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The relationship disclosed is he received a grant/ research support from Brahms Diagnostics.

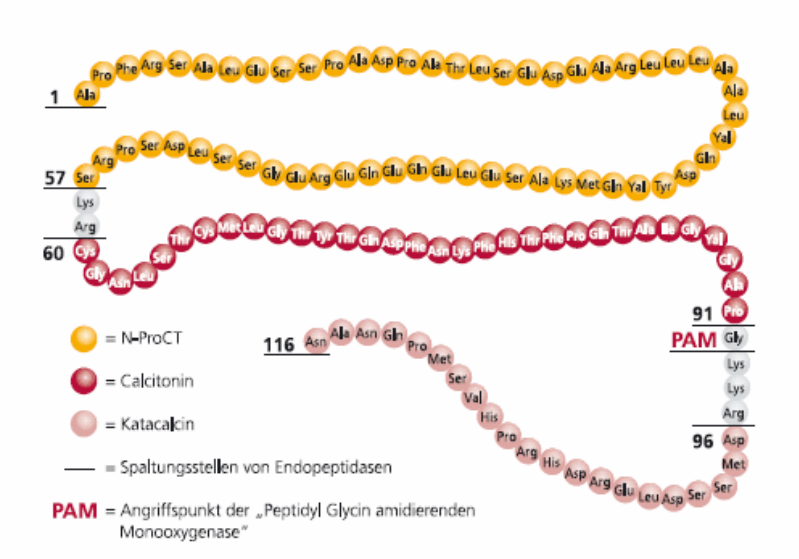
Procalcitonin Directed Antibiotic Therapy

Eric Gluck MD FCCM
Chicago, IL
February 4, 2008

Procalcitonin- Introduction

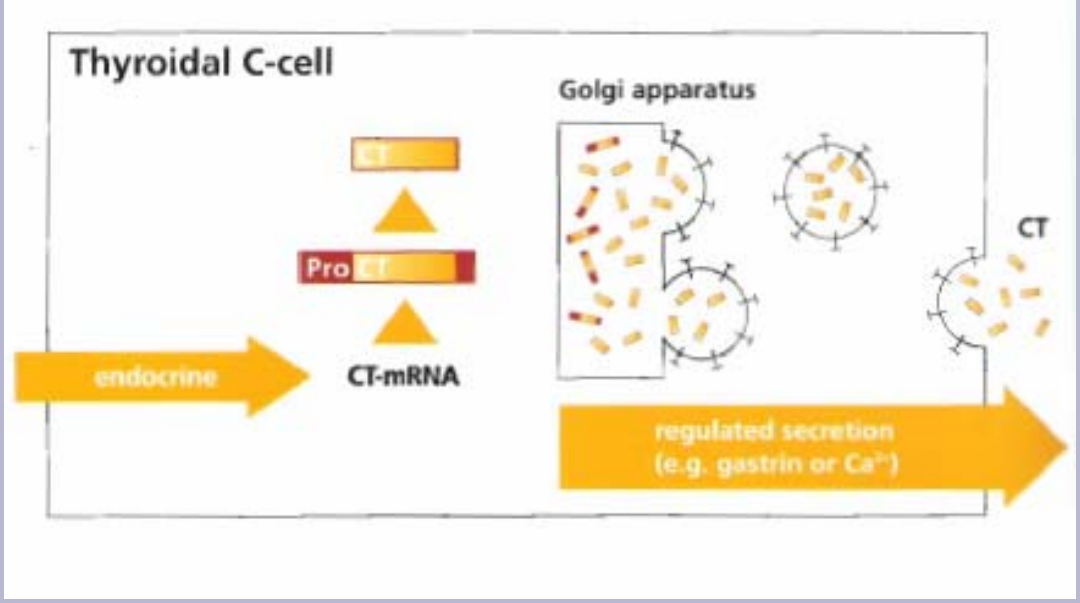
- What is Procalcitonin?
- What is the role of PCT in sepsis?

Procalcitonin - Structure



- Procalcitonin is a 116 amino-acid peptide - Precursor of the hormone Calcitonin
- Expression is induced by bacterial infection but not by viral or fungal infections.
- Plasma concentrations can vary from 0.02 – 1,000 ng/ml (normal to septic shock)
- Serum level is not dependent on kidney function
- Stable invivo and invitro – easy to measure in serum and plasma

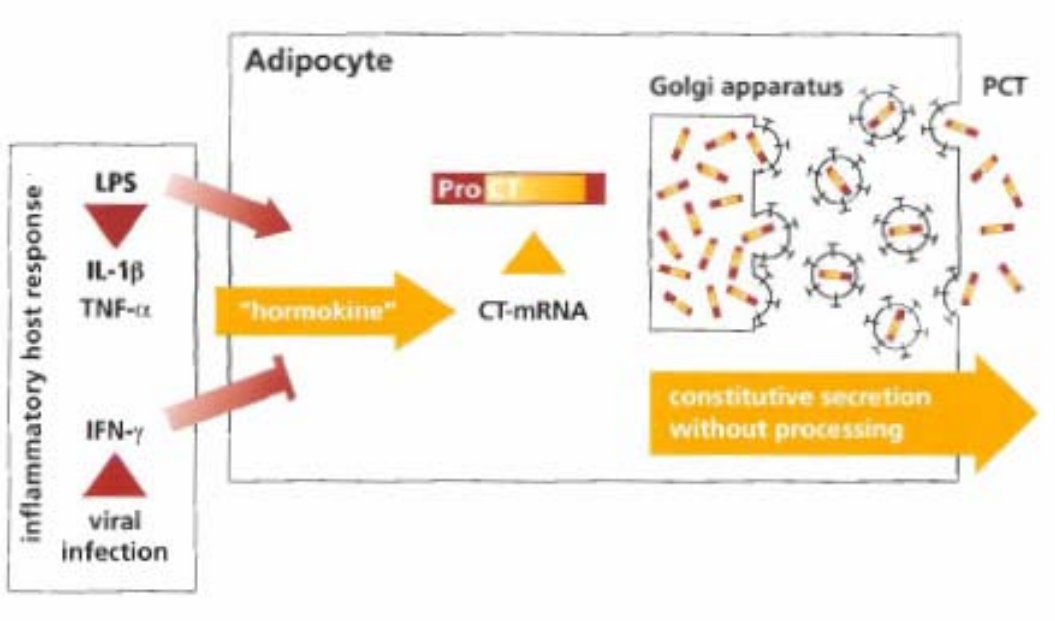
Role of PCT in the Absence of Infection



Release of Calcitonin in the context of endocrine regulation:

- Synthesis in healthy persons in the C-Cells of the thyroid
- PCT is enzymatically converted to calcitonin and then stored in endocrine granules
- Released only under certain stress (e.g. magnesium, gastrin)

Role of PCT in Sepsis

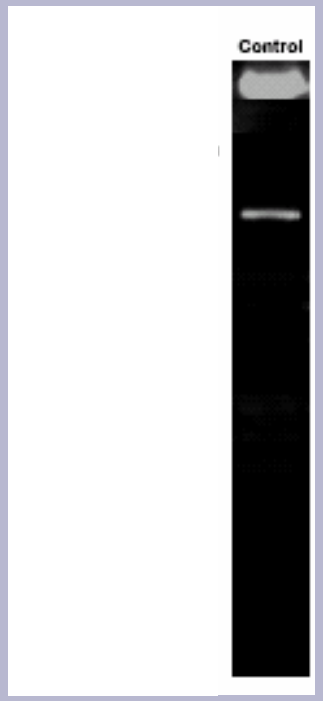


Alternative (cytokine-like) pathway during sepsis: 'Hormokine'

- Bacterial toxins (gran +/gram-) and cytokines stimulate production of PCT in all parenchymal tissues
- This process can be attenuated or blocked during viral infection by interferones.
- Non endocrine tissue ie Liver, Lung, Brain etc. do not have endocrine granules where calcitonin can be stored.
- PCT is immediately released into the bloodstream

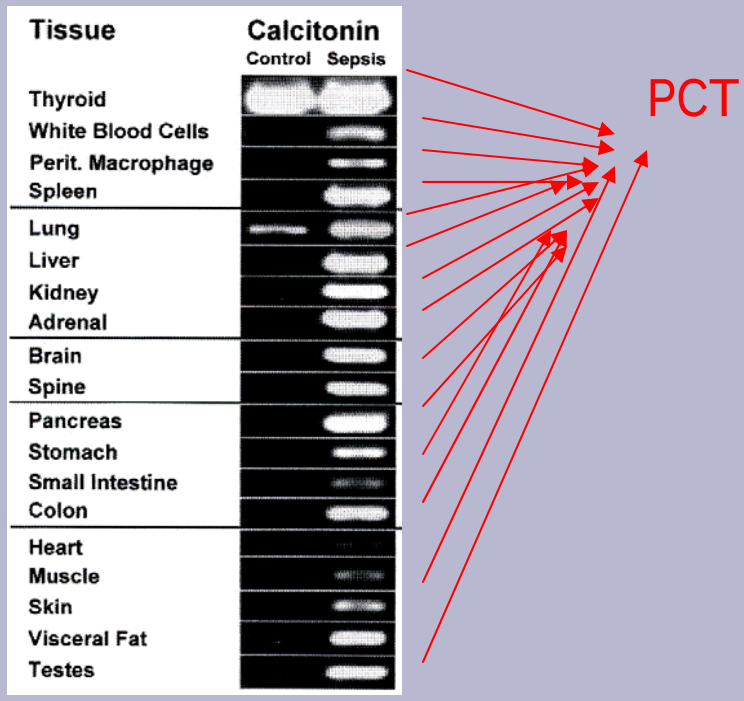
A Hormone Becomes a Cytokine

Calcitonin in healthy persons



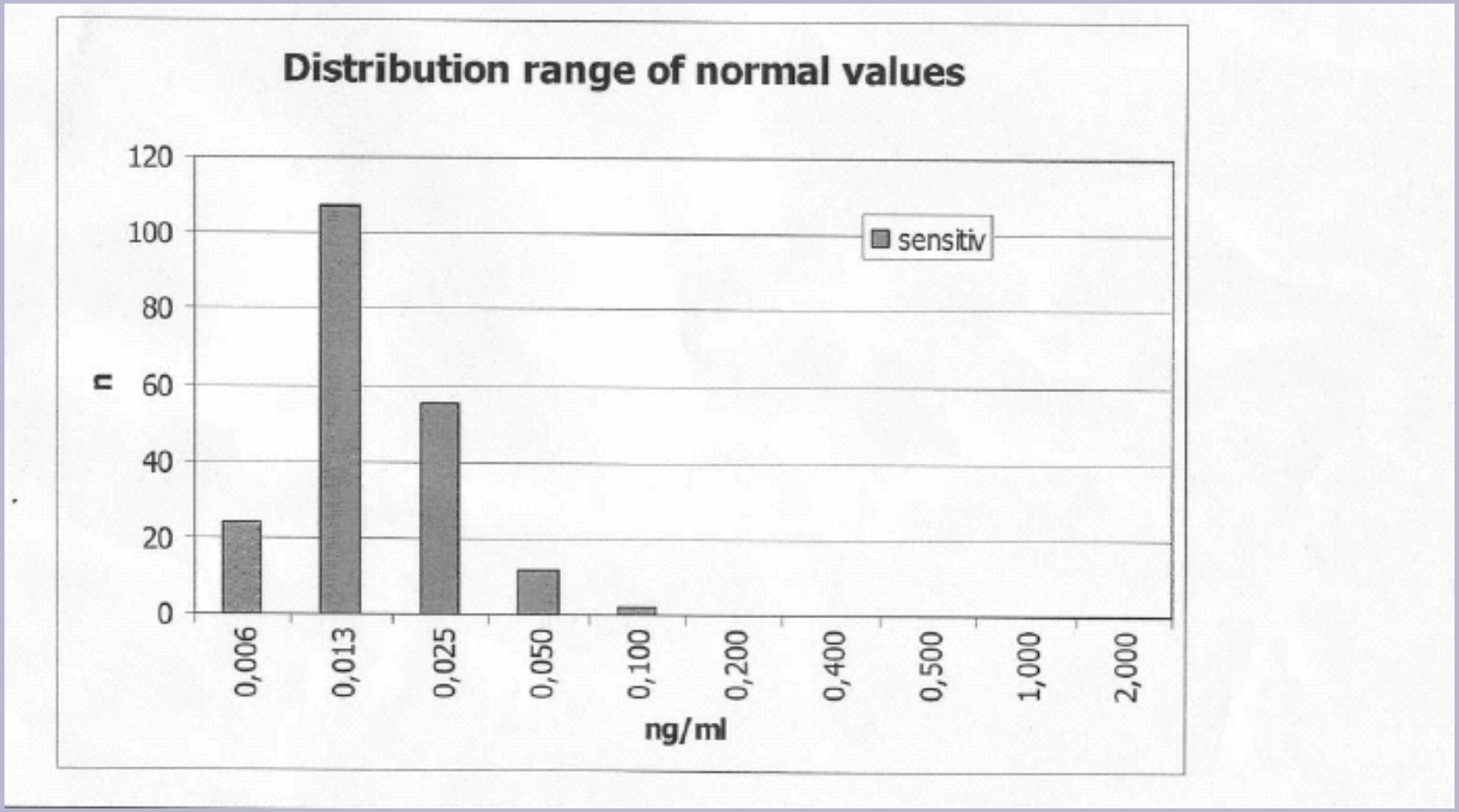
Calcitonin

PCT in bacterially infection



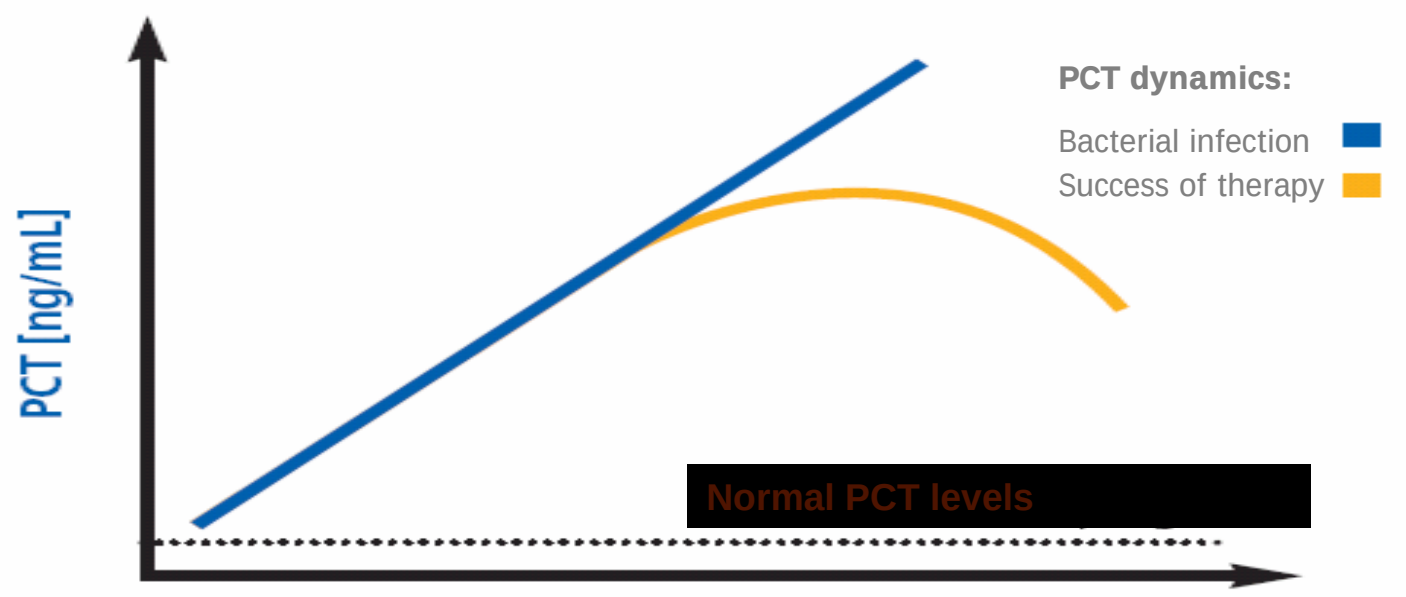
Müller B. et al., JCEM 2001

Procalcitonin - Normal Range



95% percentile < 0.025ng/ml

PCT Dynamics After Bacterial Challenge

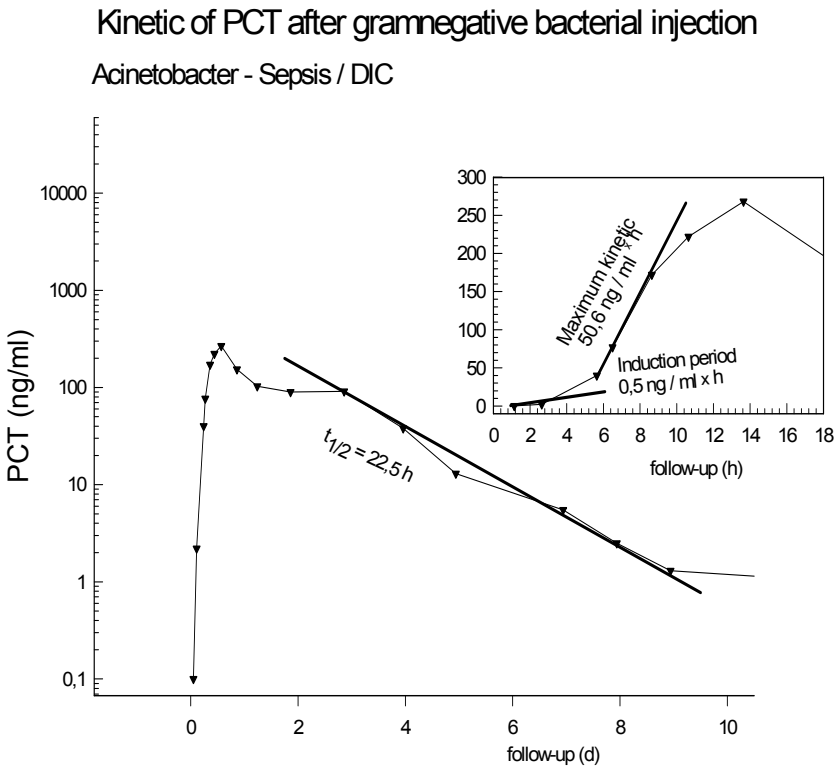


Procalcitonin

- Rapid increase usually around 3-4 hours after stimulation
- Plasma concentrations between 0.02 ng/ml und 1000 ng/ml
- Short half-life time (~ 24 h) not dependent on renal function
- Easy to measure in serum and plasma

Rapid Rise of PCT Post-Bacterial Challenge

- **Highly specific induction** of PCT by bacterial infection
- **Fast increase** (after 3-4 hours),
- **High dynamic range** (Plasma concentrations between < 0.05 ng/ml und 1000 ng/ml
- **Short half-life time** (~ 24 h) independent of renal function
- **Easy to measure** in serum and plasma, stable *in vivo* and *in vitro*



Evolutionary Basis

- Has bactericidal properties
- Present in all mammals tested
- Probably was an early host defense against infection
- Replaced by more robust defenses such as antibody system and enhanced leukocyte defenses
- Most important, perhaps, in defending the body against invasion of bacteria during feeding.

Evolutionary Basis

- Co-opted by thyroid gland to provide a stimulatory mechanism for the management of calcium during digestion.

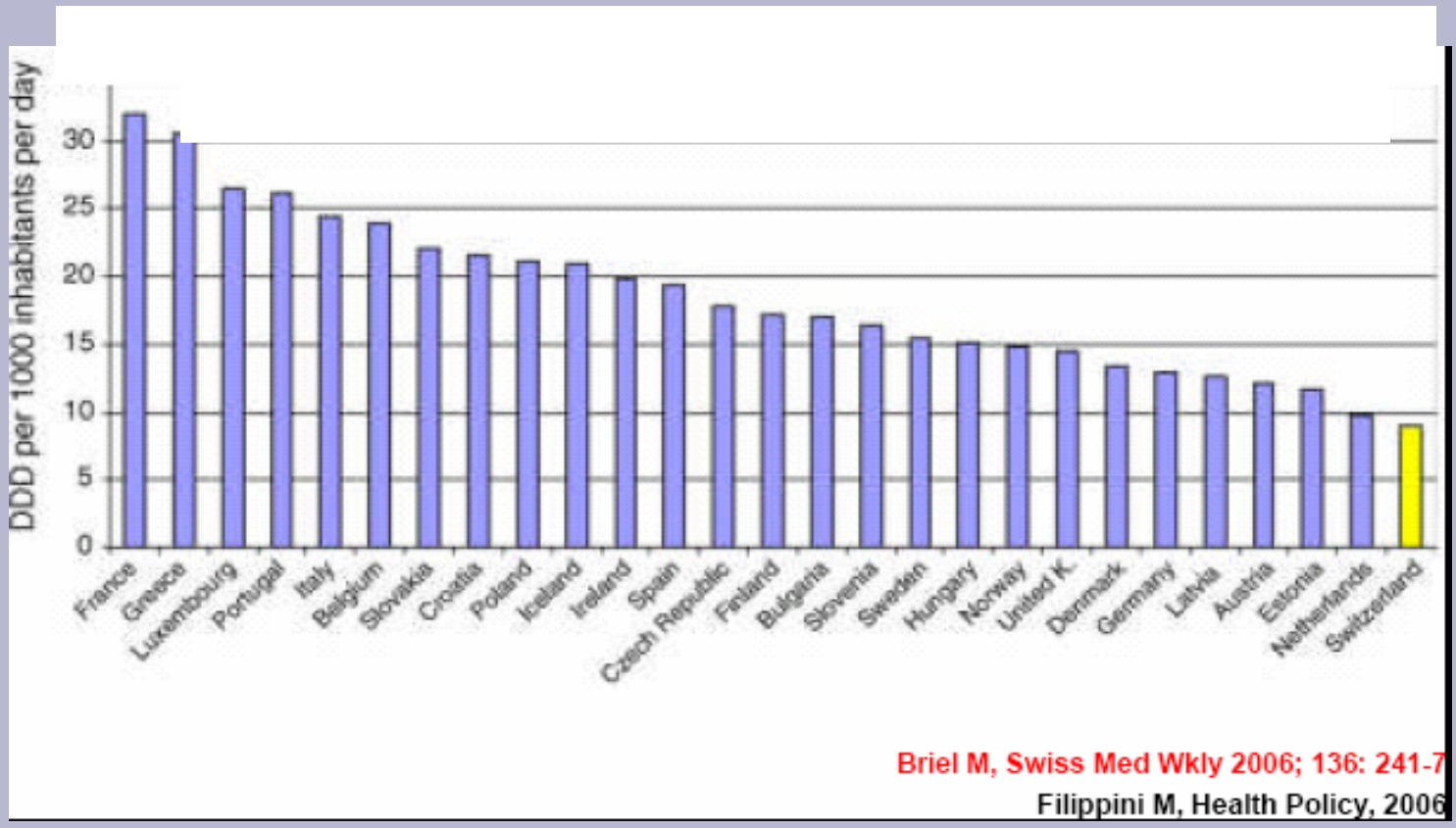
- Since there was no biological cost for maintaining the system, non endocrine cells maintained the ability to produce PCT during bacterial stimulation

Goals of PCT

- How can we use this cellular signal of infection in the management of both septic and non septic patients

- Goals
  - Provide antibiotic therapy to pts who need it as soon as possible
  - Avoid antibiotic prescription to those without infection
  - Do both with a strong likelihood of being correct, at least as good as other markers such as WBC, bands, fever, CRP

Antibiotic Use in Europe



Briel M, Swiss Med Wkly 2006; 136: 241-7

Filippini M, Health Policy, 2006

Sepsis in the US

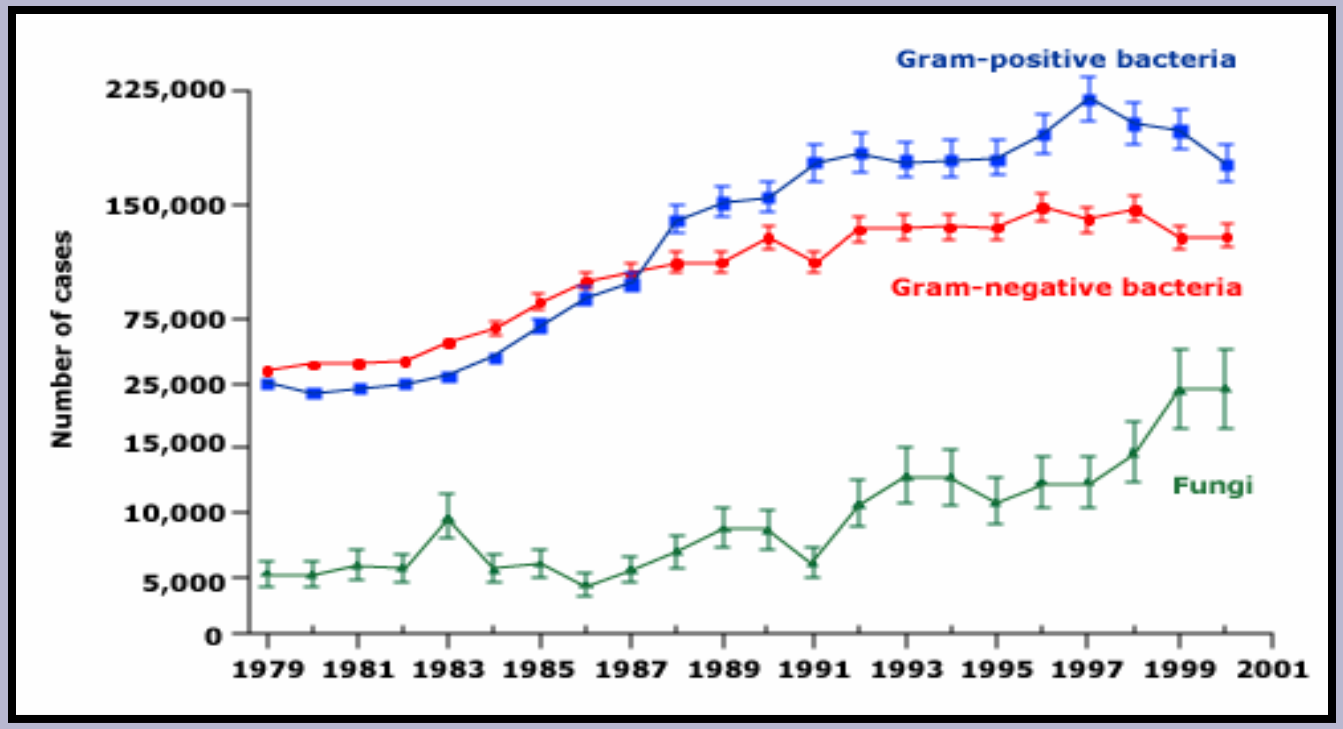


Figure 1. Number of cases of sepsis in the United States, according to causative organism from 1979 - 2000

Lower Respiratory Tract Infections : A Frequent Clinical Condition Causing High Treatment Costs

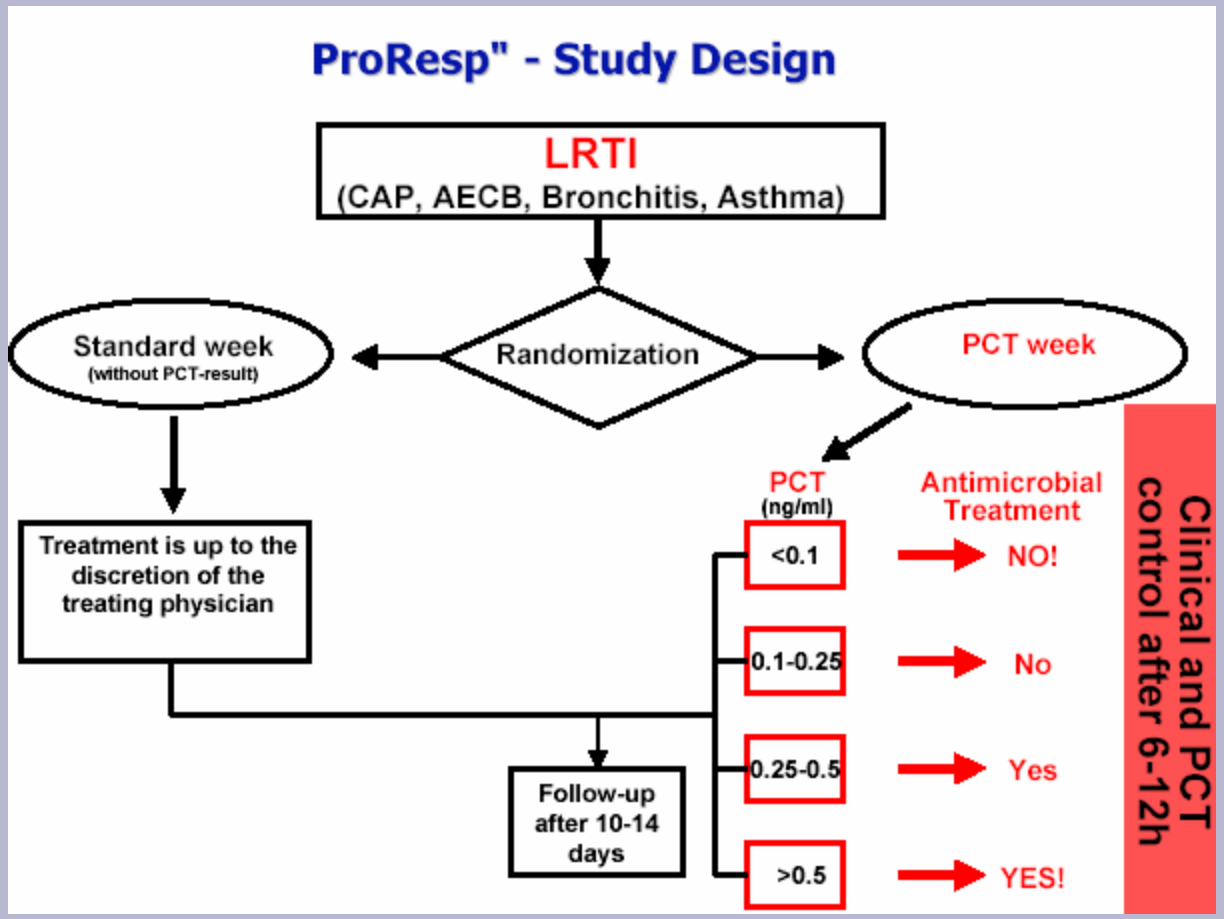
- Acute exacerbations of COPD (US).
  - Prevalence: 16 million adults,
  - Hospitalisations: 500‘000 p.a.
  - Mortality: 110‘000 deaths p.a.
- Acute Bronchitis:
  - 5% of population per year,
  - 90% consulting doctor
- Value of AB controversial: 75% non-bact. Origin, DD colonization
- Common prescription rate: 94-100% ABX

NEJM 2003; 348: 2618-25
Eur Respir J 1996; 9: 1590-5

- With antibiotic use ‘out of control’ are there interventions that can be employed to reduce the use of antibiotics without imposing a risk on our patients?

- Intervention in the ED

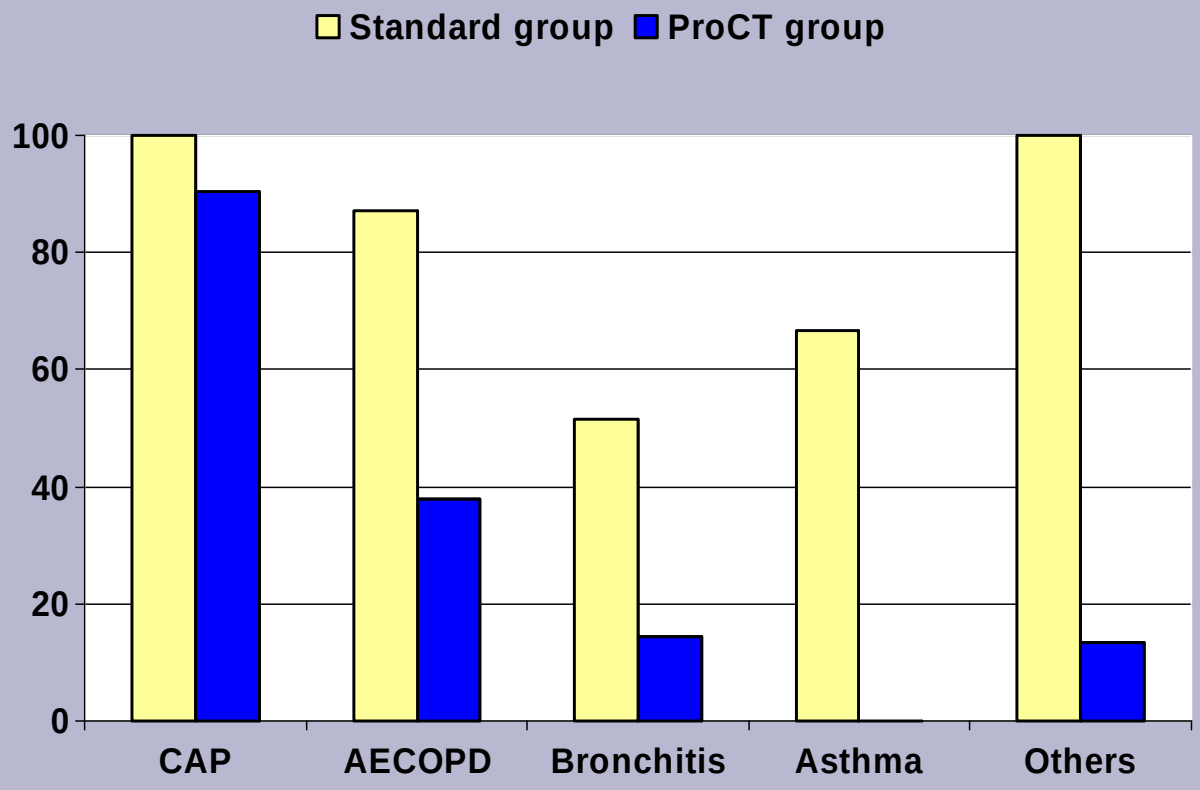
Algorithm for ED Intervention Study



Christ-Crain et al., Lancet 2004

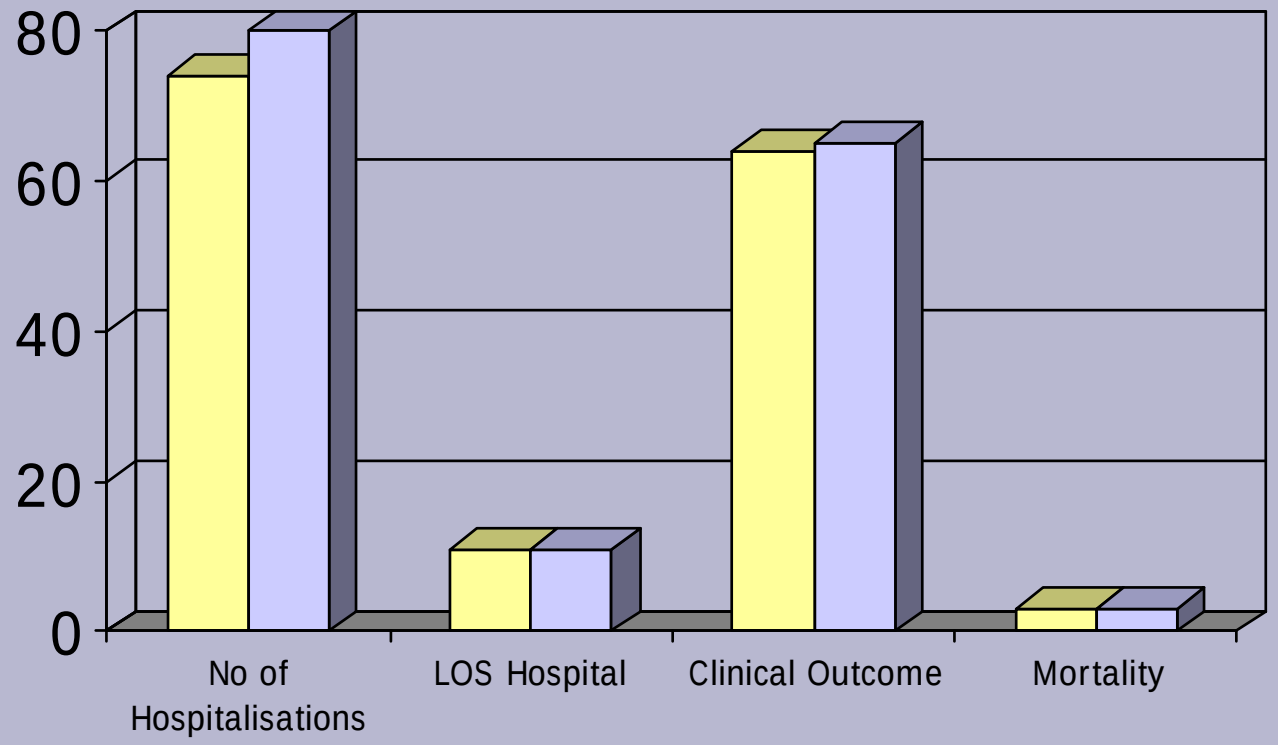
Antibiotic Therapy in LRTI

PCT identifies clinically relevant bacterial infection
Reduction of antibiotic use and costs by ~50%



Christ-Crain et al., Lancet 2004

Outcome was the Same in Both Groups



Christ-Crain et al., Lancet 2004

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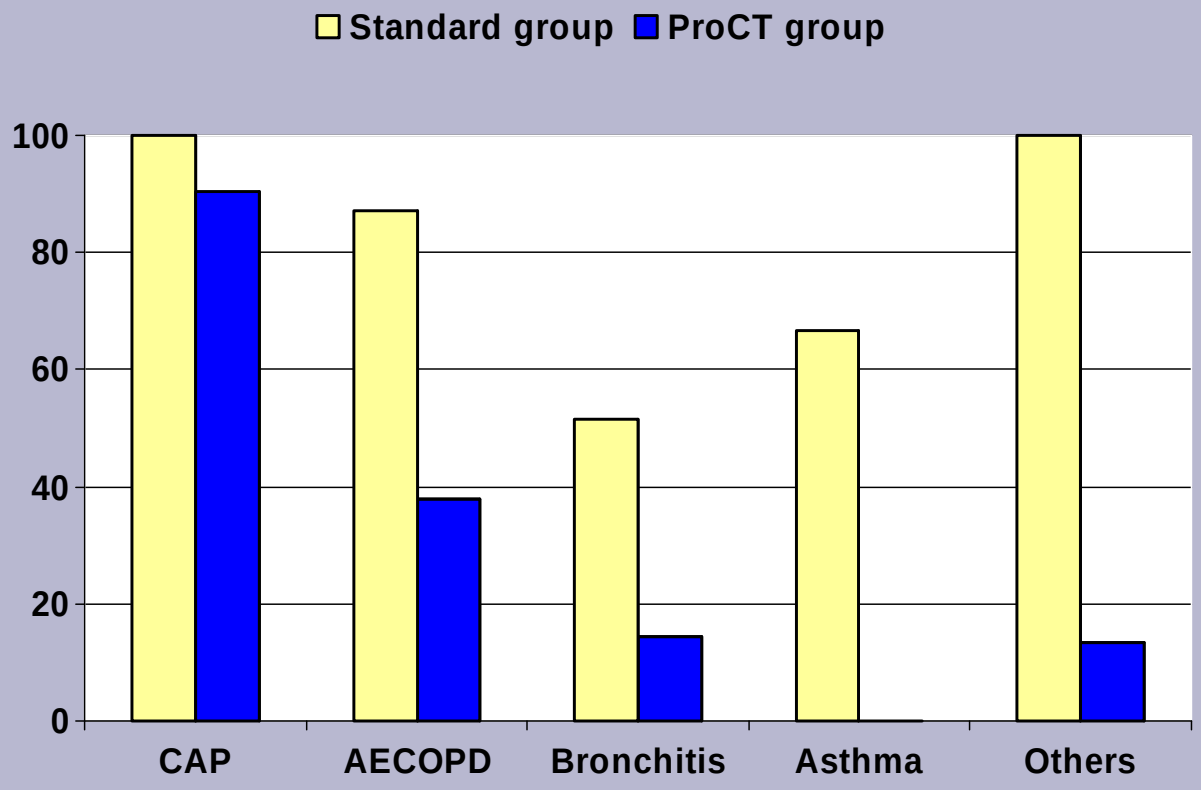


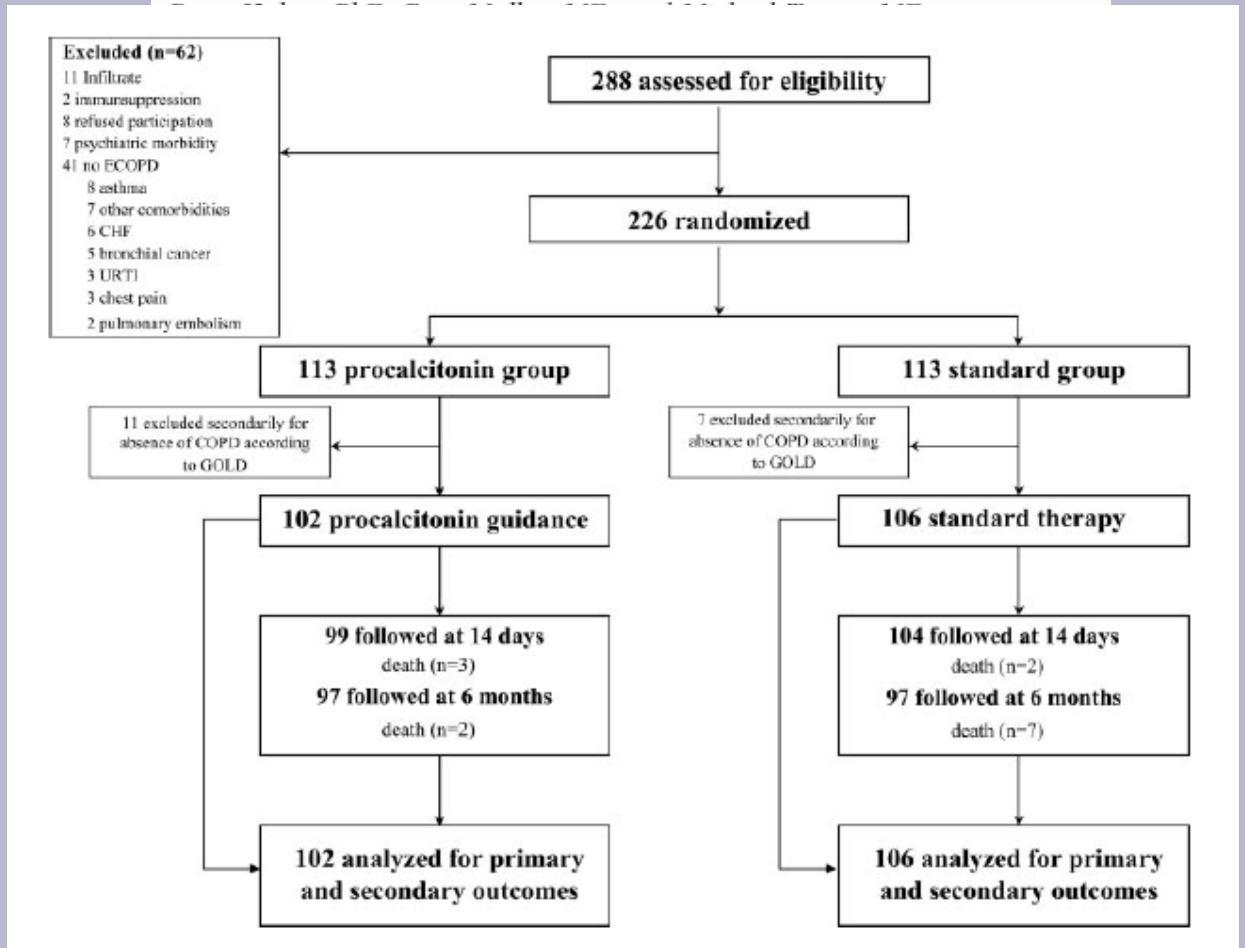
Christ-Crain et al., Lancet 2004

PCT Guided Therapy in COPD

Antibiotic Treatment of Exacerbations of COPD*

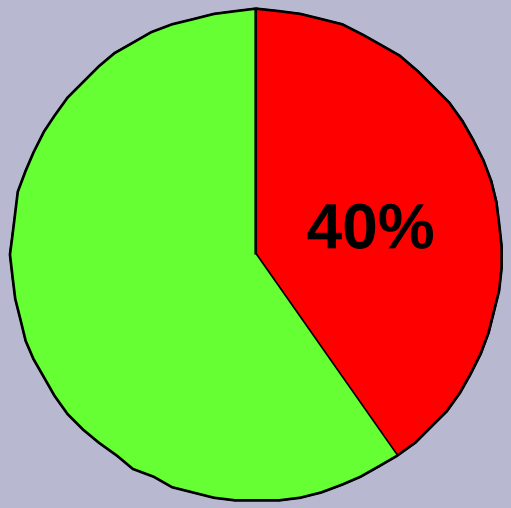
A Randomized, Controlled Trial Comparing Procalcitonin-Guidance With Standard Therapy

Daiana Stolz, MD; Mirjam Christ-Crain, MD; Roland Bingisser, MD; Jörg Leuppi, MD; David Miedinger, MD; Christian Müller, MD;

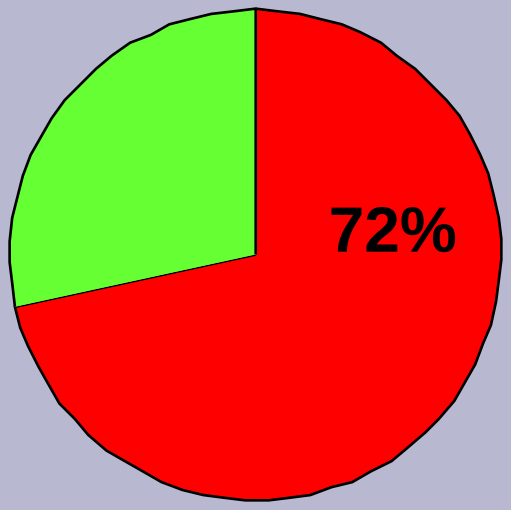


PCT Guided Therapy in AECOPD

Procalcitonin-Group



Standard-Group



p <0.0001

Antibiotics
no Antibiotics

Relative risk for antibiotic exposure
In PCT group .58

Stolz D et al, CHEST, in press

Clinical Outcome at Short-term Follow-up

Clinical success (%)	84 (82.4)	89 (83.9)	0.853
Length of hospital stay days	9 (1-15)	10 (1-15)	0.960
Duration of ICU stay in days	3.3 ± 2.7	3.7 ± 2.1	0.351
Median steroid dose in mg	250 (119-400)	280 (183-421)	0.303
Hospitalization rate for AECOPD within 6 mo	18 (17.7)	22 (20.8)	0.507

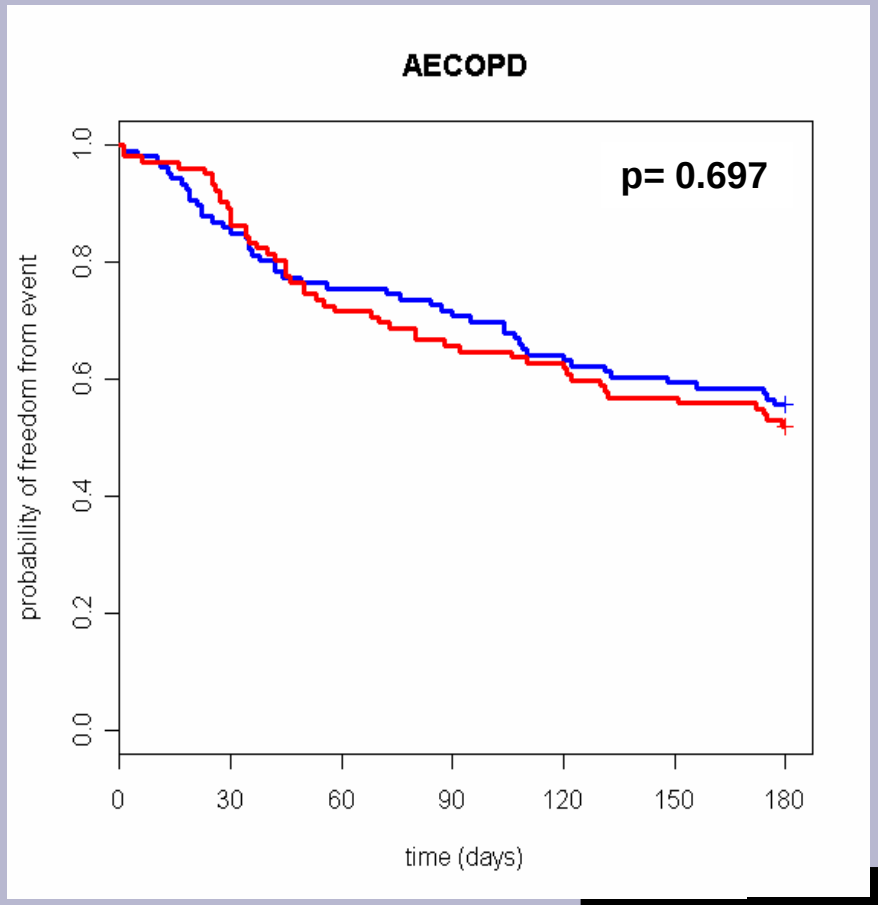
Stolz D et al, CHEST, in press

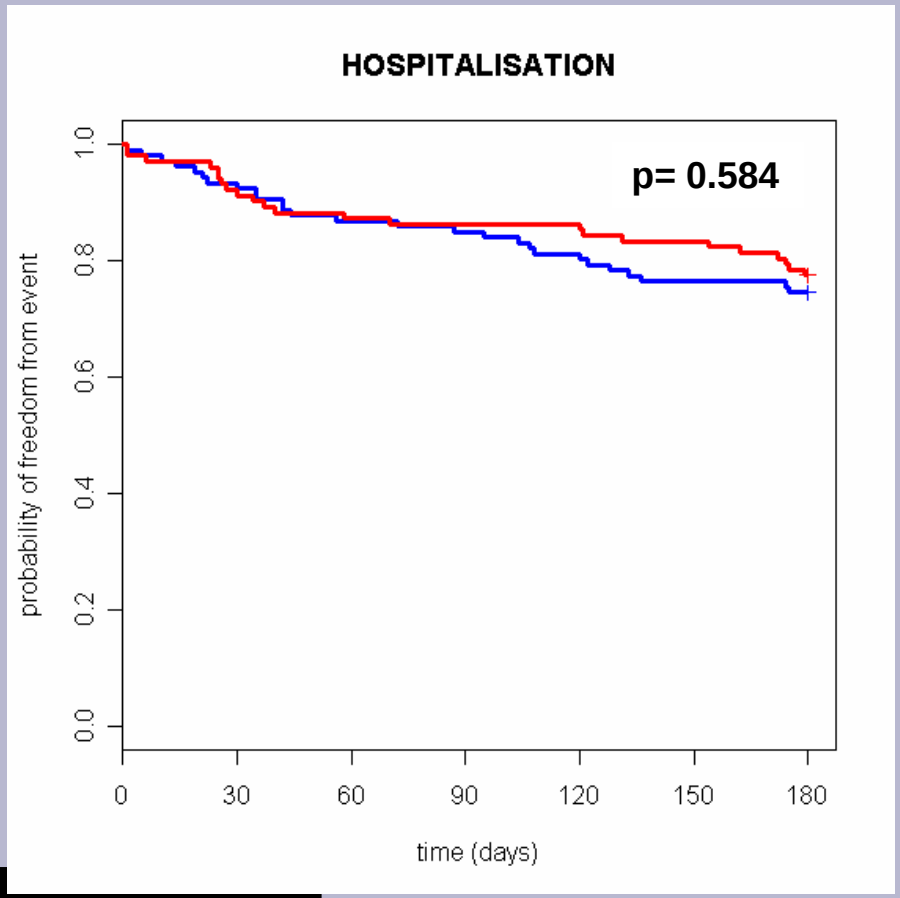
Laboratory and Lung-function Outcome at Long-Term Follow-up

Symptom score	47 ± 14	30 ± 16	24 ± 16	45 ± 16	27 ± 16	23 ± 15	0.394
FEV_1 L	0.88 ± 0.41	1.04 ± 0.48	1.07 ± 0.55	0.98 ± 0.41	1.01 ± 0.57	1.11 ± 0.57	0.068
FEV_1/FVC	43.8 ± 11.2	47.8 ± 14.7	48.0 ± 16.1	48.2 ± 12.9	51.8 ± 14.4	50.1 ± 13.5	0.215
CRP (mg/L) Median (IQR)	16 (5-53)	5 (2-16)	2 (1-9)	22(7-62)	7 (2-19)	4 (2-10)	0.856

Stolz D et al, CHEST, in press

Long-term Outcome – Time to Next Exacerbation





Procalcitonin-group

Standard-group

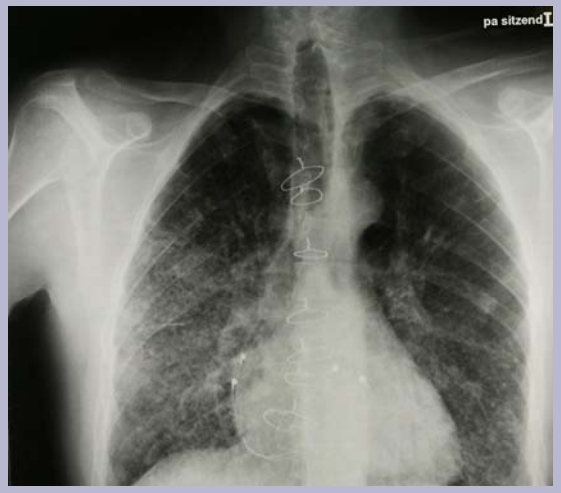
Stolz D et al, CHEST, in press

Prognosis in Patients with High and Low PCT Values on Admission

Characteristics	Procalcitonin < 0.25 ng/ml	Procalcitonin ≥ 0.25 ng/ml	p-value
Hospital stay <24 hours %	27.2%	3. 2%	0.004
Length of hospital stay in days	15 (9.5-20)	17.5 (9.5-24)	0.002
Need for ICU stay %	5.9 %	25.8%	0.001
Death during hospitalization %	2.2%	6.5%	0.211
Death within 6 months %	6.6%	16.1%	0.058

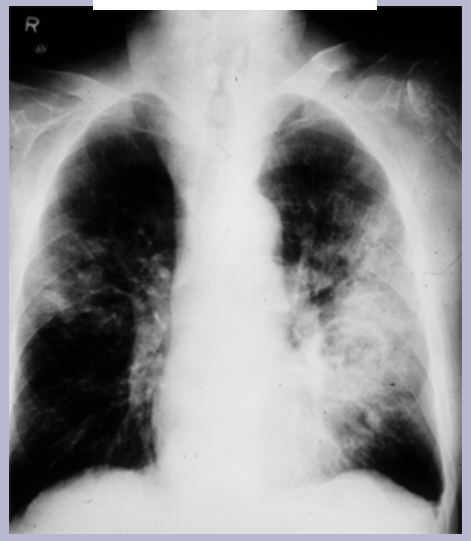
Verification of Clinical Diagnosis by Integrating the PCT Measurement into Diagnostic Assessment

Other cause



- **History: Cough, Dyspnea**
- **T: 37.6°C**
- **CRP: 119 mg/L**
- **PCT: 0.14 ng/ml**
- **Dx**

Infection



- **Hx: Cough, productive Sputum**
- **T: 38.3°C**
- **CRP: 250 mg/L**
- **PCT: 4.2 ng/ml**
- **Dx:**

Müller B. , personal communication

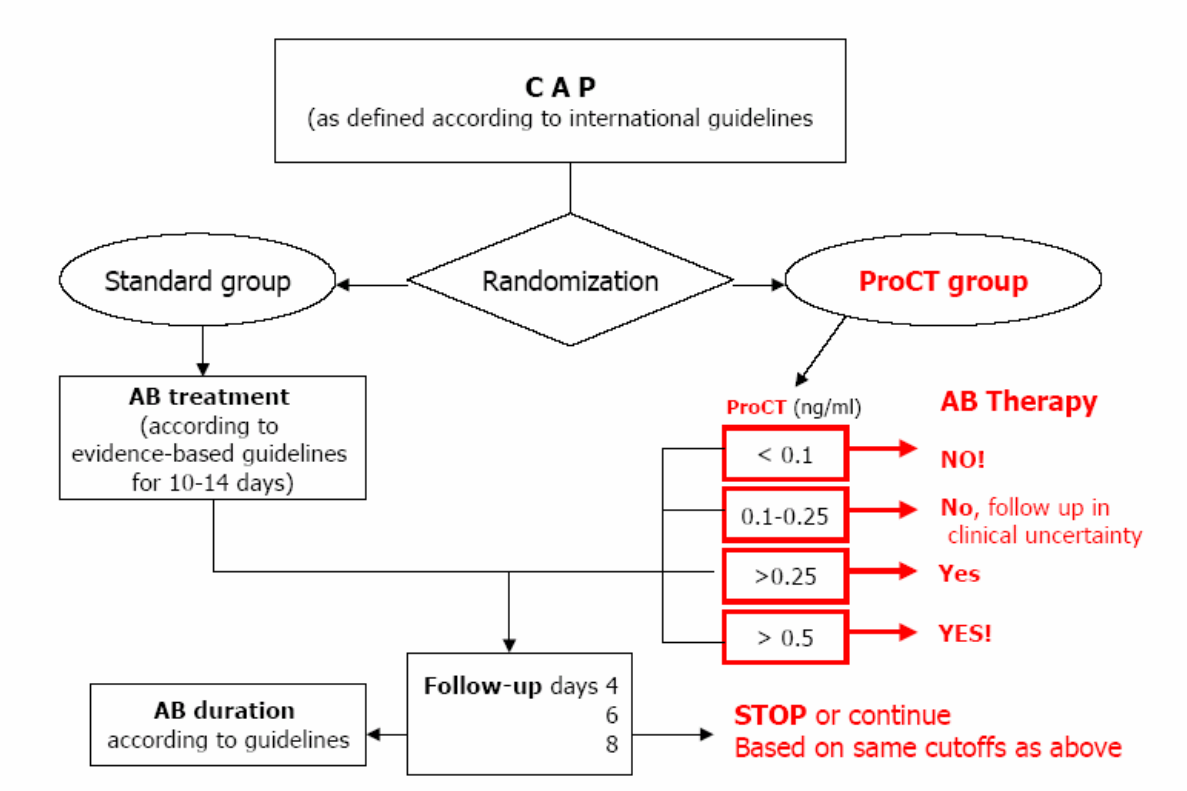
CAP: Diagnosis and Treatment

- **Duration of ABX treatment** is empiric (~ 14 days) – no data for optimal duration
- Shorter duration (7 days has been shown to give same result)
- **PCT could be used to improve accuracy of dx and determine length of treatment**
  - Reduce days of treatment -> reduce costs for AB
  - Reduce the risk for increasing antibiotic resitancy

ProCAP –Study:

Dx and guidance of Ab Rx in patients with bacterially induced CAP

Study Design

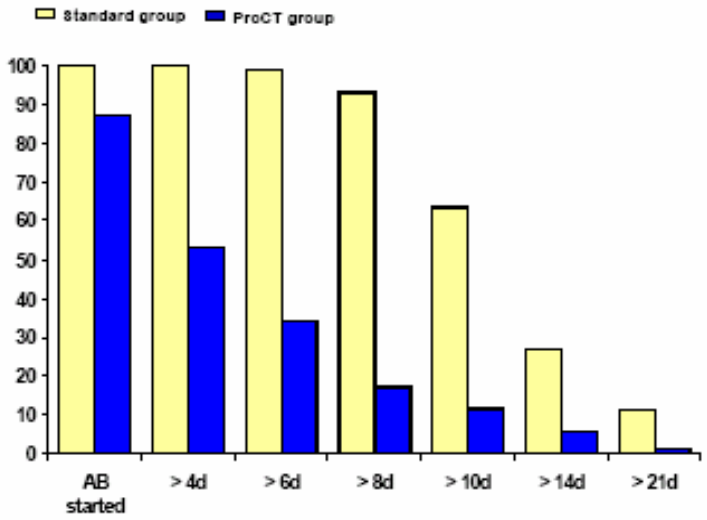


Christ-Crain et al., ISICEM Brussels 2005

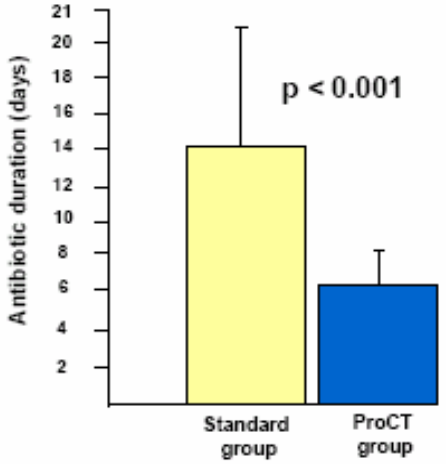
Procalcitonin guidance safely shortens antibiotic treatment in community acquired pneumonia
The "ProCAP"- Study

M. Christ-Crain, D. Stolz, R. Bingisser, C. Müller, J. Leuppi, M. Battegay, P. Huber, M. Tamm and B. Müller
Department of Internal Medicine, University Hospitals, CH-4031 Basel, Switzerland
christmj@uhbs.ch *

Antibiotic Use at days 0 to 21 in both groups



Mean antibiotic duration in both groups



Preliminary results (200 patients): Reduction of treatment days by ~50 %

*Christ-Crain et al., ISICEM Brussels 2005

Preliminary Result of ProCAP Study:

Monitoring of Abx therapy with PCT can be used to

- Decide on the **individual duration of treatment** according to the clinical situation of each patient

- Safely reduce the number of treatment days significantly (~50%)
  - Reduce costs
  - Reduce development of AB resistancy

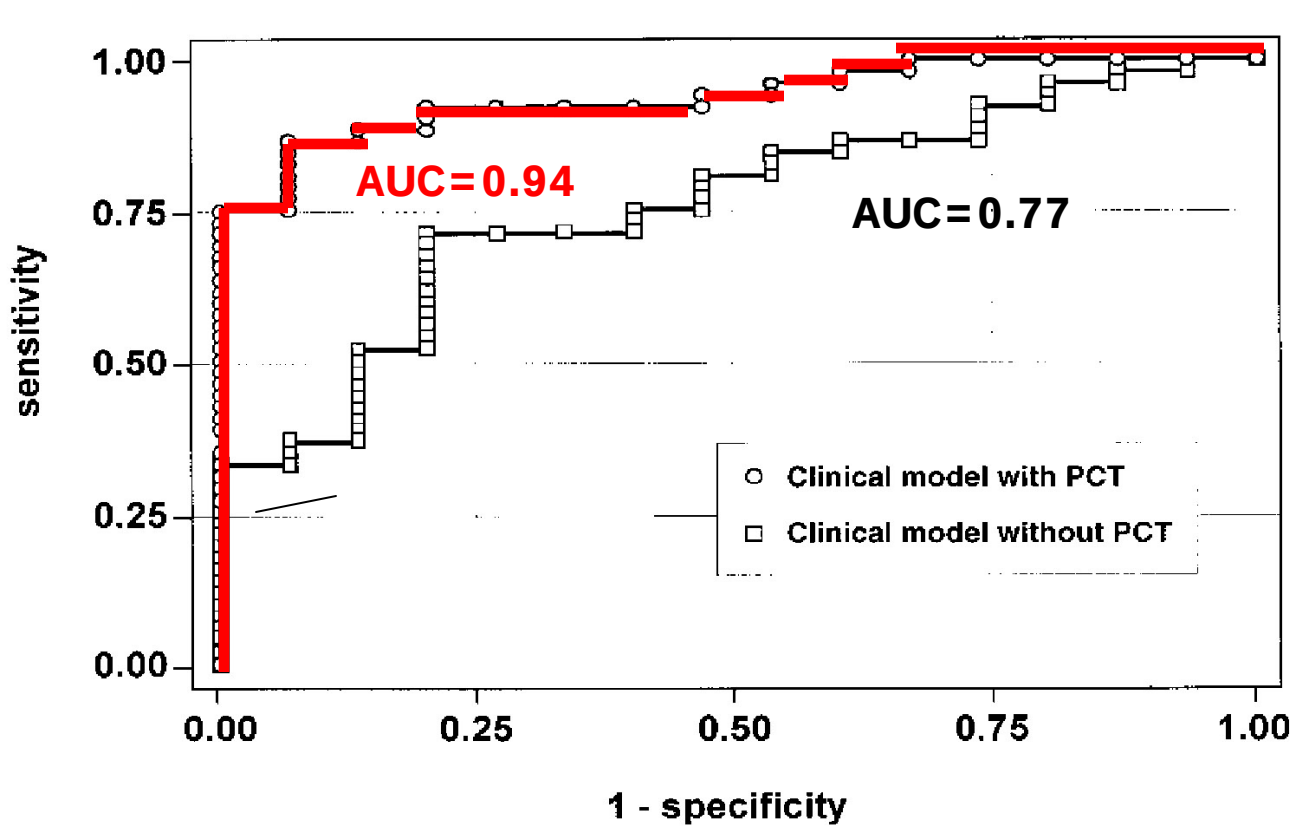
Can this PCT guidance of ABX Therapy also be used for VAP patients?

Ventilator-associated pneumonia (VAP)

- frequent complication of mechanical ventilation
- associated with prolonged hospital stay
- High ICU mortality

Early identification of patients at high risk for death or VAP recurrence may provide an opportunity to change the treatment strategy to improve outcome.

PCT Significantly Improves the Accuracy of Clinical Diagnosis

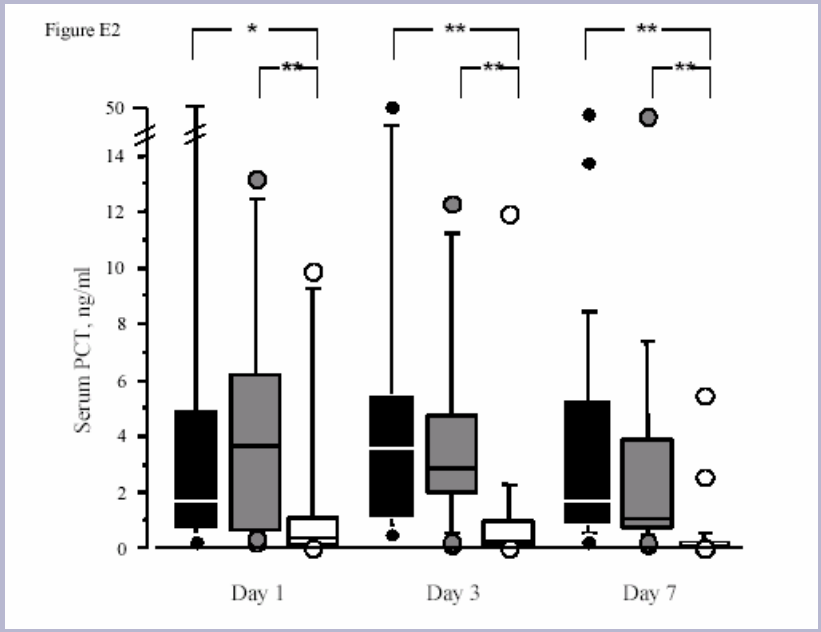


In contrast: IL-6, IL-8 or CRP did **not** have any impact on the accuracy of clinical diagnosis

Harbarth S. Am J Respir Crit Care Med 2001

PCT as Prognostic Marker of Therapeutic Failure in VAP Patients

Kinetics of serum procalcitonin in patients who died (•), had pulmonary and/or extrapulmonary infection recurrence (•) or had favorable outcome (•) from day 1 to day 7.
*p < 0.05
**p < 0.001



PCT values > 0.5 ng/ml on day 7 predict treatment failure
(AUC 0.9; sensitivity 90%, specificity 88%; odds ratio 64.2)

Luyt et al., AJRCCM 2004

1229 patients included in LRTI studies

ProResp: Patients with LRTI in the ED
(Lancet 2004, N=243)

ProCAP: Hospitalized patients with CAP
(AJRCCM, 2006, N=302)

ProCold: Patients with AECOPD in the ED
(Chest, 2007, N=226)

PARTI: Patients with ARTI in primary care,
(submitted, N= 458)

PCT Release in the Absence of Infection

- **Newborn < 48hr** -> increased PCT-values (physiological peak)
- **Primary inflammation syndrome following trauma:** multiple trauma, extensive burns, post major surgery (cardiac, transplant, abdominal)
- **Treatment that acts upon the proinflammatory CK cascade** (OKT3, injection therapy TNFα, IL-2, anti-lymphocyte globulins)
- **Certain cancers** (medullary CT-cell cancers of the thyroid, pulmonary small-cell carcinoma and bronchial carcinoma)
- **During prolonged circulatory failure** (prolonged cardiogenic shock, haemorrhagic shock, thermal shock)

Use of Procalcitonin as a Biomarker for Diagnosis Sepsis in Patients in the ICU

Aditi Patel D.O
Eric Gluck MD FCCP
Susan Dawson MT(AS)
Tony Ocasio CLS(CMS)

Procalcitonin

- TNF-alpha and Interleukins IL-1β, IL-6 and IL-8.
  - Peaks within 3 hours
  - Even if there is on-going infection it is undetectable within the blood in 24 hours

- CRP
  - Very non-specific for sepsis and is elevated in and ICU patient for many other inflammatory conditions.

- Procalcitonin:
  - Increases within 12 hours of initial systemic infection
  - Half life of 24-30 hours

Reason for Study

- The present study is to determine whether in a general cohort of ICU patients Procalcitonin levels have sufficient sensitivity and specificity to predict sepsis in pts.

Current Accepted Definitions of Sepsis

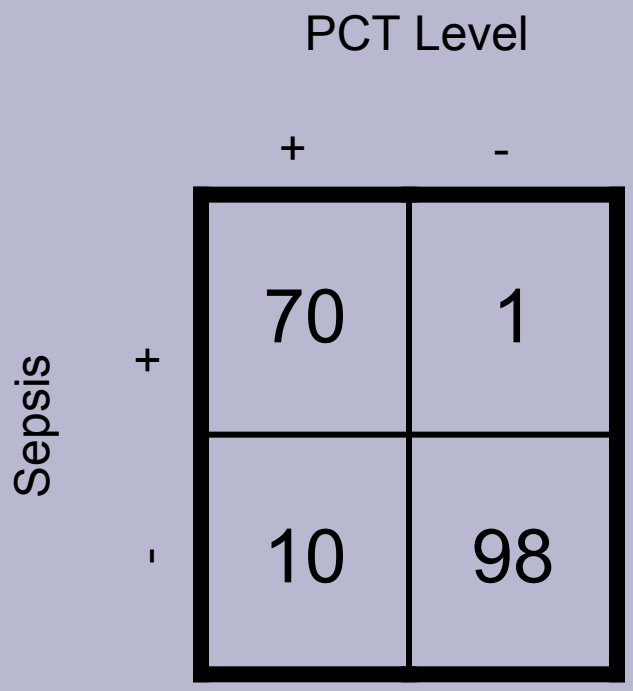
- The SIRS criteria that was used was two or more of the following:
  - Temperature >38ºC or <35ºC
  - Heart rate >90 beats/min
  - Respiratory rate >20 breaths/min or PaCO2 <32 mmHg
  - WBC >12,000 cells/mm3
    - <4000 cells/mm3
    - or >10 percent immature (band) forms
- Sepsis includes pts that have clinical signs of SIRS and a definite site or highly probable site of infection through blood cultures, sputum cultures, urine culture, or any other culture.
- Septic Shock is severe sepsis associated with hypotension that is not responsive to 3L of isotonic solution plus end organ dysfunction

Methods

- Over a 5-month period, patients staying in the ICU for more than 24 hours were consecutively enrolled in the study irrespective of initial diagnosis.
  - post op patients were excluded
- Daily blood samples were obtained for the measurement of PCT. The SIRS criteria was assessed and recorded daily.
- In phase I of the trial a total of 49 pts were studied, 23 had a single level obtained on the day of admission and the rest had daily levels obtained. In phase II of the trail, not reported in our abstract, an additional 154 pts were studied with daily PCT levels.
- PCT levels were run using the proprietary assay Brahms.
- At the end of the study period each pt was evaluated for the presence of sepsis or sirs, using the previously defined criteria, by an investigator who was blinded to the values of PCT for the pt.

Results For Phase I and II

- PCT plasma levels below 0.5ng/mL have been shown to be physiologic, and in this situation infection is unlikely.
- While PCT levels above 2ng/mL are associated with increased likelihood of sepsis.
- Total Number of Patients n=179



Analysis for all Patients

Standard formulas were used to calculate sensitivity, specificity, positive predictive values, negative predictive value, and positive and negative likelihood ratio's.

- Sensitivity: 99%
- Specificity: 91%

- Positive Predictive Value: 0.88
- Negative Predictive Value: 0.99

- Positive Likelihood Ratio: 11
- Negative Likelihood Ratio: 0.01

Analysis

- Patients were further analyzed based upon which criteria they met:
  - No SIRS, SIRS, Sepsis, or Septic Shock. (Figure 2 and 3)

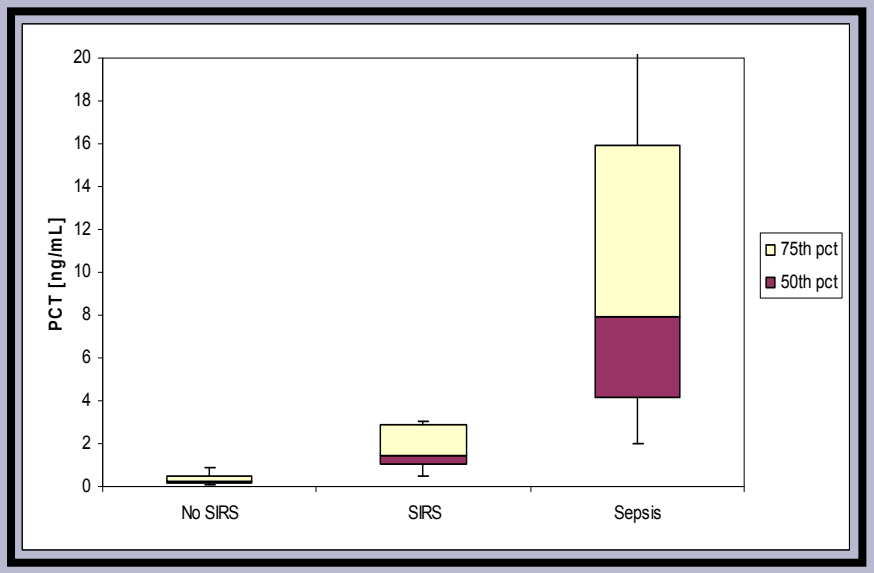


Figure 2. Comparison of procalcitonin levels in patient with No SIRS, SIRS and Sepsis

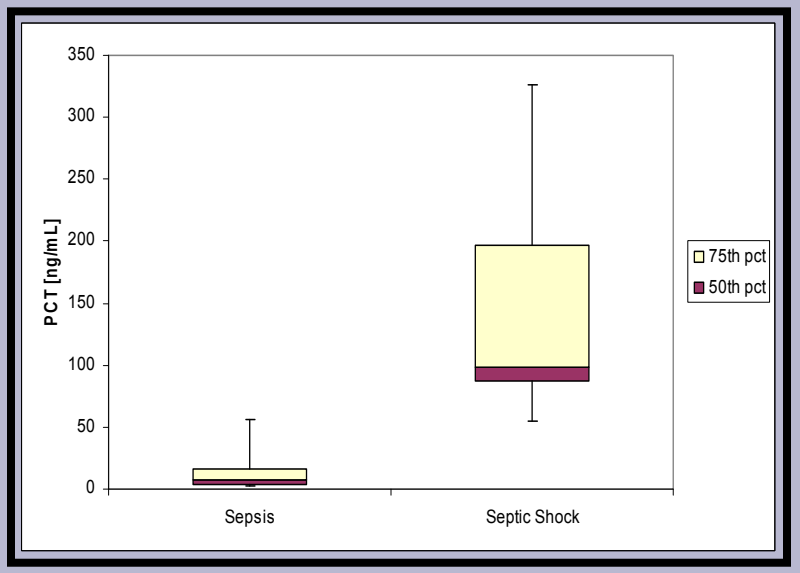


Figure 3. Comparison of procalcitonin levels in Sepsis vs. Septic Shock.

Results

- Of the total number, 9 patients in phase I and 15 patients in phase II were found to have intermediate levels between 0.5ng/mL to 2ng/mL and were not statistically evaluated This represents 12% of the pts enrolled in the study.

- These patients either had chronic infections such as positive chronic urine or wound cultures, major trauma or major burn but no signs of systemic infection

Discussion

- PCT appears to be a sensitive and specific biomarker for the presence and absence of sepsis in a mixed cohort of pts admitted to the ICU.

- As evidenced by the NPV patients with PCT levels of <0.5ng/mL could be excluded from having sepsis with a high degree of certainty

- Intermediate levels between 0.5ng/mL to 2ng/mL appear to require more clinical interpretation.

Discussion

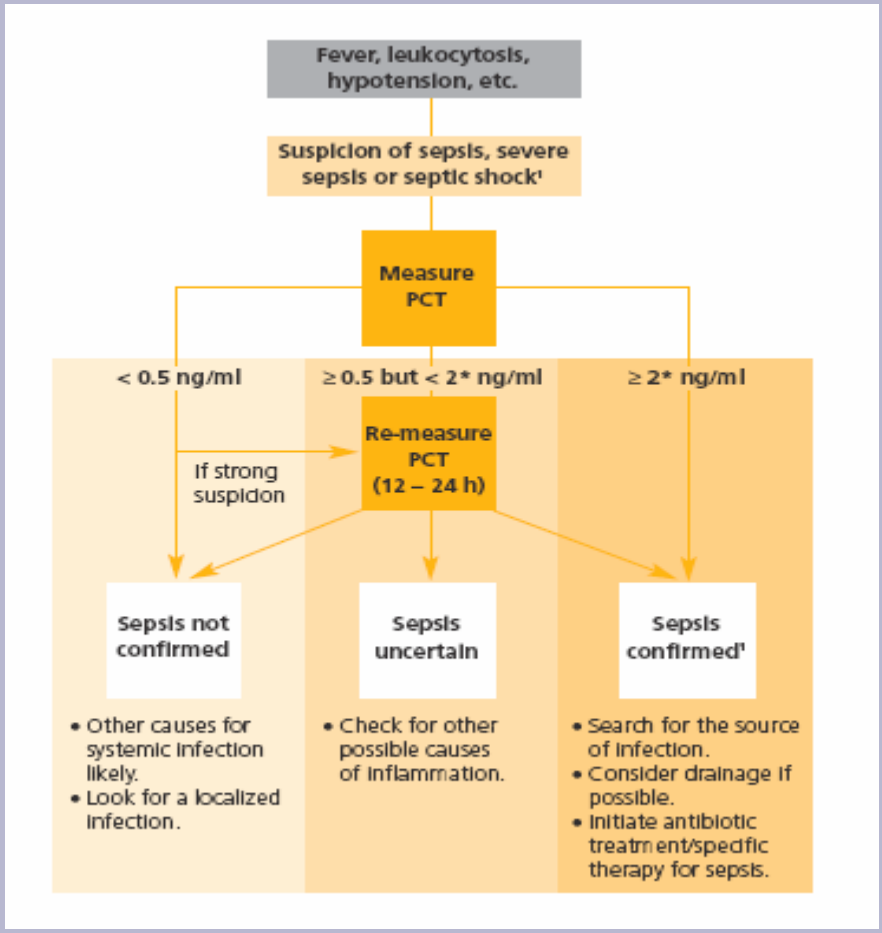


Figure 4. Flow chart of approach to drawing PCT levels in ICU patients.

Discussion

- Negative PCT levels virtually exclude the presence of bacterial or fungal infection
- Positive PCT levels suggest strongly the presence of infection with an acceptable false positive rate.
- Intermediate levels require clinical correlation but are only present in a small percentage of ICU admissions.

Summary of available data on PCT and Rx of LRTI

	Use of PCT	Proven by clinical study?
LRTI	• **Diagnosis** of clinically relevant bacterial infections of the lower respiratory tract which require **AB** treatment	**Efficacy**
CAP	• Guidance of **duration of AB therapy**	**Efficacy**
VAP	• **???**	

The End

Questions?