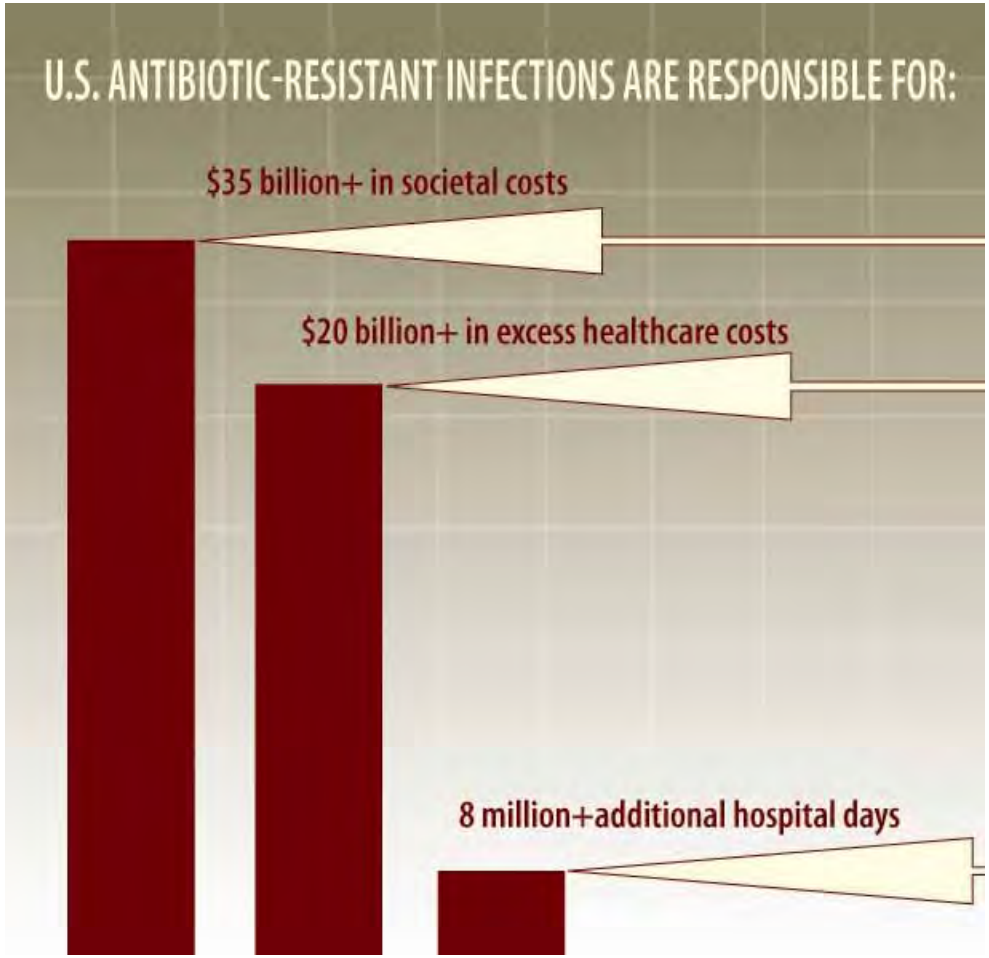
Biomarker mediated management of pneumonia

Abhishek Goyal

21/10/11

Antibiotic-resistant Infections



CDC Nov 2010

Prevent unnecessary antibiotic use

- More than $1.1 billion is spent annually on unnecessary antibiotic prescriptions for respiratory infections in adults.
- antibiotic stewardship programs
- Prevent nosocomial infections
- Stopping unnecessary antibiotic

CDC Nov 2010

Pneumonia

SMART-COP

- Low Systolic blood pressure
- Multilobar chest radiography involvement
- low Albumin level
- high Respiratory rate,
- Tachycardia
- Confusion,
- poor Oxygenation
- low arterial pH

score ≥3 points identified 92% of patients who received invasive respiratory or vasopressor support, including 84% of patients who did not need immediate admission to the ICU.

- CURB-65

  or

- CRB-65
- PSI

What is a biomarker

- "….a xenobiotically-induced variation in cellular or biochemical components or processes, structures, or functions that is measurable in a biological system." -National Academy of Science

- " A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention."

-Biomarker Definitions Working Group (2001)

If we know what a biomarker is-

What makes an ideal biomarker?

Ideal biomarker

- Rise before clinical manifestation
- Easy to measure
- Shows no major fluctuation in serum levels
- Help target intervention
- Increases pathologically in the presence of disease (high sensitivity)
- Does not increase in the absence of the disease (high specificity)
- Consistent results
- Short half life
- Cost effective

Indications in pneumonia

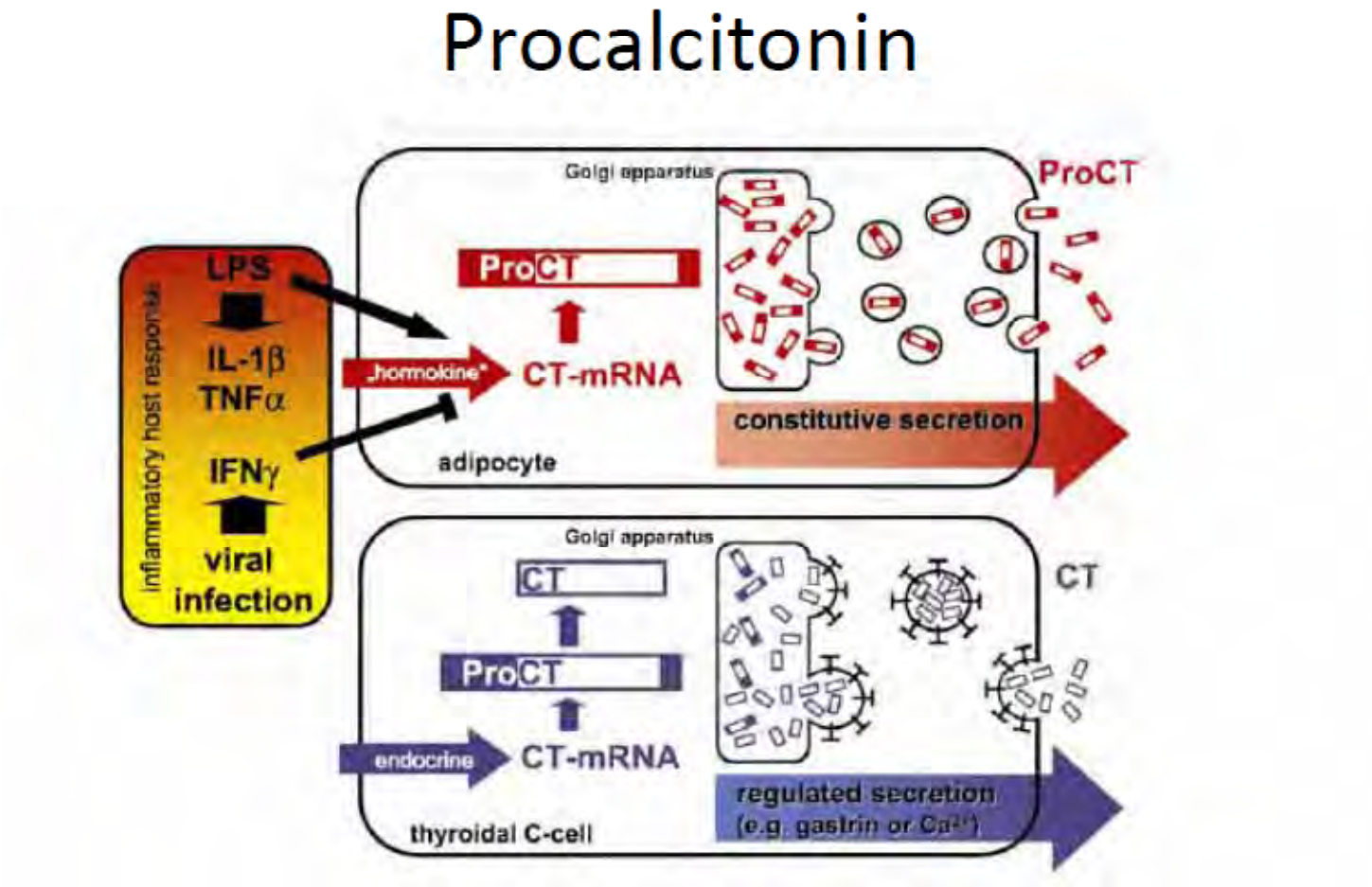
- diagnosis of severe bacterial infection
- evaluation of sepsis severity
- assessment of the appropriateness of therapy
- tailoring of antibiotic prescription (indication and duration)

Procalcitonin

- devoid of known hormonal activity.
- normally produced by thyroid C cells and then cleaved into 3 distinct molecules: calcitonin, katacalcin & N-terminal fragment.
- Release in response to bacterial toxins and proinflammatory mediators (IL-1b, TNF-a & IL-6).
- ↓↓ in patients with viral infections because of IFN-gamma.

Clin Chest Med :29;2008.591-603.

Procalcitonin



Clin Chest Med :29;2008.591-603.

Procalcitonin

- ↑ upon initial infection within 6 to 12 hours
- Because enzymatic cleavage of calcitonin is circumvented, PCT levels may increase without any concomitant calcitonin level increase.
- Sepsis indicator .

Clin Chest Med :29;2008.591-603.

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Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia

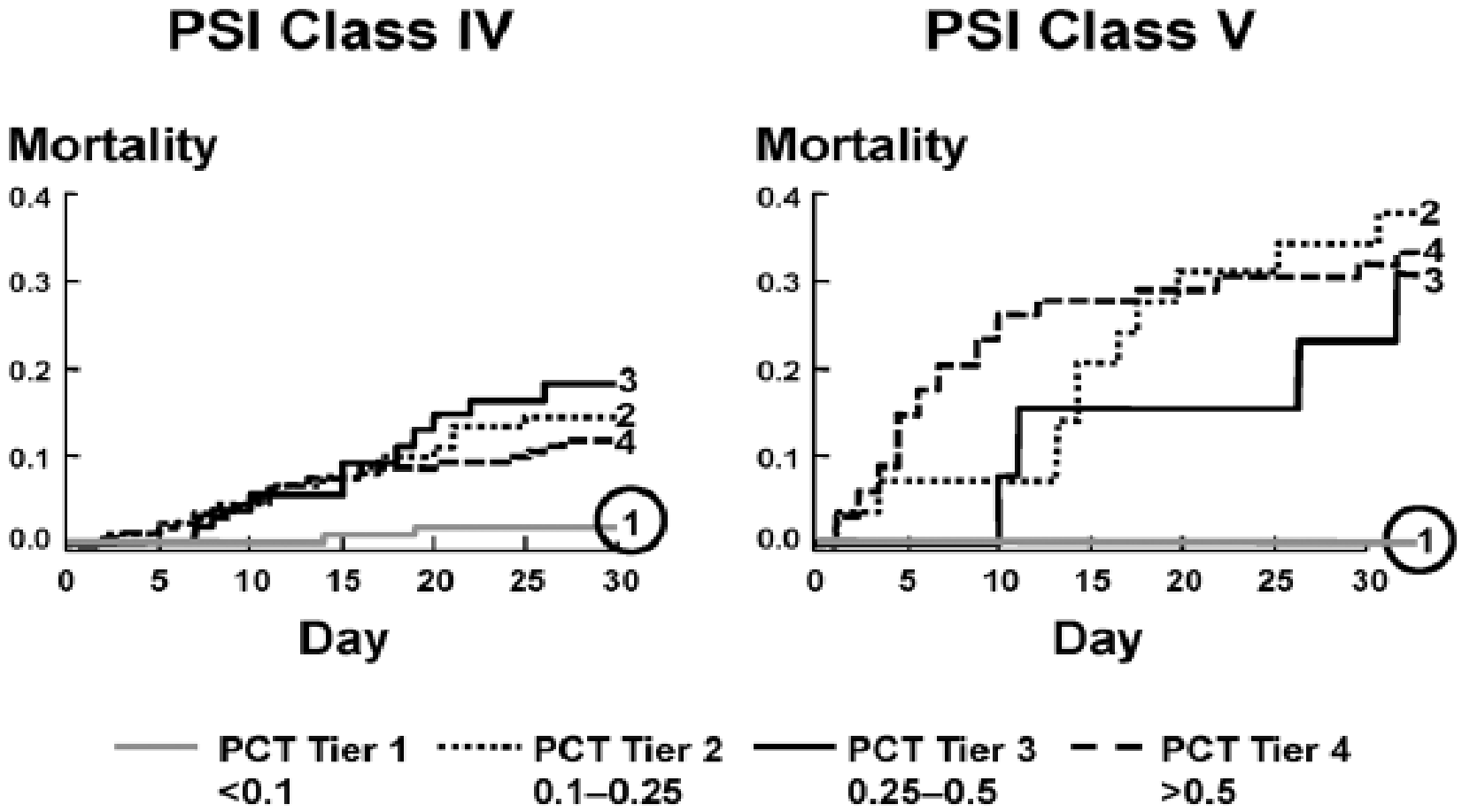
David T. Huang, MD, MPH[*,†], **Lisa A. Weissfeld, PhD**[‡], **John A. Kellum, MD**[*], **Donald M. Yealy, MD**[†], **Lan Kong, PhD**[‡], **Michael Martino, MD**[§], and **Derek C. Angus**[*] **on behalf of the GenIMS investigators**

Methods—We conducted a multi-center prospective cohort study in 28 community and teaching emergency departments. Patients presenting with a clinical and radiographic diagnosis of CAP were enrolled. We stratified procalcitonin levels *a priori* into four tiers – I: < 0.1; II: ≥ 0.1 to <0.25; III: ≥ 0.25 to < 0.5; and IV: ≥ 0.5 ng/ml. Primary outcome was 30d mortality.

Results—1651 patients formed the study cohort. Procalcitonin levels were broadly spread across tiers: 32.8% (I), 21.6% (II), 10.2% (III), 35.4% (IV). Used alone, procalcitonin had modest test characteristics: specificity (35%), sensitivity (92%), positive likelihood ratio (LR) (1.41), and negative LR (0.22). Adding procalcitonin to PSI in all subjects minimally improved performance. Adding procalcitonin to low risk PSI subjects (Class I–III) provided no additional information. However, subjects in procalcitonin tier I had low 30d mortality regardless of clinical risk, including those in higher risk classes (1.5% vs. 1.6% for those in PSI Class I–III vs. Class IV/V). Among high risk PSI subjects (Class IV/V), one quarter (126/546) were in procalcitonin tier I, and the negative LR of procalcitonin tier I was 0.09. Procalcitonin tier I was also associated with lower burden of other adverse outcomes. Similar results were seen with CURB-65 stratification.

Huang et al.Ann Emerg Med 2008, ***52:48-58.***

PCT level and PSI prognostic value



Low levels (<0.1 mg/ml) of PCT at baseline are predictive of survival, even in PSI group IV and V patients, although the distinction is less defined in PSI group V patients

Huang et al. Ann Emerg Med 2008, ***52:48-58.***

- low procalcitonin was associated with shorter length of stay, lower proportions of mechanical ventilation and ICU admission.
- while CAP patients with severe sepsis at ED presentation or later→ low procalcitonin portends a less severe course, potentially explaining the associated low mortality.

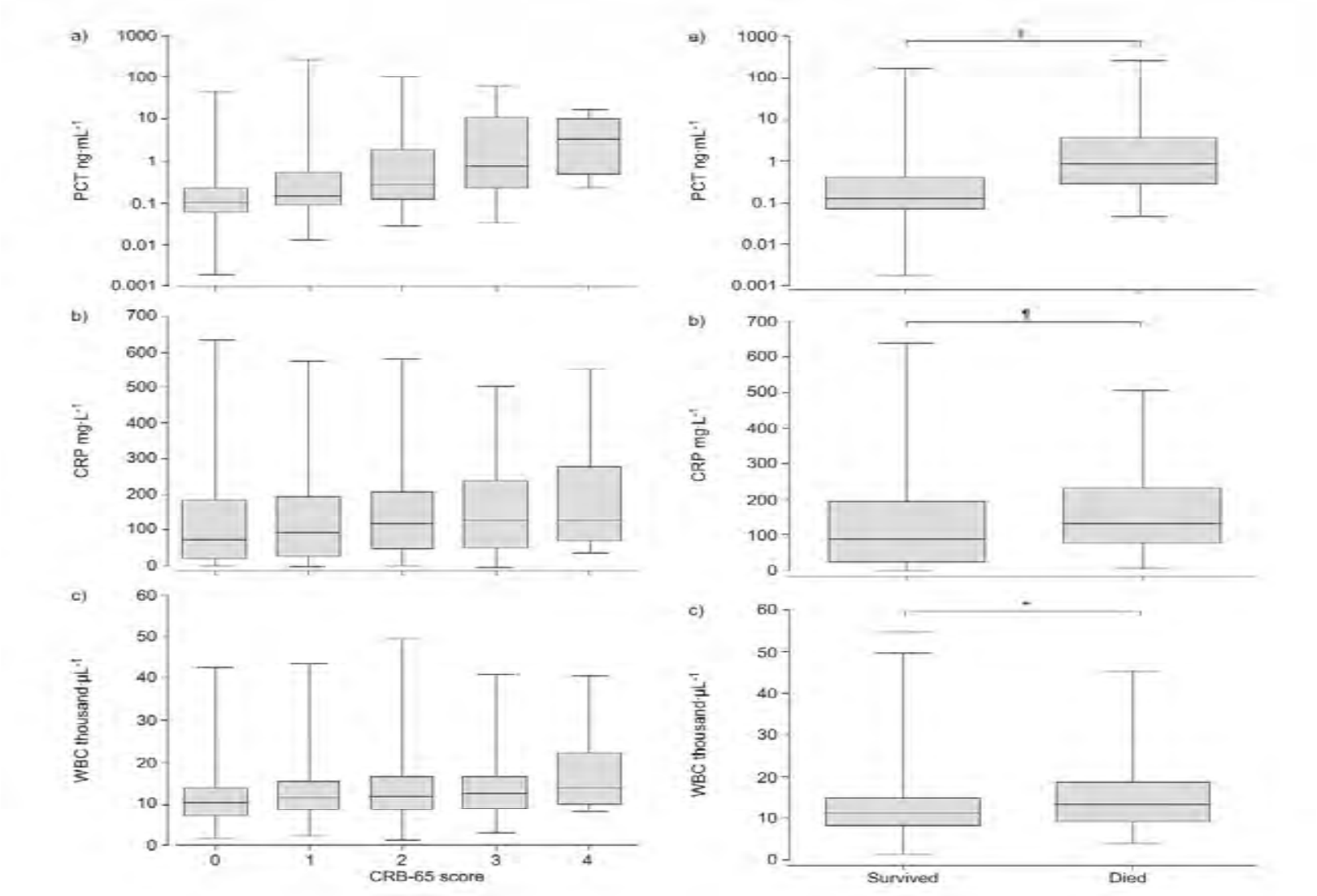
Huang et al. Ann Emerg Med 2008, ***52:48-58.***

CAPNETZ trial

- In 1671 patients with proven CAP, PCT, CRP, WBC and CRB-65 were determined at admission and patients were followed-up for 28 days for outcome.
- PCT levels at admission → better predictor of CAP severity and outcome than WBC and CRP levels, with a similar prognostic accuracy as the CRB-65 score.
- PCT threshold of 0.228 ng/ml identifies low-risk patients within all CRB-65 risk groups.

Eur Respir J 2008; 31: 349–55

CAPNETZ trial



Eur Respir J 2008; 31: 349–55

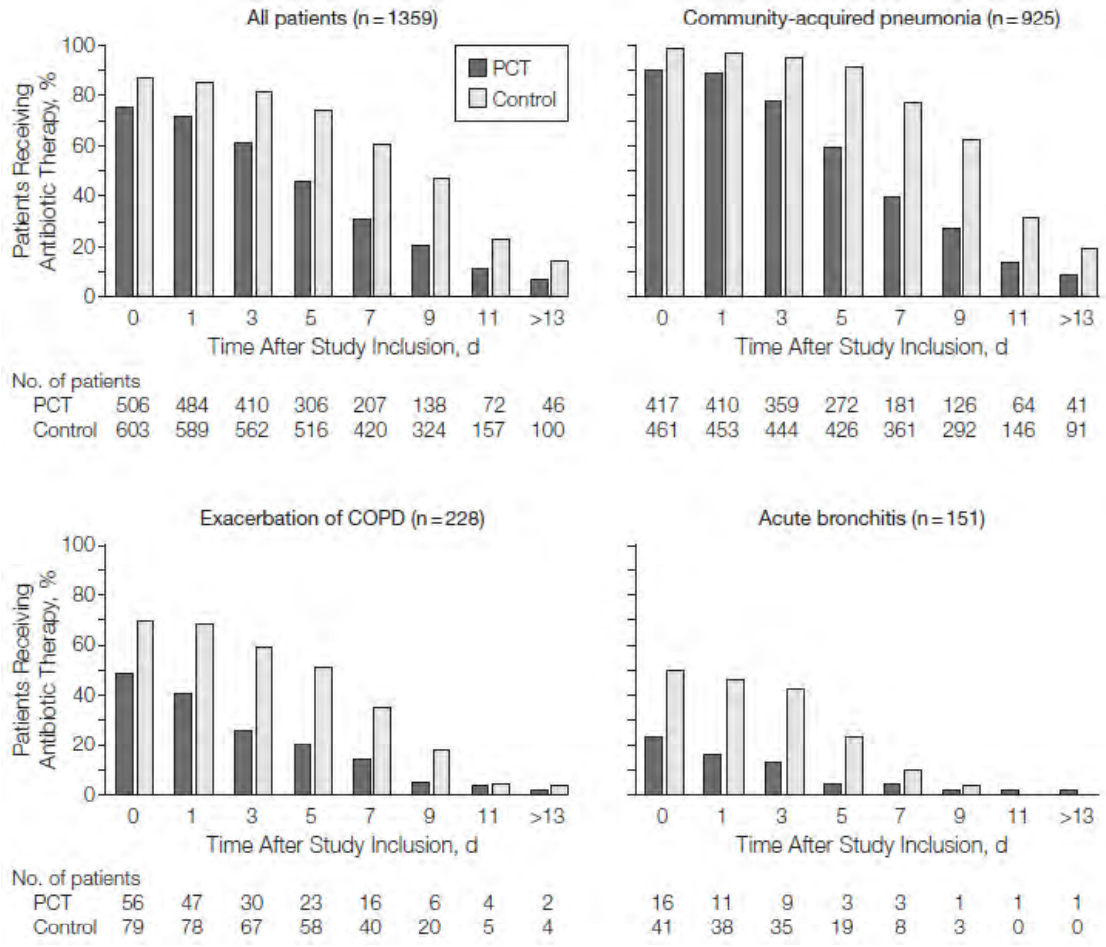
CAPNETZ trial

- procalcitonin levels did not add prognostic information for most pneumonia patients.
- Among higher-risk groups as assessed by the PSI score, low procalcitonin level reliably predicted lower mortality.

Huang et al Eur Respir J 2008; 31: 349–55

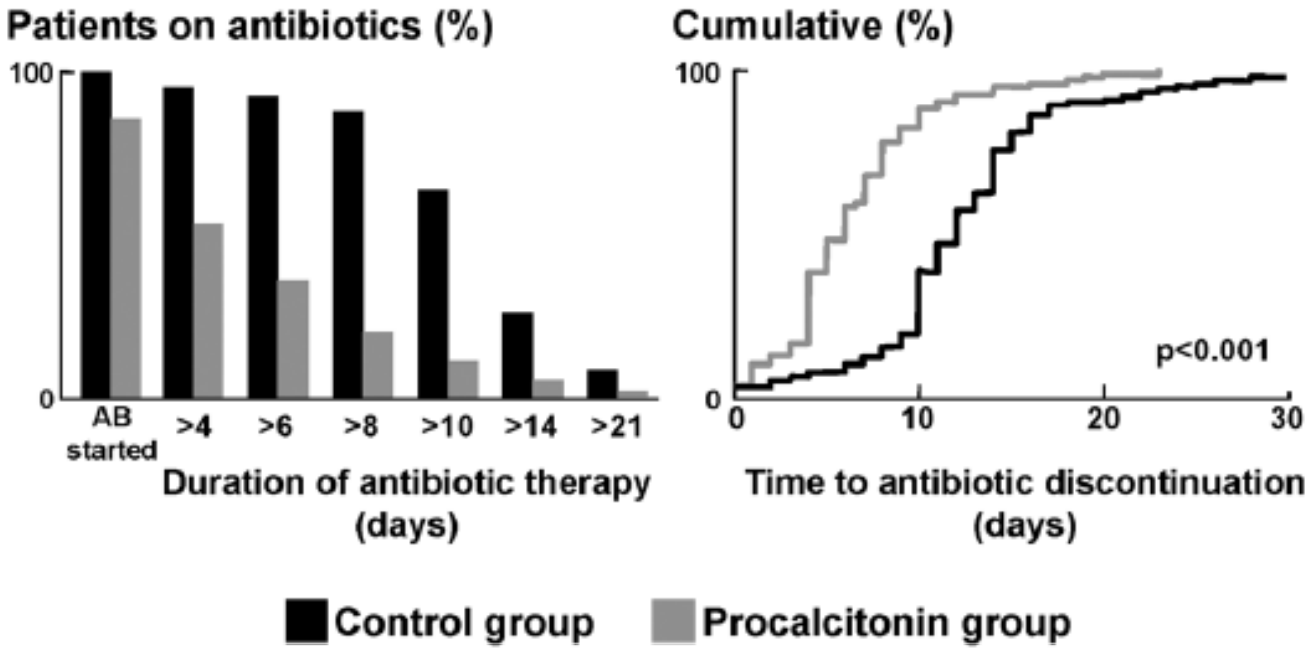
Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections

The ProHOSP Randomized Controlled Trial



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

PCT guided CAP management



Am J Resp Crit Care Med 2006, **174:84-93.**

HAP

- PCT not as a good marker of nosocomial infections as CAP.
- PCT measured in the blood or BAL fluid of VAP patients was not a good marker of this pneumonia.
- Incorporating its value into a clinical score (CPIS) did not improve its diagnostic performance

Duflo F et al. Anesthesiology 2002;96:74–9.
Luyt CE et al.Intensive Care Med 2008;34:1434–40.
Charles PE et al. BMC Infect Dis 2009;9:49.

Why PCT failed to indicate HAP

- Pneumonia may be a localized infection, with only local PCT synthesis & no systemic release → low blood level or apparent decline in patients with true pulmonary infections.
- Pre-existing severe sepsis or MODS or SIRS.
- Time lag of 24 to 48 hours between onset of bacterial infection and peak PCT release.

Why VAP is difficult to diagnose

- ARDS
- CCF
- Pulmonary contusion
- DAH
- Colonisation of E.T.

PCT kinetics

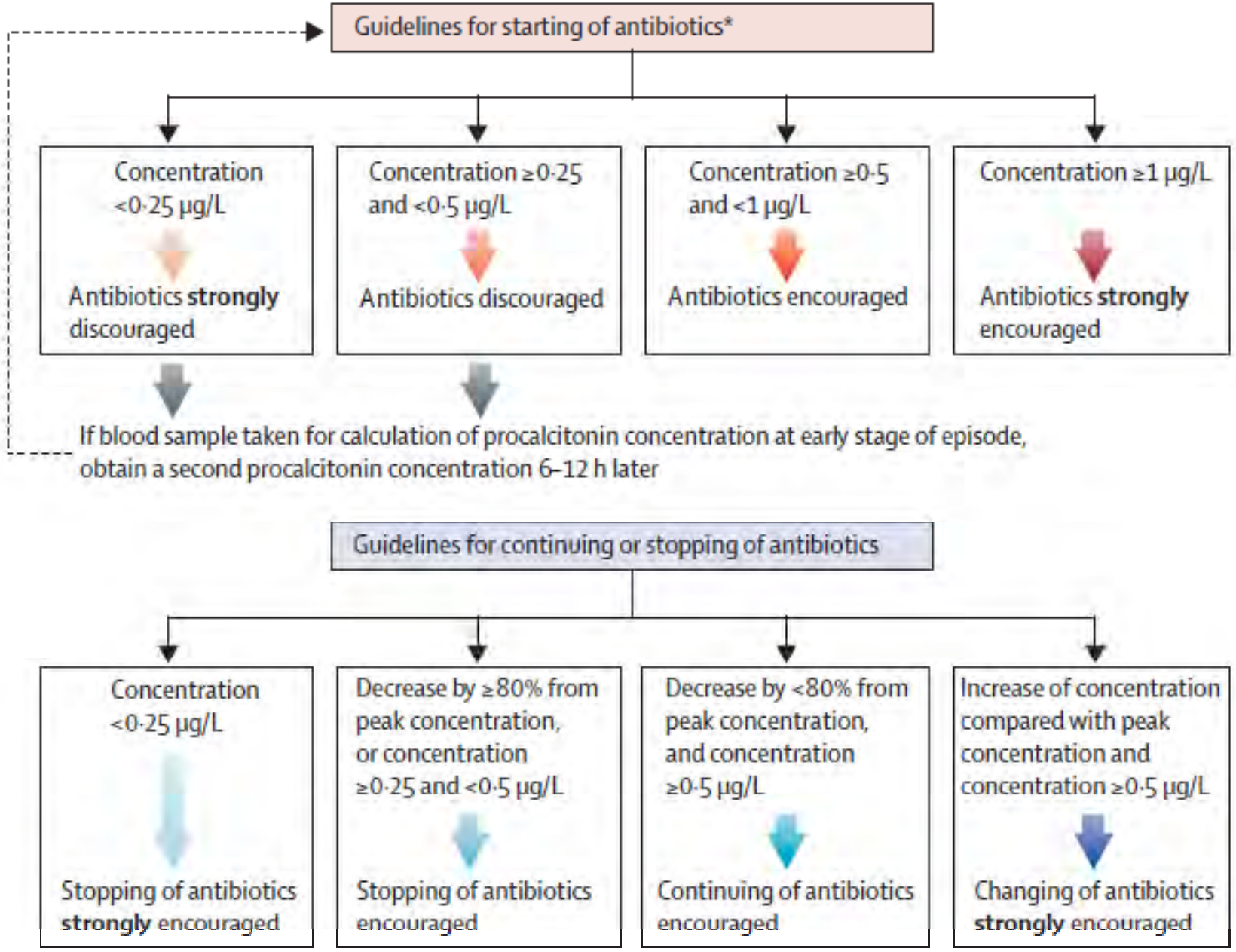
- might be useful as a diagnostic marker.
- PCT concentration rises(the day VAP is suspected) compared with a value obtained 1 to 5 days earlier, is highly suggestive of an active infection.
- In contrast, when the PCT level is low (<0.1 ng/mL) the day of suspected VAP, with no increase 24 to 48 hours later, the probability of an active infection is very low.

Semin Respir Crit Care Med 2011;32:181–187.

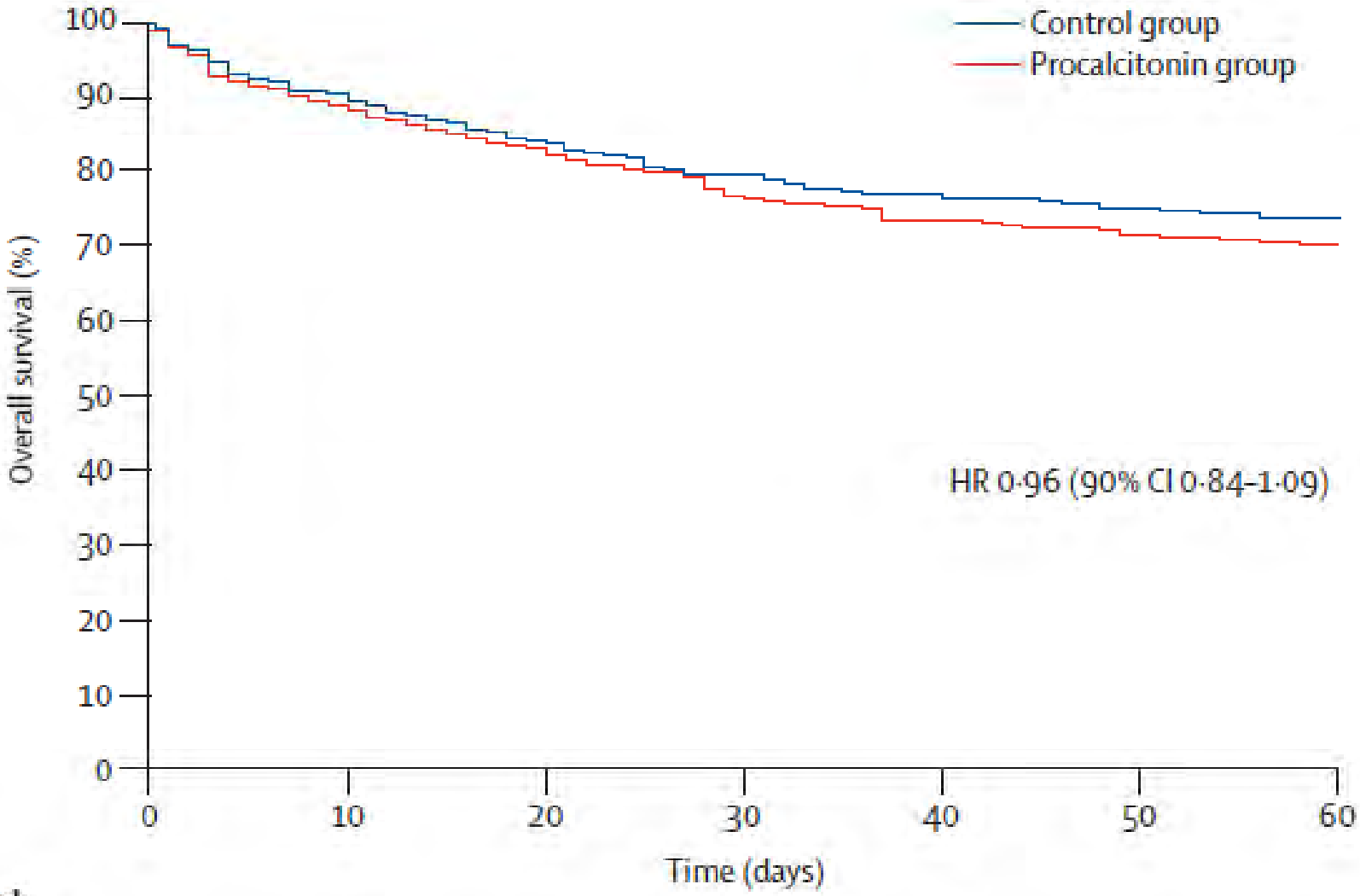
Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial

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



Lancet 2010; 375: 463–74



Number at risk							
Procalcitonin group	307	273	255	235	225	219	215
Control group	314	284	264	249	240	234	231

Lancet 2010; 375: 463–74

	Procalcitonin group (n=307)	Control group (n=314)	Between-group absolute difference	p value
Primary endpoints				
28-day mortality*	65 (21·2%)	64 (20·4%)	0·8% (–4·6 to 6·2)	NA
60-day mortality*	92 (30·0%)	82 (26·1%)	3·8% (–2·1 to 9·7)	NA
Number of days without antibiotics	14·3 (9·1)	11·6 (8·2)	2·7 (1·4 to 4·1)	<0·0001
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
SOFA score				
Day 1	7·5 (4·4)	7·2 (4·4)	0·3 (–0·4 to 1·0)	0·39
Day 7	4·1 (4·2)	4·0 (4·2)	0·1 (–0·6 to 0·8)	0·73
Day 14	2·8 (3·5)	2·8 (3·6)	0 (–0·6 to 0·7)	0·87
Day 21	2·1 (3·3)	1·9 (3·1)	0·2 (–0·4 to 0·8)	0·52
Day 28	1·5 (3·0)	0·9 (2·4)	0·6 (0·0 to 1·1)	0·0370
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
Duration of first episode of antibiotic treatment (number [%]; days [SD])				
Overall population	307 (100%); 6·1 (6·0)	314 (100%); 9·9 (7·1)	–3·8 (–4·8 to –2·7)	<0·0001
Community-acquired pneumonia	79 (26%); 5·5 (4·0)	101 (32%); 10·5 (6·4)	–5·0 (–6·6 to –3·4)	<0·0001
Ventilator-associated pneumonia	75 (24%); 7·3 (5·3)	66 (21%); 9·4 (5·7)	–2·1 (–4·0 to –0·3)	0·0210
Intra-abdominal infection	14 (5%); 8·1 (7·7)	20 (6%); 10·8 (6·7)	–2·7 (–7·7 to 2·4)	0·29
Urinary tract infection	24 (8%), 7·4 (6·3)	18 (6%), 14·5 (9·3)	–7·1 (–11·9 to –2·2)	0·0053
Infection with positive blood culture	55 (18%), 9·8 (7·7)	53 (17%), 12·8 (8·1)	–3·0 (–6·0 to 0·1)	0·06

Data are number (%), difference (95% CI), or mean (SD), unless otherwise indicated. NA=not applicable. SOFA=sequential organ-failure assessment. ICU=intensive care unit.
*Difference (90% CI).

Table 2: **Main outcome variables**

PCT as guide to start Antibiotic

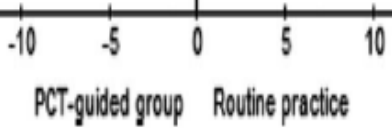
- Among the 307 patients randomized to algorithm-guided management, only 10.4% were not given antibiotics at inclusion despite having PCT concentrations of less than 0.5 ng/mL.
- 65 patients received antibiotics because their treating physicians considered that the presence of a true infection could not be excluded.

Total duration of antibiotic

Review: Procalcitonin-guided algorithms of antibiotic stewardship in the intensive care unit: systematic review and meta-analysis
Comparison: 01 Procalcitonin-guided algorithms versus routine practice
Outcome: 02 Total duration of antibiotic treatment

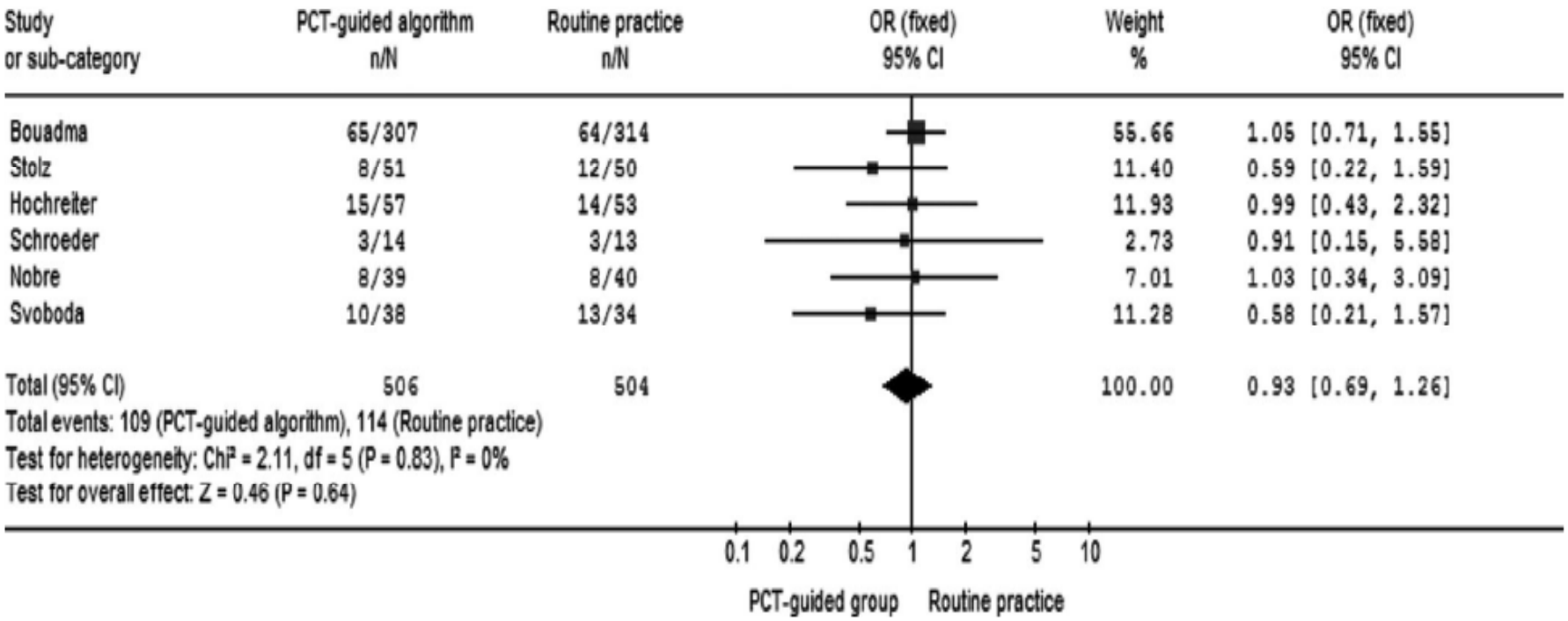
Study or sub-category	PCT-guided algorithm N	PCT-guided algorithm Mean (SD)	Routine practice N	Routine practice Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Bouadma	307	10.30(7.70)	314	13.30(7.60)		43.91	-3.00 [-4.20, -1.80]
Stolz	51	10.00(2.50)	50	15.00(3.25)		49.60	-5.00 [-6.13, -3.87]
Nobre	39	8.00(5.75)	40	14.00(8.25)		6.49	-6.00 [-9.13, -2.87]
Total (95% CI)	397		404			100.00	-4.19 [-4.98, -3.39]

Test for heterogeneity: $Chi^2 = 7.01$, $df = 2$ ($P = 0.03$), $I^2 = 71.5\%$
Test for overall effect: $Z = 10.29$ ($P < 0.00001$)



Crit Care Med 2010 Vol. 38, No. 11

28 day mortality



Crit Care Med 2010 Vol. 38, No. 11

Studies Evaluating Procalcitonin Concentration as a Diagnostic Marker of Ventilator-Associated Pneumonia

Reference	Number of Subjects		Cut-off	Sensitivity	Specificity
	VAP	No VAP	(ng/mL)	(%)	(%)
Duflo et al, 2002[22]	44	52	3.9	41	100
Ramirez et al, 2008[26]	9	11	2.99	78	97
Luyt et al, 2008[23]	32	41	2	41	61
Charles et al, 2009[24]	47	23	0.44	65	83
Jung et al, 2010[25]	48	38	0.5	54	39

Semin Respir Crit Care Med 2011;32:181–187.

Algorithm for PCT use

PCT <0.1 μg/L	Bacterial infection very unlikely	NO antimicrobials	Consider repeat in 6–24 hours; reassess based on clinical status and new result
PCT 0.1–0.25 μg/L	Bacterial infection unlikely	NO antimicrobials	Use of antimicrobials should be considered despite low PCT level if: Respiratory or hemodynamic instability; Life-threatening condition; Need for ICU admission; Evidence of empyema; Positive microbiological test (eg, pneumococcal or *Legionella* urinary antigen)
PCT >0.25–0.5 μg/L	Bacterial infection likely	YES antimicrobials	Consider clinical course and repeat PCT at days 3, 5, 7:
PCT >0.5 μg/L	Bacterial infection very likely	YES antimicrobials	Stop antimicrobial using the cutoffs above If peak PCT was very high, consider stopping antimicrobials when 80%–90% decrease If PCT remains high, consider treatment failure

Thomas et al. Clin Chest Med 32 (2011) 417–430

CRP

- pentameric protein
- 5 noncovalently bound identical subunits
- synthesized by hepatocytes.
- M.W.- 118,000 Da.
- nonspecific indicator of inflammation

CRP in CAP

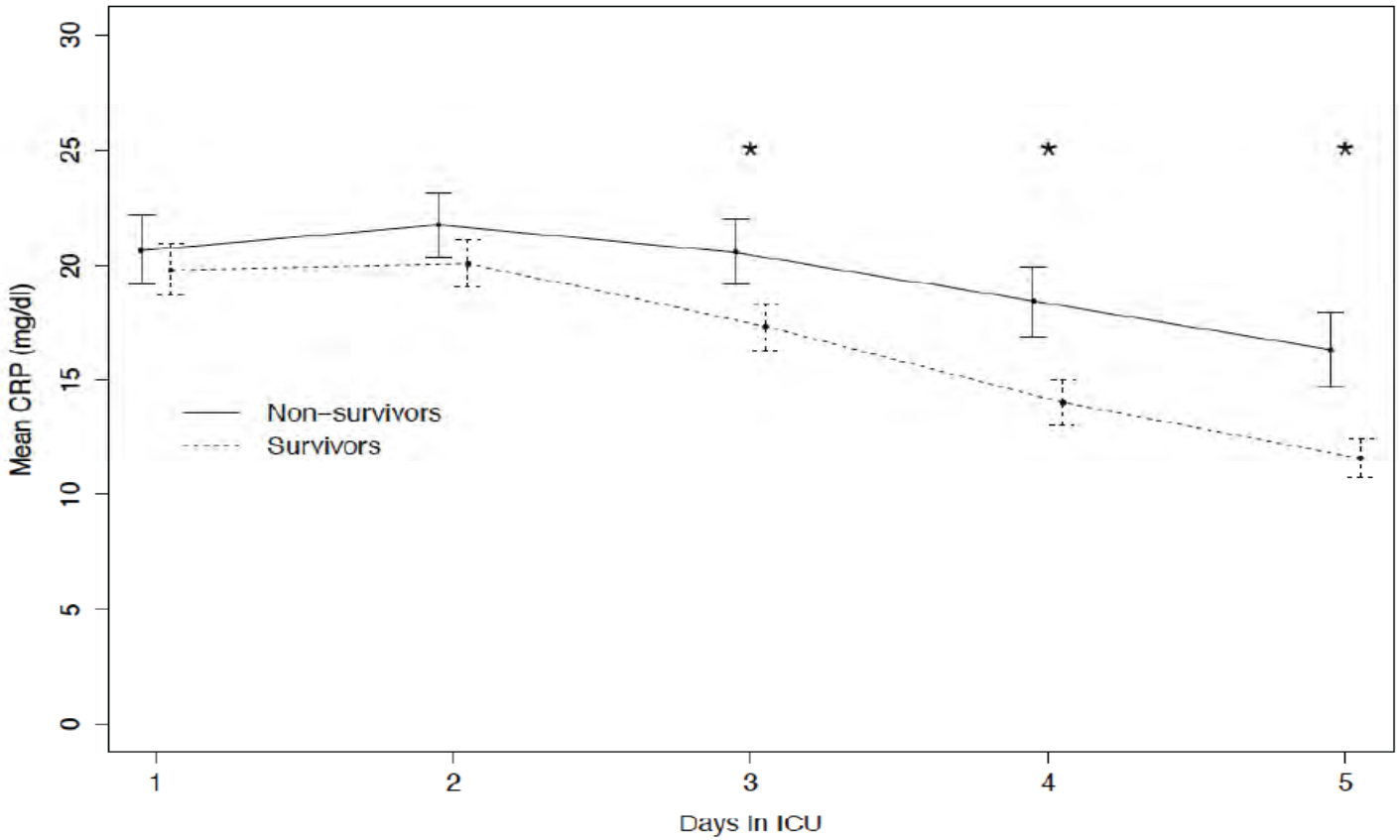
- Threshold of >40 mg/L CRP had a sensitivity of 70% and specificity of 90% to identify pneumonia.
- confirmed the low sensitivity and specificity of CRP in the D/D of LRTIs .
- only very high CRP levels (>100 mg/L) can be used as indicator for the presence of CAP.

Flanders et al. Resuscitation 2002;53:167-70.

CRP

- prospective, multicenter study involving 289 severe hospitalized CAP
- CRP was measured at admission, day 3 and day 7.
- Delayed normalization of CRP was suggestive of inappropriate treatment but was not significantly related to mortality.
- Baseline CRP levels were influenced by steroids and pneumonia etiology.

CRP in VAP



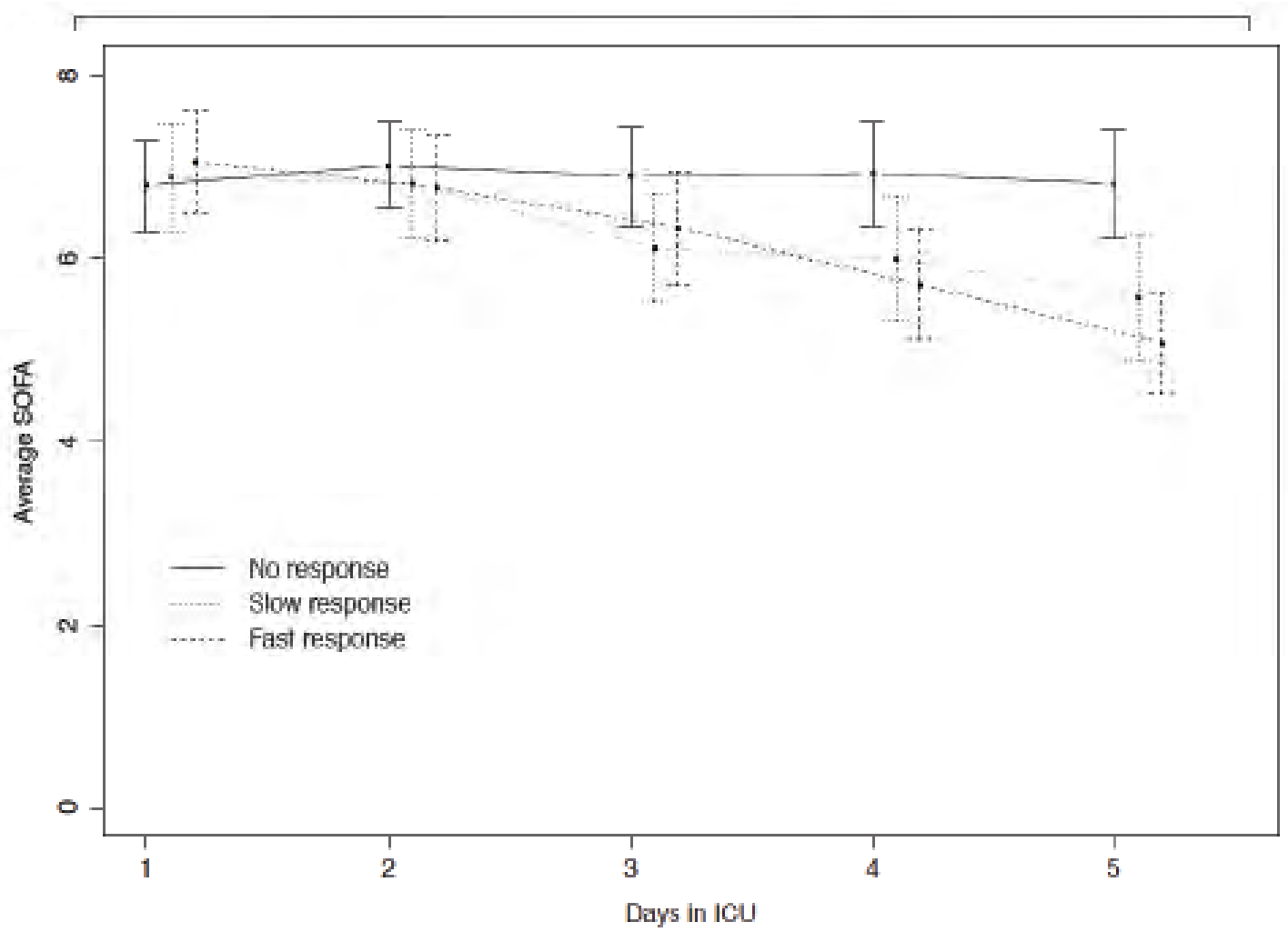
In survivors, CRP showed a marked decrease and was significantly lower in comparison to non-survivors from D3 onwards.

Povoa et al. Clin Microbiol Infect 2005;11:101–8.

CRP in VAP

- For a threshold of 9.6 mg/dL, CRP had 87% sensitivity and 88% specificity for VAP diagnosis.
- Daily CRP measurements in ICU patients enabled early diagnosis of sepsis.
- prognostic marker of VAP resolution.

Povoa et al.Clin Microbiol Infect 2005;11:101–8.



Patients with a no response pattern had more than three times the odds of dying in the ICU when compared to patients with a fast response pattern.

Povoa et al.Clin Microbiol Infect 2005;11:101–8.

CRP

- Only prognosis
- No data are available on the potential contribution of CRP for starting, pursuing, or terminating antibiotics in septic patients.
- no established role in patients with CAP or VAP.

Copeptin

- AVP is produced by hypothalamic neurons, is stored and released from the posterior pituitary gland following different stimuli such as hypotension, hypoxia, hyperosmolarity, acidosis and infections.
- vasoconstrictor and antidiuretic properties and has potency to restore vascular tone in vasodilatory hypotension .
- derived from a larger precursor (preproAVP) along with two other peptides of unknown function, neurophysin II and copeptin, the carboxy-terminal part of the precursor .
- AVP levels -short half-life and instability. (half-life 5 to 15 minutes and largely attached to platelets)

Critical Care 2008, ***12:R11***

- Copeptin - more stable peptide.
- Copeptin concentrations mirror that of AVP and are also elevated in sepsis and septic shock .
- levels have been used in diagnosis of

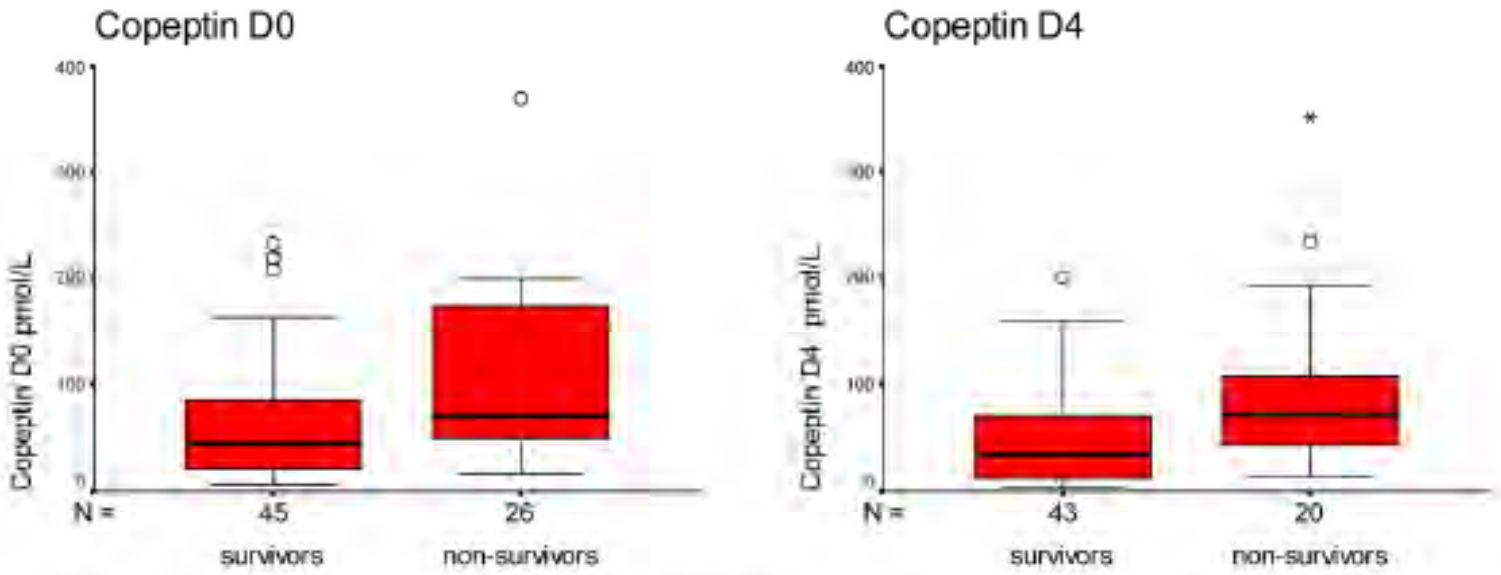
Diabetes insipidus

Cardiovascular disease

Sepsis

Pneumonia

AECOPD

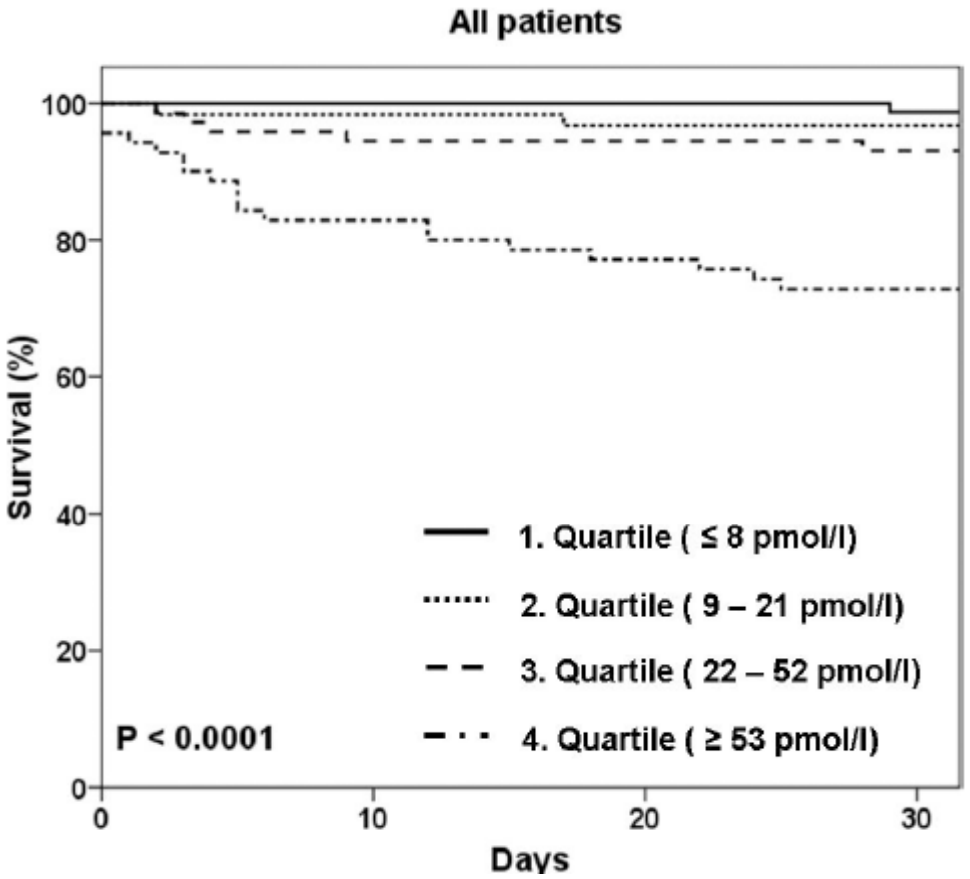


Copeptin levels in survivors and nonsurvivors. Box plots showing copeptin levels in survivors and nonsurvivors on day 0 (D0) and on day 4 (D4). Boxes represent the 25th to 75th percentiles. Circles and asterisks represent outliers.

Comparison of copeptin levels between survivors and nonsurvivors (Mann–Whitney test)

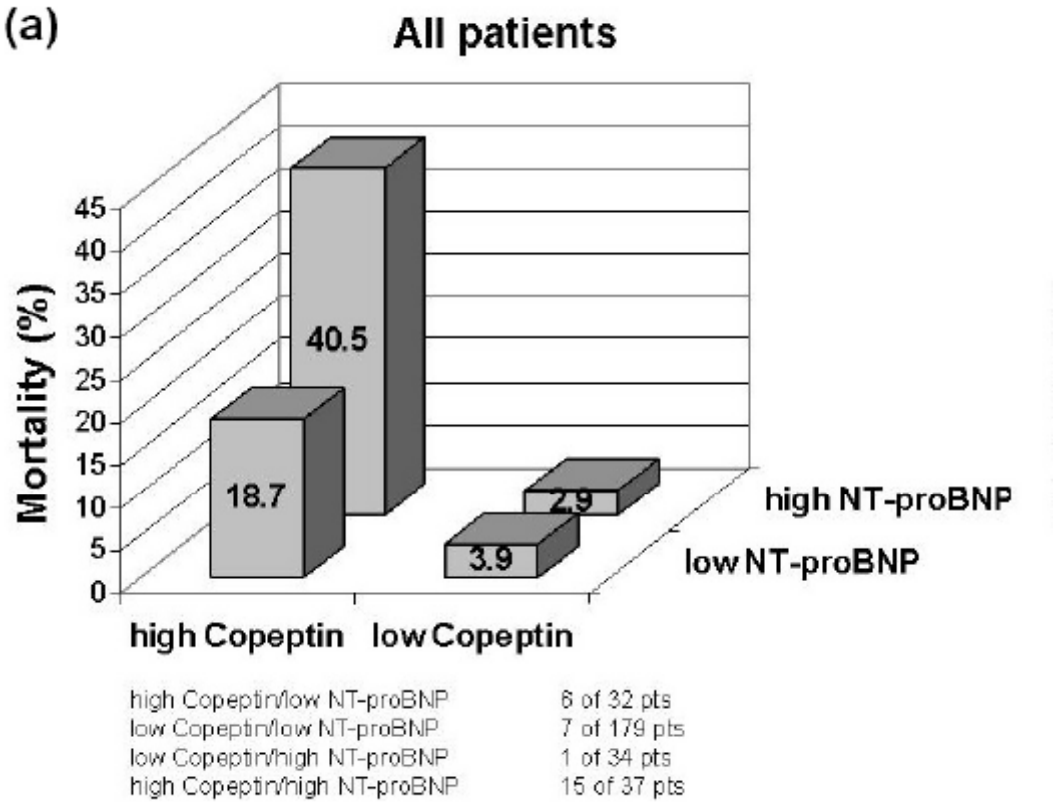
Variable		Median (pmol/l)	Interquartile range	*P* value
Copeptin on day 0	Survivor	44.7	7.8 to 81.6	0.006
	Nonsurvivor	74.2	12.3 to 136.1	
Copeptin on day 4	Survivor	34.5	2.6 to 66.4	0.006
	Nonsurvivor	72.3	38.6 to 106.0	

Mortality with copeptin level



Potocki et al. Critical Care 2010,14:R213

30 day mortality in pt with dyspnea



Potocki et al. Critical Care 2010,14:R213

- Copeptin levels were **significantly higher in patients with HF** than in patients with other diagnoses responsible for acute dyspnea.
- Copeptin was **significantly higher in non-survivors** compared to survivors at 30 days, regardless of whether ADHF was present or not.
- Copeptin is a new promising prognostic marker for short-term mortality **independent of natriuretic peptide levels in patients with acute dyspnea and even more in patients with HF**.

Potocki et al. Critical Care 2010,14:R213

Limitations

- Technical challenges in measurement in the ICU setting.
- easier to determine in the clinical laboratory
- Copeptin was superior to CRP, an established inflammatory and also prognostic marker (AUC 0.83 (95% CI 0.76 to 0.90) vs. 0.71 (0.63 to 0.80), P = 0.04.
- Non specific marker of inflammation
- Does not differentiate between CAP & CCF.

Potocki et al. Critical Care 2010,14:R213

MR-proADM

- Adrenomedullin (ADM) is a peptide of 52 amino acids
- From pheochromocytoma cells, heart, adrenal medulla, lungs, and kidneys .
- potent vasodilator, causes hypotension and has inotropic and natriuretic effects.
- The midregional fragment of the pro-ADM(AA24 to 71) is more stable than ADM itself, is secreted in equimolar amounts to ADM, and is easier to measure .
- sepsis, pneumonia, COPD ,MI, CCF→ MR-proADM levels were elevated and predicted mortality

Biochem Biophys Res Commun 1993, ***192:553-60.***

MR-proADM

- level correlated with severity of illness and death.
- High levels offer additional risk stratification in high-risk CAP patients.
- levels do not alter PSI-based risk assessment in most CAP patients.

sTREM -1

- Expressed on the surfaces of neutrophils, mature monocytes, and macrophages
- immunoglobulin superfamily.
- TREM-1 engagement acts in synergy with the Toll-like receptor signaling pathway by amplifying the inflammatory response mediated by several microbial components.
- Released in infections
- not upregulated in patients with noninfectious inflammatory disorders, for example, psoriasis, ulcerative colitis, or vasculitis.

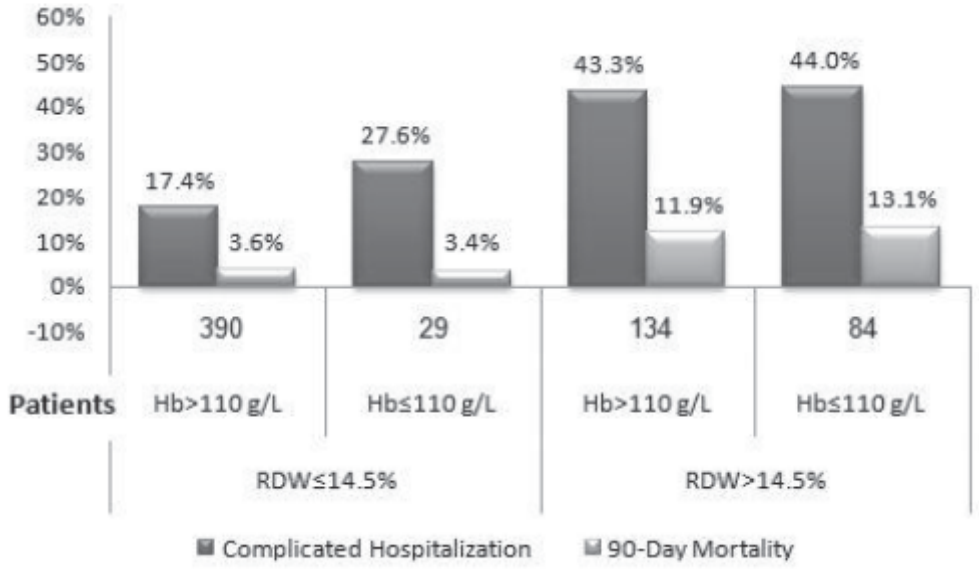
soluble Triggering Receptor Expressed by Myeloid cell (sTREM)

- reports on 148 patients suffering from suspected CAP or VAP and receiving mechanical ventilation TREM was assessed in the BAL fluid and its levels were a better predictor for bacterial infection than CPIS, TNF-alfa and IL-1 levels.
- **potential value of sTREM-1 measurement in BAL fluid for VAP diagnosis remains unclear.**
- apparently a reliable marker of pneumonia,

  especially VAP.
- **Data lacking**
- **Not routinely available**

Horonenko G et al.Chest 2007;132:58–63.
Clin Chest Med 32 (2011) 431–438

RDW in CAP



elevated RDW in young patients hospitalized with CAP is a significant risk factor for complicated hospitalization and in hospital mortality

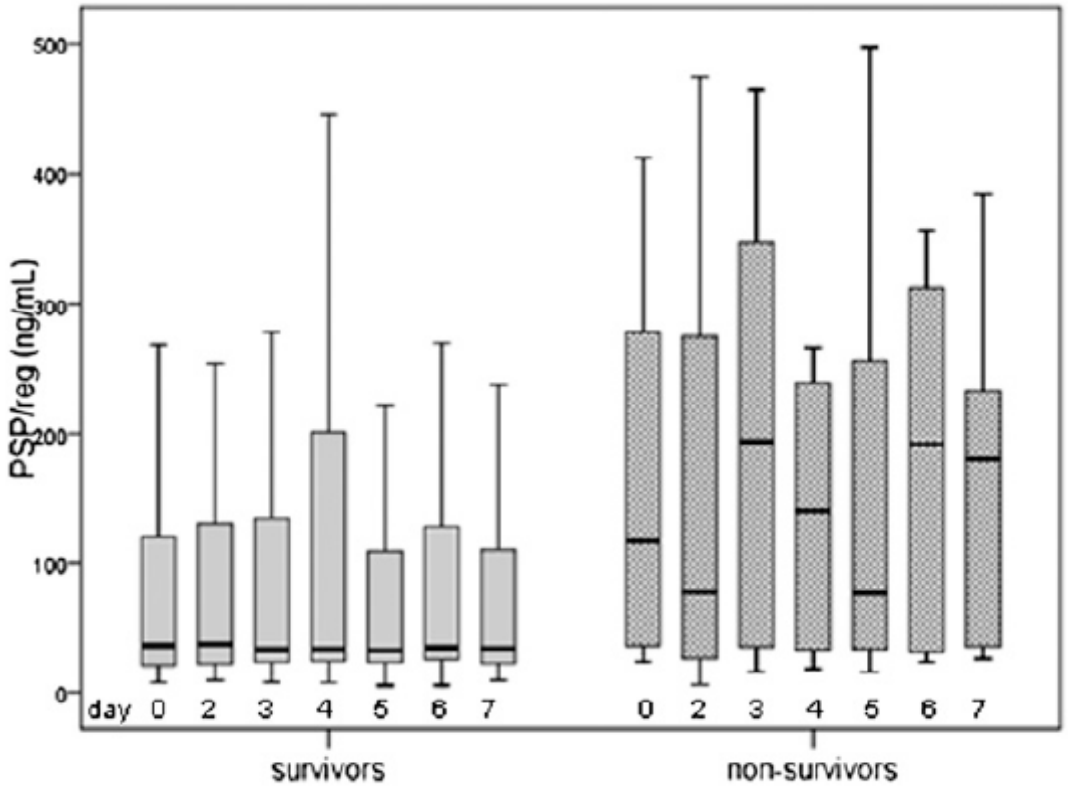
Braun et al. Critical Care 2011, 15:R194

Pancreatic stone protein (PSP)

- 16-kDa polypeptide
- family of lectin-binding proteins.
- Function suggested was the capacity to inhibit pancreatic stone formation, a role subsequently challenged.
- Independently, PSP appeared to stimulate islet b -cell growth and regeneration
- Increased in infections.

Chest 2011;140;925-932;

PSP in VAP



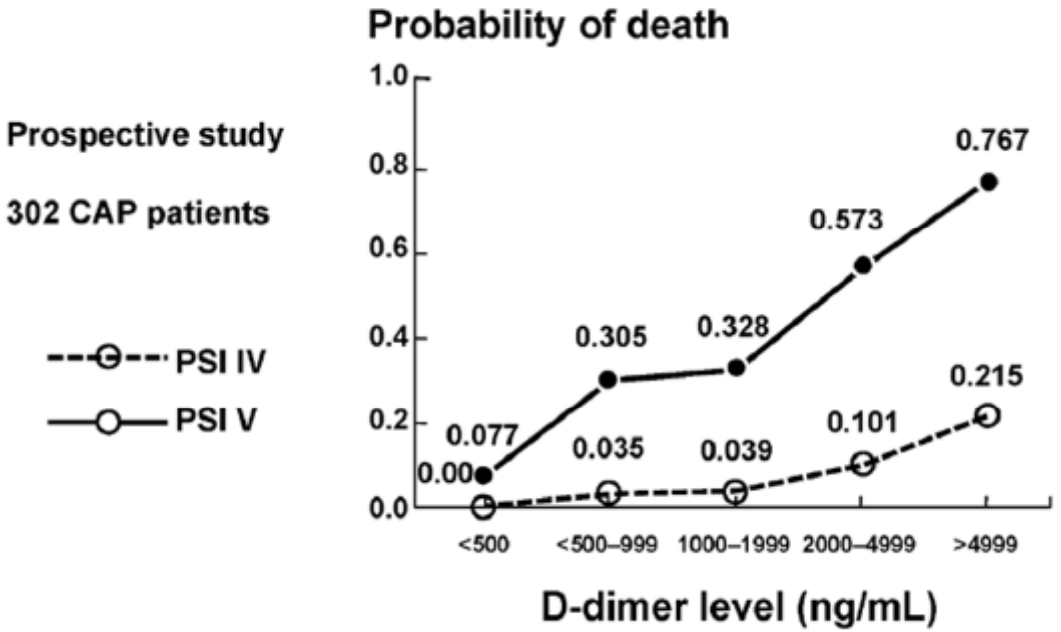
PSP has discriminative properties and may allow for identification of survivors and nonsurvivors

Chest 2011;140;925-932;

Platelets

- possible marker of CAP severity.
- thrombocytopenia and thrombocytosis → a/w mortality in patients with CAP.
- better predictors of clinical outcomes in patients with CAP when compared to abnormalities in leukocyte count.

D dimer



Chest 2004, ***126:1087-1092.***

Other anticoagulant

- prothrombin fragment
- thrombin-antithrombin complexes
- Fibrinogen

- Under evaluation ?

Single nucleotide polymorphisms

- heat shock protein 70-2
- lymphotoxin-α +250 loci
- IL-10
- 4G/5G polymorphism→ increase plasminogen activator inhibitor-1 expression doubled the likelihood of CAP in 12 year follow-up period.

Am J Resp Crit Care Med 2007, ***176:1129-***37.

Other biomarkers

- aPTT in sepsis & septic shock not CAP
- High mobility group box-1 nonhistone nucleoprotein- unreliable
- Endotoxin measurement in BAL
- BPI
- Soluble E- selectin
- plasma SP-D in SARS patients.

Scandinavian Journal of Immunology 69, 508–515.
Crit Care Med 2006, 34:1654-1660.
Br J Anaesth 2002;89:231–6.

Take home message

- Procalcitonin can not guide starting antibiotics only antibiotic stopping.
- should not be used as the sole basis for clinical decisions.
- Biomarkers are meant to complement, rather than to supersede, clinician’s judgment and/or validated severity scores.