

# Biomarkers in Sepsis

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- Circulating cells

#### 1. Cell counts

- Total leucocyte count
- Neutrophil count
- Lymphocyte count
- Platelet count

#### 2. Leucocyte surface markers

- Cell differentiation antigen CD11b
- Intercellular adhesion molecule (ICAM-1)
- CD63
- CD64
- CD66b

#### 3. Other properties

- Polymorphonuclear leucocyte migration
- Leucocyte gene expression profile
- Mean platelet volume

#### • Peptides

##### 1. Monocyte/macrophage products

- Tumour necrosis factor  $\alpha$  (TNF- $\alpha$ )
- Interleukin 1 $\alpha$
- Interleukin 1 $\beta$
- **Interleukin 6**
- Interleukin 8
- Interleukin 10
- Interleukin 18
- Macrophage migration inhibitory factor (MIF)
- **Soluble triggering receptor expressed on myeloid cells (sTREM-1)**
- High mobility group box protein 1 (HMGB-1)

##### 1. Leucocyte products

- Soluble L-selectin (=CD62L)
- Soluble P-selectin (=CD62P)

##### 2. Endothelial cell products

- Soluble vascular cell adhesion molecule (sVCAM-1=CD106)
- Soluble E-selectin (=CD62E)

##### 3. Other cell products

- Soluble intercellular adhesion molecule (sICAM-1)
- Soluble haemoglobin scavenger receptor (sCD163)
- Growth arrest specific protein 6 (Gas6)
- Soluble urokinase-type plasminogen activator receptor
- Soluble tumour necrosis factor receptor 1 (sTNFR-p55)
- Soluble tumour necrosis factor receptor 2 (sTNFR-p75)

#### • Acute phase reactants

##### 1. C reactive protein

##### 2. Ferritin

##### 3. Lactoferrin

##### 4. Neopterin

##### 5. **Procalcitonin**

##### 6. Serum amyloid A

- Other- Activated partial thromboplastin time (aPTT) waveform, Fibronectin

- Microbial products- Endotoxin

- Fungal Markers

##### 1. **$\alpha$ -1,3- $\beta$ -D Glucan**

##### 2. **Galactomannan**

# Candidate biomarkers for the diagnosis of sepsis

# Topic outline

- Biomarker- Definition
- Need of biomarkers
- Properties of Ideal Biomarker
- Biomarkers
  - Procalcitonin
  - Galactomannan
  - $\alpha$ -1,3  $\beta$ -D Glucan

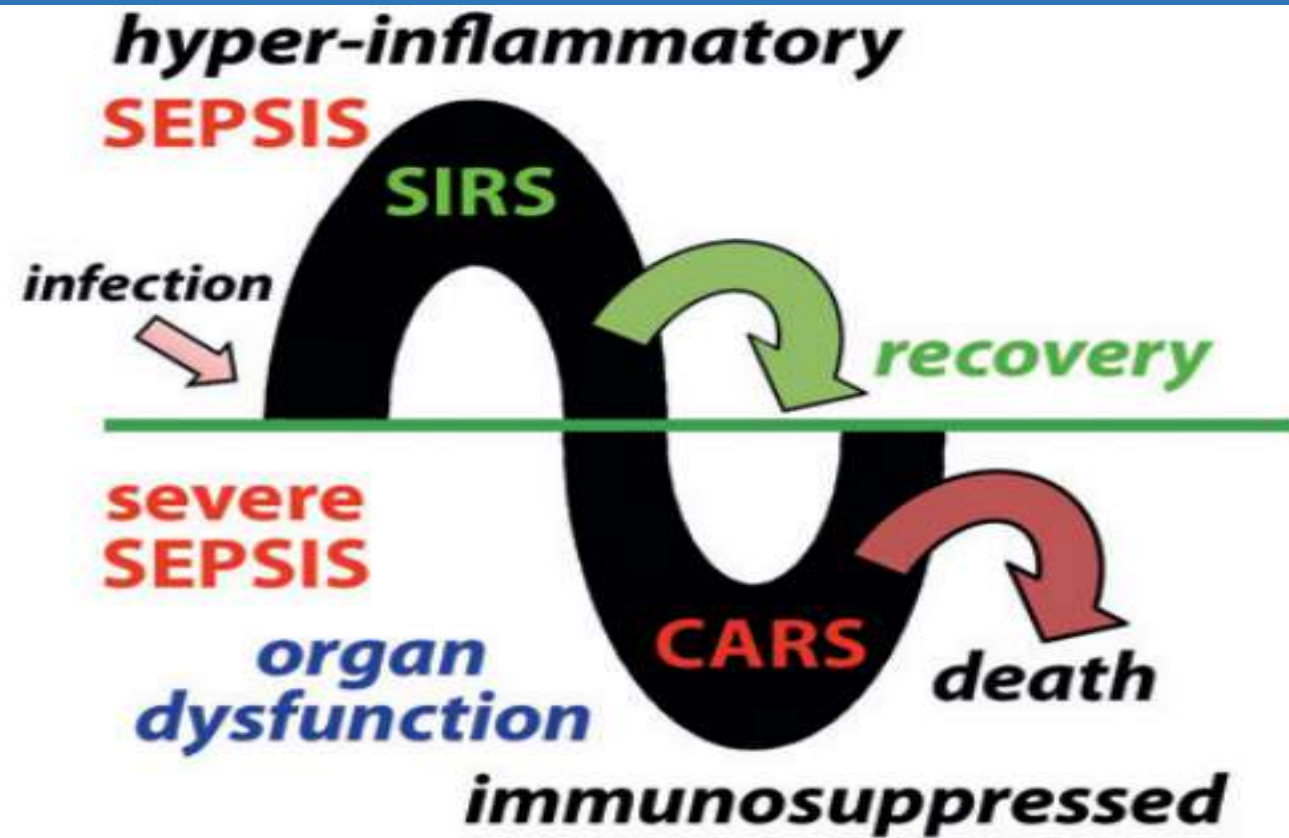


Figure 1. Sepsis may be divided into two phases. Following infection, a hyper-inflammatory phase is characterized by SIRS. This may resolve or the patient may progress to what is called severe sepsis. During this phase, there is evidence of CARS with immunosuppression and multiple organ dysfunction. This may also resolve, especially with appropriate support, but it often leads to death.

# What is a biomarker?

“almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical or biological. The response may be functional and physiological, biochemical at the cellular level, or a molecular interaction”

- WHO 1993

“ A xenobiotically induced variation in cellular or biochemical components or process, structure or function that is measurable in a biological system.”

- National Academy of Science

# What is a biomarker?

“A characteristic that is objectively measured and evaluated as an indicator of normal biological process, pathologic process or pharmacological response to a therapeutic intervention”

- Biomarker Definition Working Group (2001)

# What is the need of biomarkers in sepsis?

- Early diagnosis
- Differentiating diseases e.g. Sepsis vs. no sepsis
- Monitoring response to therapy
- Prognostication

# “SMART” biomarker

- **S**ensitive (and Specific)
- **M**easurable
- **A**vailable (Affordable and safely Attainable)
- **R**esponsive (and Reproducible) in a
- **T**imely fashion

## No “SMARTER”

- **E**valuate (validate) and
- **R**e-evaluate (revalidate) -research needs to be in a continuous cycle of appraisal and re-appraisal



# Inherent Limitations of Biomarkers

- Biomarkers are members of complex cascades and networks
- Assessing levels of an individual cytokine dissociated from the levels of its antagonists or natural inhibitors may lead to the erroneous impression that an altered cytokine level reflects derangements in a biological pathway
- Immune-reactive assays may provide qualitatively different information than bioactivity assays

# IL-6

- Not specific for sepsis
- Major role as a prognostic biomarker, not diagnostic
- Elevated levels associated with increase in mortality
- Mouse model of acute septic peritonitis also corroborative of similar findings
- Meets one of the desired attributes of an ideal biomarker of sepsis

Patel RT *et al.* Br J Surg 1994;81:1306–8.

Petilla V *et al.* Intensive Care Med 2002;28:1220–5.

Panacek EA *et al.* Crit Care Med 2004;32:2173–82

# Procalcitonin

- In 1993 Assicot and colleagues first reported elevated PCT levels in patients with invasive bacterial infection
  - 116 AA protein produced by thyroid C cells and then cleaved in to 3 distinct molecules- Calcitonin, N- terminal fragment & katacalcin
  - Devoid of known hormonal activity
  - Released from all cells in response to bacterial toxins and proinflammatory mediators (IL-1 $\beta$ , IL-6 & TNF- $\alpha$ )
  - Decreased in viral infections under influence of IFN- $\gamma$
  - Stable both in vivo and in vitro with in vivo t<sub>1/2</sub> ~24 hours
  - Increases after 2-3 hours after induction, plateau after 6-12 hours & remain high for up to 48 hours
- Assicot M *et al.* Lancet 1993;341:515–8.
  - Clin Chest Med :29;2008.591-603.
  - Faix JD. Crit Rev Clin Lab Sci, 2013; 50(1): 23–36

# Interpretation of PCT result

- The optimal cut-off depends on
  - Clinical setting (eg, emergency room, ICU, post-operative or trauma patients)
  - Site and extent of the infection (eg, RTI, meningitis, abdominal infection)
  - Co-morbidities (eg, immunosuppression)
  - Clinical implications drawn (eg diagnosis, prognosis, antibiotic stewardship)
- Should be used in the context of clinical situation
- Non infective causes of elevation-
  - First days after a major trauma, major surgical intervention, severe burns, treatment with OKT3 antibodies
  - Patients with prolonged or severe cardiogenic shock, prolonged severe organ perfusion anomalies, small cell lung cancer, medullary C-cell carcinoma of the thyroid
- False low PCT-
  - Early course of infections
  - Localised infections

#### PCT <0.05 µg/L

Healthy individuals

Determination of normal values with a high sensitive assay revealed normal values to be below 0.05 µg/L.

#### PCT <0.5 µg/L

Systemic infection (sepsis) is not likely.

Local bacterial infection is possible.

Low risk for progression to severe systemic infection (severe sepsis).

**Caution:** PCT levels below 0.5 µg/L do not exclude an infection, because localized infections (without systemic signs) may be associated with such low levels. Also if the PCT measurement is done very early after a following bacterial challenge (usually < 6 hours), these values may still be low. In this case, PCT should be re-assessed 6-24 hours later.

#### PCT ≥0.5 – <2 µg/L

Systemic infection (sepsis) is possible, but various conditions are known to induce PCT as well.<sup>19</sup>

Moderate risk for progression to severe systemic infection (severe sepsis). The patient should be closely monitored both clinically and by re-assessing PCT within 6-24 hours.

#### PCT ≥2 – <10 µg/L

Systemic infection (sepsis) is likely, unless other causes are known.<sup>11</sup>

High risk for progression to severe systemic infection (severe sepsis).

#### PCT ≥10 µg/L

Important systemic inflammatory response, almost exclusively due to severe bacterial sepsis or septic shock.

High likelihood of severe sepsis or septic shock.

# PCT as a Diagnostic Marker of Sepsis

# Procalcitonin for diagnosis of Sepsis

Sr. No.	Author, Year	Target Population	No of Studies	Observations	Comments
1	Simon et al. 2004	Hospitalized Pt Adults, Children & Neonates	12 Studies 1386 Pt.	Sn 88 Vs 75 Sp 81 vs 67	PCT Better than CRP
2	Uzzan <i>et al.</i> 2006	Critically ill adults, Post Surg/Trauma	33 Studies 3943 Pt.	Diagnostic Odds 15.47 vs 5.43 Sp 78 vs 71	PCT better than CRP
5	Tang <i>et al.</i> 2007	Critically ill, Adults	18 Studies 2097 Pt.	Sensitivity 71 % (67-76) Specificity 71% (67-76) AUC 0.78 (0.73-0.83)	Diag. performance Better in small studies Excluded Septic shock
3	Mann <i>et al.</i> 2011	Critically ill burn patients	6 Studies 194 Pt.	Most studies favor PCT Except a pediatric Study	PCT assay can be a helpful adjunct to clinical diagnosis of sepsis and holds promise
4	Yu <i>et al.</i> 2010	Neonates	22 Studies	Sensitivity 71 vs 55 Specificity 77 vs 85 Diagnostic OR 11.6 vs 8.6	More accurate than the CRP for diagnosis of LONS
6	Wacker <i>et al.</i> 2013	critically ill patients	30 Studies 3244 Pt.	Sensitivity 77% (72-81) Specificity 79% (74-84) AUC 0.85 (0.81-0.88)	7 studies common Including septic shock 4- Paediatric



# Procalcitonin Test in the Diagnosis of Bacteremia: A Meta-analysis

**Results:** The search yielded 348 publications and 1 unpublished study. Seventeen studies met the inclusion criteria and provided a sample of 2,008 subjects. There was a substantial degree of inconsistency ( $I^2=64\%$ ). The unweighted summary receiver-operating characteristic curve provided the best overall estimate of test performance, with an area under the curve of 0.84 (95% confidence interval [CI] 0.75 to 0.90). Sensitivity analysis based on study quality did not significantly change the results. Subgroup analysis including only studies that used a test threshold of 0.5 or 0.4 ng/mL yielded pooled estimates for sensitivity and specificity of 76% (95% CI 0.66 to 0.84) and 70% (95% CI 0.60 to 0.79), respectively.

**Conclusion:** We found the diagnostic performance of the procalcitonin test for identifying bacteremia in ED patients to be moderate. Future research designed to determine the utility of the procalcitonin test as a diagnostic tool used in isolation for detecting bacteremia in ambulatory patients is needed before widespread clinical use. [Ann Emerg Med. 2007;50:34-41.]



*What this study adds to our knowledge*

From 17 included studies involving 2,008 patients, procalcitonin demonstrates moderate sensitivity and specificity.

*How this might change clinical practice*

These results provide little support for the clinical use of procalcitonin to detect bacteremia. At present, there is no justification for using the test outside the research environment.

# PCT as a Predictor of Bacteremia



# Procalcitonin Levels Predict Bacteremia in Patients With Community-Acquired Pneumonia

## A Prospective Cohort Trial

*Fabian Müller, MD; Mirjam Christ-Crain, MD; Thomas Bregenzer, MD; Martin Krause, MD; Werner Zimmerli, MD; Beat Mueller, MD; and Philipp Schuetz, MD; for the ProHOSP Study Group\**

**Methods:** This was a prospective cohort study with a derivation and validation set including 925 patients with CAP who underwent blood culture sampling on hospital admission.

**Results:** A total of 73 (7.9%) patients had true bacteremia (43 of 463 in the derivation cohort, 30 of 462 in the validation cohort). The area under the receiver operating characteristics curve of PCT in the derivation and validation cohorts was similar (derivation cohort, 0.83; 95% CI, 0.78-0.89; validation cohort, 0.79; 95% CI, 0.72-0.88). Overall, PCT was a significantly better predictor for blood culture positivity than WBC count, C-reactive protein, and other clinical parameters. In multivariate regression analysis, only antibiotic pretreatment (adjusted odds ratio, 0.25;

# PCT as predictor of bacterial burden in Pyelonephritis

- AUC for prediction of Bacteremia in Pyelonephritis-
  - Clinical Model -0.71 (95% CI 0.66 to 0.76)
  - Clinical + PCT- 0.79 (95% CI: 0.75 to 0.83)
  - PCT alone - 0.73 (9 5% CI: 0.68 to 0.77)

PCT Guided algorithms to decrease Antibiotic Use



# Procalcitonin as a guide to decrease ABx use

**Table 3. Primary and Secondary Outcomes of the Different RCTs, Grouped by Study Setting**

Source	Diagnoses	Total No.	Mortality, Control vs PCT Groups, No. Dead/Total (%)	Abx Use, Control vs PCT	Relative Reduction, %	Key Findings
<b>Primary Care Settings</b>						
Briel et al, <sup>14</sup> 2008 <sup>a</sup>	Upper and lower RTI	458	1/226 (0.4) vs 0/232 (0)	Prescription: 97% vs 25% Duration (mean): 7.1 vs 6.2 d	Prescription: -74 Duration: -13	Reduction of Abx without additional days of restricted activity
Burkhardt et al, <sup>21</sup> 2010	Upper and lower RTI	550	0/275 (0) vs 0/275 (0)	Prescription: 36.7% vs 21.5% Duration (mean): 7.7 vs 7.8 d	Prescription: -42 Duration: 1	Reduction of Abx without causing health impairment
<b>ED Settings</b>						
Christ-Crain et al, <sup>22</sup> 2004	CAP, AECOPD, bronchitis	243	4/119 (3.4) vs 4/124 (3.2)	Prescription: 83% vs 44% Duration (mean): 12.8 vs 10.9 d	Prescription: -47 Duration: -15	Reduction of Abx prescriptions
Christ-Crain et al, <sup>23</sup> 2006	CAP	302	20/151 (13.2) vs 18/151 (11.9)	Prescription: 99% vs 85% Duration (mean): 12.9 vs 5.8 d	Prescription: -14 Duration: -55	Reduction of initiation and duration of Abx without adverse outcomes
Stolz et al, <sup>24</sup> 2007	AECOPD	208	9/106 (8.5) vs 5/102 (4.9)	Prescription: 72% vs 40%	Prescription: -44	Reduced Abx exposure without adverse outcome
Long et al, <sup>25</sup> 2009	CAP	127	0/64 (0) vs 0/63 (0)	Prescription: 97% vs 86% Duration (median): 10 vs 6 d	Prescription: -11 Duration: -40	Reduction of Abx use and shorter Abx duration
Kristoffersen et al, <sup>26</sup> 2009	Lower RTI	210	1/107 (0.9) vs 2/103 (1.9)	Prescription: 79% vs 85% Duration (mean): 6.8 vs 5.1 d	Prescription: 8 Duration: -25	Reduction of duration of Abx use
Schuetz et al, <sup>15</sup> 2009	CAP, AECOPD, bronchitis	1359	33/688 (4.8) vs 34/671 (5.1)	Prescription: 87.7% vs 75.4% Duration (median): 8.7 vs 5.7 d	Prescription: -14 Duration: -34	Noninferiority for clinical outcomes and decreased Abx use

# Procalcitonin as a guide to decrease ABx use

Inpatient and ICU Settings						
Svoboda et al, <sup>27</sup> 2007	<u>Postop septic shock</u>	72	13/34 (38.2) vs 10/38 (26.3)	NA	NA	<u>Trend to decrease in SOFA and ventilator/ICU days</u>
Nobre et al, <sup>28</sup> 2008	Sepsis	79	12/40 (30.0) vs 8/39 (20.5)	Duration (median): 9.5 vs 6.0 d	Duration: -37	<u>Reduction in Abx duration and ICU LOS without adverse events</u>
Stolz et al, <sup>29</sup> 2009	VAP	101	12/50 (24.0) vs 8/51 (15.7)	Abx-free days alive: 9.5 vs 13 Duration (median): 15 vs 10 d	Abx-free days alive: 27 Duration: -33	<u>Decreased Abx use without increasing mortality rate</u>
Hochreiter et al, <sup>30</sup> 2009	<u>Postop patients with infection</u>	110	14/53 (26.4) vs 15/57 (26.3)	Duration (mean): 7.9 vs 5.9 d	Duration: -25	<u>Reduction in Abx duration and ICU LOS without adverse events</u>
Schroeder et al, <sup>31</sup> 2009	<u>Postop severe sepsis</u>	27	3/13 (23.1) vs 3/14 (21.4)	Duration (mean): 8.3 vs 6.6 d	Duration: -20	<u>Shorter Abx duration</u>
Bouadma et al, <sup>32</sup> 2010 <sup>b</sup>	Sepsis	621	64/314 (20.4) vs 65/307 (21.2)	Abx-free days alive: 11.6 vs 14.3 Duration (mean): 9.9 vs 6.6 d	Abx-free days alive: 19 Duration: -33	<u>Reduction in Abx use without increase in mortality rate</u>



# Use of Serum Procalcitonin to Detect Bacterial Infection in Patients With Autoimmune Diseases

## A Systematic Review and Meta-Analysis

*Objective.* To systematically review evidence of the accuracy of the procalcitonin test for diagnosis of bacterial infection in patients with autoimmune disease.

*Methods.* The major databases Medline, EMBase, and the Cochrane Library were searched for studies published between January 1966 and October 2011 that evaluated procalcitonin, alone or in comparison with other laboratory markers such as C-reactive protein (CRP), as a diagnostic marker for bacterial infection in patients with autoimmune disease and provided sufficient data to permit construction of  $2 \times 2$  tables.

*Results.* Nine studies were included in the final meta-analysis. The area under the summary receiver operating characteristic curve values were 0.91 (95% confidence interval [95% CI] 0.88–0.93) for procalcitonin and 0.81 (95% CI 0.78–0.84) for CRP. In general, testing for procalcitonin was highly specific for identifying infectious complications, although it was not as

sensitive as testing for CRP. Pooled sensitivity was 0.75 (95% CI 0.63–0.84) for procalcitonin tests and 0.77 (95% CI 0.67–0.85) for CRP tests. Pooled specificity was 0.90 (95% CI 0.85–0.93) for procalcitonin tests and 0.56 (95% CI 0.25–0.83) for CRP tests. The positive likelihood ratio for procalcitonin (7.28 [95% CI 5.10–10.38]) was sufficiently high to qualify procalcitonin testing as a rule-in diagnostic tool, while the negative likelihood ratio (0.28 [95% CI 0.18–0.40]) was not sufficiently low to qualify procalcitonin testing as a reliable rule-out diagnostic tool.

*Conclusion.* Procalcitonin has higher diagnostic value than CRP for the detection of bacterial sepsis in patients with autoimmune disease, and the test for procalcitonin is more specific than sensitive. A procalcitonin test is not recommended to be used in isolation as a rule-out tool.



# Serum procalcitonin in patients with CKD: a systematic review and meta-analysis

- Seven studies, 803 patients and 255 bacterial infection episodes
- Sensitivity 73% (95% CI 54–86%) for PCT & 78% (95% CI 52–92%) for CRP
- Specificity 88 % ( 95% CI 79–93%) for PCT & 84% (95% CI, 52–96%) for CRP
- Both PCT and CRP have poor sensitivity but acceptable specificity in diagnosing bacterial infection In CKD
- Poor negative likelihood ratio- role as a rule-out test is question able

# The use of pleural fluid procalcitonin and C-reactive protein in the diagnosis of parapneumonic pleural effusions: a systemic review and meta-analysis<sup>☆</sup>

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**Results:** We found 6 qualifying studies including 780 patients with suspected parapneumonic effusion and 306 confirmed cases of parapneumonic effusion. Six studies examined the diagnostic performance of pleural fluid PCT, 3 also tested for serum PCT, and another 3 tested for serum CRP. The bivariate pooled sensitivity and specificity were as follows 0.67 (95% confidence interval [CI], 0.54-0.78) and 0.70 (95% CI, 0.63-0.76), respectively, for pleural fluid PCT; 0.65 (95% CI, 0.55-0.74) and 0.68 (95% CI, 0.62-0.74), respectively, for serum PCT; and 0.54 (95% CI, 0.47-0.61) and 0.77 (95% CI, 0.72-0.81), respectively, for serum CRP. There was evidence of significant heterogeneity ( $I^2=55.0\%$ ) for pleural fluid or serum PCT but not for CRP ( $I^2=0.0\%$ ).

**Conclusion:** The existing literature suggests that both pleural fluid and serum PCT tests have low sensitivity and specificity for differentiating parapneumonic effusion from other etiologies of pleural effusion. Compared with PCT, serum CRP has higher specificity and a higher positive likelihood ratio, and thus, it has a higher rule-in value than PCT.

# The role of procalcitonin in the identification of invasive fungal infection—a systemic review and meta-analysis☆☆☆

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- Low value used to differentiate from Bacterial infection
- High Value >0.5ng/L used to differentiate from Non infected
- 8 Trials, 4 vs Bacterial & 4 vs Non infected- 155 IFI episodes
- Sensitivity 82% (48-95) & specificity 80% (60-91) Vs Non infection
- Sensitivity and specificity 88% (71–96) & 81 (68–90) vs Bacterial infection

PCT to Guide initiation as well as Stopping  
Antibiotics in ARI



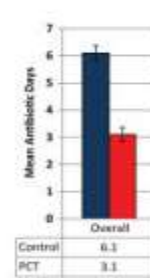
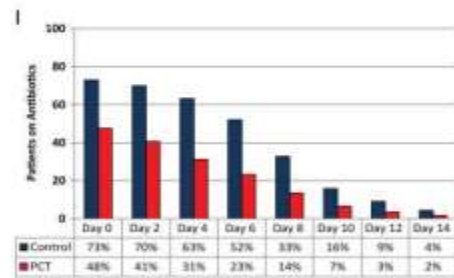
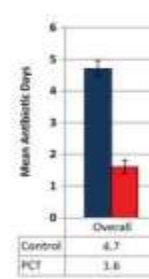
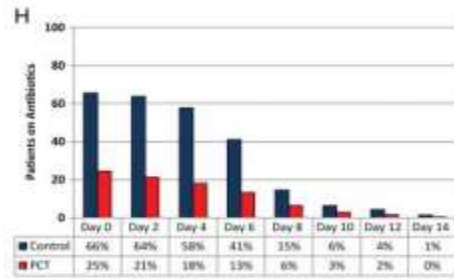
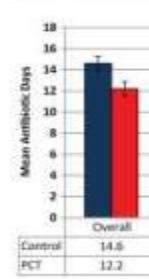
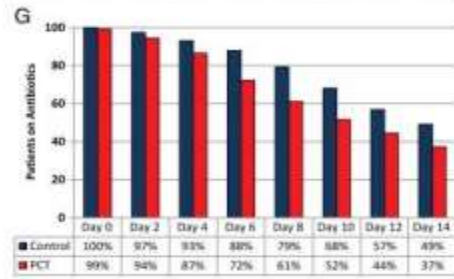
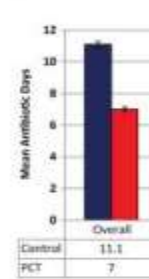
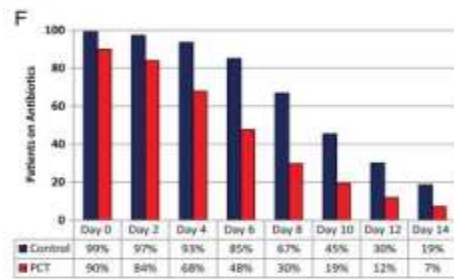
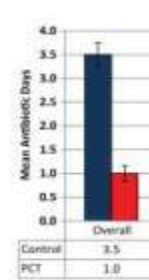
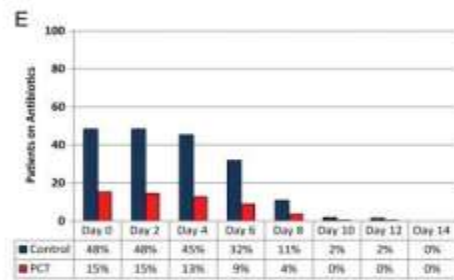
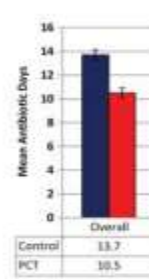
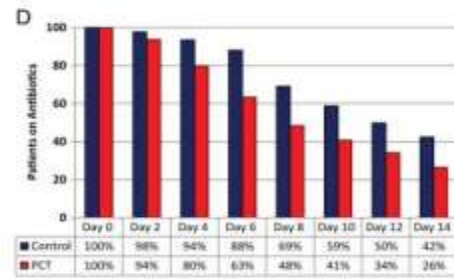
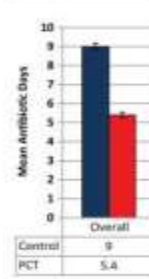
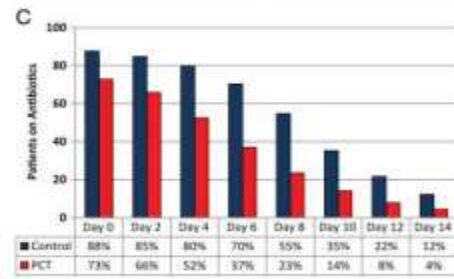
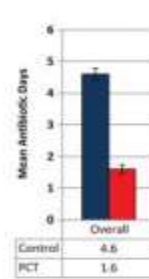
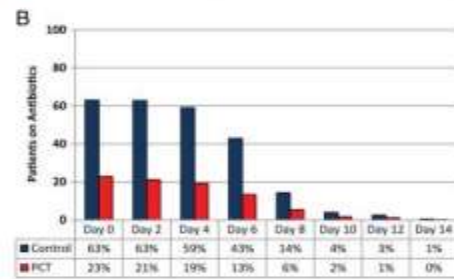
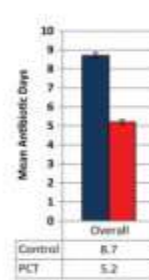
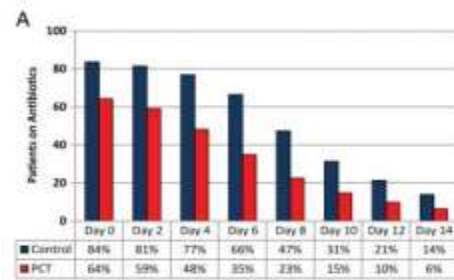
# Procalcitonin to Guide Initiation and Duration of Antibiotic Treatment in Acute Respiratory Infections: An Individual Patient Data Meta-Analysis

**Table 2. Methodological Quality of Included Trials**

First Author (Year)	Allocation Concealment	Blinded Outcome Assessment	Follow-up for Mortality	Adherence to PCT Algorithm in PCT Group
Briel (2008) [9]	Yes (central randomization, by phone)	Yes	454/458 (99%)	85% adherence
Burkhardt (2010) [10]	Yes (central randomization, by fax)	Yes	546/550 (99%)	87% adherence
Christ-Crain (2004) [11]	No (weekly randomization)	No	230/243 (95%)	83% adherence
Christ-Crain (2006) [12]	No (envelopes)	No	300/302 (99%)	87% adherence
Stolz (2007) [13]	No (envelopes)	Yes	208/208 (100%)	Not reported
Kristoffersen (2009) [14]	Yes (central randomization, web-based)	No	210/210 (100% until discharge)	59% adherence
Long (2009) [16]	No (odd and even patient ID numbers)	No	127/127 (100%)	Not reported
Schuetz (2009) [17]	Yes (central randomization, web-based)	Yes	1358/1359 (100%)	91% adherence
Long (2011) [15]	No (odd and even patient ID numbers)	No	156/156 (100%)	Not reported
Nobre (2008) [18]	Yes (sequentially numbered, opaque, sealed envelopes)	No	52/52 (100%)	81% adherence
Schroeder (2009) [21]	No (unconcealed drawing of lots)	No	8/8 (100% until discharge)	Not reported
Hochreiter (2009) [22]	No (unconcealed drawing of lots)	No	43/43 (100% until discharge)	Not reported
Stolz (2010) [19]	No (envelopes)	No	101/101 (100%)	Not reported
Bouadma (2010) [20]	Yes (central randomization, web-based)	Yes	393/394 (100%)	47% adherence

	PCT Group	Control Group	Adjusted OR (95% CI) <sup>a</sup>	P Value
Overall	n = 2085	n = 2126	...	...
Mortality, No. (%)	118 (5.7)	134 (6.3)	0.94 (.71–1.23)	.75
Treatment failure, No. (%) <sup>b</sup>	398 (19.1)	466 (21.9)	0.82 (.71–.97)	.02
Setting specific				
Primary care	n = 507	n = 501		
Mortality, No. (%)	0 (0)	1 (0.2)	...	...
Treatment failure, No. (%) <sup>c</sup>	159 (31.4)	164 (32.7)	0.95 (.73–1.24)	.69
Days with restricted activities, median (IQR)	9 (6–14)	9 (5–14)	0.05 (–.46 to .56) <sup>d</sup>	.85
Emergency department	n = 1291	n = 1314		
Mortality, No. (%)	61 (4.7)	59 (4.5)	1.03 (.7–1.5)	.90
Mortality or ICU admission, No. (%)	126 (9.8)	147 (11.2)	0.83 (.64–1.08)	.16
Treatment failure, No. (%) <sup>e</sup>	182 (14.1)	228 (17.4)	0.76 (.61–.95)	.01
Length of hospital stay, median (IQR) <sup>f</sup>	8 (4–13)	8 (4–13)	–0.42 (–1.2 to .35) <sup>d</sup>	.28
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) <sup>d</sup>	.39
Length of hospital stay, median (IQR)	21 (11–38)	24 (14–38)	–1.36 (–4.5 to 1.77) <sup>d</sup>	.39
Disease specific				
Upper ARI	n = 282	n = 267		
Mortality, No. (%)	0 (0)	1 (0.4)	...	...
Treatment failure, No. (%) <sup>c</sup>	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. (%) <sup>b</sup>	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. (%) <sup>b</sup>	8 (6.3)	12 (10.3)	0.69 (.25–1.94)	.49
Acute bronchitis	n = 249	n = 282		







# The Procalcitonin And Survival Study (PASS)

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

**tion of appropriate antimicrobial therapy improves prognosis. The objective of this trial was to determine whether a strategy of antimicrobial spectrum escalation, guided by daily measurements of the biomarker procalcitonin, could reduce the time to appropriate therapy, thus improving survival.**

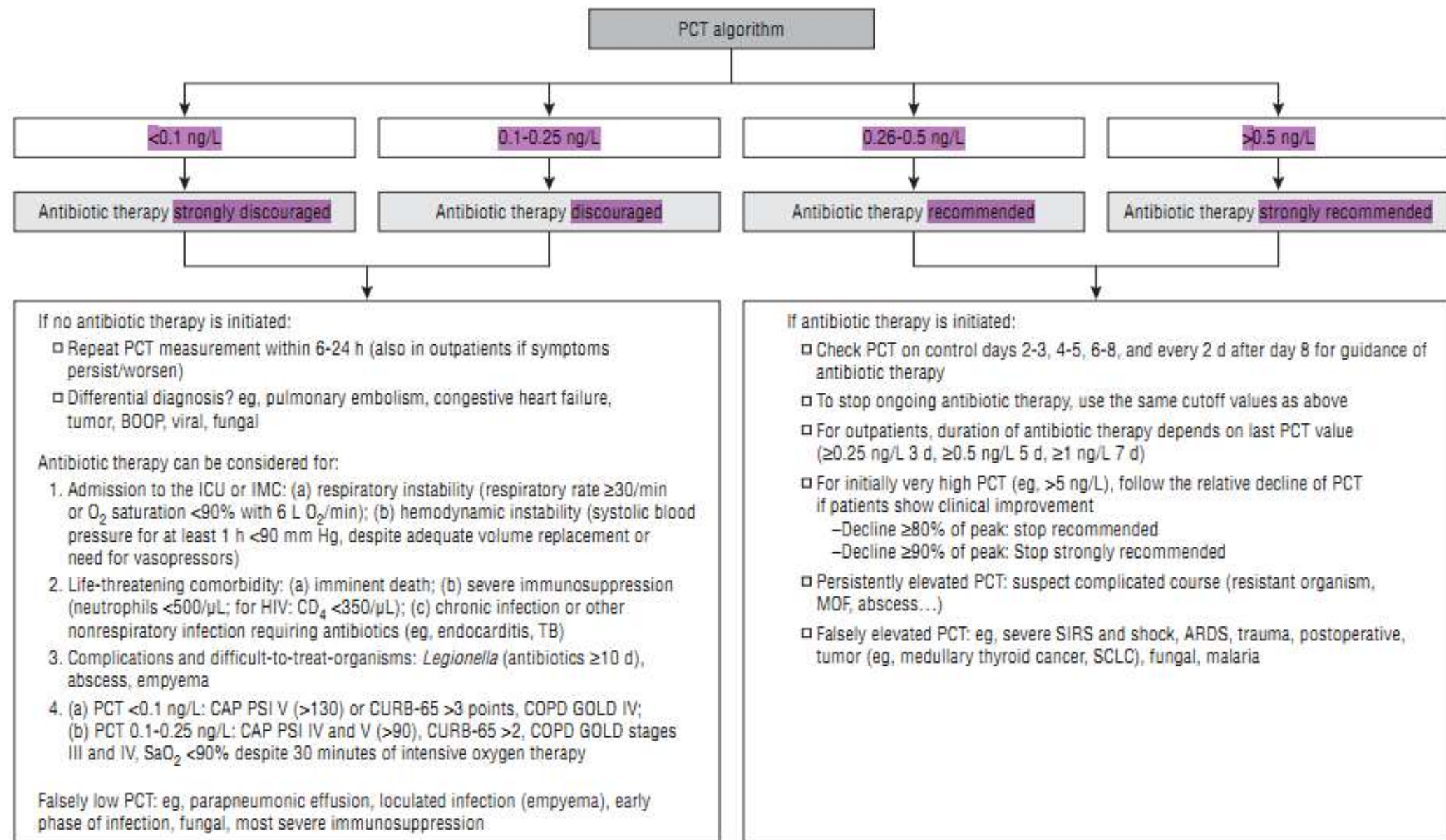
***Design:*** Randomized controlled open-label trial.

***Setting:*** Nine multidisciplinary intensive care units across Denmark.

# The Procalcitonin And Survival Study (PASS)

***Patients:*** A total of 1.200 critically ill patients

***Interventions:*** Patients were randomized either to the “standard-of-care-only arm.” receiving treatment according to the current international guidelines and blinded to procalcitonin levels, or to the “procalcitonin arm,” in which current guidelines were supplemented with a drug-escalation algorithm and intensified diagnostics based on daily procalcitonin measurements. tion, 0.6%; 95% confidence interval [CI] –4.7% to 5.9%). Length of stay in the intensive care unit was increased by one day ( $p = .004$ ) in the procalcitonin arm, the rate of mechanical ventilation per day in the intensive care unit increased 4.9% (95% CI, 3.0–



**Figure 1.** Algorithm for procalcitonin (PCT)-guided antibiotic therapy. This algorithm was available on a password-secured website to all the physicians and study



# Procalcitonin Guidance to Reduce Antibiotic Treatment of Lower Respiratory Tract Infection in Children and Adolescents (ProPAED): A Randomized Controlled Trial

**Background:** Antibiotics are overused in children and adolescents with lower respiratory tract infection (LRTI). Serum-procalcitonin (PCT) can be used to guide treatment when bacterial infection is suspected. Its role in pediatric LRTI is unclear.

**Methods:** Between 01/2009 and 02/2010 we randomized previously healthy patients 1 month to 18 years old presenting with LRTI to the emergency departments of two pediatric hospitals in Switzerland to receive antibiotics either according to a PCT guidance algorithm established for adult LRTI or standard care clinical guidelines. In intention-to-treat analyses, antibiotic prescribing rate, duration of antibiotic treatment, and number of days with impairment of daily activities within 14 days of randomization were compared between the two groups.

**Results:** In total 337 children, mean age 3.8 years (range 0.1–18), were included. Antibiotic prescribing rates were not significantly different in PCT guided patients compared to controls (OR 1.26; 95% CI 0.81, 1.95). Mean duration of antibiotic exposure was reduced from 6.3 to 4.5 days under PCT guidance (−1.8 days; 95% CI −3.1, −0.5;  $P=0.039$ ) for all LRTI and from 9.1 to 5.7 days for pneumonia (−3.4 days 95% CI −4.9, −1.7;  $P<0.001$ ). There was no apparent difference in impairment of daily activities between PCT guided and control patients.

**Conclusion:** PCT guidance reduced antibiotic exposure by reducing the duration of antibiotic treatment, while not affecting the antibiotic prescribing rate. The latter may be explained by the low baseline prescribing rate in Switzerland for pediatric LRTI and the choice of an inappropriately low PCT cut-off level for this population.



# Effectiveness and Safety of Procalcitonin-Guided Antibiotic Therapy in Lower Respiratory Tract Infections in “Real Life”

*An International, Multicenter Poststudy Survey (ProREAL)*

**Background:** In controlled studies, procalcitonin (PCT) has safely and effectively reduced antibiotic drug use for lower respiratory tract infections (LRTIs). However, controlled trial data may not reflect real life.

**Methods:** We performed an observational quality surveillance in 14 centers in Switzerland, France, and the United States. Consecutive adults with LRTI presenting to emergency departments or outpatient offices were enrolled and registered on a website, which provided a previously published PCT algorithm for antibiotic guidance. The primary end point was duration of antibiotic therapy within 30 days.

**Results:** Of 1759 patients, 86.4% had a final diagnosis of LRTI (community-acquired pneumonia, 53.7%; acute exacerbation of chronic obstructive pulmonary disease, 17.1%; and bronchitis, 14.4%). Algorithm compliance overall was 68.2%, with differences between diagnoses (bronchitis, 81.0%; AECOPD, 70.1%; and community-acquired pneumonia, 63.7%;  $P < .001$ ), outpatients (86.1%) and inpatients (65.9%) ( $P < .001$ ), algorithm-experienced (82.5%) and algorithm-naïve (60.1%) centers ( $P < .001$ ), and countries (Switzerland, 75.8%; France,

73.5%; and the United States, 33.5%;  $P < .001$ ). After multivariate adjustment, antibiotic therapy duration was significantly shorter if the PCT algorithm was followed compared with when it was overruled (5.9 vs 7.4 days; difference, -1.51 days; 95% CI, -2.04 to -0.98;  $P < .001$ ). No increase was noted in the risk of the combined adverse outcome end point within 30 days of follow-up when the PCT algorithm was followed regarding withholding antibiotics on hospital admission (adjusted odds ratio, 0.83; 95% CI, 0.44 to 1.55;  $P = .56$ ) and regarding early cessation of antibiotics (adjusted odds ratio, 0.61; 95% CI, 0.36 to 1.04;  $P = .07$ ).

**Conclusions:** This study validates previous results from controlled trials in real-life conditions and demonstrates that following a PCT algorithm effectively reduces antibiotic use without increasing the risk of complications. Preexisting differences in antibiotic prescribing affect compliance with antibiotic stewardship efforts.

**Trial Registration:** [isrctn.org](http://isrctn.org) Identifier: ISRCTN40854211

*Arch Intern Med.* 2012;172(9):715-722



# Procalcitonin Versus C-Reactive Protein for Guiding Antibiotic Therapy in Sepsis: A Randomized Trial\*

**Objective:** We sought to evaluate whether procalcitonin was superior to C-reactive protein in guiding antibiotic therapy in intensive care patients with sepsis.

**Design:** Randomized open clinical trial.

**Setting:** Two university hospitals in Brazil.

**Patients:** Patients with severe sepsis or septic shock.

**Interventions:** Patients were randomized in two groups: the procalcitonin group and the C-reactive protein group. Antibiotic therapy was discontinued following a protocol based on serum levels of these markers, according to the allocation group. The procalcitonin group was considered superior if the duration of antibiotic therapy was at least 25% shorter than in the C-reactive

protein group. For both groups, at least seven full-days of antibiotic therapy were ensured in patients with Sequential Organ Failure Assessment greater than 10 and/or bacteremia at inclusion, and patients with evident resolution of the infectious process had antibiotics stopped after 7 days, despite biomarkers levels.

**Measurements and Main Results:** Ninety-four patients were randomized: 49 patients to the procalcitonin group and 45 patients to the C-reactive protein group. The mean age was 59.8 (SD, 16.8) years. The median duration of antibiotic therapy for the first episode of infection was 7.0 (Q1–Q3, 6.0–8.5) days in the procalcitonin group and 6.0 (Q1–Q3, 5.0–7.0) days in the C-reactive protein group ( $p = 0.13$ ), with a hazard ratio of 1.206 (95% CI, 0.774–1.3;  $p = 0.13$ ). Overall, protocol overruling occurred in only 13 (13.8%) patients. Twenty-one patients died in each group ( $p = 0.836$ ).

**Conclusions:** C-reactive protein was as useful as procalcitonin in reducing antibiotic use in a predominantly medical population of septic patients, causing no apparent harm. (*Crit Care Med* 2013; 41:2336–2343)

**Key Words:** antibiotic therapy; C-reactive protein; intensive care; procalcitonin; sepsis

\*See also p. 2447.

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Currently listed as ClinicalTrials.org (NCT00934011).

Dr. Nobre conceived the study idea. Dr. C. F. Oliveira, Dr. C. R. A. Oliveira, Ms. Silva, and Ms. Pereira acquired the data. Drs. C. F. Oliveira and Nobre

Stop Antibiotics on guidance of Procalcitonin Study (SAPS): a randomised prospective multicenter investigator-initiated trial to analyse whether daily measurements of procalcitonin versus a standard-of-care approach can safely shorten antibiotic duration in intensive care unit patients - calculated sample size: 1816 patients

# PCT as a prognostic marker

- Clec'h *et al.* 2004
  - 75 Patients, Severe Sepsis & septic Shock
  - PCT >6ng/ml Independent predictor of worse outcome
- Azevedo *et al.*
  - 28 Patients, PCT at baseline, 24hrs & 48hrs
  - Baseline PCT no Sig. difference in survivors & Non-survivors
  - Rapid clearance over 24 Hrs = good prognosis
- Karlsson *et al.*
  - 242 (155 @72hrs) patients with severe sepsis & septic Shock
  - Rapid decline of >50% was associated with better outcome

- Karlsson et al . Critical Care 2010

- Azevedo *et al.* Rev Col Bras Cir 2012; 39(6): 456-460.



# sTREM-1

- Triggering receptor expressed on myeloid cells (TREM)-1 - member of the immunoglobulin superfamily, ~30-kDa glycoprotein
- Described first by Axel Bouchon and colleagues in 2000
- Expression up-regulated on phagocytic cells in the presence of **extracellular** bacteria or fungi, but not in non-infective acute/chronic inflammation
- Stimulates neutrophil and monocyte-mediated inflammatory responses
- A soluble form of TREM-1 (sTREM-1) is re-released from the activated phagocytes and can be found in body fluids
- Murine study - Mortality benefit with Anti TREM-1 Ab injected up to 1 hr of insult

# sTREM-1

Sr. No.	Author, Year	Setting, N	Sensitivity (%)	Specificity (%)	PLR	NLR	Comments
1	Gibot S, 2004 (Serum sTREM-1)	ICU, 76	96	89	8.6	0.04	Only 13 patients actually had clinical picture confusing with sepsis
2	Gibot S, 2004 (BAL sTREM-1)	ICU, 148	98	90	10.38		Uniform Mini BAL with 20MI saline, 2/3 <sup>rd</sup> return.

# sTREM-1 as a prognostic marker

- High level of sTREM-1 is associated with good prognosis
- Progressive decline in sTREM-1 level over time portends improvement and predicts survival
- Persistent elevation or increase over time despite treatment predicts poor outcome
- More than normal but not very high level of sTREM at baseline predicts poor outcome

# Galactomannan

- Galactomannan is a heat-stable heteropolysaccharide present in the cell wall of most *Aspergillus* and *Penicillium* species
- Comprised of a non-immunogenic mannan core with immunoreactive side-chains of varying lengths containing galactofuranosyl units
- Two commercial assays for the detection
  - The Pastorex kit (Sanofi Diagnostics Pasteur, Marnes-La-Coquette, France)
  - Platelia ELISA (BioRad, Marnes-La-Coquette, France)
  - Pastorex is now rarely used
- Testing is not universally available
- Details of release and kinetics of circulating galactomannan are unknown
- Galactomannan production is proportional to fungal load, levels appear to have prognostic significance
- Assays to detect galactomannan have mostly used serum and BAL fluid
- Assays use EB-A2, a monoclonal antibody derived from rats, which is directed towards the (1,5)-linked galactofuranoside side-chain residues of the GM



# Serum galacomannan – Cochrane review

- Cross-sectional studies, case –control designs and consecutive series
- In patients with neutropenia or whose neutrophils are functionally compromised
- The reference standard criteria by EORTC and MSG
- Results-

Sr No.	Cut Off	Studies (Pt.)	Sn (%)	Sp (%)
1	0.5	3 (901)	78 (61-89)	81 (72 to 88)
2	1.0	12 (1744)	75 (59-86)	91 (84-95)
3	1.5	17 (2600)	64 (50-77)	95 (91-97)



## Accuracy of BAL Galactomannan in Diagnosing Invasive Aspergillosis

### A Bivariate Metaanalysis and Systematic Review

**Background:** A serum galactomannan (GM) assay has been approved for diagnosing invasive aspergillosis (IA). However, the role of the BAL-GM assay has not been well established. Therefore, we conducted a metaanalysis to determine the overall accuracy of BAL-GM in the diagnosis of IA.

**Methods:** After a systematic review of English-language studies, the sensitivity (SEN), specificity (SPE), and positive and negative likelihood ratios (PLR and NLR, respectively) of BAL-GM for the diagnosis of IA were pooled using a bivariate metaanalysis. Hierarchic summary receiver operating characteristic curves were used to summarize overall test performance. Potential between-study heterogeneity was explored by subgroup analyses. We calculated posttest probability to evaluate clinical usefulness.

**Results:** Twelve reports, including 13 studies, met our inclusion criteria. The summary estimates of the BAL-GM assay for proven or probable IA were as follows: SEN, 0.90 (95% CI, 0.79-0.96); SPE, 0.94 (95% CI, 0.90-0.96); PLR, 14.87 (95% CI, 8.89-24.90); and NLR, 0.10 (95% CI, 0.04-0.24). The four summary estimates of the BAL-GM assay for proven IA were 0.94 (95% CI, 0.86-0.98), 0.79 (95% CI, 0.68-0.86), 4.41 (95% CI, 2.87-6.77), and 0.07 (95% CI, 0.03-0.09), respectively. Significant heterogeneity was present.

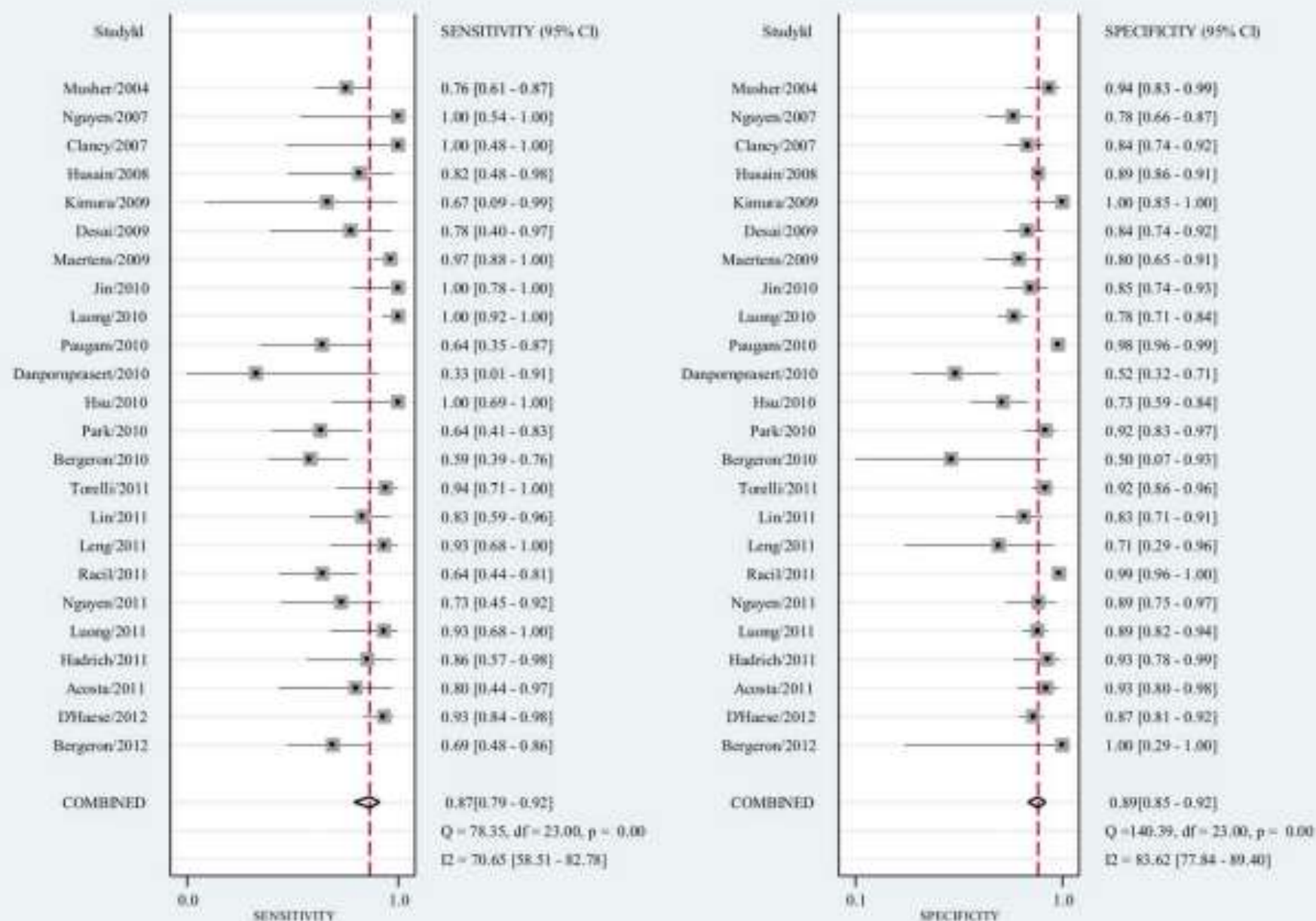
**Conclusions:** BAL-GM determination is a sensitive and specific test for the diagnosis of proven and probable IA. The measurement of BAL-GM is thus likely to be a useful tool for diagnosing IA. Further studies focused on the impact of treatment agents are needed.

CHEST 2010; 138(4):817-824

# BAL galactomannan- Recent meta-analysis

- 30 Studies, 23 cohort studies and 7 case–control studies
- 3344 patients, 614 (18.4%) proven or probable IA
- Studies mainly from American, European and Asian countries
- Cutoff of BAL-GM varied from 0.5 to 8.0 in individual studies, most commonly 0.5
- Mean DOR was 52.7 (95% CI 31.8–87.3).
- SEN- 87% (79–92), SPE was 89% (85–92)
- Summary AUC was 0.94 (0.92–0.96)
- Pooled PLR and NLR were 8.0 (5.7–11.1) and 0.15 (0.10–0.23)





**Figure 3. Forest plot of sensitivities and specificities from test accuracy studies of BAL-GM in the diagnosis of IA.**

doi:10.1371/journal.pone.0043347.g003



# BAL galacomannan- Recent meta-analysis

- BAL-GM has a better capacity for diagnosing IA than both serum GM
- Airway colonization with *Aspergillus* species & contamination may result in false positive results
- Significant heterogeneity existed in most of the analyses, sensitivity analyses heterogeneity still exist
- Most of the pooled SEN and SPE were still above 85%, indicating that BAL-GM test has excellent accuracy
- Publication bias can not be ruled out
- Misclassification bias is unavoidable –as most IFI are not substantiated by Microbiological/Histopathological gold standard

## Early Serum Galactomannan Trend as a Predictor of Outcome of Invasive Aspergillosis

The monitoring and prediction of treatment responses to invasive aspergillosis (IA) are difficult. We determined whether serum galactomannan index (GMI) trends early in the course of disease may be useful in predicting eventual clinical outcomes. For the subjects recruited into the multicenter Global Aspergillosis Study, serial GMIs were measured at baseline and at weeks 1, 2, and 4 following antifungal treatment. Clinical response and survival at 12 weeks were the outcome measures. GMI trends were analyzed by using the generalized estimation equation approach. GMI cutoffs were evaluated by using receiver-operating curve analyses incorporating pre- and posttest probabilities. Of the 202 study patients diagnosed with IA, 71 (35.1%) had a baseline GMI of  $\geq 0.5$ . Week 1 GMI was significantly lower for the eventual responders to treatment at week 12 than for the nonresponders (GMIs of  $0.62 \pm 0.12$  and  $1.15 \pm 0.22$ , respectively;  $P = 0.035$ ). A GMI reduction of  $> 35\%$  between baseline and week 1 predicted a probability of a satisfactory clinical response. For IA patients with pretreatment GMIs of  $< 0.5$  ( $n = 131$ ; 64.9%), GMI ought to remain low during treatment, and a rising absolute GMI to  $> 0.5$  at week 2 despite antifungal treatment heralded a poor clinical outcome. Here, every 0.1-unit increase in the GMI between baseline and week 2 increased the likelihood of an unsatisfactory clinical response by 21.6% ( $P = 0.018$ ). In summary, clinical outcomes may be anticipated by charting early GMI trends during the first 2 weeks of antifungal therapy. These findings have significant implications for the management of IA.



# The Performance of Real-Time PCR, Galactomannan, and Fungal Culture in the Diagnosis of Invasive Aspergillosis in Ventilated Patients with Chronic Obstructive Pulmonary Disease (COPD)

**Abstract** Emerging reports have associated chronic pulmonary obstructive disease (COPD) with invasive aspergillosis (IA), particularly in patients treated with mechanical ventilation and/or corticosteroids. This is a multicentre study in which COPD patients demonstrating a new lung infiltrate while being mechanically ventilated were prospectively evaluated for the presence of IA. From the 47 patients studied, *Aspergillus fumigatus* was recovered in culture in two patients (4.2%). While serum galactomannan (GM) was negative for 94% of patients, GM levels in respiratory

samples were  $>0.5$ ,  $>1.0$  and  $>1.5$  for 74.5, 40.5, and 21.3% of patients, respectively. PCR was positive for 10 patients in the study but did not differentiate *Aspergillus* colonization from infection. The combination of PCR and GM in respiratory samples may be an interesting alternative to diagnose IA in COPD patients.

**Keywords** Aspergillosis · *Aspergillus fumigatus* · COPD · Galactomannan · PCR

# Serum 1,3 Beta D Glucan

- (1,3)- $\beta$ -D glucan assays have been developed by Wako Pure Chemical Industries (Tokyo, Japan), Seikagaku Kogyo Corporation (Tokyo, Japan), Maruha Corporation (Tokyo, Japan) and Associates of Cape Code (Falmouth, USA)
- Assay developed by Associates of Cape Code, Fungitell, has been approved by the FDA for the diagnosis of IFI
- B-D glucan is present in the cell wall of most fungi; the notable exceptions are *Cryptococcus* spp and the zygomycetes
- The molecule is ubiquitous in the environment and has been used as a marker of fungal biomass
- Sensitivity of the Fungitell assay is in the order of 1 pg/mL, which is < cut-off of 60 pg/mL used in a recent clinical study
- False-positive (1,3)- $\beta$ -D glucan results have been documented in haemodialysis, cardiopulmonary bypass, treatment with
- immunoglobulin products, and exposure to glucan-containing gauze (eg, following major surgery)
- Environmental (1,3)--D glucan contamination may also compromise specificity



# Serum 1,3 Beta D Glucan- Diagnosis of IFI

- 23 studies, 16 included in meta-analysis
- 2979 patients, 594 with proven or probable IFIs
- For proven IFI- pooled sensitivity 79.1% (68.9–86.7) & specificity 87.7% (82.4–91.6)
- Pooled diagnostic odds ratio was 27.0 (13.8–52.8)
- PLR was 6.4(4.4–9.4), and the NLR - 0.24 (0.16–0.37).
- sAUC 0.91 (0.88–0.93)
- $I^2$  index was 92% (84%–99%)

# 1,3 Beta D Glucan- Diagnostic accuracy

- Meta analysis- Studies from 1966-2010
- 907 articles screened
- 35 studies selected-1995-2010
- 13 different countries- max from Japan & USA
- Separately for PJP and IFI

J Clin Micro Nov 2011

# Diagnostic accuracy for PJP

- Sensitivity: 96%
- Specificity: 84%
- Diagnostic Odds Ratio: 102.3
- Diagnostic accuracy same for HIV positive and negative

# Diagnostic accuracy for IFI

- Sensitivity: 80%
- Specificity: 82%
- Diagnostic Odds Ratio: 25.7

## Accuracy of $\beta$ -D-glucan for the diagnosis of *Pneumocystis jirovecii* pneumonia: a meta-analysis

*Pneumocystis jirovecii* pneumonia (PCP) can affect various types of immunocompromised patients. We sought to evaluate the diagnostic accuracy of (1  $\rightarrow$  3)- $\beta$ -D-glucan (BDG) for the diagnosis of PCP. We carried out a meta-analysis of relevant studies, identified through PubMed and Scopus. Eligible studies were those that reported BDG diagnostic data in cases with documented PCP and controls with other conditions. Cases of invasive fungal infections and healthy controls were excluded. We performed a bivariate meta-analysis of sensitivity and specificity and constructed a hierarchical summary receiver operating characteristics (HSROC) curve. Fourteen studies were included in the meta-analysis. BDG data were analysed for 357 PCP cases and 1723 controls. The average (95% confidence interval) sensitivity and specificity of BDG were 94.8% (90.8–97.1%) and 86.3% (81.7–89.9%), respectively. The positive and negative likelihood ratios were 6.9 (5.1–9.3) and 0.06 (0.03–0.11), respectively. The area under the HSROC curve was 0.965 (0.945–0.978). Serum BDG shows excellent sensitivity and very good specificity in the diagnosis of PCP. Still, in clinical practice the test results should be interpreted in the context of the underlying clinical characteristics of the individual patient.



# Novel Biomarkers

Need Validation in further studies

RESEARCH

Open Access

## Development and validation of a novel molecular biomarker diagnostic test for the early detection of sepsis

**Methods:** This was a multi-centre, prospective clinical trial conducted across four tertiary critical care settings in Australia. Sepsis patients were recruited if they met the 1992 Consensus Statement criteria and had clinical evidence of systemic infection based on microbiology diagnoses ( $n = 27$ ). Participants in the post-surgical (PS) group were recruited pre-operatively and blood samples collected within 24 hours following surgery ( $n = 38$ ). Healthy controls (HC) included hospital staff with no known concurrent illnesses ( $n = 20$ ). Each participant had minimally 5 ml of PAXgene blood collected for leucocyte RNA isolation and gene expression analyses. Affymetrix array and multiplex tandem (MT)-PCR studies were conducted to evaluate transcriptional profiles in circulating white blood cells applying a set of 42 molecular markers that had been identified *a priori*. A LogitBoost algorithm was used to create a machine learning diagnostic rule to predict sepsis outcomes.

**Results:** Based on preliminary microarray analyses comparing HC and sepsis groups, a panel of 42-gene expression markers were identified that represented key innate and adaptive immune function, cell cycling, WBC differentiation, extracellular remodelling and immune modulation pathways. Comparisons against GEO data confirmed the definitive separation of the sepsis cohort. Quantitative PCR results suggest the capacity for this test to differentiate severe systemic inflammation from HC is 92%. The area under the curve (AUC) receiver operator characteristics (ROC) curve findings demonstrated sepsis prediction within a mixed inflammatory population, was between 86 and 92%.

# Multi marker approach

- No one biomarker is likely to adequately reflect the rapidly evolving nature of a potentially septic patient's status
- Important lesson from the failure of PCT to provide helpful information in the PASS study
- Several investigators have reported attempts to use a panel of biomarkers in order to better identify patients at risk.



# Use of plasma C-reactive protein, procalcitonin, neutrophils, macrophage migration inhibitory factor, soluble urokinase-type plasminogen activator receptor, and soluble triggering receptor expressed on myeloid cells-1 in combination to diagnose infections: a prospective study

Kristian Kofoed<sup>1,2</sup>, Ove Andersen<sup>1,2</sup>, Gitte Kronborg<sup>2</sup>, Michael Tvede<sup>3</sup>, Janne Petersen<sup>1</sup>, Jesper Eugen-Olsen<sup>1</sup> and Klaus Larsen<sup>1</sup>

The AUCs for bacterial Sepsis- were

- sUPAR= 0.50 (0.40 to 0.60)
- sTREM= 0.61 (0.52 to 0.71)
- MIF= 0.63 (0.53 to 0.72)
- PCT= 0.72 (0.63 to 0.79)
- Neutrophil count= 0.74 (0.66 to 0.81)
- CRP= 0.81 (CI 0.73 to 0.86)

- composite three-marker 0.84 (0.71 to 0.91)
- composite six-marker= 0.81 to 0.92)



# A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis

**Objective:** To define a biomarker panel to predict organ dysfunction, shock, and in-hospital mortality in emergency department (ED) patients with suspected sepsis.

**Design:** Prospective observational study.

**Setting:** EDs of ten academic medical centers.

**Patients:** There were 971 patients enrolled. Inclusion criteria: 1) ED patients age  $\geq 18$ ; 2) suspected infection or a serum lactate level  $\geq 2.5$  mmol/L; and 3) two or more systemic inflammatory response syndrome criteria. Exclusion criteria: pregnancy, do-not-resuscitate status, or cardiac arrest.

**Measurements and Main Results:** Nine biomarkers were assayed from blood draws obtained on ED presentation. Multivari-

in-hospital mortality. The overall rates of each outcome were severe sepsis, 52%; septic shock, 39%; and in-hospital mortality 7%. Among the nine biomarkers tested, the optimal 3-marker panel was neutrophil gelatinase-associated lipocalin, protein C, and interleukin-1 receptor antagonist. The area under the curve for the accuracy of the sepsis score derived from these three biomarkers was 0.80 for severe sepsis, 0.77 for septic shock, and 0.79 for death. When included in multivariate models with clinical variables, the sepsis score remained highly significant ( $p < 0.001$ ) for all the three outcomes.

**Conclusions:** A biomarker panel of neutrophil gelatinase-associated lipocalin, interleukin-1ra, and Protein C was predictive of