JNI 12es Journées Nationales d'Infectiologie

OPTIMISATION DES PRESCRIPTIONS ANTIBIOTIQUES

Intérêt des marqueurs biologiques

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Déclaration de conflits d'intérêts de 2009 à 2011

Stéphanie Ruiz

- Intervenant au titre d'orateur : Sanofi-Aventis
- Participation à des groupes de travail: LFB, Pfizer
- Invitations à des congrès ou des journées scientifiques: Pfizer, MSD

ET absence de conflits d'intérêt avec Brahms

A quoi sert un biomarqueur?

Role	Description	Examples
Diagnosis of a disease	To make a diagnosis more reliably, more rapidly, or more inexpensively than available methods	Troponin Ic diagnoses myocardial infarction[6] Procalcitonin diagnoses bacterial infection[7]
Severity assessment	To identify subgroup of patients with a severe form of a disease associated with an increased probability of death or severe outcome	Procalcitonin identifies severe outcome in septic patients[8] Troponin Ic identifies severe outcome in patients with pulmonary embolism[9]
Risk assessment	To identify subgroup of patients who may experience better (or worse) outcome when expose to an intervention	Brain natriuretic peptide and postoperative outcome in noncardiac surgery[10] Troponin and long term outcome in cardiac surgery[11]
Prediction of drug effects	To identify the pharmacological response of a patient exposed to a drug (efficacy, toxicity, and pharmacokinetics)	Efficacy of clopidogrel[15]
Monitoring	To assess the response to a therapeutic intervention	Procalcitonin may guide antibiotic duration[13]

Ray P. et al, Anesthesiology, 2010

A quoi sert un biomarqueur?

Role	Description
Diagnosis of a disease	To make a diagnosis more reliably, more rapidly, or more inexpensively than available methods
Monitoring	To assess the response to a therapeutic intervention

Ray P. et al, Anesthesiology, 2010

Quelques (!) biomarqueurs utilisables dans le diagnotic d'un sepsis

Table 10 Biomarkers that have been assessed for use in the diagnosis of sepsis

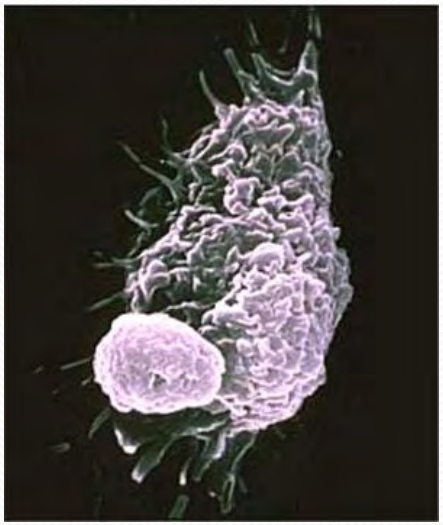
	Sepsis biomarker	Clinical study	Type of measurement	Outcome
1	aPTT** [35]	C	c	High negative predictive value
2	CD11b*** [33]	B	s	Higher values in neonates with sepsis than in those with possible infection
3	CD25 [87]	A	s	Distinguished between sepsis and SIRS
4	CD64*** [32,287]	C	s	Low sensitivity and specificity to distinguish between viral and bacterial infections
5	Complement (C3, C4, C5a) [219]	B	s	Distinguished between sepsis and SIRS
6	EA complex [230]	C	s	Diagnosis of sepsis, increased earlier than CRP
7	ELAM-1 (cellular and soluble) [129]	C(s)	c	Increased in trauma patients with sepsis compared with no sepsis
8	Endocan [127]	B	s	Distinguished between sepsis and SIRS
9	E-Selectin (cellular and soluble) [136]	B	s	Distinguished between sepsis and SIRS
10	Fibrin degradation products [36]	B	s	High negative predictive value
11	Gas6 [241]	B	s	Higher values in patients with severe sepsis compared with patients with organ failure but no sepsis

				postoperative patients
28	pFN [270]	B	s	Distinguished between sepsis and SIRS
29	PLA2-II (soluble)*** [31]	B	s	Distinguished between bacteremic and non-bacteremic infections
30	Serum lysozyme (enzyme activity) [258]	B	s	Distinguished between sepsis and organ rejection in transplanted patients
31	ST2 (soluble) [108]	A	s	Higher in septic patients compared with those with no sepsis
32	Surfactant protein (A, B, C, D) [192]	B	s	Early diagnosis of ARDS in septic patients
33	TREM-1 (soluble) [288,289]	C	s	Distinguished between sepsis and SIRS, diagnosed pneumonia
34	Troponin [193]	B	s	Diagnosis of myocardial dysfunction in septic patients

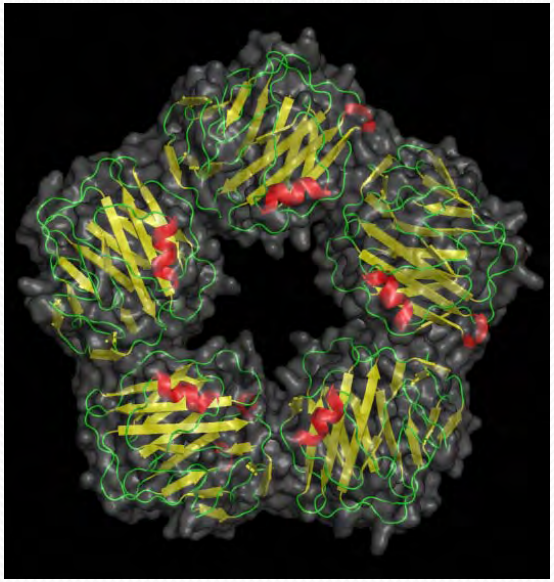
Pierrakos C et Vincent JL, Critical Care, 2010

Marqueurs du sepsis utilisés en routine

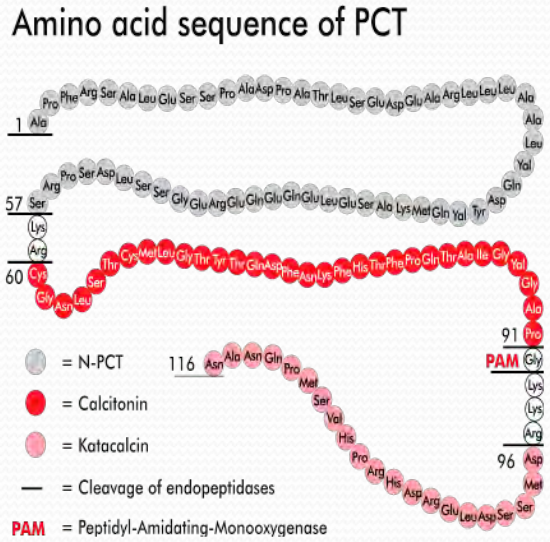
- Leucocytes, neutrophiles



- CRP

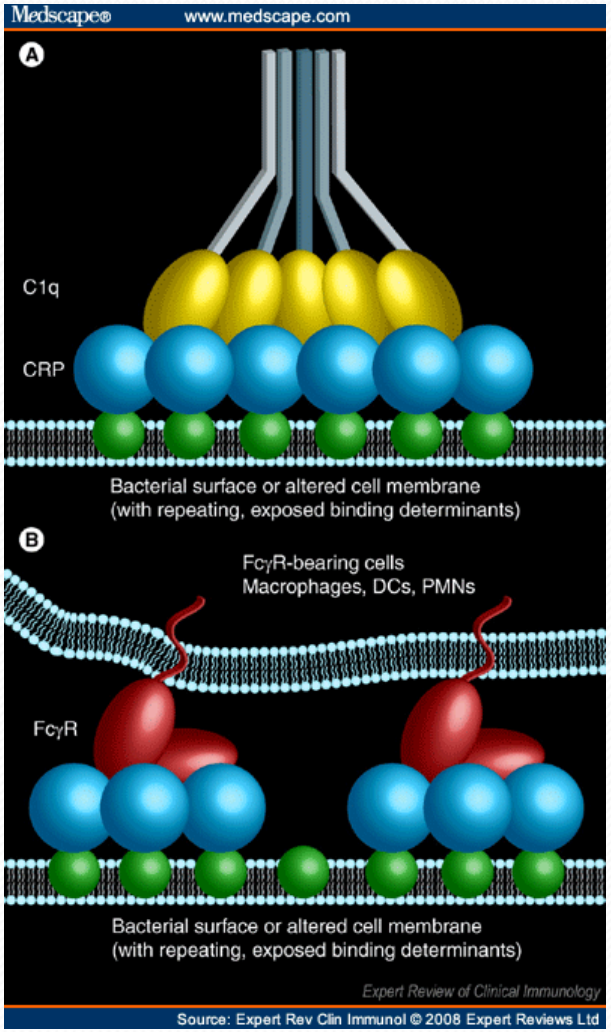


- PCT



C-Reactive Protein

- Découverte 1930
- Synthétisée par le foie
- Liaison aux résidus phosphocholines bactériens et fungiques: opsonisation phagocytose, activation du complément
- Protéine non spécifique de l'inflammation



Procalcitonine

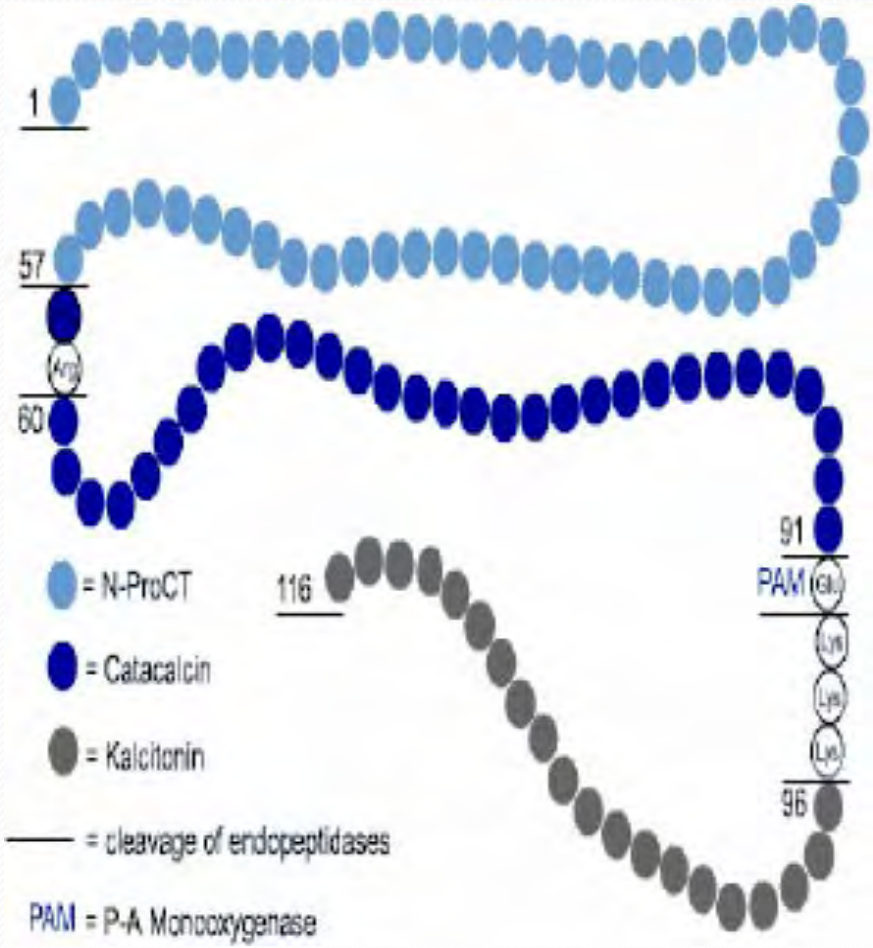
- Amino-peptide de 116 aa (12.6 kDa)

- **PCT : pro-hormone de la CT**

Concentration sanguine < 0,05 ng/ml

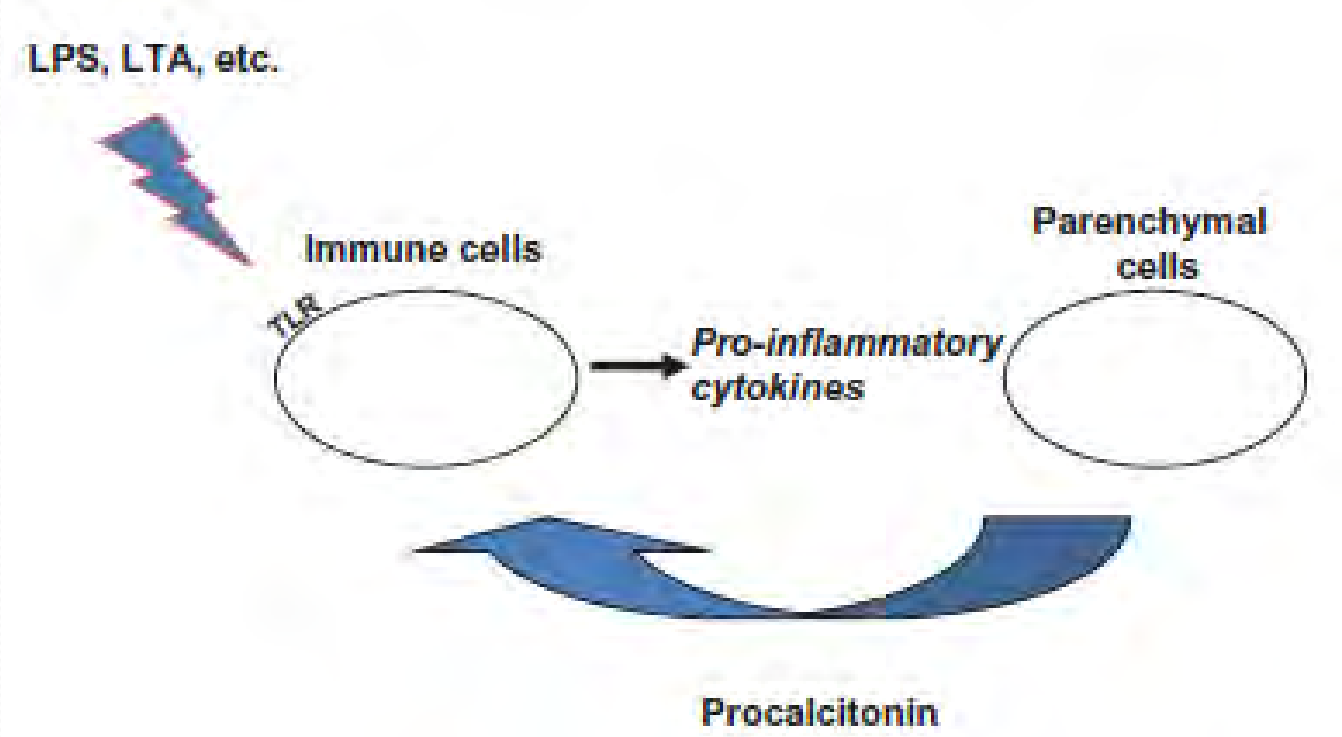
- Cellules C de la thyroïde et neuroendocriniennes du poumon.

- Protéolyse → Calcitonine (hypocalcémiante)



Procalcitonine

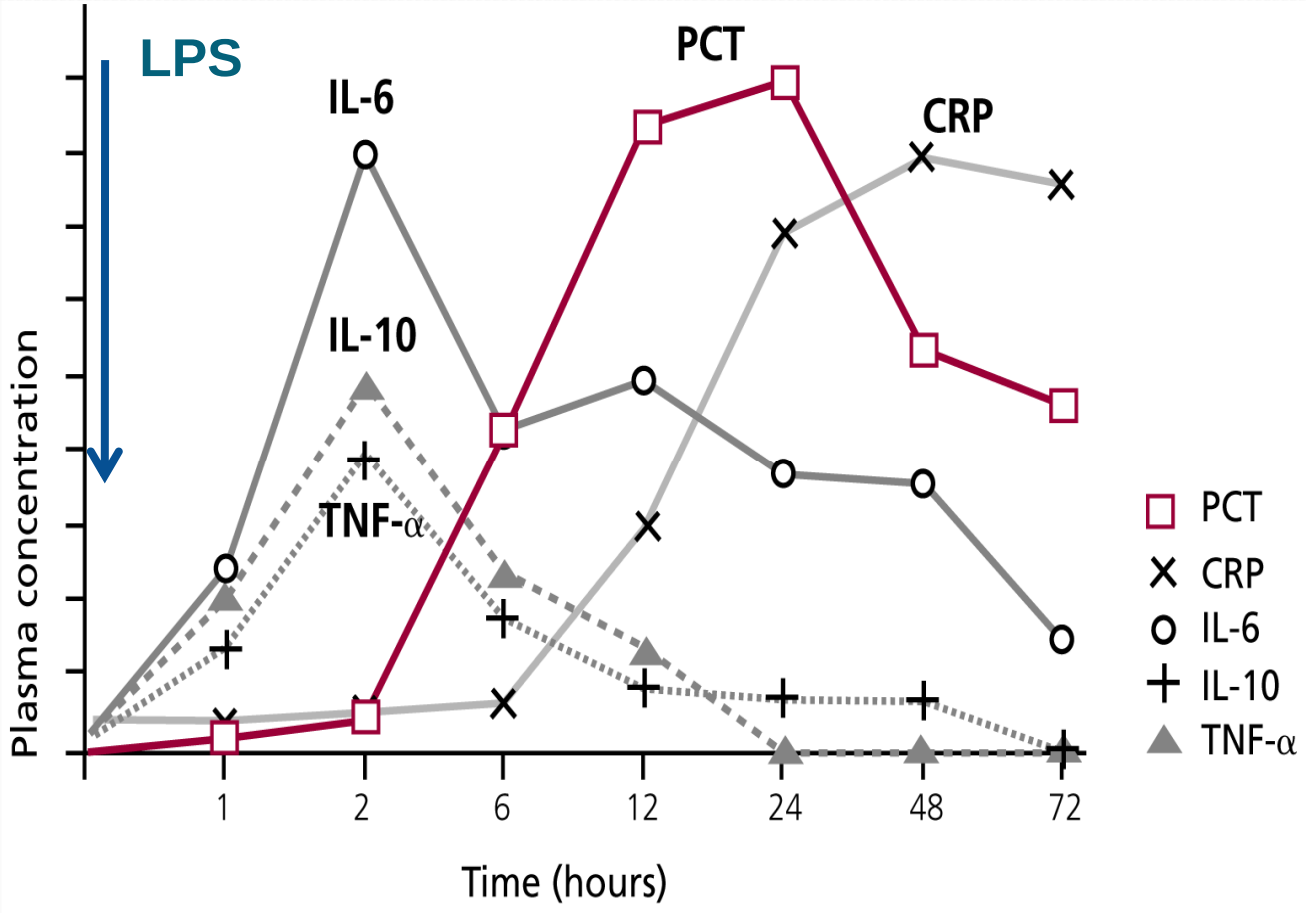
- Sepsis: ProCT retrouvée dans le sang, produite par d'autre(s) type(s) cellulaire(s) et organes



- Sepsis → "Hormokine" : Comportement d'une hormone comme une cytokine

Kenneth KL, BJP, 2010

Cinétique



Meisner M. et al., J Lab Med, 1999,

Procalcitonine

Faux positifs

- **SIRS primaire après traumatisme**
- **Paludisme, infection fongique systémique**
- **Défaillance circulatoire prolongée:** choc cardiogénique prolongé, choc hémorragique, choc thermique
- **Traitement agissant sur la cascade des CK pro-inflammatoires :** anti-rejet OKT3, TNFα, IL-2
- **Certains cancers** (cancers médullaires à CT de la thyroïde, carcinome pulmonaire à petites cellules et carcinome bronchique)

Faux négatifs

- **Infections localisées**
- **Phase précoce de l'infection**
- **Infection décapitée**

Biomarqueurs: aide à l'instauration de l'antibiothérapie?

Usefulness of Procalcitonin as a Marker of Systemic Infection in Emergency Department Patients: A Prospective Study

P. Hausfater,[1] S. Garric,[1] S. Ben Ayed,[2] M. Rosenheim,[3] M. Bernard,[2] and B. Riou[1]

[1]Service d'Accueil des Urgences, [2]Laboratoire de Biochimie C, and [3]Departement de Santé Publique, Hôpital La Pitié-Salpêtrière, Paris, France

Clinical Infectious Diseases 2002; 34:895–901

- 195 patients des urgences suspects d'infection ou de maladie inflammatoire

Valeur seuil PCT 0,5 ng/mL

Table 4. Univariate analysis of variables at admission to the emergency department, comparing the entire study group, group I (patients with systemic infection), and group II (patients with no systemic infection).

Variable	No. (%) of patients with available data	Mean value ± SD, by patient group: All (*n* = 195)	Group II (*n* = 127)	Group I (*n* = 68)	*P*[a]
Procalcitonin level, ng/mL	195 (100)	1.9 ± 9.5	0.09 ± 0.09	5.3 ± 15.6	<.001[b]
Body temperature, °C	156 (80)	38 ± 0.08	37.7 ± 0.9	38.6 ± 1.1	<.001[b]
C-reactive protein level, mg/L	184 (94.3)	82 ± 114	80 ± 102	88 ± 135	.9

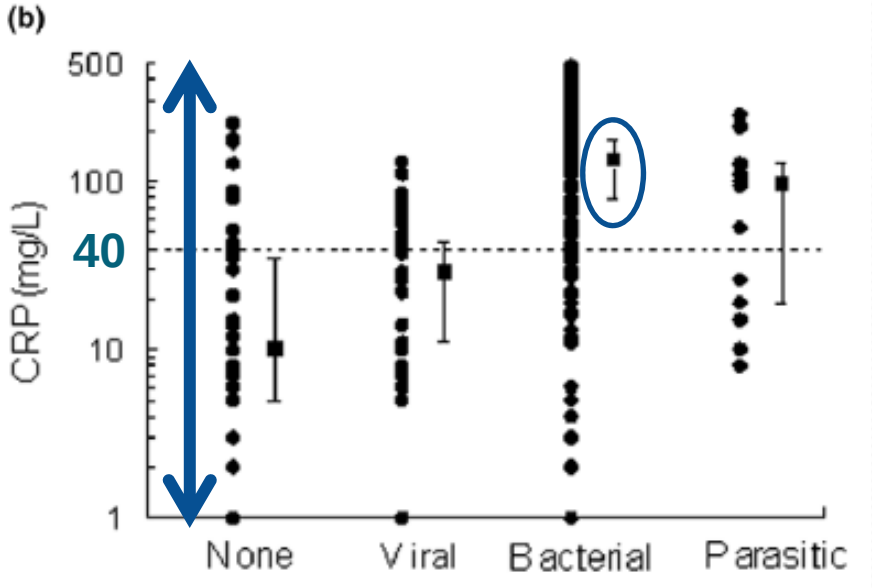
- Multivariée: seule la PCT est associée à l'infection systémique (OR 43.5; 95% CI, 7.9–1000; *P* = 0.0004)

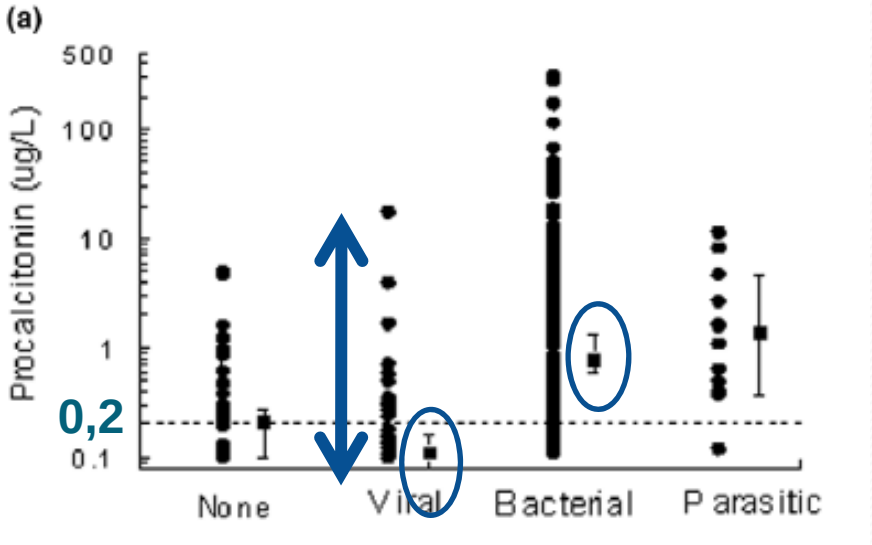
Serum procalcitonin measurement as diagnostic and prognostic marker in febrile adult patients presenting to the emergency department

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

Critical Care 2007, 11:R60

N = 243





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

Critical Care 2007, 11:R60

PCT and CRP versus emergency physician judgement in diagnosing bacterial/parasitic infection

Test and cutoff	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
CRP					
≥ 5 mg/l	0.96 (0.91–0.98)	0.16 (0.09–0.26)	0.71 (0.65–0.77)	0.63 (0.41–0.81)	0.71 (0.64–0.76)
≥40 mg/l	0.76 (0.69–0.82)*	0.62 (0.51–0.72)	0.81 (0.74–0.87)	0.54 (0.44–0.64)*	0.71 (0.65–0.77)
≥100 mg/l	0.54 (0.46–0.62)	0.90 (0.82–0.95)	0.93 (0.85–0.96)	0.47 (0.39–0.56)	0.65 (0.59–0.71)
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)	0.72 (0.66–0.77)
≥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)*	0.71 (0.65–0.77)
≥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)	0.68 (0.62–0.73)
≥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)	0.54 (0.48–0.60)
≥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)	0.46 (0.40–0.53)
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)	0.76 (0.70–0.81)

Shown is a comparison of performance of procalcitonin (PCT) and C-reactive protein (CRP) with emergency physician for the diagnosis of bacterial/parasitic infection, with the 'gold standard' being experts diagnosis. *$P < 0.05$, versus emergency physician. CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial

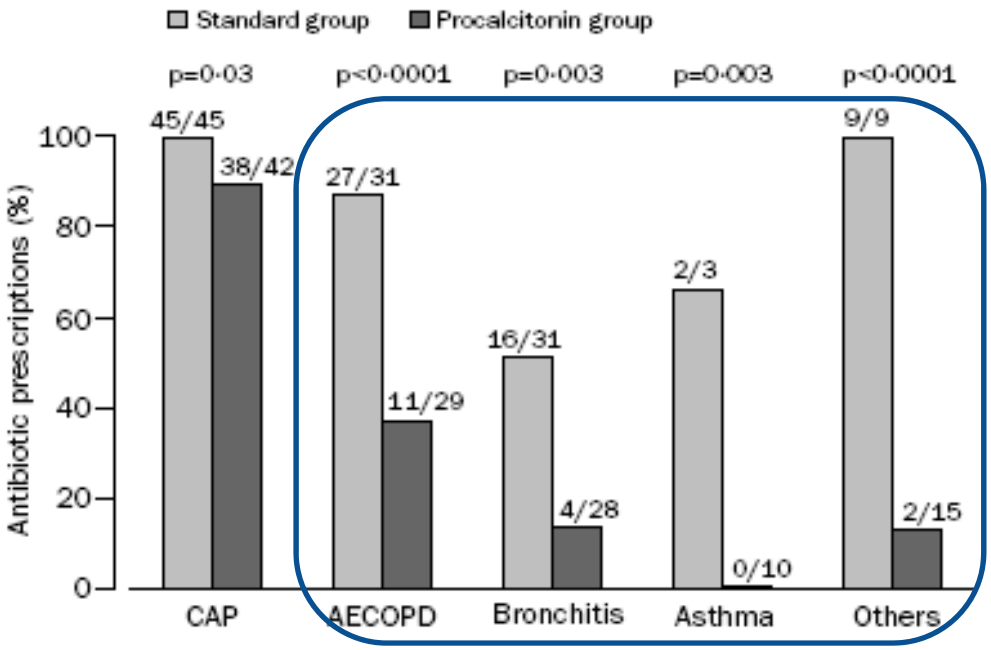
Mirjam Christ-Crain, Daiana Jaccard-Stolz, Roland Bingisser, Mikael M Gencay, Peter R Huber, Michael Tamm, Beat Müller

Lancet 2004; **363:** 600–07

Patients:
243 Patients presenting to ER with infections of the lower respiratory tract

Design:
Interventional study with Kryptor PCT;
Randomization of patients in standard group (standard antibiotic therapy) and PCT-group

Algorithm in the PCT-group:
- ✓PCT< 0.1 ng/ml : NO Antibiotic prescription
- ✓PCT<0.25 ng/ml: Antibiotics not recommended
- ✓PCT>0.25 ng/ml: Antibiotics recommended
- ✓PCT > 0.5 ng/ml: Antibiotics have to be given!

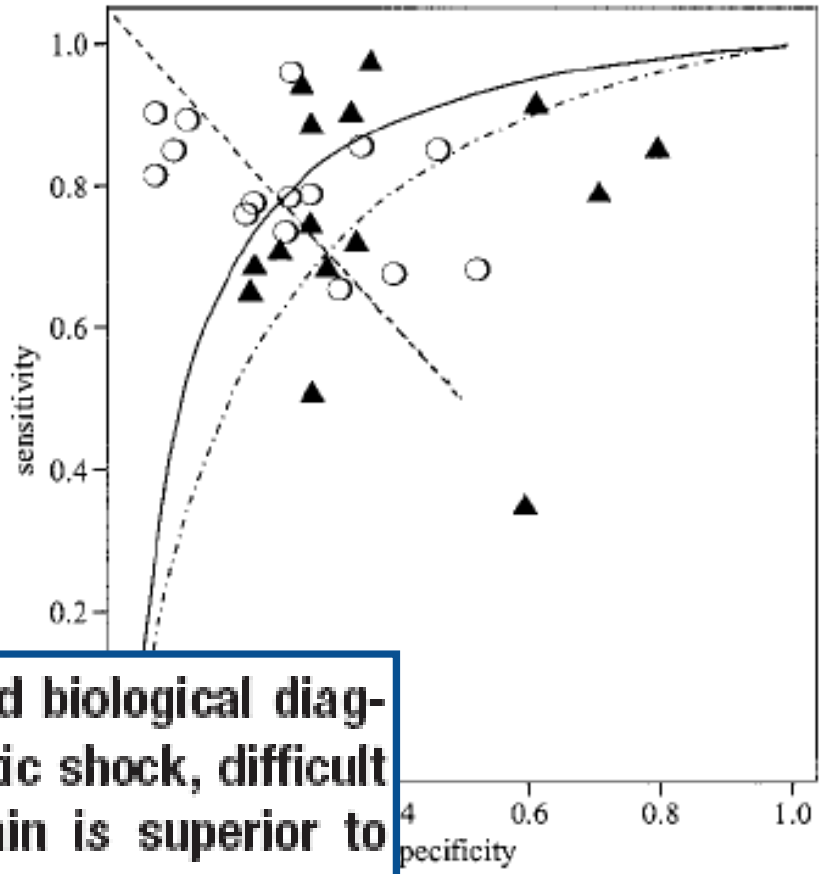


Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: A systematic review and meta-analysis

Bernard Uzzan, MD; Régis Cohen, MD, PhD; Patrick Nicolas, PharmD, PhD;
Michel Cucherat, MD; Gérard-Yves Perret, MD, PhD

Crit Care Med 2006; 34:1996–2003

- 25 études entre 1997 et 2004
- 2966 adultes
- OR diagnostique
  - PCT = 14,7 (IC: 9,1 – 27,1)
  - CRP = 5,4 (IC: 3,2 – 9,2)



er operating characteristics
(*circle, solid line*) and C-
e, dashed line), according
model; n = 15 studies.

Conclusions: **Procalcitonin represents a good biological diagnostic marker for sepsis, severe sepsis, or septic shock, difficult diagnoses in critically ill patients. Procalcitonin is superior to C-reactive protein. Procalcitonin should be included in diagnostic guidelines for sepsis and in clinical practice in intensive care units. (Crit Care Med 2006; 34:1996–2003)**

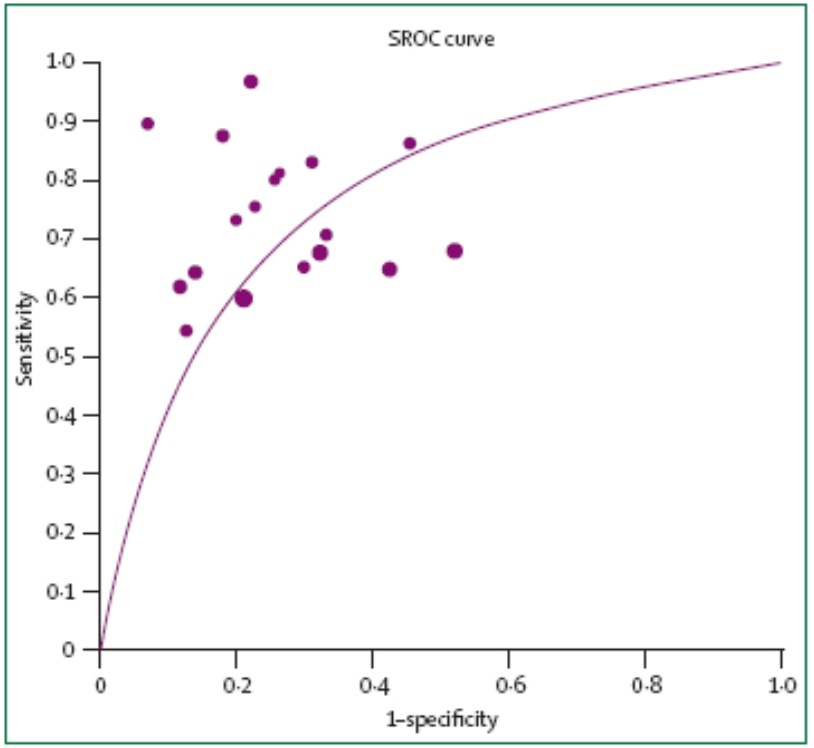
Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis

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

Lancet Infect Dis 2007; 7: 210–17

- 18 études entre 1996 et 2005
  - 2097 adultes
  - 80% en soins intensifs

- Aire sous la courbe ROC à 0,79
- Se et Sp 71 %
- VPP 3·03 (95% CI 2·51–3·65)
- VPN 0·43 (95% CI 0·37–0·48)

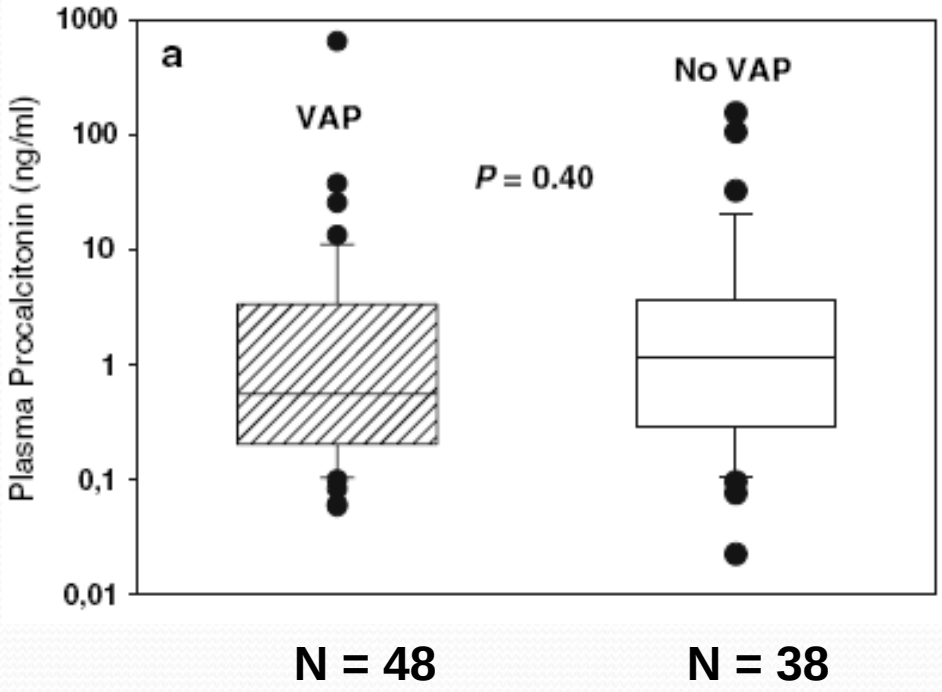


Procalcitonin cannot reliably differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome in critically ill adult patients. The findings from this study do not lend support to the widespread use of the procalcitonin test in critical care settings.

PCT et PAVM

Microbiogical data, but not procalcitonin improve the accuracy of the clinical pulmonary infection score

Jung et al, ICM, 2010



Usefulness of procalcitonin for the diagnosis of ventilator-associated pneumonia

Luyt et al, ICM, 2008

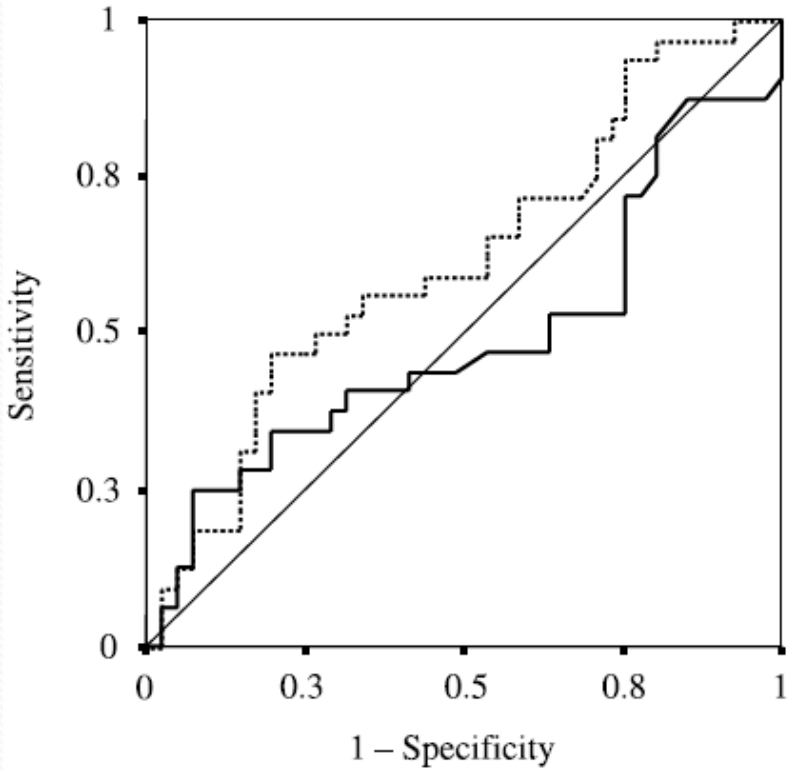


Fig. 1 ROC curves of day-1 PCT (*bold line*) and PCT increase (*dotted line*), with respective areas under the curves of 0.51 (95% CI 0.39–0.63) and 0.62 (95% CI 0.50–0.73)

CRP et PAVM

Research

Open Access

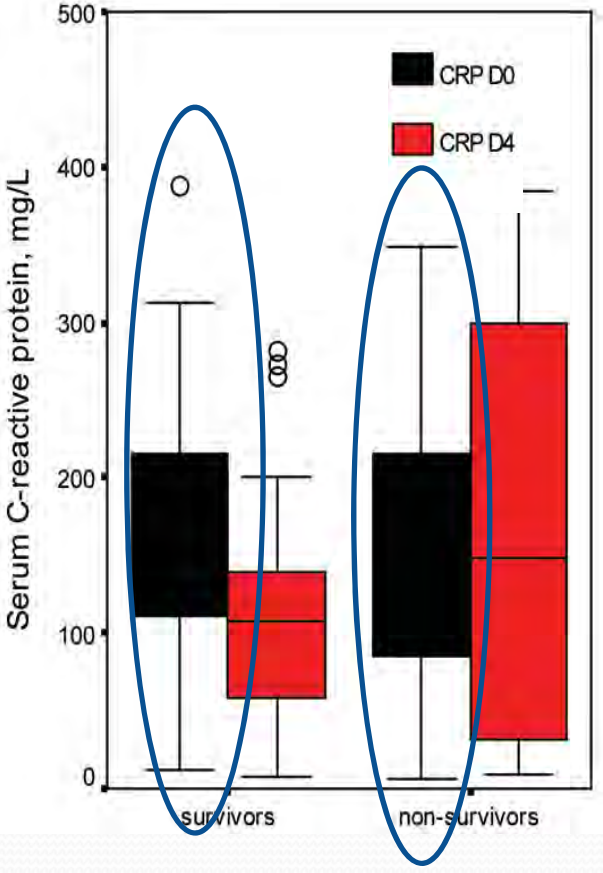
Decreases in procalcitonin and C-reactive protein are strong predictors of survival in ventilator-associated pneumonia

Renato Seligman[1,2], Michael Meisner[3], Thiago C Lisboa[2], Felipe T Hertz[2], Tania B Filippin[2], Jandyra MG Fachel[4] and Paulo JZ Teixeira[1,5]

Critical Care 2006, 10:R125

- 75 patients

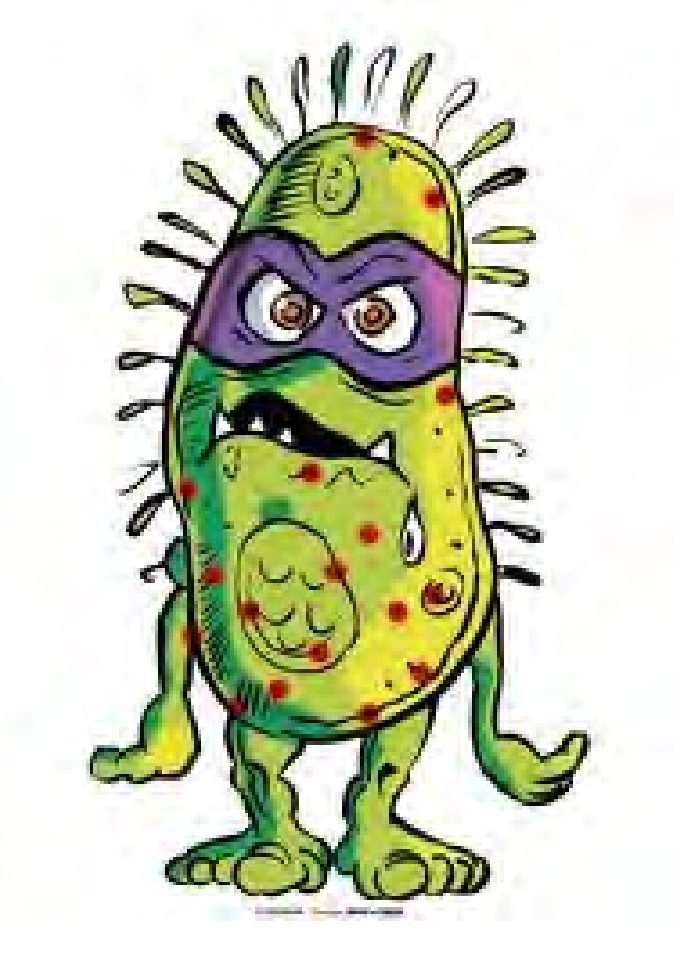
Parameter	Survivors ($n = 45$)	Non-survivors ($n = 23$)
Procalcitonin D0	0.58 (0.08–19.60)	2.18 (0.19–21.33)
Procalcitonin D4	0.30 (0.08–36.19)	3.44 (0.39–17.00)
C-reactive protein D0	160.0 (11.6–388.0)	167.5 (5.6–349.0)
C-reactive protein D4	108.0 (6.8–282.0)	148.0 (9.0–384.0)



Aide pour l'initiation?

- Le clinicien reste le meilleur élément diagnotique !
- Pas de place pour la CRP dans ce cadre
- Pas de PCT pour « voir », si l'infection est évidente
- MAIS aide à la prescription d'antibiotiques dans certaines situations floues de suspicion d'infection communautaire (exacerbation de BPCO…)
- Pas de place dans le diagnostic des infections nosocomiales en réa (sauf si cinétique)

Biomarqueurs: aide pour la durée du traitement?



Procalcitonin Guidance of Antibiotic Therapy in Community-acquired Pneumonia

A Randomized Trial

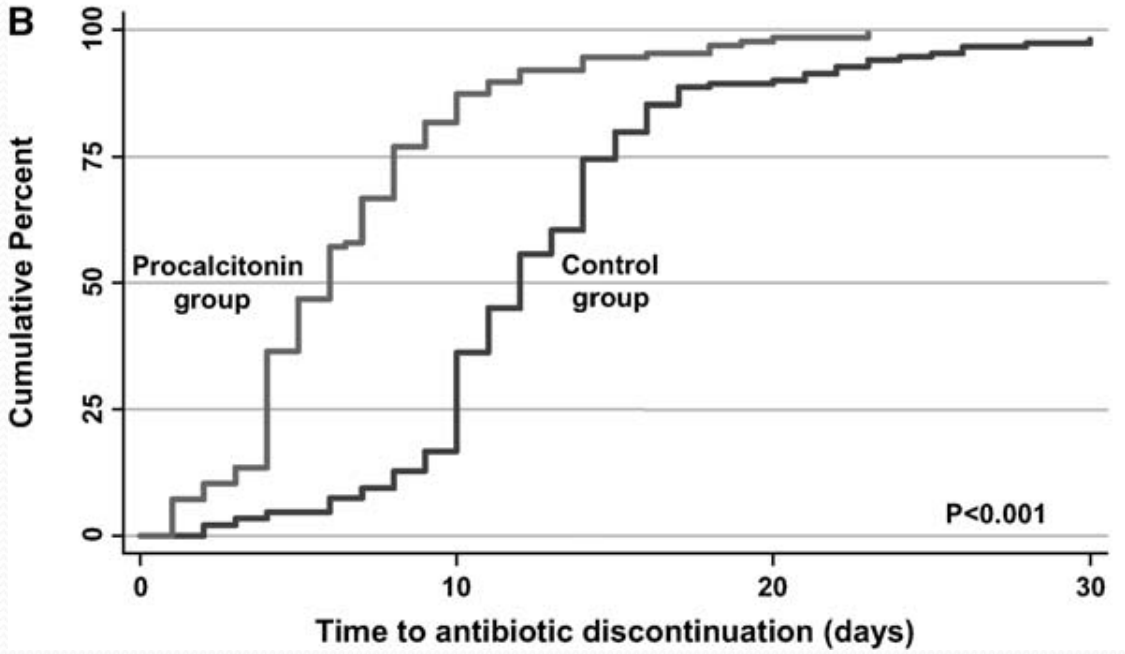
Mirjam Christ-Crain, Daiana Stolz, Roland Bingisser, Christian Müller, David Miedinger, Peter R. Huber, Werner Zimmerli, Stephan Harbarth, Michael Tamm, and Beat Müller

Am J Respir Crit Care Med Vol 174. pp 84–93, 2006

Algorithm in the PCT-group:

✓PCT< 0.1 ng/ml : NO Antibiotic prescription
✓PCT<0.25 ng/ml: Antibiotics not recommended
✓PCT>0.25 ng/ml: Antibiotics recommended
✓PCT > 0.5 ng/ml: Antibiotics have to be given!

Arrêt antibiotiques:
- si PCT < 0,25 ng/ml
- si ↓ PCT > 90 %



- 302 patients:
  - 151 groupe PCT
  - 151 groupe contrôle

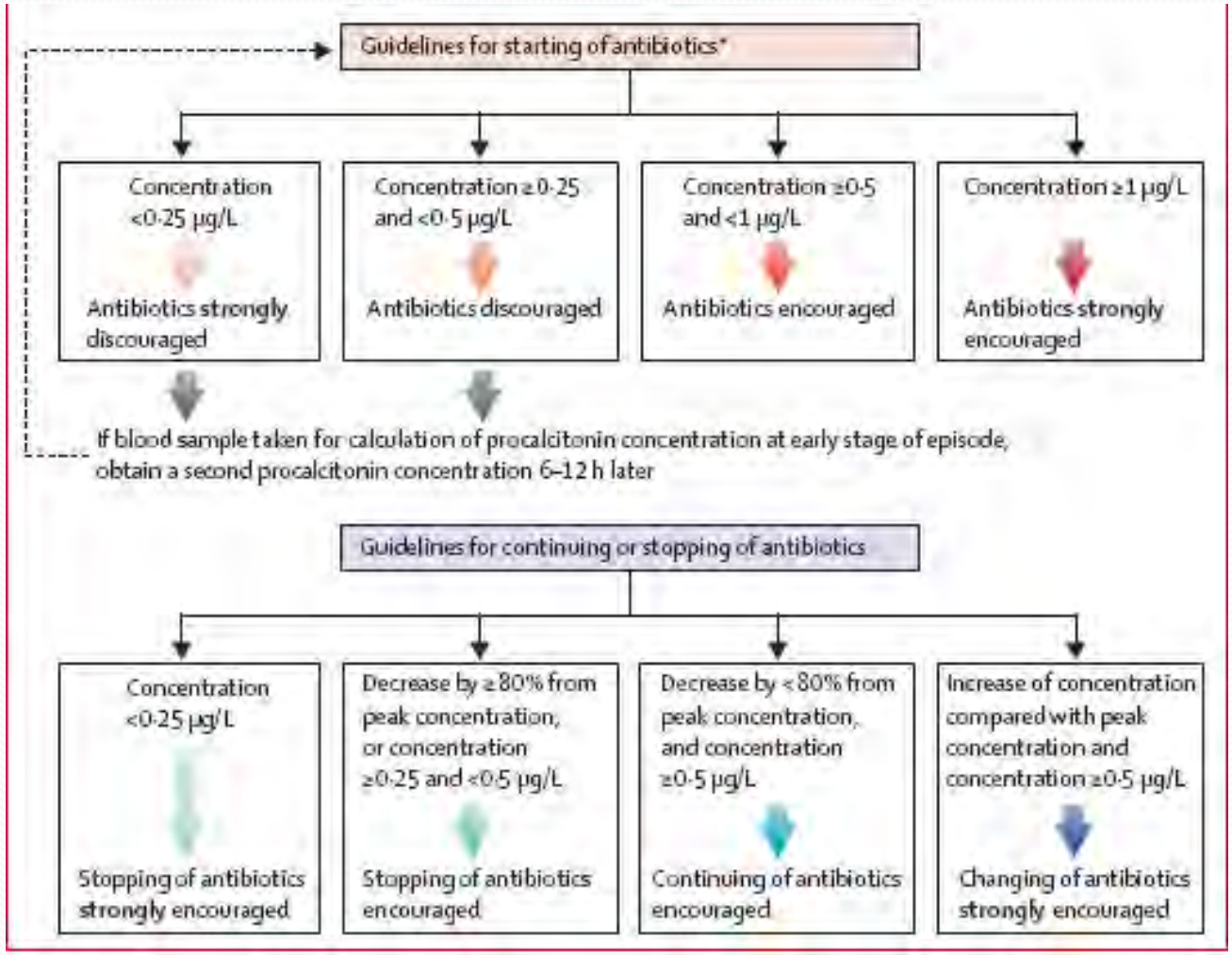
- A 6 semaines:

Complications NS (entrée en réa, rechutes, décès liés à la pneumopathie)

Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial

Lila Bouadma, Charles-Edouard Luyt, Florence Tubach, Christophe Cracco, Antonio Alvarez, Carole Schwebel, Frédérique Schortgen, Sigismond Lasocki, Benoît Veber, Monique Dehoux, Maguy Bernard, Blandine Pasquet, Bernard Régnier, Christian Brun-Buisson, Jean Chastre, Michel Wolff,* for the PRORATA trial group†*

Lancet 2010; 375: 463–74



- Groupes:

- PCT 307 patients
- contrôle 314 patients

Prorata

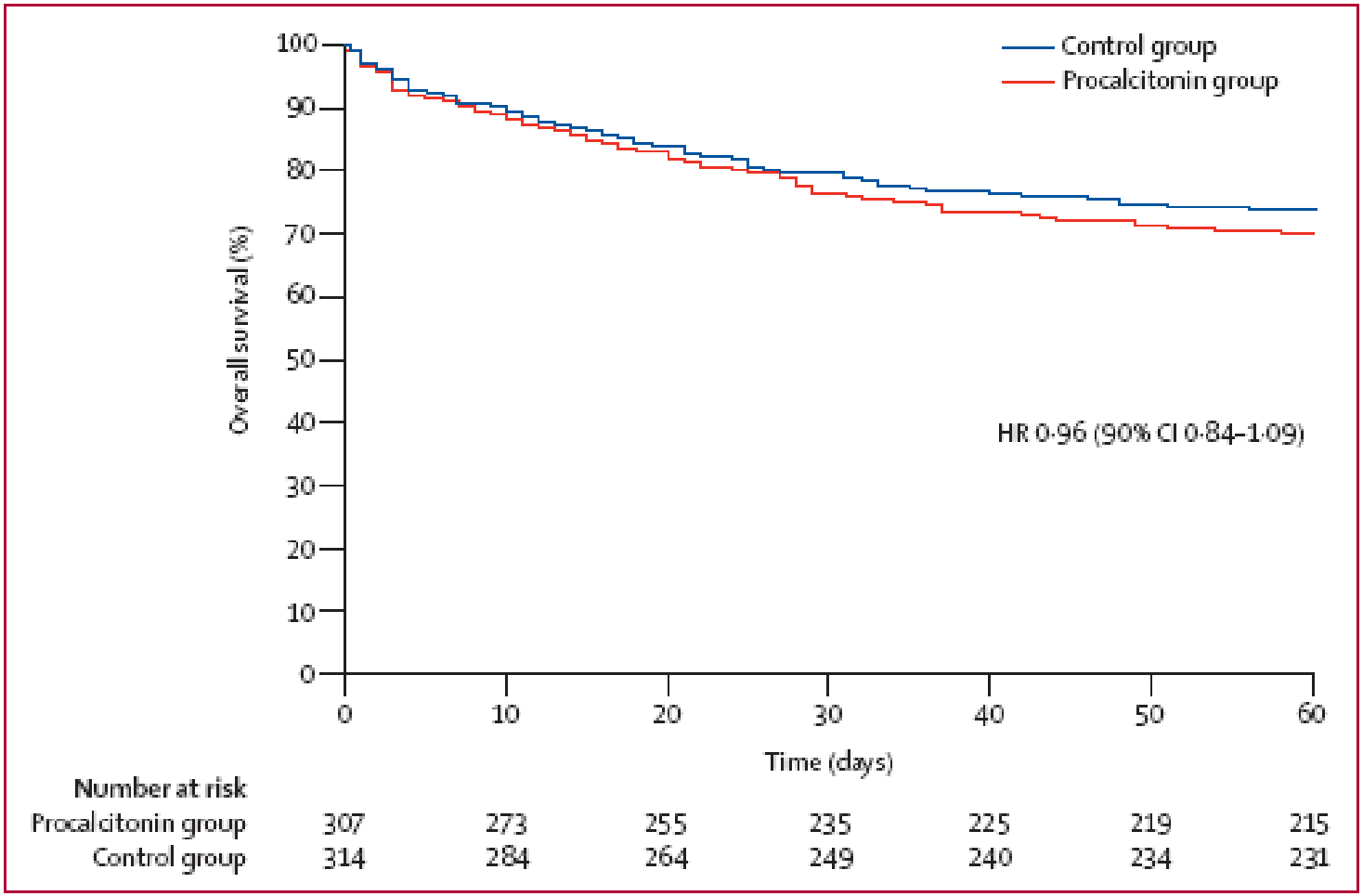
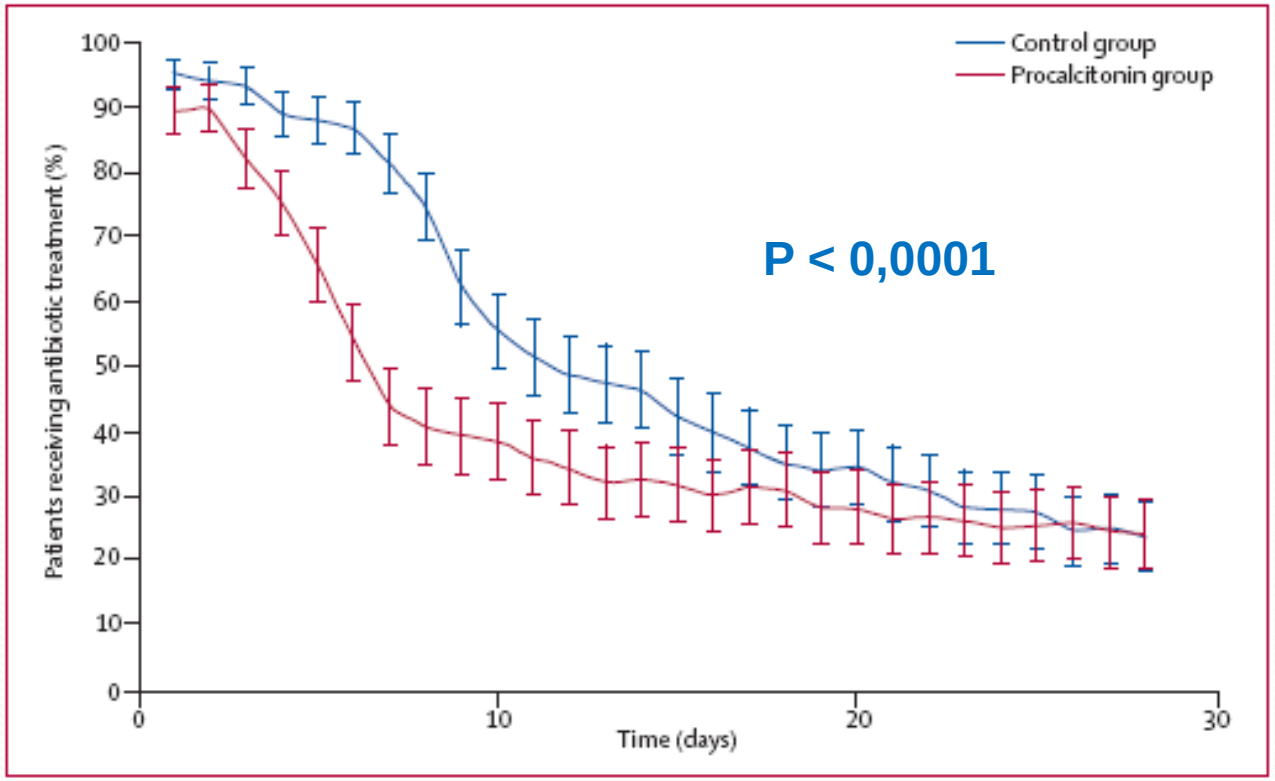


Figure 3: **Kaplan-Meier estimates of the probability of survival**
HR=hazard ratio. No significant difference (log-rank test) was recorded between patients assigned to the procalcitonin group and control group.

Prorata



	Procalcitonin group (n=307)	Control group (n=314)	Between-group absolute difference	p value
Primary endpoints				
Number of days without antibiotics	14·3 (9·1)	11·6 (8·2)	2·7 (1·4 to 4·1)	<0·0001

Prorata

	Procalcitonin group (n=307)	Control group (n=314)	Between-group absolute difference	p value
Secondary endpoints (days 1–28)				
Relapse	20 (6·5%)	16 (5·1%)	1·4% (–2·3 to 5·1)	0·45
Superinfection	106 (34·5%)	97 (30·9%)	3·6% (–3·8 to 11·0)	0·29
Number of days without mechanical ventilation	16·2 (11·1)	16·9 (10·9)	–0·7 (–2·4 to 1·1)	0·47
Length of stay in ICU from inclusion (days)	15·9 (16·1)	14·4 (14·1)	1·5 (–0·9 to 3·9)	0·23
Length of stay in hospital from inclusion (days)	26·1 (19·3)	26·4 (18·3)	–0·3 (–3·2 to 2·7)	0·87
Multidrug-resistant bacteria†	55 (17·9%)	52 (16·6%)	1·3% (–4·6 to 7·2)	0·67
Days of antibiotic exposure per 1000 inpatient days	653	812	–159 (–185 to –131)	<0·0001

La PCT pour élargir le traitement?

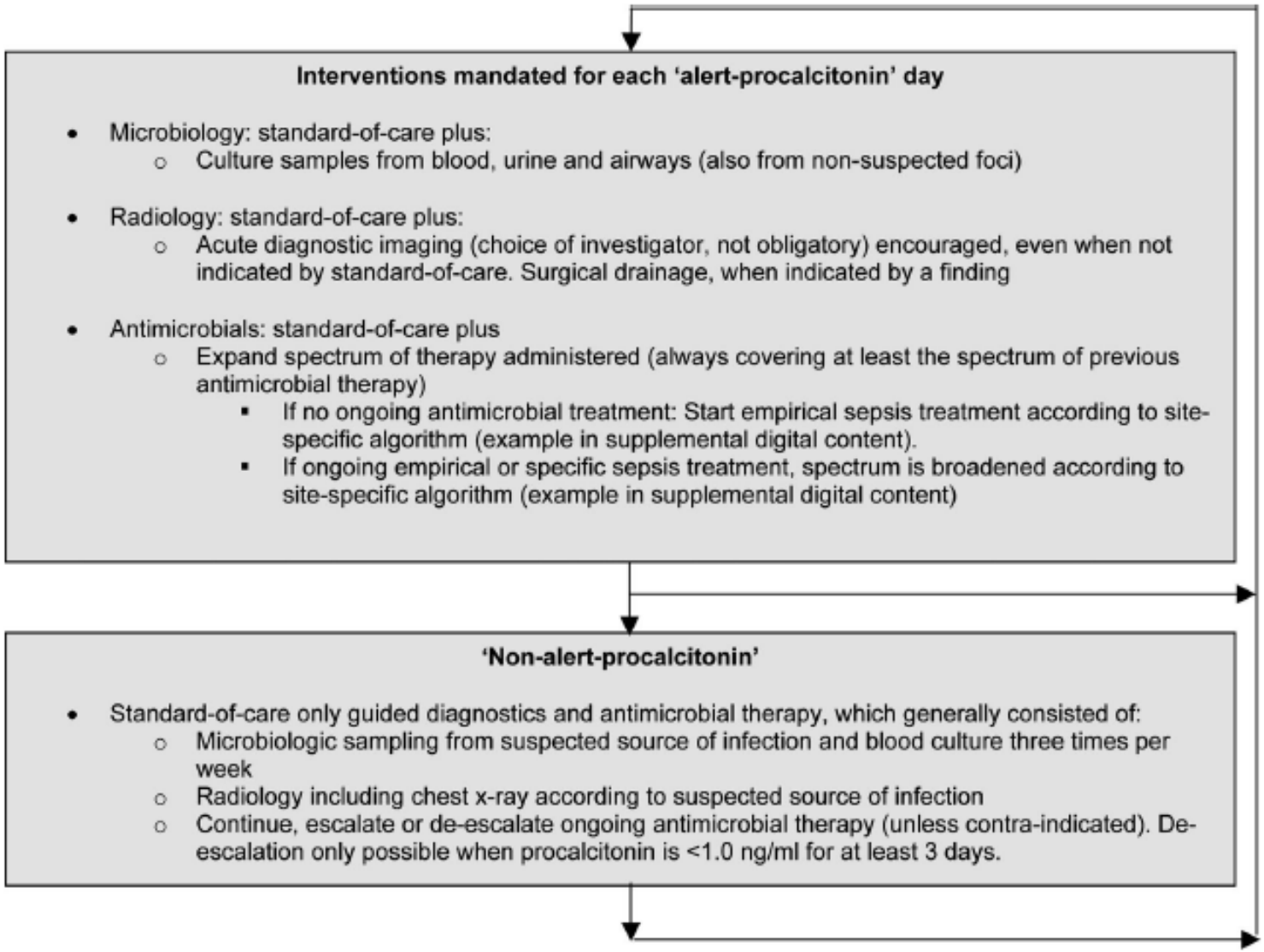
Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: A randomized trial

Jensen JU et al, Crit Care Med, 2011

- 1200 patients de réanimation danoises:
  - bras thérapeutique guidée par PCT 604
  - bras contrôle 596

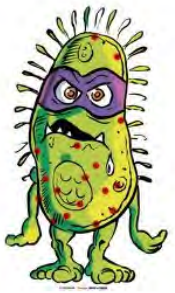
Conclusions: **Procalcitonin-guided antimicrobial escalation in the intensive care unit did not improve survival and did lead to organ-related harm and prolonged admission to the intensive care unit. The procalcitonin strategy like the one used in this trial cannot be recommended. (Crit Care Med 2011; 39:000–000)**

PASS study group



« Alert PCT » = PCT ≥ 1 ng/ml et pas de ↓ d'au moins 10% par rapport au jour précédent

Biomarqueurs: aide pour la durée du traitement?



- Probablement oui, pour diminuer la durée des antibiotiques

  → Intérêt d'une cinétique

  → Eviter les antibiotiques à tort…

- Mais ne semble pas être un guide du type d'antibiothérapie à prescrire….

Merci