



Sepsis: new definitions - novel treatments

Prof. Zsolt Molnár

zsoltmolna@gmail.com

Department of Anaesthesia and Intensive Therapy

University of Szeged, Hungary



Hungary



New definitions: “Sepsis-3”





Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Gregory S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

JAMA. 2016;315:864-870. doi:10.1001/jama.2016.0287



Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Developing a New Definition and Assessing New Clinical Criteria for Septic Shock For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Manu Shankar-Hari, MD, MSc; Gary S. Phillips, MAS; Mitchell L. Levy, MD; Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD; Clifford S. Deutschman, MD; Derek C. Angus, MD, MPH; Gordon D. Rubenfeld, MD, MSc; Mervyn Singer, MD, FRCP; for the Sepsis De

1,020,681
Views

8
Citations



Application of a Framework to Assess the Usefulness of Alternative Sepsis Criteria

Christopher W. Seymour, MD¹; Craig M. Coopersmith, MD²; Clifford S. Deutschman, MD³; Foster Gesten, MD⁴; Michael Klompas, MD⁵; Mitchell Levy, MD⁶; Gregory S. Martin, MD⁷; Tiffany M. Osborn, MD⁸; Chanu Rhee, MD^{4,5}; David K. Warren, MD⁹; R. Scott Watson, MD¹⁰; Derek C. Angus, MD¹

A Framework for the Development and Interpretation of Different Sepsis Definitions and Clinical Criteria

Derek C. Angus, MD¹; Christopher W. Seymour, MD¹; Craig M. Coopersmith, MD²; Clifford S. Deutschman, MD³; Michael Klompas, MD^{4,5}; Mitchell M. Levy, MD⁶; Gregory S. Martin, MD⁷; Tiffany M. Osborn, MD⁸; Chanu Rhee, MD^{4,5}; R. Scott Watson, MD⁹

(Crit Care Med 2016; 44:e113-e121)



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

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287



A Need for Sepsis Definitions for the Public and for Health Care Practitioners

Despite its worldwide importance, public awareness of sepsis is poor.²⁹ Furthermore, the various manifestations of sepsis make diagnosis difficult, even for experienced clinicians. Thus, the public needs an understandable definition of sepsis, whereas health care practitioners require improved clinical prompts and diagnostic approaches to facilitate earlier identification and an accurate quantification of the burden of sepsis.



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

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287



Full details are found in the accompanying article by Seymour et al.¹² In brief, electronic health record data of 1.3 million encounters at 12 community and academic hospitals within the University of Pittsburgh Medical Center health system in southwestern Pennsylvania were studied. There were 148 907 patients with suspected infection, identified as those who had body fluids sampled for culture and received antibiotics. Two outcomes—hospital mortality and mortality, ICU stay of 3 days or longer, or both—were used to assess predictive validity both overall and across deciles of baseline risk as determined by age, sex, and comorbidity. For infected patients both inside and outside of the



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

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287



Table 2. Terminology and *International Classification of Diseases* Coding

Current Guidelines and Terminology	Sepsis	Septic Shock
1991 and 2001 consensus terminology ^{9,10}	Severe sepsis Sepsis-induced hypoperfusion	Septic shock ¹³
2015 Definition	Sepsis is 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/metabolic abnormalities are profound enough to substantially increase mortality
2015 Clinical criteria	Suspected or documented infection and an acute increase of ≥ 2 SOFA points (a proxy for organ dysfunction)	Sepsis ^a and vasopressor therapy needed to elevate MAP ≥ 65 mm Hg and lactate > 2 mmol/L (18 mg/dL) despite adequate fluid resuscitation ¹³
Recommended primary ICD codes ^a		
ICD-9	995.92	785.52
ICD-10 ^a	R65.20	R65.21
Framework for implementation for coding and research	Identify suspected infection by using cultures for blood cultures and antibiotics (oral or intravenous) during a specified period ^b Within specified period around suspected infection: 1. Identify sepsis by using a clinical criterion for life-threatening organ dysfunction 2. Assess for shock criteria, using admission vital signs, vasopressors, MAP < 65 mm Hg, and lactate > 2 mmol/L (18 mg/dL) ^d	

Dysregulated Host response

Organ dysfunction in focus:
-fluid/vasopressor
-lactate
-MAP



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

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287



Screening for Patients Likely to Have Sepsis

A parsimonious clinical model developed with multivariable logistic regression identified that any 2 of 3 clinical variables—Glasgow Coma Scale score of 13 or less, systolic blood pressure of 100 mm Hg or less, and respiratory rate 22/min or greater—offered predictive validity (AUROC = 0.81; 95% CI, 0.80-0.82) similar to that of the full SOFA score outside the ICU.¹² This model was robust to multiple sensitivity analyses including a more simple assessment of altered mentation (Glasgow Coma Scale score <15) and in the out-of-hospital, emergency department, and ward settings within the external US and non-US data sets.

For patients with suspected infection within the ICU, the SOFA score had predictive validity (AUROC = 0.74; 95% CI, 0.73-0.76) superior to that of this model (AUROC = 0.66; 95% CI, 0.64-0.68), likely reflecting the modifying effects of interventions (eg, vaso-pressors, sedative agents, mechanical ventilation). Addition of lactate measurement did not meaningfully improve predictive validity but may help identify patients at intermediate risk.

Box 4. qSOFA (Quick SOFA) Criteria

Respiratory rate ≥ 22 /min

Altered mentation

Systolic blood pressure ≤ 100 mm Hg



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

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287





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

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

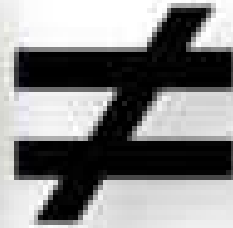
JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

Conclusions

These updated definitions and clinical criteria should clarify long-used descriptors and facilitate earlier recognition and more timely management of patients with sepsis or at risk of developing it. This process, however, remains a work in progress. As is done with software and other coding updates, the task force recommends that the new definition be designated Sepsis-3, with the 1991 and 2001 iterations being recognized as Sepsis-1 and Sepsis-2, respectively, to emphasize the need for future iterations.



My problem remains unsolved...





Pathomechanism of critical illness – New insight





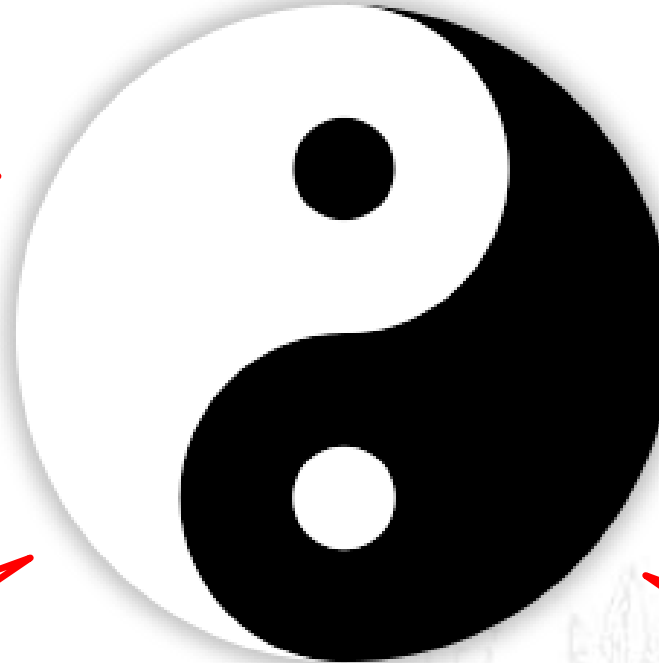
Health=balance between the antagonistic forces

Acid

Pro-
coagulation

Oxidants

Pro-
inflammation



Base

Anti-
coagulation

Anti-oxidants

Anti-
inflammation



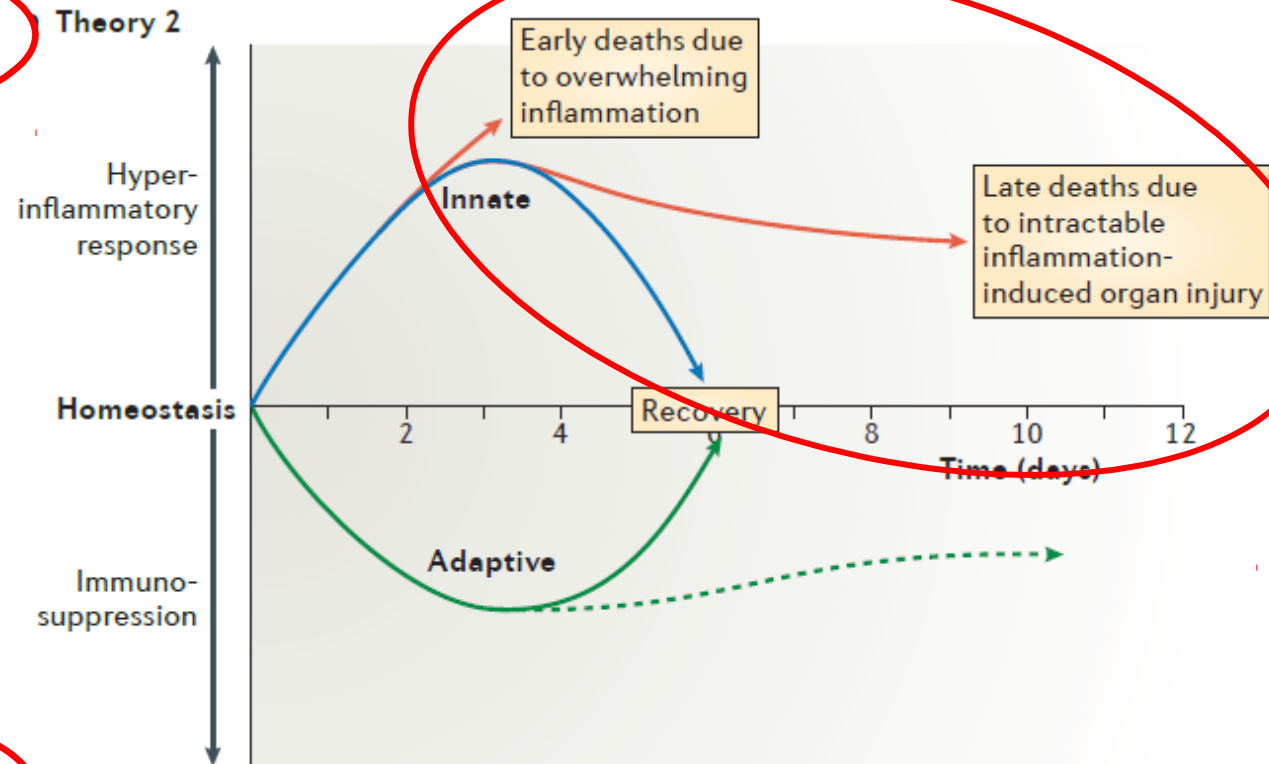
Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss¹, Guillaume Monneret² and Didier Payen³

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

Pro-inflammation

Anti-inflammation





Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss¹, Guillaume Monneret² and Didier Payen³

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

Pro-

More on that tomorrow
at 10:30 – Sepsis & Love

Anti-
inflammation

immunosuppression
and recurrent
infections



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

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

Table 2. Terminology and *International Classification of Diseases* Coding

Current Guidelines and Terminology	Sepsis	Septic Shock
1991 and 2001 consensus terminology ^{9,10}	Severe sepsis Sepsis-induced hypoperfusion	Septic shock ¹³
2015 Definition	Sepsis is 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/metabolic abnormalities are profound enough to substantially increase mortality
2015 Clinical criteria	Suspected or documented infection and an acute increase of ≥ 2 SOFA points (a proxy for organ dysfunction)	Sepsis ^a and vasopressor therapy needed to elevate MAP ≥ 65 mm Hg and lactate > 2 mmol/L (18 mg/dL) despite adequate fluid resuscitation ¹³
Recommended primary ICD codes ^a		
ICD-9	995.92	785.52
ICD-10 ^a	R65.20	R65.21
Framework for implementation for coding and research	Identify suspected infection by using concomitant orders for blood cultures and antibiotics (oral or parenteral) in a specified period ^b Within specified period around suspected infection ^c : 1. Identify sepsis by using a clinical criterion for life-threatening organ dysfunction 2. Assess for shock criteria, using administration of vasopressors, MAP < 65 mm Hg, and lactate > 2 mmol/L (18 mg/dL) ^d	

Good! 😊

Hmm? 😞



New guidelines: SSC-2016





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

Andrew Rhodes^{1*}, Laura E. Evans², Waleed Alhazzani³, Mitchell M. Levy⁴, Massimo Antonelli⁵, Ricard Ferrer⁶

21 aspects

Results: The Surviving Sepsis Guideline panel provided 93 statements on early management and resuscitation of patients with sepsis or septic shock. Overall, 32 were strong recommendations, 39 were weak recommendations, and 18 were best-practice statements. No recommendation was provided for four questions.

„Sepsis
specific”

D. ANTIMICROBIAL THERAPY

1. We recommend that administration of IV antimicrobials should be initiated as soon as possible after recognition and within one hour for both sepsis and septic shock (strong recommendation, moderate quality of evidence).
2. 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).

L. ANTICOAGULANTS

1. We recommend against the use of antithrombin for the treatment of sepsis and septic shock (strong recommendation, moderate quality of evidence).

The rest: Good Medicine

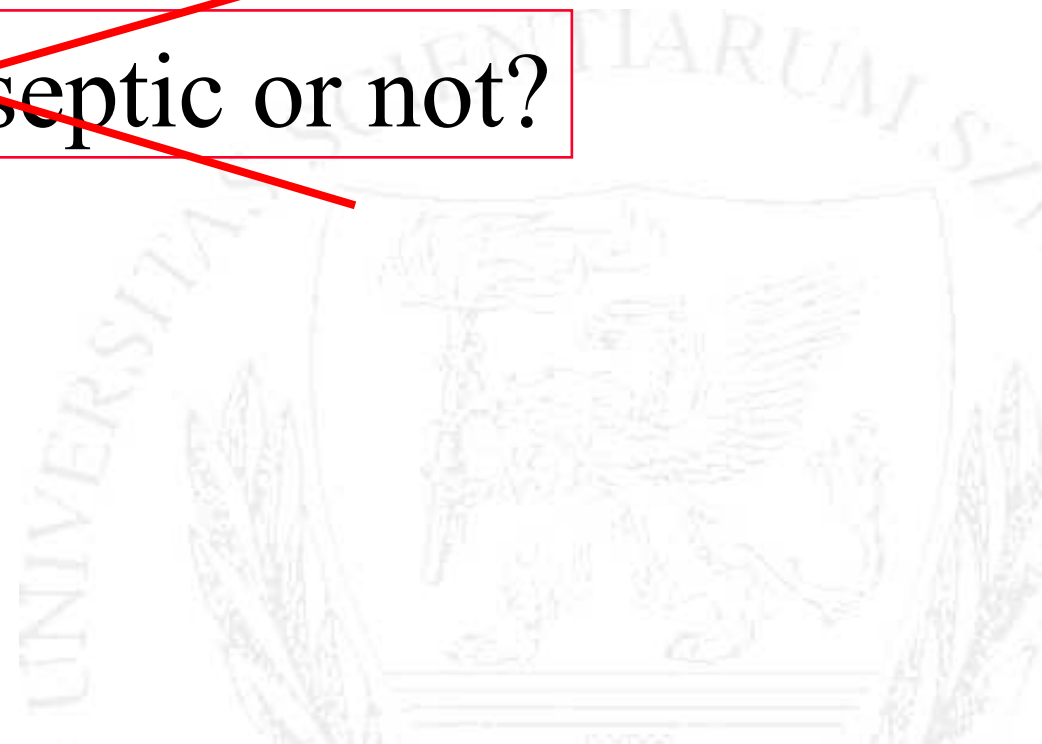


Novel treatments (?)





~~Is this patient septic or not?~~





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

Hemodynamic
instability

Respiratory
dysfunction

You don't treat SEPSIS but:
Organ dysfunction +/- infection

Etc, etc, etc....

dysfunction





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

Infection = ABs

No infection = No ABs



Signs of infection

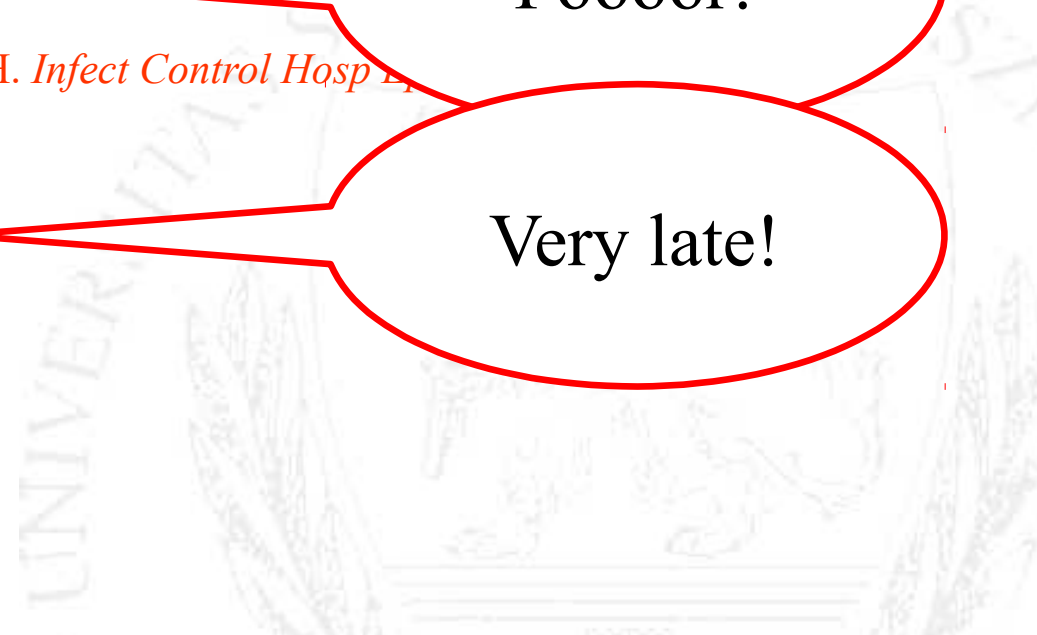
- Clinical signs:
 - Most important
- Fever ($>38^{\circ}\text{C}$), WBC ($>12\ 000$):
 - Low sensitivity ($\sim 50\%$)
- Microbiology:
 - Results: 24 hours or more

Not good
enough

Pooooor!

Very late!

Galicier L and Richet H. Infect Control Hosp Epidemiol 2004; 29: 1000-1001





We need biomarkers!

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



More on that:
17:15-18:15

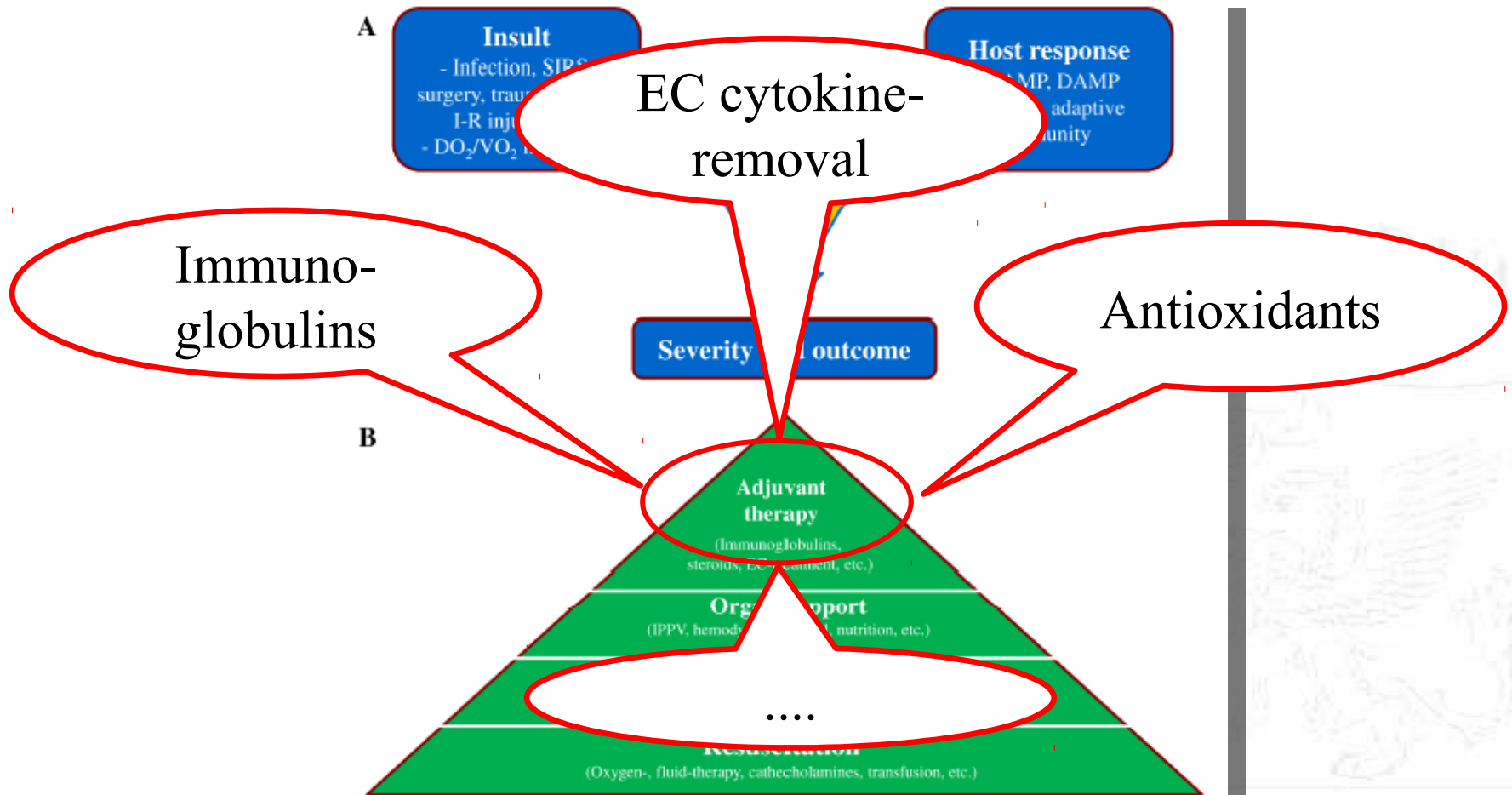




Sepsis – from pathophysiology to individualized patient care

Ildikó László MD¹, Domonkos Trásy MD¹, Zsolt Molnár MD PhD¹, János Fazakas MD PhD²

Journal of Immunology Research, 2015; Volume 2015, ID 510436, 13 pages
<http://dx.doi.org/10.1155/2015/510436>



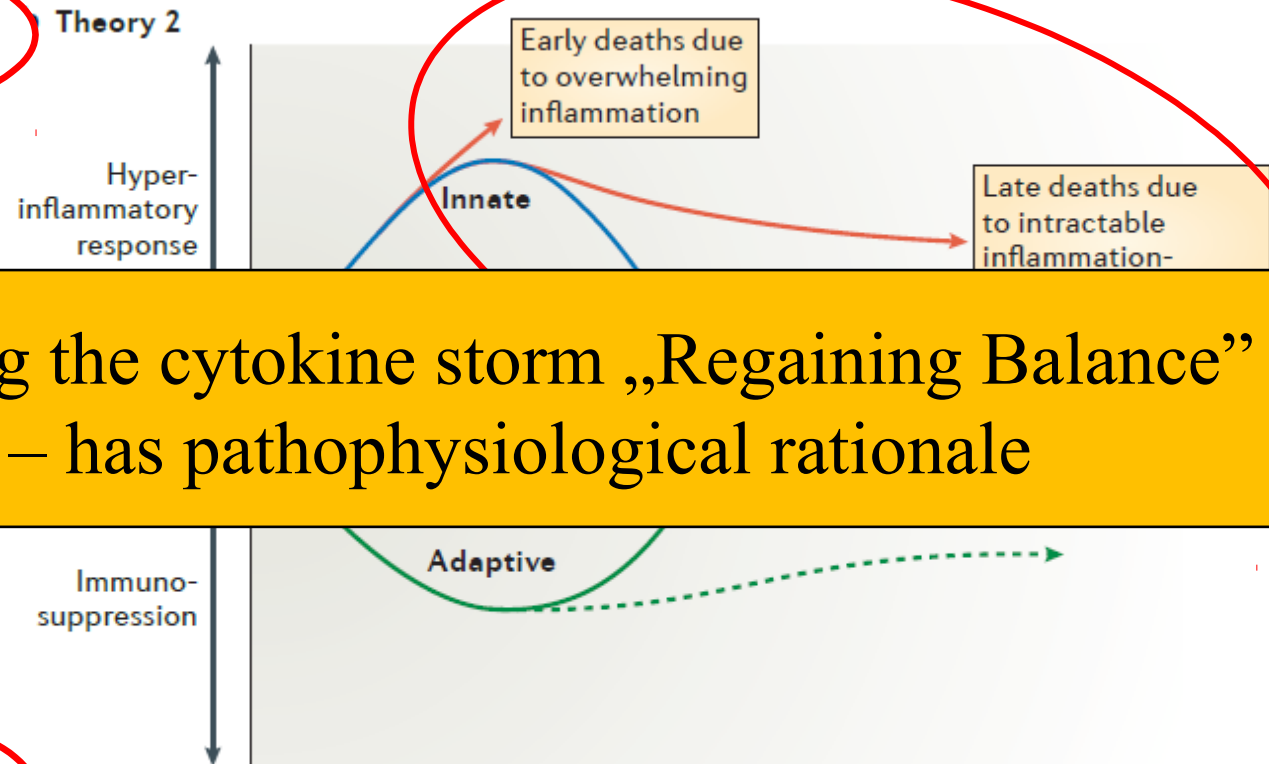


Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss¹, Guillaume Monneret² and Didier Payen³

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

Pro-
inflammation

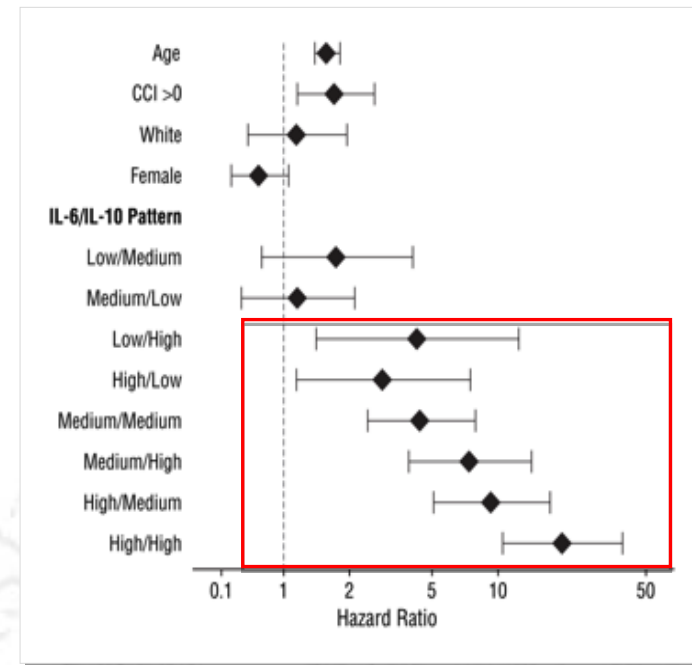
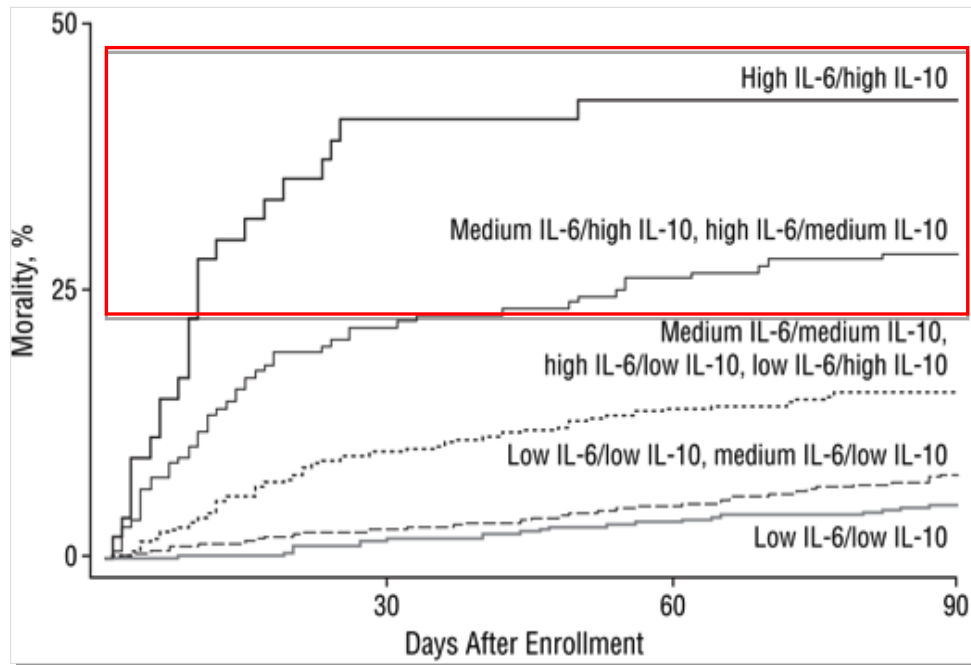


Attenuating the cytokine storm „Regaining Balance”
– has pathophysiological rationale

Anti-
inflammation



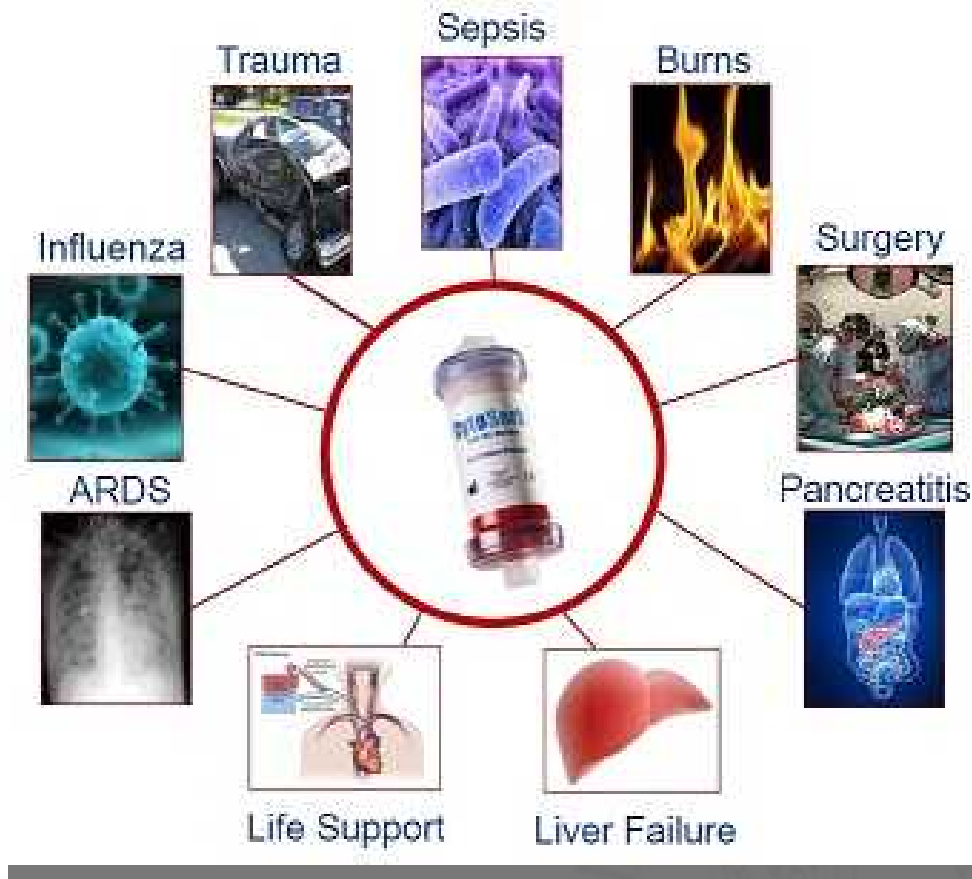
Rationale – „Regaining Balance”



Kellum JA et al., (GenIMS Study); Arch Intern Med 2007; 167:1655-63



Cytokine adsorbent...



...and not only in septic patients: all with Cytokine Storm



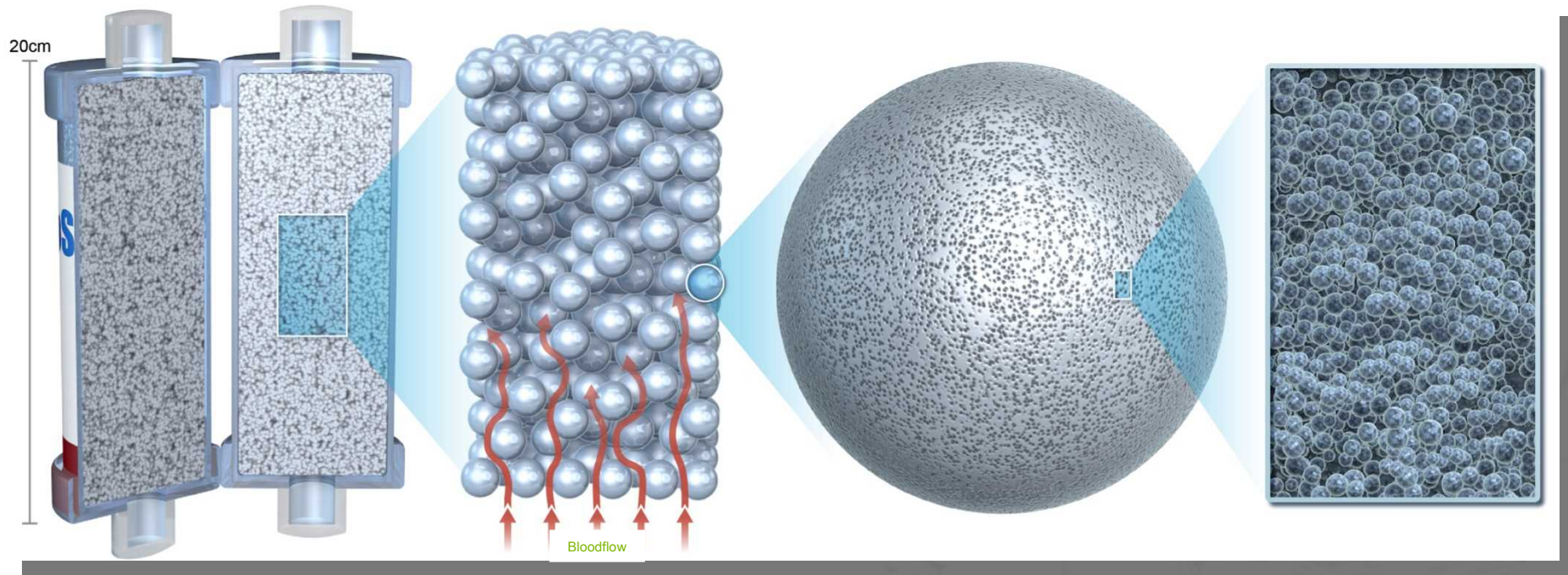
What is it?



Biocompatible, porous polymer polystyrene beads



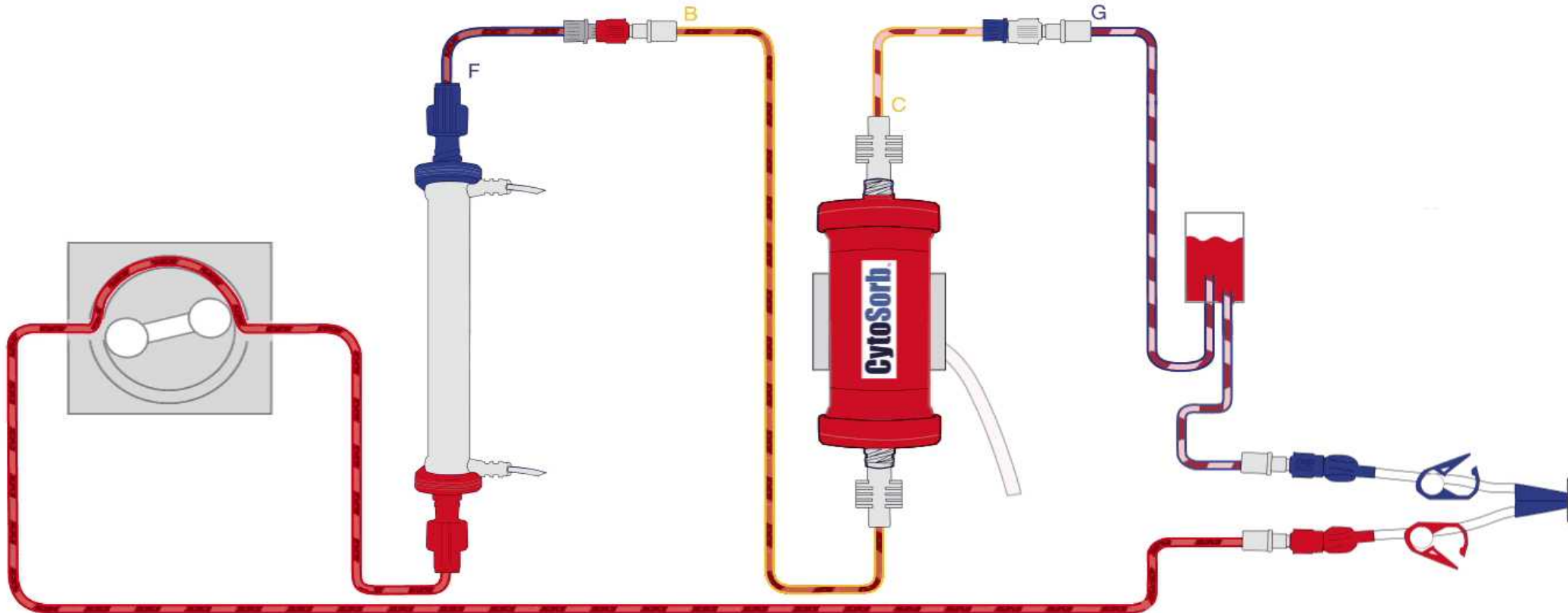
How does it work?



- 300ml cartridge with “Bead” design
- 120ml blood volume / filling volume
- Pre-filled with 0.9% sodium chloride
- Gamma-sterilized, storable for 3 years
- Low flow resistance

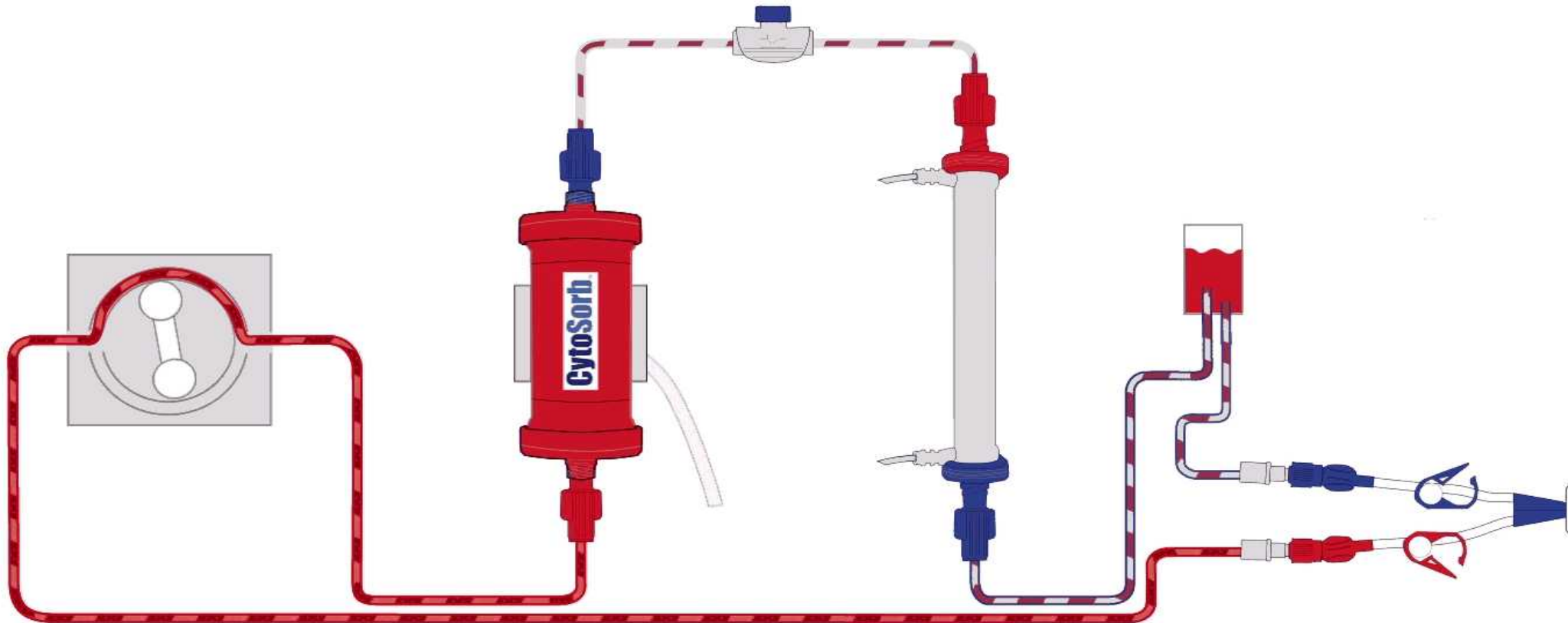


How to apply? – on RRT





How to apply? – on RRT



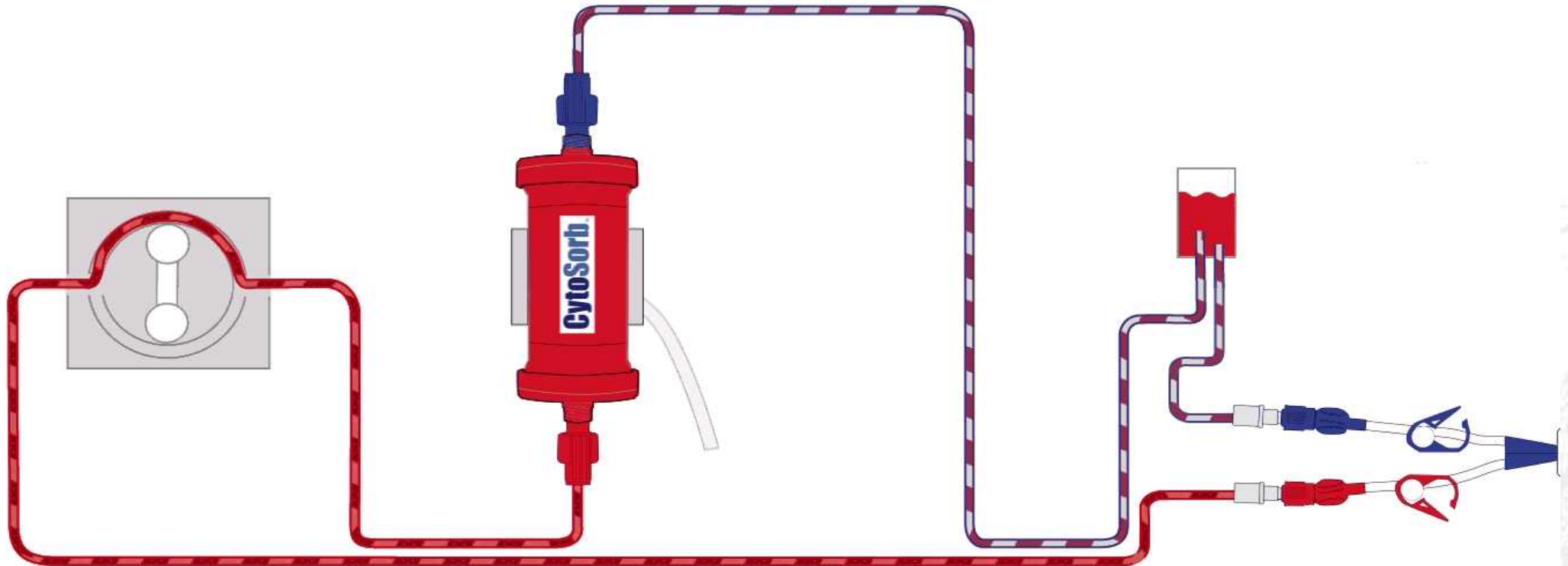


CRRT+ECMO+CytoSorb





How to apply? – on its own





At the moment: experimental data

Acute removal of common sepsis mediators does not explain the effects of extracorporeal blood purification in experimental sepsis

Peng ZY, Wang HZ, Carter MJ, Dileo MV, Bishop JV, Zhou FH, Wen XY, Rimmelé T, Singbartl K, Federspiel WJ, Clermont G, Kellum JA

Kidney Hemoadsorption Reprograms Inflammation in Experimental Gram-Negative Sepsis: Insights from In Vivo and In Silico Studies

Attenuates inflammatory response of leukocytes
Eliminates inflammatory cytokines
Keeps infection localised
Improves hemodynamics

Peng ZY, Bishop JV, Wen XY, Elder MM, Zhou F, Chuasuwan A, Carter MJ, Devlin JE, Kaynar AM, Singbartl K, Pike F, Parker RS, Clermont G, Federspiel WJ, Kellum JA.

Crit Care. 2014 Jul 3;18(4):R141



At the moment: case reports

Case Rep

Cytosorb™ in a Patient with *Legionella*-Pneumonia Associated Rhabdomyolysis: A Case Report

Proved to be safe

Attenuated inflammatory response (PCT, IL-6)

Improved organ function

Survival

First successful combination of ECMO with cytokine

Romanian Journal of Anaesthesia and Intensive Care 2014 Vol 21 No 2, 134-138

removal of cytokines
report Effects of a novel cytokine haemoadsorption system on inflammatory response in septic shock after cephalic pancreatectomy – a case report

Frank Bruenger¹, Luk

Dana Tomescu^{1,4}, Simona O. Dima², Sabina Tănăsescu¹, Cristiana Pistol Tănase³, Anca Năstase², Mihai Popescu⁴



Registry: 15 countries so far



Thank you very much for your support and cooperation for this registry!

Registry data base

The registry data base is set up with the system OpenClinica. To get an impression of how this system works, please visit our registry homepage where you can find a test data base. In the Login area you can get a test access.

For further information on the use of the data base please refer to the attached working instruction.

On the next page you'll find the results of our first intermediate analysis.

Please continue to support us in extending the data collection on the use of the CytoSorb-Adsorber so that our results are built on a broader basis in the future.

Homepage:
<http://www.cytosorb-registry.org/>

interested sites:

Study team
Jena University Hospital
Center for Clinical Studies



Prof. Dr. Frank M. Brunkhorst



Manja Schein



Viola Bahr



14 trials registered on ClinicalTrials.gov!



Attenuating the cytokine storm early?

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Example: "Heart attack" AND "Los Angeles"

Search for studies:

Search

[Advanced Search](#) | [Help](#) | [Studies by Topic](#) | [Glossary](#)

Comment Period Extended to 3/23/2015 for Notice of Proposed Rulemaking (NPRM) for FDAAA 801 and NIH Draft Reporting Policy for NIH-Funded Trials

The ACCESS trial

Adsorbtion of Cytokines Early in Septic Shock

Locations)

Verified November 2014 by Szeged University

Sponsor:

Domonkos Trásy

Information provided by (Responsible Party):

Domonkos Trásy, Szeged University

NCT02288975

First received: November 5, 2014

Last updated: November 14, 2014

Last verified: November 2014

[History of Changes](#)

[Full Text View](#)

[Tabular
View](#)

[No Study Results Posted](#)

[Disclaimer](#)

[How to Read a Study Record](#)



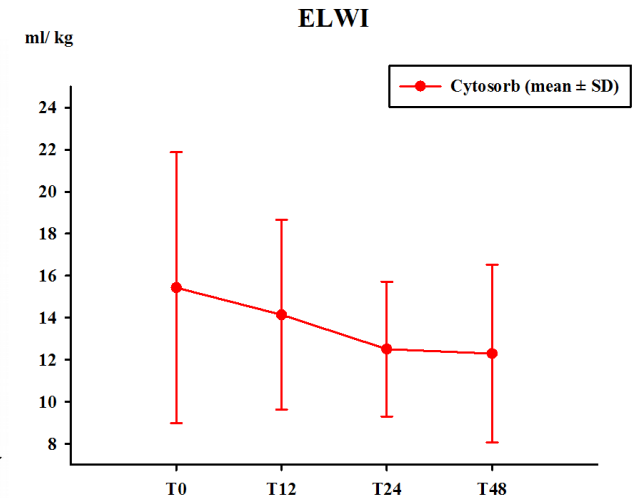
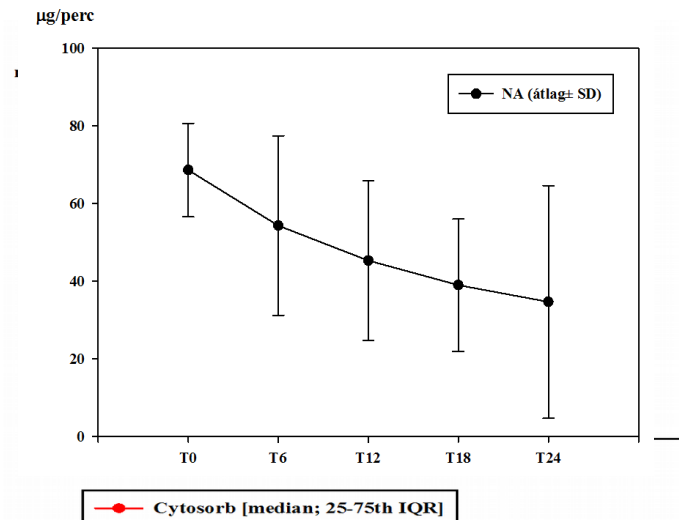
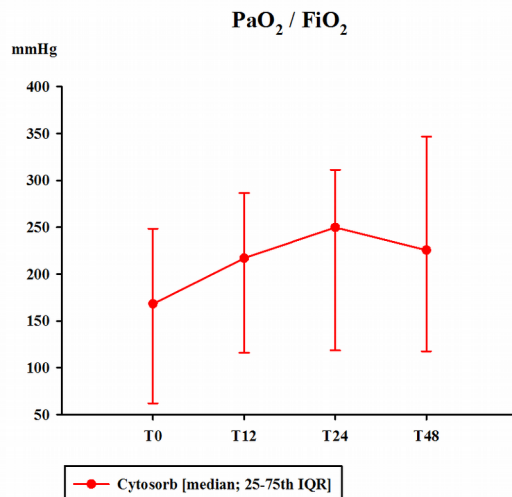
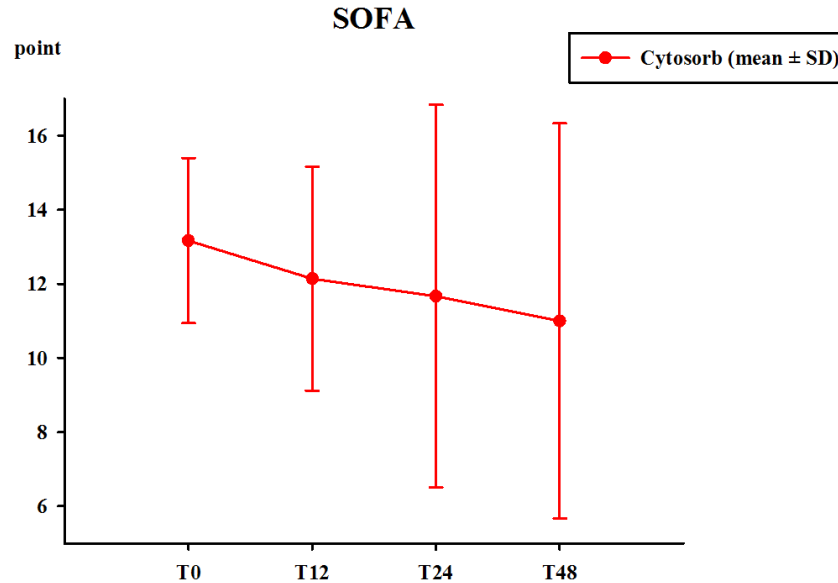
ACCESS - Inclusion criteria

- Suspected sepsis of medical etiology
- IPPV
- PCT >3 ng/ml
- Norepinephrine $\geq 10 \mu\text{g}/\text{min}$
- PiCCO confirmed normovolemia and CO
- Signs of hypoperfusion: ScvO₂, lactate, dCO₂,

8 patients over 6 months!



ACCESS – preliminary results (6pts)



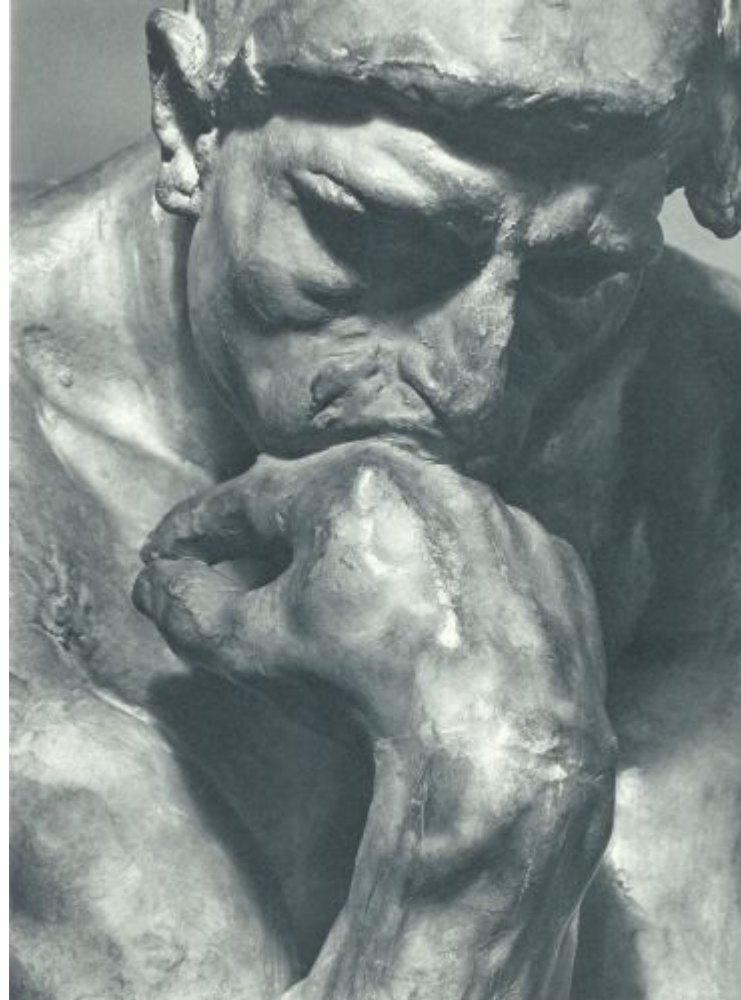


Final thoughts on sepsis





Thinking has no alternative!



Auguste Rodin: The Thinker (1880)



Free for junior doctors (<29)!

www.sepseast2016.com

Next time: November 2018!!





SepsEast 2016

3rd Central and Eastern European Sepsis Forum



YouTube: [oncall@jate](https://www.youtube.com/channel/UC...)