CytoSorbents™

Early antibiotics in septic shock: is it that important?

Prof. Zsolt Molnár[1,2,3]

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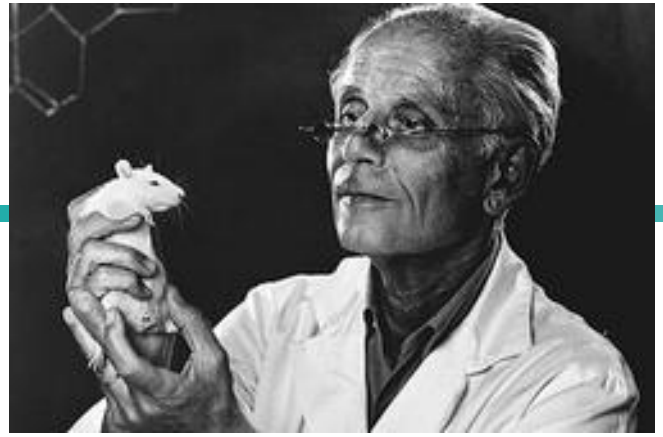
[3]Professor: Anaesthesiology and Intensive Therapy, Poznan University of Medical Sciences, Poznan, Poland

COLOURS OF SEPSIS
OSTRAVA 2020 / 22nd



János (Hans) Selye
1907-1982

32 NATURE JULY 4, 1936

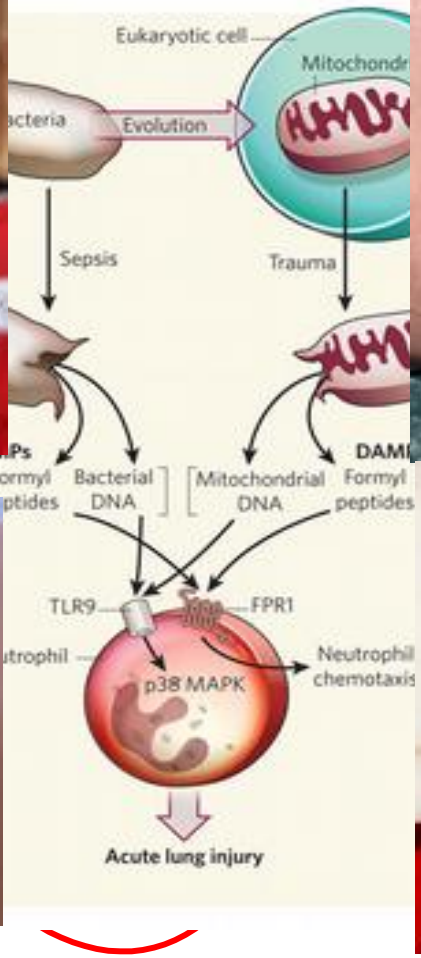
A Syndrome produced by Diverse Nocuous Agents

EXPERIMENTS on rats show that if the organism is severely damaged by acute non-specific nocuous agents such as exposure to cold, surgical injury, production of spinal shock (transcision of the cord), excessive muscular exercise, or intoxications with sublethal doses of diverse drugs (adrenaline, atropine, morphine, formaldehyde, etc.), a typical syndrome appears, the symptoms of which are independent of the nature of the damaging agent or the pharmacological type of the drug employed, and represent rather a response to damage as such.

Injury: DAMP or PAMP

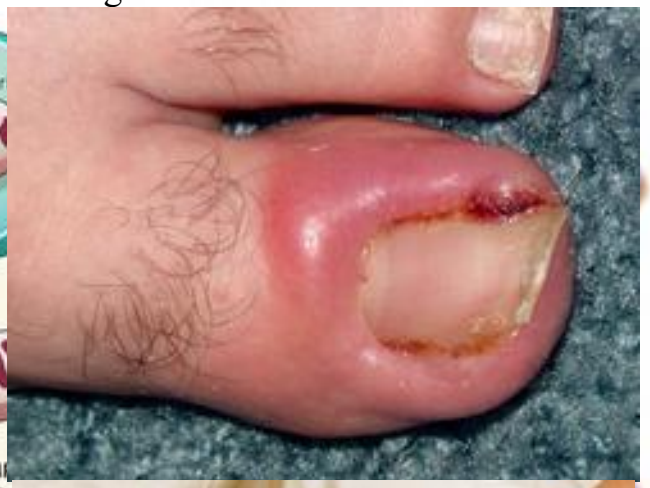
DAMP

Damage Associated Molecular Pattern



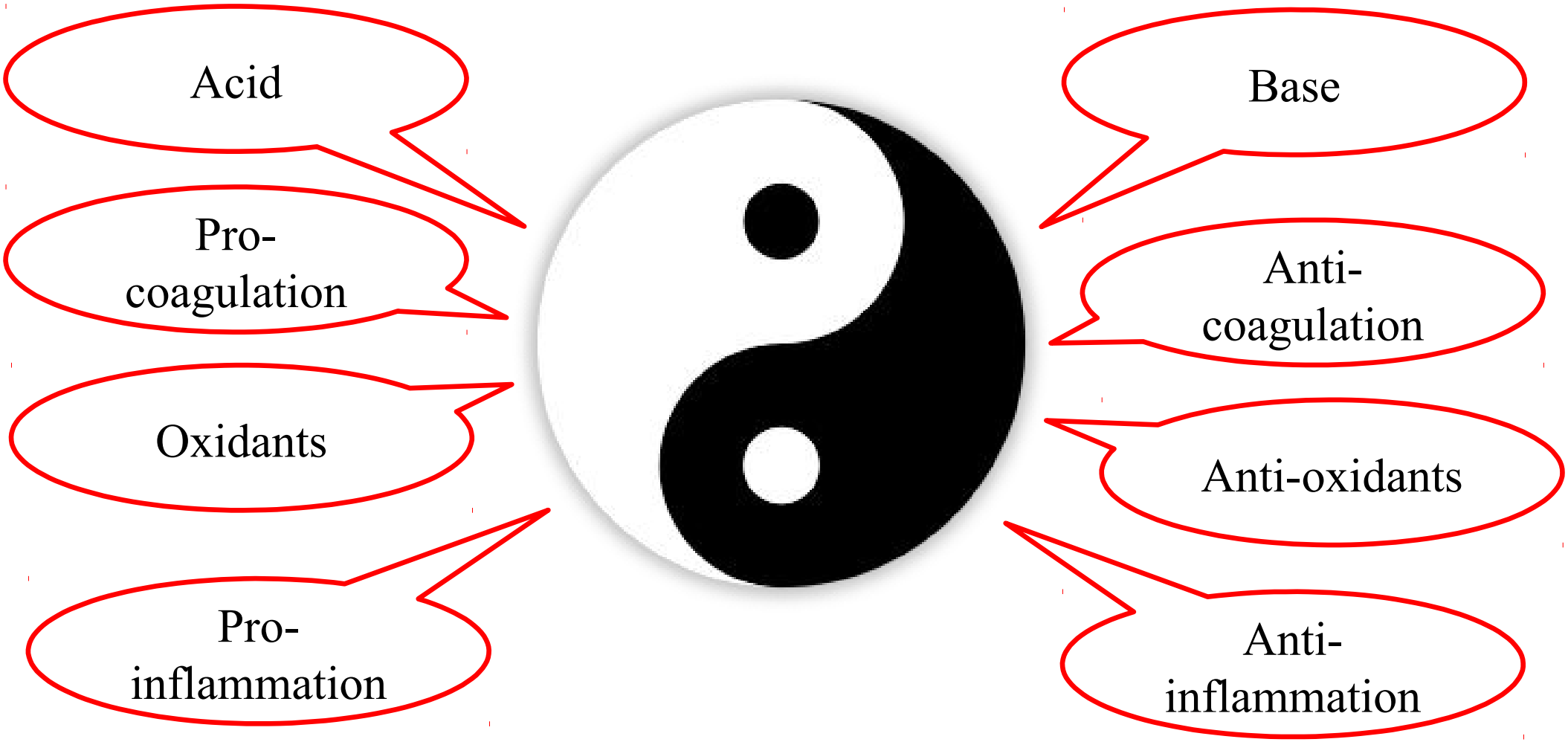
PAMP

Pathogen Associated Molecular Pattern



Interpreting biomarkers in infectious diseases in intensive care unit: the potential role of procalcitonin

Fatime Hawchar, Zsolt Molnar

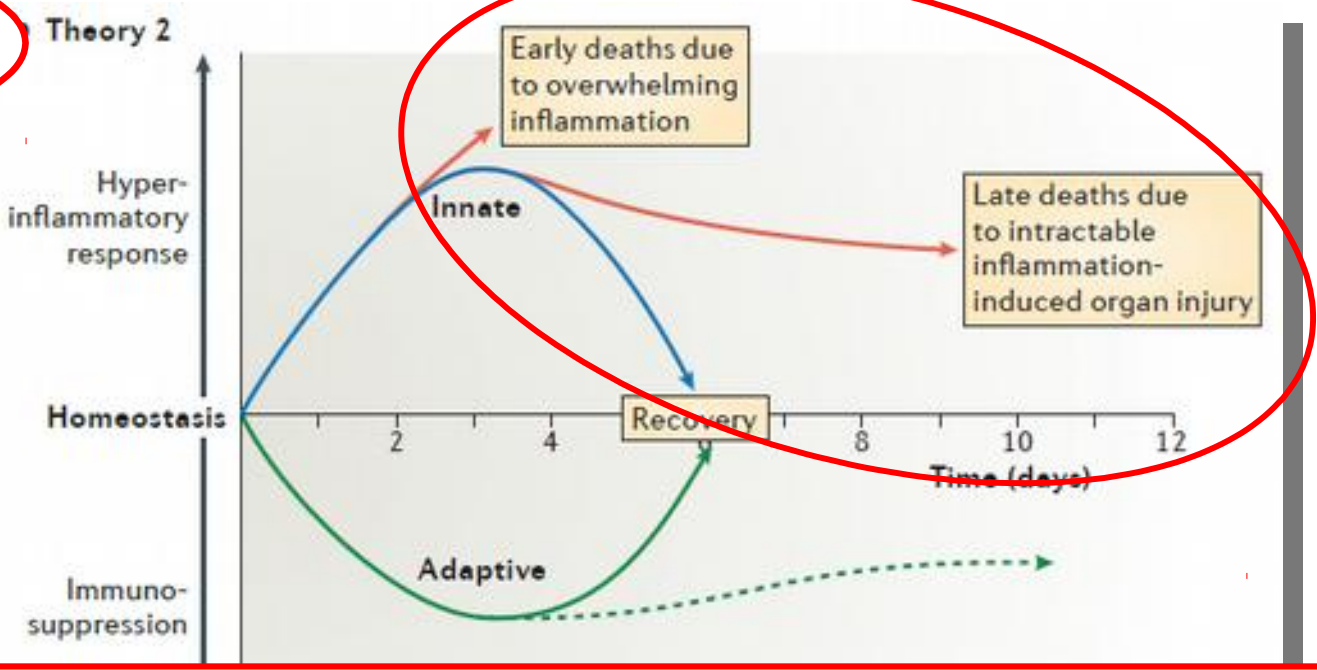


Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

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

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

Pro-inflammation



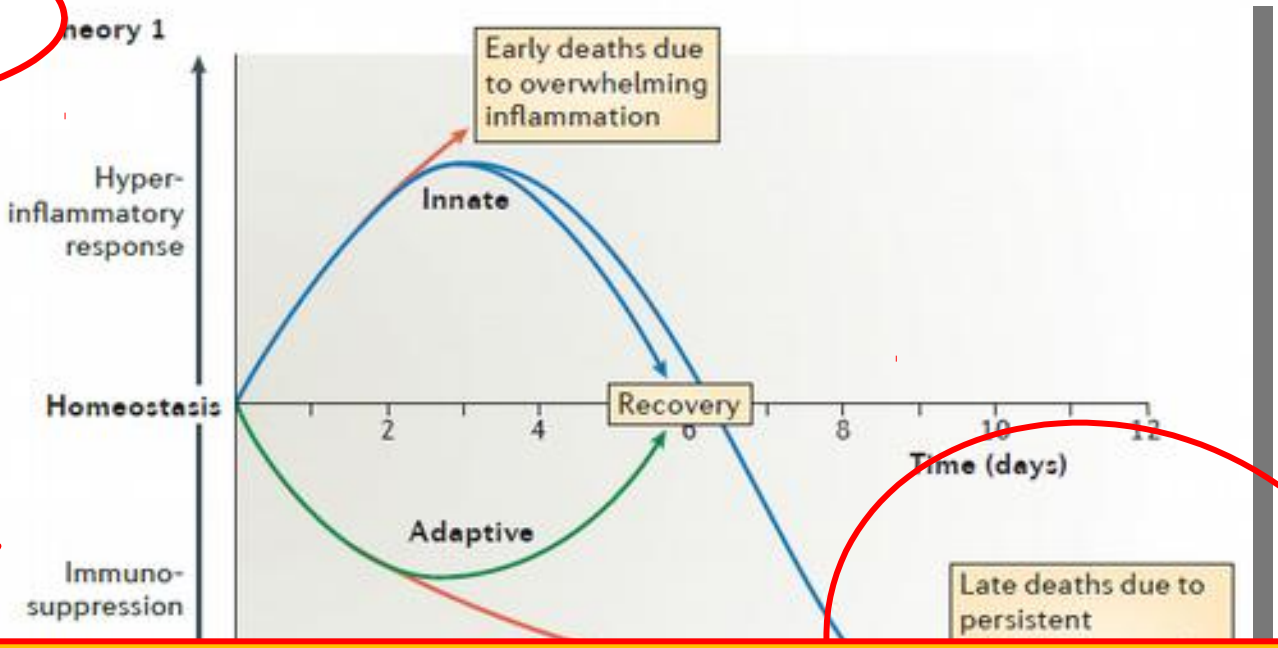
This is why SIRS was a wrong concept

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-inlflammation



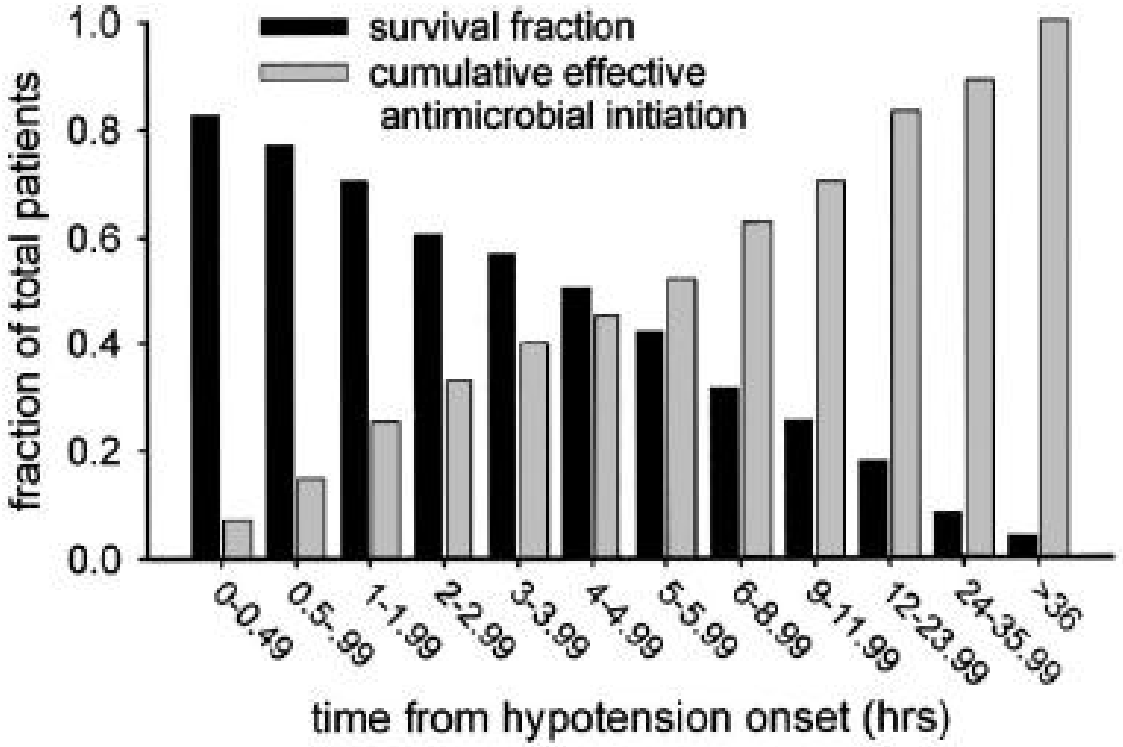
Immunosuppression is (one of) the answers for MDRPs

The mantra goes as:
„Give antibiotic(s) within the 1st hour!”

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

(Crit Care Med 2006; 34:1589–1596)



Each hour of delay in antimicrobial administration over the ensuing 6 hrs
was associated with an average decrease in survival of 7.6%.

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Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

R. Phillip Dellinger, MD; Jean M. Carlet, MD; Henry Masur, MD; Herwig Gerlach, MD, PhD; Thierry Calandra, MD; Jonathan Cohen, MD; Juan Gea-Banacloche, MD, PhD; Didier Keh, MD; John C. Marshall, MD; Margaret M. Parker, MD; Graham Ramsay, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Mitchell M. Levy, MD; for the Surviving Sepsis Campaign Management Guidelines Committee

CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

C. Antibiotic Therapy

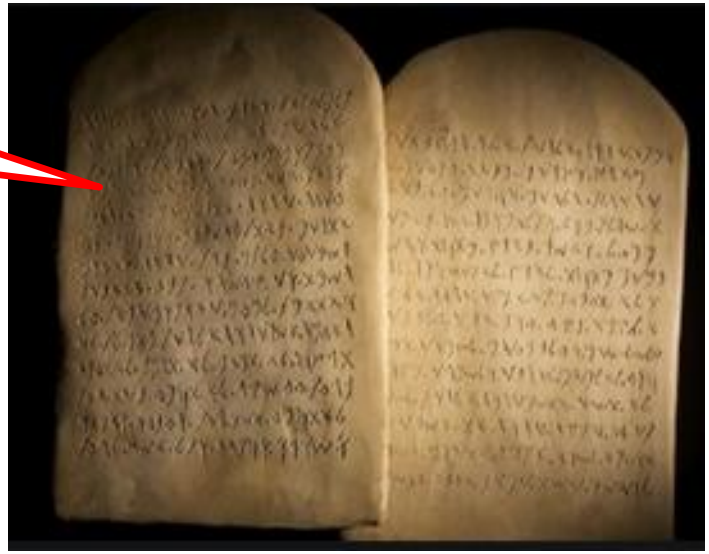
1. Intravenous antibiotic therapy should be started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained.

Grade E

D. ANTIMICROBIAL THERAPY

1. **We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock (strong recommendation, moderate quality of evidence; grade applies to both conditions).**

Give AB ASAP!!



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Antibiotics for Sepsis: Does Each Hour Really Count, or Is It Incestuous Amplification?

American Journal of Respiratory and Critical Care Medicine Volume 196 Number 7 | October 1 2017

"Each hour's delay in initiating antibiotics costs lives" is a doctrine that has attained quasireligious status. Like most (quasi) religions, this is founded more on faith and hope than hard fact."

"The "each hour delay" mantra is, however, being drummed into healthcare providers, hospital administrators, funders, and governmental bodies. Quality-improvement programs are being driven by financial penalty."

Klein Klouwenberg et al. Critical Care (2015) 19:319
DOI 10.1186/s13054-015-1035-1

CRITICAL CARE

RESEARCH Open Access

Likelihood of infection in patients with presumed sepsis at the time of intensive care unit admission: a cohort study

Peter M. C. Klein Klouwenberg[1,2,3*], Olaf L. Cremer[1], Lonneke A. van Vught[4], David S. Y. Ong[1,2,3], Jos F. Frencken[1,3], Marcus J. Schultz[5], Marc J. Bonten[2,3] and Tom van der Poll[4]

2,579 pts

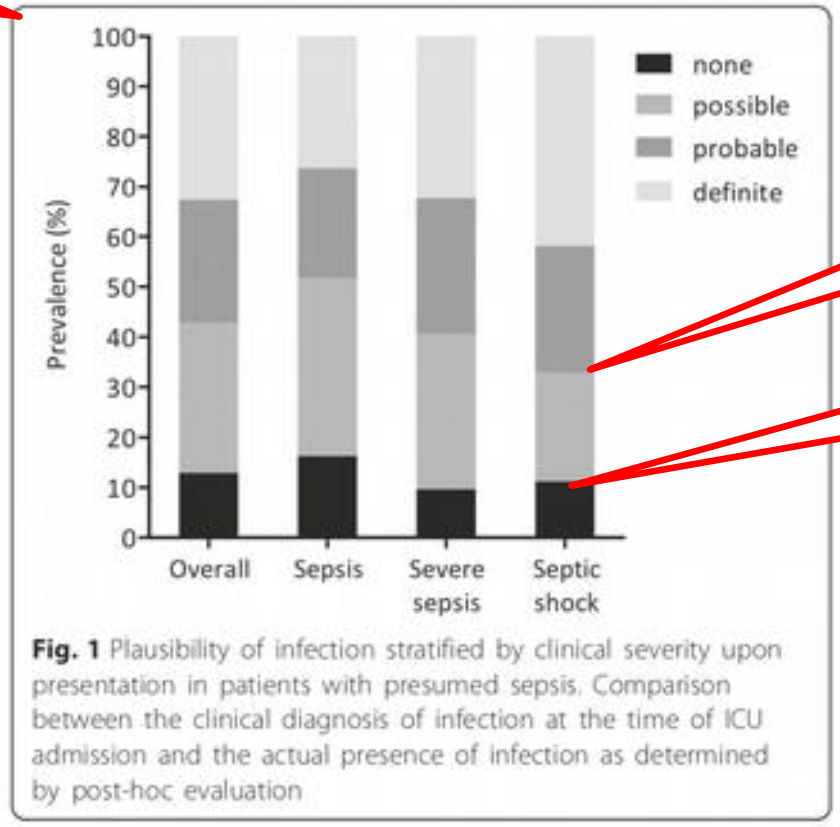

Fig. 1 Plausibility of infection stratified by clinical severity upon presentation in patients with presumed sepsis. Comparison between the clinical diagnosis of infection at the time of ICU admission and the actual presence of infection as determined by post-hoc evaluation

30%: possible

13%: none

Bloos et al. Critical Care 2014, 18:R42
http://ccforum.com/content/18/2/R42

CRITICAL CARE

RESEARCH Open Access

Impact of compliance with infection management guidelines on outcome in patients with severe sepsis: a prospective observational multi-center study

Frank Bloos[1,2*], Daniel Thomas-Rüddel[1,2], Hendrik Rüddel[1], Christoph Engel[3], Daniel Schwarzkopf[2], John C Marshall[4], Stephan Harbarth[5], Philipp Simon[6], Reimer Riessen[7], Didier Keh[8], Karin Dey[9], Manfred Weiß[10], Susanne Toussaint[11], Dirk Schädler[12], Andreas Weyland[13], Maximillian Ragaller[14], Konrad Schwarzkopf[15], Jürgen Eiche[16], Gerhard Kuhnle[17], Heike Hoyer[18], Christiane Hartog[1,2], Udo Kaisers[6] and Konrad Reinhart[1,2] for the MEDUSA Study Group

Surgical source control required ($n = 234$)[f]		
Time to antimicrobial therapy >1 hour[b]	0.80 (0.38 to 1.72)	0.552
Initial SOFA score[c]	1.19 (1.08 to 1.31)	<0.001
Age[d]	1.06 (1.03 to 1.08)	<0.001
Maximum lactate (day 1)[e]	1.08 (1.00 to 1.13)	0.046
Time to source control >6 hours	2.36 (1.22 to 4.71)	0.012
Intra-abdominal focus	1.08 (0.54 to 2.18)	0.822
Urogenital focus	0.43 (0.12 to 1.34)	0.165
Unknown focus[g]	–	–
Community-acquired infection	1.08 (0.58 to 2.04)	0.800
Inadequate empiric antimicrobial therapy	1.17 (0.61 to 2.24)	0.646
No de-escalation of antimicrobials within 5 days	0.94 (0.33 to 2.81)	0.909

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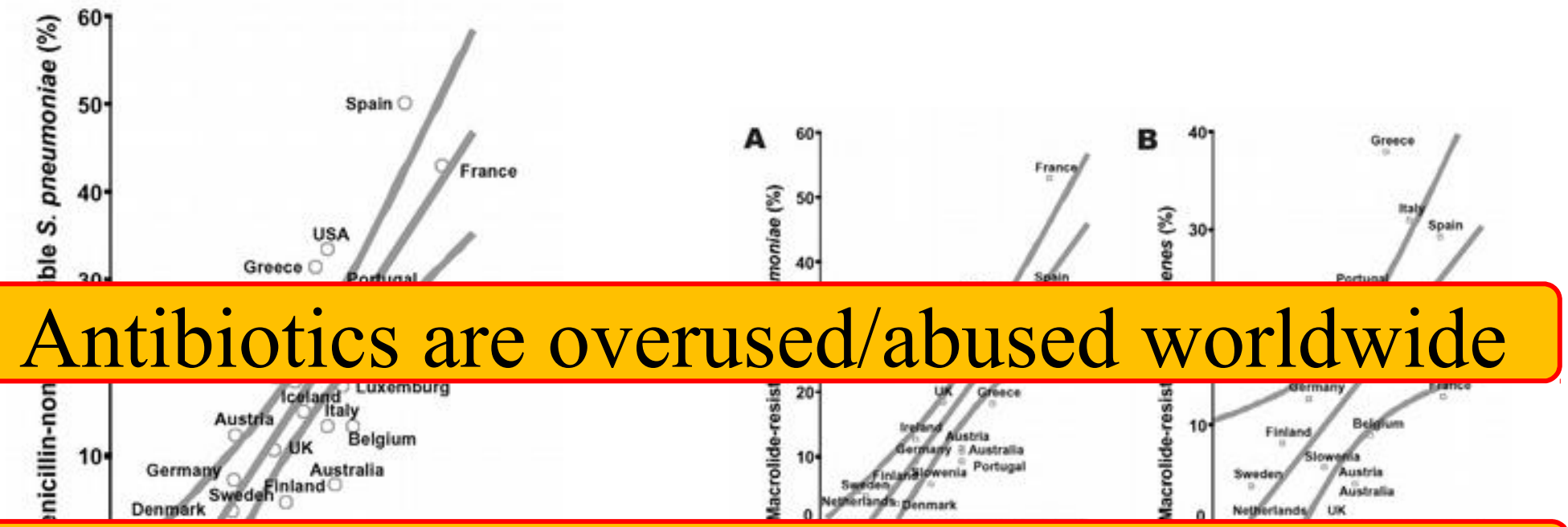
Antibiotic Selection Pressure and Resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*

Werner C. Albrich,* Dominique L. Monnet,† and Stephan Harbarth‡

EMERGING INFECTIOUS DISEASES

Volume 10, Number 3—March 2004



Antibiotics are overused/abused worldwide

MDR pathogens – „global crisis”

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REVIEW

Rationalizing antimicrobial therapy in the ICU: a narrative review

Jean-François Timsit[1,2*], Matteo Bassetti[3], Olaf Cremer[4], George Daikos[5], Jan de Waele[6], Andre Kallil[7], Eric Kipnis[8], Marin Kollef[9], Kevin Laupland[10], Jose-Artur Paiva[11], Jesús Rodríguez-Baño[12], Étienne Ruppé[2,13], Jorge Salluh[14], Fabio Silvio Taccone[15], Emmanuel Weiss[16,17] and François Barbier[18]

Intensive Care Med (2019) 45:172–189
https://doi.org/10.1007/s00134-019-05520-5

Table 1 Determinants of increased risk of MDRB infection at ICU admission and during the ICU stay

Predictors of MDRB infection	At ICU admission	During the ICU stay
Patient features	Co-morbid illness/immunosuppression/recent hospital and/or ICU stay	Higher severity of acute illness/Invasive interventions
Type of infection	Hospital-acquired > healthcare-associated > community-acquired	ICU-acquired > others
Antimicrobial selection pressure	Prior antibiotics*/antifungals	Antibiotics*/antifungals in the ICU
Colonization status	Previously documented colonization with MDRB	In-ICU acquisition of MDRB

3 times more AB on ICU then on wards

MDRB multidrug-resistant bacteria, *ICU* intensive care unit

*Especially if agents with broad-spectrum and/or potent activity against intestinal anaerobes

70% of patients receive ABs

ABs are potentially harmful

Organ injury

Wright J, Paauw DS. Complications of antibiotic therapy. *Med Clin North Am* 2013;97:667–679, xi.

Mitochondrial dysfunction

Singh R, Sripada L, Singh R. Side effects of antibiotics during bacterial infection: mitochondria, the main target in host cell. *Mitochondrion* 2014;16:50–54.

Microbiome, Fungal infections

Alverdy JC, Krezalek MA. Collapse of the microbiome, emergence of the pathobiome, and the immunopathology of sepsis. *Crit Care Med* 2017;45:337–347.

Clostridium difficile infections

Kalghatgi S, Spina CS, Costello JC, Liesa M, Morones-Ramirez JR, Slomovic S, Molina A, Shirihai OS, Collins JJ. Bactericidal antibiotics induce mitochondrial dysfunction and oxidative damage in mammalian cells. *Sci Transl Med* 2013;5:192ra85.

Research article

Open Access

Empirical use of antibiotics and adjustment of empirical antibiotic therapies in a university hospital: a prospective observational study

Julian Mettler[1], Mathew Simcock[1,2], Pedram Sendi[1,2], Andreas F Widmer[1], Roland Bingisser[3], Manuel Battegay[1], Ursula Fluckiger[1] and Stefano Bassetti*[1,4]

BMC Infectious Diseases 2007, 7:21

Table 4: Characteristics of patients receiving adequate or inadequate empirical antibiotic treatment (univariate analysis).

Characteristic	Patients (n) receiving adequate empirical antibiotic treatment	Patients (n) receiving inadequate empirical antibiotic treatment	p-value	OR (95% CI) for adequate therapy
Number of patients	418 (77.6%)	121 (22.4%)		
Women	170 (70.2%)	72 (29.8%)	**< 0.001**	**0.47 (0.31–0.70)**
Age				
Median age and range (years)	67 [18–100]	72 [17–97]	**0.038***	
< 40 years	74 (77.1%)	22 (22.9%)	0.904	0.97 (0.57–1.64)
41 – 60 yr.	91 (87.5%)	13 (12.5%)	**0.007**	**2.31 (1.12–4.30)**
> 60 years	253 (74.6%)	86 (25.4%)	**0.034**	**0.62 (0.40–0.97)**
Ward:				
Medicine/Geriatrics	281 (78.3%)	78 (21.7%)	0.399	1.19 (0.80–1.76)
Surgery	135 (78.9%)	36 (21.1%)	0.733	1.09 (0.70–1.65)
Medical and surgical intensive care	25 (71.4%)	10 (28.6%)	0.408	0.73 (0.34–1.55)
Neurology	1 (25.0%)	3 (75.0%)	**0.040†**	**0.10 (0.01–0.94)**
Died in hospital	25 (80.6%)	6 (19.4%)	0.671	1.22 (0.49–3.04)

28%

So, what to do?!

International guidelines…

American Thoracic Society Documents

Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection: 2009 Update by the Infectious Diseases

Is there infection for a start?!

Issam I. Raad,[6] Bart J. A. Rijnders,[10] Robert J. Sherertz,[7] and David K. Warren[8]

and the Infectious Diseases Society of America

Joseph S. Solomkin,[1] John E. Mazuski,[2] John S. Bradley,[3] Keith A. Rodvold,[7,8] Ellie J. C. Goldstein,[5] Ellen J. Baron,[6] Patrick J. O'Neill,[9] Anthony W. Chow,[35] E. Patchen Dellinger,[10] Soumitra R. Eachempati,[11] Sherwood Gorbach,[12] Mary Hilfiker,[4] Addison K. May,[13] Avery B. Nathens,[17] Robert G. Sawyer,[14] and John G. Bartlett[15]

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

Infection = ABs

No infection = No ABs

Signs of infection

- Clinical signs:
  - Most important

Not good enough

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

Galicier L and Richet H. *Infect Control Ho*

Poooor!

- Microbiology:
  - Results: 24 hours or more

Very late!

We need biomarkers!

Pierrakos and Vincent *Critical Care* 2010, **14**:R15
http://ccforum.com/content/14/1/R15

CRITICAL CARE

WARNING!

Using biomarkers is not easy

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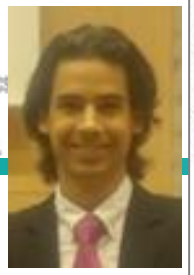


Research Article

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

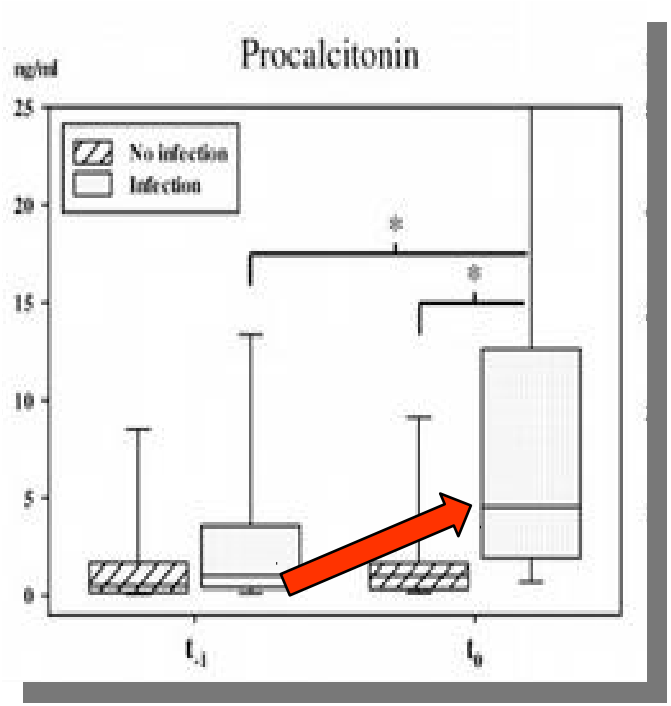
Domonkos Trásy,[1] Krisztián Tánczos,[1] Márton Németh,[1] Péter Hankovszky,[1] András Lovas,[1] András Mikor,[1] Edit Hajdú,[2] Angelika Osztroluczki,[1] János Fazakas,[3] and Zsolt Molnár[1]

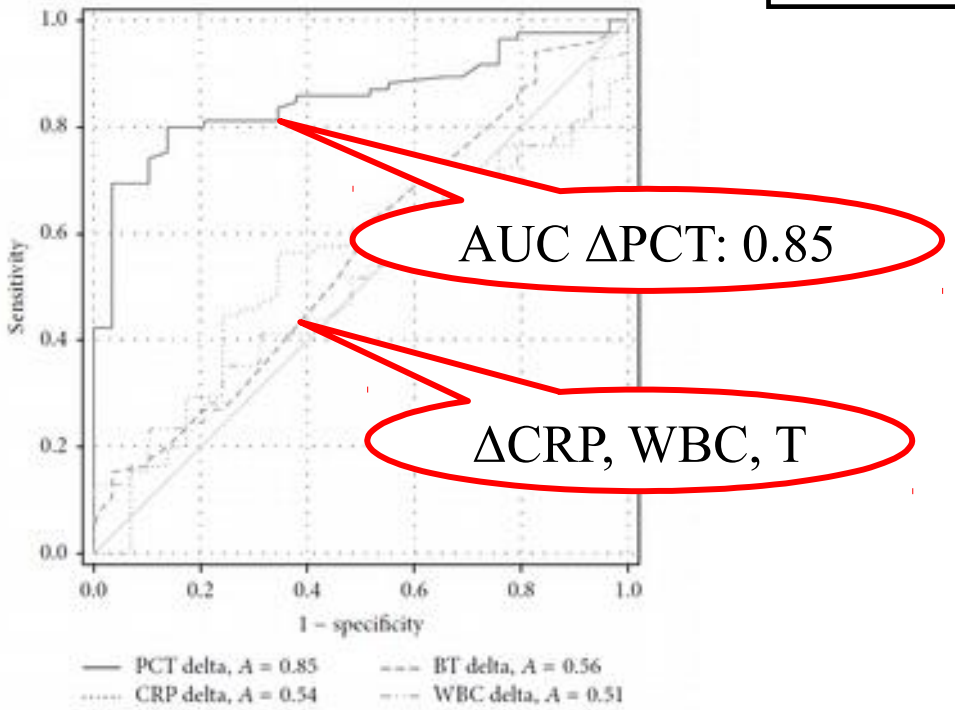
Journal of Immunology Research
Volume 2016, Article ID 3530752, 9 pages
http://dx.doi.org/10.1155/2016/3530752

Patients with suspected infection = 209

PCT available at T_{-1} = 114

- Infection = 85
- No-infection = 29





AUC ΔPCT: 0.85

ΔCRP, WBC, T

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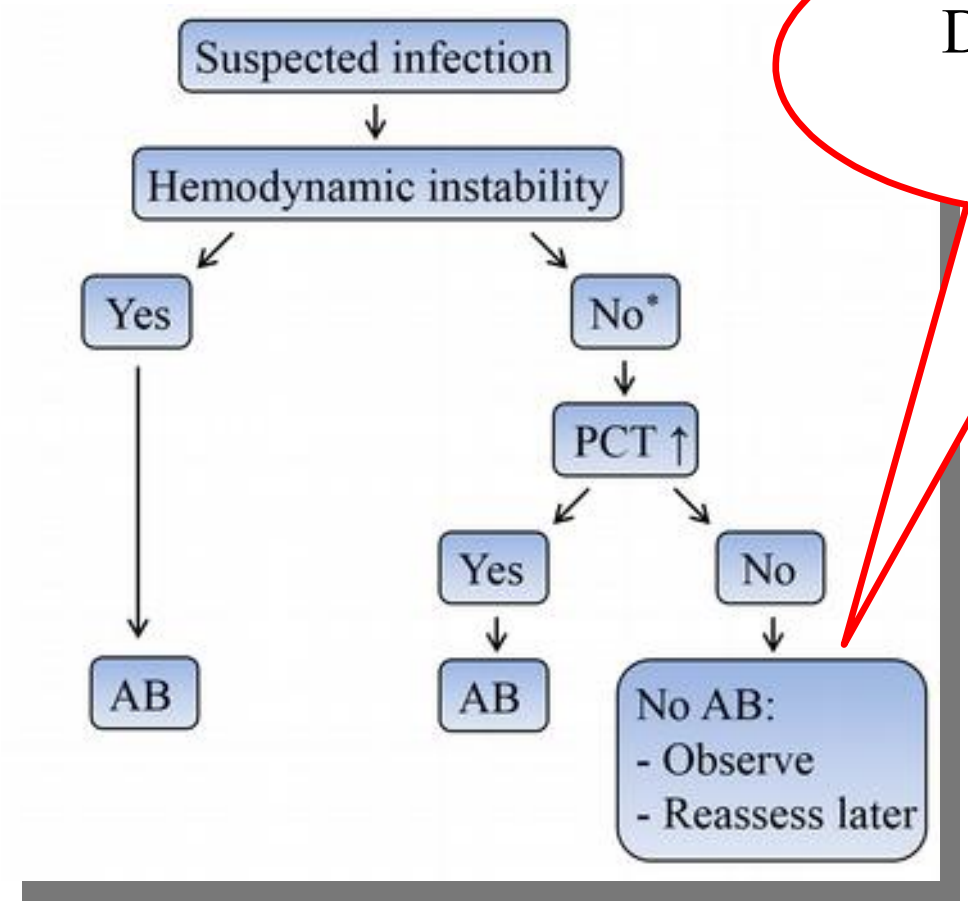
Interpreting Procalcitonin at the Bedside

J. Fazakas, D. Trásy, and Z. Molnár

2016
Annual Update in Intensive Care and Emergency Medicine 2016



Dare not to give AB

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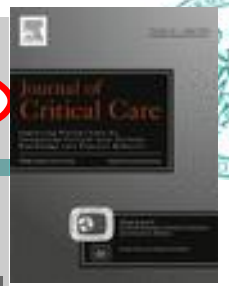
Early procalcitonin kinetics and appropriateness of empirical antimicrobial therapy in critically ill patients
A prospective observational study

EProK-study

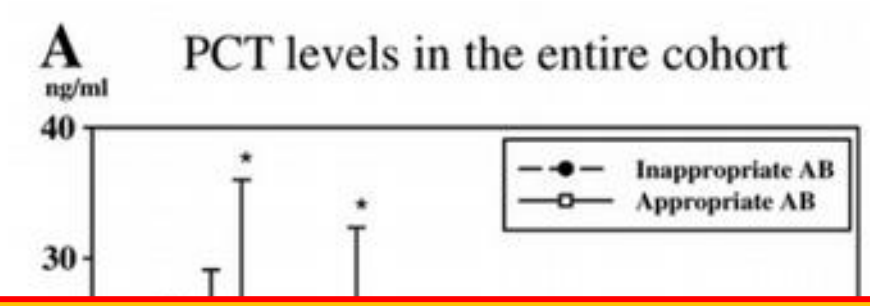
Domonkos Trásy, MD [a,*], Krisztián Tánczos, MD [a], Márton Németh, MD [a], Péter Hankovszky, MD [a], András Lovas, MD [a], András Mikor, MD [a], Ildikó László, MD [a], Edit Hajdú, MD [b], Angelika Osztroluczki [a], János Fazakas, MD [c], Zsolt Molnár, MD [a] The EProK study group

Journal of Critical Care 34 (2016) 50–55



Patients with suspected infection= 209

Proven infection = 141
Appropriate AB = 108 (77%)
Inappropriate AB = 33 (23%)
No infection/micro = 68



≥ 73%

Pattern of PCT kinetics – could be used early for individualizing treatment: timing, monitoring

PCT t_0-t_{36}	0.73	0.63 -0.83	<0.001
PCT t_0-t_{54}	0.86	0.77 -0.94	<0.001

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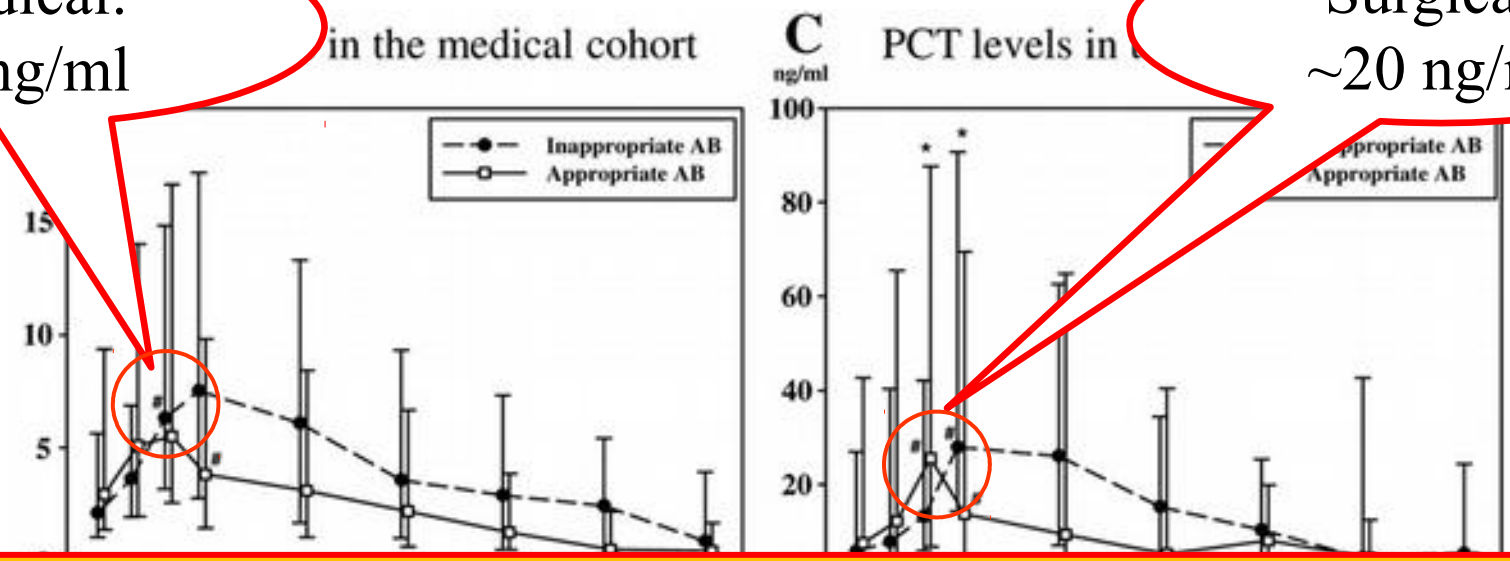
Early procalcitonin kinetics and appropriateness of empirical antimicrobial therapy in critically ill patients
A prospective observational study

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

Journal of Critical Care 34 (2016) 50–55

Medical:
~ 5ng/ml

Surgical:
~20 ng/ml



Preference of kinetics over absolute values!

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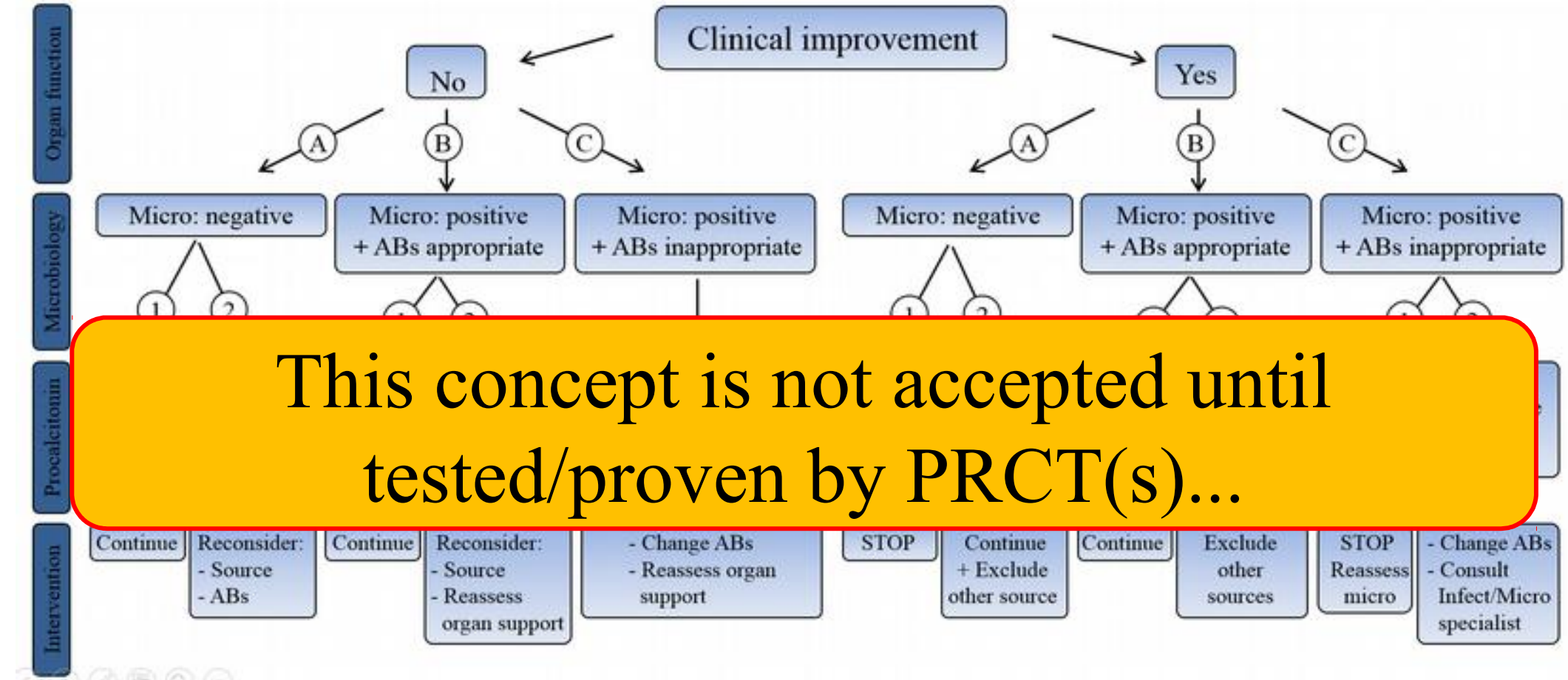
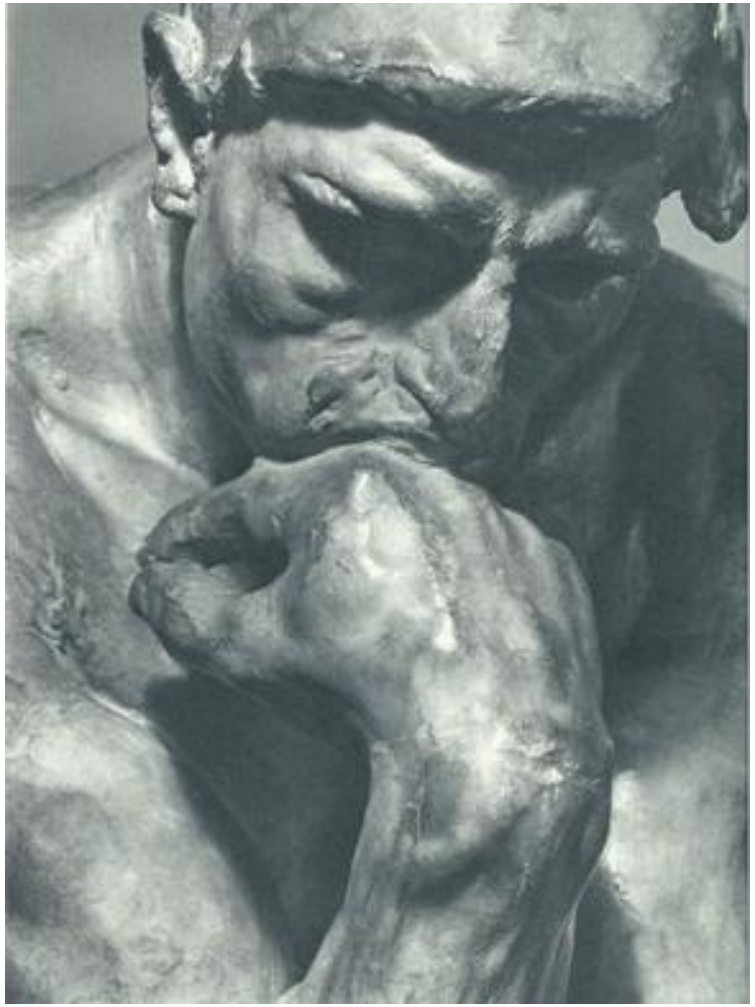
Interpreting Procalcitonin at the Bedside

J. Fazakas, D. Trásy, and Z. Molnár



This concept is not accepted until tested/proven by PRCT(s)...

Thinking has no alternative!



Auguste Rodin: The Thinker (1880)

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Thank you!

500 participants
From 30 countries!

A long way since 2012...

SepsEast 2012
1st Central and Eastern European Sepsis Forum

SepsEast 2014
2nd Central and Eastern European Sepsis Forum

SepsEast 2016
3rd Central and Eastern European Sepsis Forum

The „new” SepsEast team

Ovidiu Bedreag
Organizind Committee

Dorel Sandesc
Chair of Organizing Committee

Jan Benes
Chair SepsEast

Konstanty Szuldrzynski
Secretary SepsEast

SepsEast 2020: www.sepseast.org

24-26 September, Timisoara, Roamnia