Ασθενής με οξέως επηρεασμένους βιοδείκτες χωρίς κλινικά σημεία λοίμωξης στη ΜΕΘ: ανάλυση περίπτωσης

Ηρακλής Τσαγκάρης

Καθηγητής Πνευμονολογίας-Εντατικής Θεραπείας ΕΚΠΑ

Biomarkers

- Characteristic that is objectively measured and evaluated as an indicator of normal biological process, pathogenic process, or pharmacologic response to a therapeutic intervention

- Usefulness is evaluated by:
  - Capacity to provide timely information beyond what is readily available from routine physiologic and clinical data (Speed + Accuracy)
  - Sensitivity and specificity

Potential Role(s) for Biomarkers

- Identify patient with ↑ probability of disease, adverse outcome, or benefit from intervention
- Identify presence or absence of pathologic state or process
- Aid in risk stratification/prognosis
- Monitor response to an intervention or treatment
- Serve as surrogate endpoint

Biomarkers in Sepsis

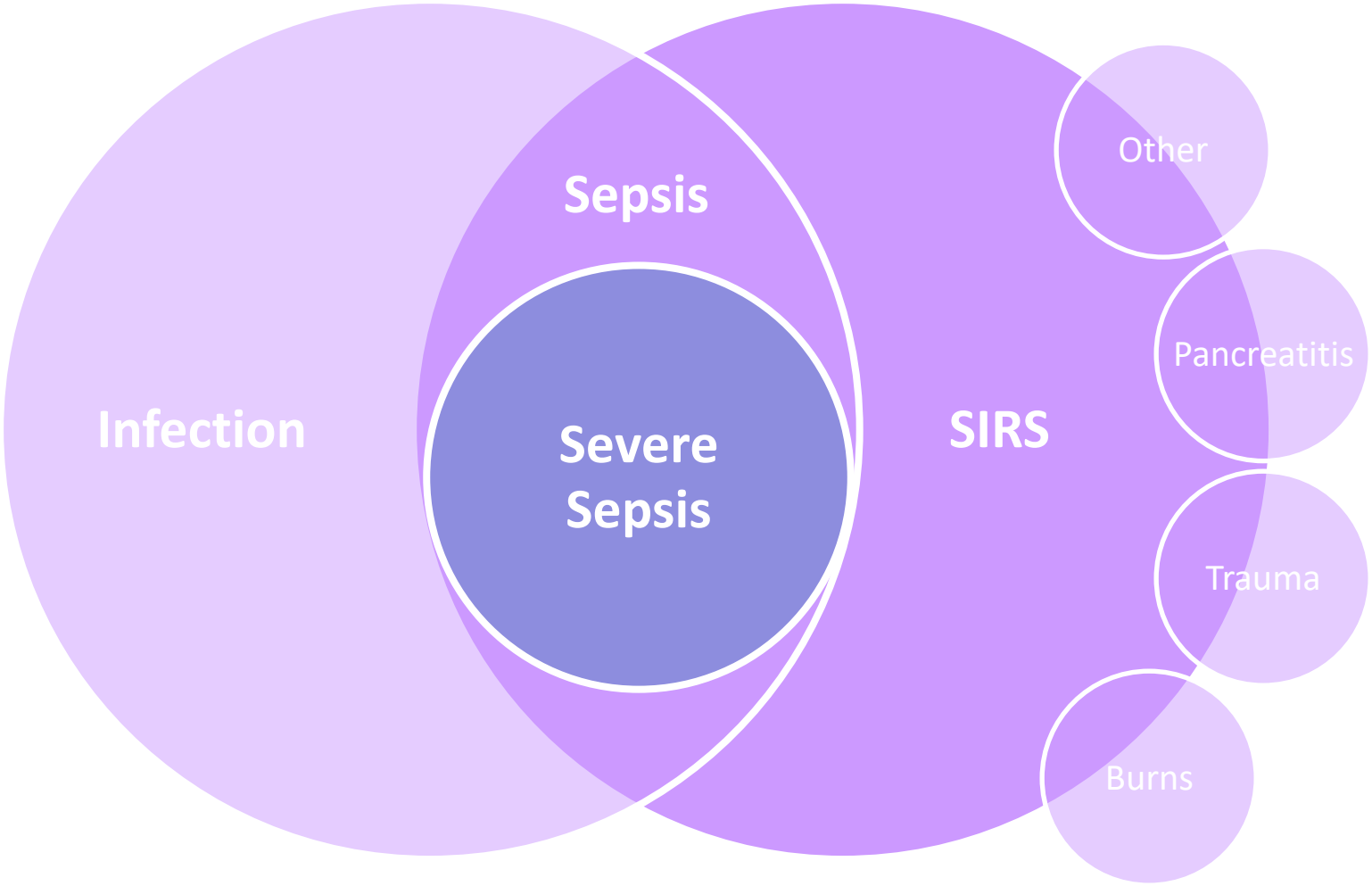
- To date >150 different biomarkers have been proposed or evaluated for their use in diagnosis, management, or prognostic ability in patients with sepsis and septic shock.
- Many biomarkers involve components of the innate or adaptive immune system or the response seen in patients with sepsis or SIRS.

Biomarkers in Sepsis Diagnosis

Table 3. "Sepsis-3" definitions and identifying features, adapted from Singer et al. [22].

Sepsis	Septic Shock
Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.	Septic shock is a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.
Organ dysfunction can be identified as an acute change in total SOFA score greater or equal to 2 points consequent to the infection.	Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors and having a serum lactate level > 2 mmol/L despite adequate volume resuscitation.

Relationship Between SIRS, Sepsis and Severe Sepsis



Diagnostic Criteria for Sepsis

General Variables

- SIRS/Sepsis Criteria
- Altered Mental Status
- Significant Edema - Positive Fluid Balance
- Hyperglycemia in Absence of DM

Inflammatory Variables

- CRP > 2 SD above Nl
- PCT > 2 SD above Nl

Hemodynamic Variables

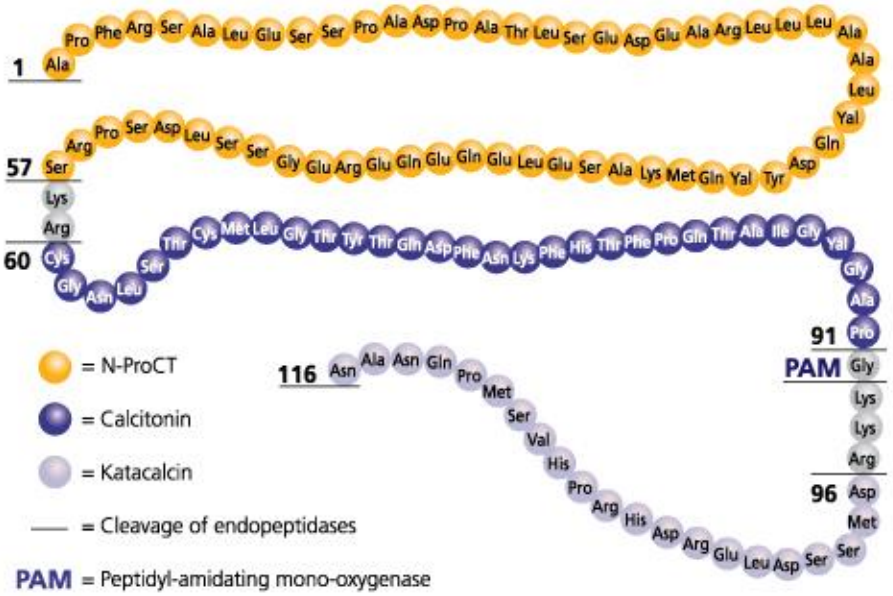
- Arterial Hypotension
- SvO2 > 70%
- Cardiac Index > 3.5 L/min/m^2

Procalcitonin as Biomarker

- Badly Named
- Misunderstood

Procalcitonin - Structure

- Procalcitonin is a 116 amino-acid peptide - Precursor of the hormone Calcitonin

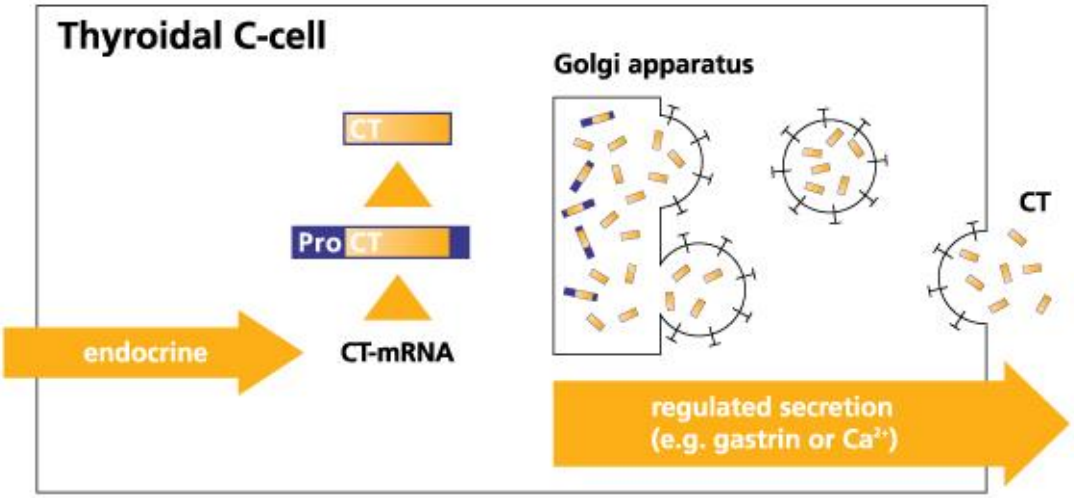


9

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)

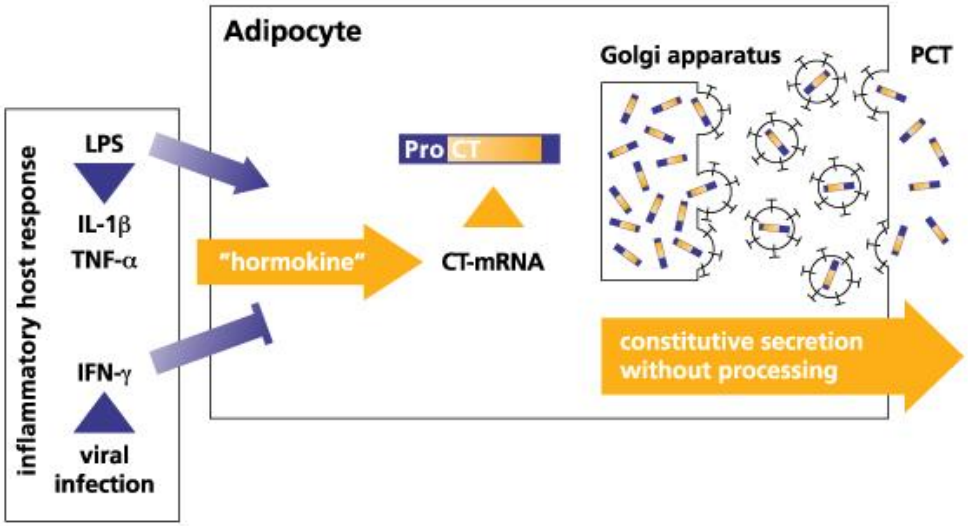


10

Role of PCT in sepsis

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

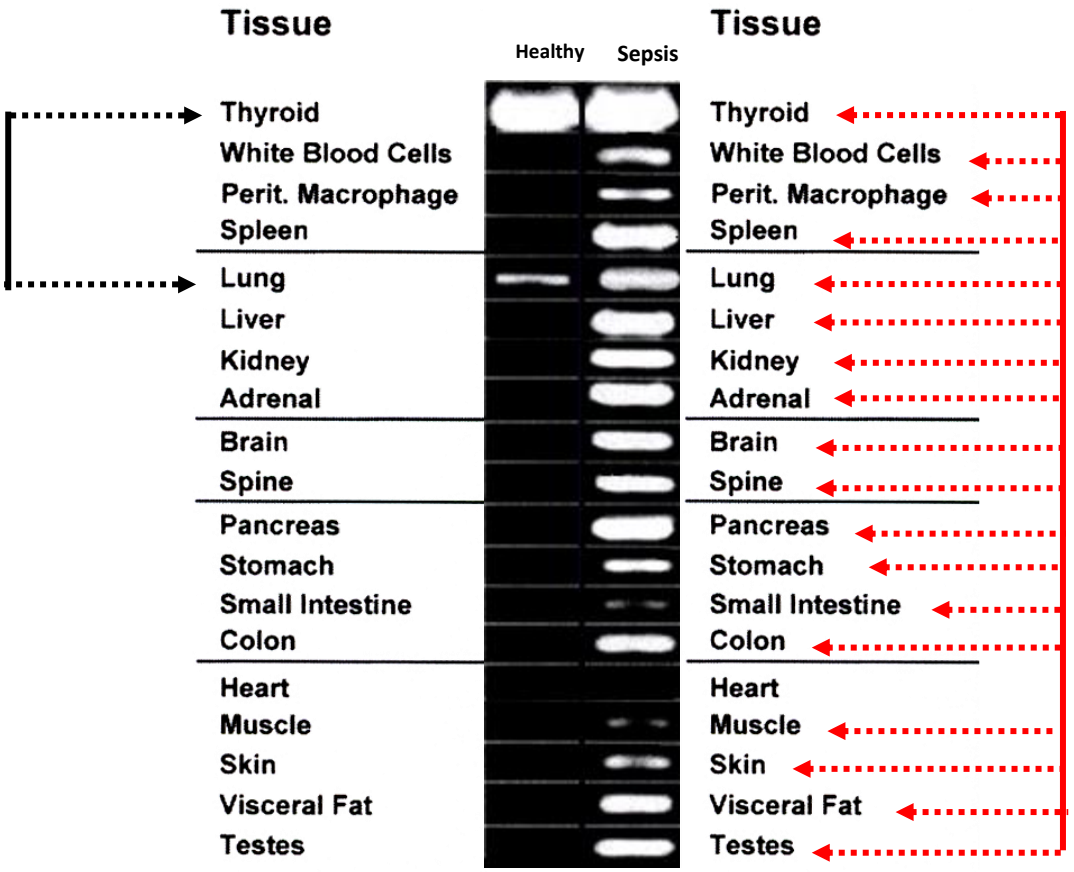
- Alternative (cytokine-like) pathway during sepsis: 'Hormokine'
- Bacterial toxins (gran +/gram-) and cytokines stimulate production of Procalcitonin in all parenchymal tissues
- This process can be attenuated or blocked during viral infection by interferones.
- Non endocrine tissue ie Liver, Lung,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



11

A hormone that becomes a cytokine…

Calcitonin:



PCT:

12

Evolutionary Basis

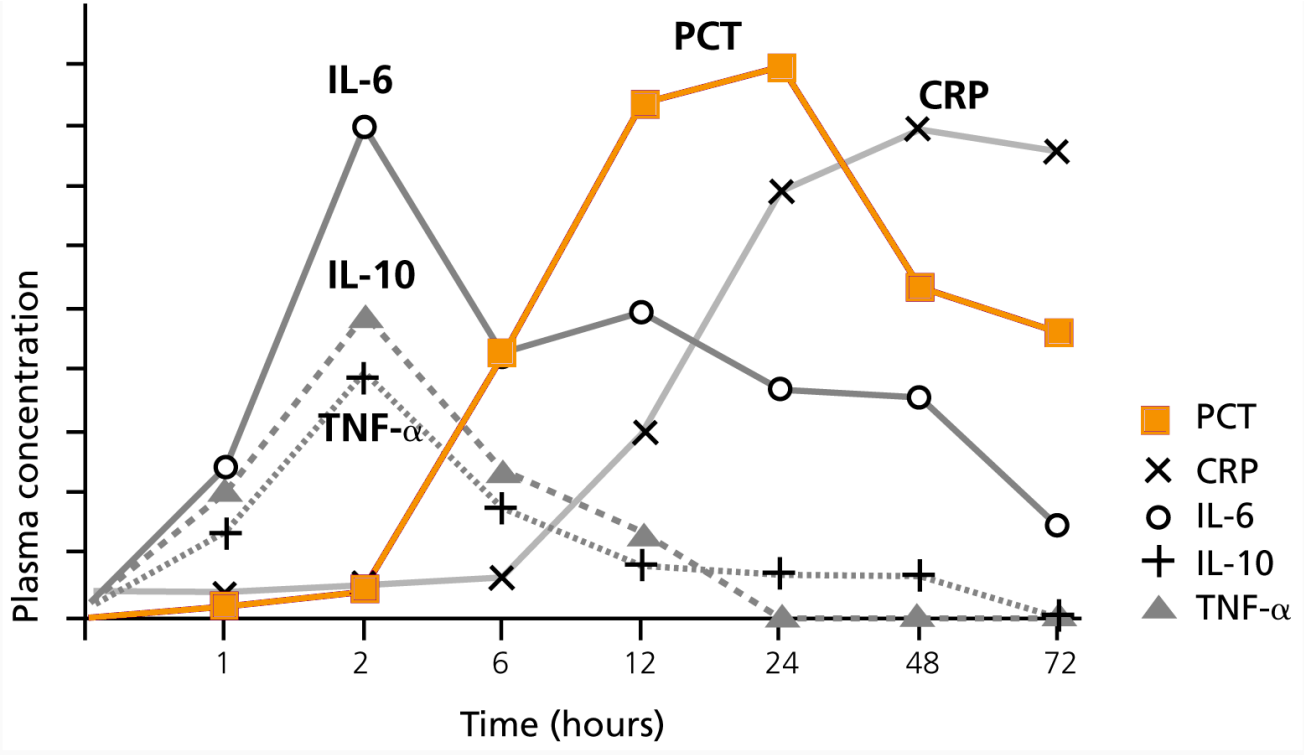
- Has bactericidal properties
- Present in all mammals tested
- Probably was an early host defense against infection
- Replaced by more robust defenses such as antibody system and enhanced leukocyte defenses
- Most important, perhaps, in defending the body against invasion of bacteria during feeding.

13

- 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

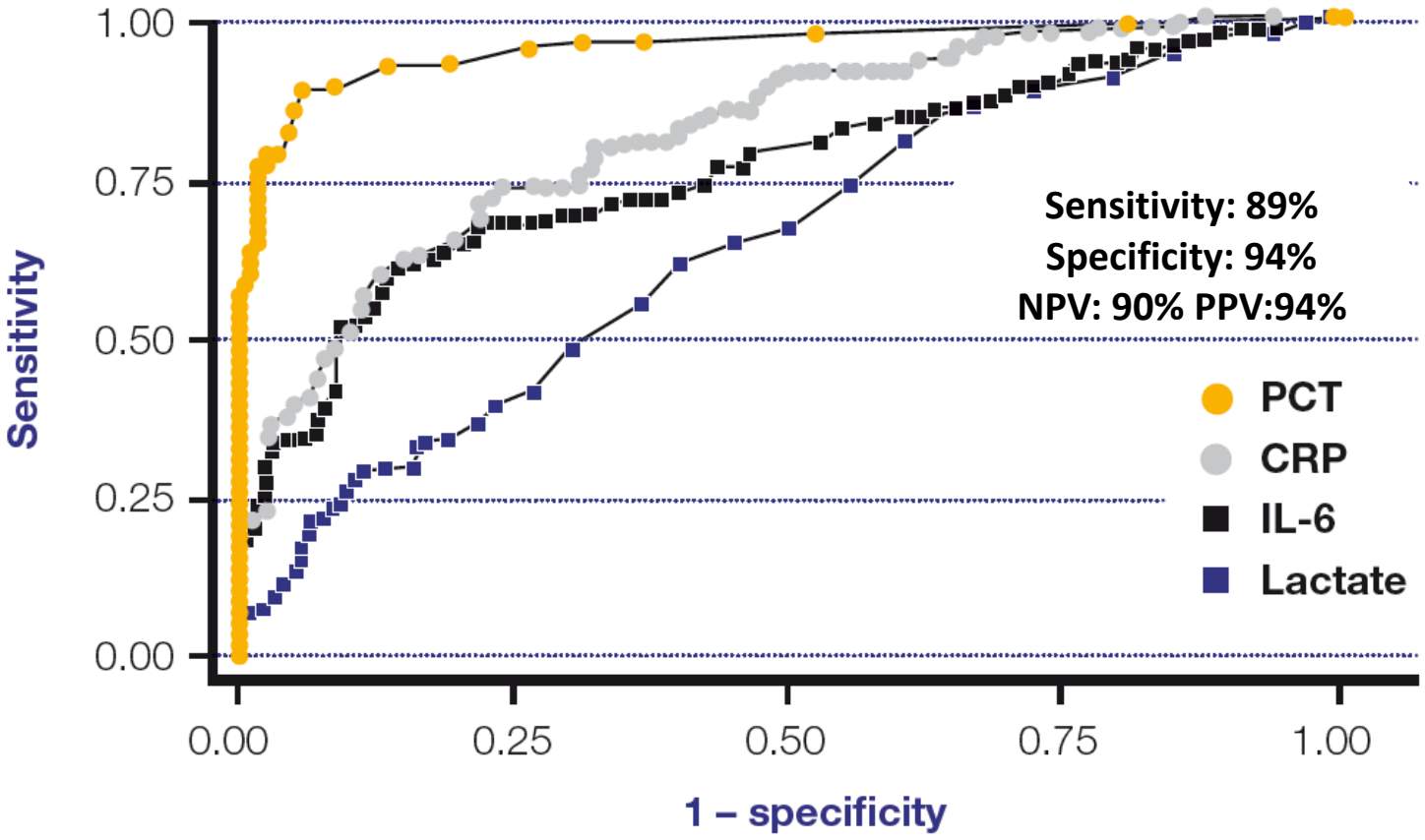
14

PCT kinetics provide important information on prognosis of sepsis patients



- Clinical symptoms alone are often insufficient for early and accurate diagnosis
- PCT levels, can be observed within 3-6 hours after an infectious challenge with a peak - up to 1000 ng/ml - after 6-12 hrs. Half-life: ~24hrs
- Specific to bacterial origin of infection and reflects the severity of the infection

Adding PCT results to clinical assessment improves the accuracy of the early clinical diagnosis of sepsis



- PCT levels accurately differentiate sepsis from noninfectious inflammation*
- PCT has been demonstrated to be the best marker for differentiating patients with sepsis from those with systemic inflammatory reaction not related to infectious cause

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)

17

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.

18

Current Accepted Definitions of Sepsis

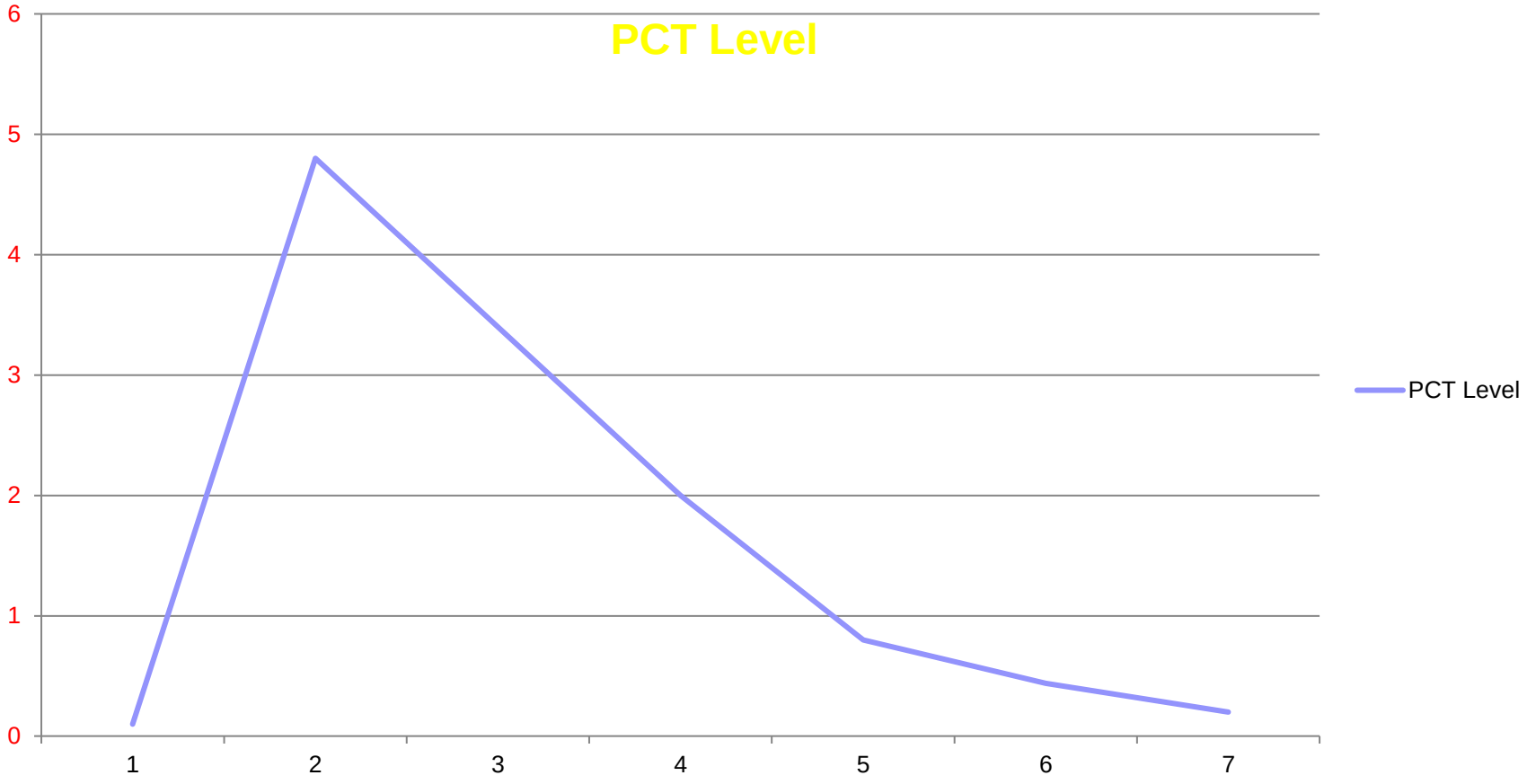
- The SIRS criteria that was used was two or more of the following:
  - Temperature >38ºC or <35ºC
  - Heart rate >90 beats/min
  - Respiratory rate >20 breaths/min or PaCO2 <32 mmHg
  - WBC >12,000 cells/mm3
    - <4000 cells/mm3
    - or >10 percent immature (band) forms
- Sepsis includes pts that 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

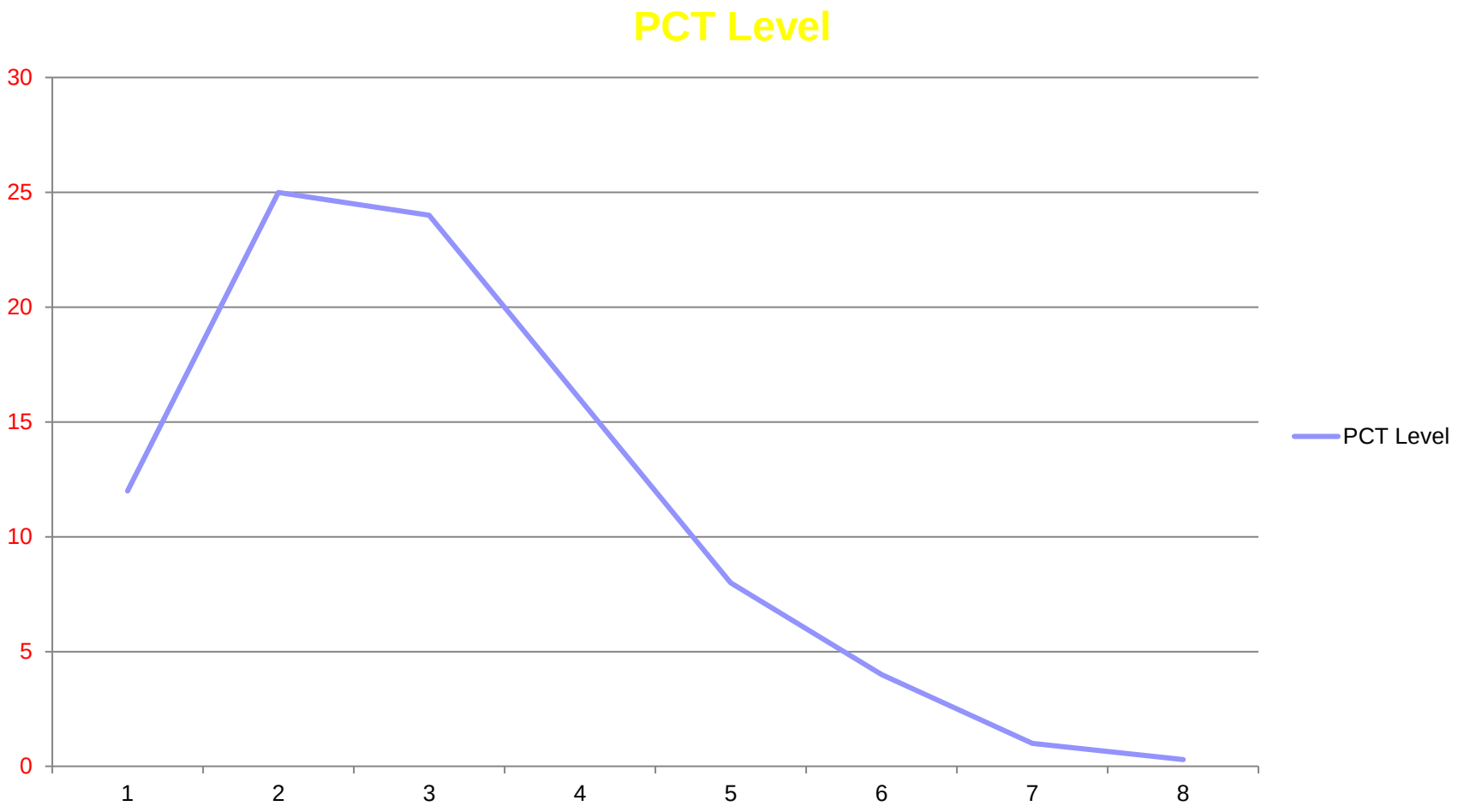
19

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.

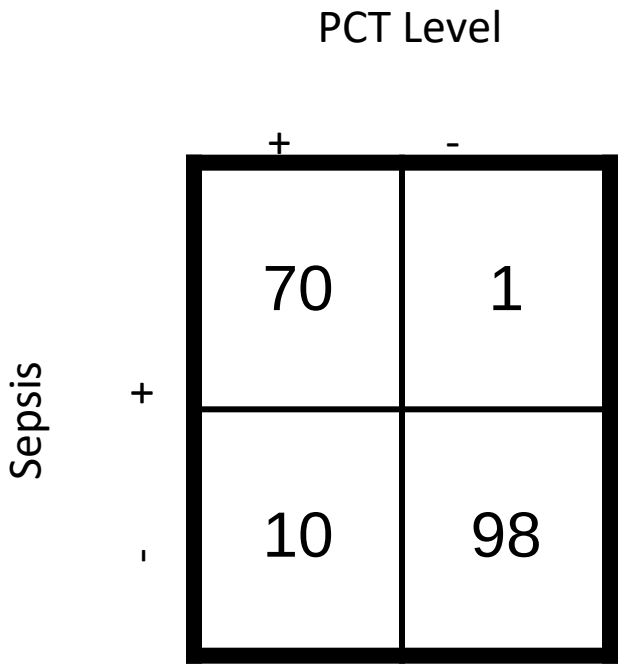
20


PCT Level
6
5
4
3
2
1
0
1
2
3
4
5
6
7
PCT Level


PCT Level
30
25
20
15
10
5
0
1
2
3
4
5
6
7
8
PCT Level

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



23

Analysis for all pts.

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

24

Analysis

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

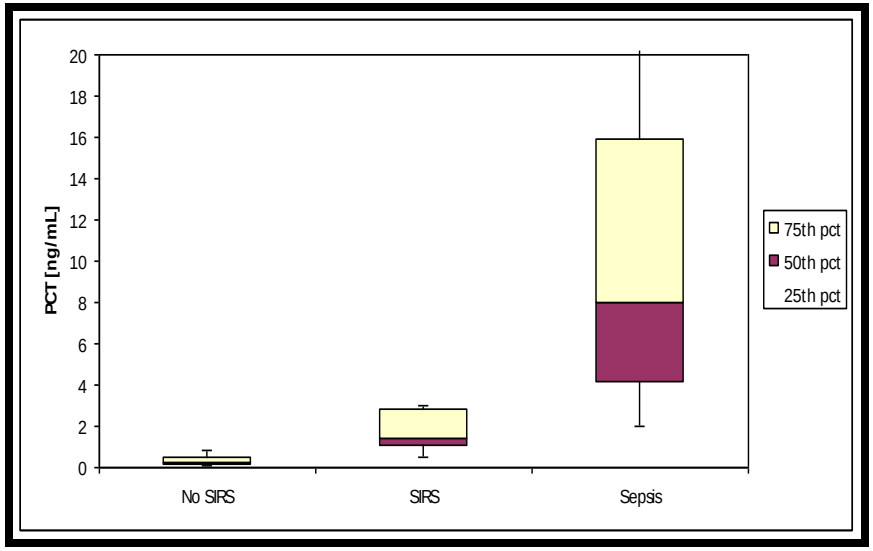


Figure 2. Comparison of procalcitonin levels in patient with No SIRS, SIRS and Sepsis

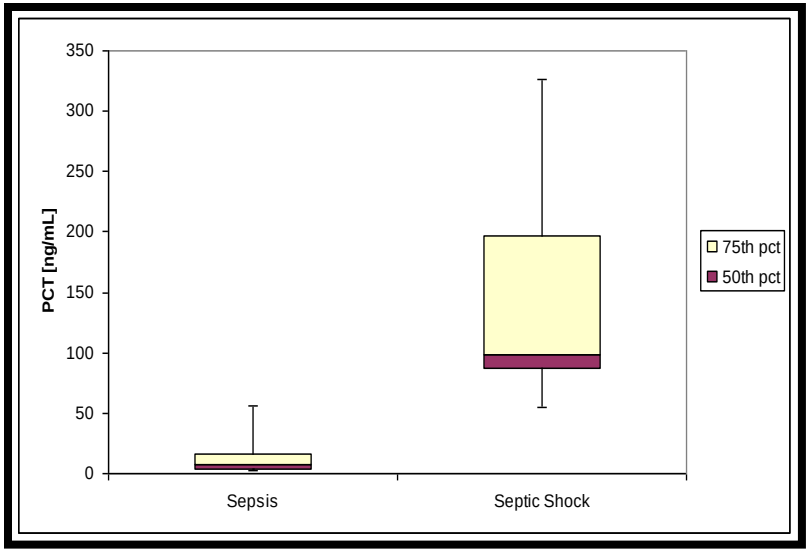


Figure 3. Comparison of procalcitonin levels in Sepsis vs. Septic Shock.

25

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.

26

Effect of Procalcitonin-Based Guidelines vs. Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: The ProHOSP Randomized Controlled Trial

Philipp Schuetz, MD; Mirjam Christ-Crain, MD;
Robert Thomann, MD; Claudine Falconnier, MD;
Marcel Wolbers, PhD; Isabelle Widmer, MD;
Stefanie Neidert, MD; Thomas Fricker, MD;
Claudine Blum, MD; Ursula Schild, RN;
Katharina Regez, RN; Ronald Schoenenberger, MD;
Christoph Henzen, MD; Thomas Bregenzer, MD;
Claus Hoess, MD; Martin Krause, MD; Heiner C. Bucher, MD;
Werner Zimmerli, MD; Beat Mueller, MD

Journal of the American Medical Association.
2009;302(10):1059-1066.

Overview

- **Unnecessary antibiotic use**
  - **Contributes to increasing bacterial resistance**
  - **Increases medical costs and the risks of drug-related adverse events**
- **Lower respiratory tract infections (LTRI)**
  - **Most frequent indication for antibiotic prescriptions in the Northwestern hemisphere**
  - **75% of patients are treated with antibiotics**
  - **Predominantly viral origin of infection**
- **Procalcitonin (PCT) algorithm**
  - **Reduced antibiotic use in patients with LTRIs**

Schuetz P et al. *J Am Med Assoc*. 2009;302(10):1059-66.

Overview

- **Objective**
  - **Examine whether a PCT algorithm can reduce antibiotic exposure without increasing the risk for serious adverse outcomes.**

Schuetz P et al. *J Am Med Assoc*. 2009;302(10):1059-66.

Study Design

- **Multicenter, noninferiority, randomized controlled trial**
- **Patients**
  - **Randomized to administration of antibiotics based on PCT algorithm**
  - **Cutoff ranges for initiating or stopping antibiotics (PCT group) or standard guidelines (control)**
  - **Serum PCT was measured locally**
- **Main Outcome Measures**
  - **Composite adverse outcomes of death, intensive care unit admission, disease-specific complications, or recurrent infection within 30 days**
  - **Antibiotic exposure and adverse effects from antibiotics**

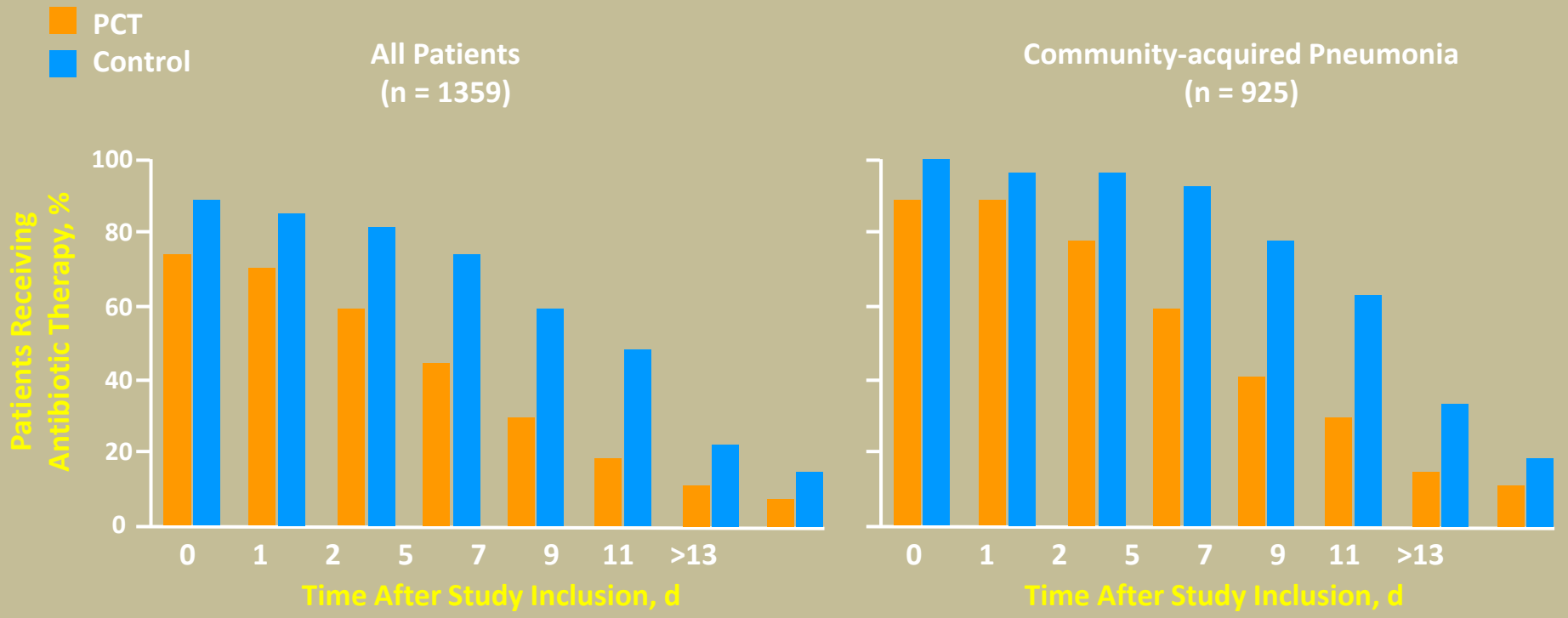
Schuetz P et al. *J Am Med Assoc*. 2009;302(10):1059-66.

Flow Diagram of Patients in Trial

1381 Randomized

687 Randomized to Receive Antibiotics Based on PCT Algorithm	**694 Randomized to Receive Antibiotics Based on Standard Guidelines**
16 Withdrew Informed Consent **1 Lost to Follow-up** **34 Died**	**6 Withdrew Informed Consent** **0 Lost to Follow-up** **33 Died**
636 Completed 30-d Interview	**655 Completed 30-d Interview**
671 Included in Primary Analysis **16 Excluded** **(Withdrew Informed Consent)**	**688 Included in Primary Analysis** **6 Excluded** **(Withdrew Informed Consent)**

Antibiotic Exposure in Patients Receiving Antibiotic Therapy



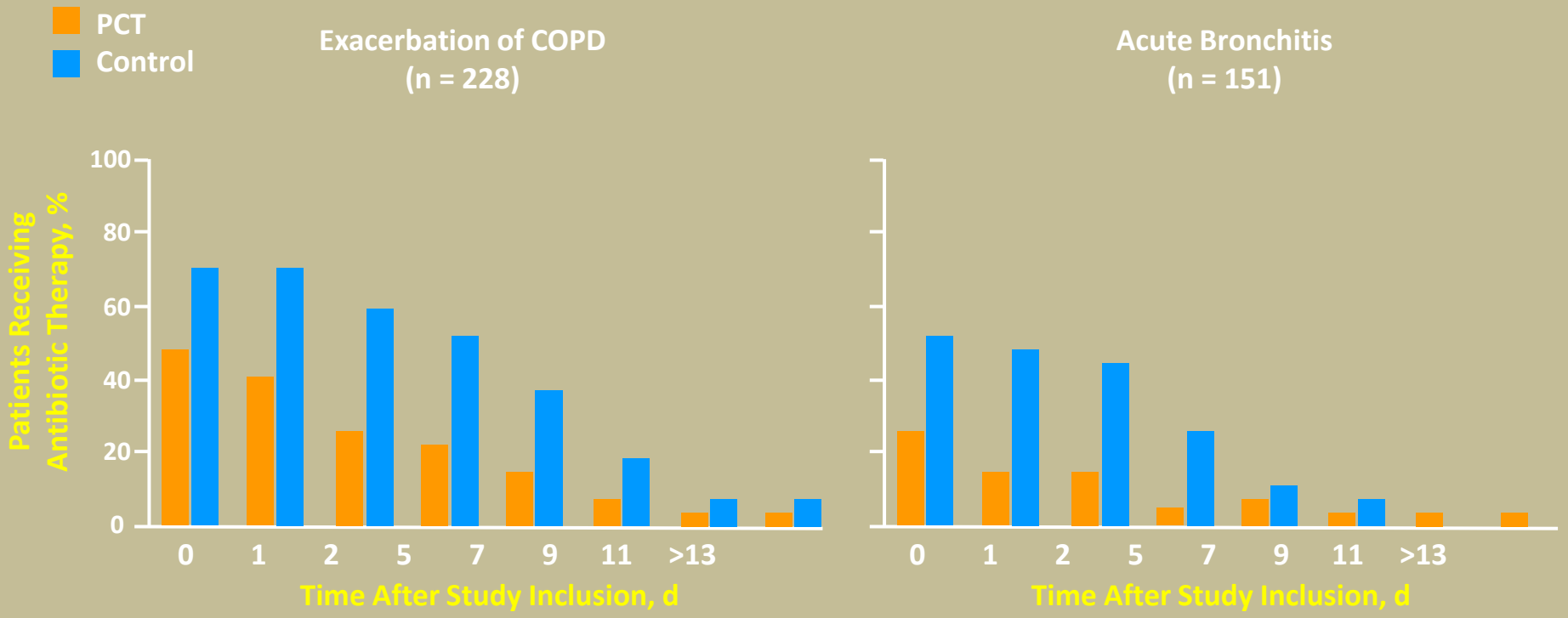
No. of Patients

PCT	506	484	410	306	207	138	72	46
Control	603	589	562	516	420	324	157	100

PCT	417	410	359	272	161	126	64	41
Control	461	453	444	428	361	292	146	91

Schuetz P et al. *J Am Med Assoc*. 2009;302(10):1059-66.

Antibiotic Exposure in Patients Receiving Antibiotic Therapy



No. of Patients

PCT	56	47	30	23	16	6	4	2
Control	79	78	67	56	40	20	5	4

PCT	16	11	9	3	3	1	1	1
Control	41	38	35	19	8	3	0	0

PCT: Procalcitoin
COPD: Chronic Obstructive Pulmonary Disease

Schuetz P et al. *J Am Med Assoc*. 2009;302(10):1059-66.

Procalcitonin (PCT) algorithm for stewardship of antibiotic therapy in patients with LRTI

< 0.1 µg/l	0.1 - 0.25 µg/l	>0.25 – 0.5 µg/l	>0.5 µg/l
Bacterial etiology very unlikely	Bacterial etiology unlikely	Bacterial etiology likely	Bacterial etiology very likely
NO antibiotics !	No antibiotics	Antibiotics yes	Antibiotics YES !

Control PCT after 6-24 hours

Initial antibiotics can be considered in case of:

- Respiratory or hemodynamic instability
- Life-threatening comorbidity
- Need for ICU admission
- PCT < 0.1 µg/l: CAP with PSI V or CURB65 >3, COPD with GOLD IV
- PCT < 0.25 µg/l: CAP with PSI ≥IV or CURB65 >2, COPD with GOLD > III
- Localised infection (abscess, empyema), L.pneumophilia
- Compromised host defense (e.g. immuno-suppression other than corticosteroids)
- Concomitant infection in need of antibiotics

Consider the course of PCT

If antibiotics are initiated:

- Repeated measurement of PCT on days 3, 5, 7
- Stop antibiotics using the same cut offs above
- If initial PCT levels are >5-10 µg/l, then stop when 80-90% decrease of peak PCT
- If initial PCT remains high, consider treatment failure (e.g. resistant strain, empyema, ARDS)
- Outpatients: duration of antibiotics according to the last PCT result:
  - >0.25-0.5 µg/l: 3 days
  - >0.5 - 1.0 µg/l: 5 days
  - >1.0 µg/l: 7 days

Conclusions

- **An algorithm with PCT cutoff ranges was noninferior to clinical guidelines in terms of adverse outcomes**
  - **Reduced antibiotic exposure**
  - **Reduced associated adverse effects**

- **In countries with higher antibiotic prescription rates PCT guidance may have clinical and public health implications**

Mortality in Sepsis: A New Standard

Trial Name	ProCESS	ARISE	ProMISe
Title	A Randomized Trial of Protocol-Based Care for Early Septic Shock	Goal-Directed Resuscitation for Patients with Early Septic Shock	Protocolised Management in Sepsis (ProMISe)
Location	U.S. 31 Emergency Departments	Australia/New Zealand 51 Emergency Departments	U.K. Multi-Center
Population	1935 adult subjects with septic shock (refractory hypotension or LA ≥ 4mmol/L)	1600 adult sepsis subjects with septic shock (refractory hypotension or LA ≥ 4mmol/L)	1260 adult sepsis subjects with septic shock (refractory hypotension or LA ≥ 4mmol/L)
Intervention	EGDT	EGDT	EGDT
Control	Protocol-Based Care (no CVC) Usual Care	Usual Care	Usual Care
Primary Outcome	60 Day Mortality	90 Day Mortality	90 Day Mortality
Primary Outcome Result (relative risk)	**EGDT 21% Protocol Based 18.1% Usual Care 18.9%**	**EGDT 18.6% Usual Care 18.8%**	**TBD**
Publication Date	May 2014	October 2014	Mar 2014
Journal	NEJM	NEJM	TBD

Adapted from:

Yealy DM et al. A Randomized Trial of Protocol-Based Care for Early Septic Shock. N Engl J Med 2014; 370:1683-1693.
Peake SL et al. Goal-Directed Resuscitation for Patients with Early Septic Shock. N Engl J Med 2014; 371:1496-1506.
Power GS et al., The Protocolised Management in Sepsis (ProMISe) trial statistical analysis plan. Crit Care Med; 2013 Dec;15(4):311-7.

Procalcitonin Algorithm in Critically Ill Adults with Undifferentiated Infection or Suspected Sepsis

- **Design:**
  - Multi Center (11 Australian ICUs), single-blinded, prospective, RCT
- **Population:**
  - 400 subjects with suspected bacterial infections/sepsis
- **Intervention:**
  - Universal cut-off of PCT (0.1ng/mL) to reduce antibiotic exposure
- **Primary Outcome:**
  - Time to antibiotic cessation at 28 days, hospital DC or death
  - Antibiotic free days

  ** 90% power calculated to determine a ***3.75 day*** difference between groups

- **Secondary Outcome:**
  - MAIN: number of antibiotic Daily Defined Dose (DDD)
- **Additional *a priori Outcomes:***
  - ICU & Hospital LOS and Mortality, all-cause 90-day mortality
  - Predictive value of initial PCT to determine site and sepsis severity, microbiologically confirmed infections within 72 hours.
  - Predictive value of baseline and serial PCT of mortality
  - Safety endpoints: readmission, emergence of resistant microorganisms, and number of algorithm violations

Shehabi Y et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or sepsis. Amer J Resp Crit Care Med 2014 Nov 15;190(10):1102-10

Primary & Secondary Outcome Results

Population	All Cohort (n=394)	PCT Guided (n=196)	Standard Care (n=198)	P Value
Primary Outcome				
Time to AB cessation (IQR)	10 (6-21)	9(6-20)	11(6-22)	0.58
AB free Days (IQR)	19 (9-22)	20(11-22)	17(7-22)	0.18
Secondary Outcome				
DDD, median (IQR)		1200 (500-3,000)	1500 (750-4000)	<0.001

Adapted from Shehabi Y et al. Procalcitonin algorithm in critically ill adults with undifferentiated infection or sepsis. Amer J Resp Crit Care Med 2014 Nov 15;190(10):1102-10

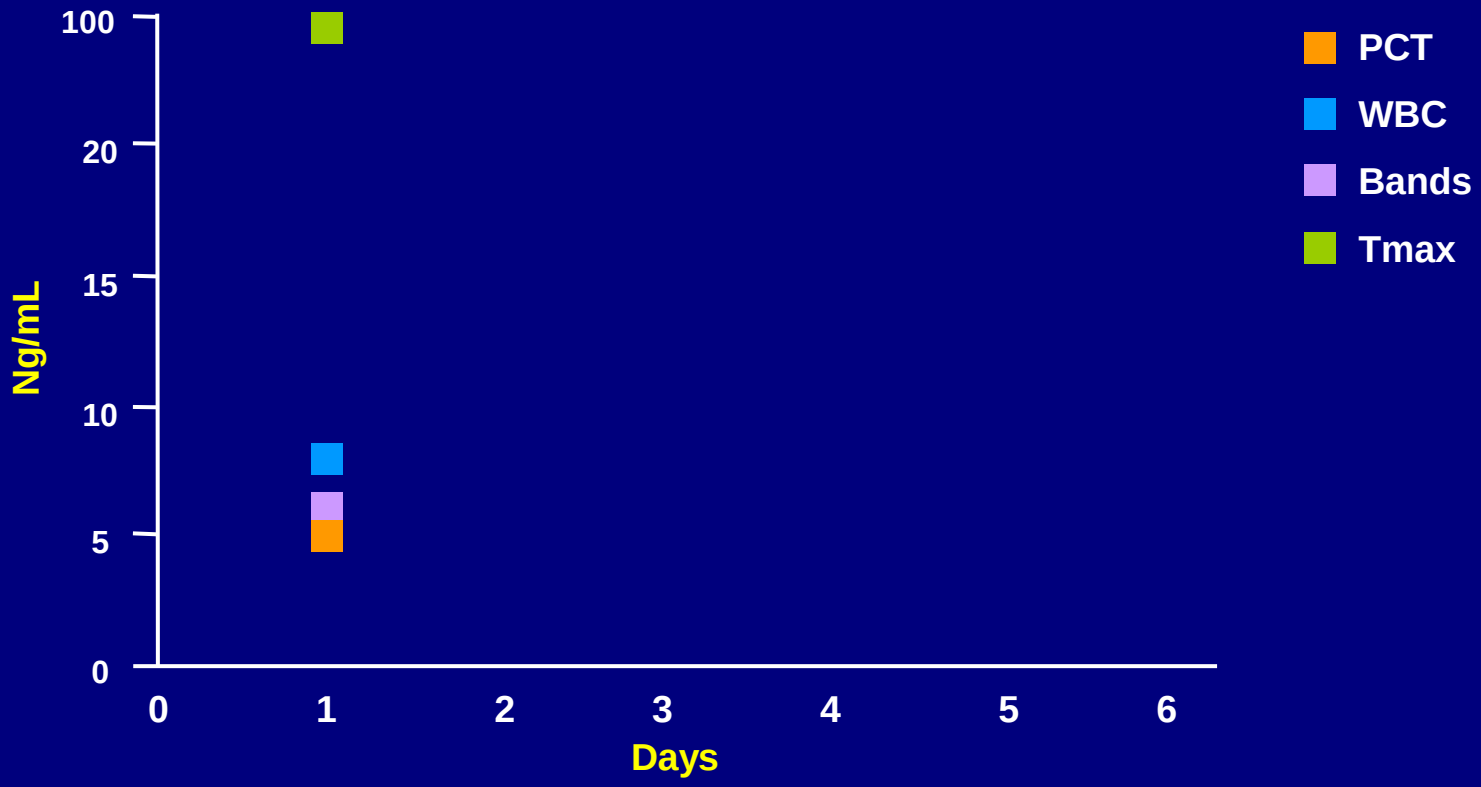
Interactive examples from everyday clinical practice

Case 1

- 78 y/o female found unresponsive at home by family. Noted to be in respiratory distress. Intubated in the ED for apnea. Prior h/o DM, HTN, UTI, AV block, pacemaker, mild dimentia and AKA. In ED WBC 14.6 with 31 bands, AG 14, BUN 53, PCT 2.7. Patient had been receiving TPN via porto-cath at home.

Case 1

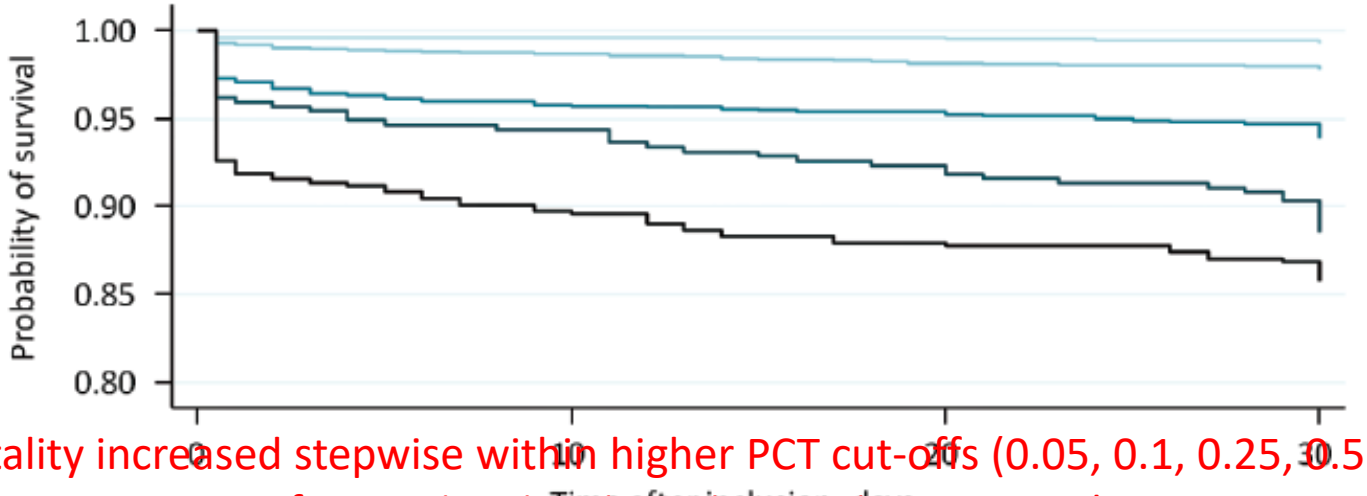
- 78 y/o female found unresponsive at home by family. Noted to be in respiratory distress. Intubated in the ED for apnea. Prior h/o DM, HTN, UTI, AV block, pacemaker, mild dimentia and AKA. In ED WBC 14.6 with 31 bands, AG 14, BUN 53, PCT 2.7. Patient had been receiving TPN via porto-cath at home.



- Σχετίζεται η PCT με την έκβαση στο γενικό πληθυσμό των σθενών στα ΤΕΠ?

Ramon Sager, Yannick Wirz, Devendra Amin, Adina Amin, Pierre Hausfater, Andreas Huber, Sebastian Haubitz, Alexander Kutz, Beat Mueller and Philipp Schuetz*

Are admission procalcitonin levels universal mortality predictors across different medical emergency patient populations? Results from the multi-national, prospective, observational



Mortality increased stepwise within higher PCT cut-offs (0.05, 0.1, 0.25, 0.5 ng/mL) from 1%, 3%, 7%, 13% to 15%, respectively.

PCT, ng/mL	Number at risk			
<0.5	1095	1091	1091	1089
0.5–0.1	3418	3372	3355	3348
0.1–0.25	1508	1444	1438	1428
0.25–0.5	393	371	363	355
>0.5	556	499	489	483

Addition of PCT also improved the prognostic accuracy of the quick sequential organ failure assessment (qSOFA) score from an AUC of from 0.61 to 0.76 ($p < 0.001$).

Journal of Hospital Infection 77 (2011) 58–63

Available online at www.sciencedirect.com

Journal of Hospital Infection

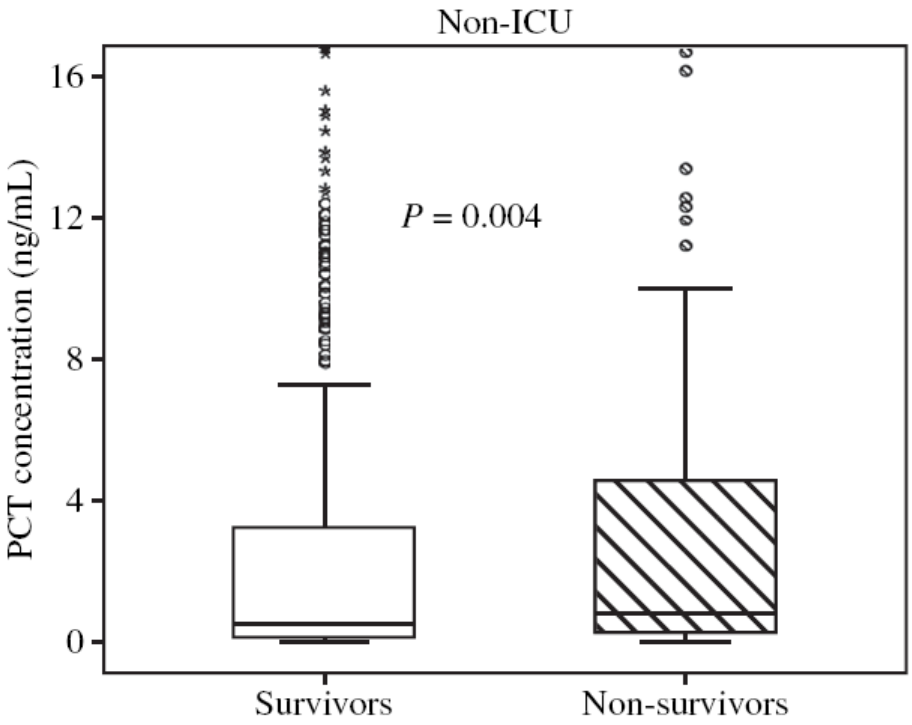
journal homepage: www.elsevierhealth.com/journals/jhin

Procalcitonin as an early indicator of outcome in sepsis: a prospective observational study

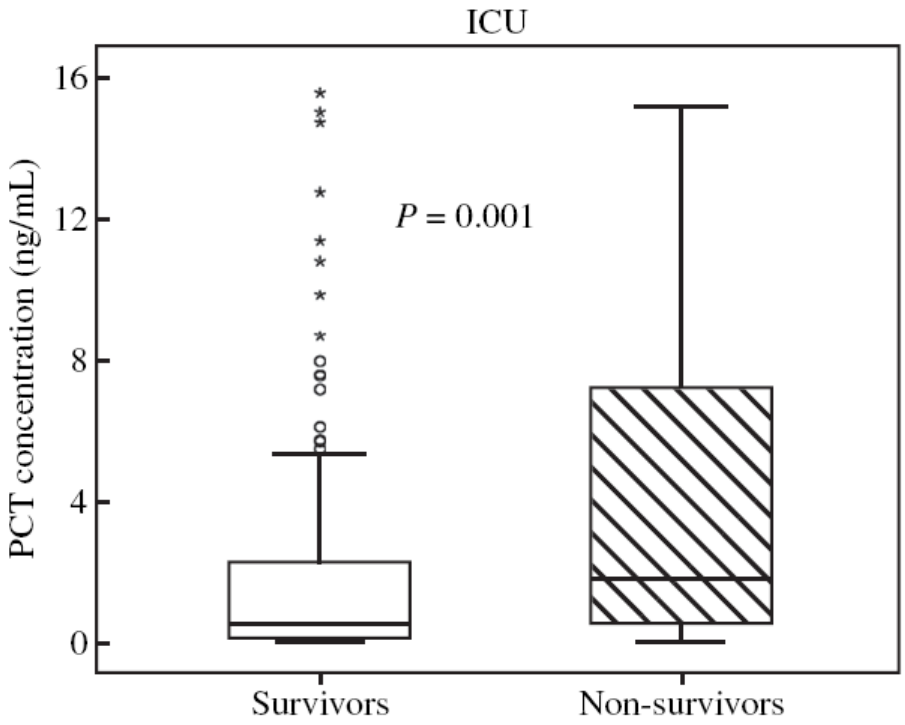
E.J. Giamarellos-Bourboulis [a,*], I. Tsangaris [b], Th. Kanni [a], M. Mouktaroudi [a], I. Pantelidou [a], G. Adamis [c], S. Atmatzidis [d], M. Chrisofos [e], V. Evangelopoulou [f], F. Frantzeskaki [b], P. Giannopoulos [g], G. Giannikopoulos [h], D. Gialvalis [i], G.M. Gourgoulis [a], K. Kotzampassi [j], K. Katsifa [k], G. Kofinas [l], F. Kontopidou [a], G. Koratzanis [m], V. Koulouras [n], A. Koutsikou [o], M. Koupetori [p], I. Kritselis [q], L. Leonidou [r], A. Mega [s], V. Mylona [m], H. Nikolaou [t], S. Orfanos [b], P. Panagopoulos [a], E. Paramythiotou [b], A. Papadopoulos [a], X. Papanikolaou [l], M. Pavlaki [u], V. Polychronopoulos [v], A. Skoutelis [w], A. Theodotou [x], M. Vassiliaghou [y], E.E. Douzinas [z], C. Gogos [r], A. Armaganidis [b] on behalf of the Hellenic Sepsis Study Group

PCT and survival

922 pts



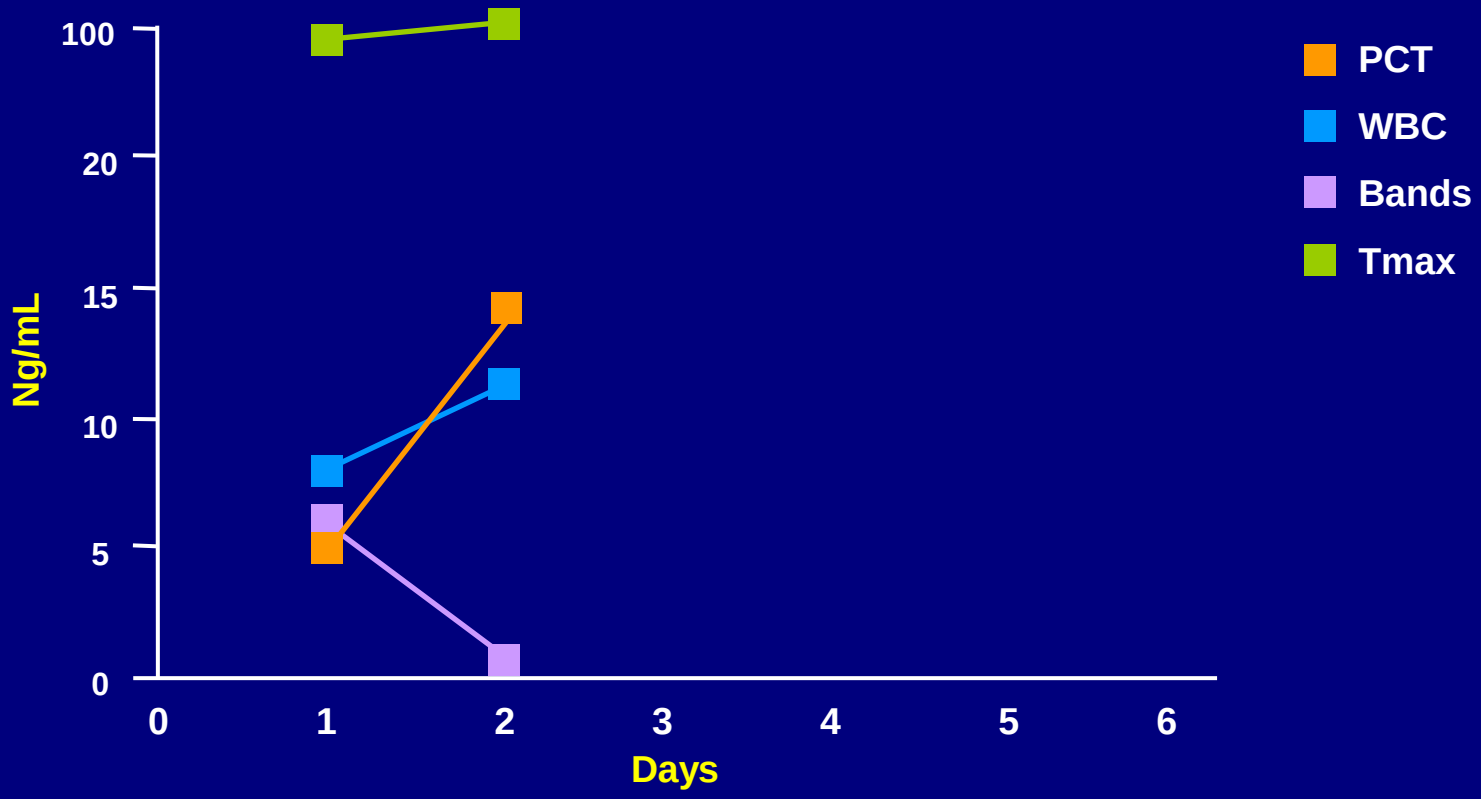
234 pts



J Hosp Infect 2011; 77: 58-63

Case 1

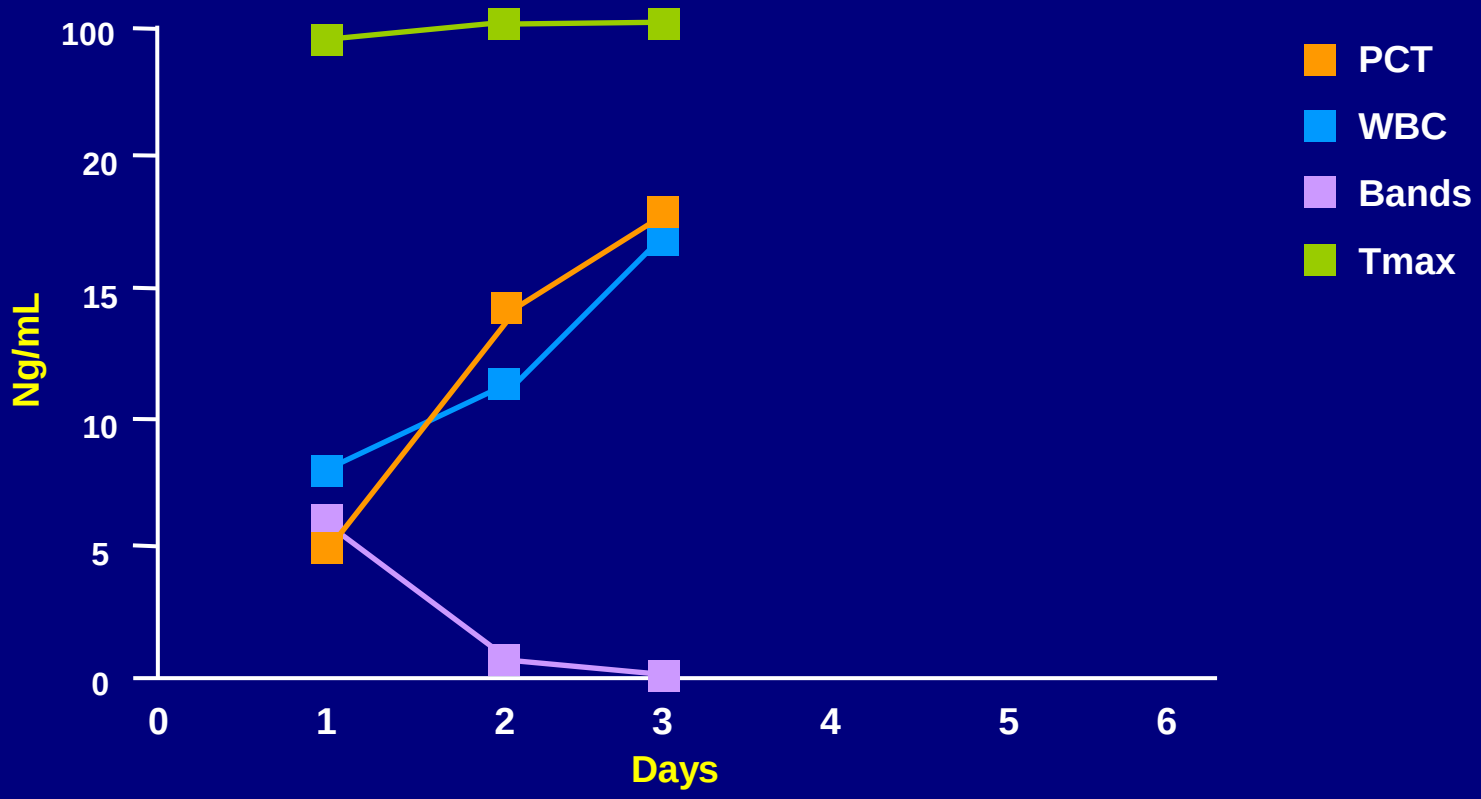
- 78 y/o female found unresponsive at home by family. Noted to be in respiratory distress. Intubated in the ED for apnea. Prior h/o DM, HTN, UTI, AV block, pacemaker, mild dimentia and AKA. In ED WBC 14.6 with 31 bands, AG 14, BUN 53, PCT 2.7. Patient had been receiving TPN via porto-cath at home.



- Interestingly, our secondary analysis identified that simply assessing whether PCT decreases or increases from baseline to day 1 revealed a three-fold higher mortality in patients with a short-term increase in PCT levels. This simple finding could prove particularly useful during early critical care management.

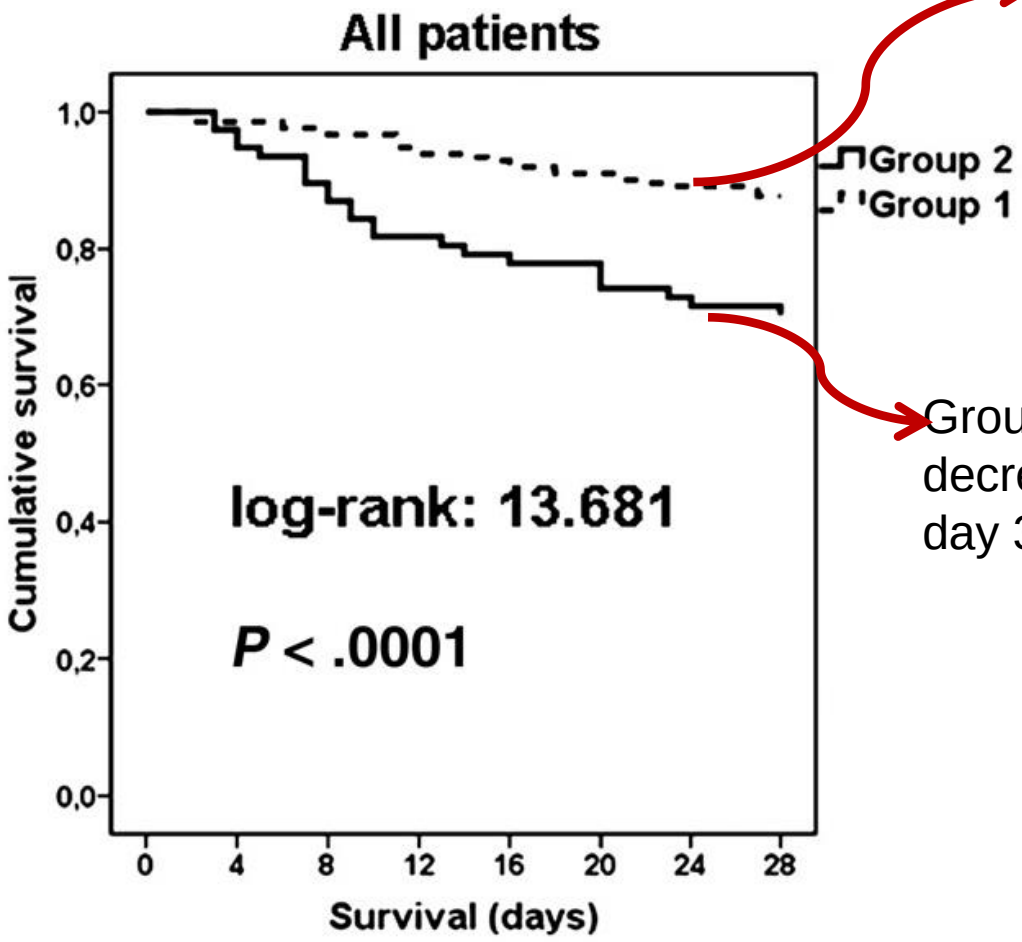
Case 1

- 78 y/o female found unresponsive at home by family. Noted to be in respiratory distress. Intubated in the ED for apnea. Prior h/o DM, HTN, UTI, AV block, pacemaker, mild dimentia and AKA. In ED WBC 14.6 with 31 bands, AG 14, BUN 53, PCT 2.7. Patient had been receiving TPN via porto-cath at home.



Does PCT carry a prognostic role?

289 pts



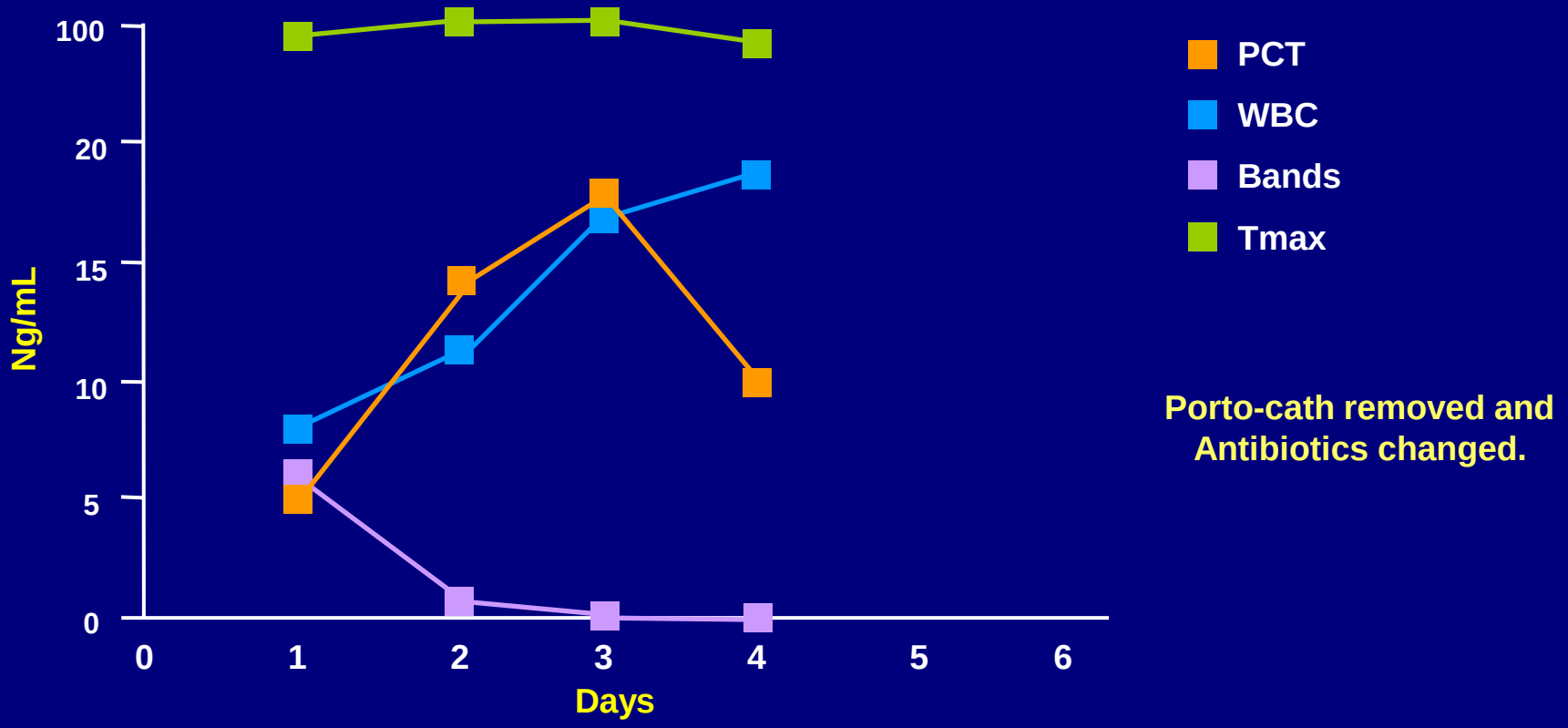
Group 1: ↓PCT on day 3 by >30% or PCT on day 3 <0.25 ng/mL

Group 2: ↑ PCT or decrease of PCT on day 3 by <30%.

Georgopoulou, J Crit Care 2011

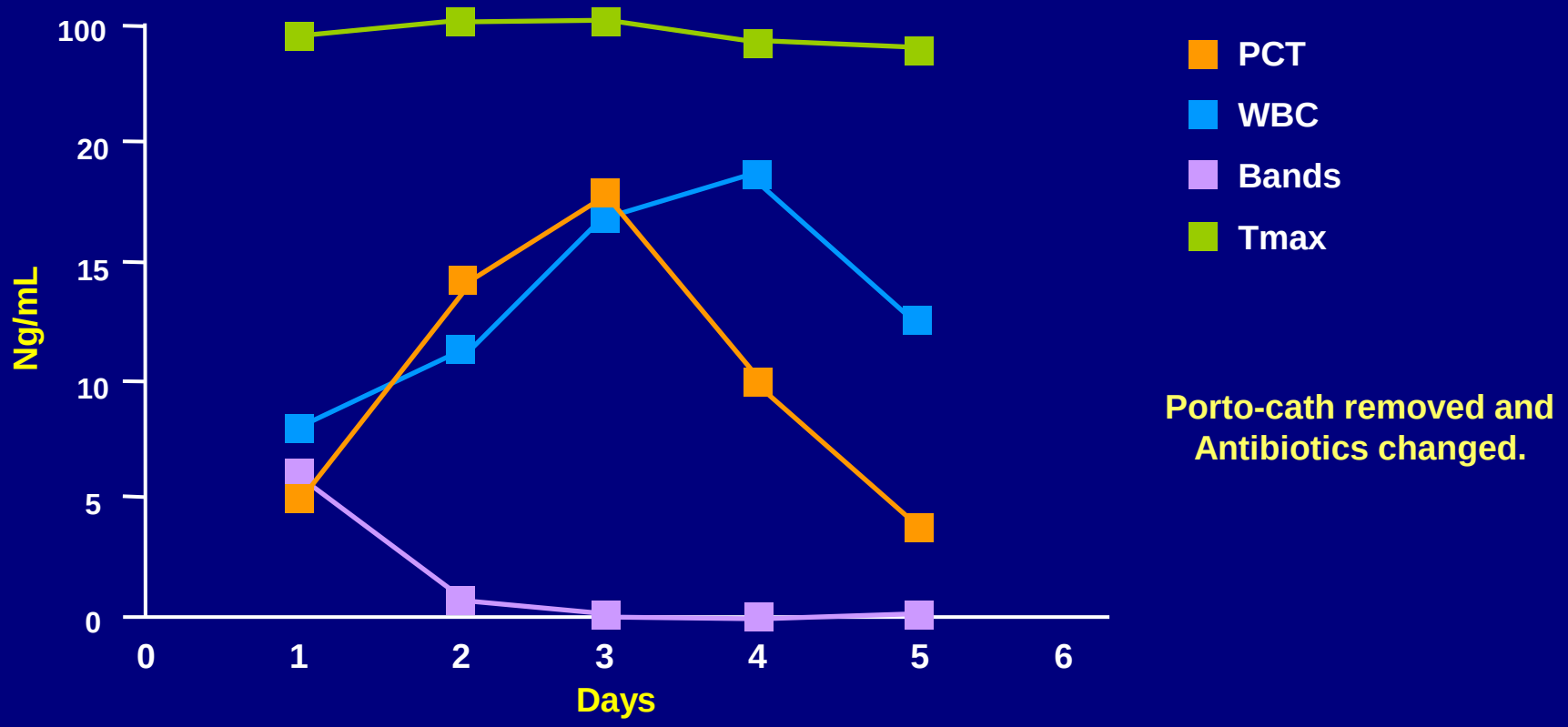
Case 1

- 78 y/o female found unresponsive at home by family. Noted to be in respiratory distress. Intubated in the ED for apnea. Prior h/o DM, HTN, UTI, AV block, pacemaker, mild dimentia and AKA. In ED WBC 14.6 with 31 bands, AG 14, BUN 53, PCT 2.7. Patient had been receiving TPN via porto-cath at home.



Case 1

- 78 y/o female found unresponsive at home by family. Noted to be in respiratory distress. Intubated in the ED for apnea. Prior h/o DM, HTN, UTI, AV block, pacemaker, mild dimentia and AKA. In ED WBC 14.6 with 31 bands, AG 14, BUN 53, PCT 2.7. Patient had been receiving TPN via porto-cath at home.

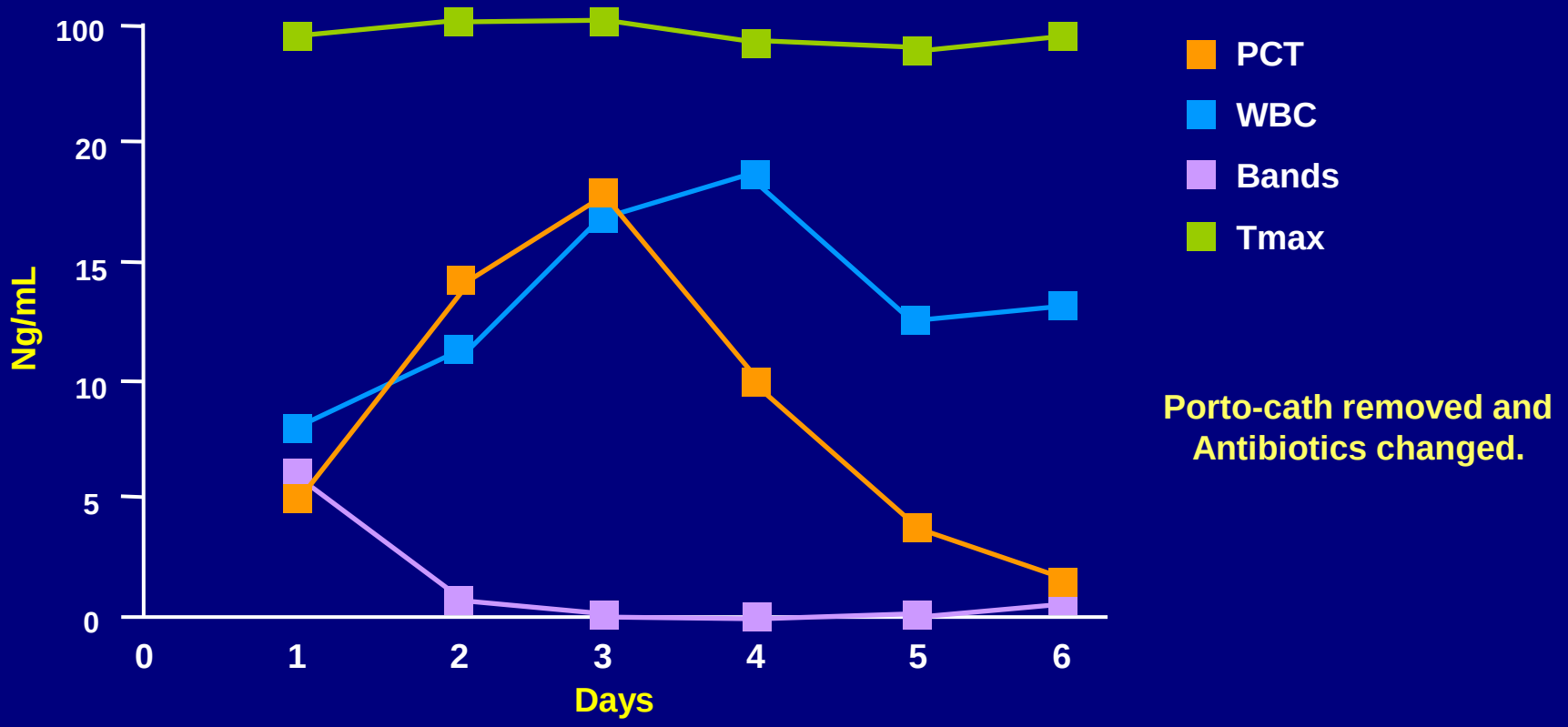


Blood stream infections and PCT

- PCT : assess whether blood cultures that test positive have been contaminated. Several studies found that PCT showed good discrimination between BSI and contamination with an AUC of 0.86
- Additionally, in a PCR diagnostic (SeptiFast) test, a PCT value of <0.37 ng/ml had a 99% negative predictive value for this assay.
- PCT correlates with types of pathogens. Different PCT cut-off levels suggest different bacterial species, with higher concentrations for Gram-negative Bacteriaceae (AUC 0.81 at cut-off 6.47 ng/ml)

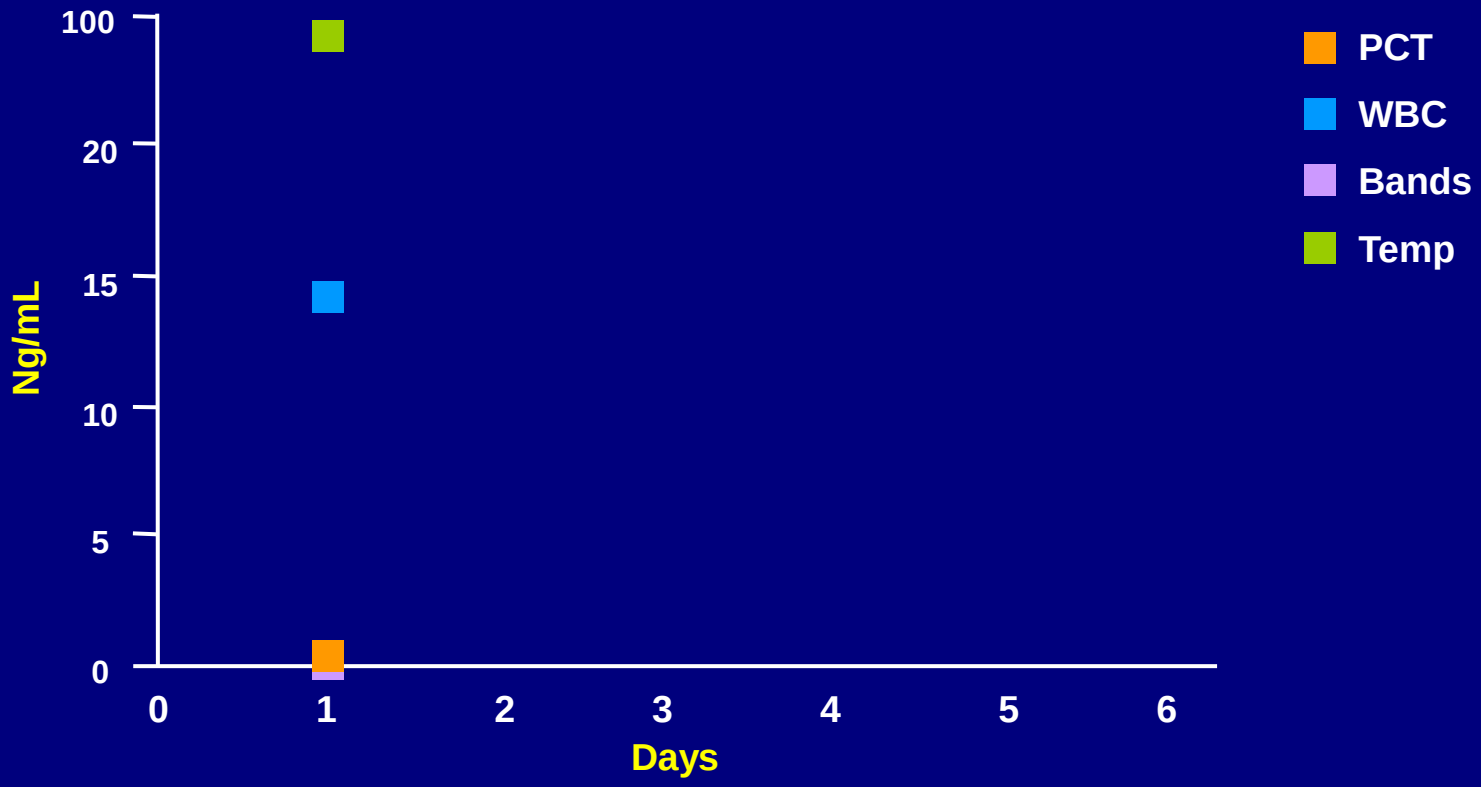
Case 1

- 78 y/o female found unresponsive at home by family. Noted to be in respiratory distress. Intubated in the ED for apnea. Prior h/o DM, HTN, UTI, AV block, pacemaker, mild dimentia and AKA. In ED WBC 14.6 with 31 bands, AG 14, BUN 53, PCT 2.7. Patient had been receiving TPN via porto-cath at home.



Case 2

- 70 Year old male presented with fever, chills, and lethargy. Seizure at home. Received flu vaccine and pnumovax one week ago. Second seizure in the ED. In ED WBC 15. 3, AG 13, myoglobin 379 temp 38.5 HR 104-22 RR 28



- Vikse J, Henry BM, Roy J, Ramakrishnan PK, Tomaszewski KA, Walocha JA. The role of serum procalcitonin in the diagnosis of bacterial meningitis in adults: a systematic review and meta-analysis. Int J Infect Dis. 2015;38:68–76.

- Wei TT, Hu ZD, Qin BD, Ma N, Tang QQ, Wang LL, Zhou L, Zhong RQ. Diagnostic accuracy of procalcitonin in bacterial meningitis versus nonbacterial meningitis: a systematic review and meta-analysis. Medicine. 2016;95(11)

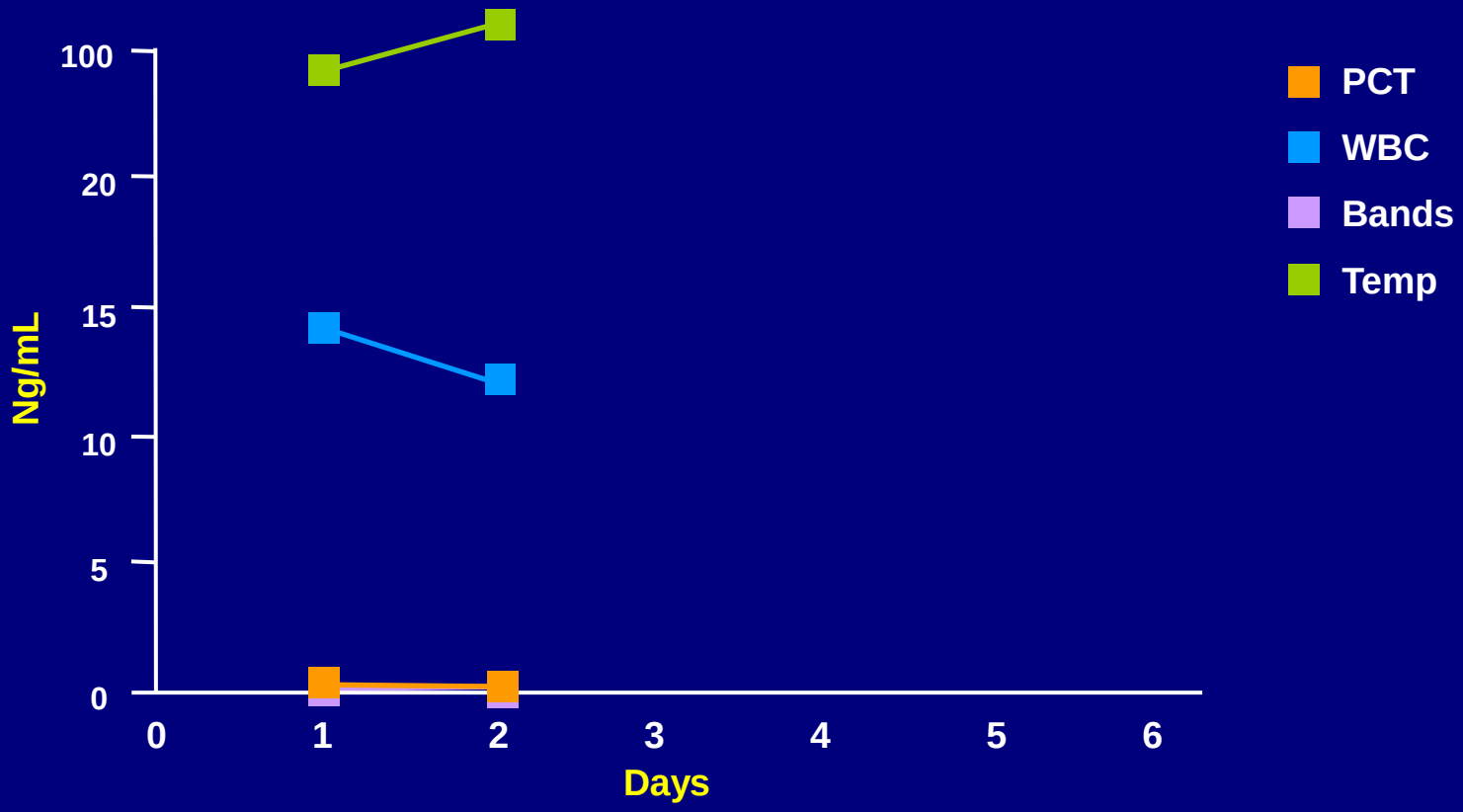
2058 subjects: sensitivity of 0.95, specificity of 0.97, a positive likelihood ratio of 31.7, and a negative likelihood ratio of 0.06.

The diagnostic performance was even better when combined with cerebrospinal fluid lactate.

Serum PCT was found to be more sensitive and specific than cerebrospinal fluid PCT

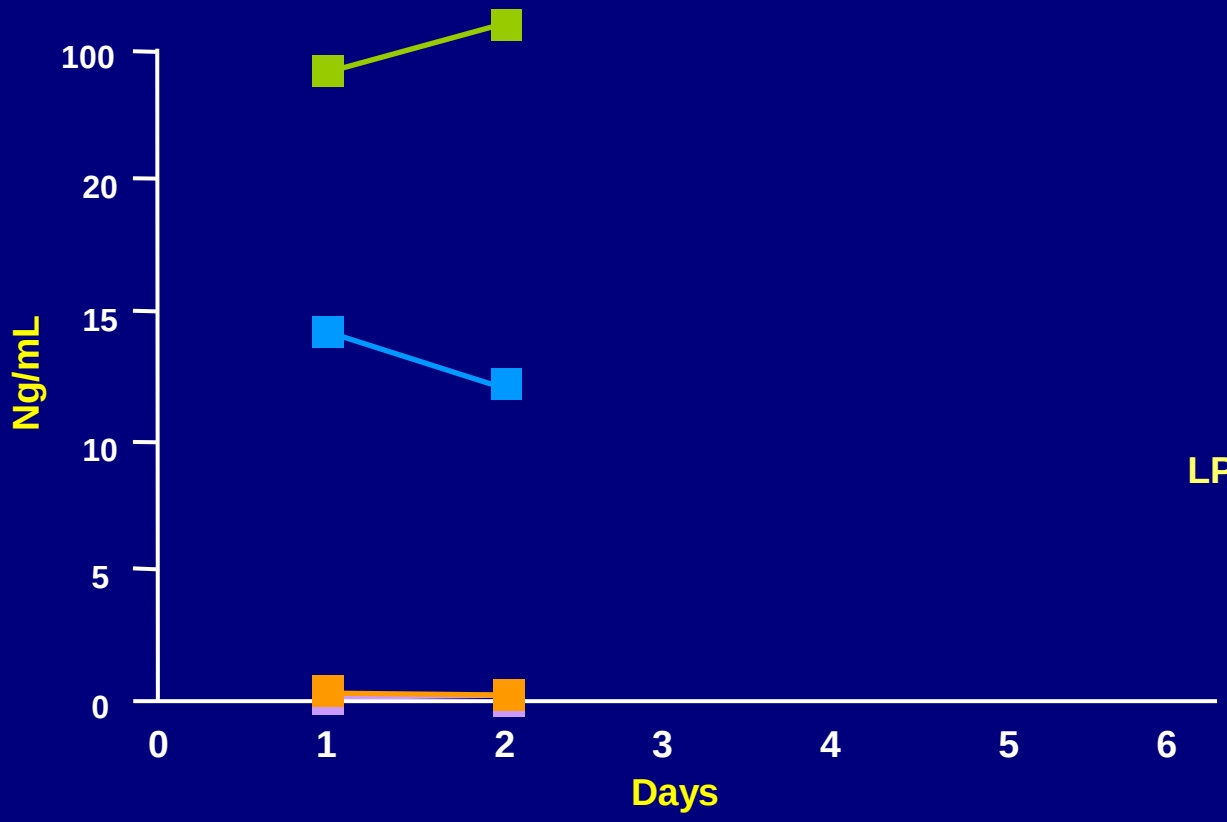
Case 2

- 70 Year old male presented with fever, chills, and lethargy. Seizure at home. Received flu vaccine and pnumovax one week ago. Second seizure in the ED. In ED WBC 15. 3, AG 13, myoglobin 379 temp 38.5 HR 104-22 RR 28



Case 2

- 70 Year old male presented with fever, chills, and lethargy. Seizure at home. Received flu vaccine and pnumovax one week ago. Second seizure in the ED. In ED WBC 15. 3, AG 13, myoglobin 379 temp 37.8 HR 104-22 RR 28



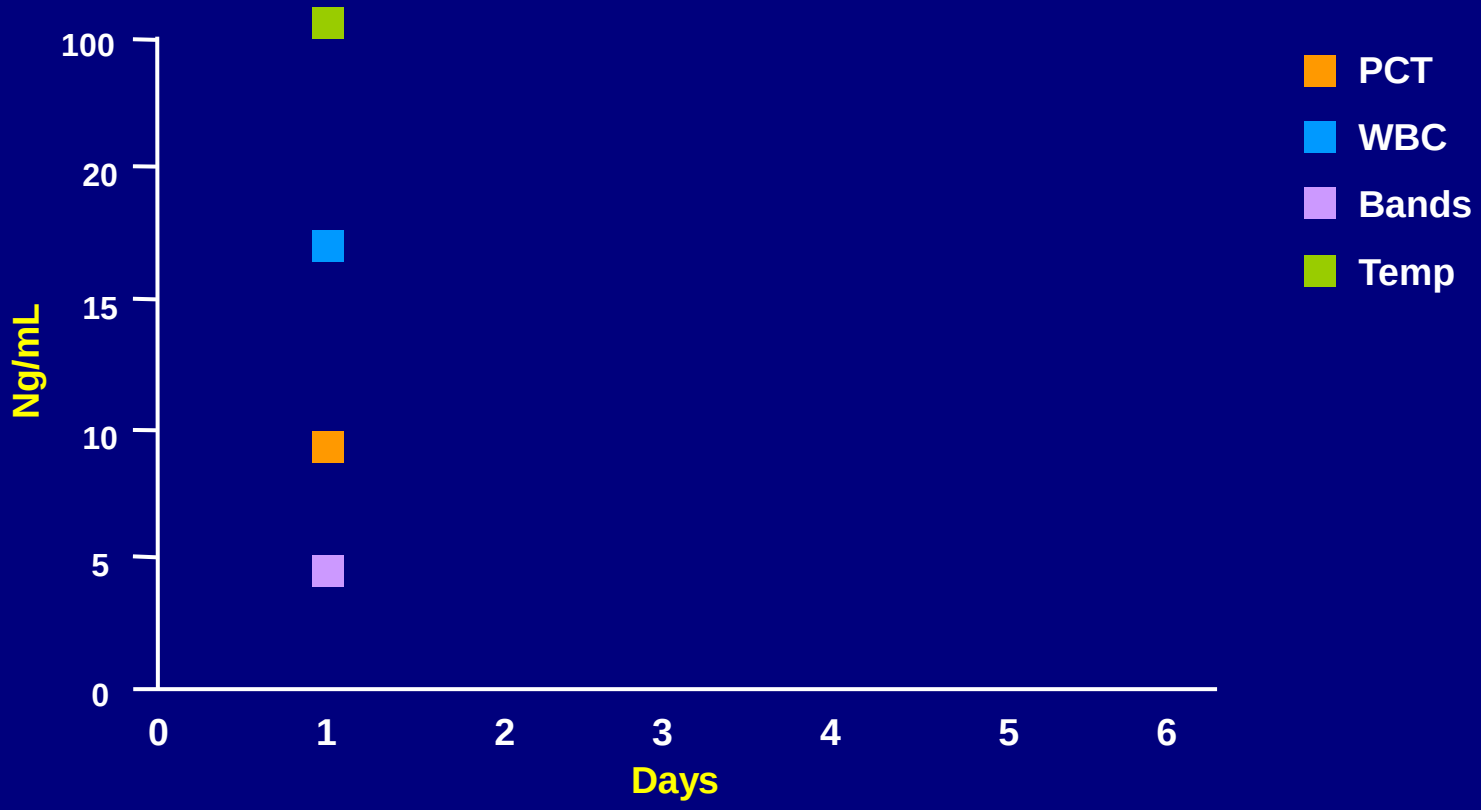
LP 25 wbc all lymphocytes.
Final dx Encephalitis

Case 3

- 50 year old M to ED s/p cardiac arrest. Had CP for three hours prior to calling EMS. ACLS successful. CXR congested lungs. BP 96/65, 110, 18. ABG 7.23/35/290. AG 20 TROP>50. Off to cardiac cath for stent placement.

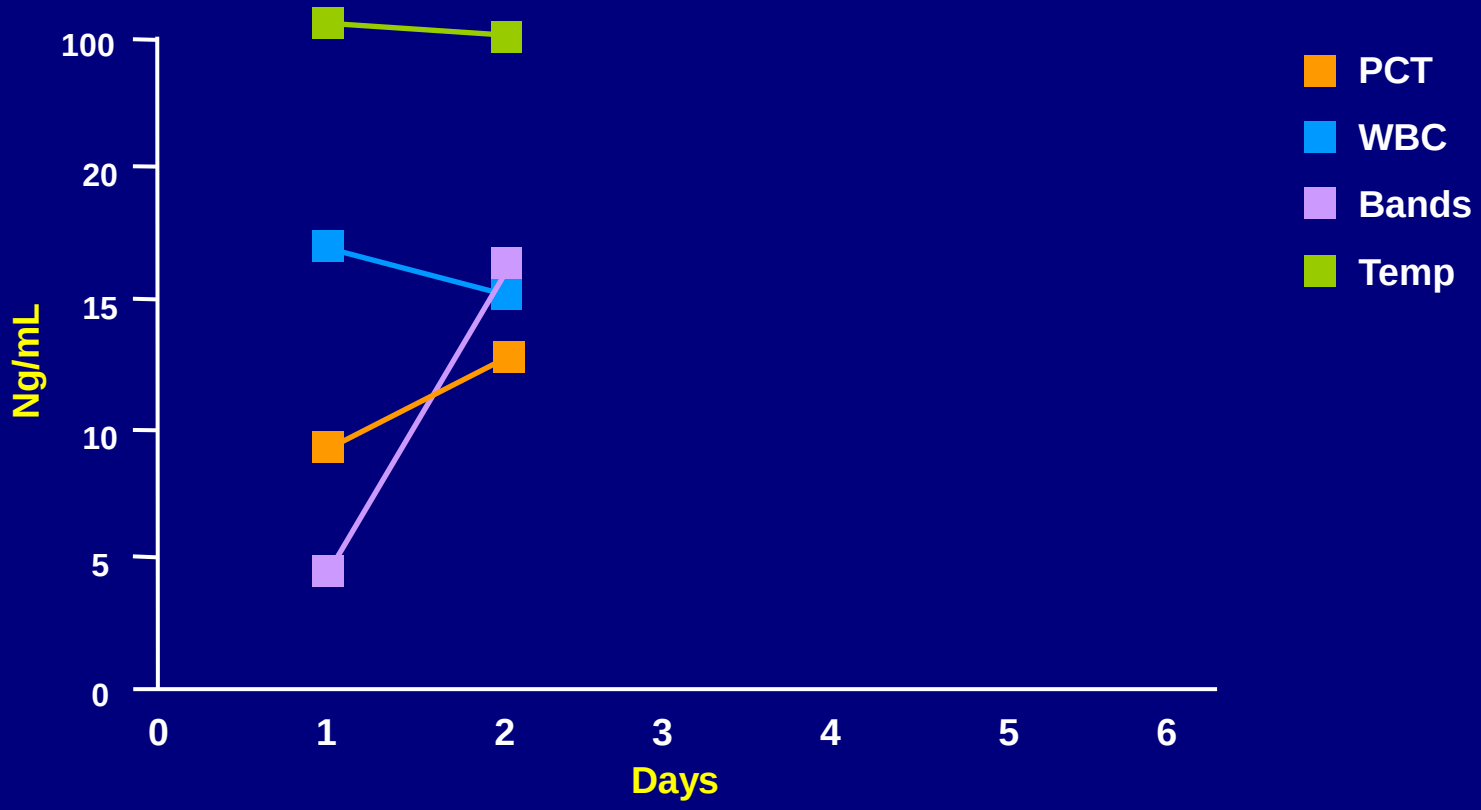
Case 3

- 50 year old M to ED s/p cardiac arrest. Had CP for three hours prior to calling EMS. ACLS successful. CXR congested lungs. BP 96/65, 110, 18. ABG 7.23/35/290. AG 20 TROP>50. Off to cardiac cath for stent placement.



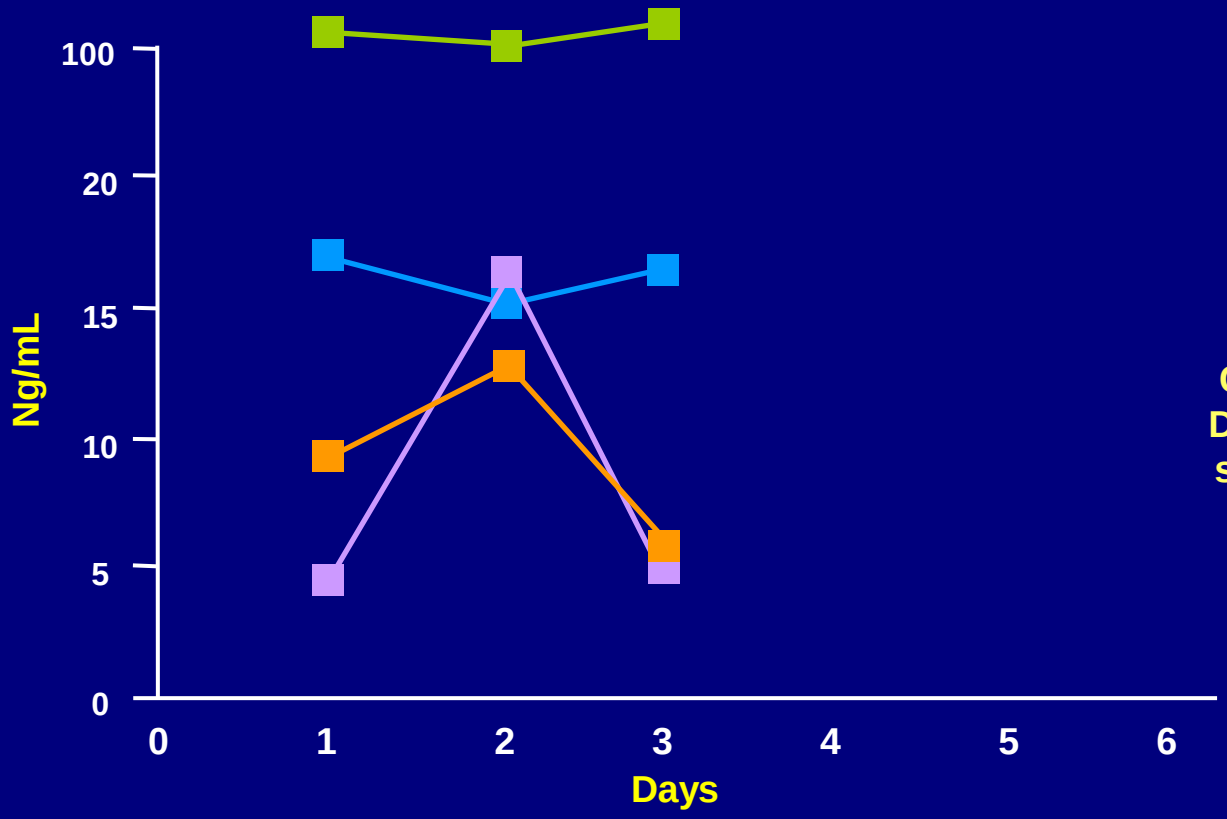
Case 3

- 50 year old M to ED s/p cardiac arrest. Had CP for three hours prior to calling EMS. ACLS successful. CXR congested lungs. BP 96/65, 110, 18. ABG 7.23/35/290. AG 20 TROP>50. Off to cardiac cath for stent placement.



Case 3

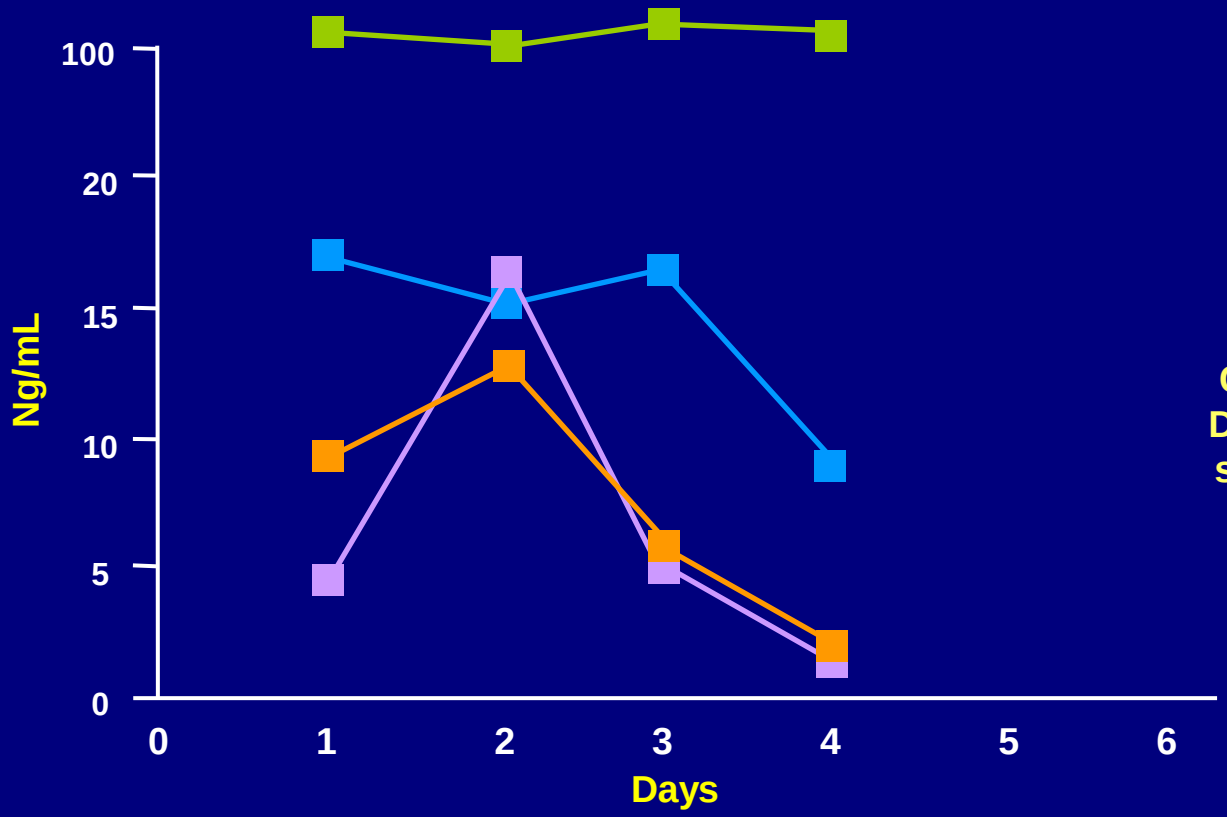
- 50 year old M to ED s/p cardiac arrest. Had CP for three hours prior to calling EMS. ACLS successful. CXR congested lungs. BP 96/65, 110, 18. ABG 7.23/35/290. AG 20 TROP>50. Off to cardiac cath for stent placement.



CT on day two in ICU CT of Abd. Demonstrates loops of distended small bowel, small accumulation of fluid thickened bowel wall consistent with small bowel ischemia.

Case 3

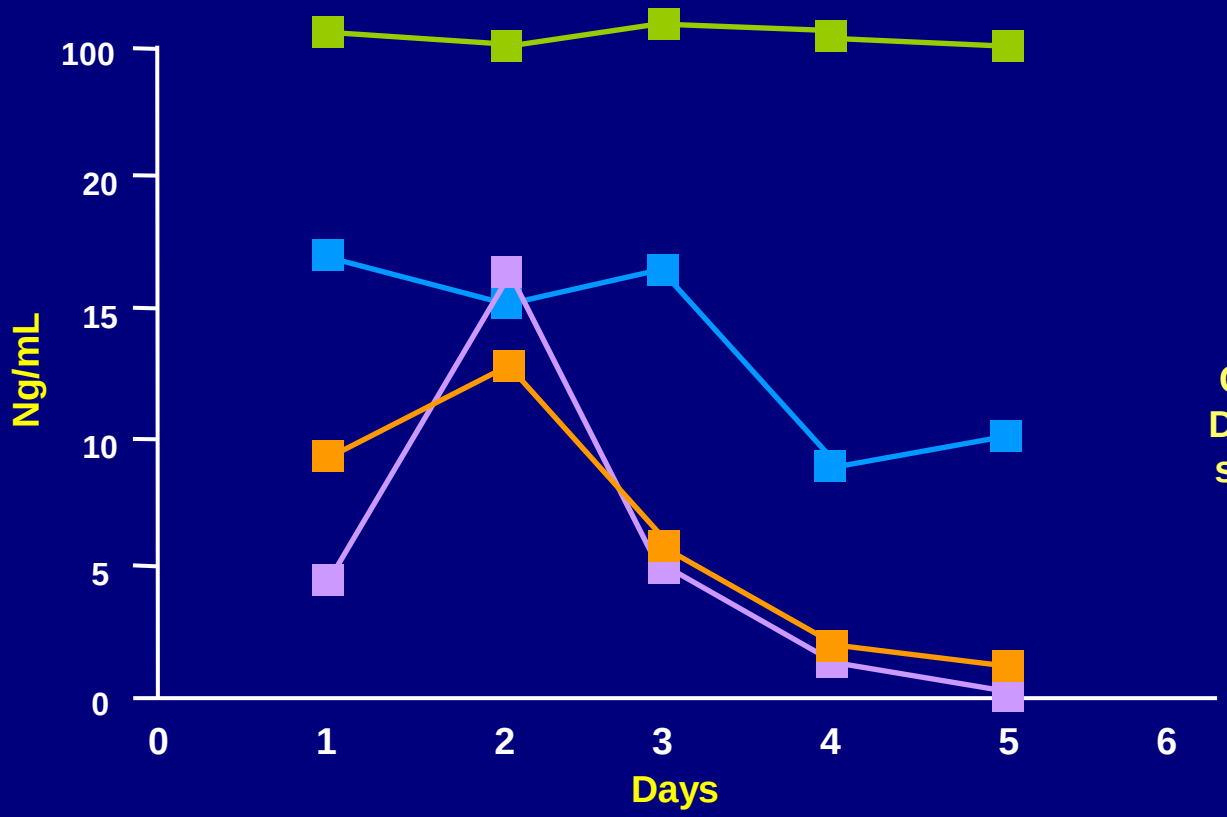
- 50 year old M to ED s/p cardiac arrest. Had CP for three hours prior to calling EMS. ACLS successful. CXR congested lungs. BP 96/65, 110, 18. ABG 7.23/35/290. AG 20 TROP>50. Off to cardiac cath for stent placement.



CT on day two in ICU CT of Abd. Demonstrates loops of distended small bowel, small accumulation of fluid thickened bowel wall consistent with small bowel ischemia.

Case 3

- 50 year old M to ED s/p cardiac arrest. Had CP for three hours prior to calling EMS. ACLS successful. CXR congested lungs. BP 96/65, 110, 18. ABG 7.23/35/290. AG 20 TROP>50. Off to cardiac cath for stent placement.



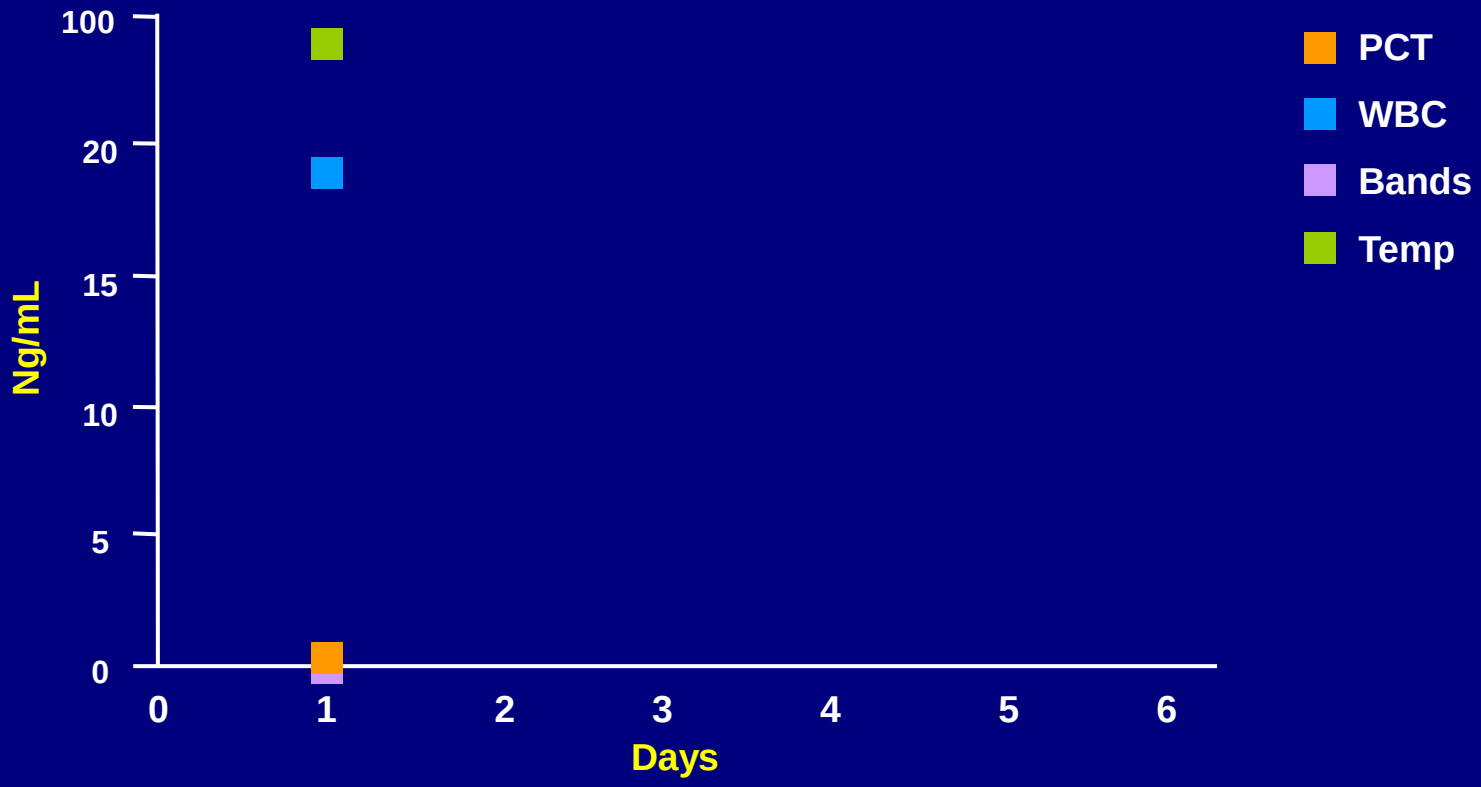
CT on day two in ICU CT of Abd. Demonstrates loops of distended small bowel, small accumulation of fluid thickened bowel wall consistent with small bowel ischemia.

Case 4

- 68 y/o male with h/o CHF, COPD, CAD previously hospitlaized two months ago for exacerbation of COPD. Presents with difficulty breathing, SOB. No chest pain, but has cough with clear to yellow sputum. ABG in ED 7.11/76/91 BNP 1301 Trop < .03 WBC 18,000, 0 Bands.

Case 4

- 68 y/o male with h/o CHF, COPD, CAD previously hospitlaized two months ago for exacerbation of COPD. Presents with difficulty breathing, SOB. No chest pain, but has cough with clear to yellow sputum. ABG in ED 7.11/76/91 BNP 1301 Trop < .03 WBC 18,000, 0 Bands.



H1N1 pts in ICU: Can PCT rule out bacterial infection?

Journal of Infection (2015) xx, 1–9

ELSEVIER

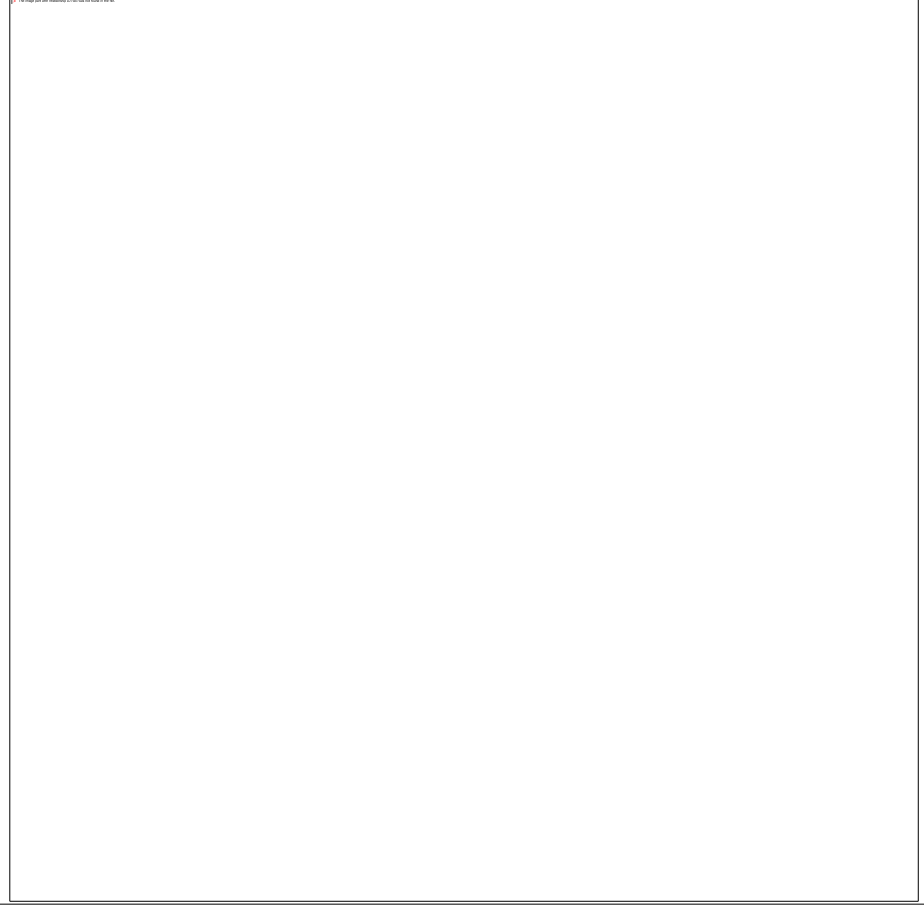
BIAM British Infection Association

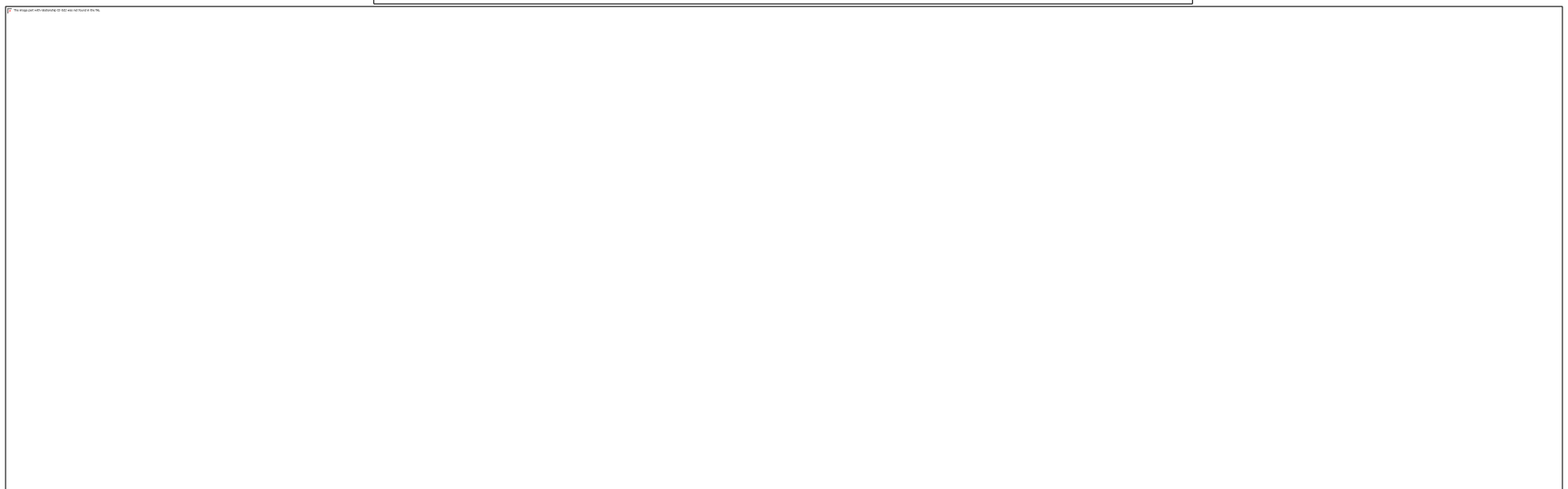
www.elsevierhealth.com/journals/jinf

Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: A CHAID decision-tree analysis

Alejandro H. Rodríguez [a,*], Francesc X. Avilés-Jurado [b], Emili Díaz [c], Philipp Schuetz [d], Sandra I. Trefler [a], Jordi Solé-Violán [e], Lourdes Cordero [f], Loreto Vidaur [g], Ángel Estella [h], Juan C. Pozo Laderas [i], Lorenzo Socias [j], Juan C. Vergara [k], Rafael Zaragoza [l], Juan Bonastre [m], José E. Guerrero [n], Borja Suberviola [o], Catia. Cilloniz [p], Marcos I. Restrepo [q], Ignacio Martín-Loeches [r], on behalf of the SEMICYUC/GETGAG Working Group [1]

J Infect. 2016 Feb;72(2):143-51





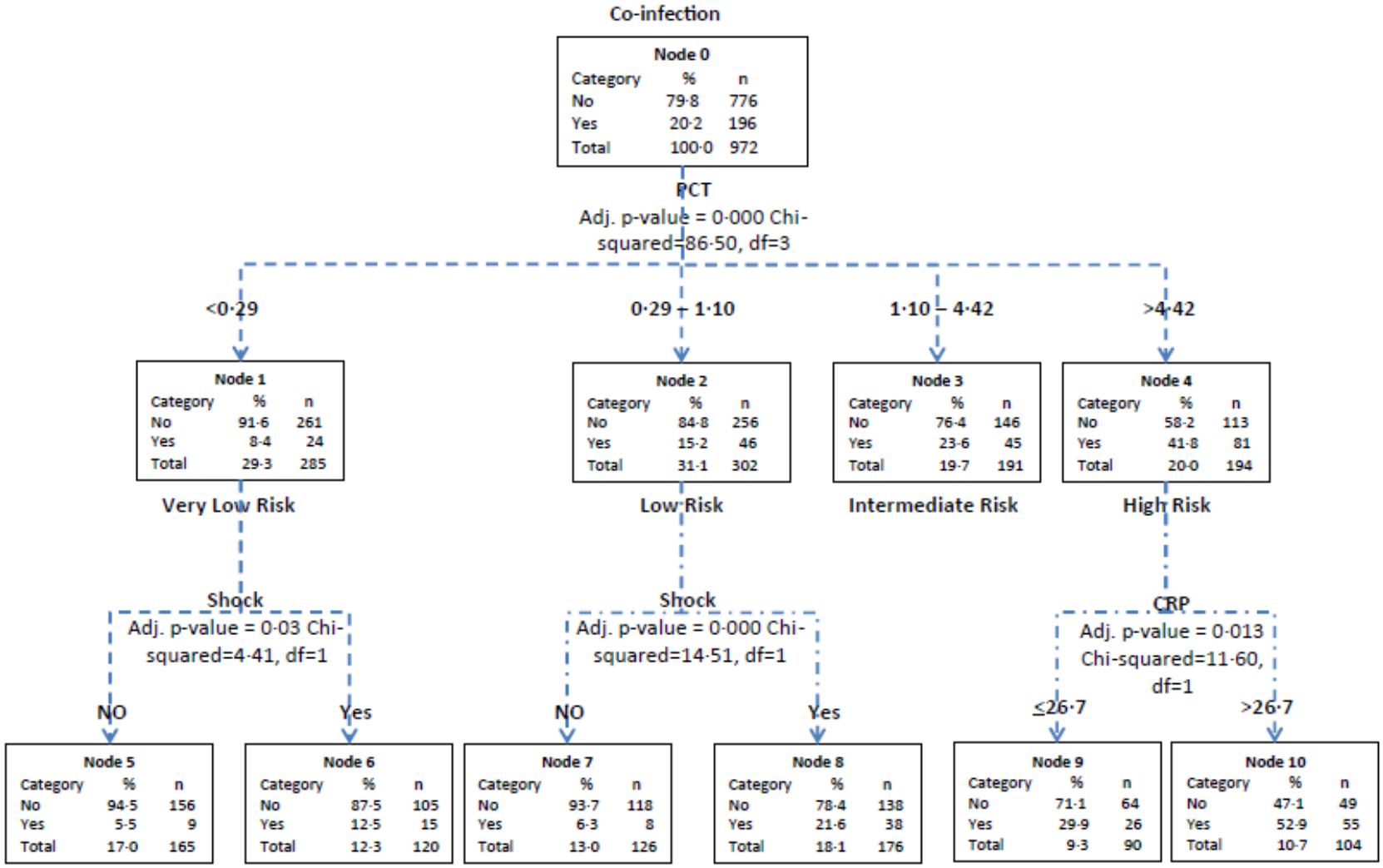
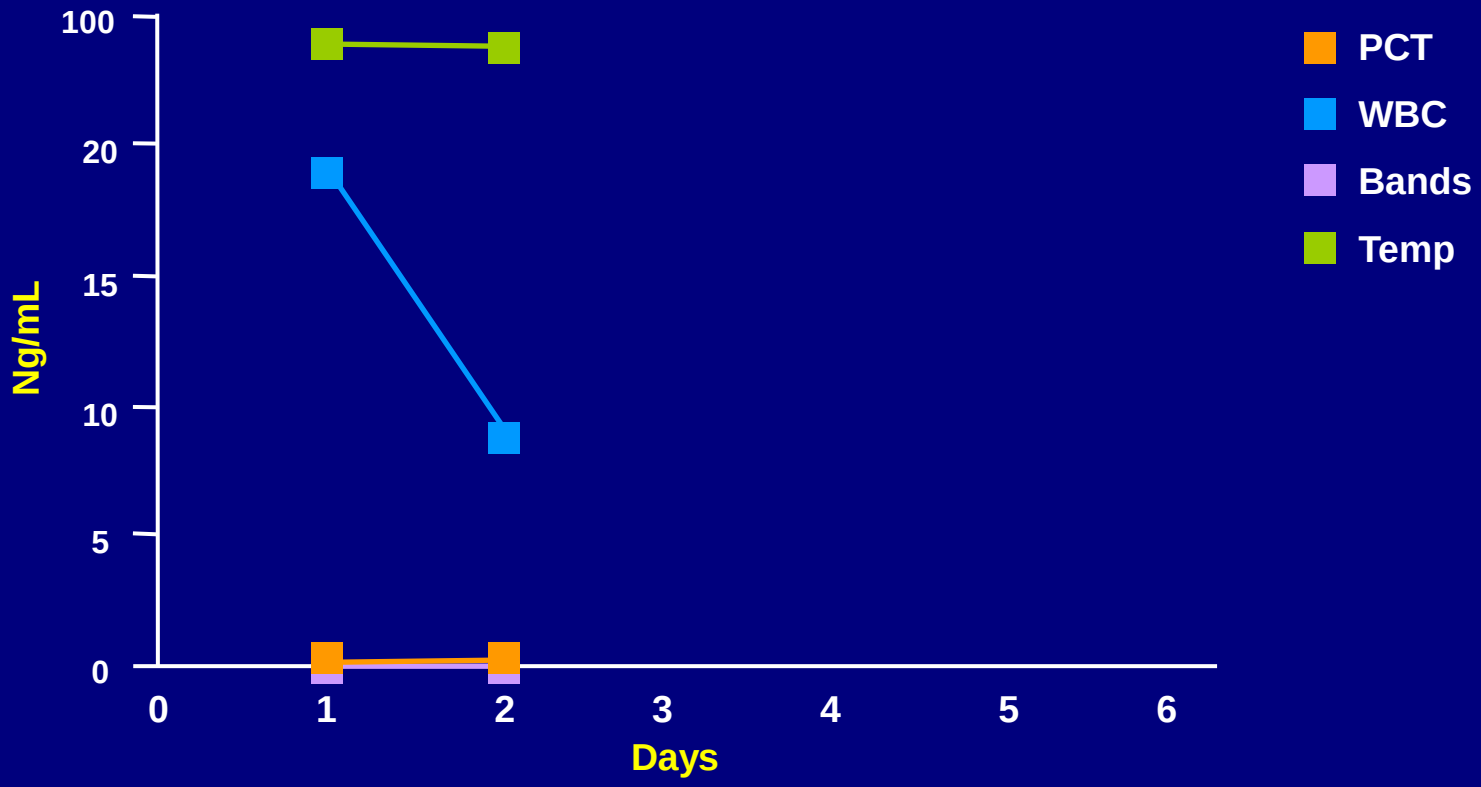


Figure 2 Tree created by the CHAID model (Chi-squared Automatic Interaction Detection) for community-acquired respiratory coinfection (CARC). PCT: procalcitonin; CRP: C-reactive protein.

Case 4

- 68 y/o male with h/o CHF, COPD, CAD previously hospitlaized two months ago for exacerbation of COPD. Presents with difficulty breathing, SOB. No chest pain, but has cough with clear to yellow sputum. ABG in ED 7.11/76/91 BNP 1301 Trop < .03 WBC 18,000, 0 Bands.



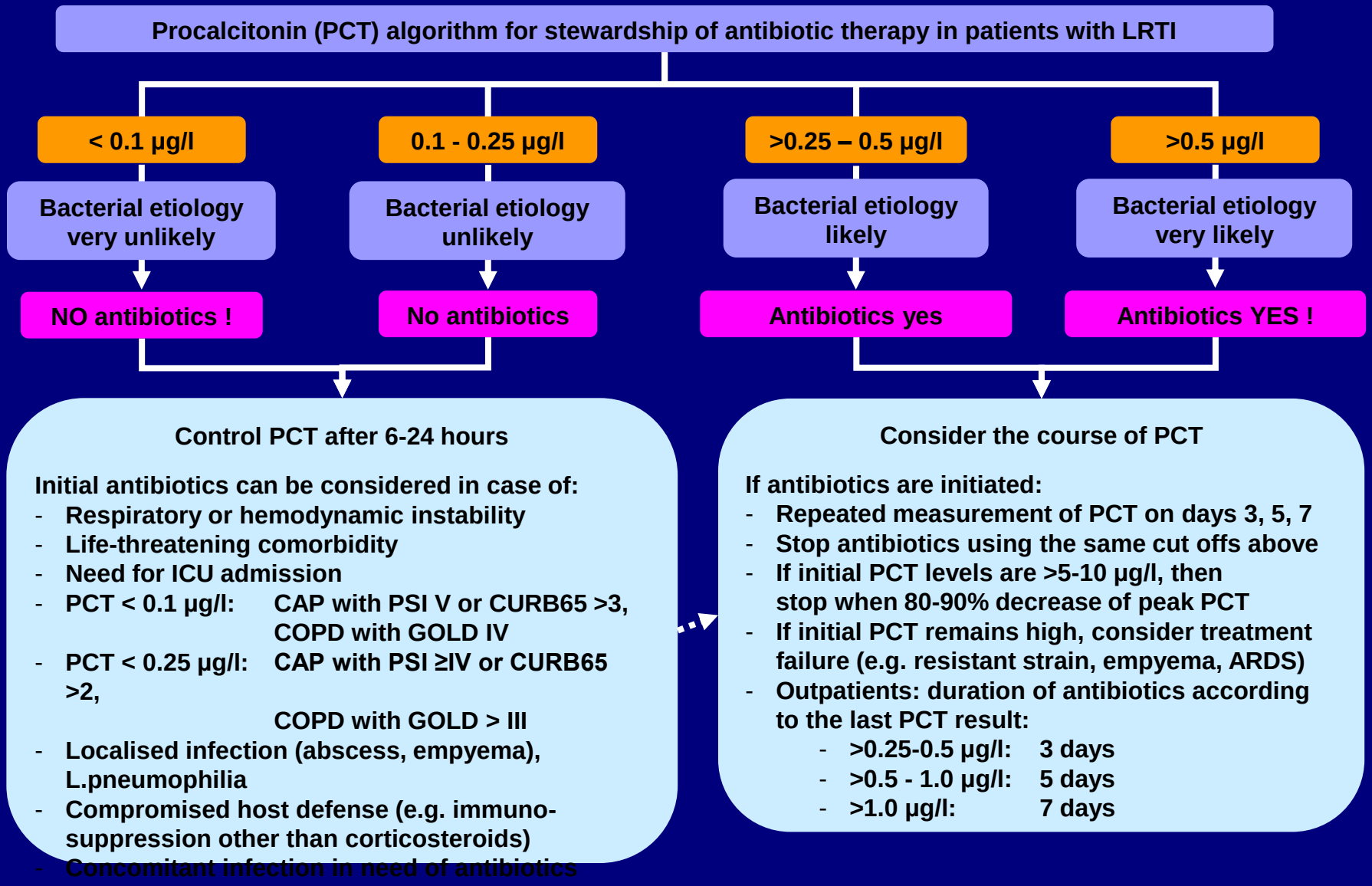
- *Albrich WC, Dusemund F, Bucher B, Meyer S, Thomann R, Kühn F, Bassetti S, Sprenger M, Bachli E, Sigrist T, Schwietert M, Amin D, Hausfater P, Carre E, Gaillat J, Schuetz P, Regez K, Bossart R, Schild U, Mueller B, ProREAL Study Team.*
- Effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infections in "real life": an international, multicenter poststudy survey (ProREAL).
- *Arch Intern Med. 2012 May 14; 172(9):715-22.*

- Worse outcome in patients with a diagnosis of CHF and an elevated PCT concentration (>0.21 ng/mL) if they were not treated with antibiotics ($p = 0.046$).
- Patients with low PCT values (<0.05 ng/mL) had a better outcome if they did not receive antibiotic therapy ($p = 0.049$).
- Similar results were also found in a secondary analysis of a previous randomized trial (PROHOSP)

Effect of Procalcitonin-Based Guidelines vs. Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections: The ProHOSP Randomized Controlled Trial

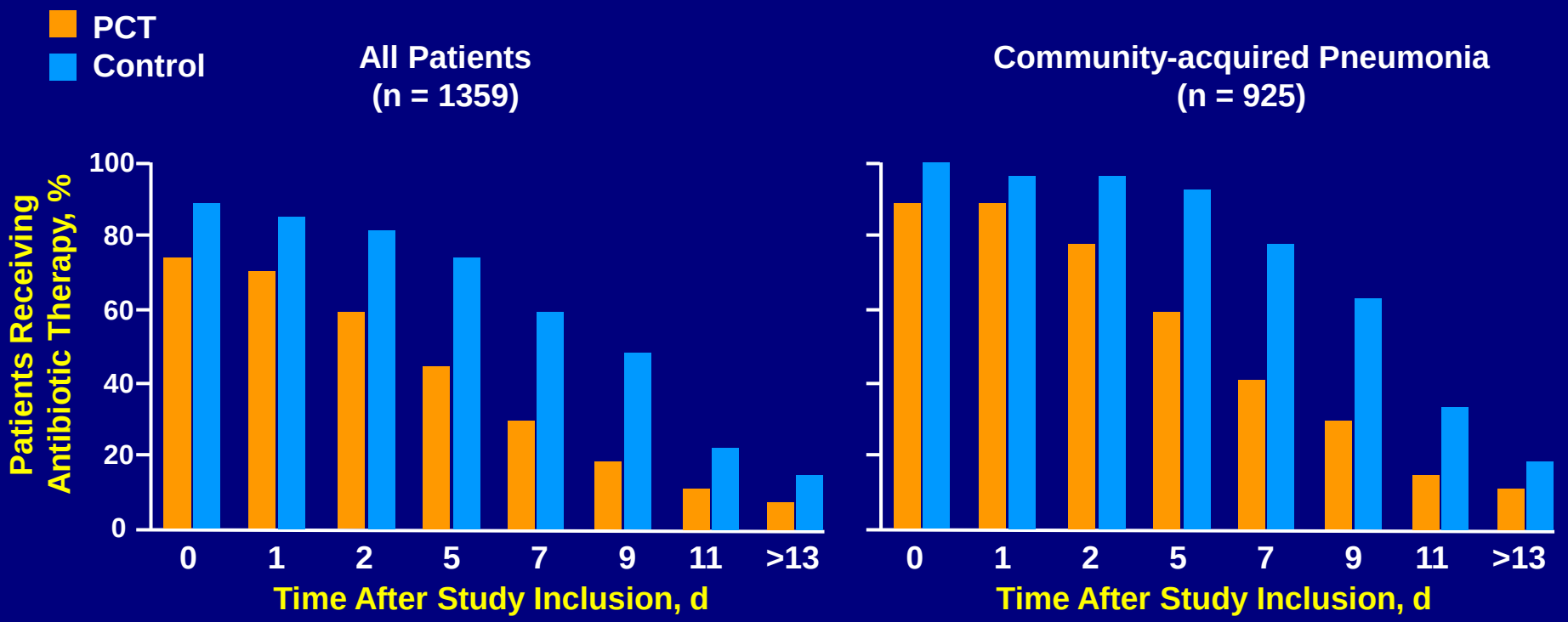
Philipp Schuetz, MD; Mirjam Christ-Crain, MD;
Robert Thomann, MD; Claudine Falconnier, MD;
Marcel Wolbers, PhD; Isabelle Widmer, MD;
Stefanie Neidert, MD; Thomas Fricker, MD;
Claudine Blum, MD; Ursula Schild, RN;
Katharina Regez, RN; Ronald Schoenenberger, MD;
Christoph Henzen, MD; Thomas Bregenzer, MD;
Claus Hoess, MD; Martin Krause, MD; Heiner C. Bucher, MD;
Werner Zimmerli, MD; Beat Mueller, MD

Journal of the American Medical Association.
2009;302(10):1059-1066.



PCT: procalcitonin, CAP: community-acquired pneumonia, PSI: pneumonia severity index, COPD: chronic obstructive pulmonary disease, GOLD: global initiative for obstructive lung disease

Antibiotic Exposure in Patients Receiving Antibiotic Therapy

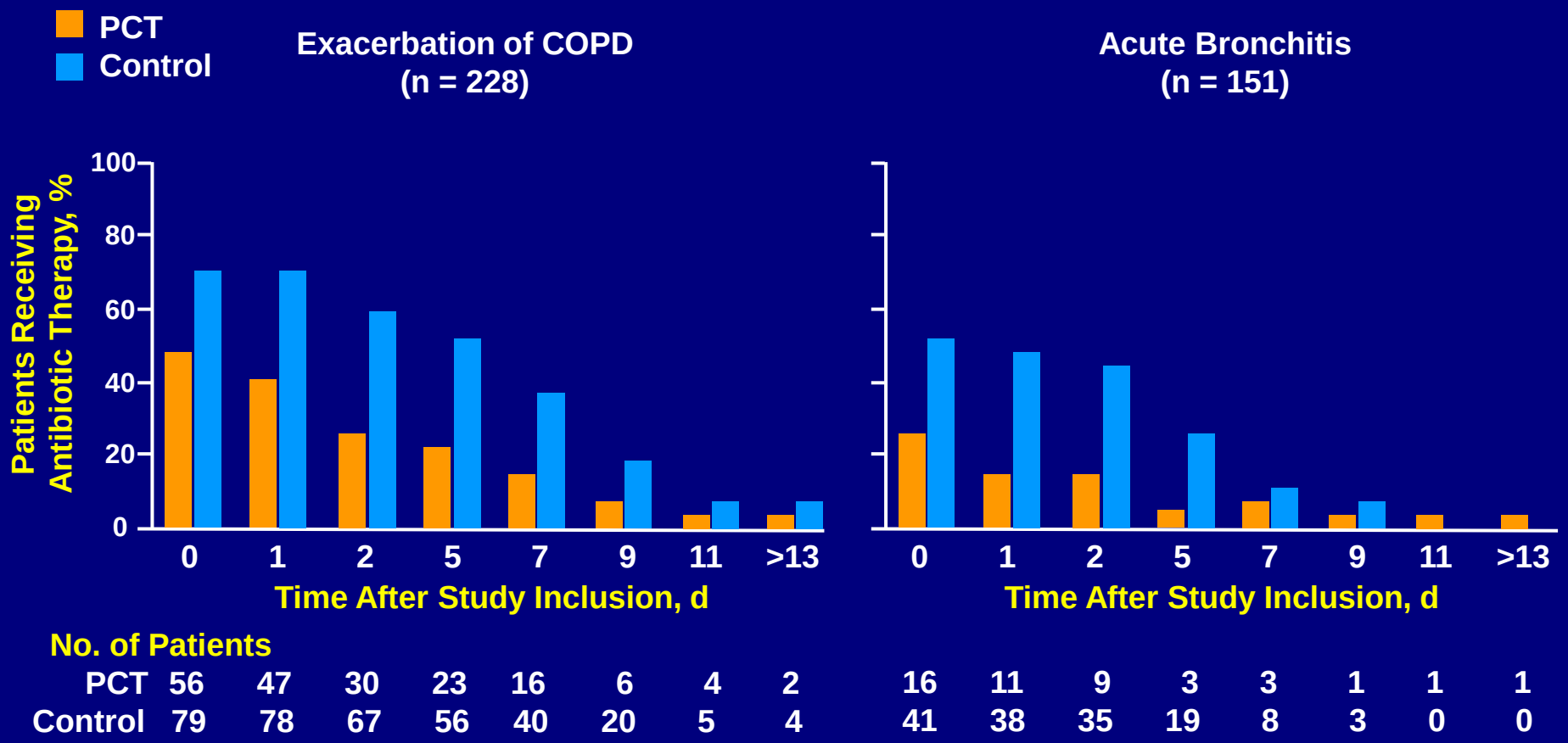


No. of Patients

PCT	506	484	410	306	207	138	72	46	417	410	359	272	161	126	64	41
Control	603	589	562	516	420	324	157	100	461	453	444	428	361	292	146	91

Schuetz P et al. *J Am Med Assoc*. 2009;302(10):1059-66.

Antibiotic Exposure in Patients Receiving Antibiotic Therapy



No. of Patients

	Exacerbation of COPD (n = 228)								Acute Bronchitis (n = 151)							
	0	1	2	5	7	9	11	>13	0	1	2	5	7	9	11	>13
PCT	56	47	30	23	16	6	4	2	16	11	9	3	3	1	1	1
Control	79	78	67	56	40	20	5	4	41	38	35	19	8	3	0	0

PCT: Procalcitoin
COPD: Chronic Obstructive Pulmonary Disease

Schuetz P et al. *J Am Med Assoc*. 2009;302(10):1059-66.

Case 5

- 75 year old female admitted through ED with severe SOB and then had apnea in ED and cardiac arrest. Has h/o CHF, DM,PVD, OSA. One round of ACLS protocol, inl. Intubation, resuscitated the pt. BP 85/40, 120, 18 on vent, 99.9 WBC 20.7,
  4 bands, Hgb 6.5, INR 6, AG 9, BNP 1369.
  Requires 15 mcg of Levo for BP control

Προβλέπει η PCT τη διασωλήνωση και την εισαγωγή στη ΜΕΘ σε ασθενείς με πνευμονία της κοινότητας?

Accepted Manuscript

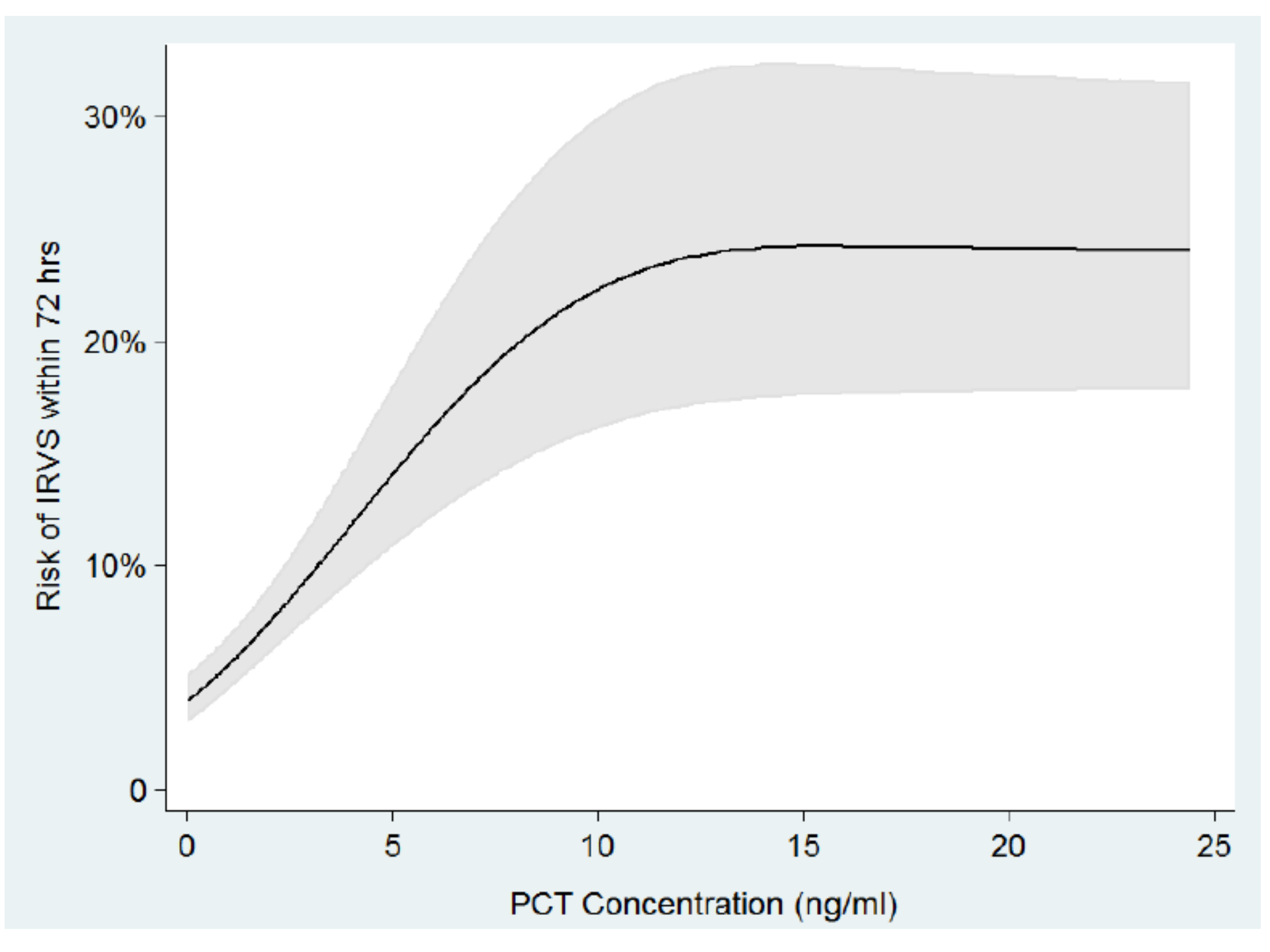
Procalcitonin as an Early Marker of the Need for Invasive Respiratory or Vasopressor Support in Adults with Community-Acquired Pneumonia

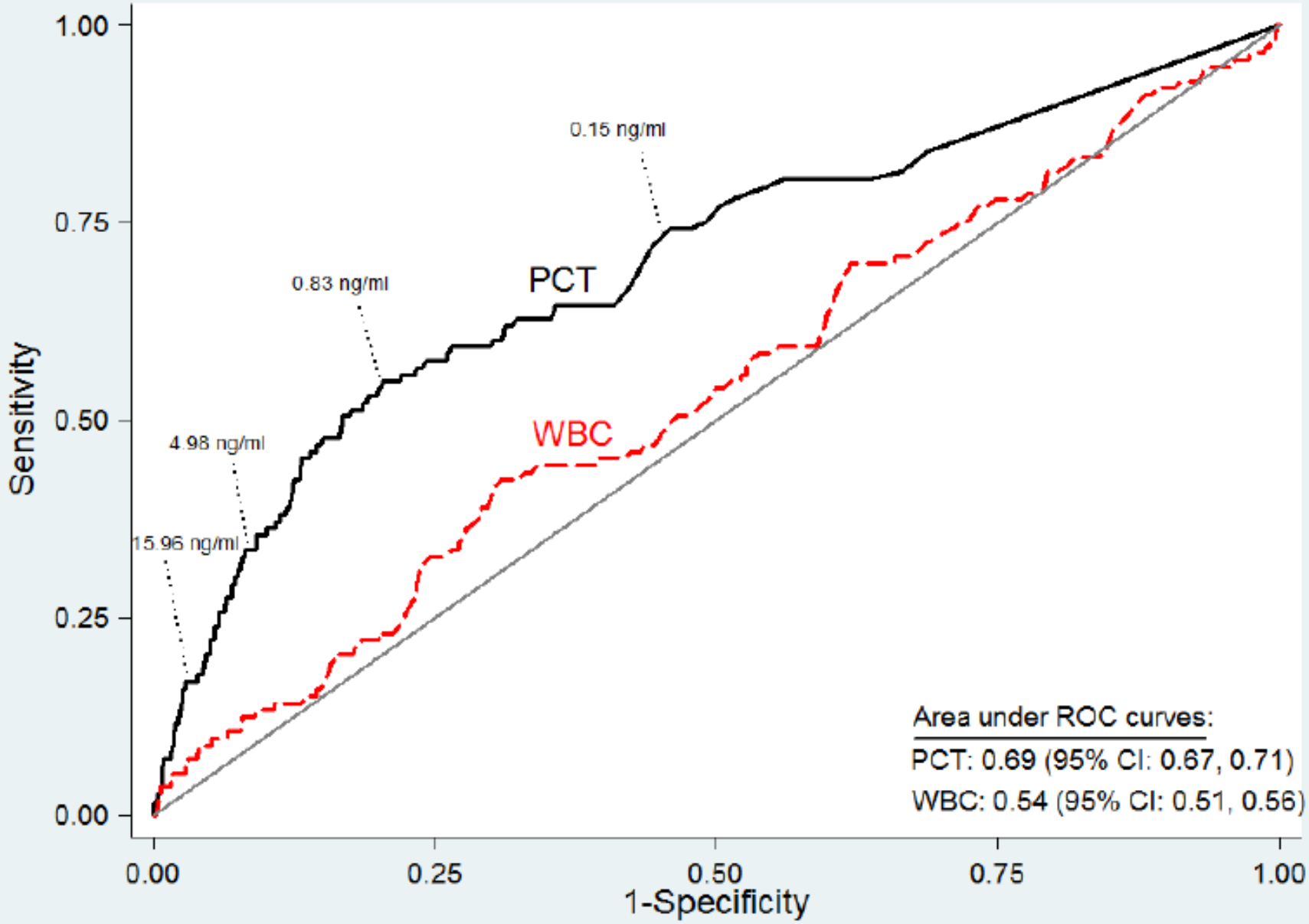
Wesley H. Self, MD, MPH, Carlos G. Grijalva, MD, MPH, Derek J. Williams, MD, MPH, Alison Woodworth, PhD, Robert A. Balk, MD, Sherene Fakhran, MD, Yuwei Zhu, MD, MS, D. Mark Courtney, MD, MSCI, James Chappell, MD, PhD, Evan J. Anderson, MD, Chao Qi, PhD, Grant W. Waterer, MD, PhD, Christopher Trabue, MD, Anna M. Bramley, MPH, Seema Jain, MD, Kathryn M. Edwards, MD, Richard G. Wunderink, MD

Chest. 2016 Oct;150(4):819-828

Results: Of 1770 enrolled patients, 115 (6.5%) required IRVS. Using the logistic regression model, procalcitonin concentration had a strong association with IRVS risk. Undetectable procalcitonin (<0.05 ng/ml) was associated with a 4.0% (95% CI: 3.1%, 5.1%) risk of IRVS. For concentrations <10 ng/ml, procalcitonin had an approximate linear association with IRVS risk; for each 1 ng/ml increase in procalcitonin, there was a 1-2% absolute increase in the risk of IRVS. With a procalcitonin concentration of 10 ng/ml, the risk of IRVS was 22.4% (95% CI: 16.3%, 30.1%) and remained relatively constant for all concentrations > 10 ng/ml. When added to each pneumonia severity score, procalcitonin contributed significant additional risk information for prediction of IRVS.

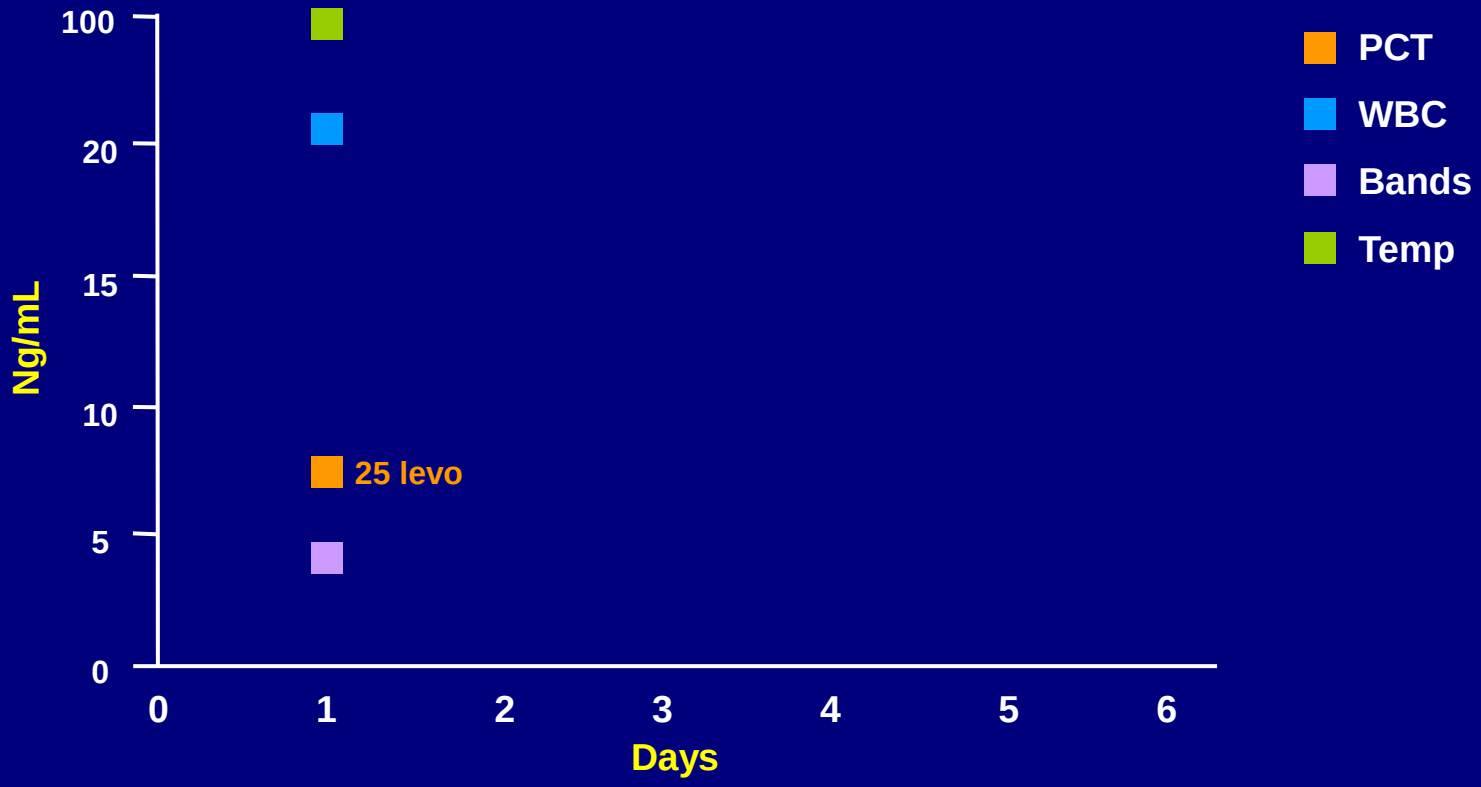
Conclusions: Serum procalcitonin concentration was strongly associated with the risk of requiring IRVS among adults hospitalized with CAP and is potentially useful for guiding decisions about intensive care unit admission.


30%
20%
10%
0
Risk of IRVS within 72 hrs
0
5
10
15
20
25
PCT Concentration (ng/ml)


1.00
0.75
0.50
0.25
0.00
Sensitivity
0.00
0.25
0.50
0.75
1.00
1-Specificity
0.15 ng/ml
0.83 ng/ml
4.98 ng/ml
15.96 ng/ml
PCT
WBC
Area under ROC curves:
PCT: 0.69 (95% CI: 0.67, 0.71)
WBC: 0.54 (95% CI: 0.51, 0.56)

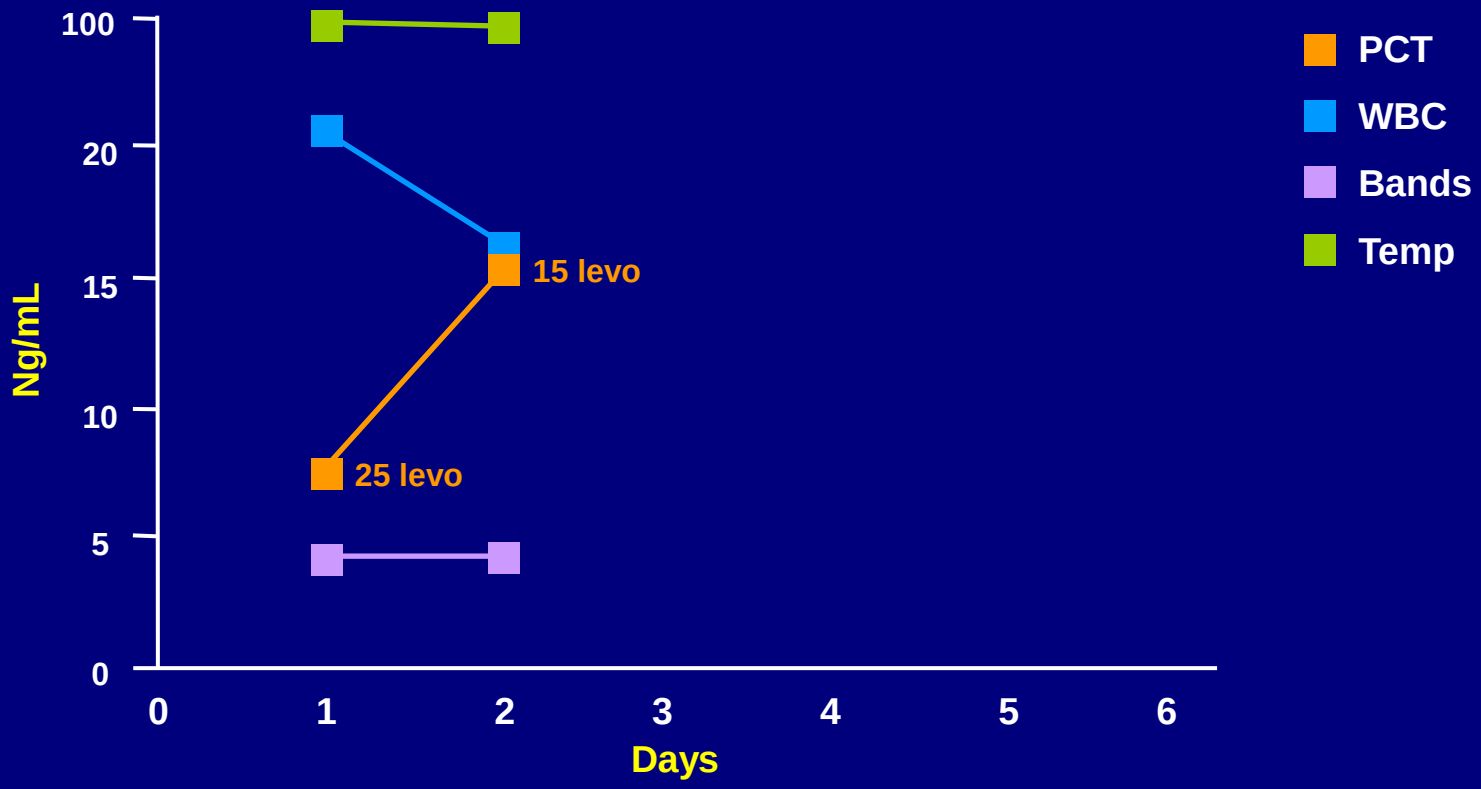
Case 5

- 75 year old female admitted through ED with severe SOB and then had apnea in ED and cardiac arrest. Has h/o CHF, DM,PVD, OSA. One round of ACLS protocol resuscitated the pt. BP 85/40, 120, 18 on vent, 99.9 WBC 20.7, 4 bands, Hgb 6.5, INR 6, AG 9, BNP 1369. Requires 15 mcg of Levo for BP control



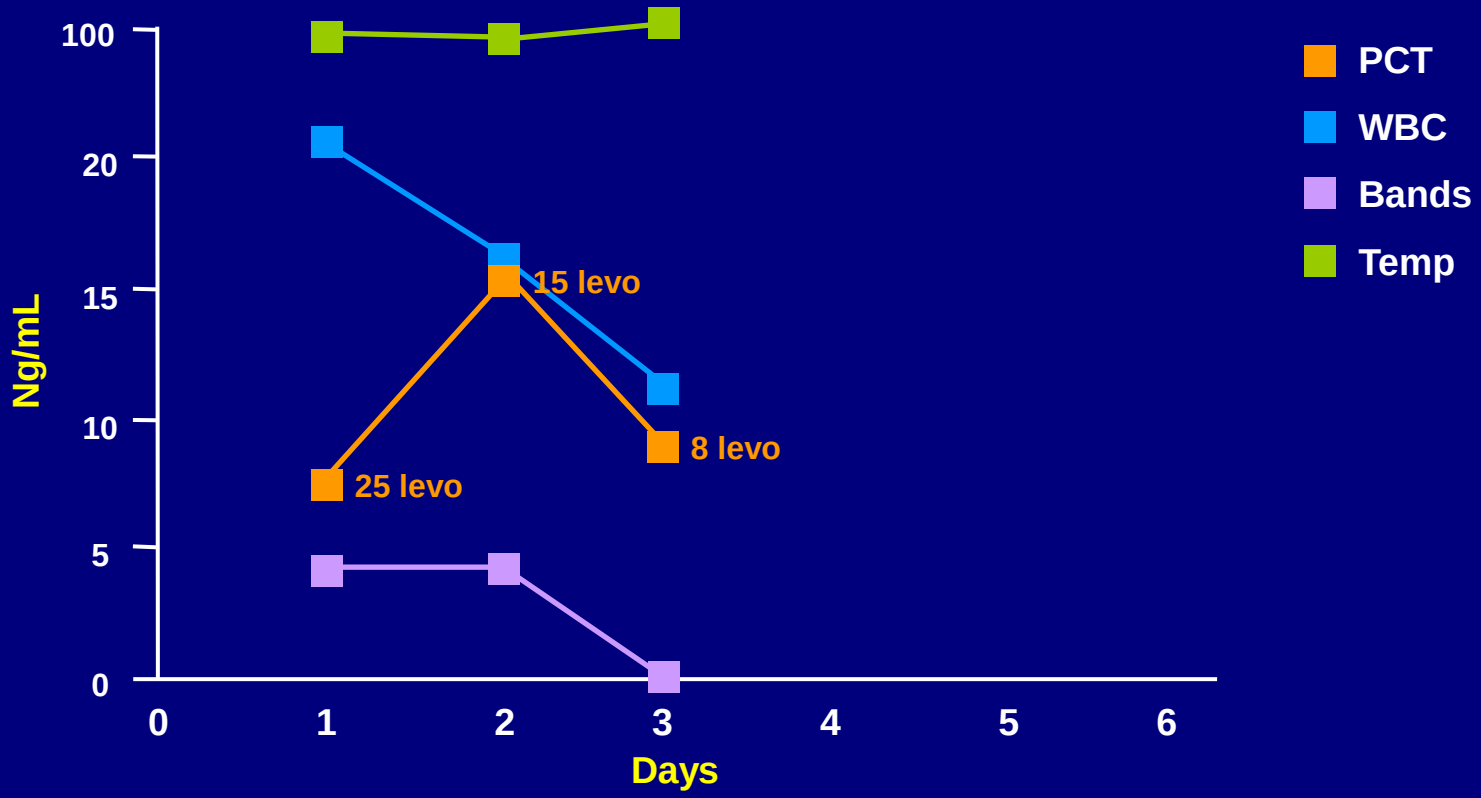
Case 5

- 75 year old female admitted through ED with severe SOB and then had apnea in ED and cardiac arrest. Has h/o CHF, DM,PVD, OSA. One round of ACLS protocol resuscitated the pt. BP 85/40, 120, 18 on vent, 99.9 WBC 20.7, 4 bands, Hgb 6.5, INR 6, AG 9, BNP 1369. Requires 15 mcg of Levo for BP control



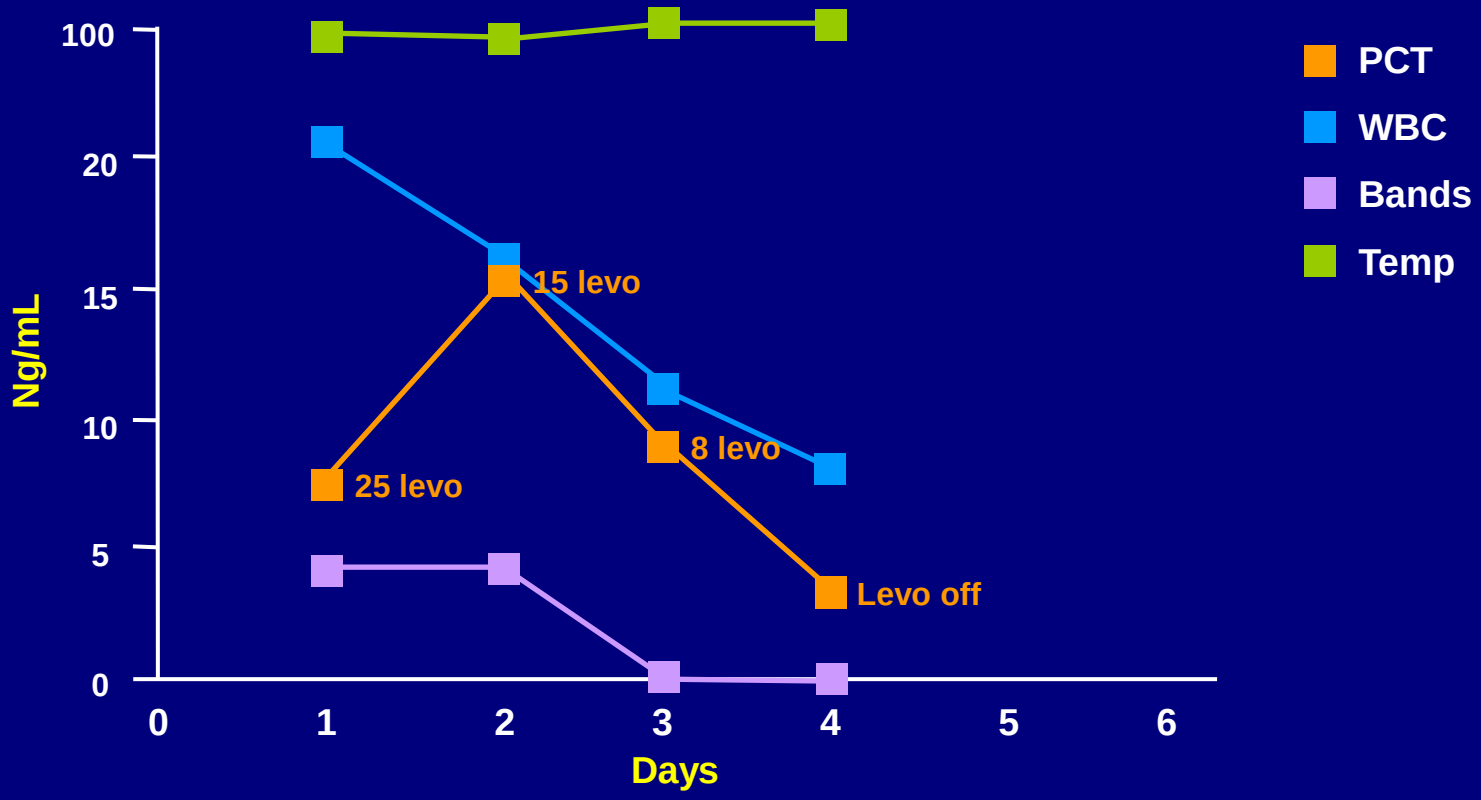
Case 5

- 75 year old female admitted through ED with severe SOB and then had apnea in ED and cardiac arrest. Has h/o CHF, DM,PVD, OSA. One round of ACLS protocol resuscitated the pt. BP 85/40, 120, 18 on vent, 99.9 WBC 20.7, 4 bands, Hgb 6.5, INR 6, AG 9, BNP 1369. Requires 15 mcg of Levo for BP control



Case 5

- 75 year old female admitted through ED with severe SOB and then had apnea in ED and cardiac arrest. Has h/o CHF, DM,PVD, OSA. One round of ACLS protocol resuscitated the pt. BP 85/40, 120, 18 on vent, 99.9 WBC 20.7, 4 bands, Hgb 6.5, INR 6, AG 9, BNP 1369. Requires 15 mcg of Levo for BP control



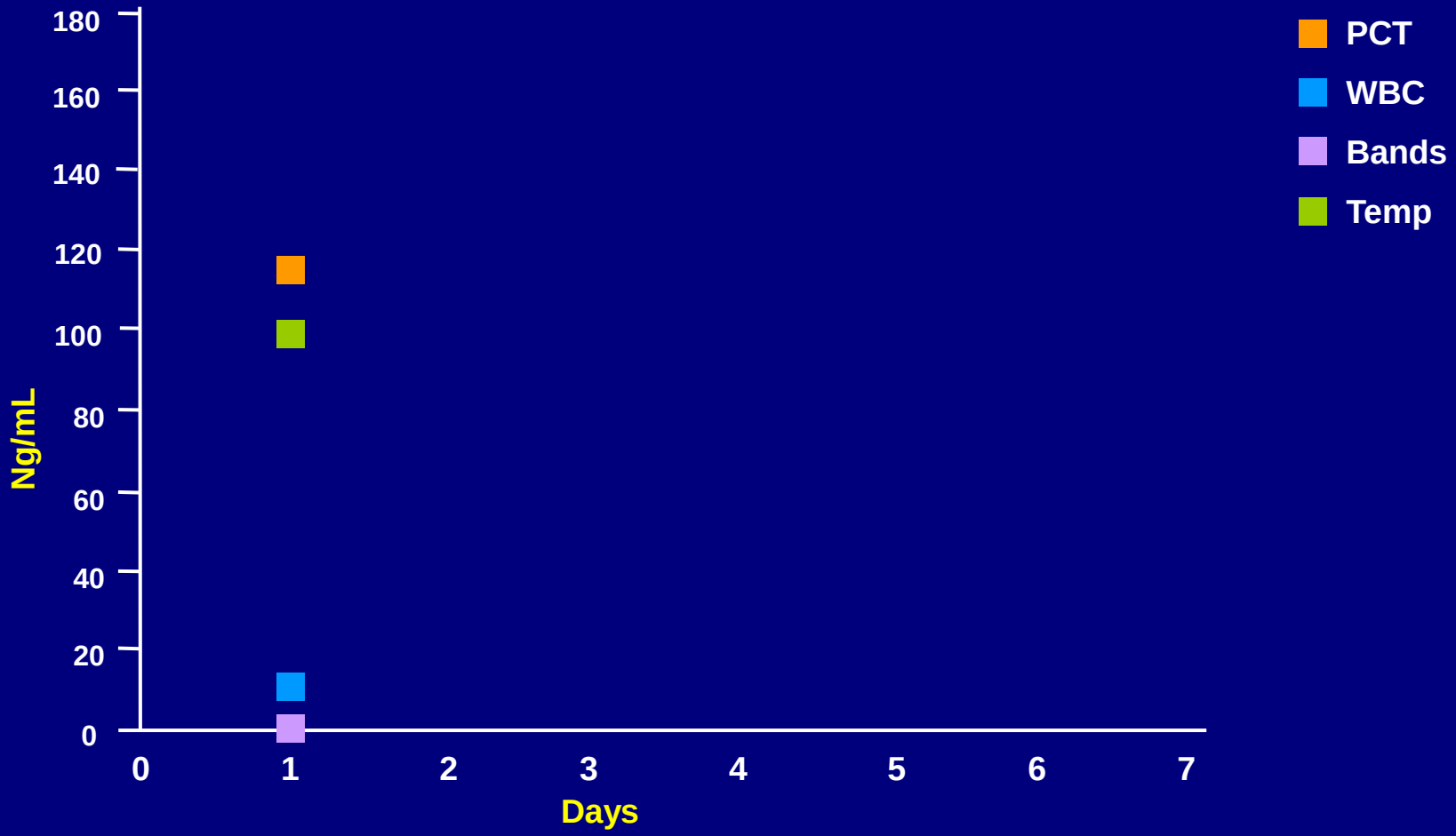
Η PCT είναι ακριβή. Ή μήπως όχι?

Case 6

- 74 year old female nursing home pts with porto-cath for chemotherapy. h/o MRSA in past. tx to hosp for decreased BP and MS changes.

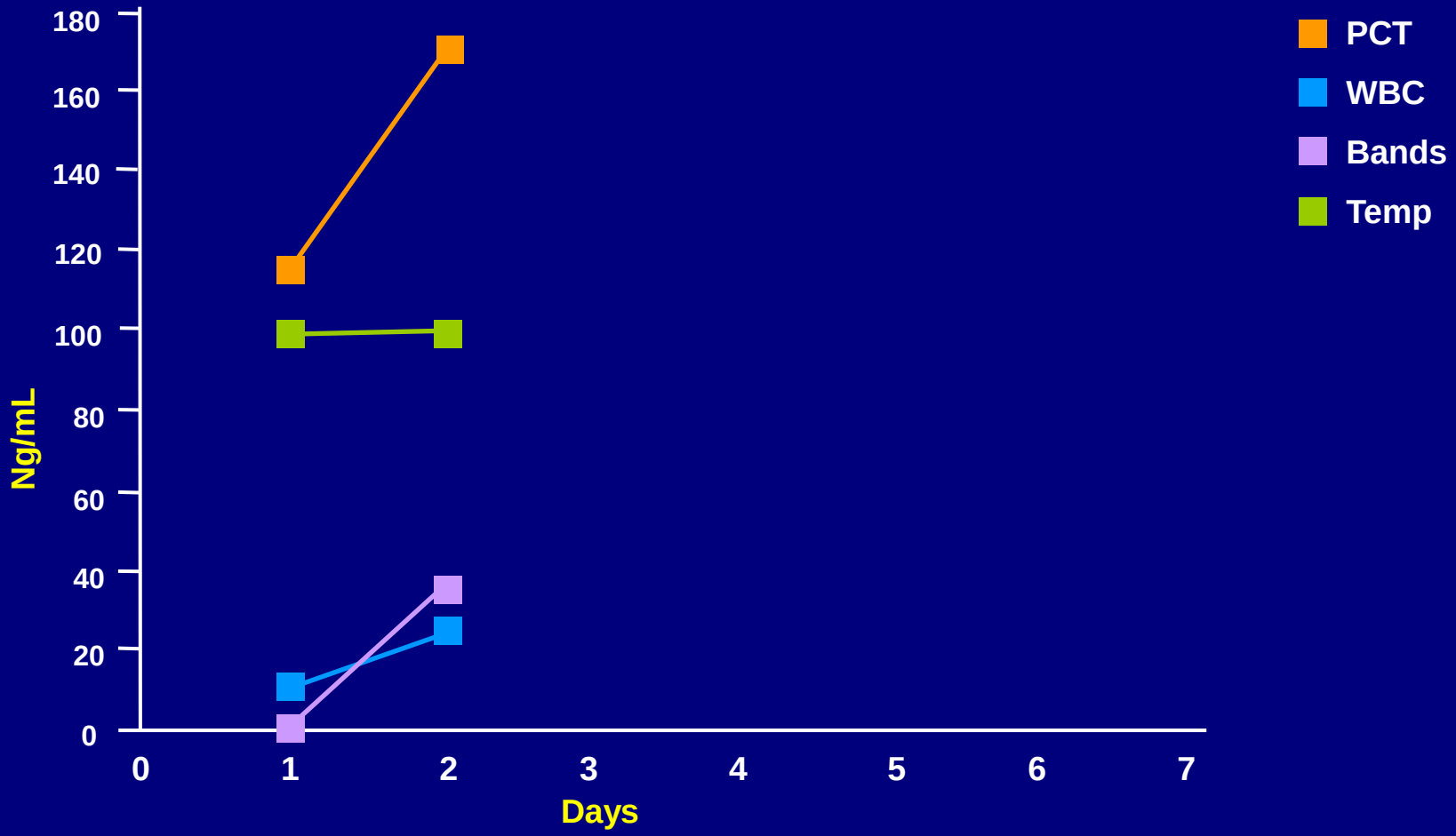
Case 6

- 74 year old female nursing home pts with porto-cath for chemotherapy. h/o MRSA in past. tx to hosp for decreased BP and MS changes.



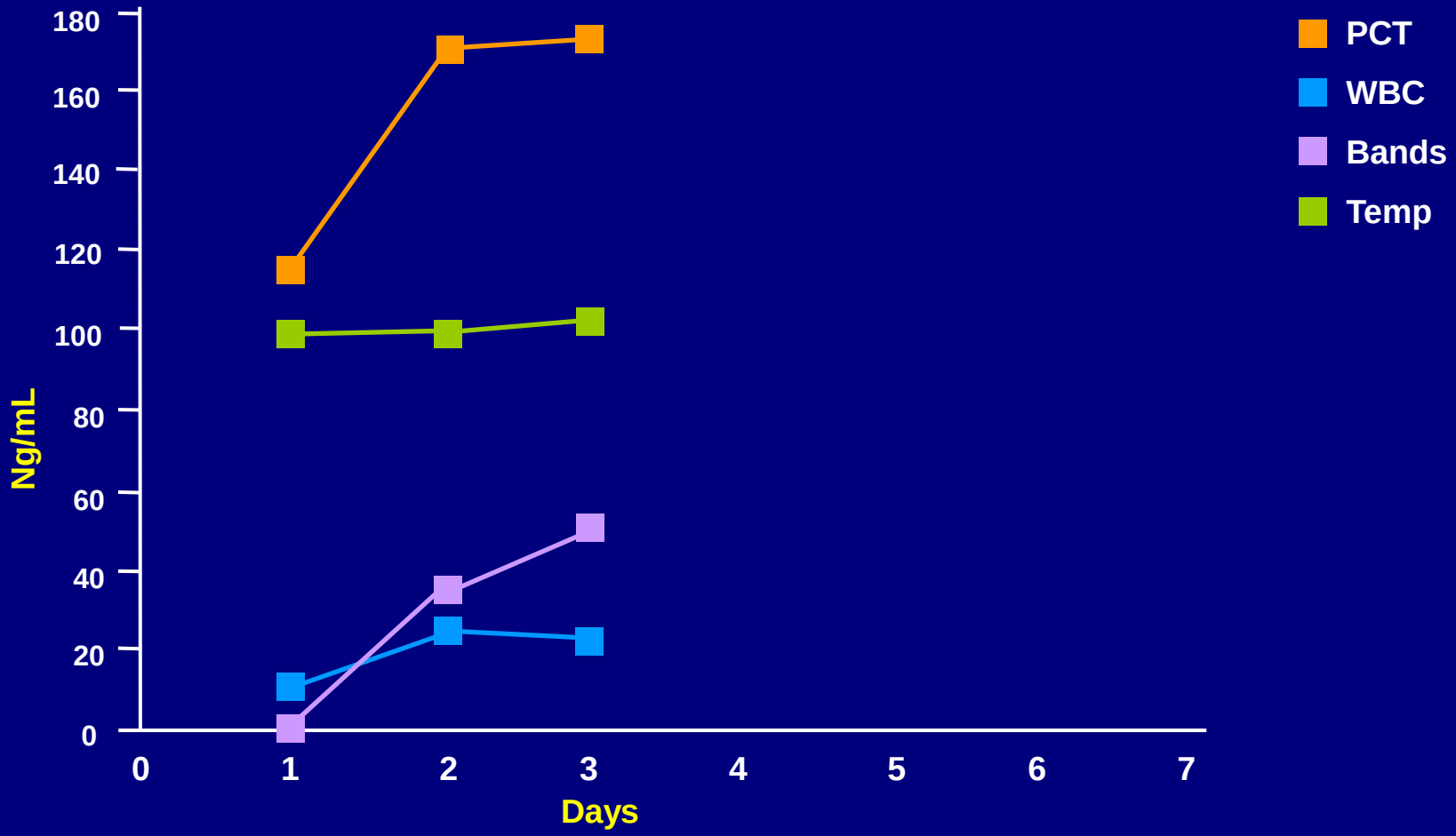
Case 6

- 74 year old female nursing home pts with porto-cath for chemotherapy. h/o MRSA in past. tx to hosp for decreased BP and MS changes.



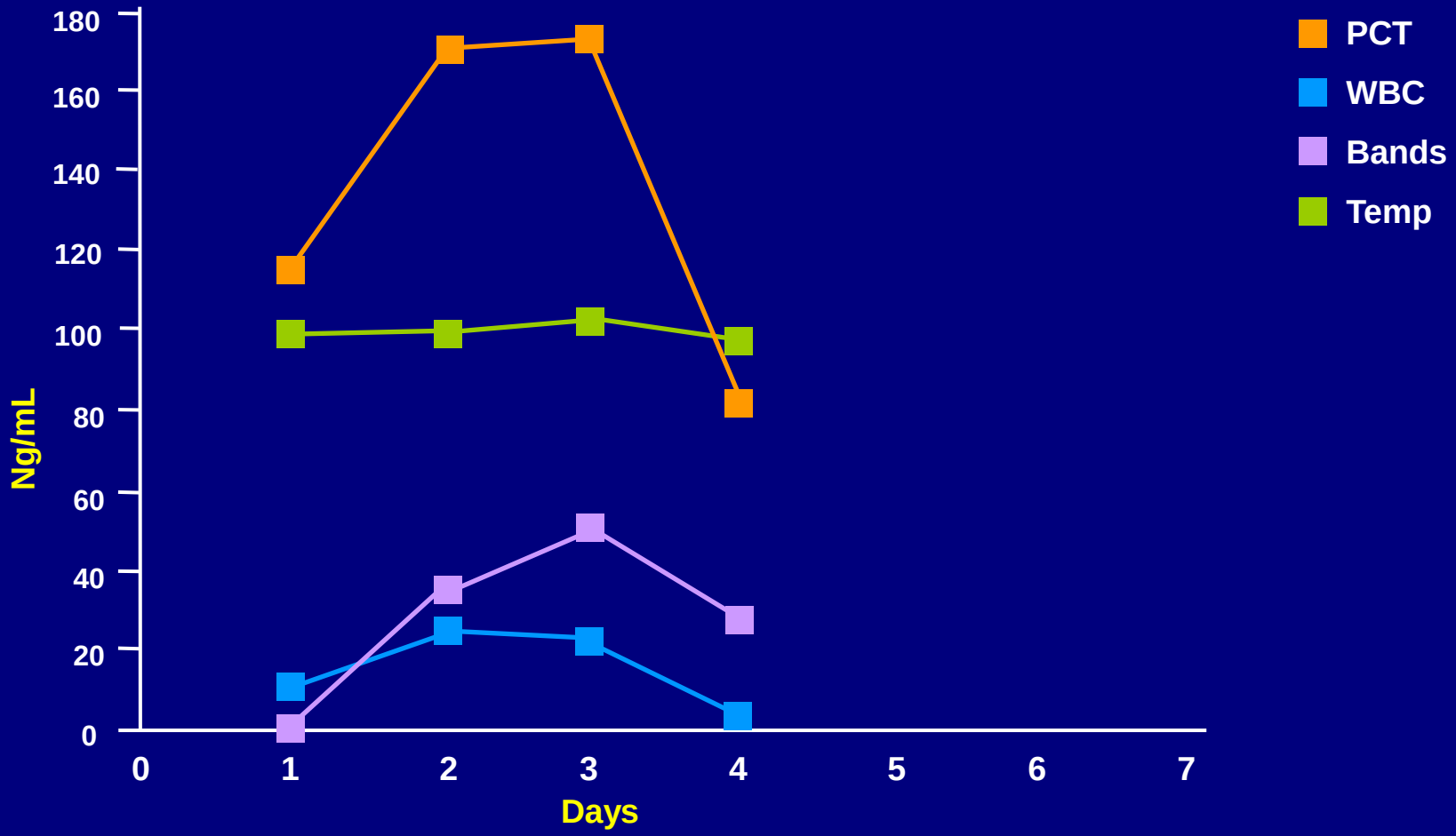
Case 6

- 74 year old female nursing home pts with porto-cath for chemotherapy. h/o MRSA in past. tx to hosp for decreased BP and MS changes.



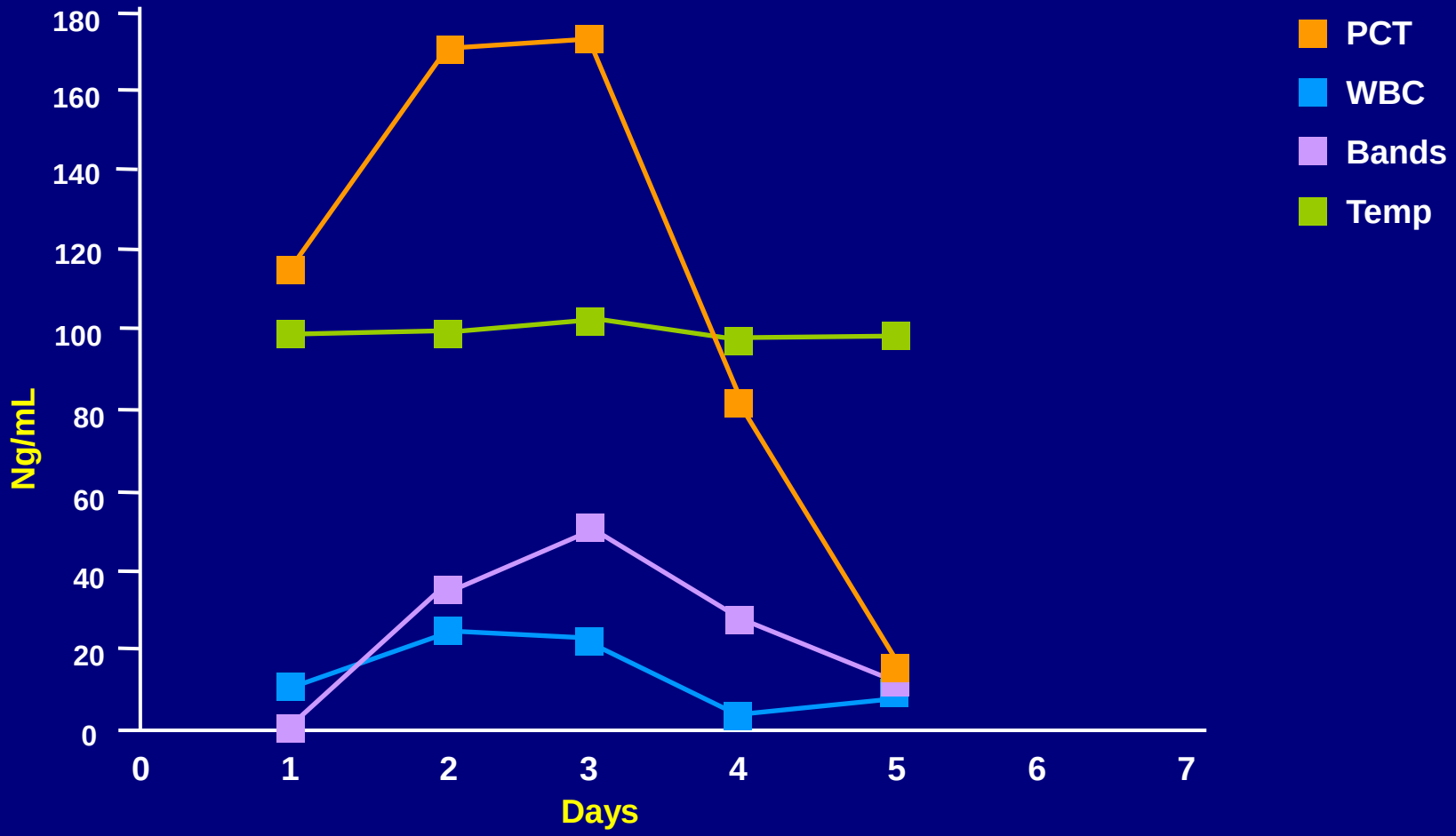
Case 6

- 74 year old female nursing home pts with porto-cath for chemotherapy. h/o MRSA in past. tx to hosp for decreased BP and MS changes.



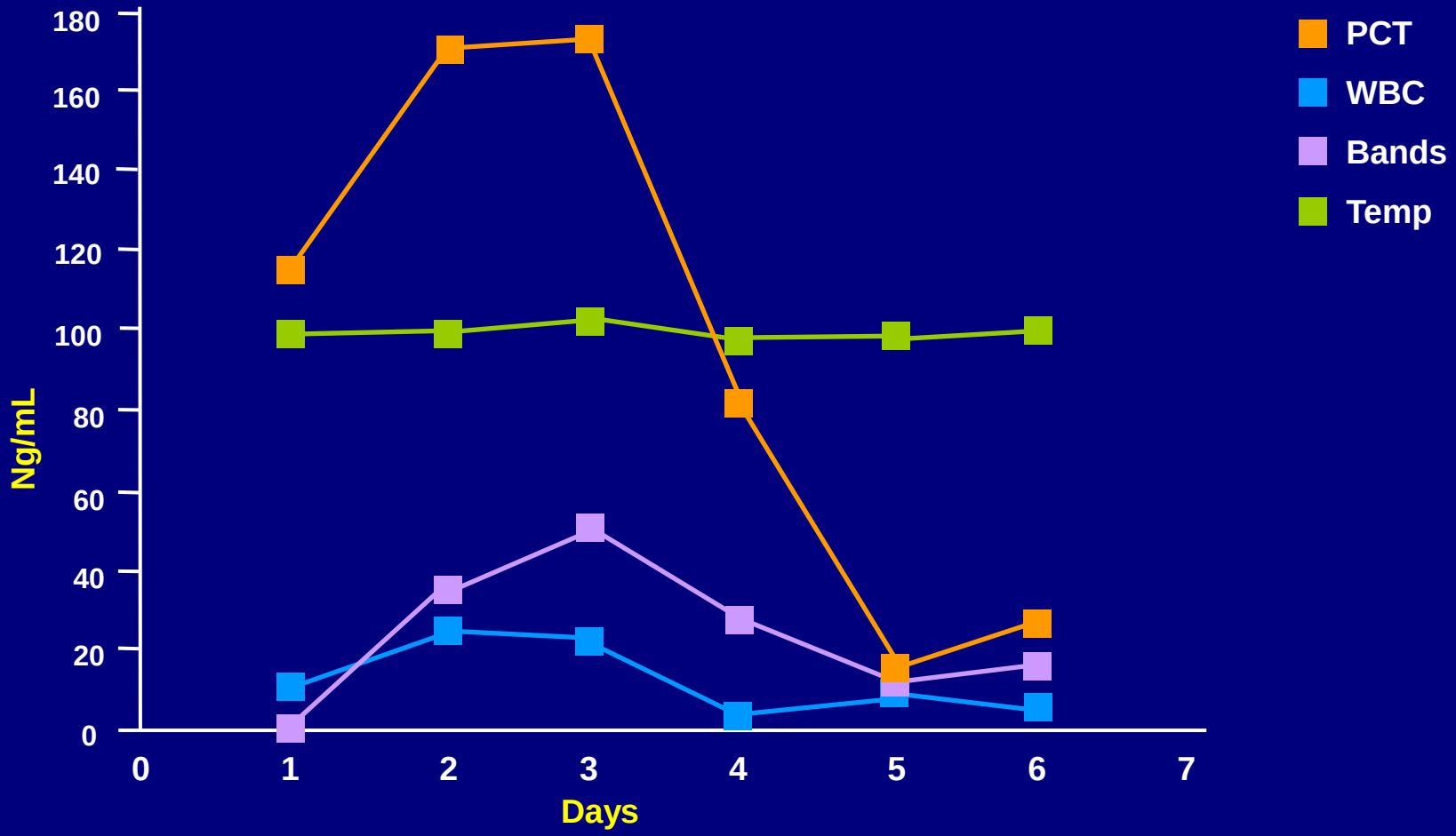
Case 6

- 74 year old female nursing home pts with porto-cath for chemotherapy. h/o MRSA in past. tx to hosp for decreased BP and MS changes.



Case 6

- 74 year old female nursing home pts with porto-cath for chemotherapy. h/o MRSA in past. tx to hosp for decreased BP and MS changes.

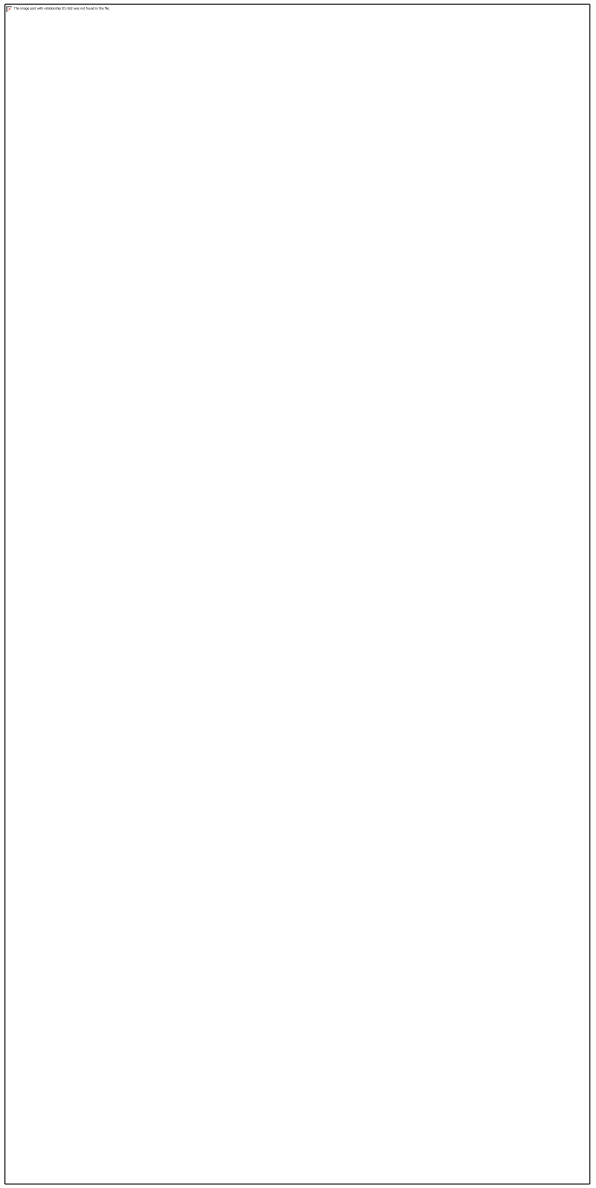


Influence of renal dysfunction on the accuracy of procalcitonin for the diagnosis of postoperative infection after vascular surgery

Julien Amour, MD, PhD; Aurélie Birenbaum, MD; Olivier Langeron, MD, PhD; Yannick Le Manach, MD; Michèle Bertrand, MD; Pierre Coriat, MD; Bruno Riou, MD, PhD; Maguy Bernard, MD, PhD; Pierre Hausfater, MD, PhD

CCM, 2008;36:1147

- 276 pts scheduled for elective major aortic surgery
- Infection was diagnosed in 67 patients.
- 75 pts (27%) had postoperative renal dysfunction.

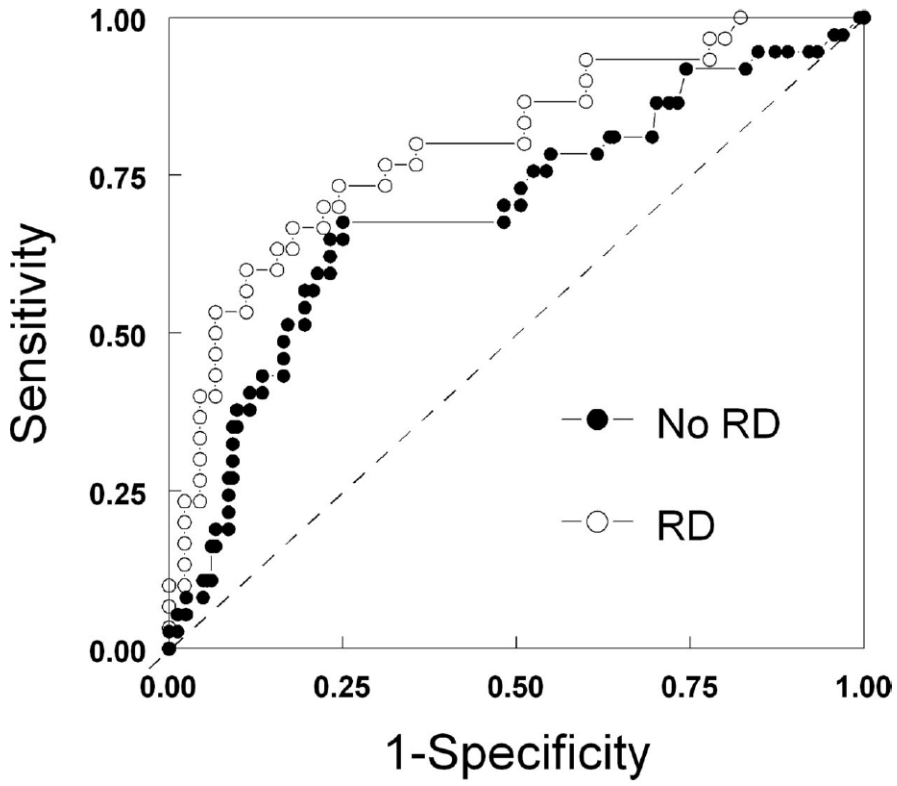


Comparison of procalcitonin in patients without (*full circles and full line, n=201) and* with postoperative renal dysfunction (*open circle* and *dotted line, n =75) in the control group* (*Panel A) and the infection group (Panel B).*

Influence of renal dysfunction on the accuracy of procalcitonin for the diagnosis of postoperative infection after vascular surgery

Julien Amour, MD, PhD; Aurélie Birenbaum, MD; Olivier Langeron, MD, PhD; Yannick Le Manach, MD; Michèle Bertrand, MD; Pierre Coriat, MD; Bruno Riou, MD, PhD; Maguy Bernard, MD, PhD; Pierre Hausfater, MD, PhD

CCM, 2008;36:1147



Variables associated with poor outcome: including ventilation>2 days, reintubation, shock (defined as catecholamine administration> 12hrs, any renal replacement therapy, and death)

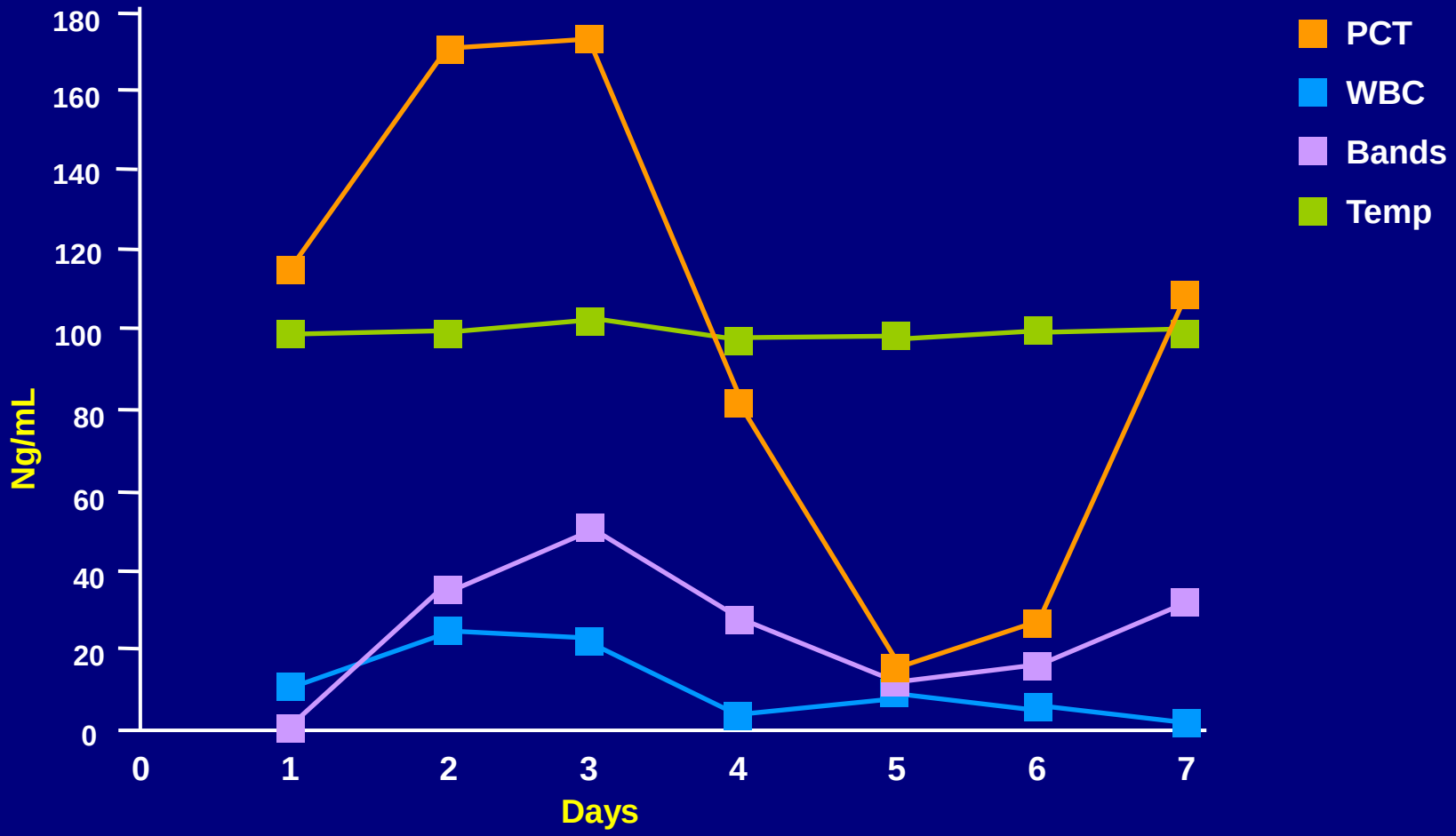
Variables	Good Outcome, n (%) (n = 199)	Poor Outcome, n (%) (n = 77)	Odds Ratio (95% CI)	*p* Value
Elevated cardiac troponin I	10 (5)	22 (29)	4.95 (1.90–12.93)	.001
Elevated procalcitonin[b]	50 (25)	49 (64)	3.24 (1.72–6.12)	<.001
Diabetes	18 (9)	22 (29)	3.28 (1.44–7.49)	.005
Elevated lactates	24 (11)	28 (42)	3.12 (1.46–6.63)	.003
ASA class 3 or 4	76 (38)	49 (64)	2.13 (1.13–4.02)	.020

Καταστάσεις όπου η PCT μπορεί να είναι ελαττώνεται χωρίς να ελέγχεται η λοίμωξη

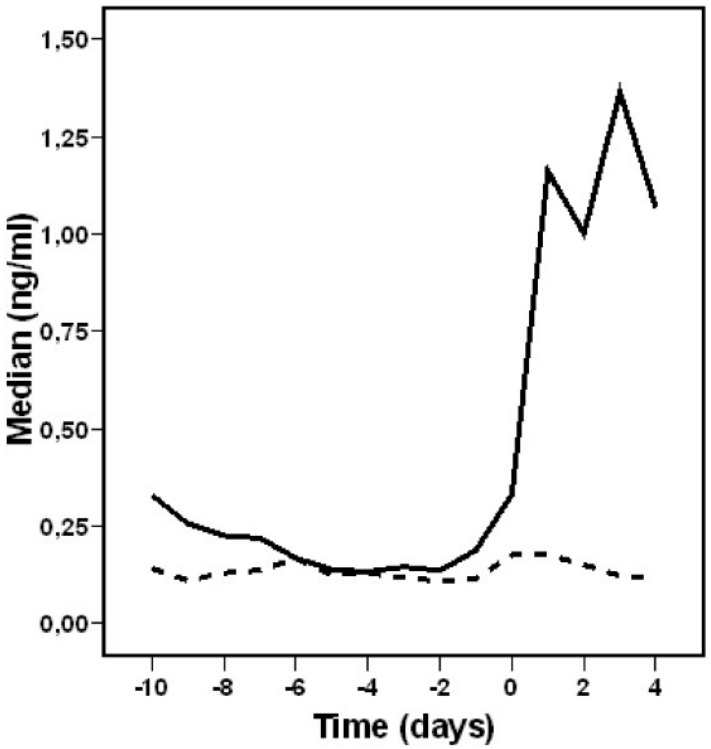
- Εντερική διατροφή
- Αιμοκάθαρση

Case 6

- 74 year old female nursing home pts with porto-cath for chemotherapy. h/o MRSA in past. tx to hosp for decreased BP and MS changes.



Chronic critically ill



- A two-fold increase of PCT between fever onset and the previous day was associated with proven infection (p 0.001) (OR = 8.55; 2.4-31.1),
- a four-fold increase of PCT of any of the 6 preceding days was associated with a positive predictive value exceeding 69.65%.
- A PCT value less than 0.5 ng/ml on the third day after the advent of fever was associated with favorable survival (p 0.01).

Accepted Manuscript

Effect of Procalcitonin Testing on Healthcare Utilization and Costs in Critically Ill Patients in the United States

Robert A. Balk, MD, Samuel A. Bozzette, MD, PhD, Zhun Cao, PhD, Sameer S. Kadri, MD, MS., Craig B. Lipkin, MS, Scott B. Robinson, MA, MPH

Background: There is a growing use of Procalcitonin (PCT) to facilitate the diagnosis and management of severe sepsis. We investigated the impact of 1-2 PCT determinations on ICU day 1 on healthcare utilization and cost in a large research database.

Conclusions: Use of PCT testing on the first day of ICU admission was associated with significantly lower hospital and ICU length of stay, as well as decreased total, ICU, and pharmacy cost of care. Further elucidation of clinical outcomes requires additional data.

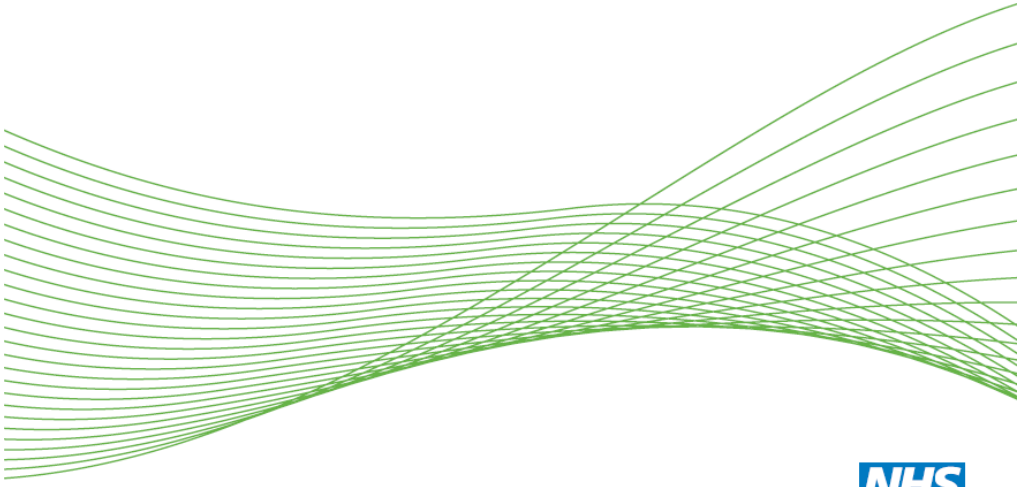
Chest 2017 Jan;151(1):23-33

HEALTH TECHNOLOGY ASSESSMENT

VOLUME 19 ISSUE 96 NOVEMBER 2015
ISSN 1366-5278

Procalcitonin testing to guide antibiotic therapy for the treatment of sepsis in intensive care settings and for suspected bacterial infection in emergency department settings: a systematic review and cost-effectiveness analysis

Marie Westwood, Bram Ramaekers, Penny Whiting, Florian Tomini, Manuela Joore, Nigel Armstrong, Steve Ryder, Lisa Stirk, Johan Severens and Jos Kleijnen



DOI 10.3310/hta19960

NHS
National Institute for Health Research

2016 ‘Surviving Sepsis Campaign’ guidelines

- (a) PCT levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but who subsequently have limited clinical evidence of infection and
- (b) that measurement of PCT can be used to support shortening the duration of antimicrobial therapy in sepsis patients

Recommendations 2021	Recommendation Strength and Quality of Evidence	Changes From 2016 Recommendations
INFECTION		
11. For adults with suspected sepsis or septic shock but unconfirmed infection, we recommend continuously re-evaluating and searching for alternative diagnoses and discontinuing empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected.	***Best practice statement***	
12. For adults with possible septic shock or a high likelihood for sepsis, we recommend administering antimicrobials immediately, ideally within 1 hr of recognition.	***Strong,*** *low quality of evidence (Septic shock)* ***Strong,*** *very low quality of evidence (Sepsis without shock)*	**CHANGED from previous:** "We recommend that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock" ***strong recommendation,*** *moderate quality of evidence*
13. For adults with possible sepsis without shock, we recommend rapid assessment of the likelihood of infectious versus noninfectious causes of acute illness.	***Best practice statement***	
14. For adults with possible sepsis without shock, we suggest a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 hr from the time when sepsis was first recognized.	***Weak,*** *very low quality of evidence*	**NEW from previous:** "We recommend that administration of IV antimicrobials should be initiated as soon as possible after recognition and within 1 hr for both a) septic shock and b) sepsis without shock" ***strong recommendation,*** *moderate quality of evidence*
15. For adults with a low likelihood of infection and without shock, we suggest deferring antimicrobials while continuing to closely monitor the patient.	***Weak,*** *very low quality of evidence*	**NEW from previous:** "We recommend that administration of IV antimicrobials should be initiated as soon as possible after recognition and within 1 hr for both a) septic shock and b) sepsis without shock" ***strong recommendation,*** *moderate quality of evidence*
16. For adults with suspected sepsis or septic shock, we suggest against using procalcitonin plus clinical evaluation to decide when to start antimicrobials, as compared to clinical evaluation alone.	***Weak,*** *very low quality of evidence*	
17. For adults with sepsis or septic shock at high risk of MRSA, we recommend using empiric antimicrobials with MRSA coverage over using antimicrobials without MRSA coverage.	***Best practice statement***	**NEW from previous:** "We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage." ***Strong recommendation,*** *moderate quality of evidence*

Recommendations 2021	Recommendation Strength and Quality of Evidence	Changes From 2016 Recommendations
18. For adults with sepsis or septic shock at low risk of MRSA, we suggest against using empiric antimicrobials with MRSA coverage, as compared with using antimicrobials without MRSA coverage.	***Weak,*** *low quality of evidence*	**NEW from previous:** "We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage." ***Strong recommendation,*** *moderate quality of evidence*
19. For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we suggest using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent.	***Weak,*** *very low quality of evidence*	
20. For adults with sepsis or septic shock and low risk for multidrug resistant (MDR) organisms, we suggest against using two gram-negative agents for empiric treatment, as compared to one gram-negative agent.	***Weak,*** *very low quality of evidence*	
21. For adults with sepsis or septic shock, we suggest against using double gram-negative coverage once the causative pathogen and the susceptibilities are known.	***Weak,*** *very low quality of evidence*	
22. For adults with sepsis or septic shock at high risk of fungal infection, we suggest using empiric antifungal therapy over no antifungal therapy.	***Weak,*** *low quality of evidence*	**NEW from previous:** "We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage." ***Strong recommendation,*** *moderate quality of evidence*
23. For adults with sepsis or septic shock at low risk of fungal infection, we suggest against empiric use of antifungal therapy	***Weak,*** *low quality of evidence*	**NEW from previous:** "We recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage. " ***Strong recommendation,*** *moderate quality of evidence*
24. We make no recommendation on the use of antiviral agents.	***No recommendation***	
25. For adults with sepsis or septic shock, we suggest using prolonged infusion of beta-lactams for maintenance (after an initial bolus) over conventional bolus infusion.	***Weak,*** *moderate-quality evidence*	

Recommendations 2021	Recommendation Strength and Quality of Evidence	Changes From 2016 Recommendations
26. For adults with sepsis or septic shock, we recommend optimising dosing strategies of antimicrobials based on accepted pharmacokinetic/pharmacodynamic (PK/PD) principles and specific drug properties.	***Best practice statement***	
27. For adults with sepsis or septic shock, we recommend rapidly identifying or excluding a specific anatomical diagnosis of infection that requires emergent source control and implementing any required source control intervention as soon as medically and logistically practical.	***Best practice statement***	
28. For adults with sepsis or septic shock, we recommend prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established.	***Best practice statement***	
29. For adults with sepsis or septic shock, we suggest daily assessment for de-escalation of antimicrobials over using fixed durations of therapy without daily reassessment for de-escalation.	***Weak,*** *very low quality of evidence*	
30. For adults with an initial diagnosis of sepsis or septic shock and adequate source control, we suggest using shorter over longer duration of antimicrobial therapy.	***Weak,*** *very low quality of evidence*	
31. For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we suggest using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone.	***Weak,*** *low quality of evidence*	