Procalcitonin kinetics guided antibiotic management of the critically ill patient

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Department of Anaesthesiology and Intensive Therapy

19/11/2016, XXXVII Turkish Congress of Microbiology

Epidemiology of sepsis

- Sepsis has severe impact on all health care
- Rates increased in USA between 2004-2009:

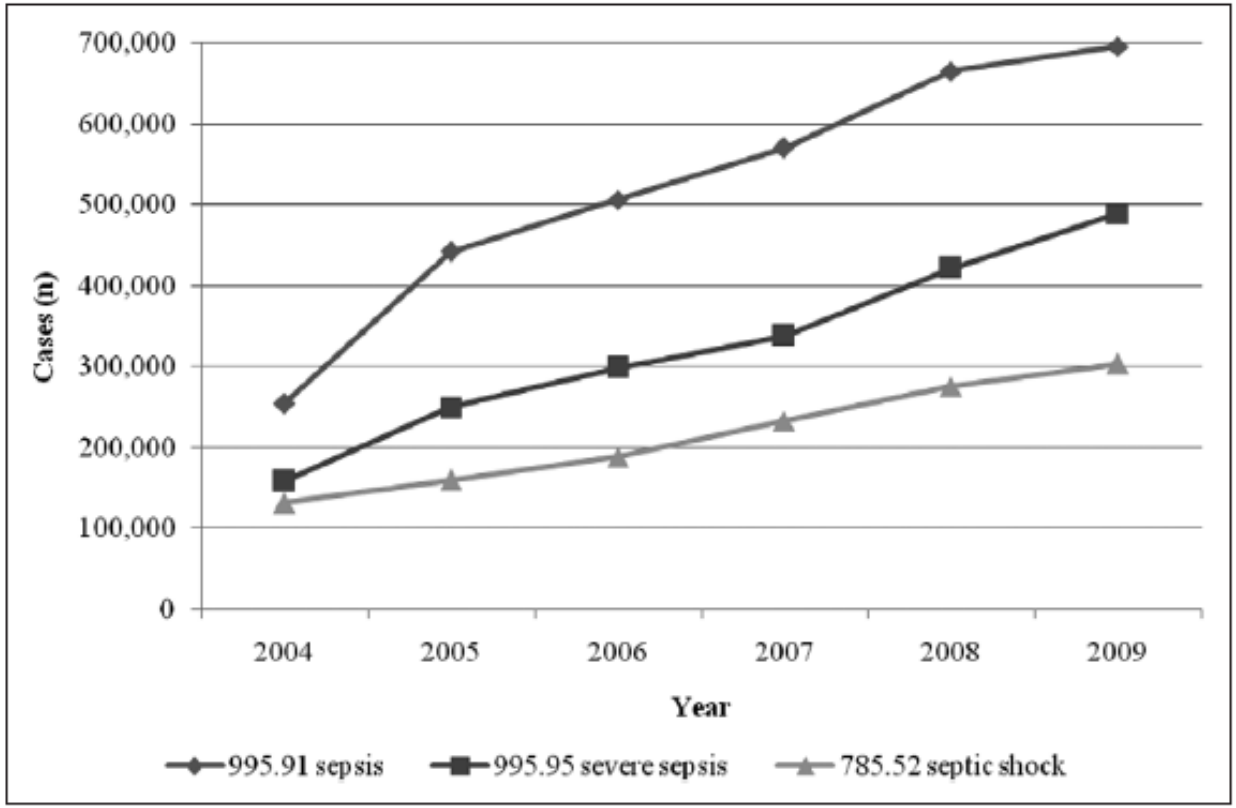

Figure 4. Use of *International Statistical Classification of Diseases*, 9th Edition, codes for sepsis (995.91), severe sepsis (995.92), and septic shock (785.52).

Gaieski DF et al. *Crit Care Med*, 2013

Improvement in sepsis

- Mortality results are decreasing
- Recognition of sepsis is increasing
- Novel interventions
- New pharmacotherapeutical strategies
- Surviving Sepsis Campaign

What is sepsis?

Sepsis is not a definitive diagnosis

- „Sepsis-syndrome” and Las Vegas - 1980:
  - Fever or hypothermia (> 38.3°C or < 35.0 °C)
  - Tachycardia (>90/min)
  - Leukocytosis or leukopenia (> 12 000cells/mm^3, < 4000cells/mm^3, or > 10% immature forms)
  - Hypotension (<90mmHg)

The New England
Journal of Medicine

Volume 317 SEPTEMBER 10, 1987 Number 11

A CONTROLLED CLINICAL TRIAL OF HIGH-DOSE METHYLPREDNISOLONE IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

ROGER C. BONE, M.D., CHARLES J. FISHER, JR., M.D., TERRY P. CLEMMER, M.D., GUS J. SLOTMAN, M.D., CRAIG A. METZ, M.S., ROBERT A. BALK, M.D., AND THE METHYLPREDNISOLONE SEVERE SEPSIS STUDY GROUP

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CRITICAL CARE MEDICINE

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Sepsis syndrome: A valid clinical entity

ROGER C. BONE, MD; CHARLES J. FISHER, JR, MD; TERRY P. CLEMMER, MD; GUS J. SLOTMAN, MD; CRAIG A. METZ, MS; ROBERT A. BALK, MD; THE METHYLPREDNISOLONE SEVERE SEPSIS STUDY GROUP*

Sepsis is not a definitive diagnosis

- 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

accp/sccm consensus conference

Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis

THE ACCP/SCCM CONSENSUS CONFERENCE COMMITTEE:

Roger C. Bone, M.D., F.C.C.P., Chairman
Robert A. Balk, M.D., F.C.C.P.
Frank B. Cerra, M.D.
R. Phillip Dellinger, M.D., F.C.C.P.
Alan M. Fein, M.D., F.C.C.P.
William A. Knaus, M.D.
Roland M. H. Schein, M.D.
William J. Sibbald, M.D., F.C.C.P.

Sepsis definition – SSC 2012

Infection, documented or suspected, and some of the following:

General variables

- Fever (> 38.3°C)
- Hypothermia (core temperature < 36°C)
- Heart rate > 90/min^{-1} or more than two SD above the normal value for age
- Tachypnea

Sepsis definitions: time for change

Jean-Louis Vincent, Steven M Opal, John C Marshall, Kevin J Tracey

Lancet 2013; 381: 774–75

- Plasma C-reactive protein more than two SD above the normal value
- Plasma procalcitonin more than two SD above the normal value

Hemodynamic variables

- Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two SD

Sepsis is not a „disease” but a „consensus”

- Thrombocytopenia (platelet count < 100,000 μL^{-1})
- Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)

Tissue perfusion variables

- Hyperlactatemia (> 1 mmol/L)
- Decreased capillary refill or mottling

The most recent sepsis definition

JAMA The Journal of the American Medical Association

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February 23, 2016, Vol 315, No. 8 >

< Previous Article Next Article >

Special Communication | February 23, 2016

CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) FREE

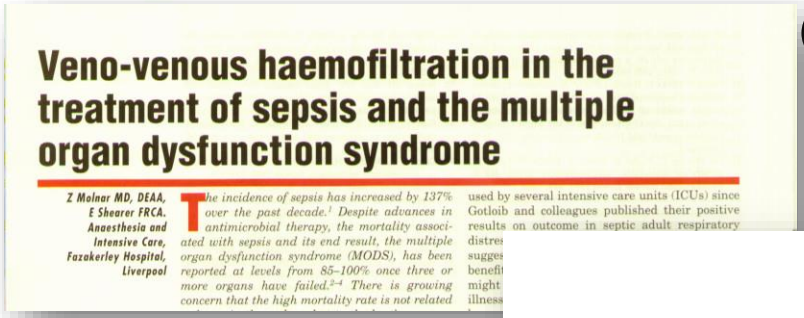
Mervyn Singer, MD, FRCP[1]; Clifford S. Deutschman, MD, MS[2]; Christopher Warren Seymour, MD, MSc[3]; Manu Shankar-Hari, MSc, MD, FFICM[4]; Djillali Annane, MD, PhD[5]; Michael Bauer, MD[6]; Rinaldo Bellomo, MD[7]; Gordon R. Bernard, MD[8]; Jean-Daniel Chiche, MD, PhD[9]; Craig M. Coopersmith, MD[10]; Richard S. Hotchkiss, MD[11]; Mitchell M. Levy, MD[12]; John C. Marshall, MD[13]; Greg S. Martin, MD, MSc[14]; Steven M. Opal, MD[12]; Gordon D. Rubenfeld, MD, MS[15,16]; Tom van der Poll, MD, PhD[17]; Jean-Louis Vincent, MD, PhD[18]; Derek C. Angus, MD, MPH[19,20]

Box 3. New Terms and Definitions

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.
  - The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
  - A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.
- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.
- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA, ie, alteration in mental status, systolic blood pressure ≤100 mm Hg, or respiratory rate ≥22/min.
- Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.
- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

Pathomechanism

Pathomechanism



Veno-venous haemofiltration in the treatment of sepsis and the multiple organ dysfunction syndrome

Z Molnar MD, DEAA, E Shearer FRCA. Anaesthesia and Intensive Care, Fazakerley Hospital, Liverpool

The incidence of sepsis has increased by 137% over the past decade.[1] Despite advances in antimicrobial therapy, the mortality associated with sepsis and its end result, the multiple organ dysfunction syndrome (MODS), has been reported at levels from 85–100% once three or more organs have failed.[2–4] There is growing concern that the high mortality rate is not related

used by several intensive care units (ICUs) since Gotloib and colleagues published their positive results on outcome in septic adult respiratory

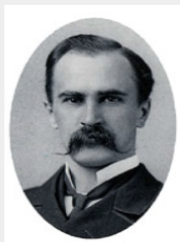
Insult
Endotoxin, Trauma, Sterile inflammation, Operation, etc.

Humoral activity
Interferon, Complement

It

t

„Except on few occasions, the patients seems to die from the body´s response to infection rather than from it.“



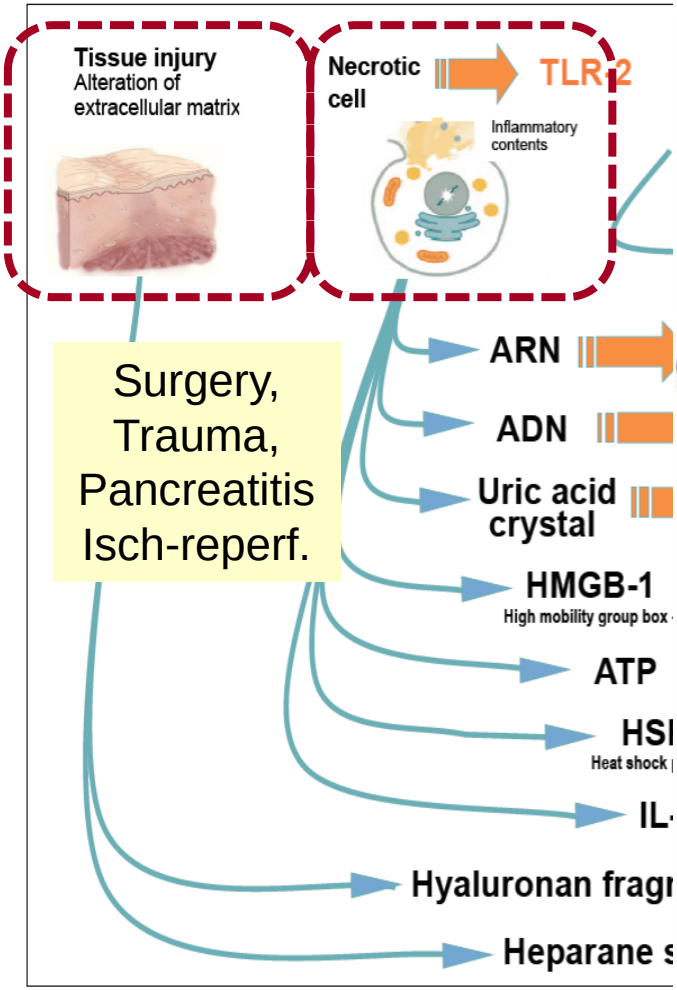
Sir William Osler; The Evolution of Modern Medicine 1904

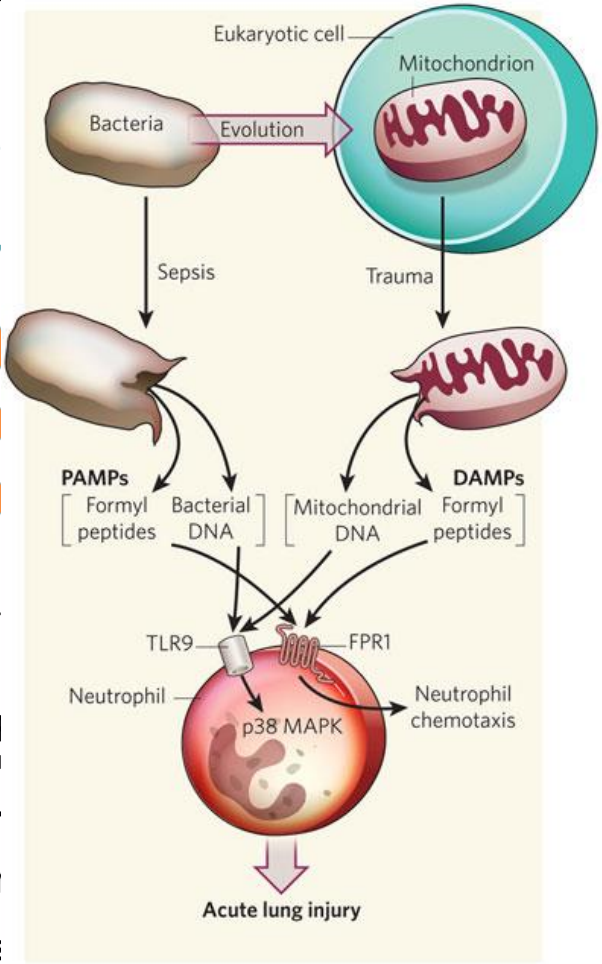
MSOF

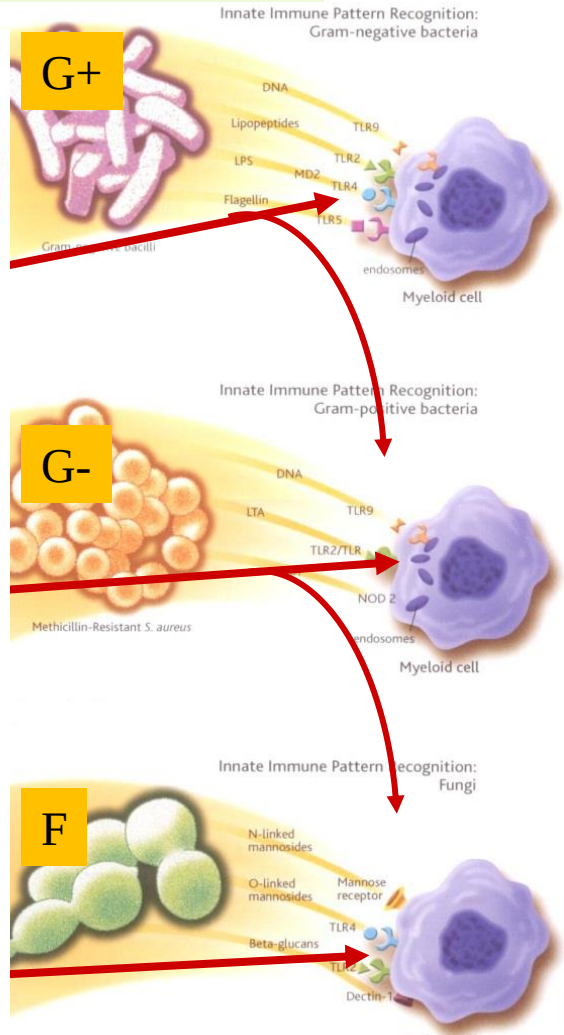
Molnár and Shearer *Br J Int Care Med* 1998; 8: 12

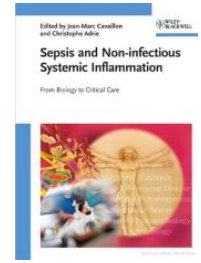
DAMP = Damage Associated Molecular Pattern
PAMP = Pathogen Associated Molecular Pattern

„DAMP → SIRS" **versus** **„PAMP → SIRS"**









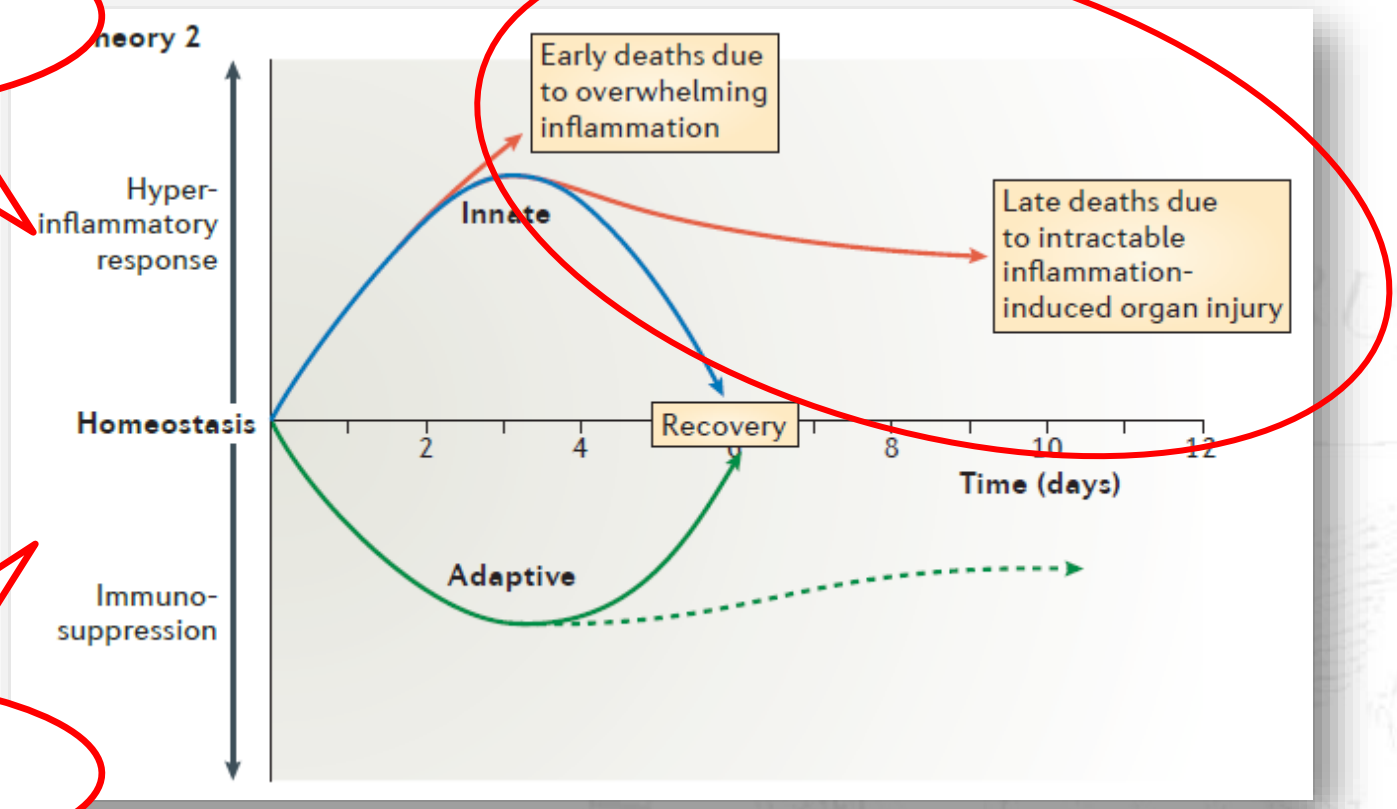
Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss[1], Guillaume Monneret[2] and Didier Payen[3]

Nature Reviews | Immunology Volume 13 | December 2013 | 862-874

Pro-inflammation

Anti-inflammation



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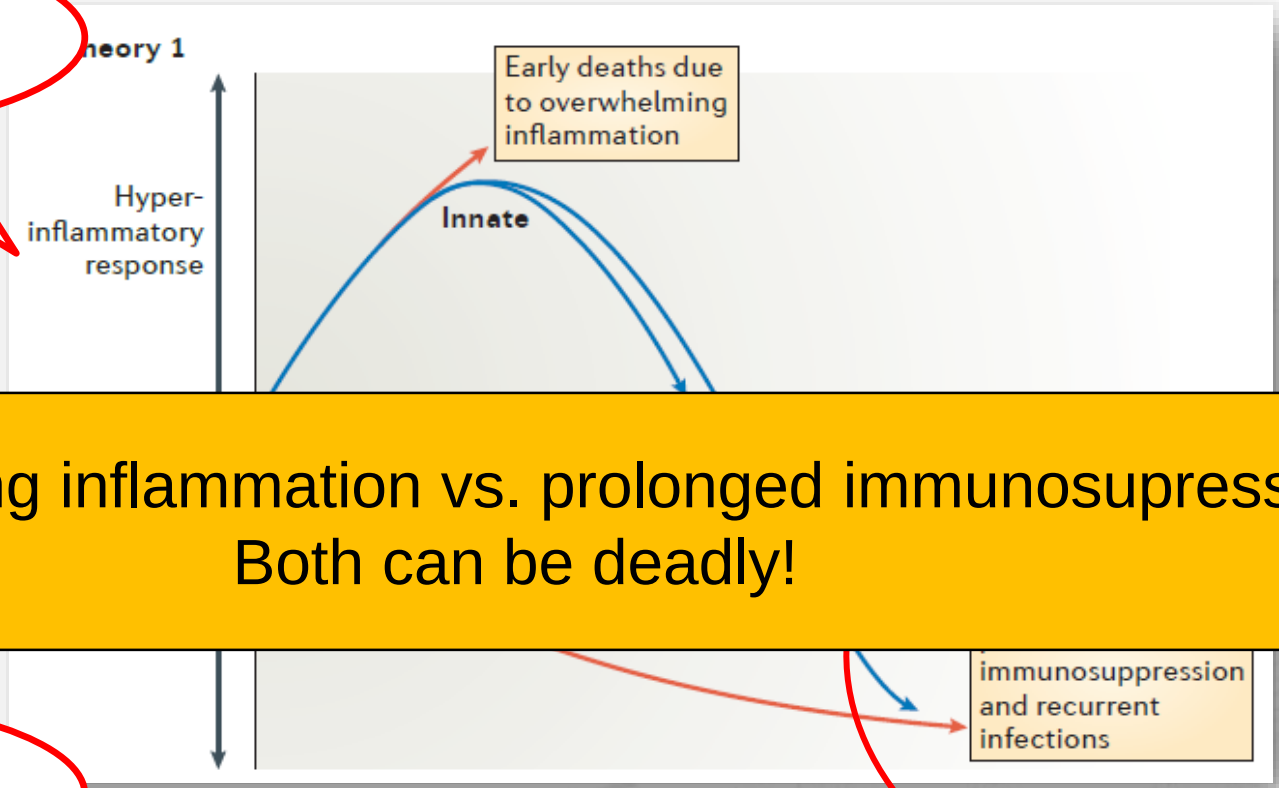


Overwhelming inflammation vs. prolonged immunosupression:
Both can be deadly!

Anti-inflammation

~~Is this patient septic or not?~~

I have never treated „SEPSIS” in my life!
But…

Does the patient have **infection** or not?

Infection = ABs

No infection = No ABs

Signs of infection

- Clinical signs:
  - Most important

Not good enough

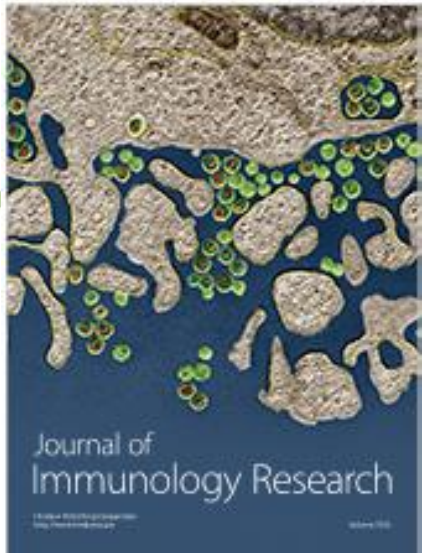
- Fever (>38ºC), WBC (>12 000):
  - Low sensitivity (~50%)

Galicier L and Richet H. *Infect Control Hosp*

Poooor!

- Microbiology:
  - Results: 24 hours or more

Very late!



Pathogen ⟶ PAMPs
Tissue injury ⟶ DAMPs
} Inflammatory respones

Leucocyte, lymphocyte, endothelial cells, parenchymal cells
MBL, NOD protein, P substance

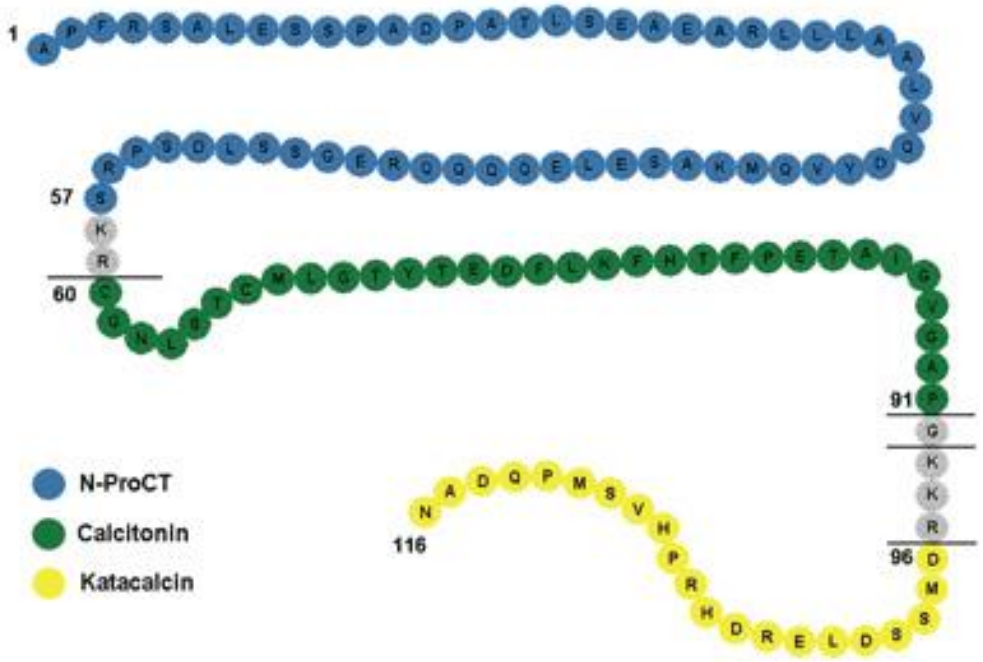
Dysregulated, generalized immune response

Coagulation	Complement system	Cytokines and chemokines	Acute phase proteins	Stress hormones	Hormokines	Cytoplasmatic factors
			α1-glycoprot.	ACTH	ADM	HS protein
			Ferritin	AVP	CGRP	HMG-1
			Fibronectin	GH	PCT	NO
			Haptoglobin	Cortisol	IL-6	
			LPS prot.	Prolactin	Leptin	
			SAA	Histamine	MIF	
			CRP	Noradrenaline		
				Adrenalin		
				Endorphin		

Immunoregulation	Proinflammatory	Anti-inflammatory
IFN-γ	IL-1β endothelin	IL-1RA
Il-2	IL-6 adheston molecules	IL-4
IL-4	IL-8 chemokines	IL-6
IL-5	IL-11 elastase	IL-10
IL-7	IL-12 growth factors	IL-11
IL-11	IL-18 LTs	IL-13
	IL-23 NO	IL-16
	TNFα protease	IL-18RA
	IFNγ PGs	TGF-β3
	ROI	Leptin
	MIF	NO
	TBs	TNF

László I et al. *J Immunol Res*, 2015

Procalcitonin (PCT)



- CD16, CD14 expression
- increases leucocyte-derived cytokins
- effects leucocyte migration
- augments nitric-oxid secretion

PCT versus CRP

László I et al. *J Immun Research*; 2015

Table 1: Comparison of CRP versus PCT (advantages and disadvantages).

	CRP	PCT
Differentiating bacterial infection from SIRS	– [27]	Specific for bacteria [28, 29]
Response to infection	Slower (days) [27]	2–6 hours [30]
Peak response after infection	2-3 days [27]	12–48 hours [27]
Half-life	Several days [27]	20–35 hours [31]
Plasma kinetic	Slow [27]	Rapid [27]
Price	+	++++
Correlating disease severity and progression	Slightly [27]	+++ [32]
Correlating effective therapy	+	+++ [33, 34]
Prognostic factor for mortality	Weak or nonexistent [27]	Good predictor [31, 32]
Differentiating G+ from G–	– [35]	++ [35]
Response to other factors	Virus, autoimmune diseases, local infections, surgery, trauma [27]	Surgery, trauma, burn, cardiogenic shock, liver cirrhosis [36–38]
Fungal infection	same as bacterial [35]	Slightly elevated [35]
Immunosuppression	Formation can be changed [27]	The induction is reduced [27]
Biological effect	Opsonin for phagocytosis [27]	Chemokine [27]
Sensitivity/specificity	Sensitive but nonspecific [27]	Sensitive and specific [27, 39]
General use	Outpatient care [27]	In intensive care [27]

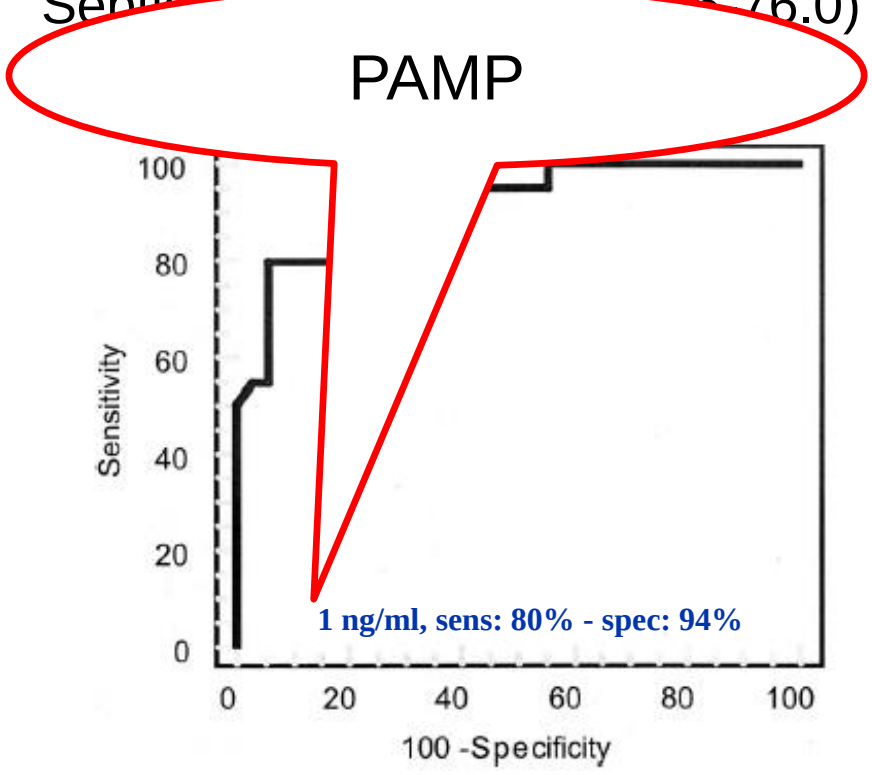
Differential diagnostic value of procalcitonin in surgical and medical patients with septic shock

Clec'h et al. *Crit Care Med* 2006; 34:102-107

Medical patients:

SIRS: PCT = 0.3 (0.1-1.0) ng/ml

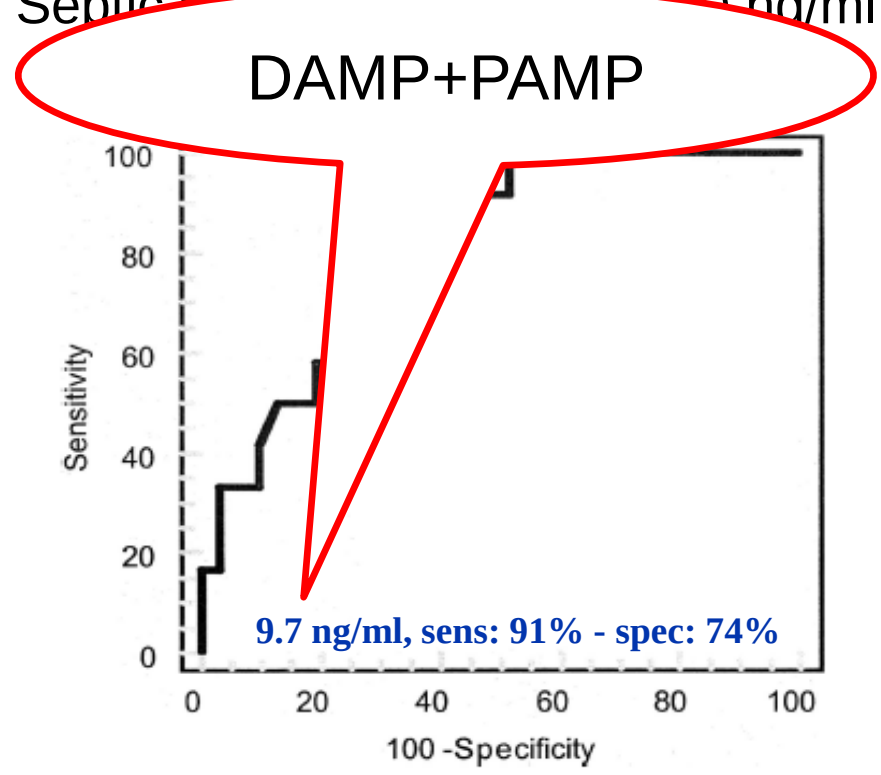
Septic [illegible] 76.0) ng/ml



Surgical patients:

SIRS: PCT = 5.7 (2.6-8.4) ng/ml

Septic [illegible] ng/ml



In clinical practice

61 years old male

- past medical history: unwell for 2 days, cough, yellowish sputu
- fever
- leucc 4520
- organ respi
- PCT: 1.2 ng/ml

47 years old female

- past medical history: breast reconstruction surgery with feeling
- WCC
- PCT: 3.7 ng/ml

Sepsis ≠ homogenious group of patients
ie
One size does not fit all

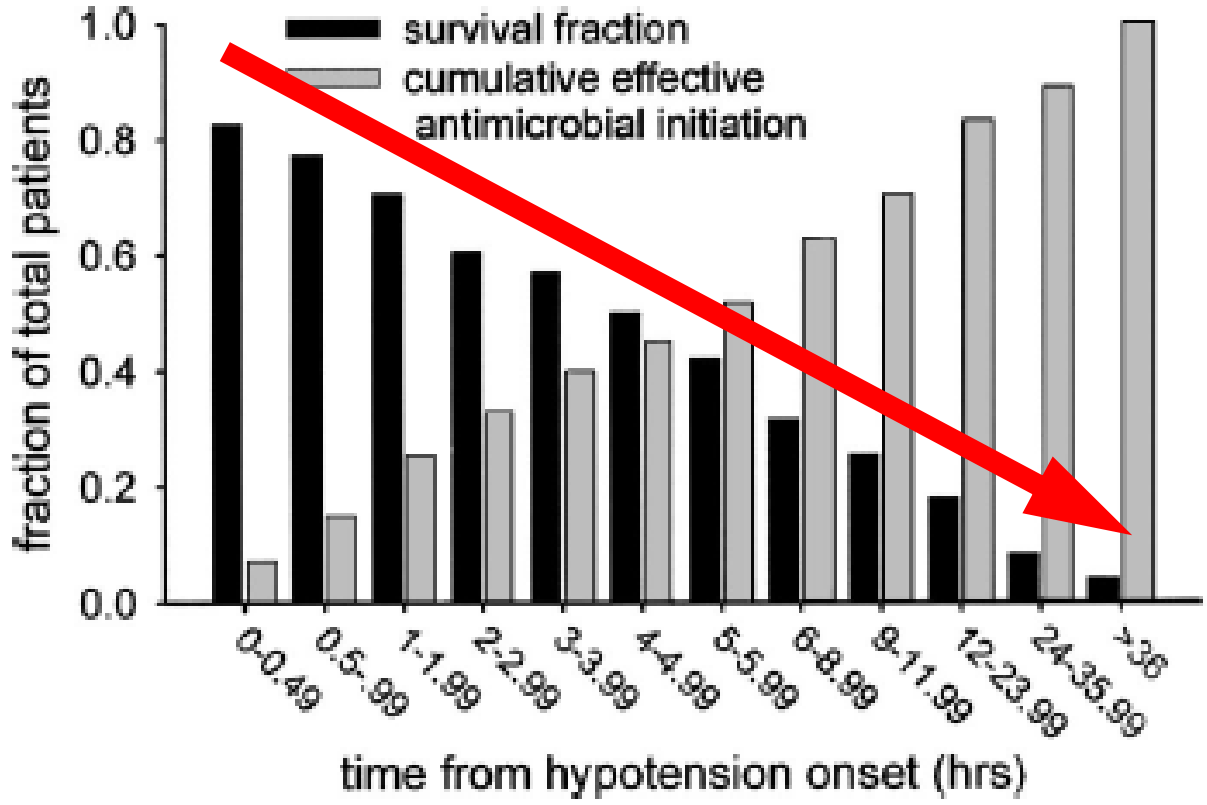
The diagnostic challange

- COLORFUL manifestation

RECOGNISING THE SEPTIC PATIENT

- initiating supportive therapy
- decision making:
  - SIRS or sepsis?
- initiating proper antibiotics

Delay in antibiotic therapy



Kumar A et al. *Crit Care Med*, 2006

Optimal antibiotic treatment

- 30-60 % of antibiotics prescribed on ICUs are:
  - unnecessary
  - inappropriate
  - suboptimal

Luyt CE et al. *Crit Care*, 2014

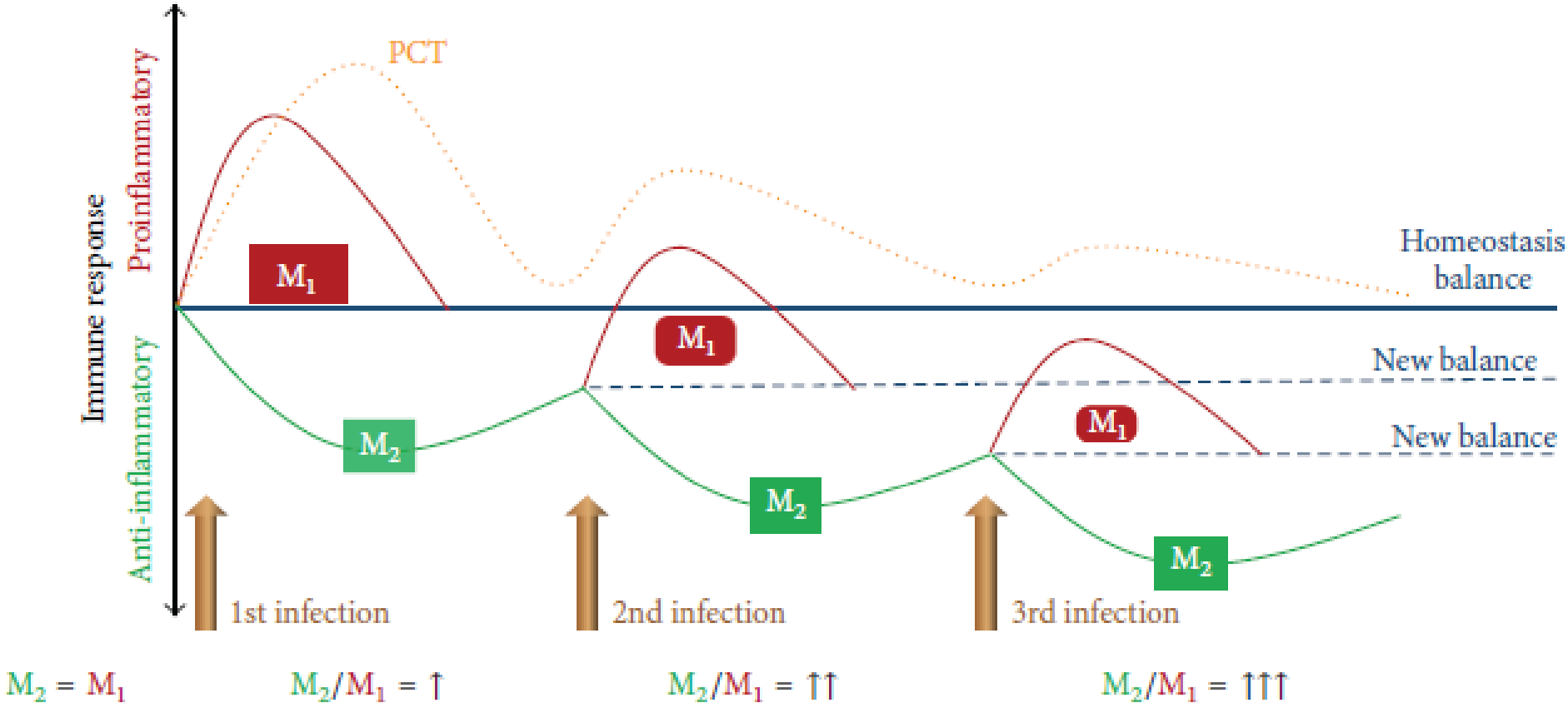
↓

- dissemination of antimicrobial-resistant microorganisms

Questions are

- Should we initiate antibiotic treatment?
- Is it an appropriate antibiotic?
- For how long should I administer the antibiotic?

PCT response to consequent infectious insults



László I et al. *J Immunol Res*, 2015

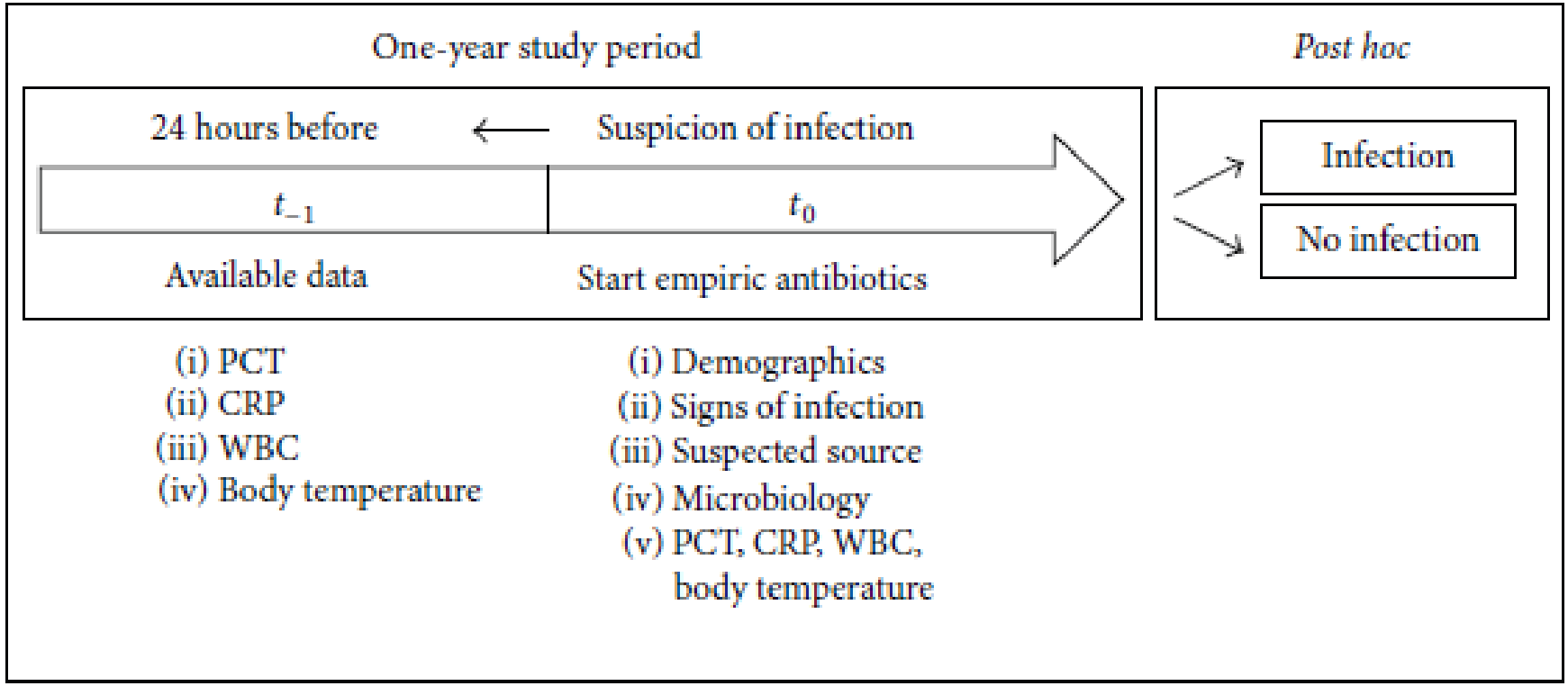
Hindawi Publishing Corporation
Journal of Immunology Research
Volume 2016, Article ID 3530752, 9 pages
http://dx.doi.org/10.1155/2016/3530752

Research Article

Delta Procalcitonin Is a Better Indicator of Infection Than Absolute Procalcitonin Values in Critically Ill Patients: A Prospective Observational Study

Domonkos Trásy,[1] Krisztián Tánczos,[1] Márton Németh,[1] Péter Hankovszky,[1] András Lovas,[1] András Mikor,[1] Edit Hajdú,[2] Angelika Osztroluczki,[1] János Fazakas,[3] and Zsolt Molnár[1]

ΔPCT as an indicator of infection



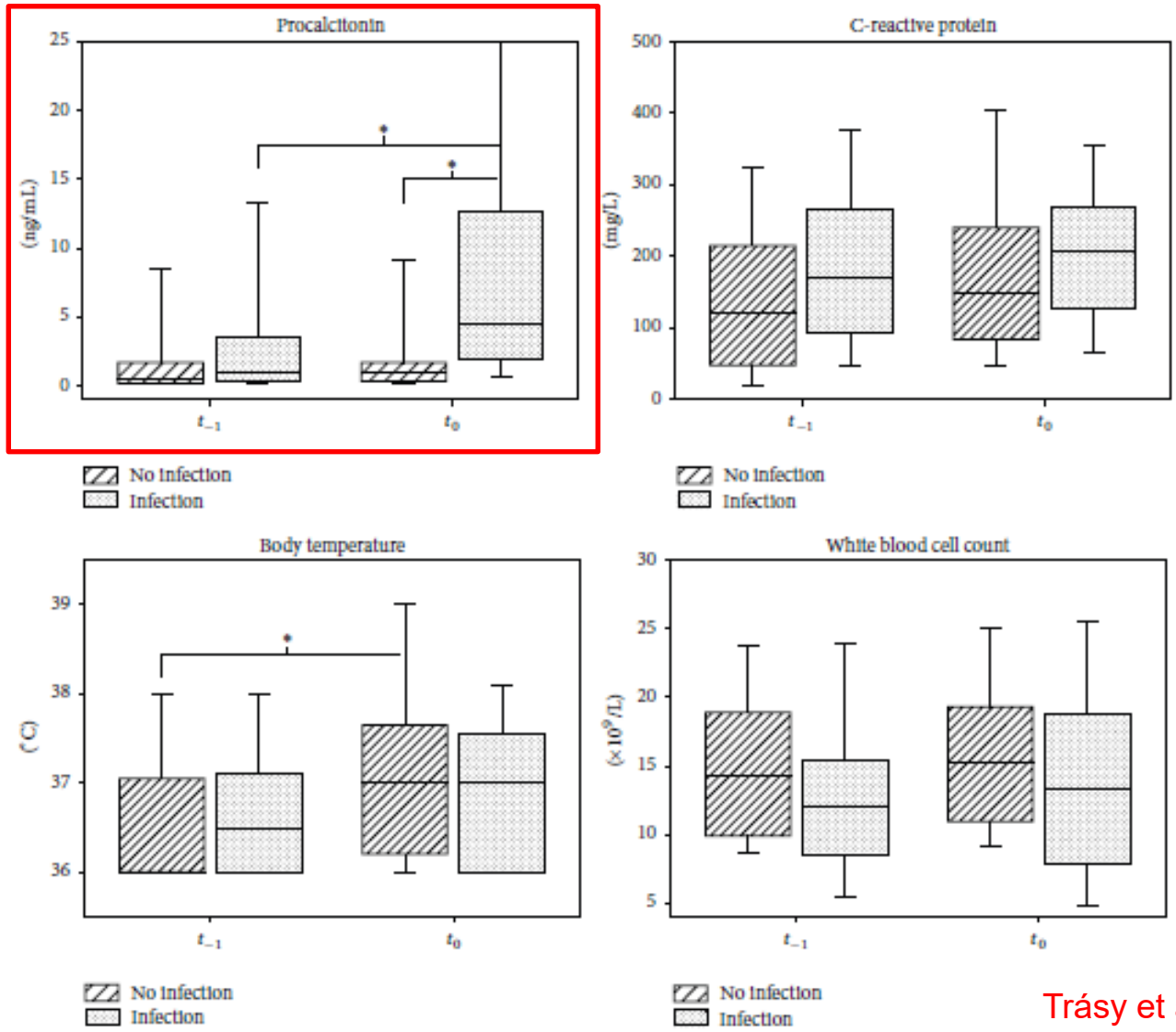
Trásy et al. *J Immunol Res*, 2016

Demographics of the investigation

	Total $n = 114$	NI-group $n = 29$	I-group $n = 85$	p value
Fever (<36°C; >38°C)	55 (48.2%)	13 (44.8%)	42 (49.4%)	0.670
WBC (>12 or <4 × 10^9/L)	82 (71.9%)	22 (75.9%)	60 (70.6%)	0.585
Impaired gas exchange	82 (71.9%)	18 (62.1%)	64 (75.3%)	0.171
Impaired consciousness	59 (51.8%)	9 (31.0%)	50 (58.8%)	0.010
Hemodynamic instability	74 (64.9%)	13 (44.8%)	61 (71.8%)	0.009
PCT (ng/mL)	3.37 (9.22)	1.12 (1.36)	4.62 (10.72)	0.018
CRP (mg/L)	182.75 (158.5)	147.60 (156.50)	208.80 (140.60)	0.301

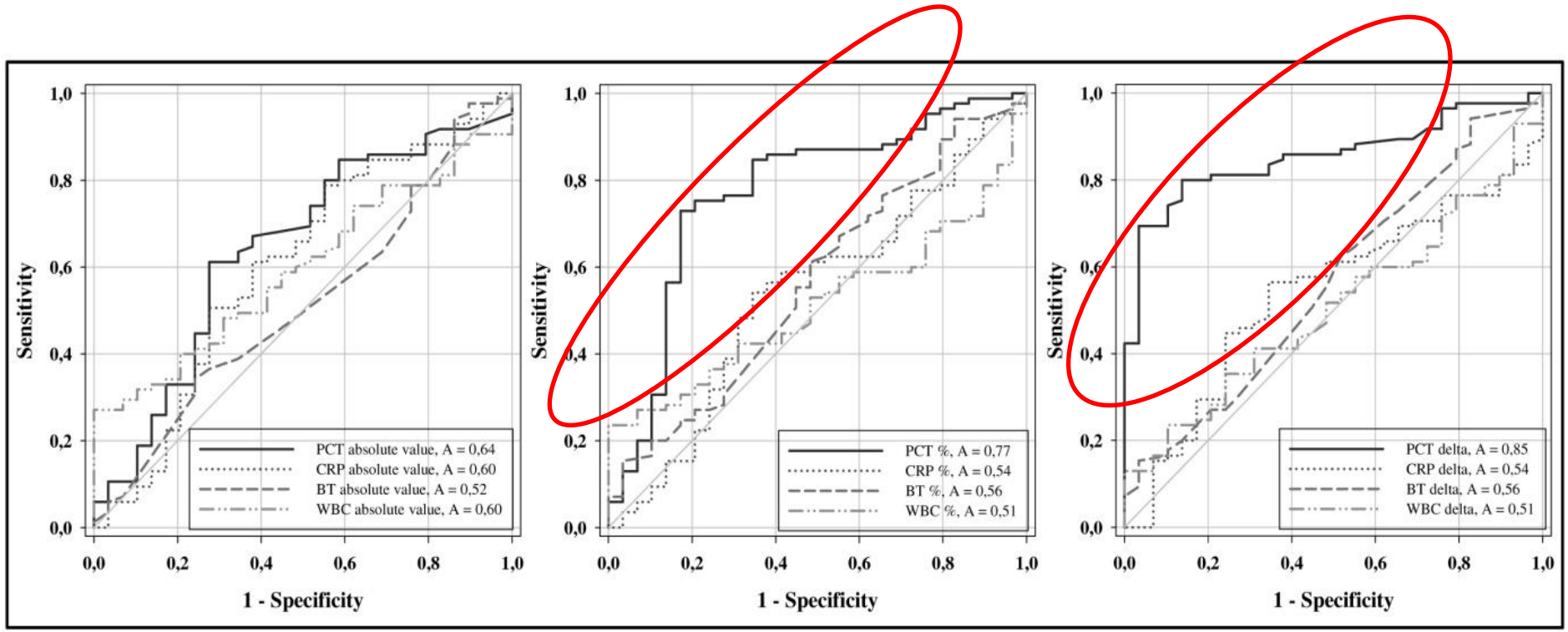
Trásy et al. *J Immunol Res*, 2016

Absolute values of PCT, CRP, temperature and WCC



Trásy et al. *J Immunol Res*, 2016

ΔPCT as an indicator of infection



Trásy et al. *J Immunol Res*, 2016

Contents lists available at ScienceDirect

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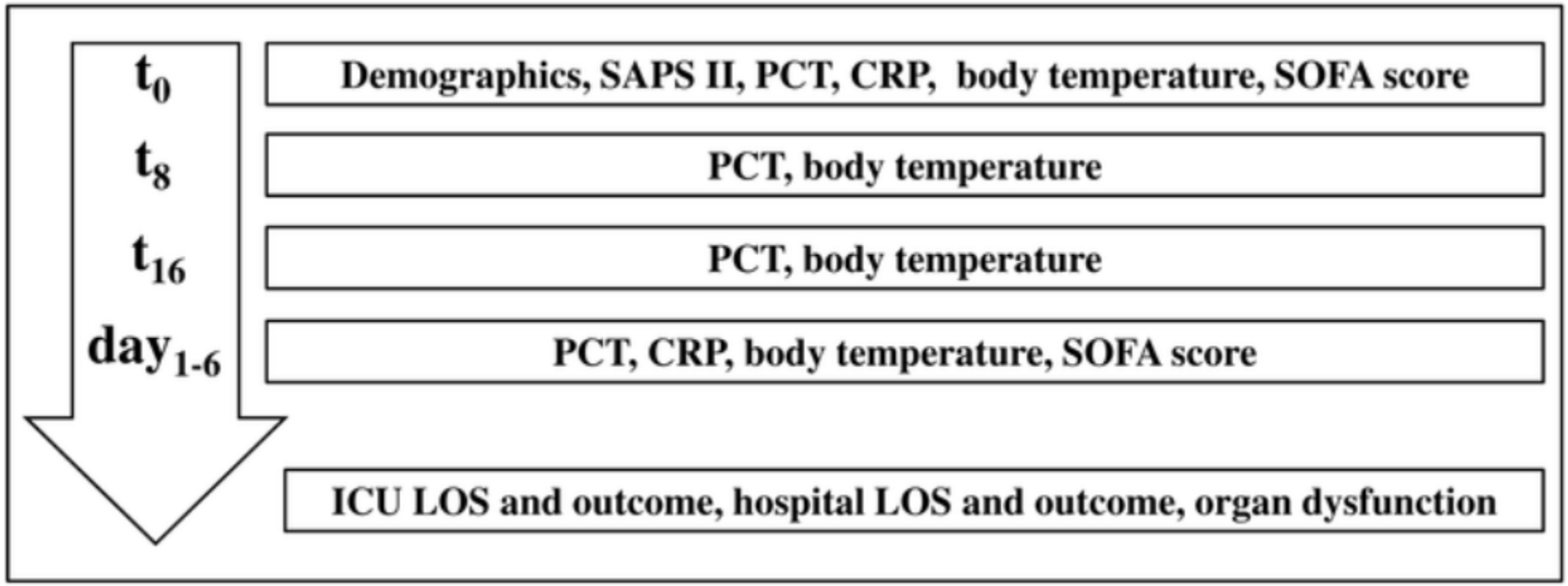
journal homepage: www.jccjournal.org

Sepsis/Infection

Early procalcitonin kinetics and appropriateness of empirical antimicrobial therapy in critically ill patients☆
A prospective observational study

Domonkos Trásy, MD [a,*], Krisztián Tánczos, MD [a], Márton Németh, MD [a], Péter Hankovszky, MD [a], András Lovas, MD [a], András Mikor, MD [a], Ildikó László, MD [a], Edit Hajdú, MD [b], Angelika Osztroluczki [a], János Fazakas, MD [c], Zsolt Molnár, MD [a] The EProK study group

Early PCT kinetics may indicate effective empirical antibiotic therapy



Trásy et al. J Crit Care, 2016

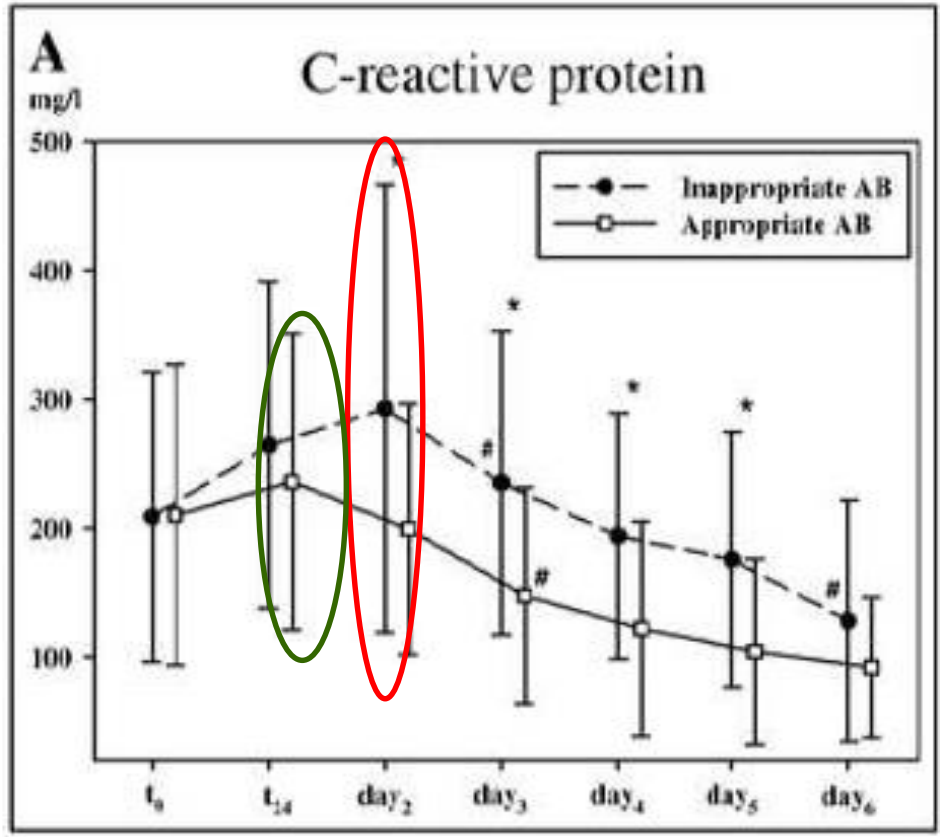
Early PCT kinetics may indicate effective empirical antibiotic therapy

Best cut-off values to indicate inappropriate antibiotic treatment:

- PCT increase of > 55% during the first 16 hours
- PCT increase of > 70% during the first 24 hours

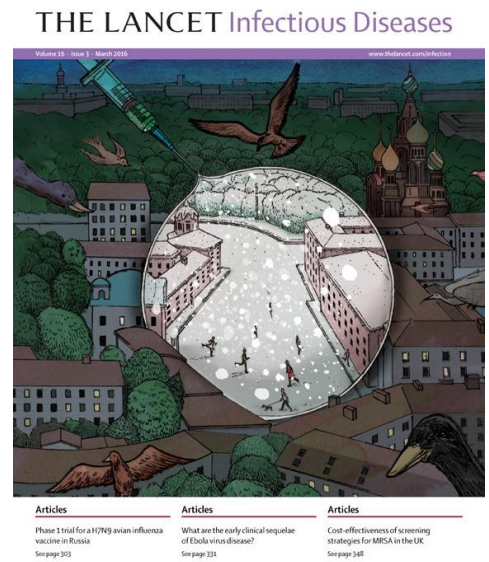
Trásy et al. under review

CRP kinetics in the same study



under submission

Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial



Background of the investigation:

- duration of AB treatment is associated with groving resistance
- safety of PCT guided therapy is scarce
- assessment of efficiacy and safety of PCT guided AB therapy on ICU

de Jong E et al. *Lancet Infect Dis*, 2016

Efficacy and safety of PCT guiding

- satisfactory drop in PCT might help to discontinue AB
- is it a safe practice?
- **S**top **A**ntibiotics on **P**rocalcitonin Guidance **S**tudy
- Study design:
  - 1546 patients
  - stop antibiotics if:
  - PCT decreased by 80%
  - absolute value < 0.5 µg/L

de Jong E et al. *Lancet Infect Dis*, 2016

Results of SAPS I.

	Procalcitonin-guided group (n=761)	Standard-of-care group (n=785)	Between-group absolute difference in means (95% CI)	p value
Antibiotic consumption (days)				
Daily defined doses in first 28 days	7·5 (4·0 to 12·8)	9·3 (5·0 to 16·5)	2·69 (1·26 to 4·12)	<0·0001
Duration of treatment	5·0 (3·0 to 9·0)	7·0 (4·0 to 11·0)	1·22 (0·65 to 1·78)	<0·0001
Antibiotic-free days in first 28 days	7·0 (0·0 to 14·5)	5·0 (0 to 13·0)	1·31 (0·52 to 2·09)	0·0016
Mortality (%)				
28-day mortality	149 (19·6%)	196 (25·0%)	5·4% (1·2 to 9·5)	0·0122
1-year mortality	265 (34·8%)	321 (40·9%)	6·1% (1·2 to 10·9)	0·0158
Adverse events				
Reinfection	38 (5·0)	23 (2·9)	−2·1% (−4·1 to −0·1)	0·0492
Repeated course of antibiotics	175 (23·0)	173 (22·0)	−1·0% (−5·1 to 3·2)	0·67
Time (days) between stop and reinstitution of antibiotics	4·0 (2·0 to 8·0)	4·0 (2·0 to 8·0)	−0·22 (−1·31 to 0·88)	0·96
Costs				
Total cumulative costs of antibiotics	€150 082	€181 263	NA	NA
Median cumulative costs antibiotics per patient	€107 (51 to 229)	€129 (66 to 273)	€33·6 (2·5 to 64·8)	0·0006
Length of stay (days)				
On the intensive care unit	8·5 (5·0 to 17·0)	9·0 (4·0 to 17·0)	−0·21 (−0·92 to 1·60)	0·56
In hospital	22·0 (13·0 to 39·3)	22·0 (12·0 to 40·0)	0·39 (−2·69 to 3·46)	0·77

Data are median (IQR), n (%), or mean (95% CI). Between-group absolute differences were calculated using the mean values, percentage differences, and 95% CIs. NA=not applicable.

Table 2: Primary and secondary outcome measures

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Results of SAPS II.

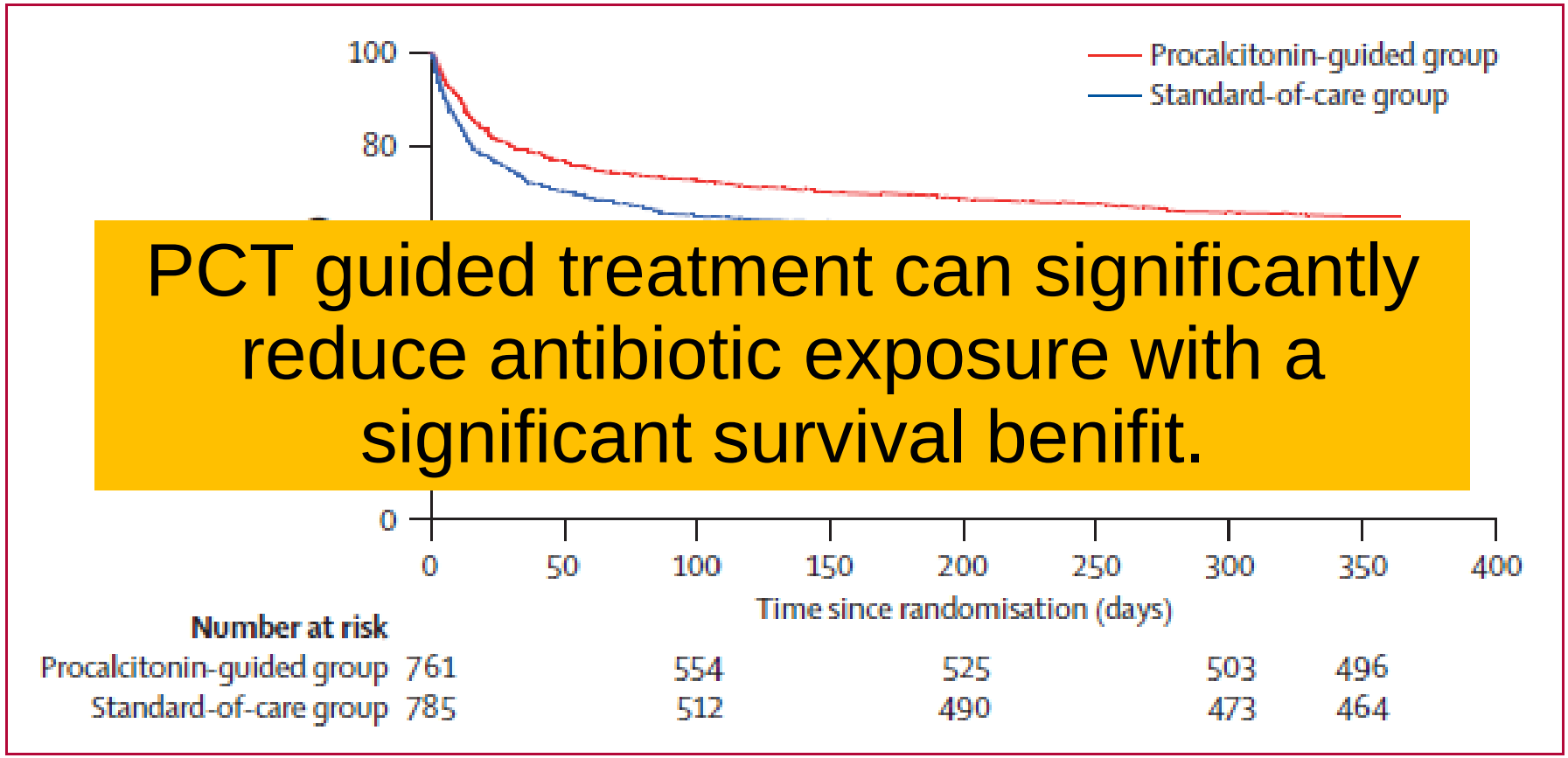

Figure 2: **Kaplan-Meier plot for probability of survival from random assignment to day 365, in the modified intention-to-treat population**

de Jong E et al. *Lancet Infect Dis*, 2016

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Case Report

Extreme Procalcitonin Elevation without Proven Bacterial Infection Related to Amphetamine Abuse

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Table 1: Blood chemistry results and their kinetics during stay in intensive care unit.

	Reference range	Day 1	Day 2	Day 4	Day 6	Day 10
PCT (ng/mL)	<0.5	1432	1640	1007	170.6	15.18
CRP (mg/L)	<5	8.5	n/a	n/a	n/a	n/a
WCC (cells/μL)	3700–9500	22690	18160	13960	11250	15950
PLT (cells/μL)	143000–332000	340000	204000	120000	115000	405000
INR		1.33	1.61	1.22	n.a.	n/a
LDH (U/L)	<530	2010	4754	7240	5150	n/a
GOT (U/L)	<37	651	2016	4207	1442	n/a
GPT (U/L)	<40	144	384	2016	463	n/a
CK (U/L)	<195	42960	125500	92700	20580	1325
Trop-T (μg/mL)	<0.04	0.117	0.192	n/a	n/a	n/a

PCT: procalcitonin; CRP: C-reactive protein; WCC: white cell count; PLT: platelet count; INR: international normalised ratio; LDH: lactate dehydrogenase; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase; CK: creatine kinase; Trop-T: troponin-T.

Conclusions I

- Sepsis is NOT a definitive diagnosis
- New definitions of sepsis approximates us to the underlying pahophysiology
- Rather the respons of the body than the infection on it’s own causes the harm
- There is grave overlap between response to infection and sterile cell injury

Conclusions II

- Biomarkers can help us in decision making
- PCT has high sensitivity and specificity

Nothing will ever replace the well trained, experienced, thinking human

Conclusions III.

- Defining and diagnosing sepsis are challanges
- Overlapping pathomechanism in sepsis and SIRS (DAMP, PAMP)
- Initiating adequate empiric antibiotic treatment in time is crucial

Conclusions IV.

- PCT can help the decision making
- Early PCT kinetics may indicate effective empirical antibiotic therapy
- PCT kinetics can be useful in the cessation of antibiotic treatment

Thank you for your attention