



Sepsis course – IV: Biochemical signs of sepsis

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Sepszis: nem definitív betegség

- „Sepsis-syndrome” and Las Vegas:
 - Fever or hypothermia ($> 38\text{ }^{\circ}\text{C}$ or $< 36\text{ }^{\circ}\text{C}$)
 - Tachycardia ($>90/\text{min}$)
 - Leukocytosis or leukopenia ($> 12\ 000\text{ cells}/\text{mm}^3$, $< 4000\text{ cells}/\text{mm}^3$, or $> 10\%$ immature forms)
 - Hypotension ($<90\text{ mmHg}$)

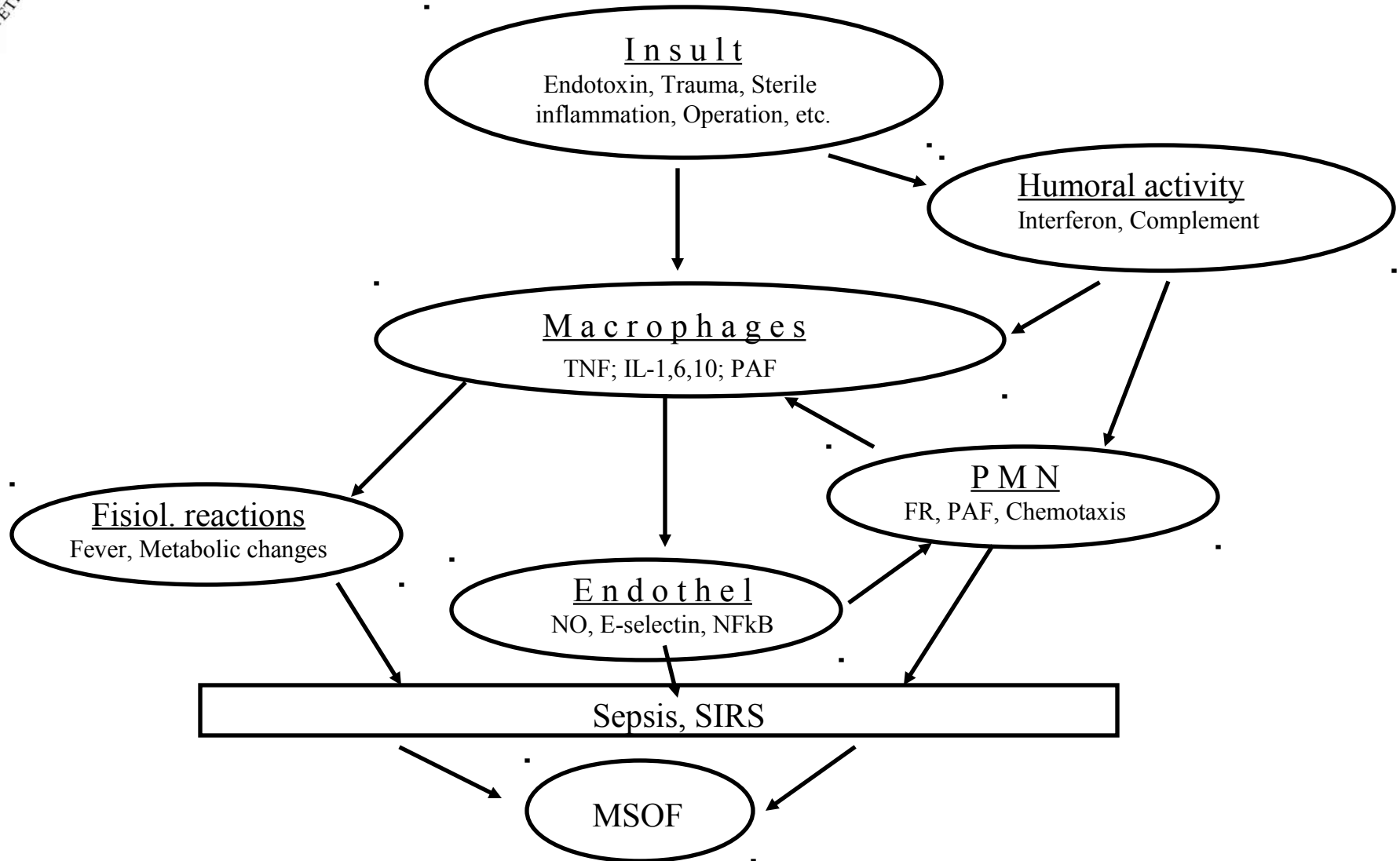
Bone RC, et al. *N Engl J Med* 1987; 317: 654

- Consensus conference ACCP/SCCM:
 - Infection
 - Bacteraemia
 - Systemic inflammatory response syndrome (SIRS)
 - Sepsis = SIRS + Infection
 - Severe sepsis (Sepsis + one organ dysfunction)
 - Septic shock (hypoperfusion despite adequate fluid load)
 - Multiple System Organ Failure (MSOF)

ACCP/SCCM. *Crit Care Med* 1992; 20: 864



Pathomechanism





Case

- 65 year old man
- Malaise, fever for 2 days – A&E
- On assessment
 - Frail looking patient
 - Sleepy, but answers for questions
 - Sweaty, cold hands, peripheral cyanosis
 - Tachypnoe
 - P = 130/m, BP = 75/35 mmHg
 - SpO₂ = 85%, PaO₂ = 62 mmHg
 - T: 39 C



Is he septic?



Why is it important?

- Antibiotics
- IgM, rh-APC, selenium
- Operation
- Progression



Objective signs of organ dysfunction

	<u>0</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>
CNS (GCS)	15	13-14	10-12	7-9	≤6
CVS (P, inotr., lactate)	≤120	120-140	>140	Inotr.	seLactate>5
Resp (PaO ₂ /FiO ₂) >300	226-300	151-225	76-150	≤75	
Ren (seCreat)	≤100	101-200	201-350	351-500	>500
Liver (seBi)	≤20	21-60	61-120	121-240	>240
Hemat (TCT)	>120	81-120	51-80	21-50	≤20

Cook R et al. *Crit Care Med* 2001; 29: 2046

- Most frequently found early signs:

- Arterial hypoxemia: 60%
- Arterial hypotension: 57%
- Metabolic acidosis: 47%

Bogár L. *Infektológia* 2007; 14: 1-6

- Atrial fibrillation: >10%
- Altered level of consciousness: >10%

Low DE, et al. *J Gastrointest Surg* 2007; 11: 1395



Conventional biochemical markers

- Fever ($>38^{\circ}\text{C}$), WBC ($>12\ 000$):
 - Low sensitivity ($\sim 50\%$)

Galicier L and Richet H. *Infect Control Hosp Epidemiol* 1985; 6: 487

- Blood culture:
 - Late result ~ 24 h
 - Low sens/spec, especially in VAP related sepsis ($\sim 30\%$)

Meakins JL. In: *Crit Care: State of the Art* 1991; 12: 141

Luna CM et al. *Chest* 1999; 116: 1075

- TNF- α , IL-1, 2, 6, 8:
 - Short half life
 - Expensive tests

Thompson D et al. *Ann Clin Biochem* 1992; 29: 123



Citokines

- Physiology
 - Low MW
 - Intercellular messengers
 - Production:
 - Response for an insults
 - Morphologically different cells
- Pathophysiological importance
 - Close link between clinical signs and citokine levels
Cannon JG et al. J Infect Dis 1990; 161:79-84
 - I.v. citokines resulted sepsis syndrome in animals
Okusawa et al. Shock 1988; 7: A487
 - Anti-citokines improved clinical condition
Ohlson K et al. Nature 1990; 348:550-2



C-reaktive protein (CRP)

- Physiology
 - Acute phase protein
 - Trigger: IL-6, 8; TNF- α
 - Synthesis: liver
 - Normal level: <10 mg/l

Castell JV et al. *Hepatology* 1990; 12:1179-86

- Patophysiology
 - Non-viral sepsis marker
 - Sensitive, but non-specific („always elevated”)

Mimoz O et al. *Intensive Care Med* 1998; 24:185-88



PCT

- Physiology
 - Thyroid C-cells
 - 126 amino acid
 - Calcitonin-katacalcin
 - PCT half life: 25-30 h
 - Levels: <0.1ng/ml

Le Moullec JM et al. *FEBS* 1984; 93-97
Meissner M. BRAHMS Diagnostica, Berlin pp: 14-60

- Pathophysiology
 - Non-viral sepsis
 - Synthesis: Leukocytes, lungs
 - Levels: >2-100 ng/ml

Oberhoffer M et al. *Shock* 1997; 7: A487
Nylen ES et al. *Am J Med Sci* 1996; 312: 12-18



PCT measurements

- Immun-luminometry
 - Antibody coated tubes
- Quick test
 - PCT-Q
 - Bedside test: result in 30 minutes
 - <0.5; 2; 10<

Gendrel D, Bouhon CJ. *Infection* 1997; 133



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- TNF- α , IL-1, 2, 6, 8:

- Short half life

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Thompson D et al. *Ann Clin Biochem* 1992; 29: 123

- Meta-analysis PCT vs CRP

- Sensitivity (%): 88(80-93) vs 75(62-84)

- Specificity (%): 81(67-90) vs 67(56-67)

Simon L et al. *Clin Infect Dis* 2004; 39: 206



Statistics

		Disease		
		<i>Pos</i>	<i>Neg</i>	
Test	<i>Pos</i>	True pos (TP)	Fals pos (FP)	$TP/(TP+FP)$ = Pos. pred.
	<i>Neg</i>	Fals neg (FN)	True neg (TN)	$TN/(FN+TN)$ = Neg. pred.
		$TP/(TP+FN)$ = Sens	$TN/(FP+TN)$ = Spec	



Diagnostic and prognostic value of procalcitonin in patients with septic shock

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

	Septic Shock	Nonseptic Shock	<i>p</i> 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.



From SIRS to septic shock

RESULTS:	TNF-α [pg/ml]			IL -6 [pg/ml]			PCT [ng/ml]		
	mean	SE	n	mean	SE	n	mean	SE	n
SIRS	24,2	4.3	332	269	22	333	1,3	0.2	333
p	< 0.0001			< 0.0001			< 0.0001		
Sepsis	50,8	9.2	108	435	52	108	2	0	108
p	n.s.			< 0.02			< 0.0001		
Sev.Sepsis	59,1	17	20	970	168	20	8,7	2.5	20
p	n.s.			n.s.			< 0.0006		
Septic Shock	118	18.4	120	996	57	120	38,6	5.9	120

Oberhoffer M et al. *Intensive Care Med* 1996; 22: S1



Predictive value - mortality

Table 2. Comparison of laboratory values and APACHE III and LOD scores between hospital survivors and nonsurvivors among patients with suspected septic infection at admission

	Survivors n = 66	Nonsurvivors n = 42	p Value
AT III, %	66 (48–82)	46 (37–65)	<.001
CRP, mg/L	164 (105–215)	137 (65–188)	.09
Platelet count $\times 10^9/L$	118 (60–202)	64 (36–129)	.0017 ^a
WBC $\times 10^9/L$	13.6 (11.2–18.4)	14.8 (6.8–20.8)	.60
Thromboplastin time, %	57 (37–67.5)	46 (26–60.5)	.02 ^a
APACHE III score	52 (39–68)	95 (72–115)	<.001
Day 1 LOD score	5 (3–7.25)	10 (7–12.25)	<.001

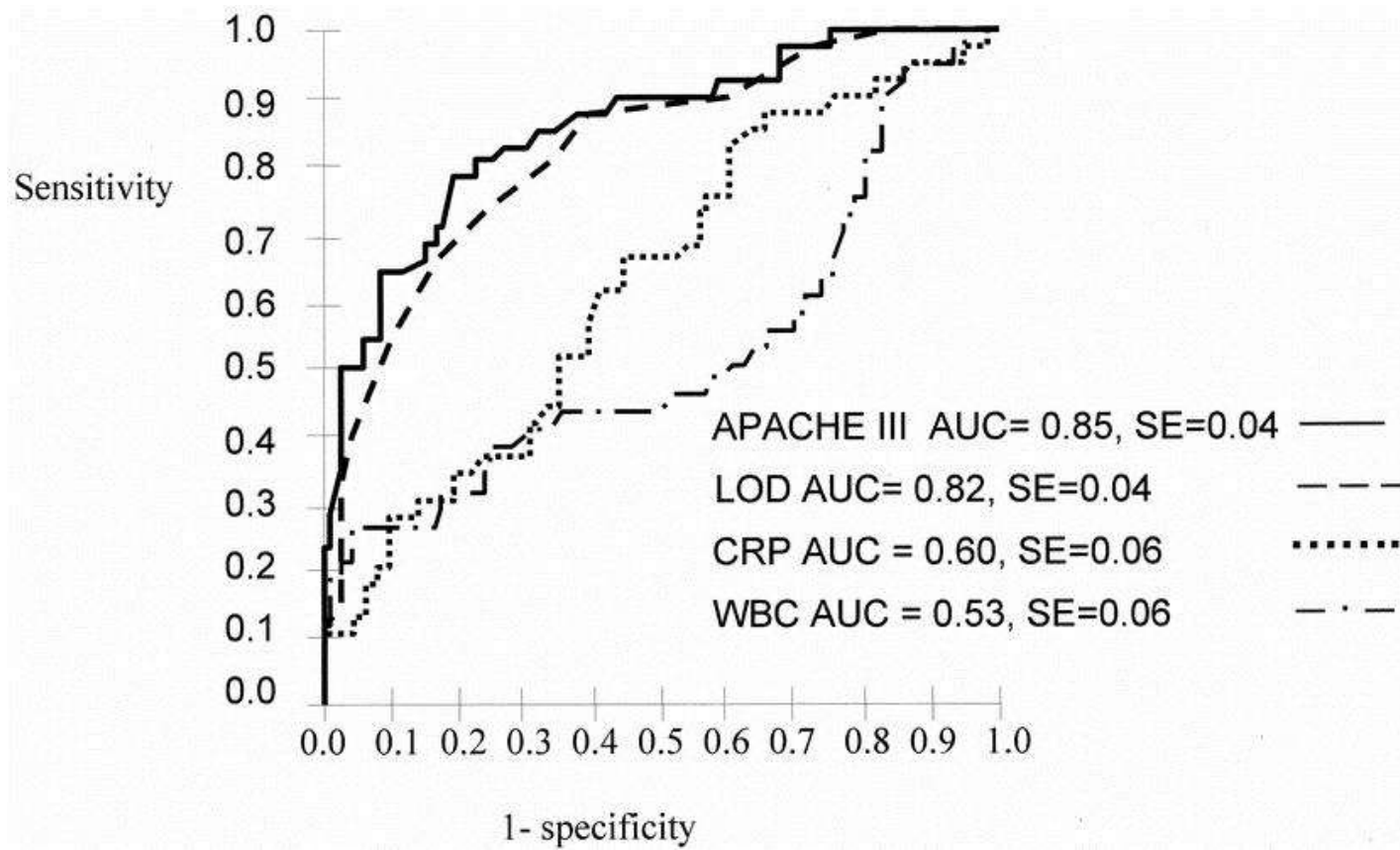
APACHE, Acute Physiology and Chronic Health Evaluation; LOD, Logistic Organ Dysfunction; AT, antithrombin; CRP, C-reactive protein concentration; WBC, white blood cell count.

^a $p < .05$. Data presented as median (interquartile range).



Predictive value - ROC

Receiver operating characteristics (ROC) görbék





SIRS or sepsis?

Parameter	Best cutoff	AUC (mean \pm SE)	<i>P</i> value
CRP (mg/dl)	14.5	0.554 \pm 0.062	0.378
TNF- α (pg/ml)	11.5	0.607 \pm 0.06	0.085
IL-2 (pg/ml)	1288.5	0.641 \pm 0.058	0.022
IL-6 (pg/ml)	68.5	0.515 \pm 0.62	0.805
IL-8 (pg/ml)	31.5	0.663 \pm 0.057	0.008
PCT (ng/ml)	2.415	0.969 \pm 0.016	0.000

P values are for AUC as a predictor of sepsis.

AUC, area under the Receiver Operating Characteristic (ROC) curve;

CRP, C-reactive protein; IL, interleukin; PCT, procalcitonin; TNF, tumour necrosis factor.



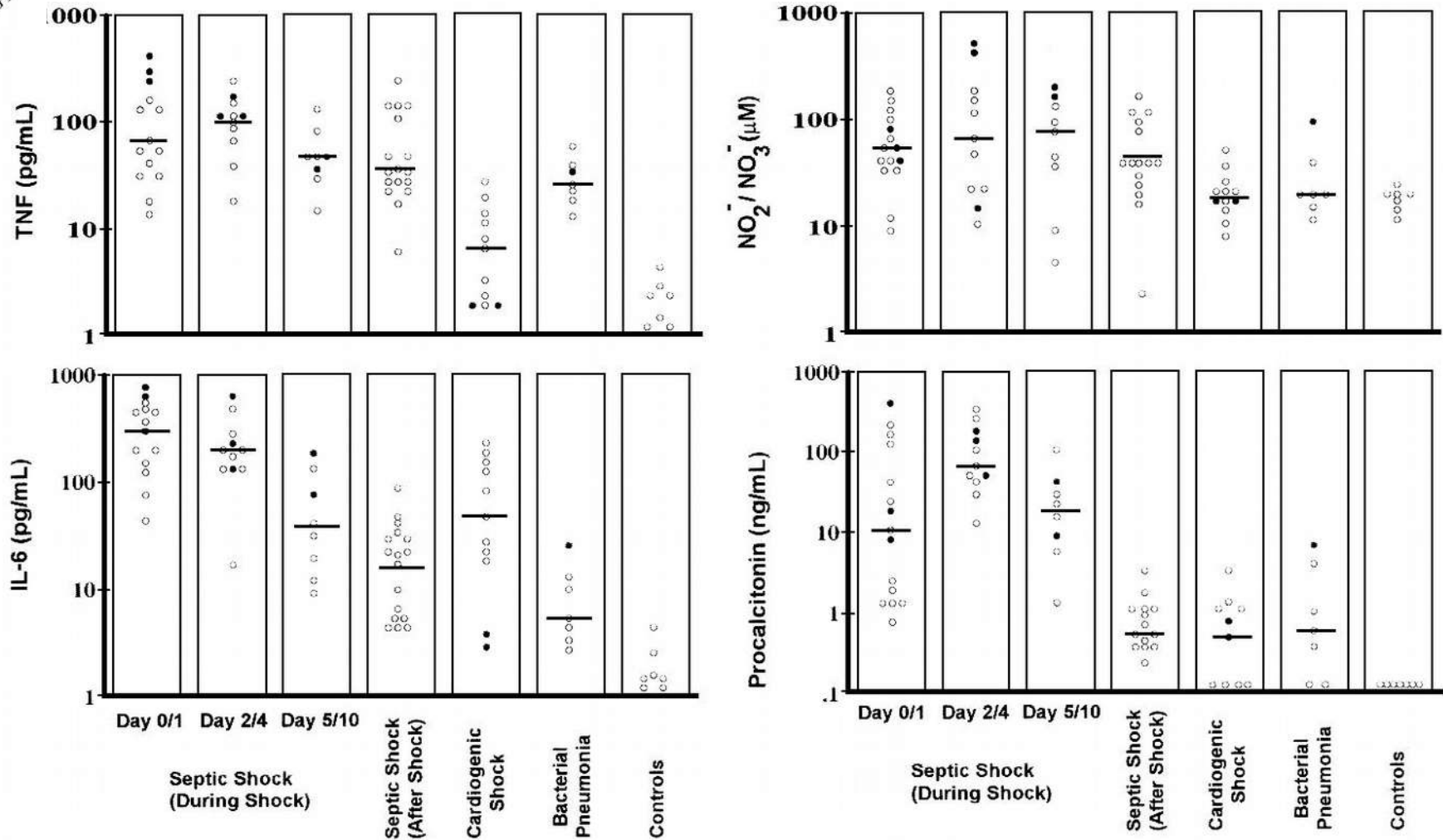
SIRS or sepsis?

Parameter	CRP	TNF- α	IL-2	IL-6	IL-8	PCT
Sensitivity (%)	58	55	63	51	68	85
Specificity (%)	58	66	55	53	57	91
Negative predictive value (%)	68	65	65	56	69	95
Positive predictive value (%)	53	54	50	42	53	89

CRP, C-reactive protein; IL, interleukin; PCT, procalcitonin; TNF, tumour necrosis factor.



Markers and shock





PCT and postoperative mortality

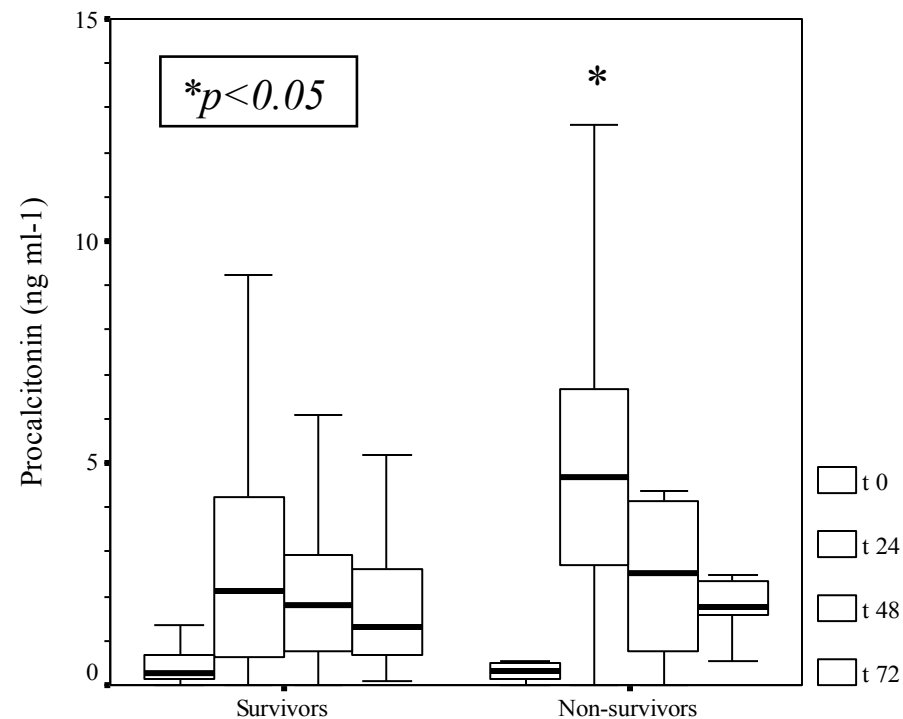
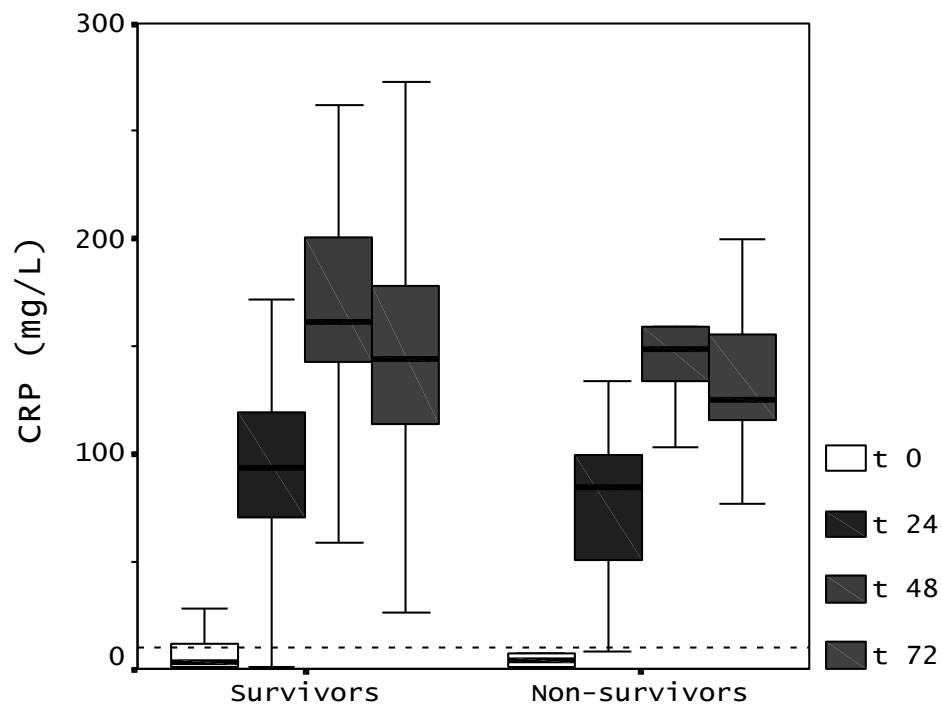
	<u>Survivors</u> (n=130)	<u>Non-survivors</u> (n=23)	<u>p</u>
Age (years)	57 (50-67)	63 (54-72)	NS
Sex (Male/Female)	90/40	19/4	NS
Length of operation (min)	240 (180-360)	260 (236-375)	NS
SAPS II	15 (10-20)	19 (13-26)	0.022

Data are presented as medians and interquartile ranges in ().
For statistical analysis Mann-Whitney U test and chi-square test were used, respectively.

Szakmány T, Molnár Z. *Can J Anaesth* 2003; 50: 1082-3



PCT postoperative mortality

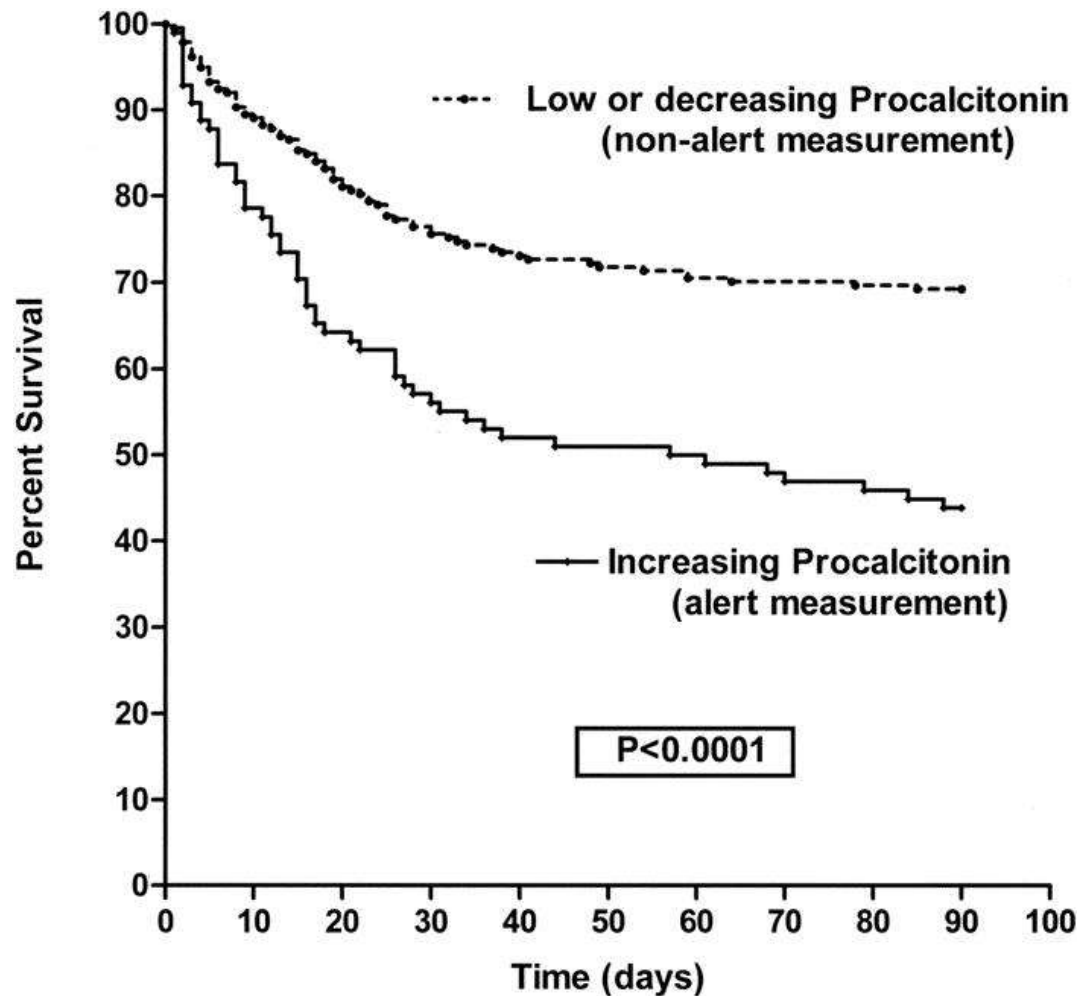


Data are presented as minimum, maximum, 25-75% percentile and median.
For statistical analysis Mann-Whitney U test was used.



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

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



- PCT change/24h
- ≥ 1 ng/ml or increasing (alert)
- < 1 ng/ml or decreasing (non-alert)



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

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

Table 4. Ninety-day mortality risk and procalcitonin (PCT) day-to-day changes

Days with PCT Decrease or Increase After PCT ≥ 1.0 ng/mL	90-Day Mortality Rate with PCT Day-to-Day Change, %		Relative Risk of PCT Increasing (95% Confidence Interval)	p Value for Risk Difference	Patients, No.
	Decreasing (Nonalert)	Increasing (Alert)			
1	30.7	56.1	1.8 (1.4–2.4)	<.0001	336
2	28.7	62.2	2.2 (1.6–3.0)	<.0001	261
3	26.0	72.4%	2.8 (2.0–3.8)	<.0001	233

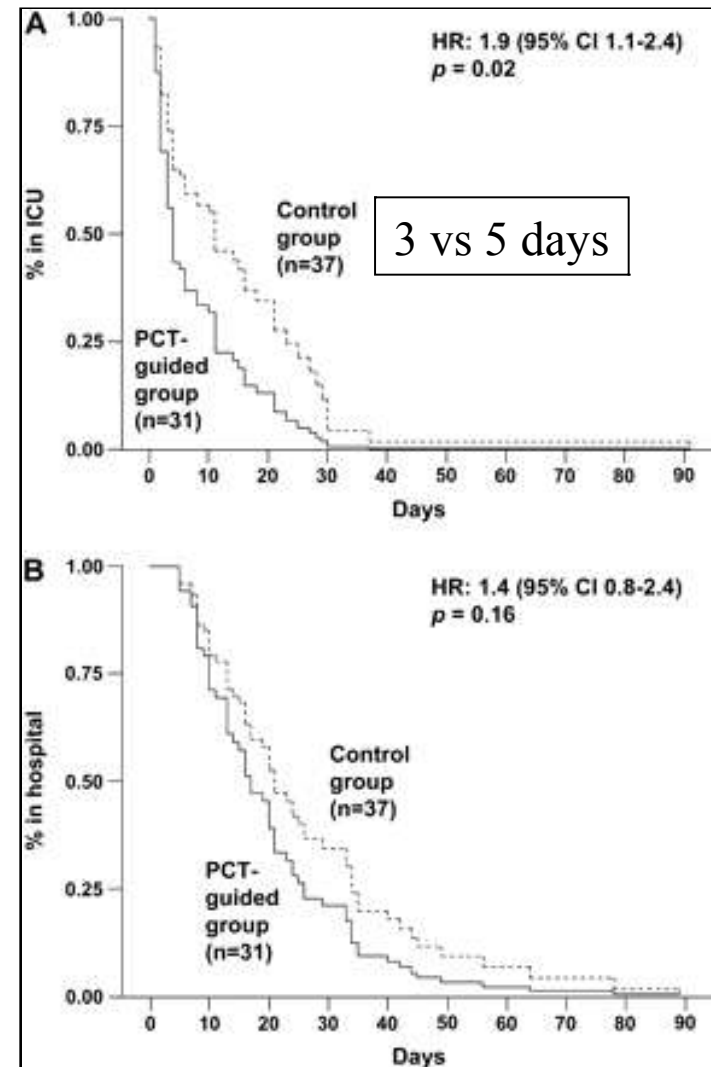
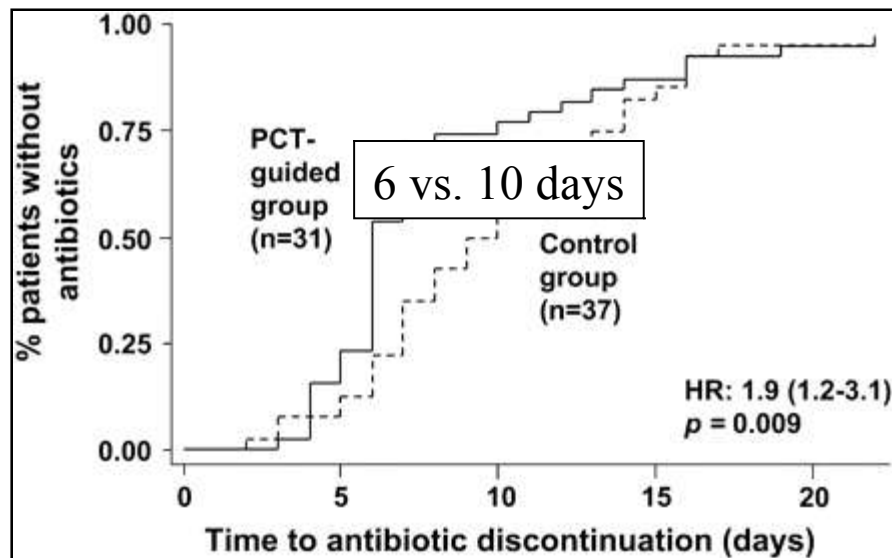
Mortality risks for patients with increasing and decreasing PCT. *p* values are estimated with the chi-square test. Categories are “alert PCT” vs. “nonalert PCT.” Constantly low PCT values are counted as nonalert PCT. Patients can be included in several categories; that is, patients with an increasing PCT trend for 3 days are also included in categories with increasing PCT trend for 1 and 2 days.



Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial

Nobre V, et al. *Am J Respir Crit Care Med*. 2008;177:498-505

- PCT vs control
- PCT-group (after day 3):
 - 90% decrease in PCT
 - <0.25 ng/ml





Summary

- Why PCT?
 - Most reliable biochemical marker of sepsis
 - Fast, sensitive, specific
 - Good severity and prognostic index
- In practice
 - Tailoring antibiotic therapy
 - Dynamic changes rather than absolute values
 - Daily measurements



But don' forget

Sepsis marker research
=
Beating around the bush