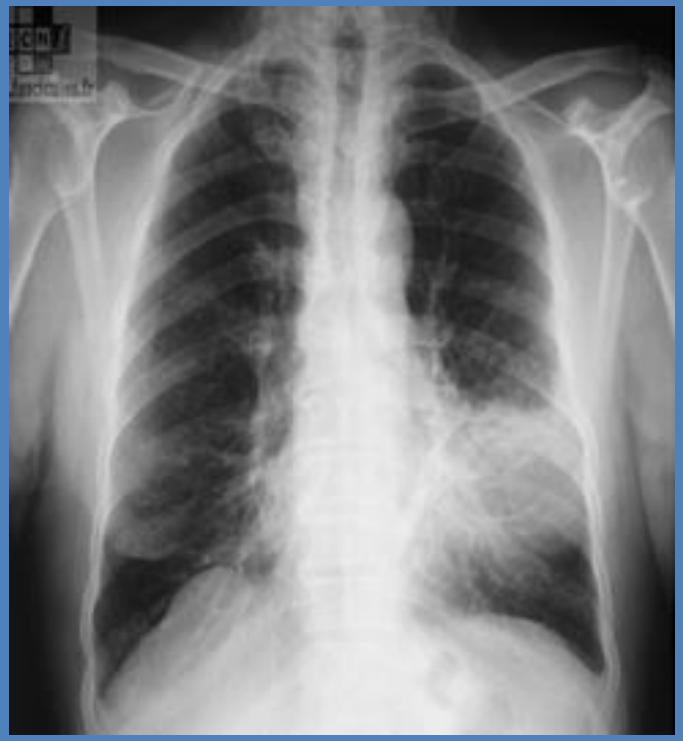
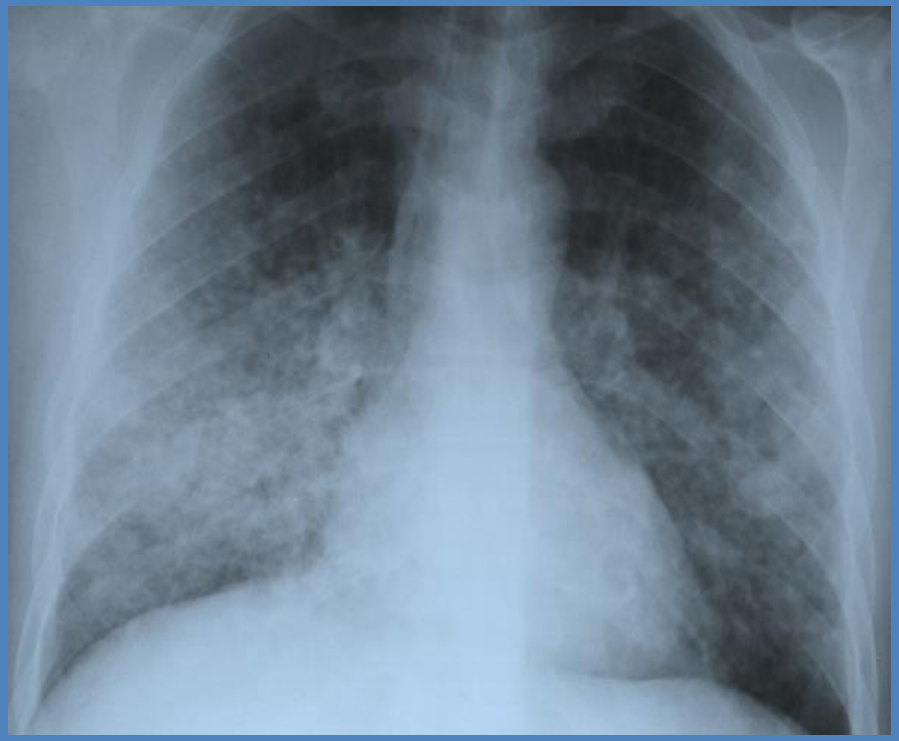
Place actuelle des biomarqueurs de l'infection en réanimation

Pr Ag Anis Chaari
Service de réanimation médicale
CHU Habib Bourguiba - Sfax

Rationnel de l'utilisation d'un biomarqueur





Diagnostic pas toujours facile !!

Quel(s) outils utiliser ?

- **Examen clinique avant tout (++).**
- **Electrocardiogramme → SCA ?**
- **Monitorage hémodynamique invasif ou non.**
- **Biomarqueurs.**

Biomarqueur ?

Un paramètre mesuré objectivement servant comme indicateur de processus physiologiques normaux, de processus pathologiques ou d'une réponse pharmacologique suite à une intervention thérapeutique.

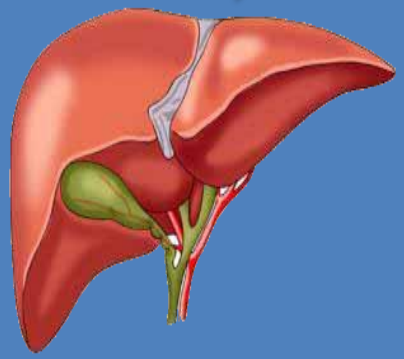
Samraj et al Shock. 2013 ; 40(5): 358–365.

C reactive Protein (CRP)

Conflit entre
l'immunité de l'hôte
et l'agent pathogène

IL6 (+++)

Cytokines pro inflammatoires

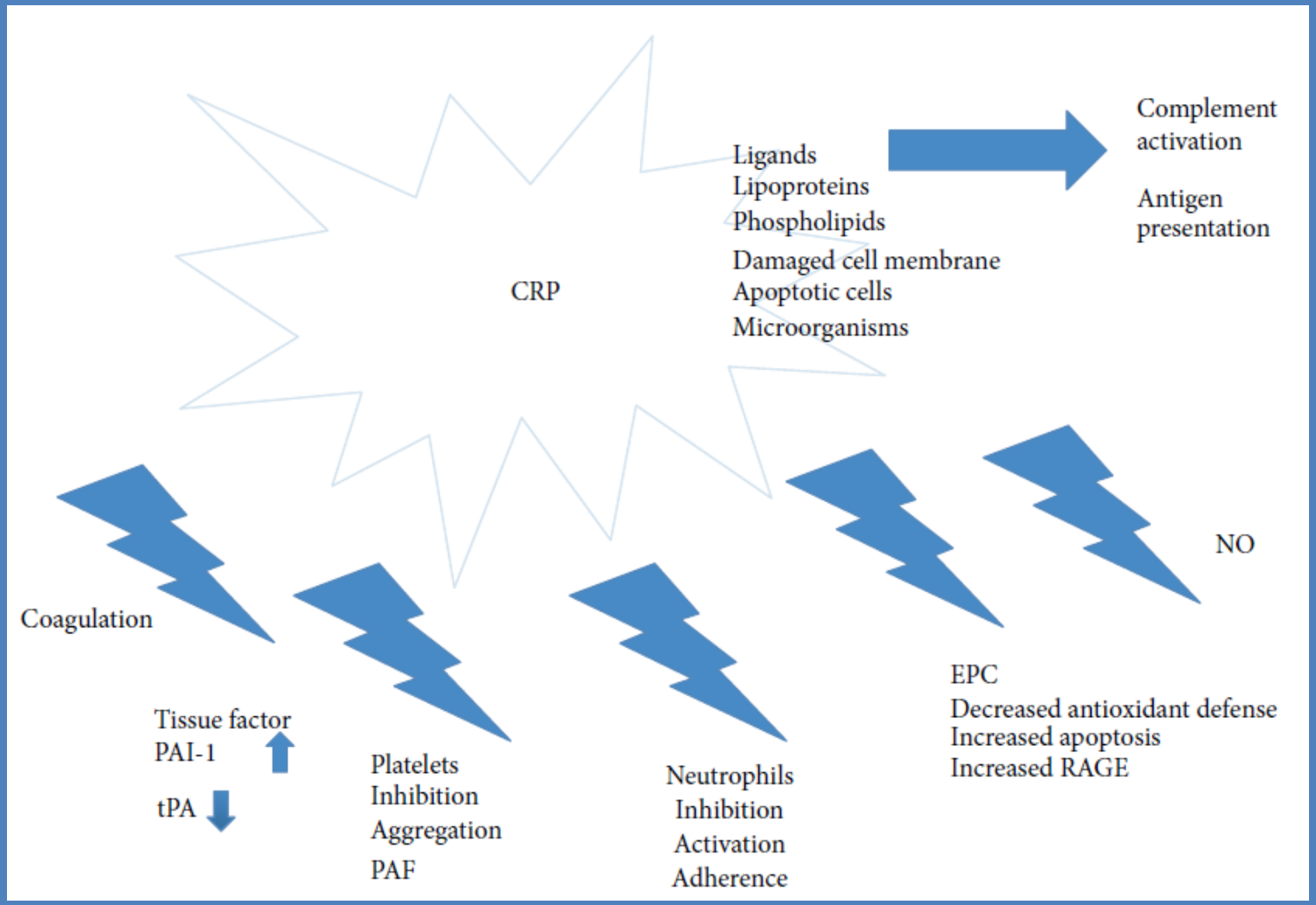


CRP

- **Début: H6.**
- **Max : H24 – H48.**
- **½ vie = 19 H.**

Lemarié et al. Réanimation (2013) 22:306-313

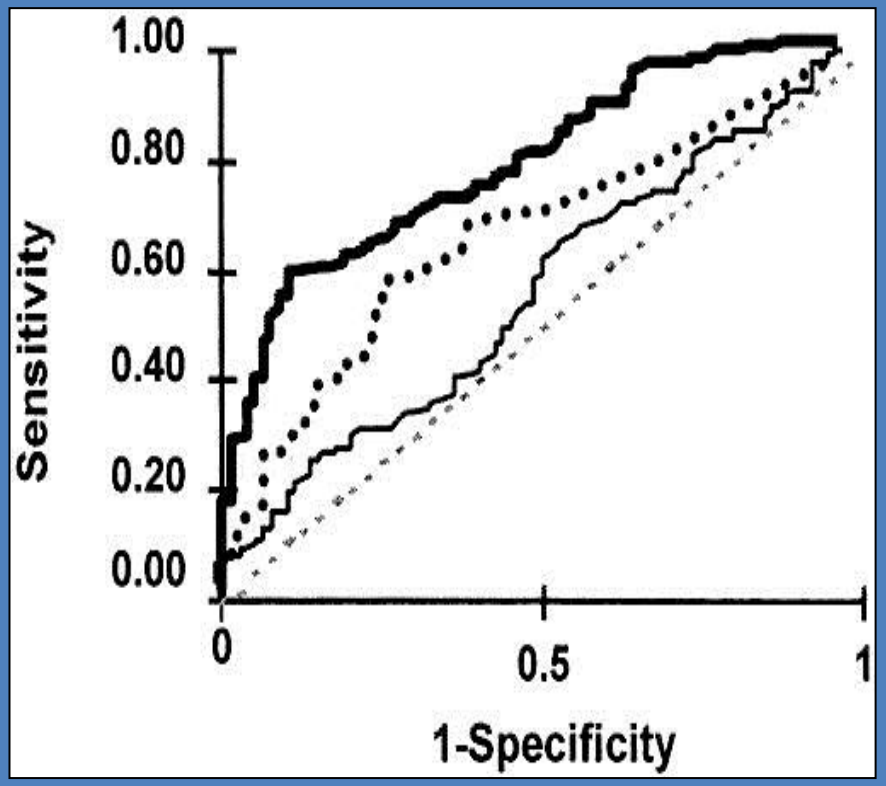
C reactive Protein (CRP)



Lelubre et al. Biomed Res Int. 2013;2013:124021

C reactive Protein (CRP)

S'agit-il d'un sepsis ou d'un SIRS isolé ?



CRP

Meilleur cutoff : 79 mg/L.

Sensibilité: 71,8 %.

Spécificité: 66,6 %.

ASC : 0,78.

Ugarte et al. Crit Care Med 1999; 27(3):498-504.

C reactive Protein (CRP)

Comparison of procalcitonin and C-reactive protein as markers of sepsis

Aldo Luzzani, MD; Enrico Polati, MD; Romolo Dorizzi, MD; Alessio Rungatscher, MD; Raffaella Pavan, MD; Alberto Merlini, MD

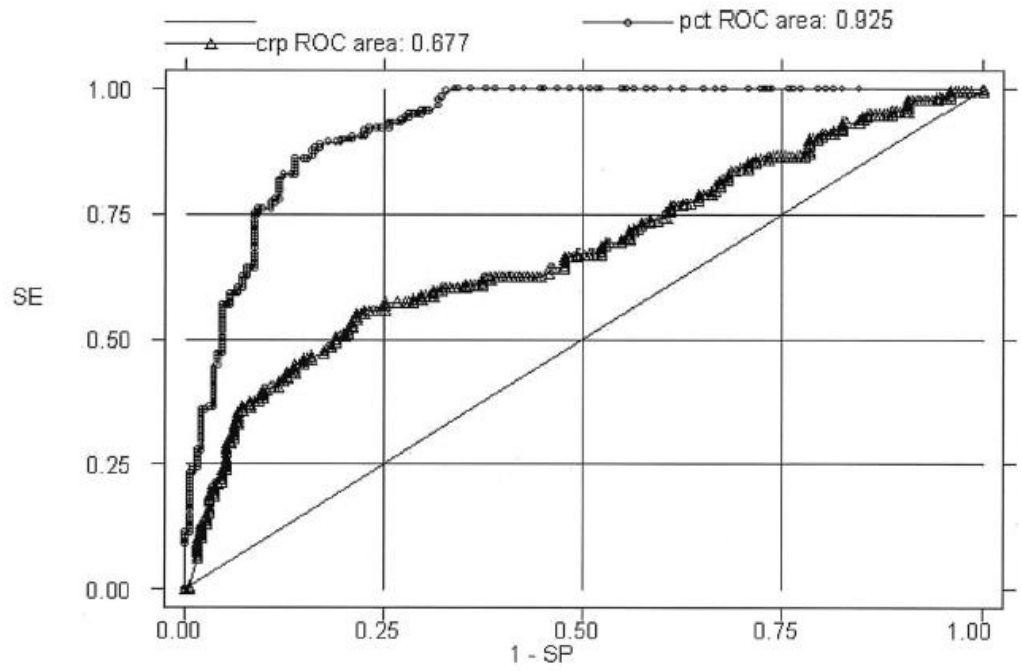
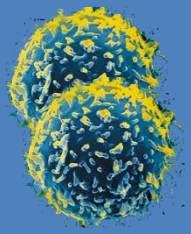


Figure 2. Receiver operating characteristic (*ROC*) curve comparing procalcitonin (*pct*; *circles*) and C-reactive protein (*crp*; *triangles*) for prediction of sepsis.

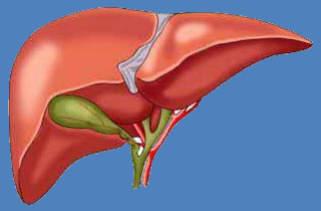
Luzzani et al. Crit Care Med. 2003; 31(6):1737-41.

Procalcitonine

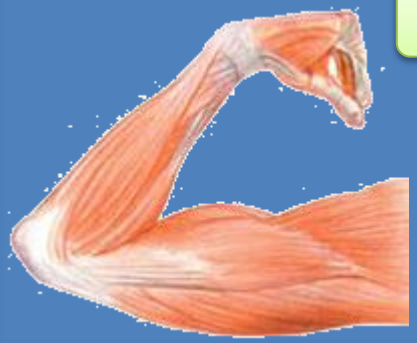
Infection bactérienne (+++)



IL1β, TNFα, IL6



Procalcitonine



Calcitonine

Procalcitonine

Procalcitonine

- ↗ de la production de cytokines pro-inflammatoire,
- Modulation de l'activité de la NOSi
- Interférence avec les hormones déterminant le tonus vasculaire.

Henriquez Camacho et al, Biomed Res Int. 2014;2014:547818.

Procalcitonine

Attention aux faux positifs

- Pathologie traumatique.
- Etat de choc cardiogénique ou chirurgie cardiaque.
- Les coups de chaleurs et les brûlures étendues,
- Maladies auto-immunes, SAM et GVH.

Henriquez Camacho et al, Biomed Res Int. 2014;2014:547818.

Quel(s) intérêt(s) pour les biomarqueurs ?

1. Aide au diagnostic

- Diagnostic précoce (+++).
- Tout retard d'antibiothérapie aggrave le pronostic.

2. Suivi de l'efficacité thérapeutique ?

3. Limitation de la durée de l'antibiothérapie ?

4. Intérêt pronostique ?

1. Aide au diagnostic

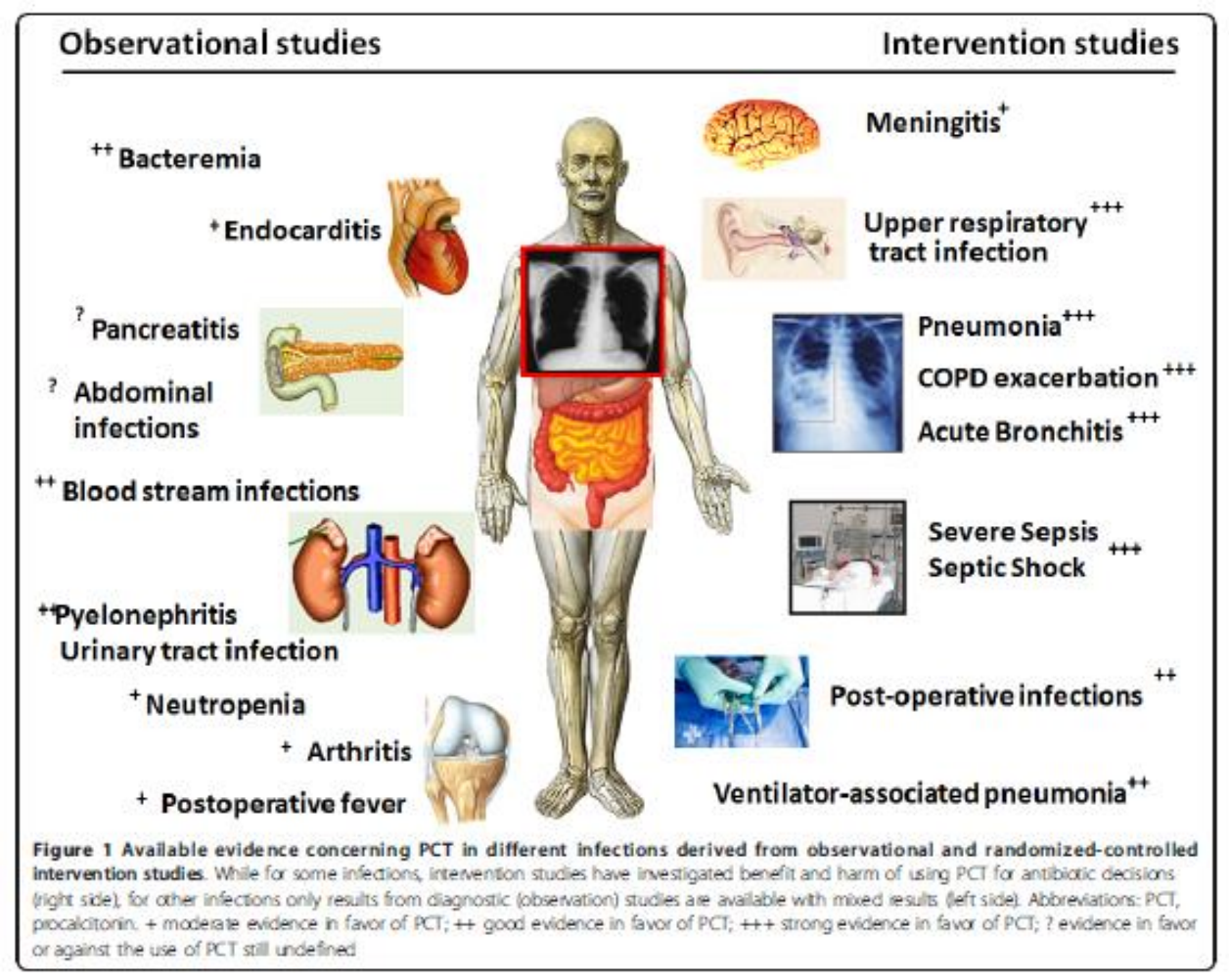


Figure 1 Available evidence concerning PCT in different infections derived from observational and randomized-controlled intervention studies. While for some infections, intervention studies have investigated benefit and harm of using PCT for antibiotic decisions (right side), for other infections only results from diagnostic (observation) studies are available with mixed results (left side). Abbreviations: PCT, procalcitonin. + moderate evidence in favor of PCT; ++ good evidence in favor of PCT; +++ strong evidence in favor of PCT; ? evidence in favor or against the use of PCT still undefined

Schuetz et al. BMC Med. 2011. 22;9:107.

2. Initiation de l'antibiothérapie

Infections respiratoires basses (+++)

IRB (Asthme/ DABPCO/ Asthme) : 10 % des causes de morbi-mortalité.

- ❑ **Origine souvent virale.**
- ❑ **75 % des prescriptions d'antibiotiques**

→ **Exposition non justifiée aux ATBs**

→ **Coûts (++)**

Acquisition de résistances (++)

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

	Standard group (n=119)		Procalcitonin group (n=124)		p*
	Initial	Final	Initial	Final	
Quality-of-life score (mean [SD])	39·3 (13·2)	22·9 (15·1)	41·3 (14·3)	21·9 (14·7)	0·60
Visual analogue scale (mean [SD], %)	43·1 (21·0)	64·1 (21·5)	42·5 (20·4)	65·1 (21·8)	0·78
Body temperature (mean [SD], °C)	37·7 (1·1)	37·0 (0·4)	37·8 (1·0)	36·9 (0·3)	0·06
White-blood-cell count (mean [SD], $\times 10^9$/L)	12·4 (6·7)	10·3 (5·1)	11·7 (6·5)	9·7 (4·4)	0·26
C-reactive protein (mean [SD], mg/L)	97·8 (106·1)	25·8 (43·7)	82·8 (93·9)	18·2 (33·3)	0·24
Procalcitonin (mean [SD], µg/L)	1·6 (4·2)	0·12 (0·2)	1·6 (7·7)	0·12 (0·4)	0·10
Admitted	88 (74%)		101 (81%)		0·16
Number of days admitted (mean [SD])	11·2 (10·6)		10·7 (8·9)		0·89
Need for stay in intensive care unit	6 (5%)		5 (4%)		0·71
Died	4 (3%)		4 (3%)		0·95
Follow-up	110 (92%)		112 (90%)		0·56
Follow-up of survivors	110/115 (96%)		112/120 (93%)		0·44
Antibiotic prescription foreseen	99 (83%)		99 (80%)		0·50
Antibiotics prescribed	99 (83%)		55 (44%)		<0·0001
Duration of antibiotic treatment (mean [SD], days)	12·8 (5·5)		10·9 (3·6)		0·03
Antibiotic use per 1000 days of follow-up (mean [SD])	661 (398)		332 (433)		<0·0001
Antibiotic costs per patient (mean [SD], US$)	202·5 (250·6)		96·3 (172·8)		<0·0001

Data are mean (SD) or number of patients (%).*If initial and final data are given, p values denote comparisons between final data of patients in the standard group and final data in the procalcitonin group.

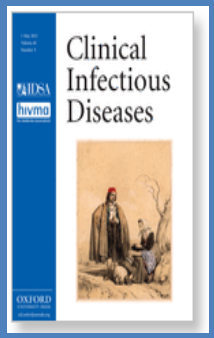
Table 5: **Clinical outcome in all patients with lower respiratory tract infections according to treatment algorithm**

Christ-Crain et al. Lancet 2004 21; 363(9409):600-7.

2. Initiation de l'antibiothérapie

Infections respiratoires basses (+++)

Procalcitonin to Guide Initiation and Duration of Antibiotic Treatment in Acute Respiratory Infections: An Individual Patient Data Meta-Analysis



- 14 essais cliniques retenus (3 de réa).
- 4211 patients inclus.
- Répartition en deux groupes :
  - PCT(+): 2085.
  - PCT(-): 2126.

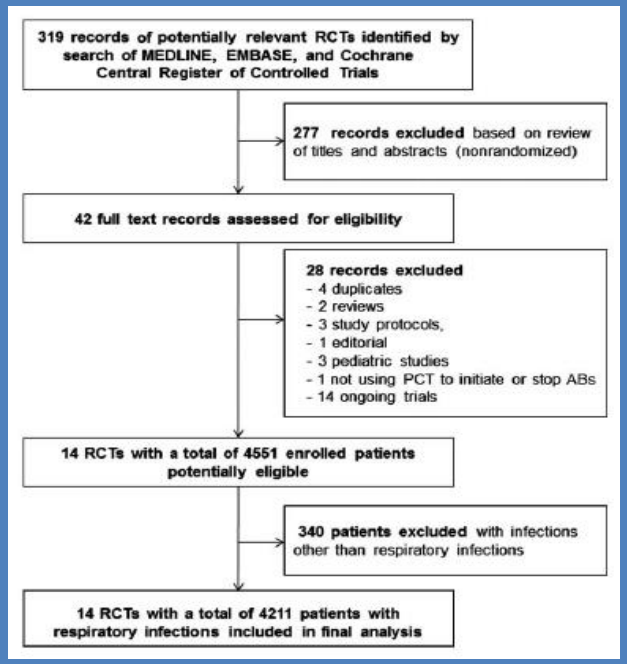


Table 4. Clinical Endpoints Overall and Stratified by Setting and Acute Respiratory Infection Diagnosis

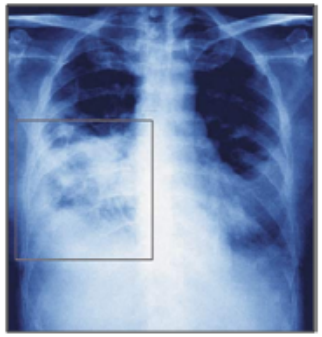
	PCT Group	Control Group	Adjusted OR (95% CI)[a]	*P* Value
Overall	n = 2085	n = 2126	…	…
Mortality, No. (%)	118 (5.7)	134 (6.3)	0.94 (.71–1.23)	.75
Treatment failure, No. (%)[b]	398 (19.1)	466 (21.9)	0.82 (.71–.97)	.02
Intensive care unit	n = 287	n = 311		
Mortality, No. (%)	57 (19.9)	74 (23.8)	0.84 (.54–1.31)	.44
Length of ICU stay, median (IQR)	12 (6–23)	12 (6–22)	1.01 (–1.26 to 3.28)[d]	.39
Length of hospital stay, median (IQR)	21 (11–38)	24 (14–38)	–1.36 (–4.5 to 1.77)[d]	.39
Upper ARI	n = 282	n = 267		
Mortality, No. (%)	0 (0)	1 (0.4)	…	…
Treatment failure, No. (%)[c]	93 (33.0)	92 (34.5)	0.95 (.73–1.24)	.69
Community-acquired pneumonia	n = 999	n = 1028		
Mortality, No. (%)	92 (9.2)	111 (10.8)	0.89 (.64–1.23)	.47
Treatment failure, No. (%)[b]	190 (19.0)	240 (23.4)	0.77 (.62–.96)	.02
Ventilator-associated pneumonia	n = 126	n = 116		
Mortality, No. (%)	8 (6.3)	12 (10.3)	0.69 (.25–1.94)	.49
Treatment failure, No. (%)[b]	8 (6.3)	12 (10.3)	0.69 (.25–1.94)	.49

2. Initiation de l'antibiothérapie

Infections respiratoires basses

Cutoff ?

PCT algorithm for patients with respiratory tract infection



PCT (ug/L)	Bacterial Infection?	Recommendation for antibiotics	Important considerations and overruling criteria
10	Very likely	AB YES!	**- Consider the course of PCT** **- If antibiotics are initiated:** - Repeat PCT on days 3, 5, 7; stop antibiotics using the same cut offs - if peak PCT levels are very high, then stop when 80-90% decrease of peak - If PCT remains high, consider treatment failure
2			
1			
0.5	likely	AB Yes	
0.25	unlikely	AB No	**- If Antibiotics are withheld, control PCT after 6-24 hours** **- Initial antibiotics can be considered in case of:** - Respiratory or hemodynamic instability, severest comorbidities, ICU admission - **PCT < 0.1** ug/L: CAP with PSI V or CURB >3, COPD with GOLD IV - **PCT < 0.25** ug/L: CAP with PSI IV & V or CURB >2, COPD with GOLD III & IV
0.1	very unlikely	AB NO!	
0.01			

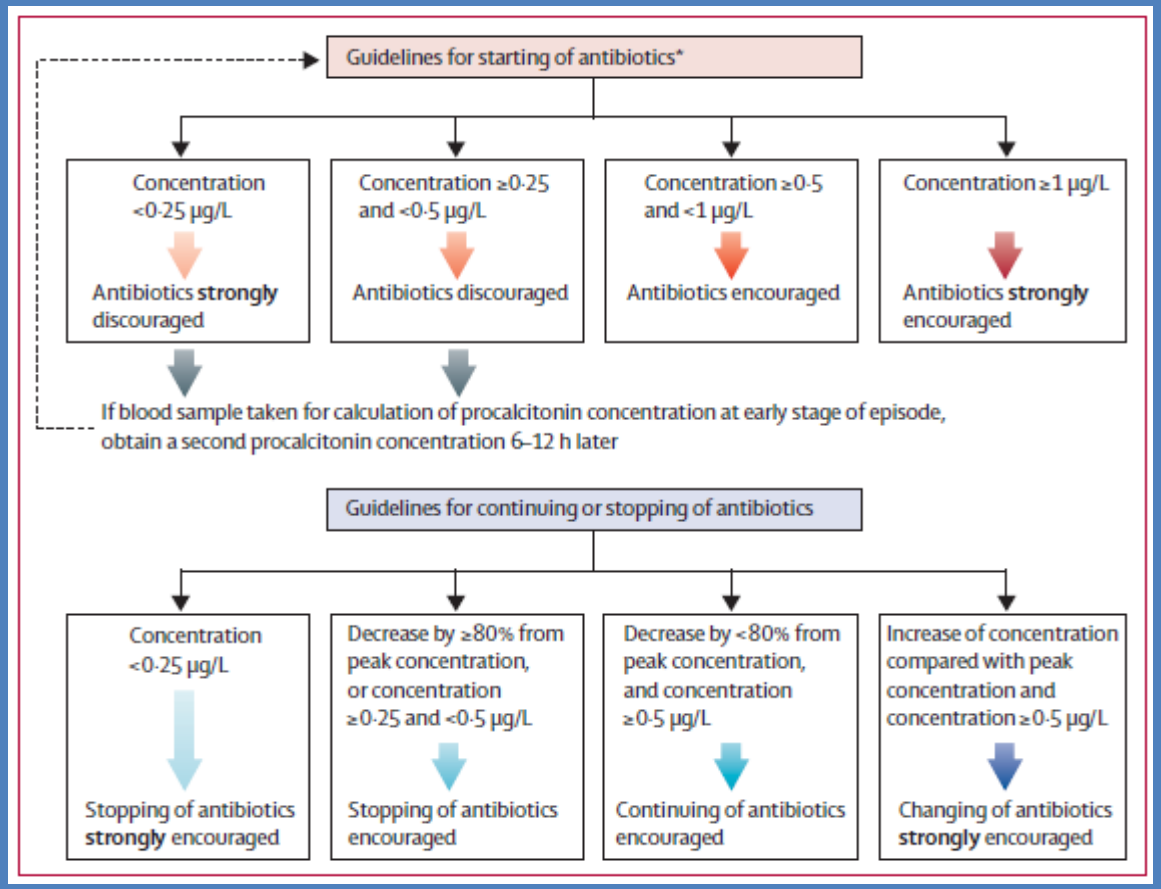
Figure 2 PCT algorithm in patients with respiratory tract infections in the Emergency Department. The clinical algorithm for antibiotic stewardship in patients with respiratory tract infections in the Emergency Department encourages (>0.5 μg/l or >0.25 μg/l) or discourages (<0.1 μg/l or <0.25 μg/l) initiation or continuation of antibiotic therapy more or less based on PCT specific cut-off ranges. Abbreviations: AB, antibiotic; LRTI, lower respiratory tract infection; PCT, procalcitonin; PSI, Pneumonia Severity Score.

Schuetz et al. BMC Med. 2011. 22;9:107.

3. Limitation de la durée de l'antibiothérapie

Données relative à la réanimation ?

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



Bouadma L et al. Lancet. 2010 . 6;375(9713):463-74.

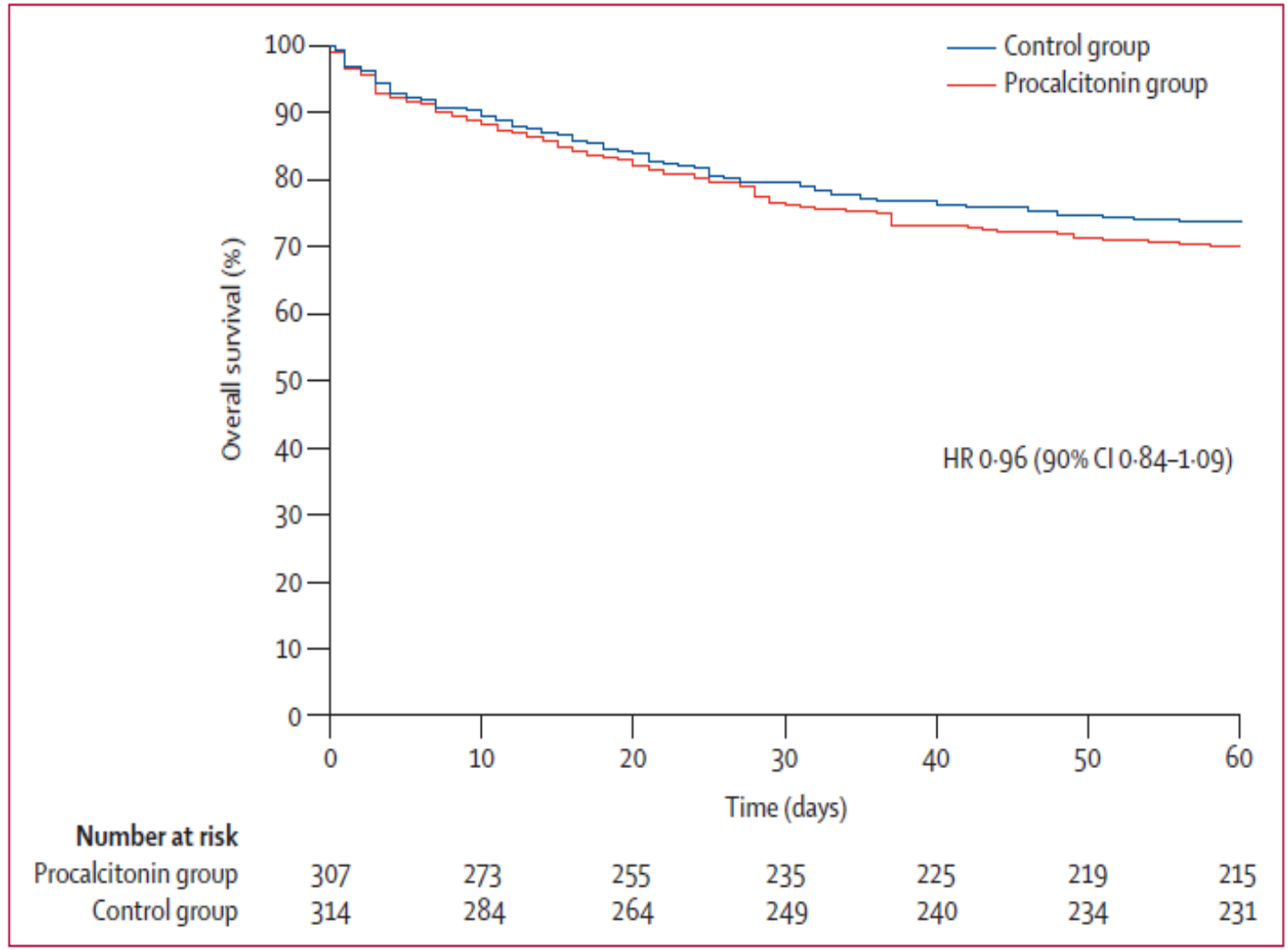


Figure 3: Kaplan-Meier estimates of the probability of survival

4. Valeur pronostique ?

Predictive value of procalcitonin decrease in patients with severe sepsis: a prospective observational study

CRITICAL CARE

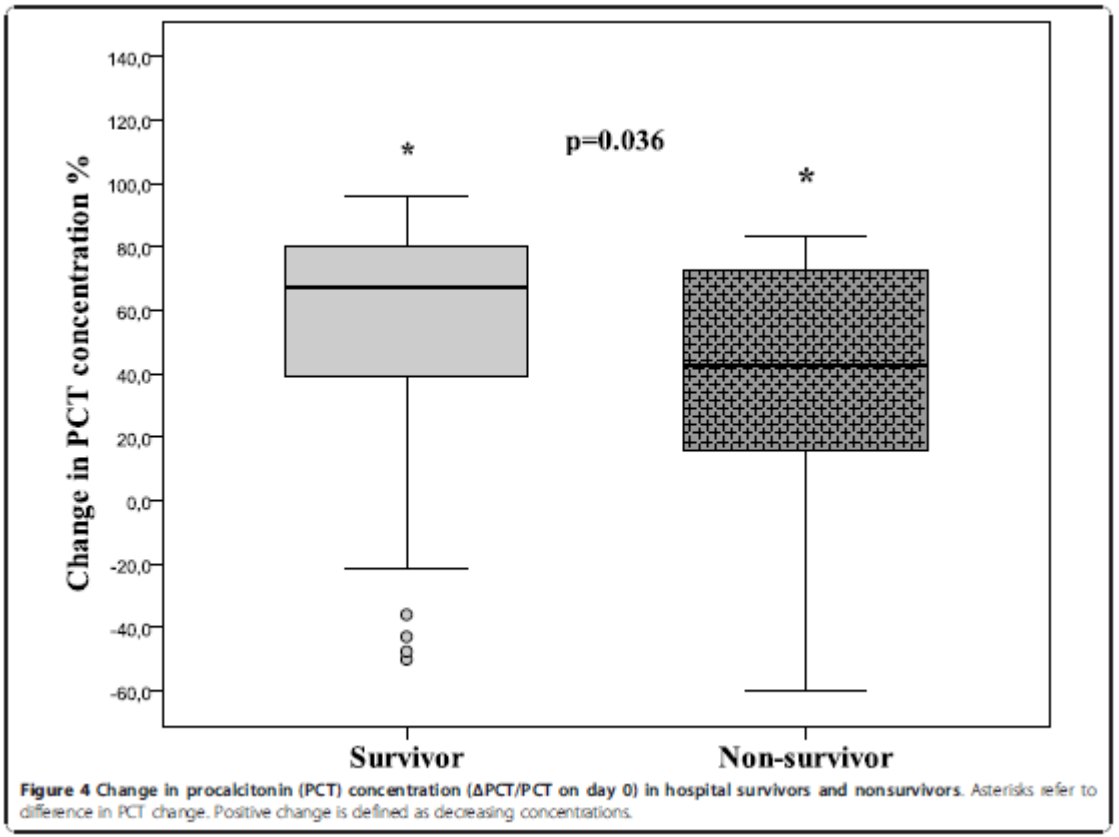


Figure 4 Change in procalcitonin (PCT) concentration (ΔPCT/PCT on day 0) in hospital survivors and nonsurvivors. Asterisks refer to difference in PCT change. Positive change is defined as decreasing concentrations.

Karlsson et al. Crit Care. 2010;14(6):R205

Autres marqueurs ?

S-TREM-1 (Triggering Receptor Expressed on Myeloïd Cell-1)

- SuperIg exprimée par les cellules myéloïdes lors d'une exposition à un agent bactérien ou fungique.
- Sepsis → Libération par la phagocyte de la forme soluble de cette Ig.

Bloos et al. Virulence 5:1, 154–160; January 1, 2014

Accuracy of plasma sTREM-1 for sepsis diagnosis in systemic inflammatory patients: a systematic review and meta-analysis

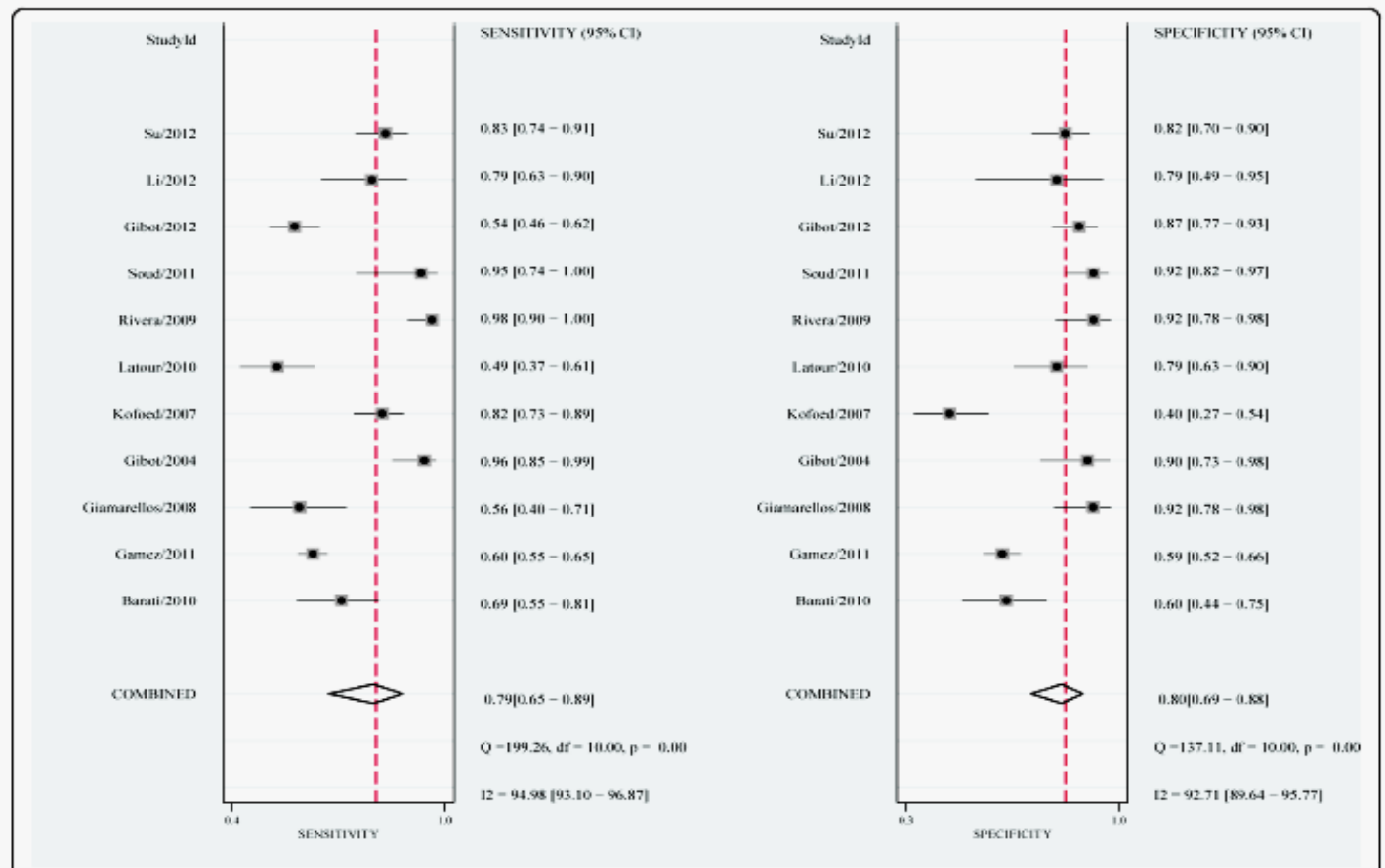


Figure 3 Forrest plot of the sensitivity and specificity of sTREM-1 for the diagnosis of sepsis. Forrest plot of the sensitivity and specificity of each individual study, pooled sensitivity and specificity, and I^2 statistic for heterogeneity.

Wu et al. Critical Care 2012, 16:R229

Autres marqueurs ?

- suPAR (urokinse Plasminogen Activator Receptor): Protéine membranaire exprimée par les cellules immunitaires.
- Multiplex PCR-based Pathogen detection: Détection de séquences spécifiques de rRNA de bactéries ou d'agents fongiques (6 – 8 H).
- Dosage de cytokines.
- LBP (Lipopolysaccharid Binding Protein).

Bloos et al. Virulence 5:1, 154–160; January 1, 2014

Finalement, quel est le meilleur biomarqueur ?

Table 1. Diagnostic value and limitations of biomarkers to separate infectious from non-infectious causes of inflammation

Biomarker	Source	Sens.	Spec.	AUC	LR^+	LR^-	Limitations
C-reactive protein[21]	Metaanalysis ($n = 1386$)	0.75	0.67	–	2.43	0.42	Slow kinetic, independent of infection severity, increased in many inflammatory diseases
Procalcitonin[35]	Metaanalysis ($n = 3244$)	0.77	0.79	0.89	4.0	0.29	Increased in various non-infectious causes of SIRS (i.e., cardiac arrest, severe trauma)
Interleukin-6[57]	Cohort study ($n = 327$)	0.82	0.75	0.86	–	–	Limited data, conflicting results
sTREM-1[78]	Metaanalysis ($n = 1795$)	0.79	0.80	0.87	4.0	0.26	Present in inflammatory disease without infection
LBP[57]	Cohort study ($n = 327$)	0.57	0.85	0.73	–	–	Non-specific marker of inflammation
suPAR[98]	Cohort study ($n = 273$)	–	–	0.62	–	–	Limited data; low diagnostic value for sepsis

Data give sensitivity (sens.), specificity (spec.), area under the curve (AUC) from receiver operating characteristics, positive (LR^+) and negative (LR^-) likelihood ratios of a biomarker for differentiation of infectious vs. non-infectious causes of inflammation. LBP, lipopolysaccharide binding protein; suPAR, soluble urokinase plasminogen activator receptor; sTREM 1, soluble triggering receptor expressed on myeloid cells 1.

Bloos et al. Virulence 5:1, 154–160; January 1, 2014

Finalement, quel est le meilleur biomarqueur ?

Conclusion

- Aucun biomarqueur ne peut servir comme « gold standard »

  → Hétérogénéité des patients septique (sévérité, type d'infection, qualité et précocité de la prise en charge ….)

- Quelle serait la place des biomarqueurs ?
  - TOUJOURS à l'appui des données de la clinique (+++).
  - Combinaison des biomarqueurs ?