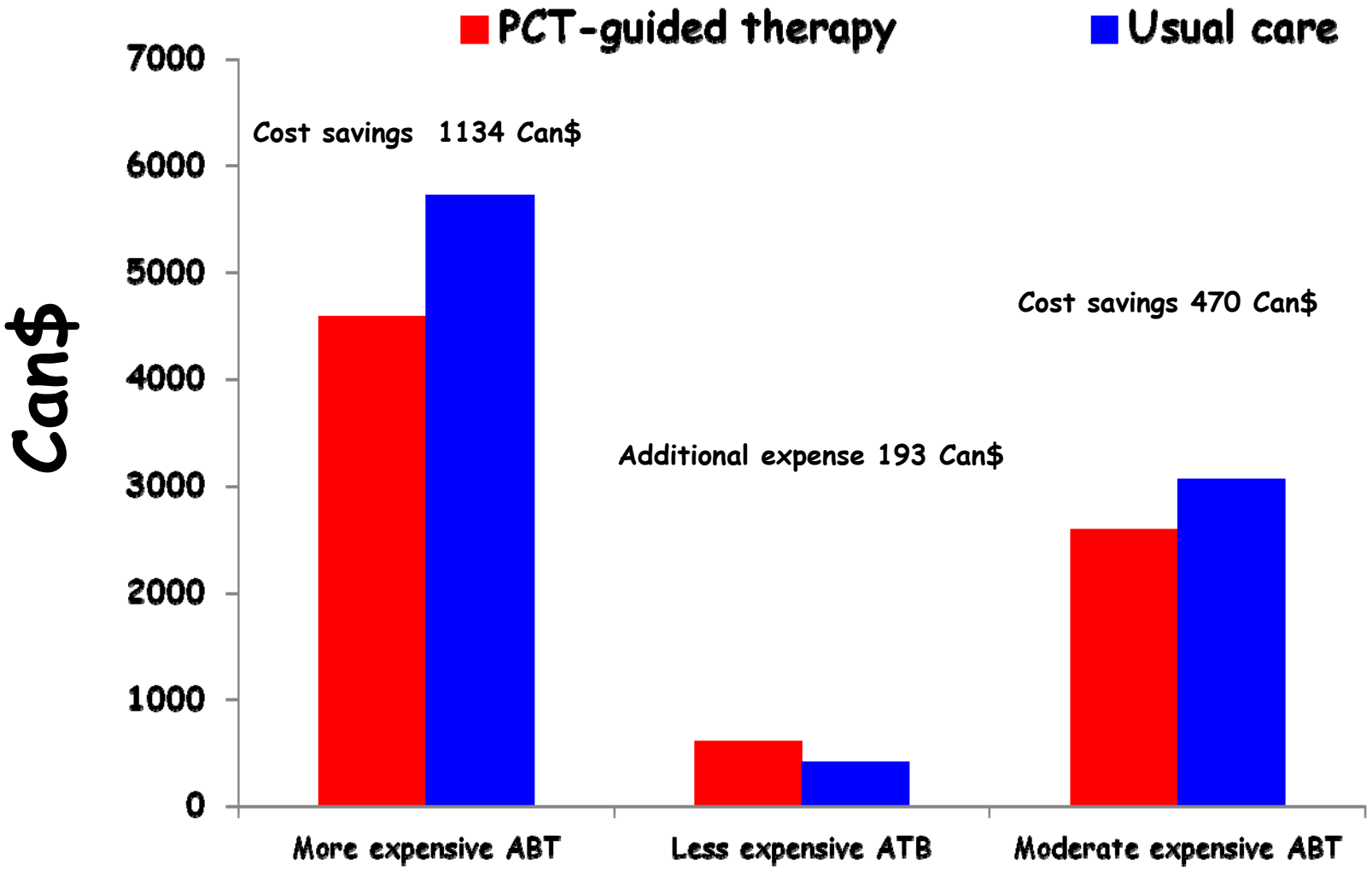
28-day mortality



Procalcitonin for reduced antibiotic exposure in the critical care setting: A systematic review and an economic evaluation*

Daren K. Heyland, MD, FRCPC, MSc; Ana P. Johnson, PhD; Steven C. Reynolds, MD, FRCPC;



Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: A randomized trial*

PASS STUDY: DESIGN

PCT group*
(n = 604)

↓

Predefined diagnostic (microbiology, radiology) and therapeutic interventions (ATB, surgical drainage

Standard-care group
(n = 596)

↓

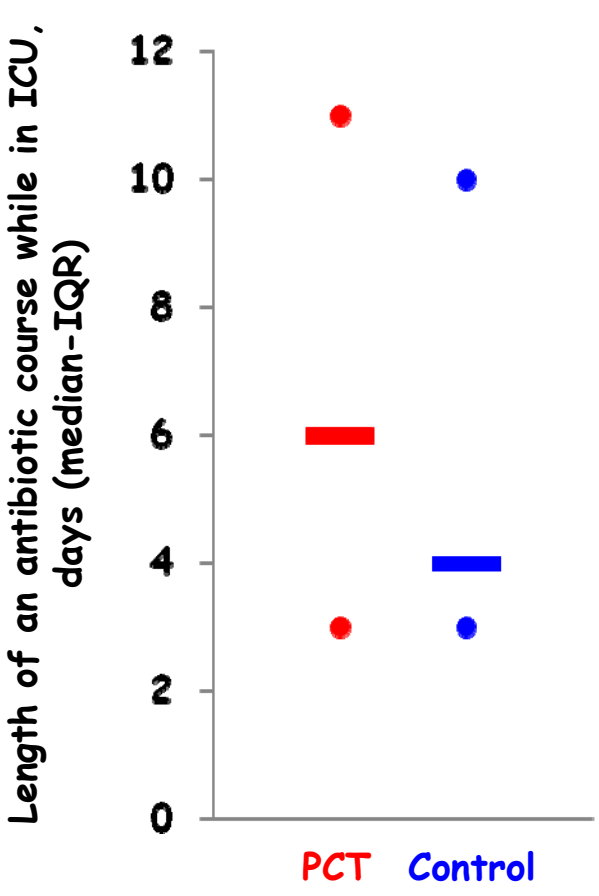
According to current international guidelines

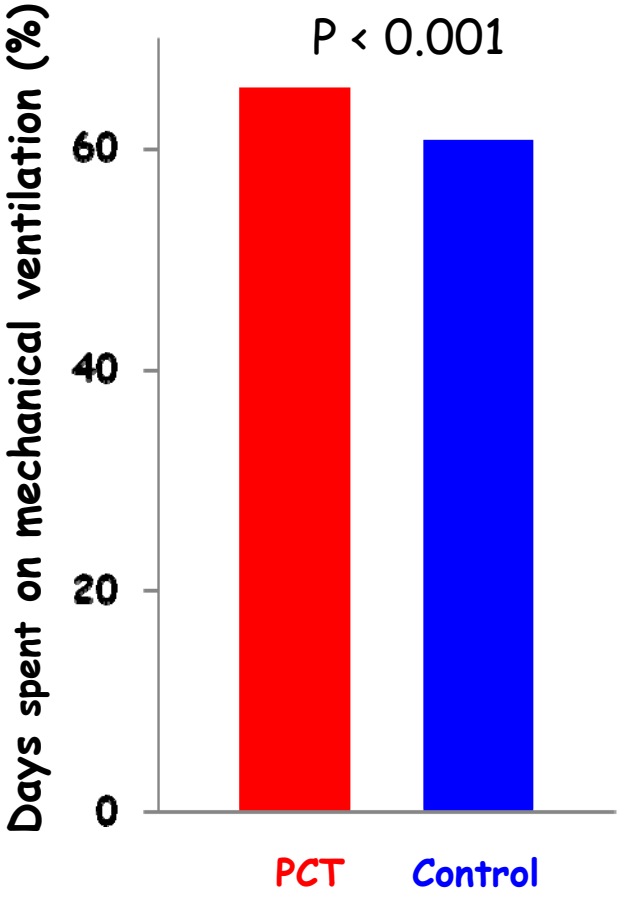
* Daily measurements

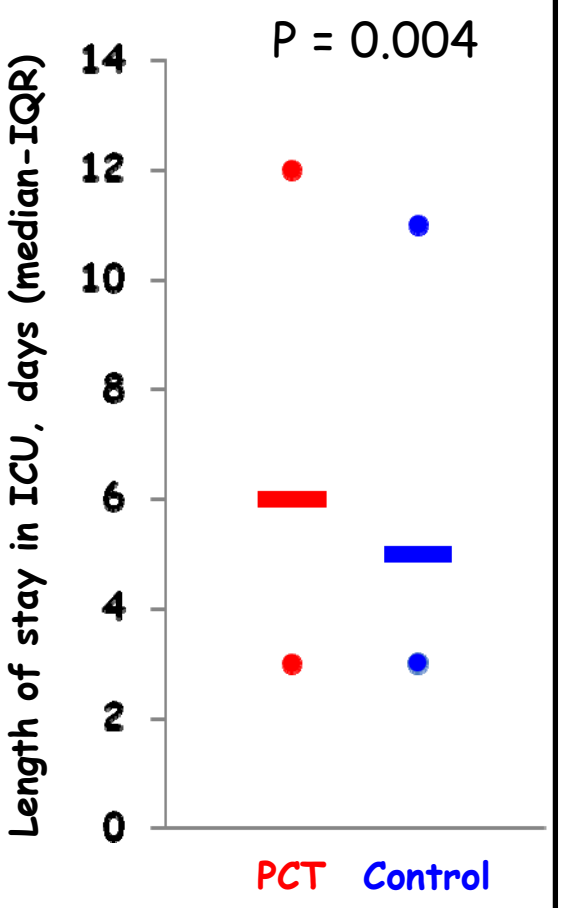
Jensen JU et al. Crit Care Med 2011;38:2048

Results

N = 1200 patients Mortality at D28: RR 0.98 [95%CI 0.83-1.16] (p = 0.83)







Conclusions: en réanimation

1. La PCT peut aider évaluer la gravité d'une infection grave et à prédire la positivité des hémocultures
2. En réanimation: PCT peu performante pour décider de débuter ou non l'antibiothérapie
3. L'arrêt des antibiotiques, même "précoce" peut être décidé, chez un malade stabilisé, en suivant un algorithme fondé sur la cinétique de PCT*

* Hayashi Y & DL. Paterson, Clin Infect Dis 2011