

La PCT :

Quand faut-il la demander dans la gestion des IR ?

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**Centre Régional Universitaire des Urgences, CHU Dijon
2018, SPLF GREPI 6**



LIENS D'INTERET

Radiometer

Roche Diagnostics

Abbott

Novartis

Boehringer Ingelheim

AstraZeneca

Novartis

T2E

EmC2

À VOS AGENDAS !

Emc² #3

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IN MONTE-CARLO**

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OBJECTIFS

- **Rappel sur le rôle des biomarqueurs et l'évaluation biostatistique usuelle**
- **LA PCT pour les urgentistes**
- **La PCT pour les pneumologues**
- **Analyse des études d'impact : BPCO et/ou pN ?**
- **En pratique ?**

Cahier des charges d'un biomarqueur

- ~~Dépistage (IC)~~
- Diagnostic d'une maladie fréquente et grave (sepsis, pN)
 - Qualités équivalentes au gold-standard (sepsis, pN ?)
 - Facile à mesurer et rendu rapide (< 1 heure)
 - Disponible 24h/j en routine
 - Pas trop cher !!
 - Qualités diagnostiques ET pronostiques si possible
 - Modification de la prise en charge ou de l'orientation
- Études interventionnelles ou d'impact montrant leur utilité sur des critères de jugement pertinents (morbi-mortalité, %ATB, %en réa...)
 - Connaissances par le clinicien des biomarqueurs du labo !!!

... et du point de vue biochimique

Principales caractéristiques d'un biomarqueur « idéal »

- spécificité optimale d'organe ou de tissu
- Bonnes performances diagnostique et pronostique
- Praticabilité (acceptable pour le patient)
- Stabilité *in vivo* et *in vitro*
- Variation biologique minimale
- Valeurs de référence et seuils décisionnels pour des sous populations (âge, sexe, etc...)
- Qualités analytiques :
 - Bonne sensibilité analytique (sensibilité fonctionnelle)
 - Précision et justesse
 - Automatisation
 - Standardisation
 - Coût peu élevé et rapport bénéfice/coût favorable

(d'après Clerico et al., Adv Clin Chem 2009)

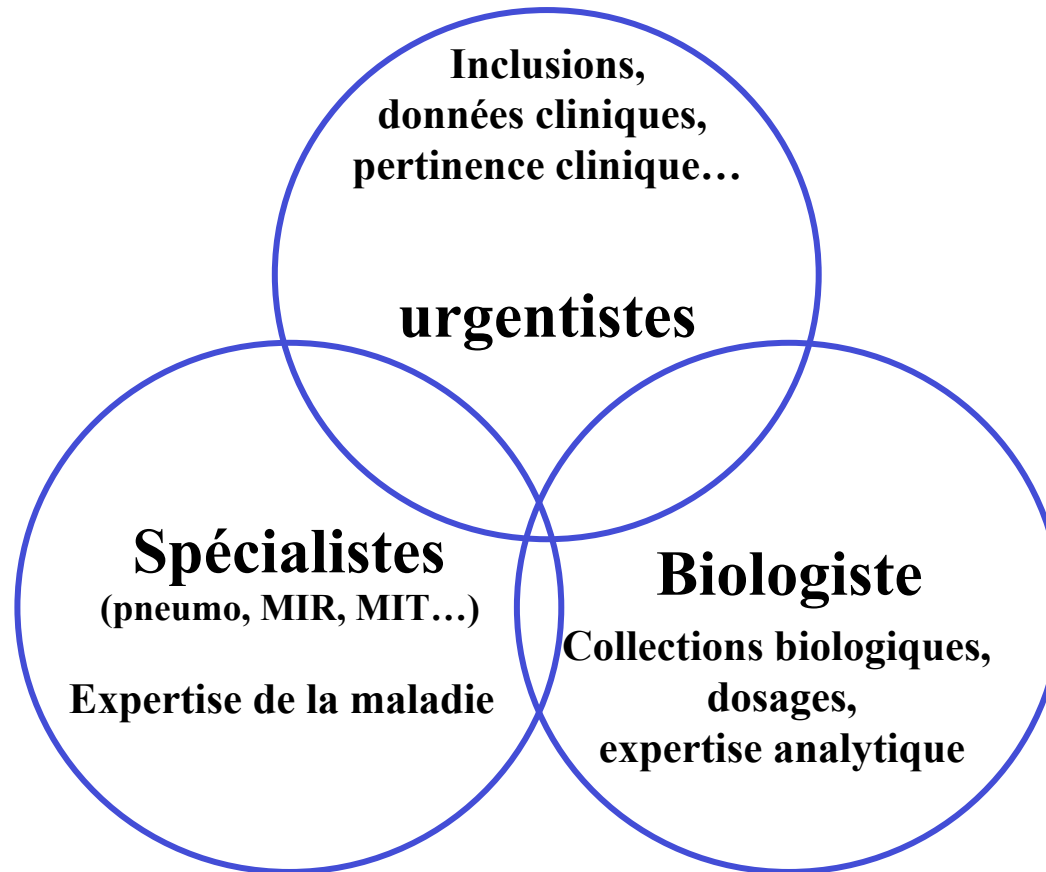
A quoi sert un biomarqueur ?

- Test diagnostique
- Evaluation de la sévérité
- Evaluation du risque
- Prédiction d'un effet thérapeutique
- Monitoring thérapeutique

METHODOLOGIE

- **S^{ce} d'Urgence**
- **Population représentative de MES patients (âgés++, difficiles, réa ≠ Urg)**
- **Dosage du [biomarqueur]_{sang} dès l'admission en aveugle**
- **Diagnostic final de la maladie (ICA ou sepsis) par experts ou grâce au « Gold-standard » ?**
- **Comparaison [biomarqueur]_{sang} et maladie (ICA ou sepsis)**
- **Courbe ROC et détermination des Sens, Spéc, VPP, VPN... et valeur seuil**
- **Etudes d'impact +++**

Une collaboration tripartite



Quand les conditions SONT FACILES !!!

Pas besoin de biomarqueur

The screenshot shows a medical software interface with a navigation bar at the top containing tabs: **Général**, **ACCUEIL**, **EXAMEN**, **IMG-CS**, **ODT**, **SOINS**, and **ZHTCD**. Below the navigation bar, there are several colored boxes and labels:

- IAO** (red box)
- MRT** (blue box)
- Attente** (purple box)
- Brancard pré-Hospi** (purple box)
- Attente** (purple box)
- Radiologie** (grey box)
- Scanner** (grey box)
- Autre Explo/Consult** (grey box)
- Echographie** (grey box)
- Imagerie Babinski** (grey box)
- Box 1** (blue box)
- Box 2** (blue box)
- Box 3** (green box)
- Box 4** (green box)
- Attente P** (orange box)
- Attente CS** (green box)
- Cs** (green box)
- Plâtre** (blue box)
- Amphi** (black box)
- Psy** (red box)
- PB** (black box)
- Box 1** (orange box)
- Box 2** (orange box)
- Box 3** (orange box)
- Box 4** (orange box)

Two chest X-ray images are overlaid on the interface. The left image is a standard chest X-ray, and the right image is a more obscured or processed version. A small yellow box with text is visible near the bottom right of the X-ray images.

At the bottom of the interface, there is a toolbar with icons and labels: **Quête**, **Somme**, **Résultats**, **Action**, **Consigne**, **Actes**, **Document**, **Plan Soins**, **VIDAL®**, **Protocoles**, **Clavier**, **Blanc**, and **Menu Spécif**. A timestamp in the bottom right corner reads: 05/10/2006 14:29 BICHET Nicolas.

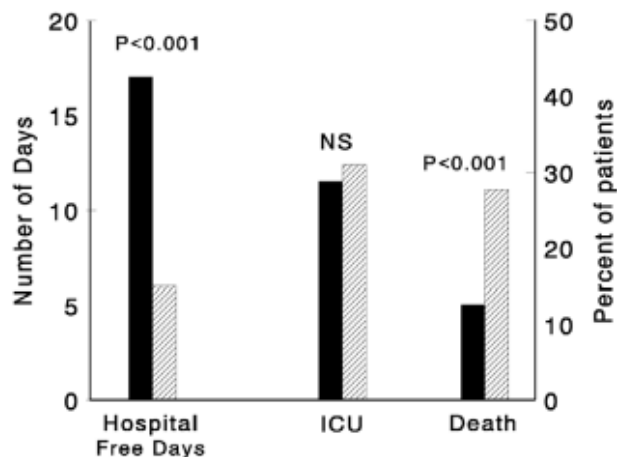
Mais, c' est PARFOIS difficile !!!

The screenshot displays a complex hospital information system interface. On the left, a vertical sidebar contains various icons and labels: Général, Actuelle, Patient, Dossier, Etiquettes, Déplacer, Recherche, Localisation, Messages, Commande, Anonymes, Tableau, and Fenêtre. The main area is dominated by a large, multi-colored grid representing a schedule or patient list, with columns labeled ACCUEIL, EXAMEN, IMG-CS, ODT, SOINS, and ZHTCD. A prominent purple box labeled 'Attente' highlights a section of the grid. Below the grid, there are several empty boxes labeled 'Attente Pst', 'Attente CS', 'P', 'Cs', 'Plâtre', 'Amphi', 'Psy', 'PB', and 'Transf'. To the right, a 'Radiologie' window shows a chest X-ray, with a smaller window displaying a CT scan. Other windows include 'Scanner', 'Echographie', 'Imagerie Babinski', 'Explo/Consult', and 'SAUV'. Numerous small, colored boxes with text like '0.03/0.00 KANIKI' and '2.19/1.06 HAUSER' are scattered throughout the interface, representing individual patient appointments or tasks. The interface also shows a 'CyberLink' toolbar at the top.

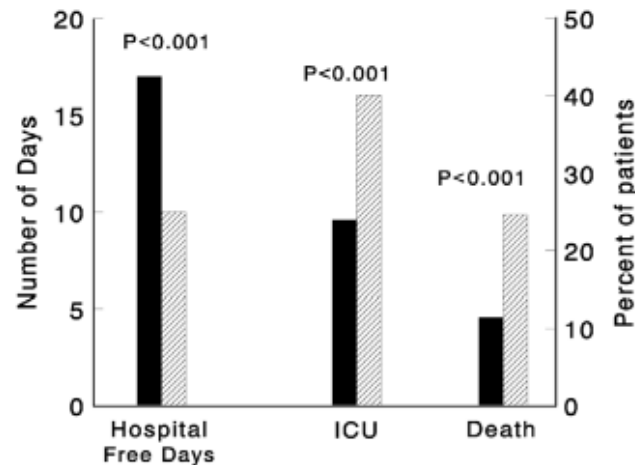
Assessment of the diagnostic performance of the emergency physicians (n = 514)

| Diagnosis | Sensitivity | Specificity | Positive predictive value | Negative predictive value | Accuracy |
|---------------------------|-------------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| CPE | 0.71 [0.65–0.77] | 0.80 [0.75–0.84] | 0.74 [0.70–0.87] | 0.78 [0.72–0.82] | 0.76 [0.72–0.80] |
| CAP | 0.86 [0.80–0.90]^a | 0.76 [0.71–0.80] | 0.66 [0.59–0.71] ^a | 0.91 [0.87–0.93] ^a | 0.79 [0.75–0.82] |
| Acute exacerbation of CRD | 0.71 [0.64–0.78] | 0.83 [0.79–0.87] | 0.66 [0.59–0.73] ^a | 0.86 [0.82–0.89] ^a | 0.81 [0.78–0.84] ^a |
| Pulmonary embolism | 0.75 [0.66–0.83] | 0.78 [0.74–0.82] | 0.43 [0.36–0.51] ^a | 0.93 [0.90–0.96] ^a | 0.78 [0.74–0.81] |
| Asthma | 0.67 [0.42–0.85] | 0.97 [0.95–0.98] ^a | 0.42 [0.24–0.61] ^a | 0.99 [0.98–1.00] ^a | 0.96 [0.94–0.98] ^a |

(a) **Emergency Diagnosis**



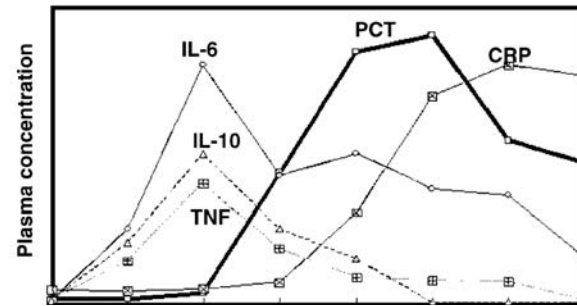
(b) **Emergency Treatment**



514 patients âgés admis pour dyspnée/IRA
 ± 1/3 d'erreur diagnostique

Ray, *Critical Care* 2006 ; Chandra *AmJEmergMed* 2010 ; Sikka *AmJEmergMed* 2012

PCT plus sensible, précoce que la CRP

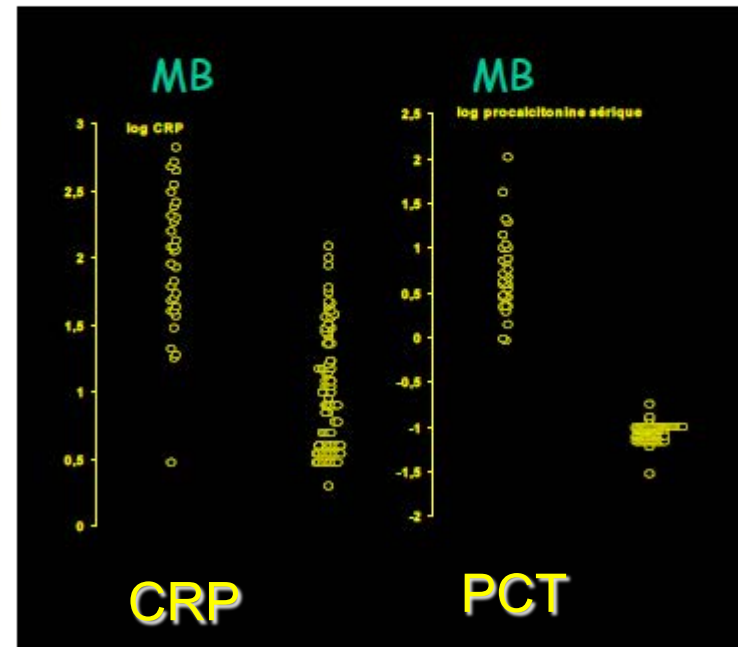


Monneret et al., *Acta Paediatr* 1997

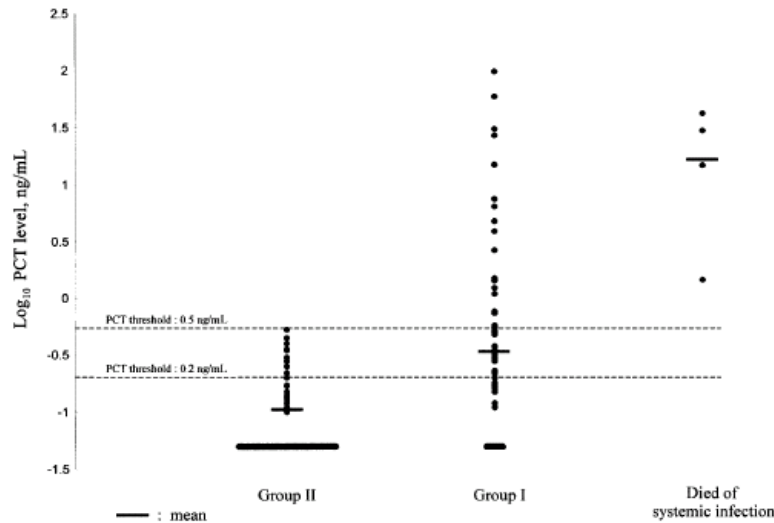
APPORT DIAGNOSTIQUE DE LA PCT

Viallon A et al, ICM 2000; CID 1999

- ◆ Sur 71 méningites de l'adulte à examen direct négatif (dont 30 MB) : PCT prédictive de MB au seuil de 0,93 ng/ml
- ◆ Sur 21 patients porteurs d'une infection du liquide d'ascite : le seuil diagnostique pour la PCT est de 0,75 ng/ml (sensibilité 95%, spécificité 98%).



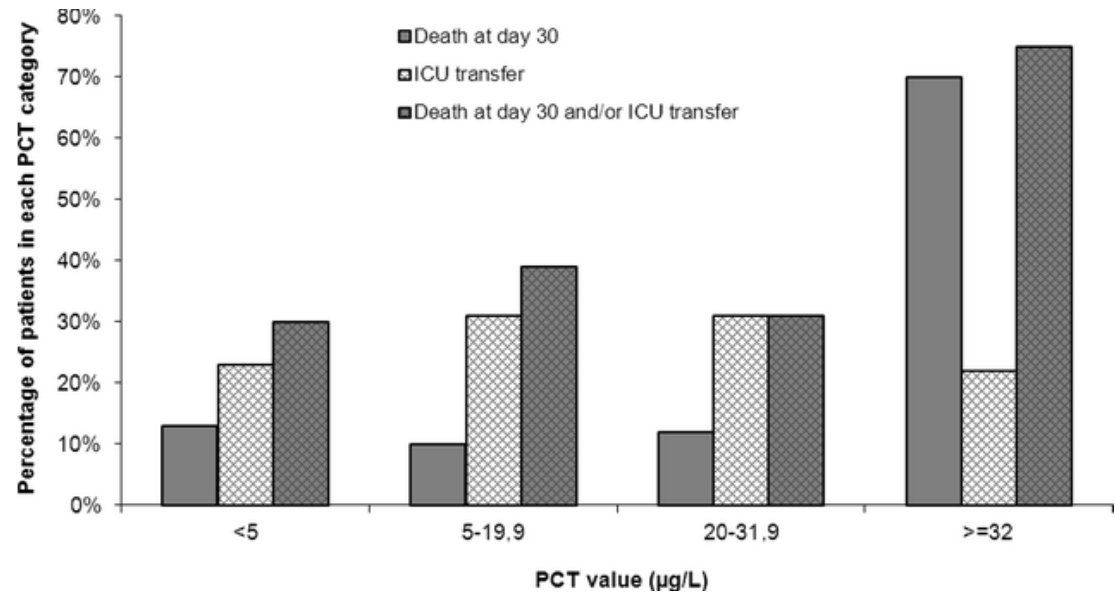
PCT au SAU +/- diagnostique et pronostique ?



Clinical Infectious Diseases 2002;34:895-901

PCT (seuil 0.2 ng/ml): Sen 62% Spe 88%

PCT au SAU
+/- liée aux complications



Peschanski *AnnIntensiveCare* 2016

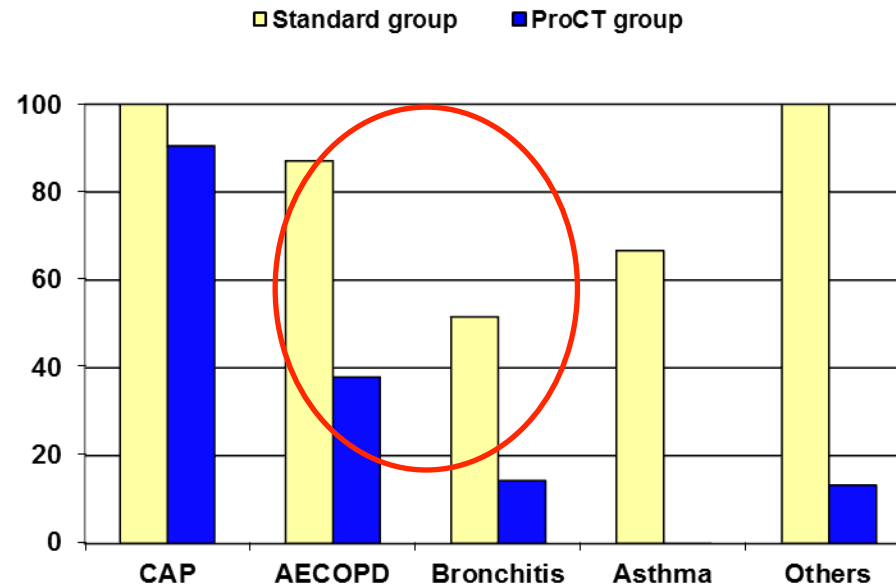
PCT: marqueur de tri dans les infections respiratoires basses (IRB) de l'adulte

- 243 patients suspects d'IRB aux urgences
 - 119 pts: prise en charge « standard »
 - 124 patients: traitement ATB guidé par résultat PCT:
 - PCT < 0,1: pas d'ATB
 - PCT < 0,25: pas d'ATB recommandé
 - PCT > 0,25: ATB recommandés

PCT-guided Antibiotic Therapy in Lower Respiratory Tract Infections (LRTI)

Christ-Crain et al., Lancet 2004

- ProRESP :étude interventionnelle dans Service d'Urgence



Dans le groupe guidé par la PCT, réduction de la prescription ATB d'environ 50 %

Avec évolution et pronostic identique au groupe standard

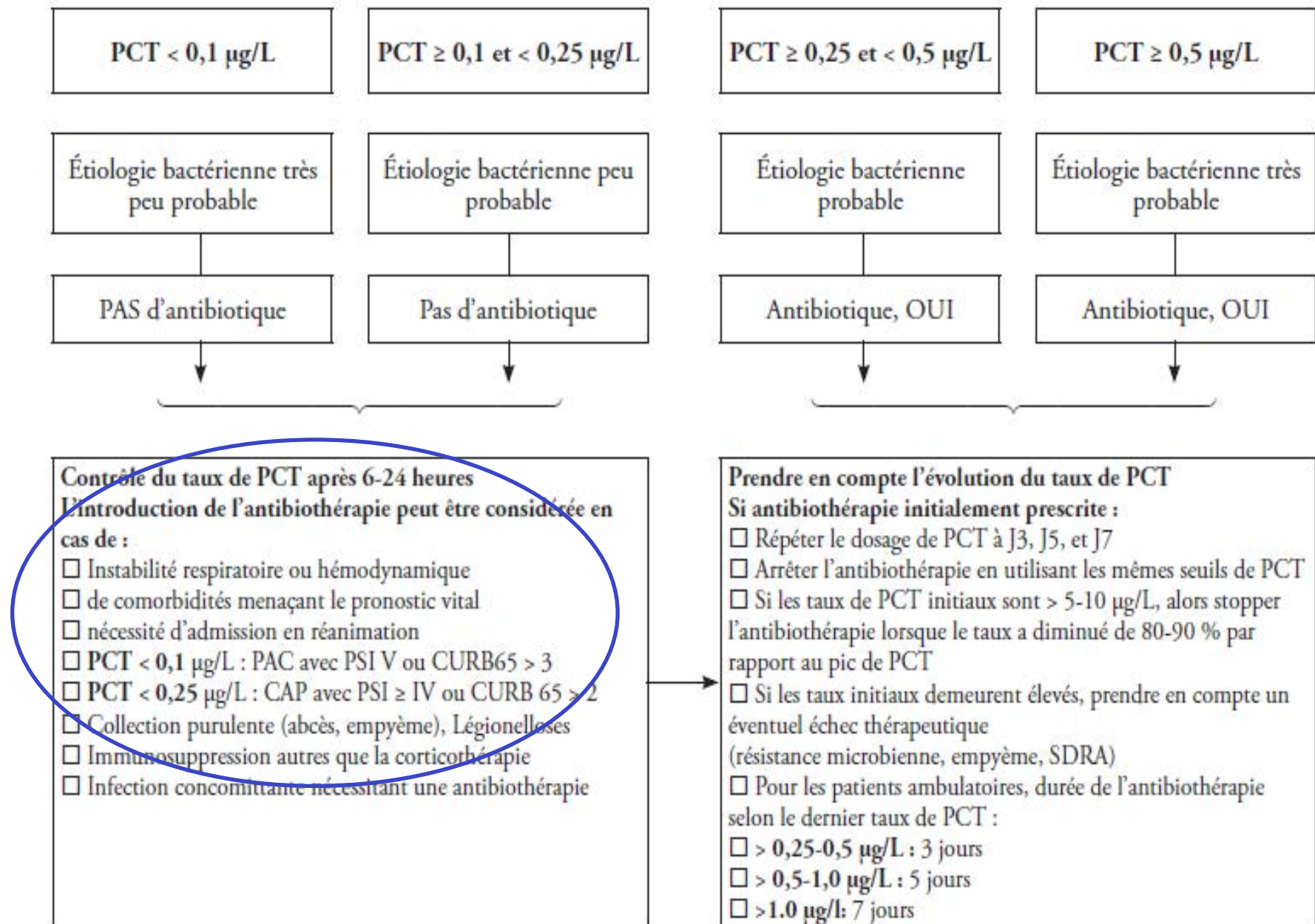
Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections

The ProHOSP Randomized Controlled Trial

JAMA. 2009;302(10):1059-1066

Philipp Schuetz

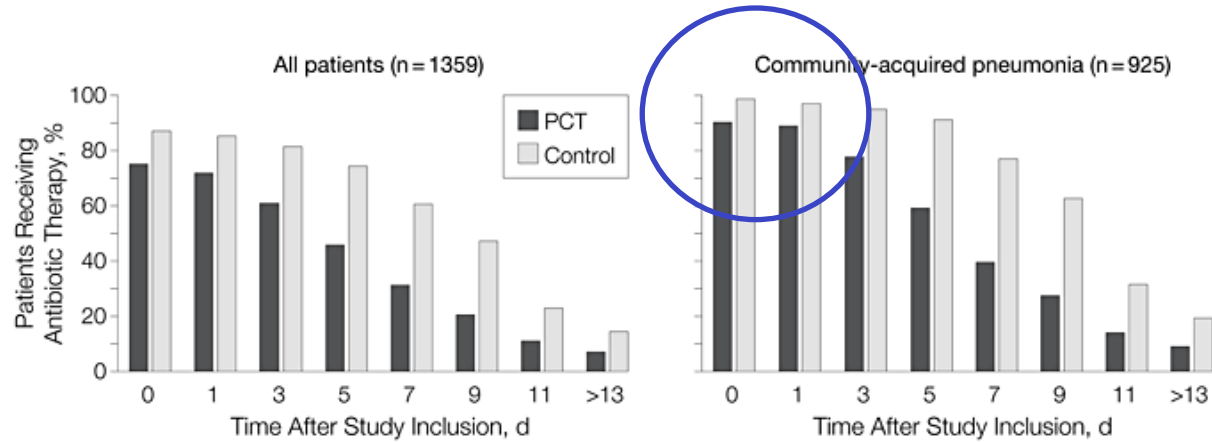
- Infection respiratoire basse:
 - ≥ 1 signe respiratoire : toux, expectoration, dyspnée, tachypnée, douleur de type pleural
 - Présence de râles ou de crépitants,
 - Ou ≥ 1 signe d'infection : $T \geq 38.0^{\circ}\text{C}$, frissons ou leucocyte $\geq 10000/\mu\text{L}$ ou $< 4000/\mu\text{L}$
-
- Mais, ce ne sont pas des patients avec IRA !!



Abréviations : PCT procalcitonine, PSI pneumonia severity index, CURB65 : Confusion, blood Urea nitrogen, Respiratory rate, Blood pressure, âge (65 ans)

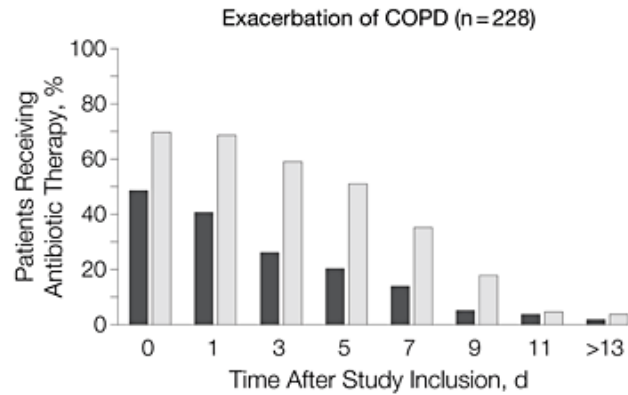
Fig. 1 – Algorithme décisionnel de la prescription d'antibiotique basé sur le taux de procalcitonine (PCT) (selon Schuetz *et al.* [12]).

Antibiotic Exposure in Patients Receiving Antibiotic Therapy

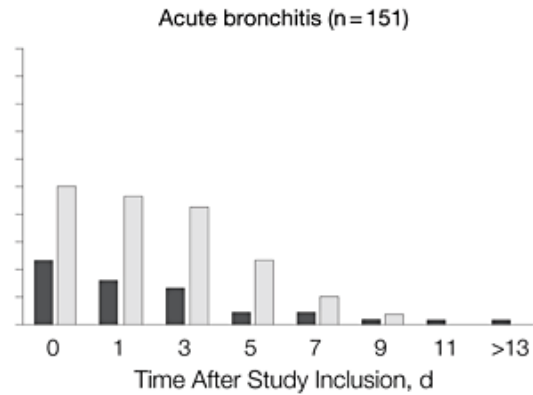


| No. of patients | | 0 | 1 | 3 | 5 | 7 | 9 | 11 | >13 |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| PCT | 506 | 484 | 410 | 306 | 207 | 138 | 72 | 46 | |
| Control | 603 | 589 | 562 | 516 | 420 | 324 | 157 | 100 | |

| No. of patients | | 0 | 1 | 3 | 5 | 7 | 9 | 11 | >13 |
|-----------------|-----|-----|-----|-----|-----|-----|-----|----|-----|
| PCT | 417 | 410 | 359 | 272 | 181 | 126 | 64 | 41 | |
| Control | 461 | 453 | 444 | 426 | 361 | 292 | 146 | 91 | |



| No. of patients | | 0 | 1 | 3 | 5 | 7 | 9 | 11 | >13 |
|-----------------|----|----|----|----|----|----|---|----|-----|
| PCT | 56 | 47 | 30 | 23 | 16 | 6 | 4 | 2 | |
| Control | 79 | 78 | 67 | 58 | 40 | 20 | 5 | 4 | |



| No. of patients | | 0 | 1 | 3 | 5 | 7 | 9 | 11 | >13 |
|-----------------|----|----|----|----|---|---|---|----|-----|
| PCT | 16 | 11 | 9 | 3 | 3 | 1 | 1 | 1 | |
| Control | 41 | 38 | 35 | 19 | 8 | 3 | 0 | 0 | |

JAMA

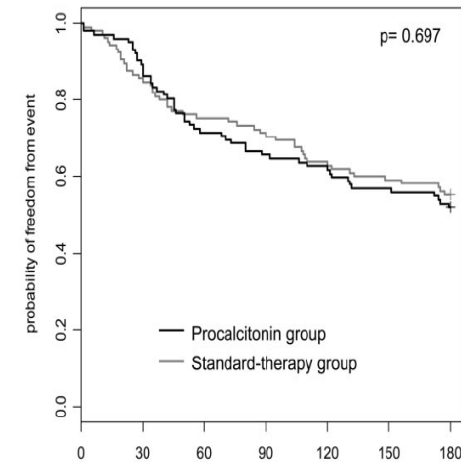
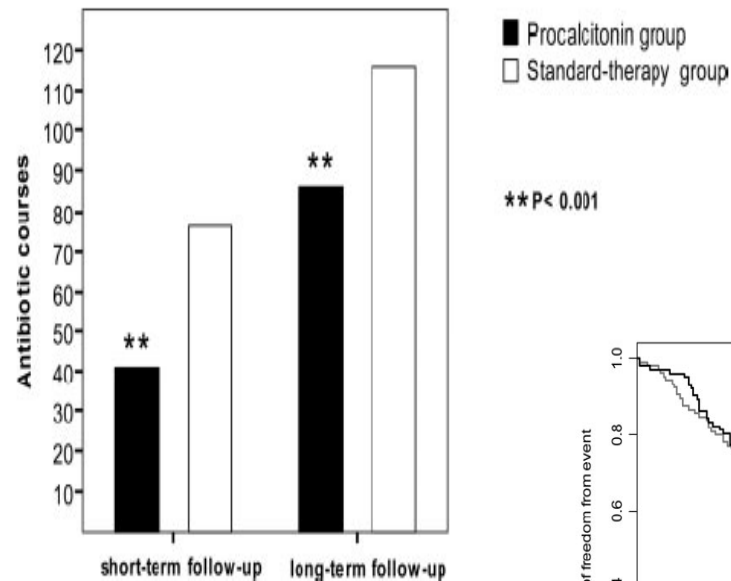
Schuetz *JAMA* 2009



Antibiotic Treatment of Exacerbations of COPD*

A Randomized, Controlled Trial Comparing Procalcitonin-Guidance With Standard Therapy

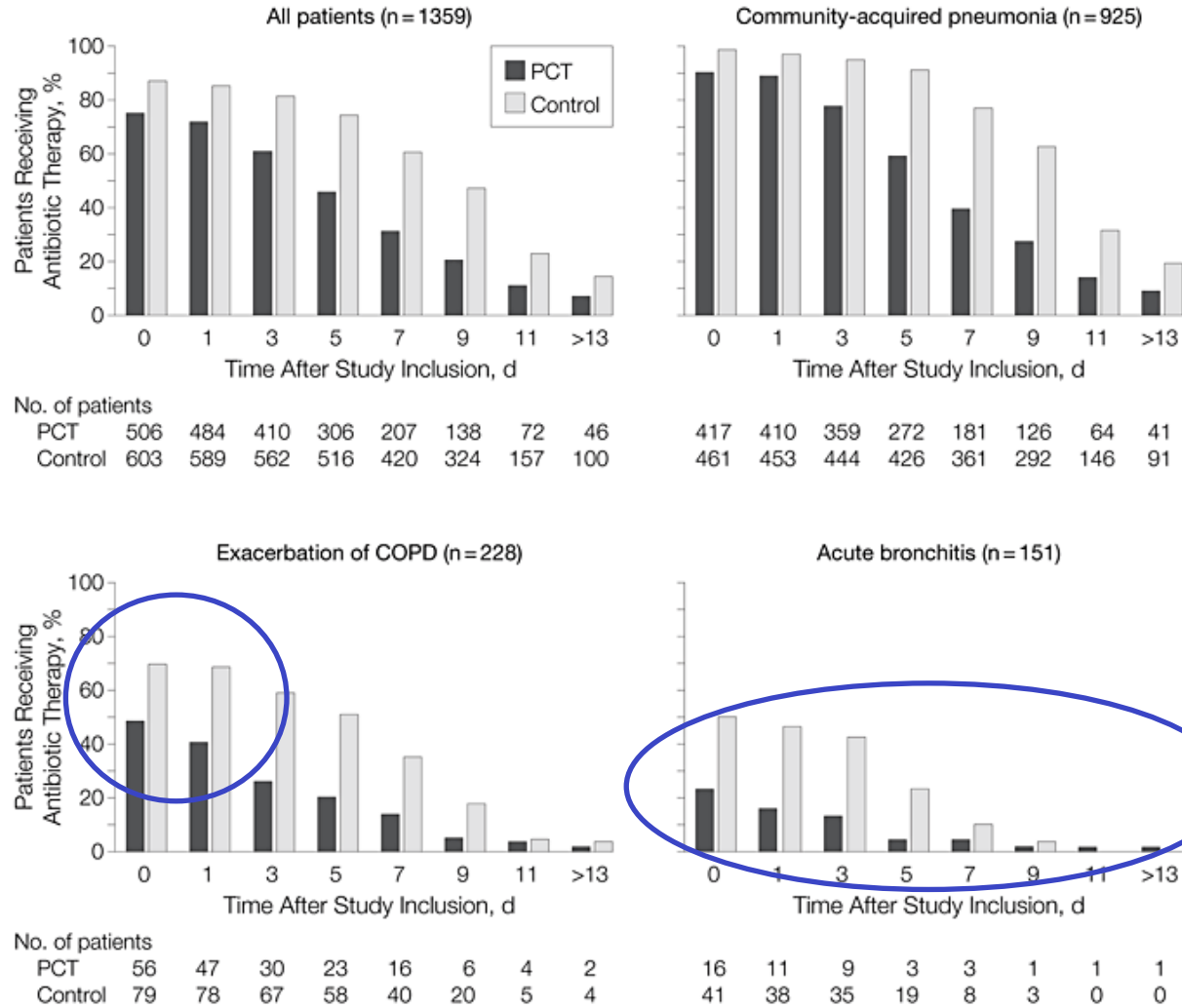
- 208 patients hospitalisés
- Décompensation de BPCO
- PCT : ATB
 - < 0,1 µg/L : déconseillé
 - 0,1-0,25 µg/L : selon contexte
 - > 0,25 µg/L : suggérée
- % consommation d'ATB



No. at Risk

| | 0 | 30 | 60 | 90 | 120 | 150 | 180 |
|------------------------|-----|----|----|----|-----|-----|-----|
| Procalcitonin group | 102 | 91 | 73 | 67 | 64 | 58 | 53 |
| Standard-therapy group | 106 | 91 | 80 | 76 | 68 | 63 | 59 |

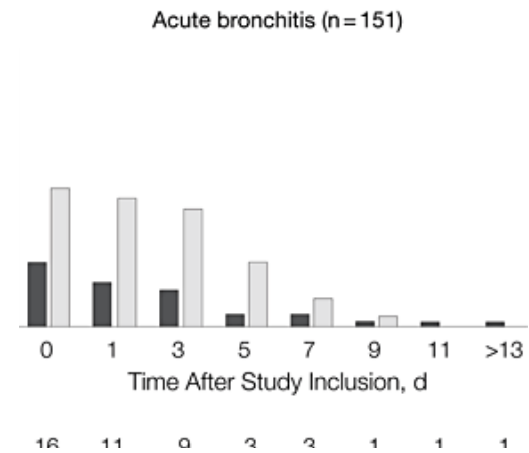
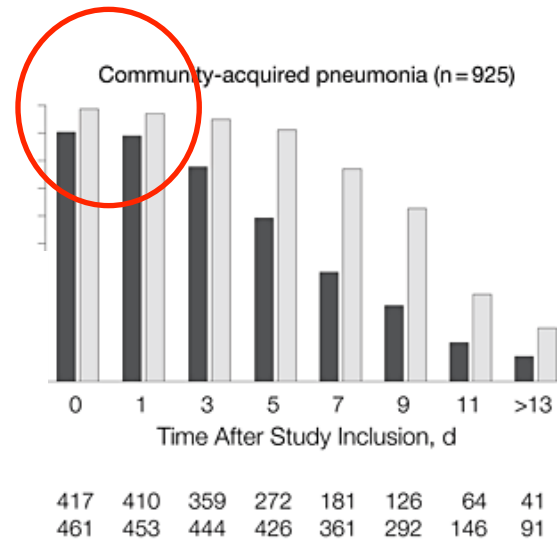
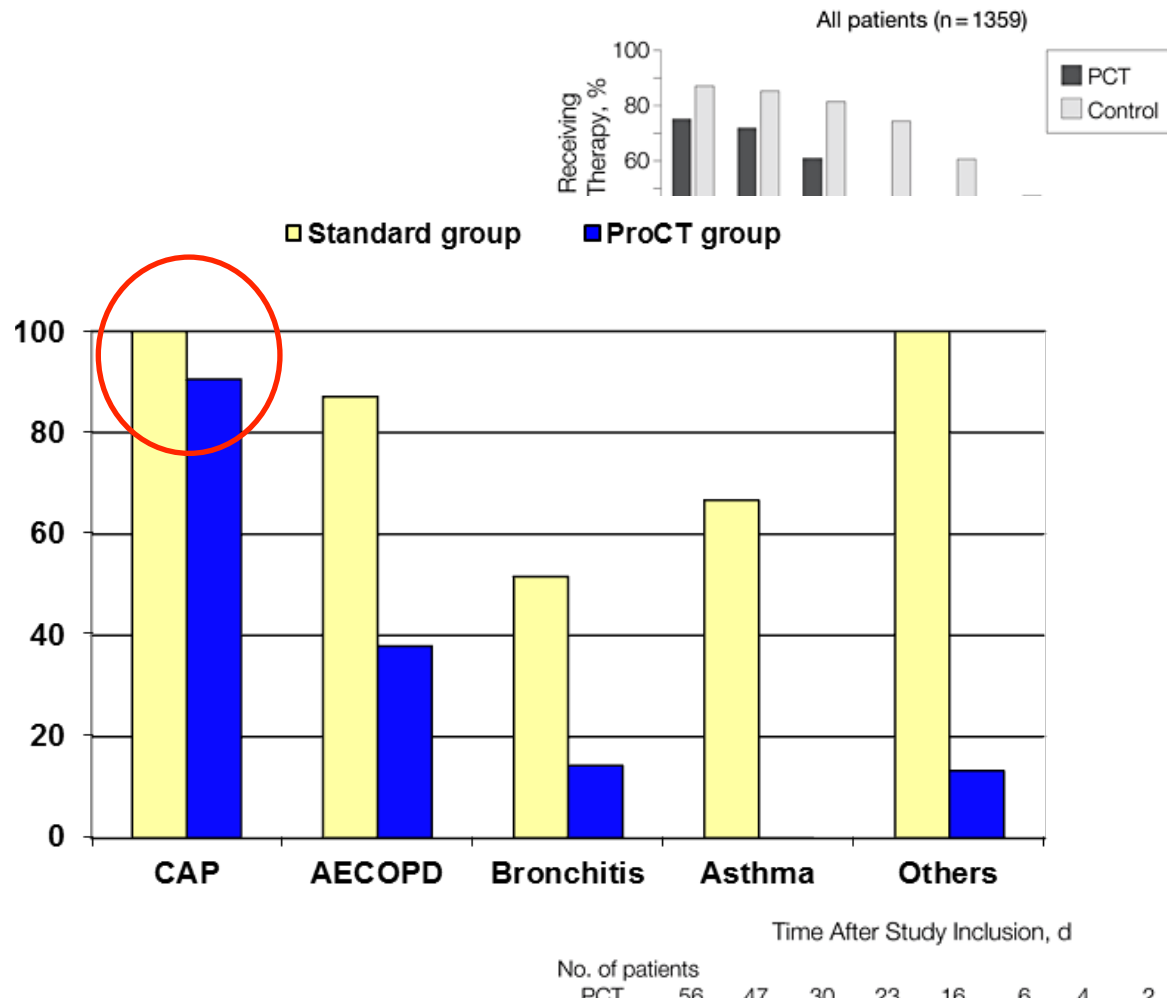
Chez les patients avec BPCO non graves : 50% de moins d'ATB



JAMA

Schuetz *JAMA* 2009

Patients avec CAP : PCT d'utilité "discutable" aux urgences

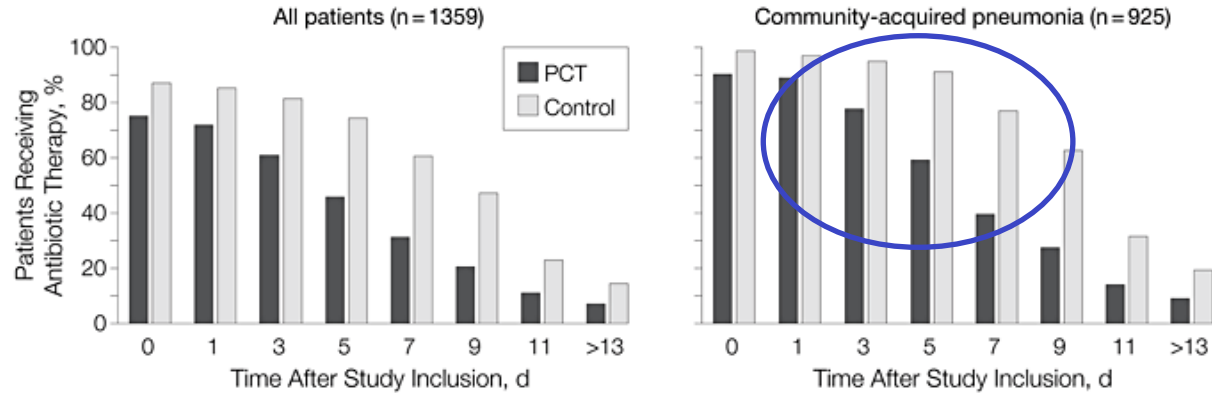


PCT aucun intérêt dans le diagnostic aux urgences

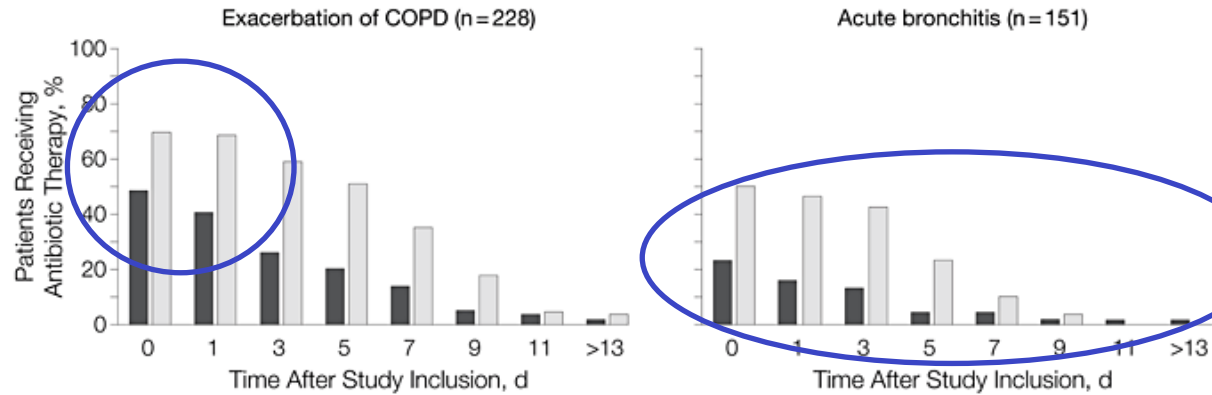
OBJECTIFS

- Rappel sur le rôle des biomarqueurs et l'évaluation biostatistique usuelle
- LA PCT pour les urgentistes
- **La PCT pour les pneumologues**
- Analyse des études d'impact : BPCO et/ou pN ?
- En pratique ?

Chez les patients hospitalisés : réduction de la durée de l'ATB



| No. of patients | | All patients (n=1359) | | | | | | | | Community-acquired pneumonia (n=925) | | | | | | | |
|-----------------|-----|-----------------------|-----|-----|-----|-----|-----|-----|-----|--------------------------------------|-----|-----|-----|-----|-----|-----|-----|
| | | 0 | 1 | 3 | 5 | 7 | 9 | 11 | >13 | 0 | 1 | 3 | 5 | 7 | 9 | 11 | >13 |
| PCT | 506 | 484 | 410 | 306 | 207 | 138 | 72 | 46 | | 417 | 410 | 359 | 272 | 181 | 126 | 64 | 41 |
| Control | 603 | 589 | 562 | 516 | 420 | 324 | 157 | 100 | | 461 | 453 | 444 | 426 | 361 | 292 | 146 | 91 |



| No. of patients | | Exacerbation of COPD (n=228) | | | | | | | | Acute bronchitis (n=151) | | | | | | | |
|-----------------|----|------------------------------|----|----|----|----|---|----|-----|--------------------------|----|----|----|---|---|----|-----|
| | | 0 | 1 | 3 | 5 | 7 | 9 | 11 | >13 | 0 | 1 | 3 | 5 | 7 | 9 | 11 | >13 |
| PCT | 56 | 47 | 30 | 23 | 16 | 6 | 4 | 2 | | 16 | 11 | 9 | 3 | 3 | 1 | 1 | 1 |
| Control | 79 | 78 | 67 | 58 | 40 | 20 | 5 | 4 | | 41 | 38 | 35 | 19 | 8 | 3 | 0 | 0 |

JAMA

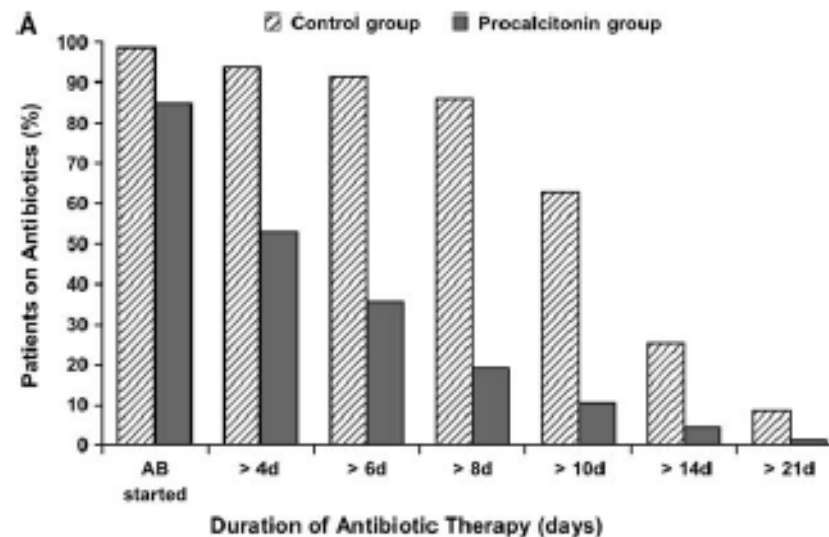
Schuetz *JAMA* 2009

Procalcitonin Guidance of Antibiotic Therapy in Community-acquired Pneumonia

A Randomized Trial

Mirjam Christ-Crain, Dalana Stoltz, Roland Bingisser, Christian Müller, David Miedinger, Peter R. Haber, Werner Zimmerli, Stephan Harbarth, Michael Tamm, and Beat Müller

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



**Réduction de 65% de la durée de traitement
ATB des PAC si guidé par la PCT**

(12.9 vs. 5.8 jours)

Effect of Procalcitonin-Guided Treatment in Patients with Infections: a Systematic Review and Meta-Analysis

Chen, Wang, Li, Hwang, Li, Song, et al. *Chest*, 2011; 140: 1161-1169

Infection 2009; 37: 497-507

Figure 2. Forrest plot of pooled odds ratios (OR) for antibiotics prescribed from four randomized trials. CI: confidence interval; PCT procalcitonin.

ATB Initiation

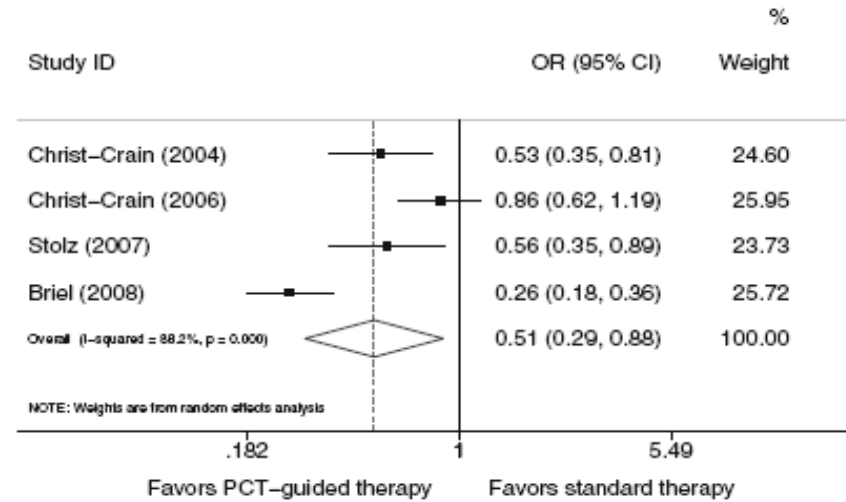
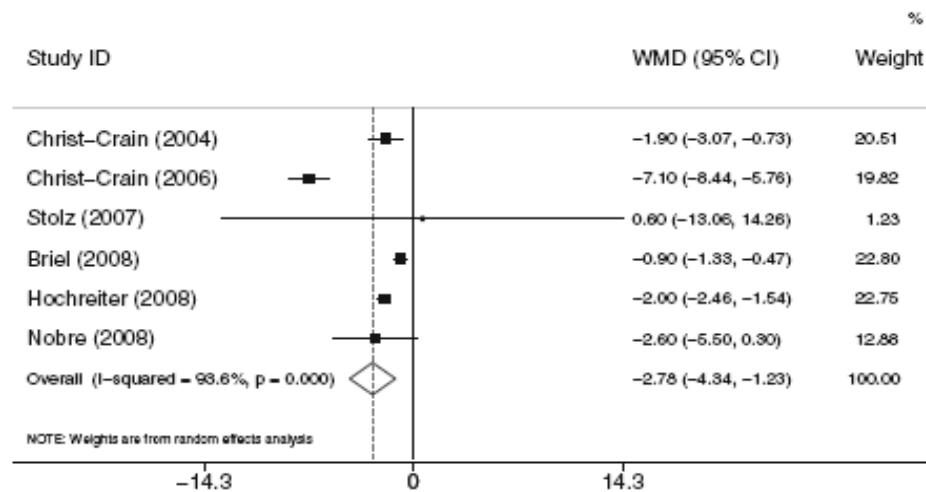


Figure 3. Forrest plot of pooled weighted mean difference for duration of antibiotic therapy from six randomized trials. WMD: Weighted mean difference. CI: confidence interval.

ATB duration

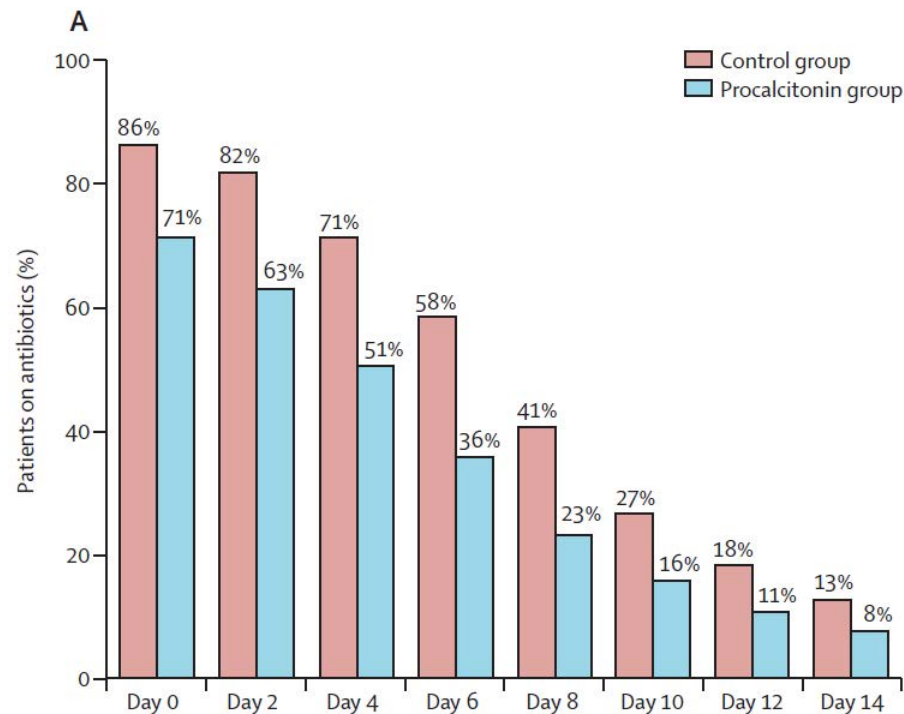


Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis

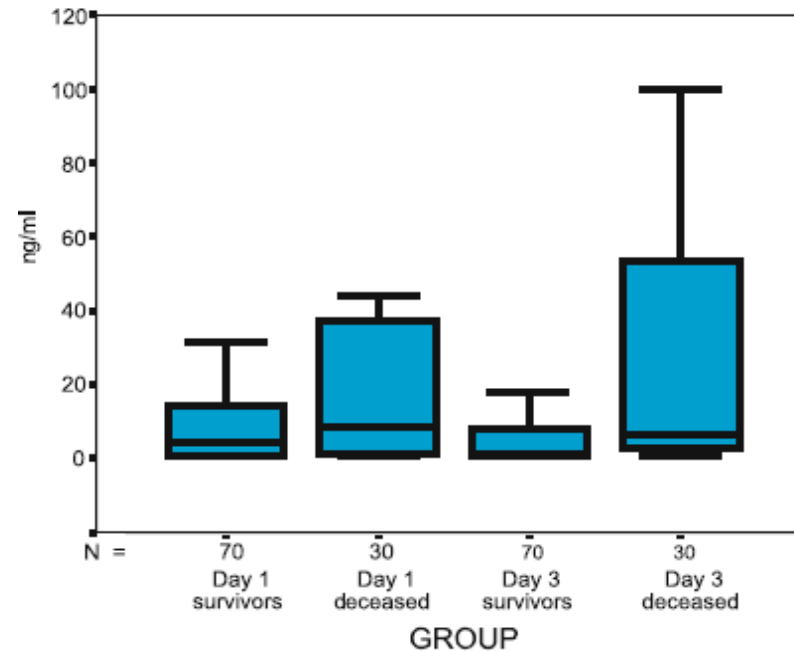
Lancet Infect Dis 2018;
18: 95-107

Philipp Schuetz, Yannick Wirz*, Ramon Sager*, Mirjam Christ-Crain, Daiana Stolz, Michael Tamm, Lila Bouadma, Charles E Luyt, Michel Wolff,*

Interpretation Use of procalcitonin to guide antibiotic treatment in patients with acute respiratory infections reduces antibiotic exposure and side-effects, and improves survival. Widespread implementation of procalcitonin protocols in patients with acute respiratory infections thus has the potential to improve antibiotic management with positive effects on clinical outcomes and on the current threat of increasing antibiotic multiresistance.

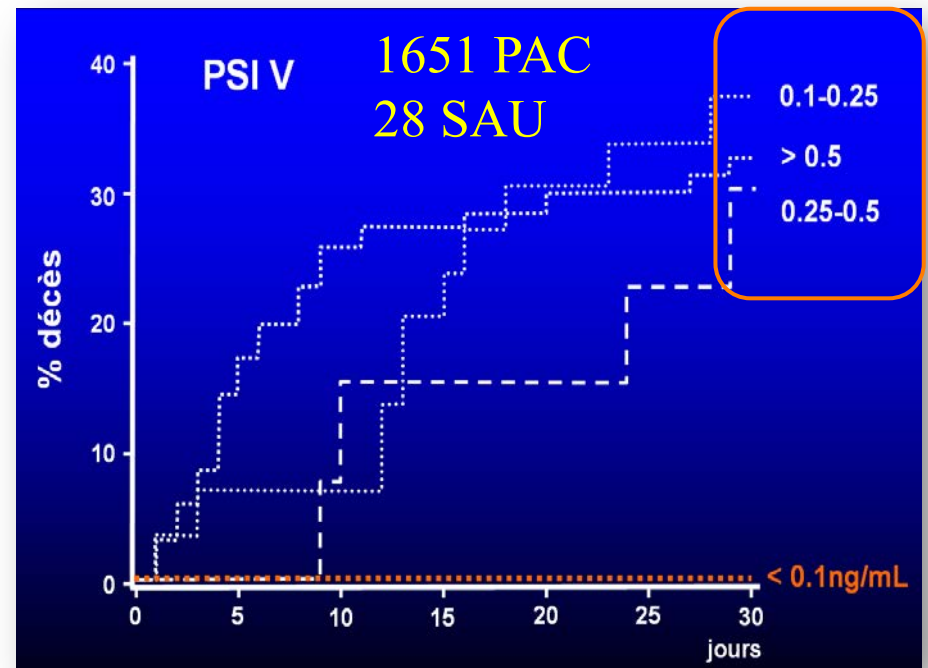
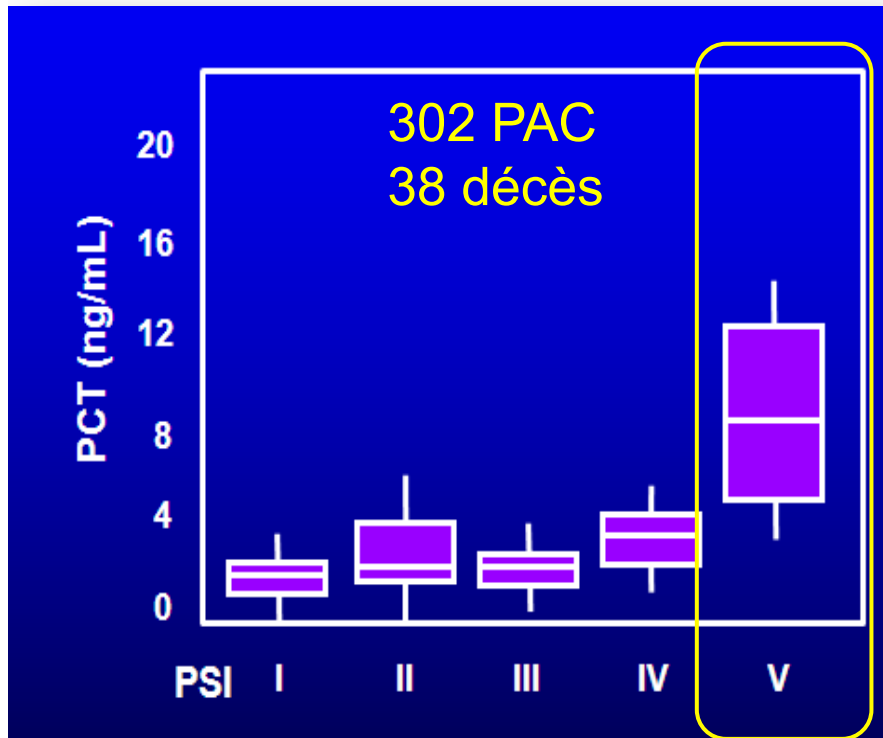


Rôle +/- pronostique de la PCT ?



g.1 Box plot of procalcitonin (PCT) levels on days 1 and 3 in survivors and nonsurvivors; $p = 0.03$ survivors' vs. nonsurvivors' PCT value on day 1, $p < 0.001$ survivors' vs. nonsurvivors' PCT value on day 3, $p = 0.01$ survivors' vs. nonsurvivors' PCT change on day 1 to day 3

PCT +/- corrélée à la sévérité de l'infection



Procalcitonin as an Early Marker of the Need for Invasive Respiratory or Vasopressor Support in Adults With Community-Acquired Pneumonia

CHEST 2016; 150(4):819-828

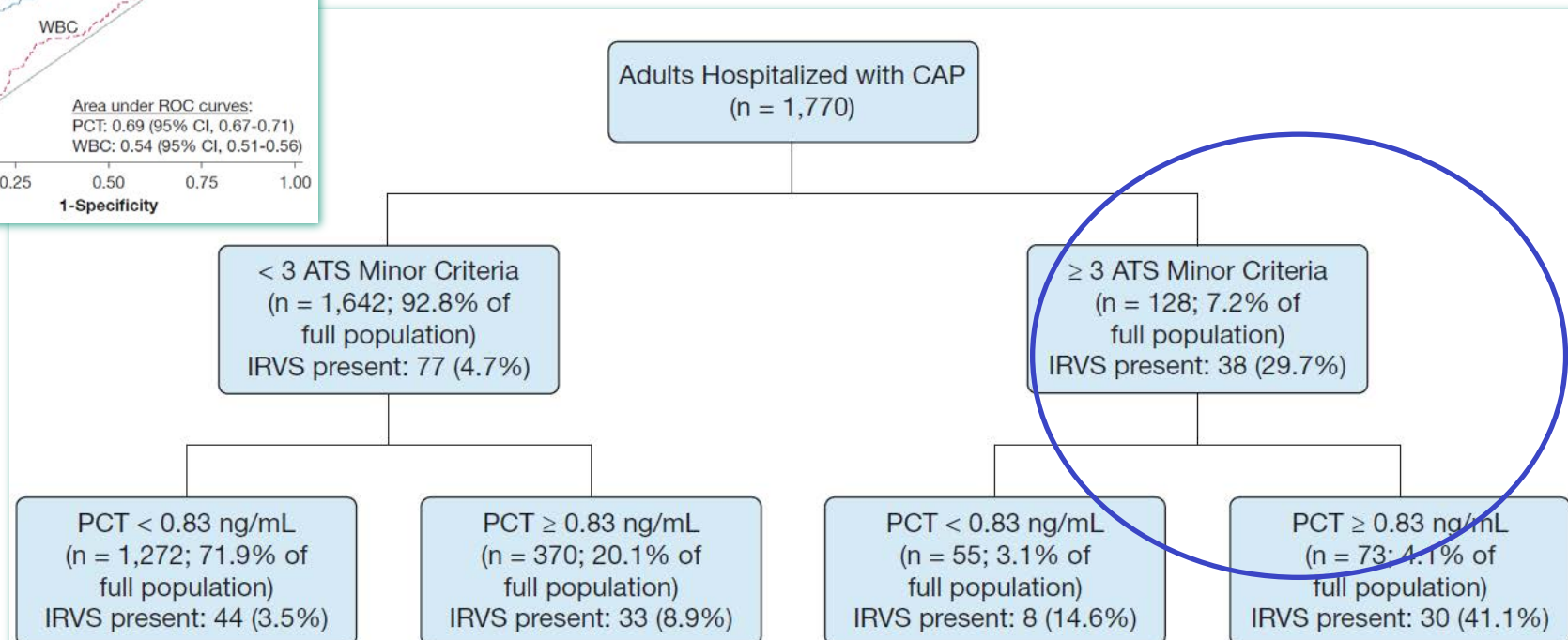
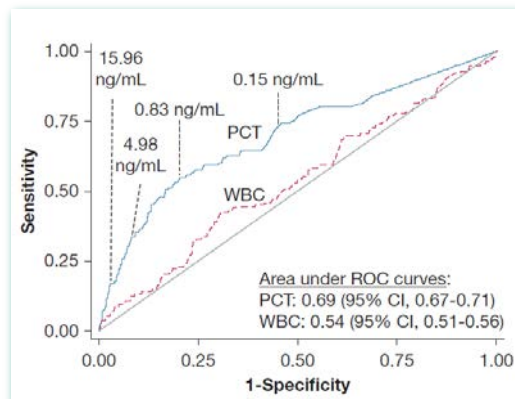
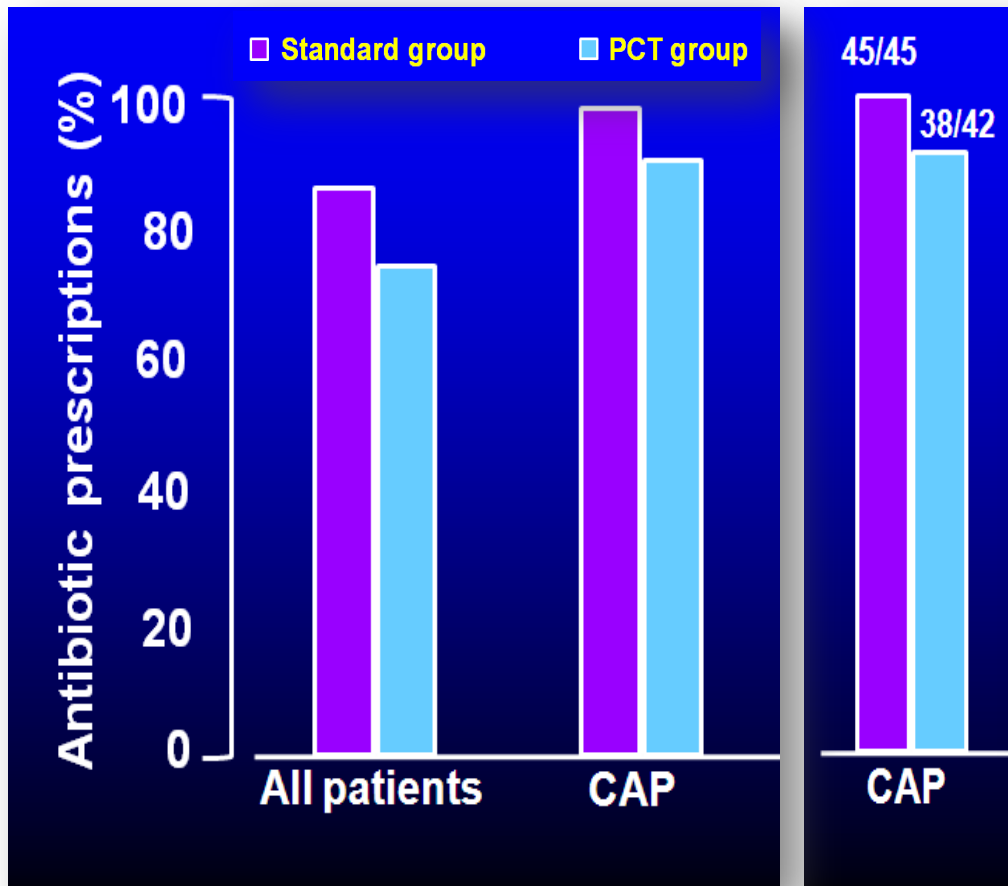


Figure 5 – Classification tree using a combination of ≥ 3 ATS minor criteria or $PCT \geq 0.83$ ng/mL (which was the 75th percentile of PCT con-

OBJECTIFS

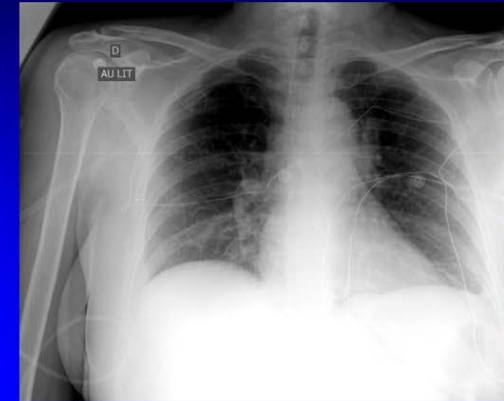
- Rappel sur le rôle des biomarqueurs et l'évaluation biostatistique usuelle
- LA PCT pour les urgentistes
- La PCT pour les pneumologues
- **Les contradicteurs des études : BPCO et/ou pN ?**
- En pratique ?


PCT et PAC

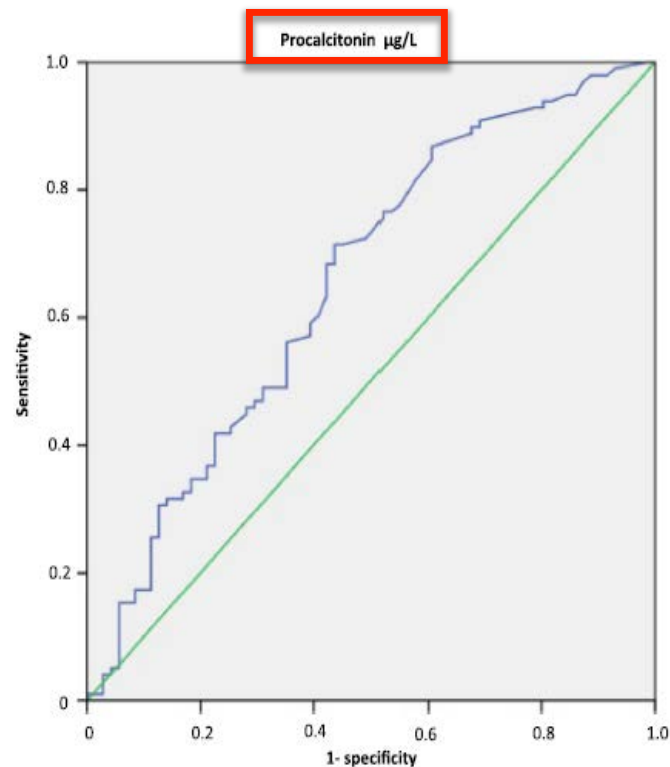


PAC « quasi-certaine »
Gain modeste
Sujets âgés ?

- Mme A, 87 ans
 - démence
 - institution
 - cardiopathie
 - ACFA
- AEG (24h)
 - dyspnée
 - confusion
 - crépitants



Diagnostic accuracy of C-reactive protein and procalcitonin in suspected community-acquired pneumonia adults visiting emergency department and having a systematic thoracic CT scan  Le Bel *et al. Critical Care* (2015) 19:366

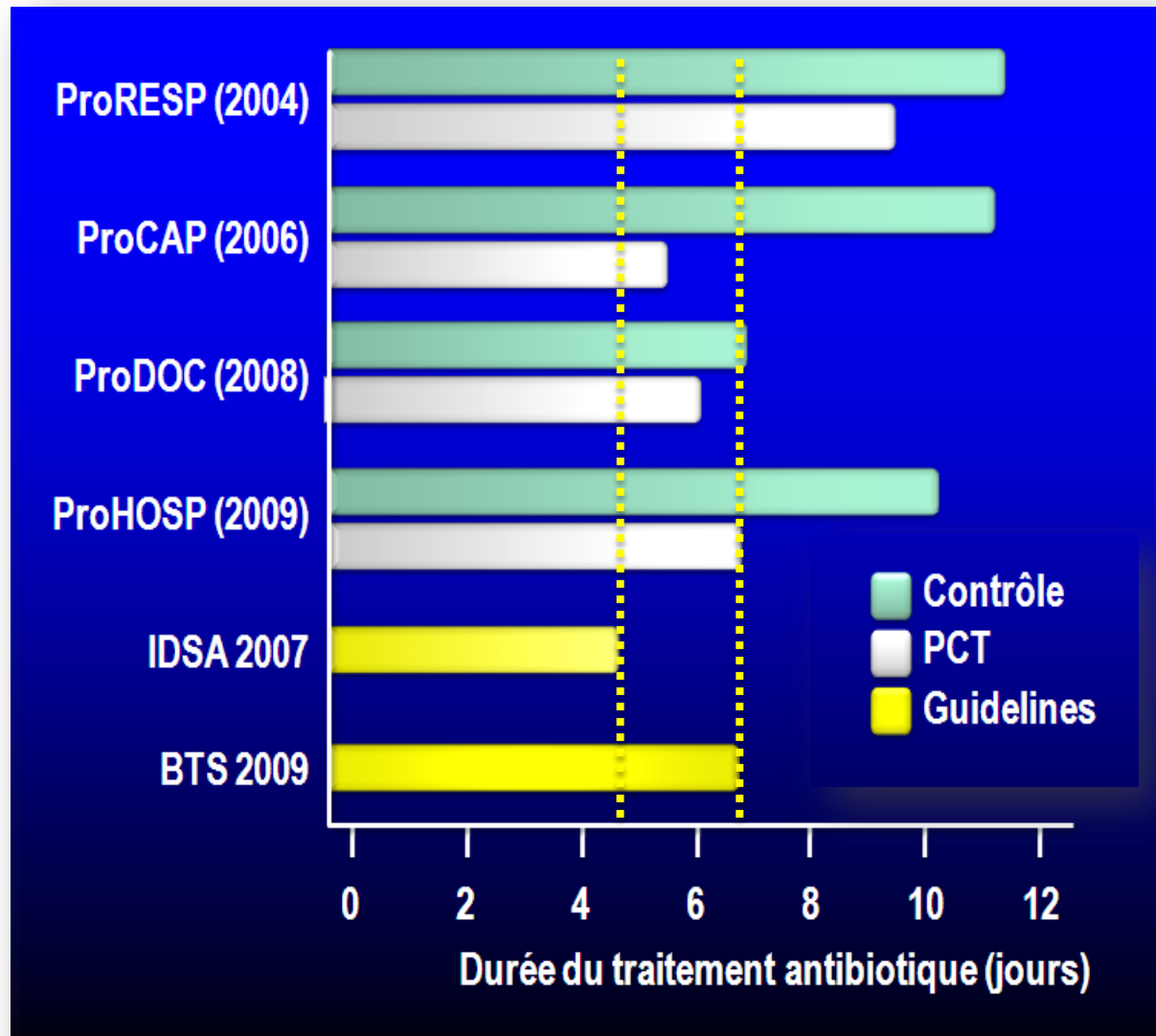


Chest X-ray results and CT scan results

Pulmonary infiltrates were seen on chest X-ray in 127 (63.5 %) patients. Thoracic CT-scan excluded a CAP diagnosis in 16.5 % of these 127 patients; on the contrary, thoracic CT-scan revealed a parenchymal infiltrate in 27 % of the 73 patients without infiltrate on chest X-ray.

Conclusions: For patients with suspected CAP visiting emergency departments, diagnostic accuracy of CRP and PCT are insufficient to confirm the CAP diagnosis established using a gold standard that includes thoracic CT scan.

PCT + durée d'antibiothérapie vs. recommandations



Procalcitonin algorithm to guide initial antibiotic therapy in acute exacerbations of COPD admitted to the ICU: a randomized



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tive randomized controlled trial of 302 severe acute exacerbation of COPD with or without pneumonia admitted in ICU failed to demonstrate the ability of a PCT-guided strategy to safely reduce antibiotic exposure, in particular among patients without antibiotics at inclusion. Prompt initiation of antibiotherapy in this population improves 3-month survival regardless of the level of PCT.

ORIGINAL ARTICLE

Procalcitonin-Guided Use of Antibiotics for Lower Respiratory Tract Infection

D.T. Huang, D.M. Yeal

Pas de différence de consommation d'ATB : 4j

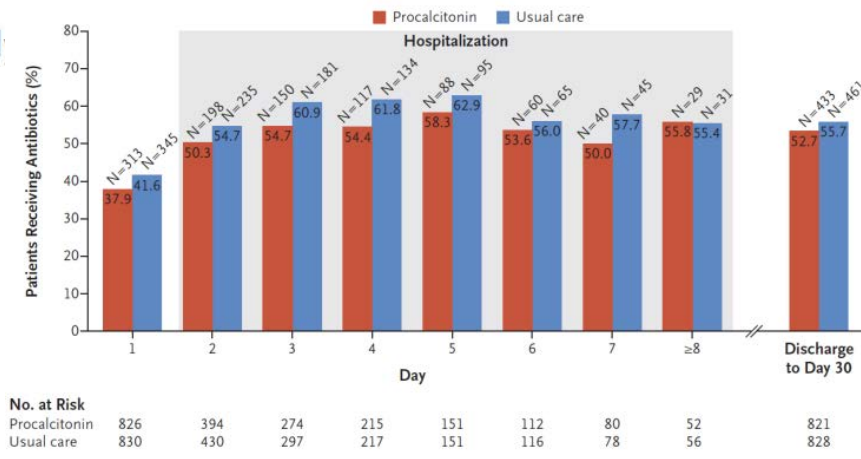


Figure 3. Antibiotic Exposure over Time.

CONCLUSIONS, en pratique

- IRB/EBPCO non graves en urgence : PCT probablement utile
- BPCO grave en urgence/réa : PCT peu utile
- PAC en urgence : PCT peu utile
- PAC graves : PCT apporte peu
- Pour diminuer la durée de l'ATB : PCT possiblement utile

...to be continued