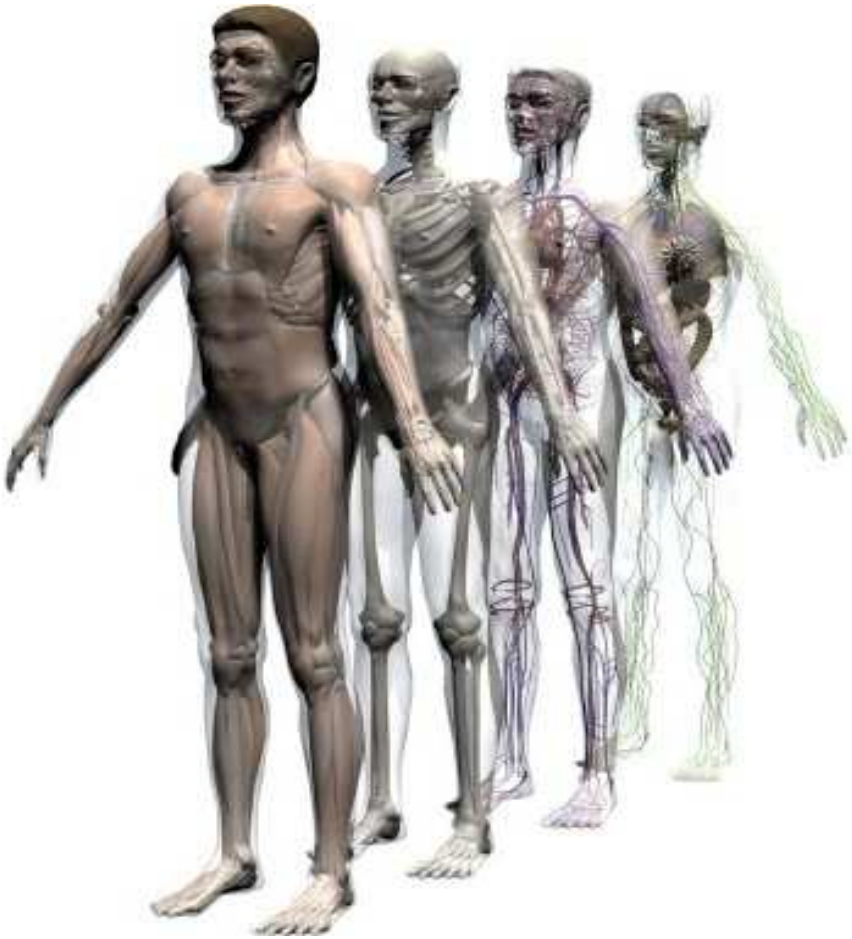


Procalcitonin a kritikus állapot prediktora

Fazakas János, PhD, egyetemi docens
Semmelweis Egyetem, Transzplantációs és Sebészeti Klinika

Procalcitonin a kritikus állapot prediktora

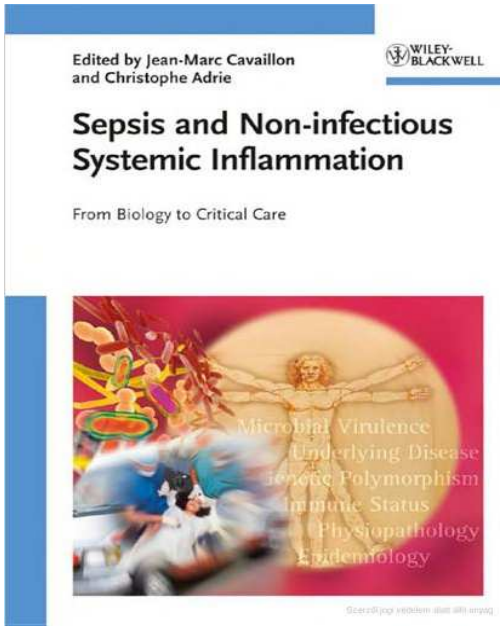
… PCT abszolút érték a SBO vagy ITO felvételnél … (PCT indukció ?)

… maximális PCT érték … (PCT indukció nagysága ?)

… PCT értékek változása – kinetika … (PCT reindukció ???)

… akut kritikus állapot, immunszupprimált állapot, krónikus kritikus állapot…..

Veleszületett immunválasz + „DAMP / PAMP”



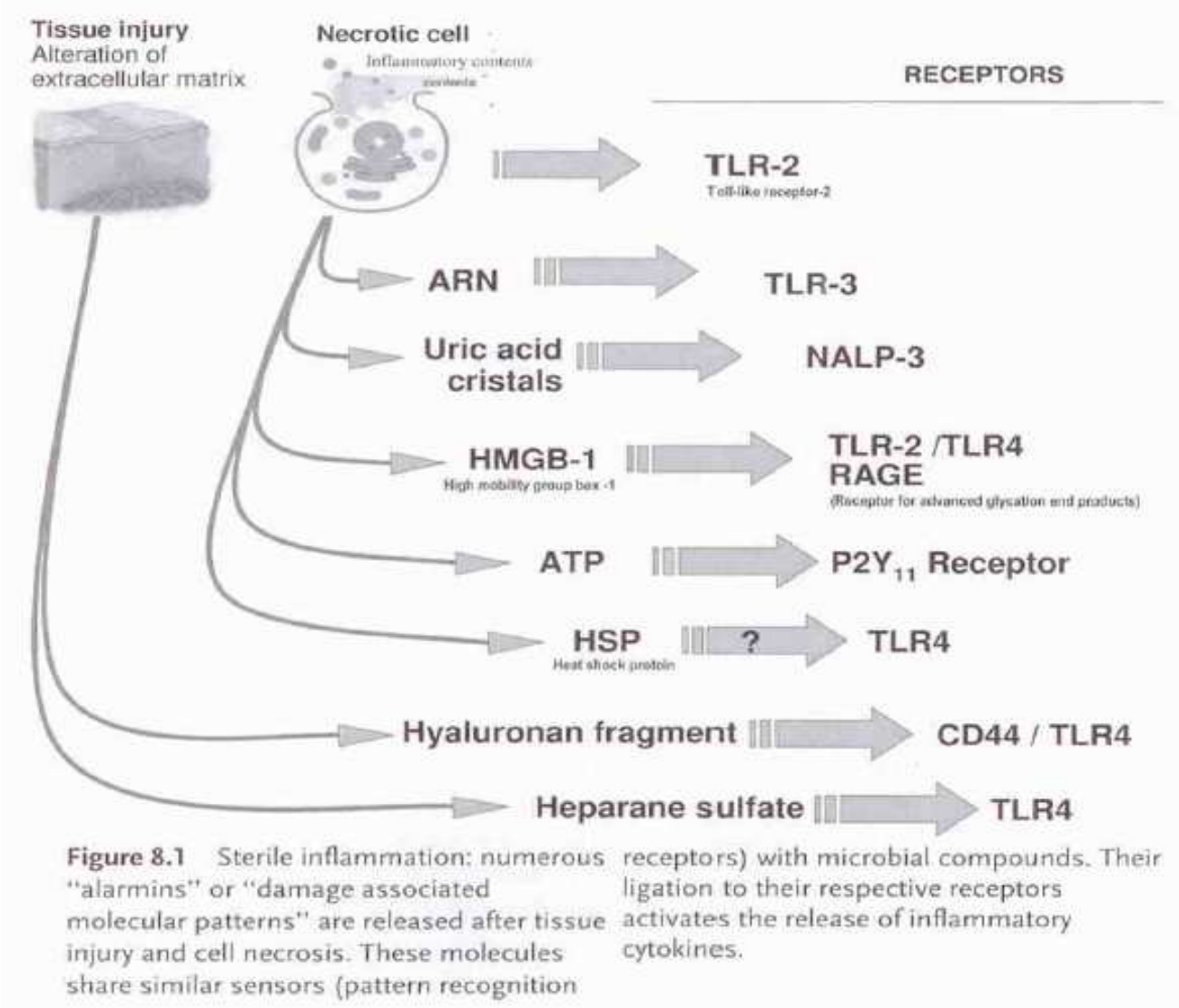


Figure 8.1 Sterile inflammation: numerous "alarmins" or "damage associated molecular patterns" are released after tissue injury and cell necrosis. These molecules share similar sensors (pattern recognition receptors) with microbial compounds. Their ligation to their respective receptors activates the release of inflammatory cytokines.

gyulladásos triggerelés: sejt stressz, inzultus, kórokozó

leucocyta, lymphocyta, „endothel”, „parenchima” sejtek
TLR4, CD14, MD2, mannoz-MBL, NOD, NALP, „P” anyag

humorális válasz „repertoár”

kaszkád aktiváció alvadás, komplement	citokinek + velük összefüggő faktorok	akut fázis fehérjék	stressz hormonok	hormokinek	citoplazma faktorok

immun-reguláció

IFN-γ
Il-2
IL-4
IL-5
IL-7
IL-11

pro-inflammáció

MIF
IL-1β
IL-6
IL-8
IL-12
IL-11
IL-18
NO
PGs
TNF-α

adhesio molek.
kemokinek
elasztáz
endhotelin
növekedési fakt.
IL-1 decoy
LTs
proteázok
ROI
TBs

anti-inflammáció

IL-4
IL-6
IL-10
IL-11
IL-13
IL-ra
Leptin
NO
TNF
TGF-β

α1-glikoprot.
ferritin
fibronectin
haptoglobin
LPS prot.
SAA

CRP

ACTH
AVP
GH
cortisol
prolactin
histamin
NA, Adr.
endorphin

ADM
CGRP

PCT

IL-6
leptin
MIF

HS protein
HMG-1
NO

Szepszis irányelvek ?

INTENSIVE CARE MEDICINE

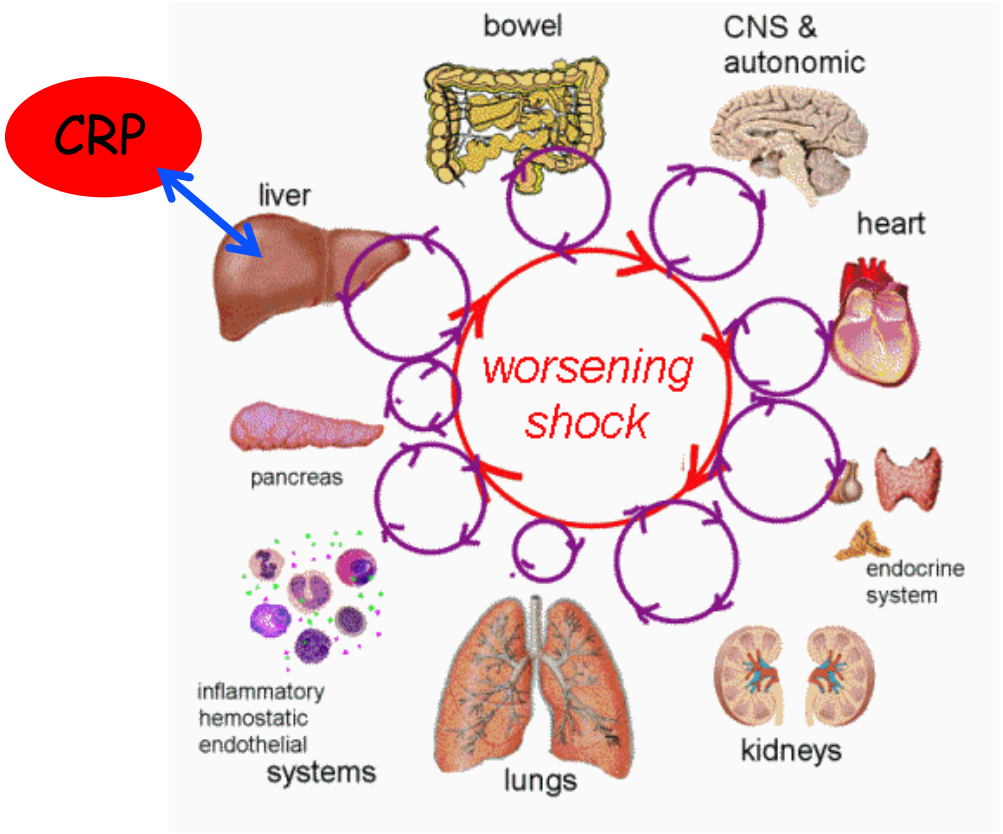
Is C-reactive protein a good prognostic marker in septic patients?

Silvestre J . Intensive Care Med. 2009;35:909-13

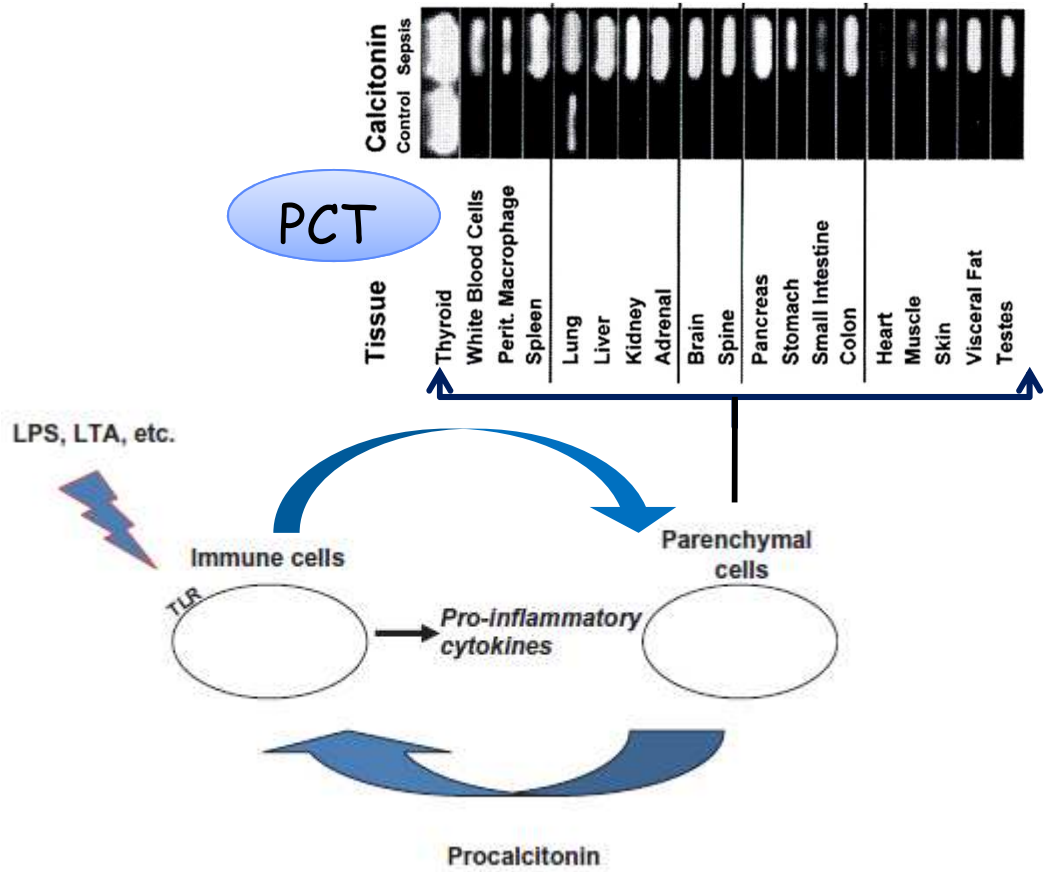
	All (n = 158)	Survivors (n = 104)	Nonsurvivors (n = 54)	P values
Age (years)	58.6 ± 16.9	55.9 ± 17.1	63.8 ± 15.3	0.005
Sex (M/F)	98/60	63/41	35/19	0.656
APACHE II	21.2 ± 7.5	18.8 ± 6.3	26.0 ± 7.3	<0.001
SAPS II	47.2 ± 15.1	41.5 ± 11.7	58.2 ± 14.7	<0.001
SOFA	8.1 ± 3.6	6.7 ± 2.7	10.6 ± 3.6	<0.001
CRP (mg/dL)		25.3 ± 13.7	28.2 ± 13.1	0.15
Temperature (°C)		38.0 ± 0.9	37.9 ± 1.1	0.81
WCC (×1,000) mL^{-1}		15.4 ± 10.9	16.2 ± 13.7	0.7
Primary admission diagnosis (N)				0.289
Respiratory	64	46	18	
Cardiovascular	15	11	4	
Neurology	14	10	4	
Surgical	32	15	17	
Trauma	14	10	4	
Obstetrics	6	3	3	
Others	13	9	4	
Comorbidities (N)				
Neoplasm	21	12	9	
Chronic pulmonary disease	19	14	5	
Congestive heart failure	16	11	5	
Diabetes	9	6	3	
Ulcer disease	5	3	2	
Myocardial infarct	3	2	1	
Chronic renal disease	2	1	1	
Dementia	2	1	1	
Mild liver disease	1	0	1	
AIDS	1	0	1	

…kritikusabb állapot… … több szerv… …több procalcitonin…

Immunsejt alapú termelődés

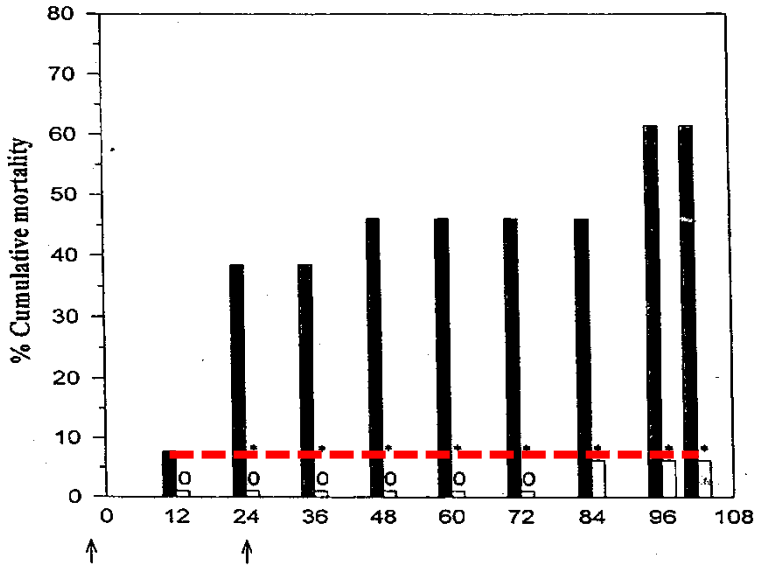


Szöveti alapú termelődés



Procalcitonin in sepsis and systemic inflammation: a biomarker and a therapeutic target. Br J Pharm 2010, 159: 253-264

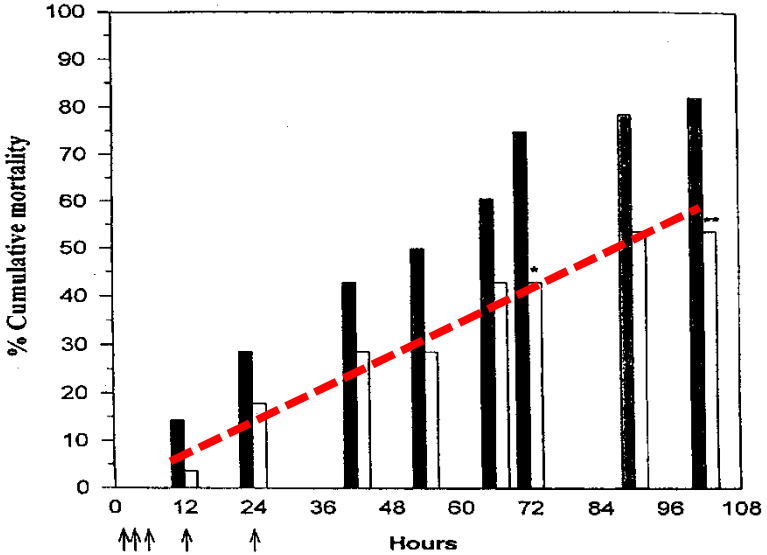
PCT toxikus tulajdonsága



Nylen ES et al, *Crit Care Med* 1998; 26: 1001

Sötét oszlop: kontrol (*E. coli)*

Világos oszlop: PCT-antiszérum előkezelés + *E. coli*



Sötét oszlop: kontrol (*E. coli)*

Világos oszlop: PCT-antiszérum kezelés + *E. coli*

ACCURACY OF PROCALCITONIN FOR OUTCOME PREDICTION IN UNSELECTED POSTOPERATIVE CRITICALLY ILL PATIENTS

Schenider et al. *Shock* 2009; 31: 568-573

… PCT abszolút érték a SBO vagy ITO felvételnél …

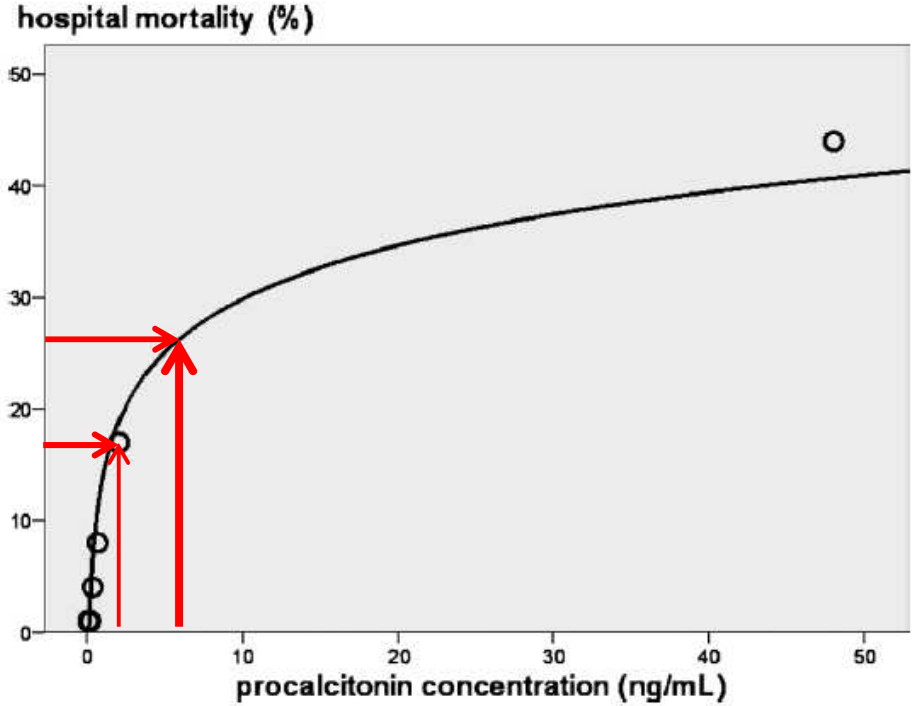
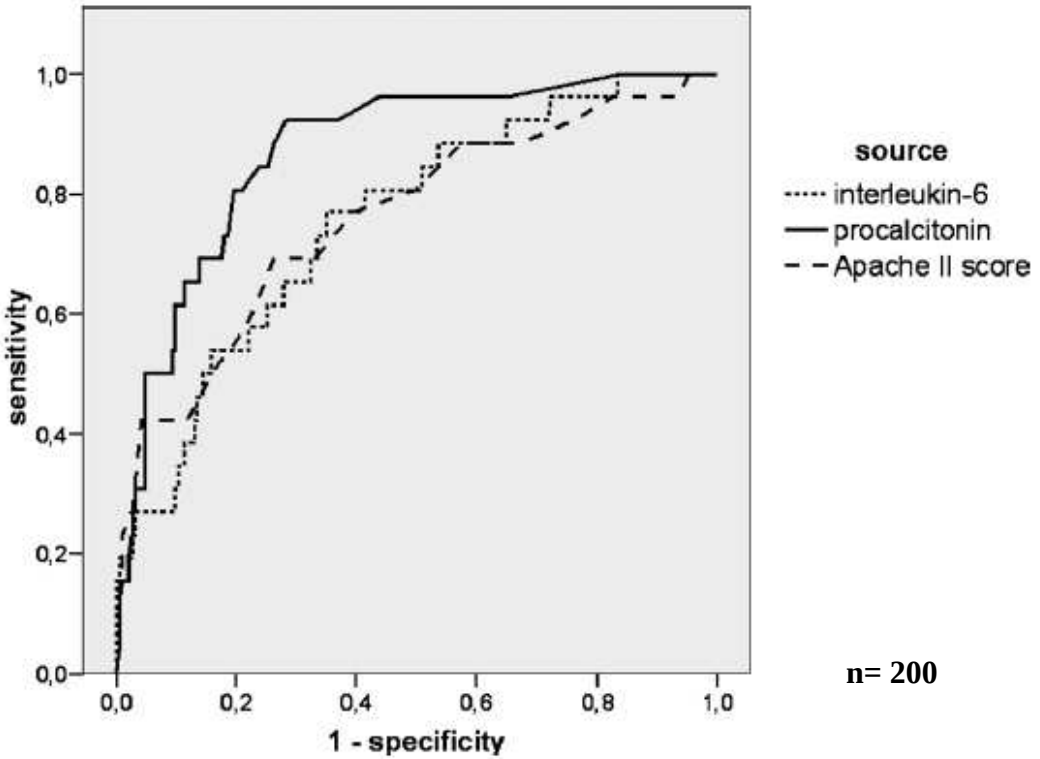


FIG. 1. **Univariate association between PCT concentration on day 1 after ICU admission and mortality.** Circles represent mean values of 0% to 16.7%, 16.7% to 33.3%, 33.3% to 50.0%, 50.0% to 66.7%, 66.7% to 83.3%, and 83.3% to 100% sixtiles of PCT concentrations. The association follows a logarithmic equation ($P = 0.001$).



n= 200

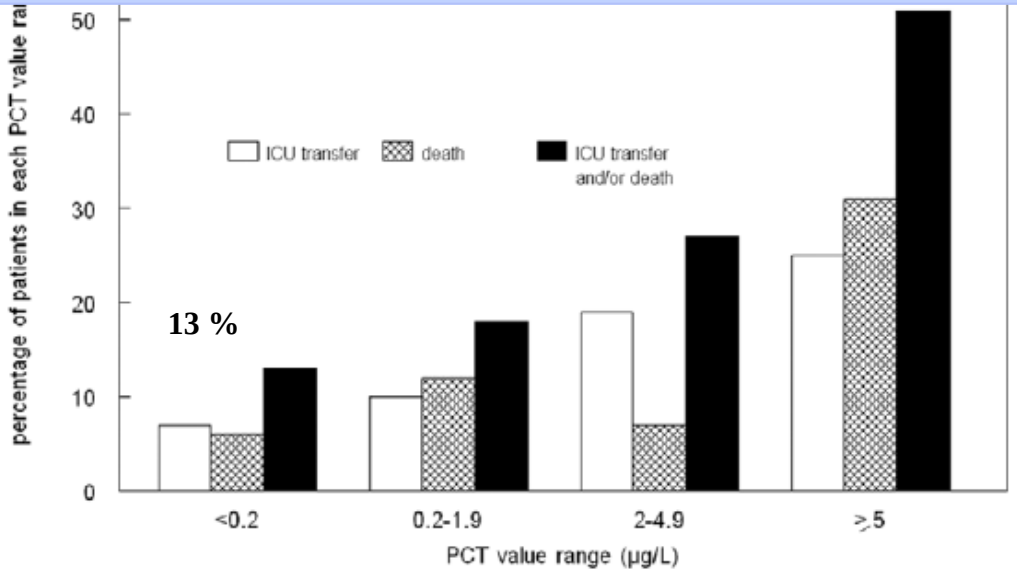
FIG. 2. **ROC curves of independent prognostic determinants of mortality.**

Research

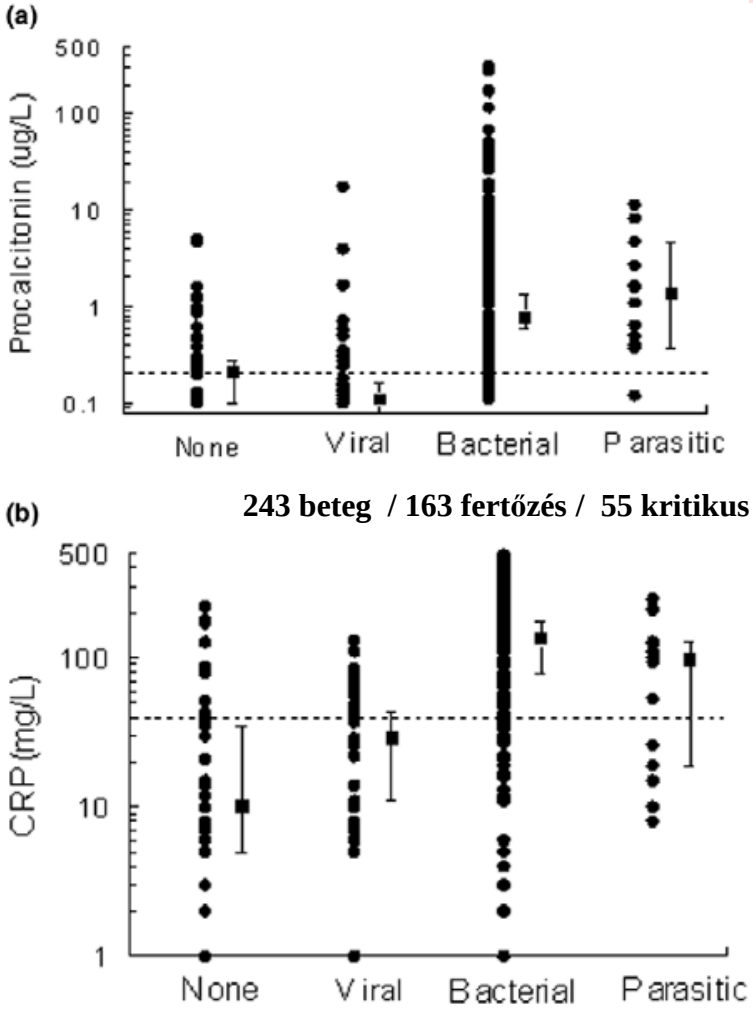
Open Access

Serum procalcitonin measurement as diagnostic and prognostic marker in febrile adult patients presenting to the emergency department

PCT abszolút érték a SBO felvételnél > 2 ng/ml független prediktor



Relation between critical illness (death or ICU transfer) and PCT value range. A total of 55 patients had critical illness, 31 of which were intensive care unit (ICU) transfers and 30 died (including six patients admitted to the ICU). PCT, procalcitonin.



243 beteg / 163 fertőzés / 55 kritikus áll.

Crit Care **2007, 11: R60,** *Crit Care* **2009, 13:R38**

Procalcitonin increase in early identification of critically ill patients at high risk of mortality

475 beteg / 3900 mérés

Jensen JU et al. *Crit Care Med* 2006; 34: 2596-2602

Table 3. Independent predictors of 90-day all-cause mortality after intensive care unit admission

Risk Variable	Univariate Hazard Ratio (95% CI)	Univariate *p* Value	Multivariate Hazard Ratio (95% CI)[a]	Multivariate *p* Value
Initial PCT level	1.002 (1.000–1.004)	.016	—	NS
PCT max	1.003 (1.002–1.004)	<.001	1.003 (1.000–1.005)	.034
PCT increase[b]	1.8 (1.4–2.4)	<.001	1.8 (1.3–2.7)	.002
CRP max	—	.057	—	NS
CRP increase[b]	—	.23	—	NI
WBC max	—	.14		NI
WBC increase[b]		.43		NI
Age[c]	1.031 (1.022–1.040)	<.001	1.03 (1.02–1.04)[d]	<.001
Clinical sepsis	2.6 (1.9–3.6)	<.001	—	NS
Trauma	0.25 (0.14–0.45)	<.001	0.48 (0.23–0.99)	.047
Acute uremia	2.2 (1.4–3.2)	<.001	—	NS
Chronic *uremia*	—	.35	—	NI
Abdomina				NI
Peritoniti				<.001
Pneumon				NI
Chronic l				NI
Diabetes				NI
Liver insu				NS
Cancer (solid tumor)	—	.38	—	NI

The maximum procalcitonin level and the increase of PCT on first ICU day are independent predictors of mortality

CI, confidence interval; PCT, procalcitonin; NS, nonsignificant; CRP, C-reactive protein; NI, not included in the multivariate analysis (did not meet Cox inclusion criteria in the univariate analysis); WBC, white blood cell count.

[a]Hazard ratio estimate according to the Cox regression model; [b]increase in PCT the first day after reaching ≥1.0 ng/mL, increase in CRP the first day after reaching ≥9.0 mg/L, increase in leukocytes the first day after reaching ≥9.0×10^9/L; [c]age in years; [d]hazard ratio increase for every year the patient age increases. Hazard ratios are only mentioned if stringency is $p < .05$ and are otherwise replaced by dashes. A multivariate Cox regression model for independent predictors of 90-day mortality. All variables initially included are shown. A stringency level of 0.10 was used to include variables in the multivariate analysis. PCT max, initial PCT level, CRP max, and age were included as continuous variables. A PCT day-by-day increase (PCT increase) for 1 day after exceeding 1.0 ng/mL was found to be an independent predictor of 90-day mortality. This was also found for 30-day mortality. Some diagnoses are poorly represented, mainly because patients with these diagnoses are admitted to other intensive care units of our hospital.

Research article

Open Access

Serum procalcitonin elevation in critically ill patients at the onset of bacteremia caused by either gram negative or gram positive bacteria

Charles et a.l: BMC Infectious Disease 2008;8:38-46

… maximális PCT érték …

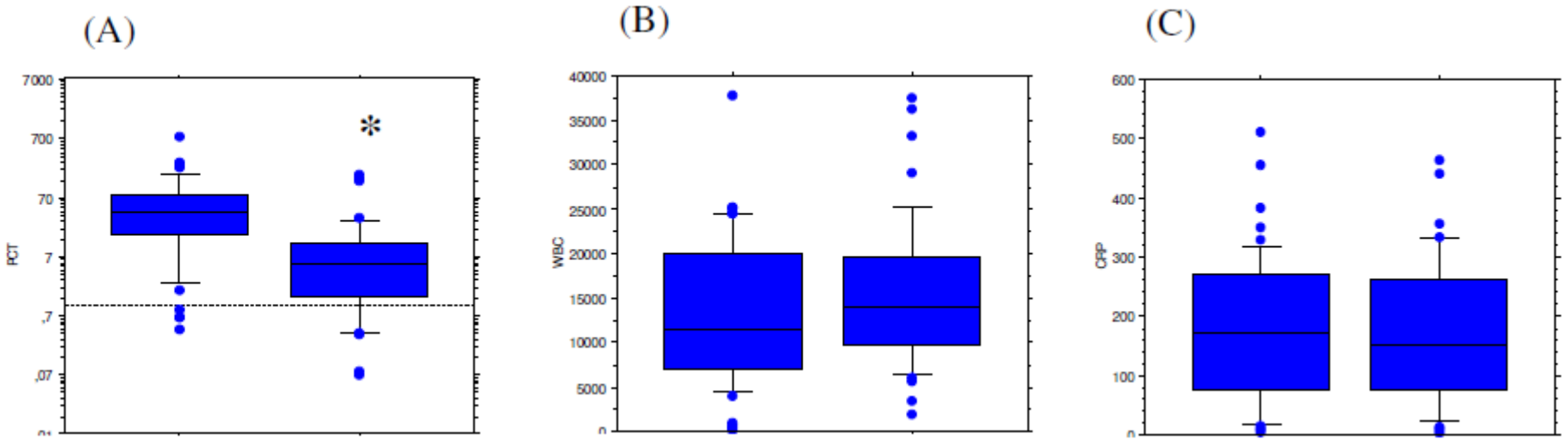


Table 4: Diagnostic accuracy of serum procalcitonin for the discrimination between gram positive and gram negative bacteremia in critically ill patients with clinical sepsis and positive blood cultures.

PCT cutoff value (ng/mL)	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Likelihood ratio +	Likelihood ratio -
PCT > 16.0 95% CI	75.0% [61.0–86.0]	82.2% [68.0–92.0]	83.0% [69.0–92.0]	74.0% [60.0–85.0]	4.21 [1.91–10.7]	0.30 [0.15–0.57]

Diagnostic and prognostic value of procalcitonin in patients with septic shock

Clec'h C et al. *Crit Care Med* 2004; 32: 1166-1169

… PCT abszolút érték a SBO felvételnél …

n = 90/16	Septic Shock	Nonseptic Shock	*p* Value
PCT, ng/mL	14 (0.3–767)	1 (0.15–36)	.0003
CRP, mg/L	122 (6–444)	68 (3–134)	NS
Lactate, mmol/L	2.4 (0.5–18)	3.2 (1–25)	NS

NS, not significant.

… maximális PCT érték …

Table 3. Prognostic value of procalcitonin (ng/mL) in septic shock

… PCT értékek változása

	Patients Who Died	Patients Who Survived	*p* Value
D1	16 (0.15–767)	6 (0.2–123)	.045
D3	14 (0.2–300)	3 (0.2–52)	.03
D7	15 (0.9–197)	1.1 (0.14–49)	.003
D10	6.5 (0.3–135)	1.05 (0.11–53)	.02

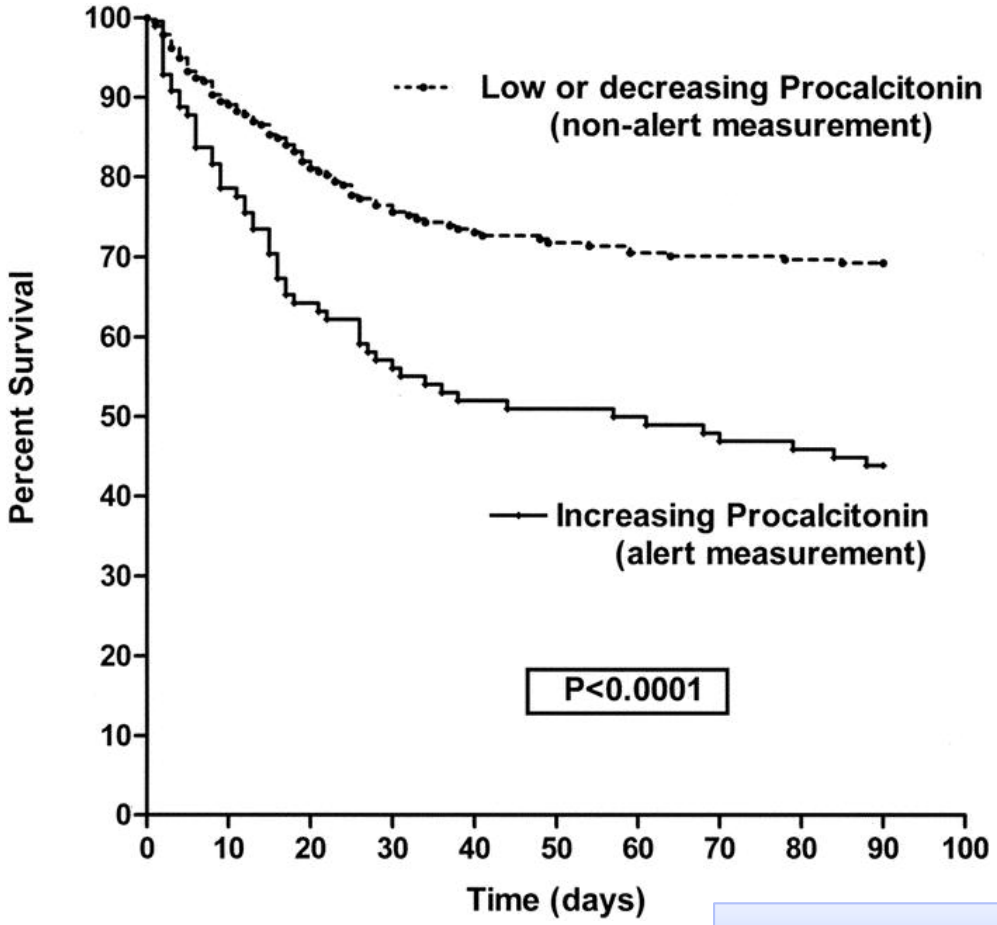
Csökkenő dinamika!!!

Data are expressed as median (range). Blood samples for procalcitonin assays were taken on the first (D1), third (D3), sixth (D7), and tenth (D10) days of shock.

Procalcitonin increase in early identification of critically ill patients at high risk of mortality*

Jens Ulrik Jensen, MD; Lars Heslet, MD, MDsc; Tom Hartvig Jensen, MD; Kurt Espersen, MD, PhD; Peter Steffensen, MSc; Michael Tvede, MD

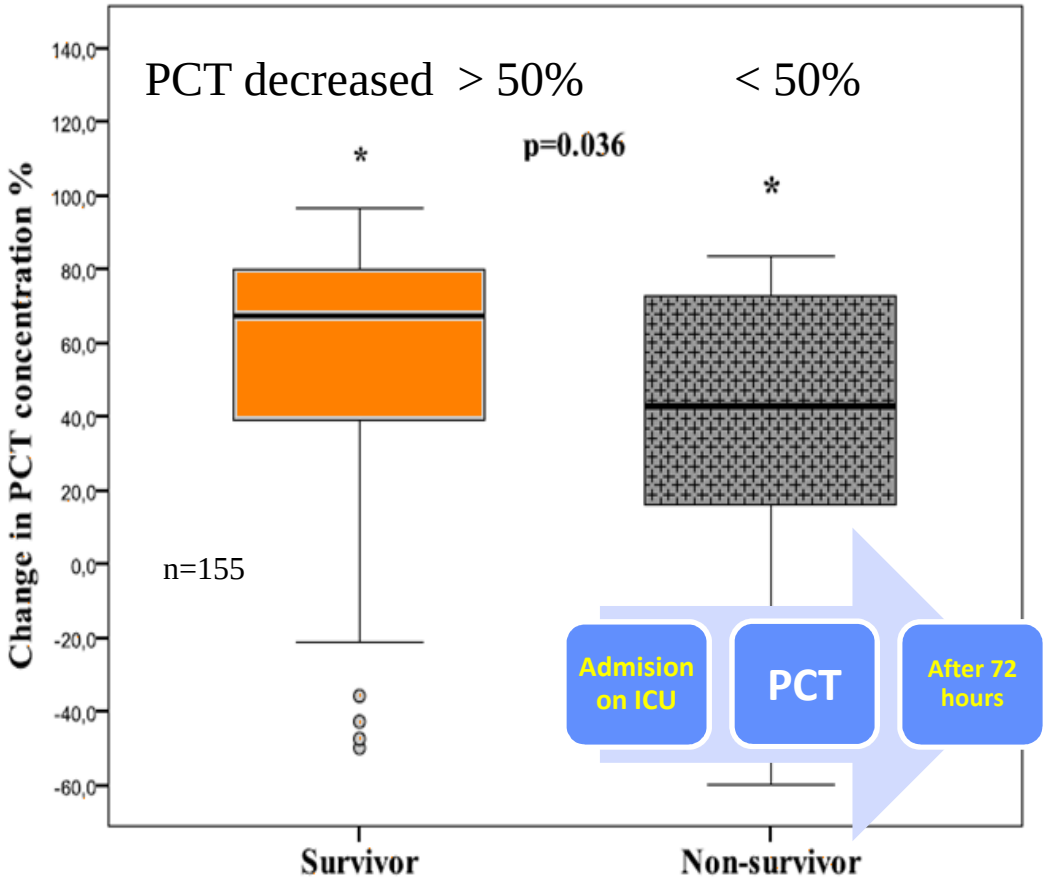
Crit Care Med 2006; 34: 2596-2602



Predictive value of procalcitonin decrease in patients with severe sepsis: a prospective observational study

Sari Karlsson[1*], Milja Heikkinen[2], Ville Pettilä[3], Seija Alila[4], Sari Väisänen[2], Kari Pulkki[2], Elina Kolho[5], Esko Ruokonen[6], the Finnsepsis Study Group[1]

Critical Care 2010, 14:R205



PCT értékek változása !!!

Limfocita

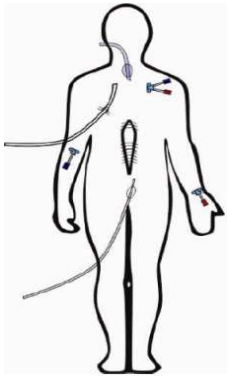
↓ % CD4, ↑ % LT reg

↑ Apoptozis LT-LB

↓ Proliferáció LT-LB

↓ citokin termelés LT

↓ IgGAM termelés LB



Anti ↑↑↑
Veleszületett ↑↑↑

Pro ↓↓
Adaptáció ↓↓

Monocita

↑ CD40-CD48-CD64, TREM-1

↑ anti-inflam. citokinek

↓ pro-inflam. citokinek

↓ CD14-CD86-CD71, ↓ HLA DR

↓ Antigén prezentáció

↓ Szabadgyök képződés

↓ Citotoxicitás

1. A beteg
2. A beteg
3. A beteg

Számszerű ↓
Funkció ↓
Kommunikáció ↓

jelentkezik
vos kezelte
upprimált

NK sejtek (LT)

↓ NK aktivitás

Dendritikus sejt

↓ MHC II antigén expressio

↓ Antigén prezentáció

↑ apoptozis

↓ citokin termelés

Neutrofil

↓ CD64

↑ apoptozis

↓ Válasz kemokinekre

↓ citokin termelés

↓ Szabadgyök képződés

PATIENT-CENTRED ACUTE CARE TRAINING PACT
AN ESICM MULTIDISCIPLINARY DISTANCE LEARNING PROGRAMME FOR INTENSIVE CARE TRAINING

Research article

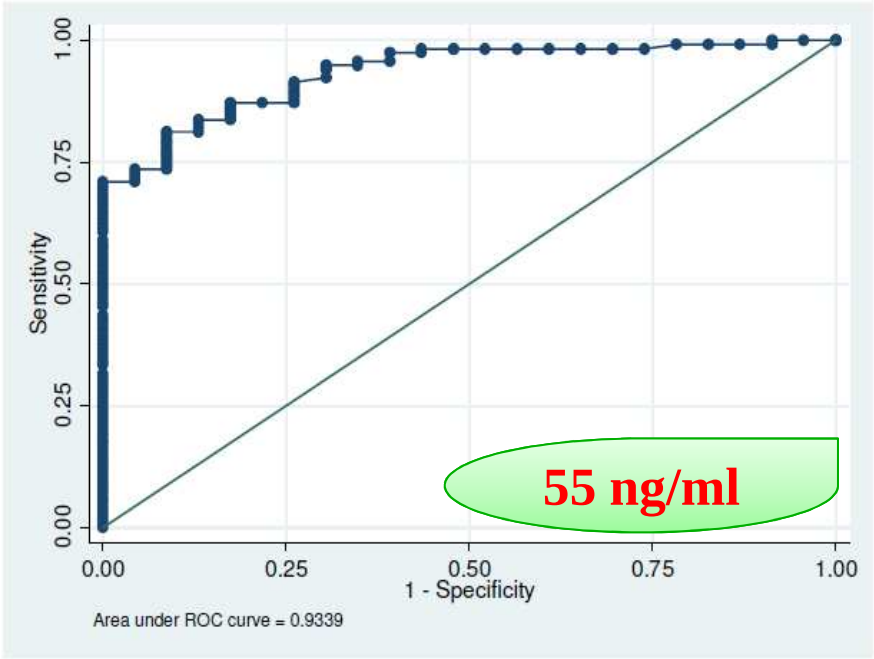
Open Access

Impact of previous sepsis on the accuracy of procalcitonin for the early diagnosis of blood stream infection in critically ill patients

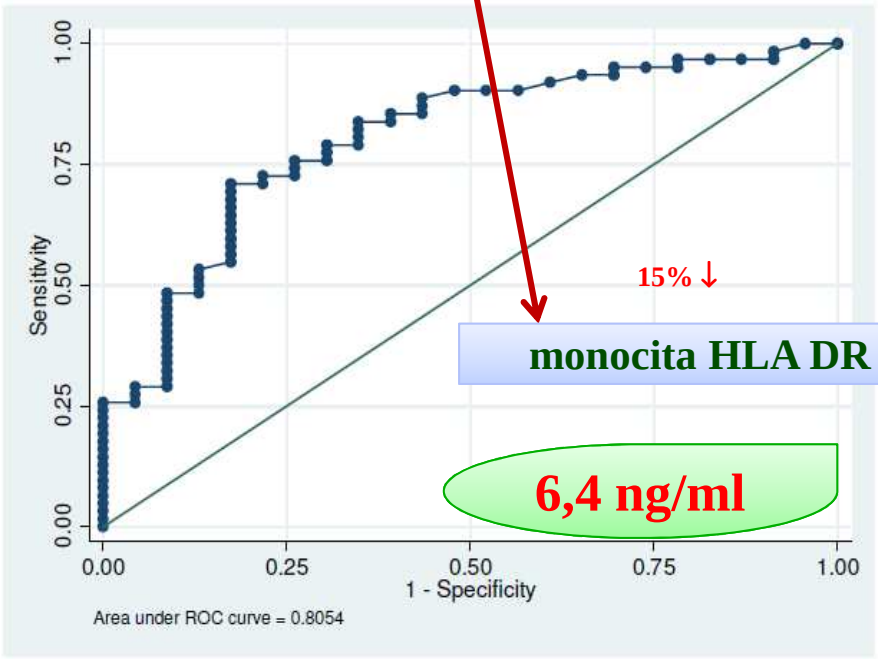
… PCT a beteg felvételnél alacsonyabb
… PCT maximális szint alacsonyabb
… PCT értékek változása **hasonló**

Charles at al.: BMC Infectious Disease 2008;8:163-173

López-Collazo *et al. Critical Care* 2010, 14:435



(A) n=100, ITO-14, ab



(B) n=50, ITO-14, ab-szteroid

Receiver operating characteristic (ROC) curve of serum procalcitonin (PCT) for the diagnosis of blood stream infection in critically ill patients with either primary (*Fig.* A), or secondary (*Fig.* B) sepsis. Plain circles indicate PCT values. Area under the ROC curve = 0.934, 95% CI: 0.881–0.970; vs. 0.805, 95% CI: 0.699–0.879, respectively; $p < 0.050$.

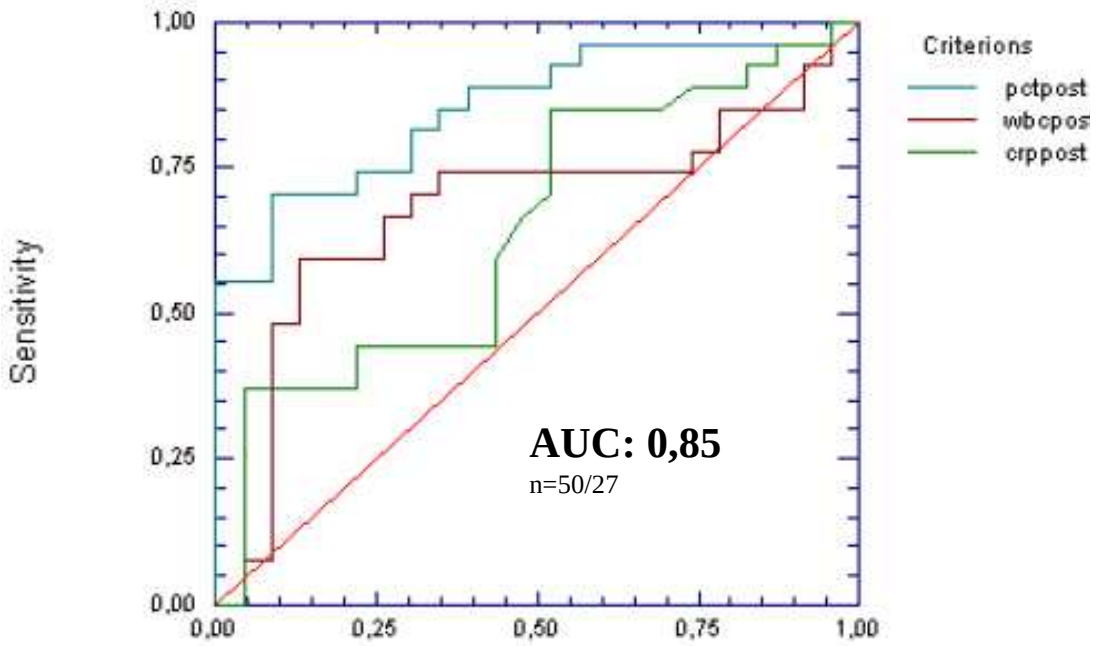
Research article

Open Access

Diagnostic and prognostic value of procalcitonin among febrile critically ill patients with prolonged ICU stay

Tsangaris at al.: BMC Infectious Disease 2009;9:213-221

A láz napján mért PCT értéket hasonlítsuk össze a korábbi napokon mért értékekkel



… PCT a beteg felvételnél **még** alacsonyabb
… PCT maximális szint **még** alacsonyabb
… PCT értékek változása **hasonló**

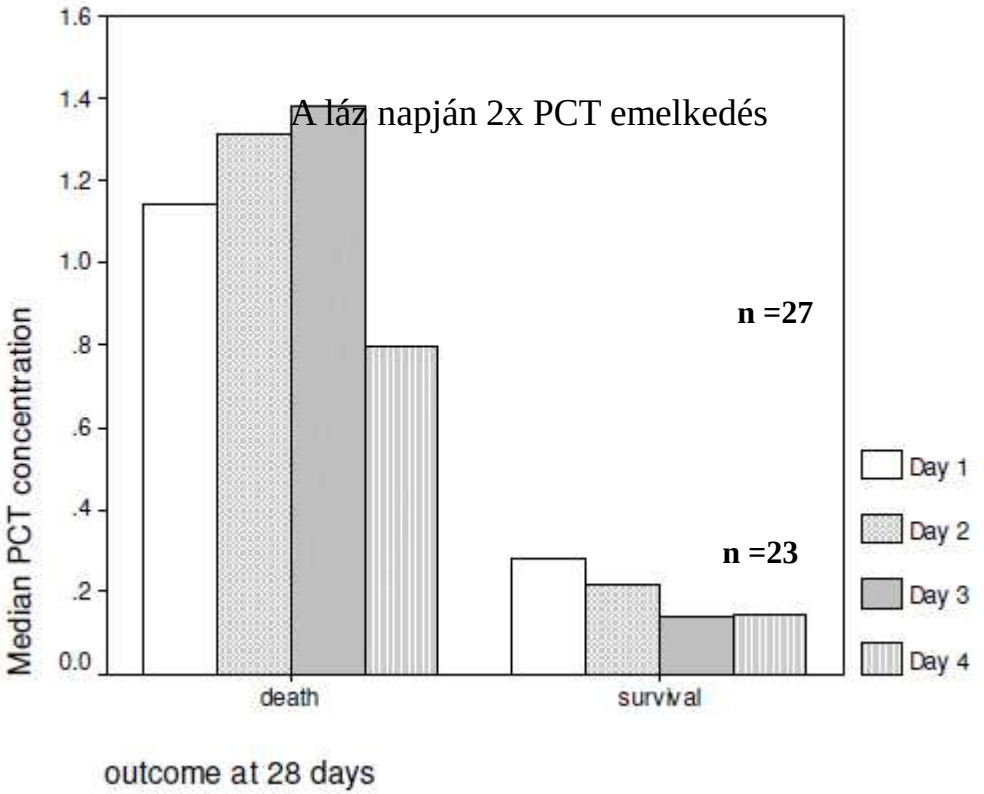


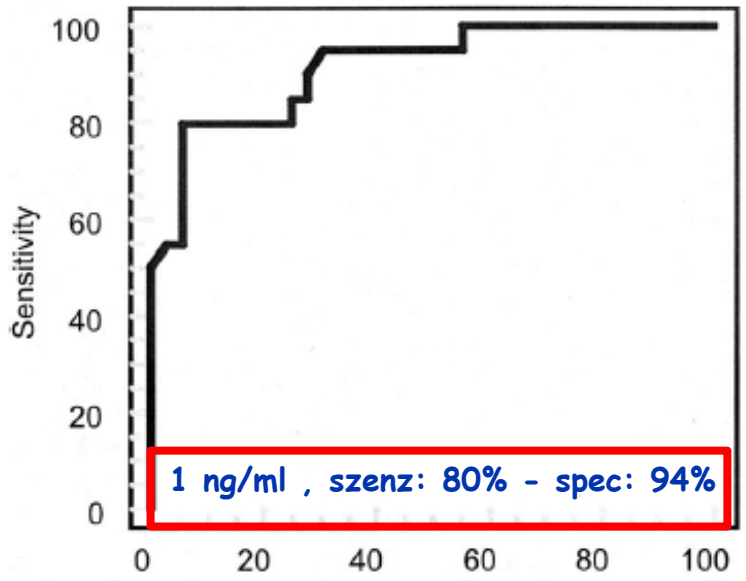
Figure 3
PCT values for patients with (constant line) and without (dotted line) proven infection before and after the onset of fever (D1). PCT: Procalcitonin, D1: Day1 (day of fever onset).

Clec'h et al.: Differential diagnostic value of procalcitonin in surgical and medical patients with septic shock

Belgyógyászati betegek:

SIRS PCT: 0,3 ng/ml (0,1-1)

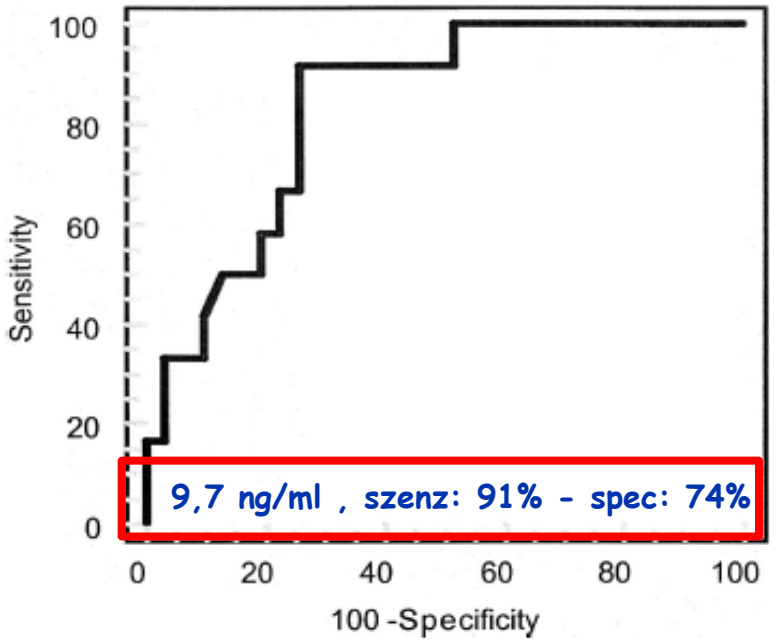
Szeptikus shock PCT: 8,4 ng/ml (3,6-76)



Sebészeti betegek:

SIRS PCT: 5,7 ng/ml (2,6-8.35)

Szeptikus shock PCT: 34 ng/ml (7-76)



Belgyógyászati beteg = PAMP és lehet DAMP
Sebészeti beteg = biztos DAMP és lehet PAMP

Crit Care Med. 2006, 34:102-107

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

Jensen et al. *Crit Care Med* 2011; 39: 2048-2058

- 1200 critically ill patients: 60% medical, 40% surgical patients, **alert PCT = 1 ng/ml**
  - Control group:
    - Standard-of-care-only
  - PCT group
    - Standar-of-care ±
    - **„alert PCT" > 1ng/ml, ↓ <10%/day**
      - ***Diagnostic measures***
      - ***Escalation of AB therapy (not treatment)***
    - „non alert PCT" <1 ng/ml, ↓ >10% /day

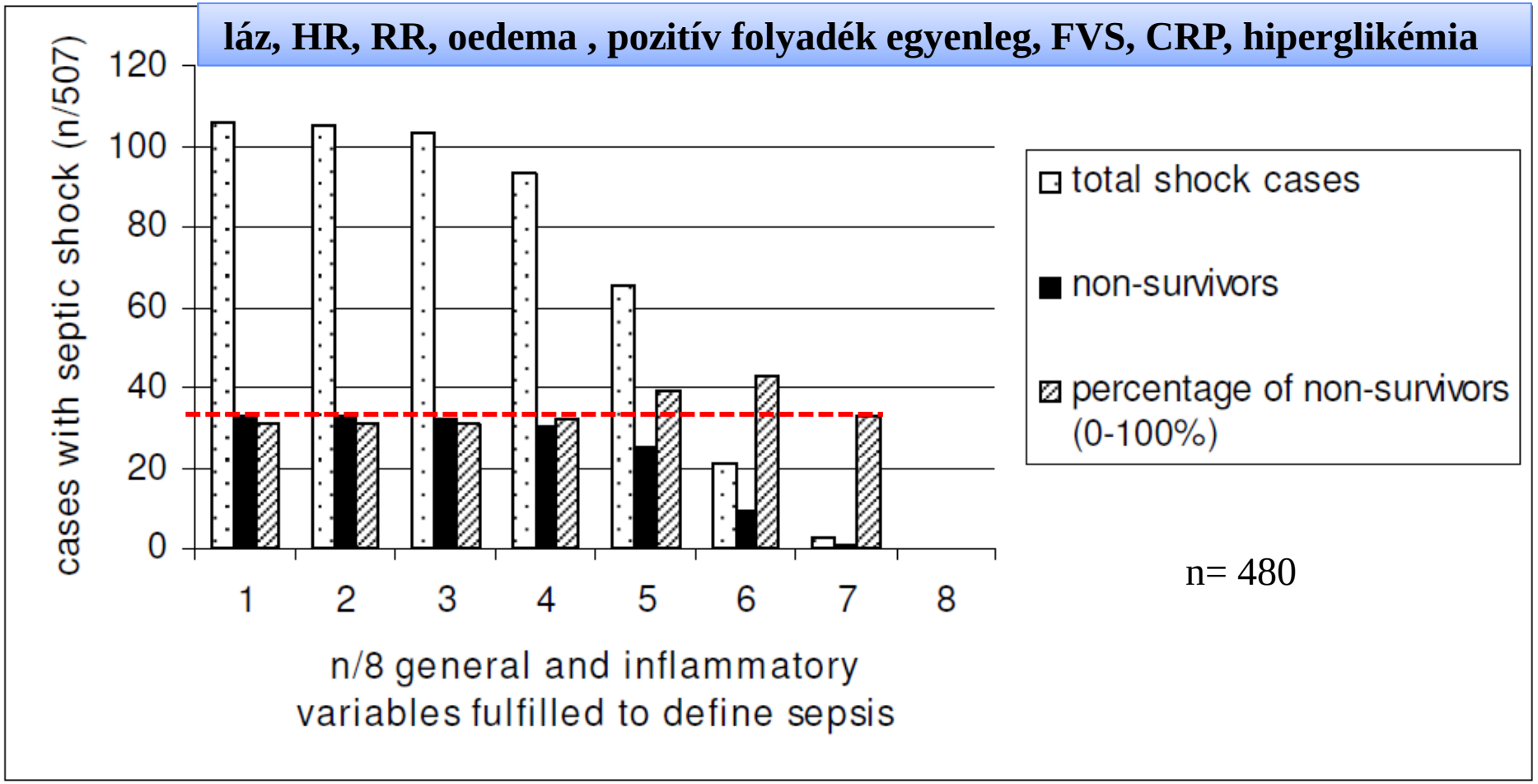
Repeatedly high PCT levels predict severe sepsis or septic shock

Repeatedly PCT ≅ 1 ," OR: 2.2; CI, 1.2– 4.1

Repeatedly PCT >2 ," OR: 3.0; CI, 1.9–4.8

PCT as outcome predictor at baseline:
OR: 1.4; CI:1.1–1.9

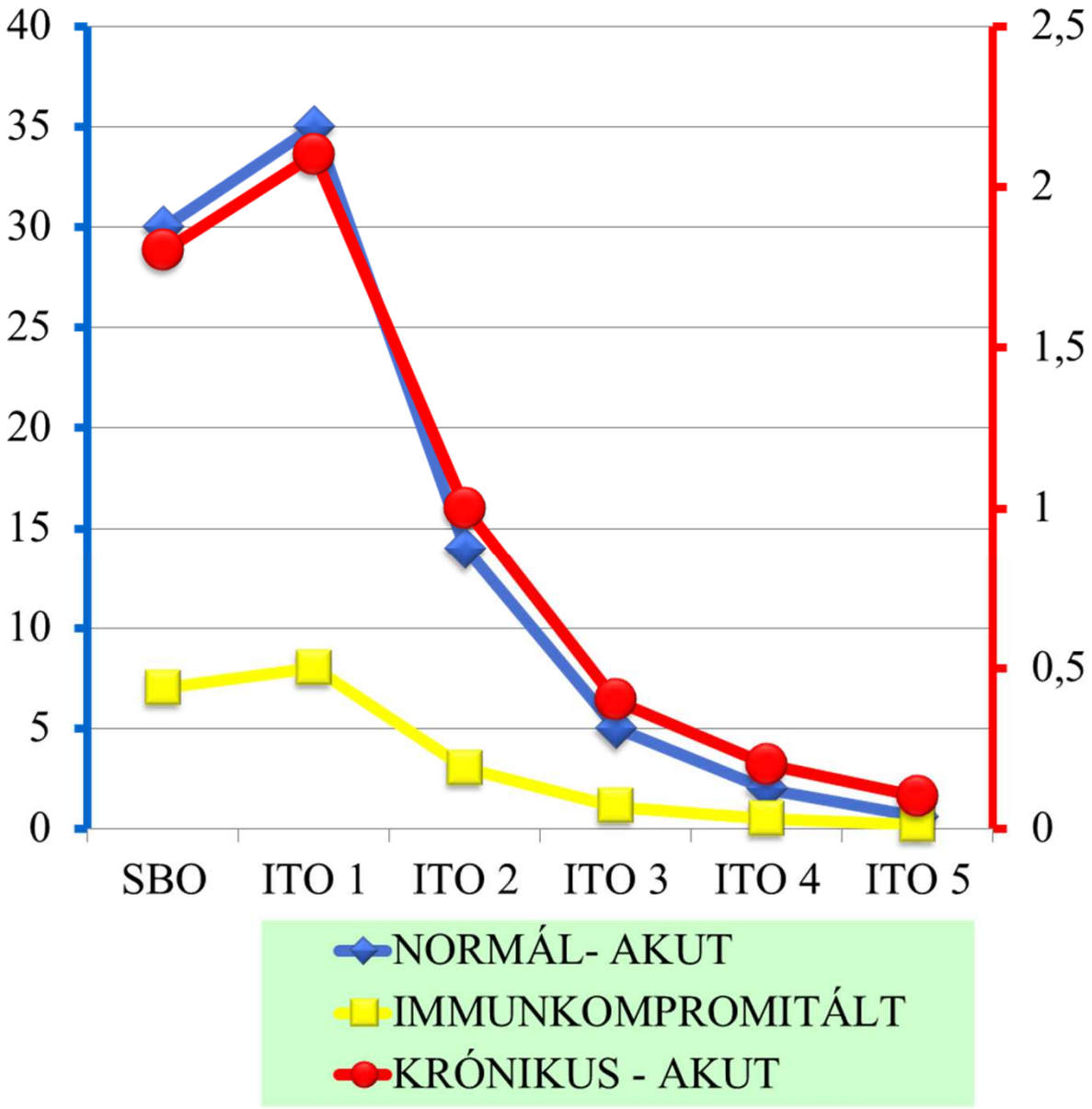
How many general and inflammatory variables need to be fulfilled when defining sepsis due to the 2003 SCCM/ESICM/ACCP/ATS/SIS definitions in critically ill surgical patients: a retrospective observational study



Weiss *et al. BMC Anesthesiology* 2010, **10**:22

Összefoglalva

1. … PCT a <u>beteg felvételnél</u>
2. … PCT <u>maximális érték</u>
3. … PCT értékek <u>változása</u>
   - Alig csökken
   - Több mint „…feleződik”



Összefoglalva

SBO→

Szűrés →

Diagnózis →

Rizikó felmérés →

Prognózis →

ITO kezelés →

Monitorozás →

Prediktív →

Mortalitás vagy a kezelés vége