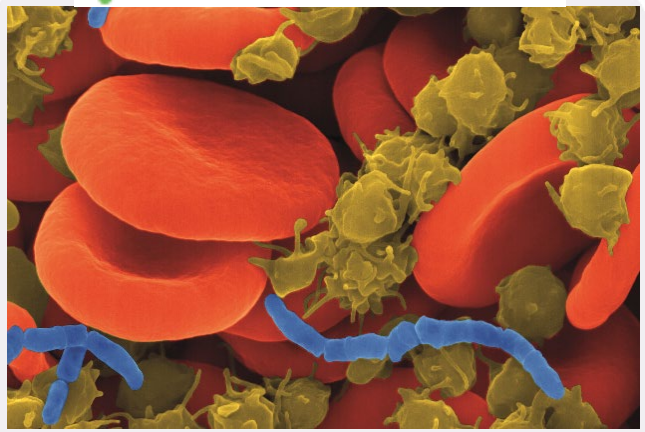
Personalizing Sepsis Phenotypes – preclinical and clinical evidence

Marcin Osuchowski

COLOURS OF SEPSIS

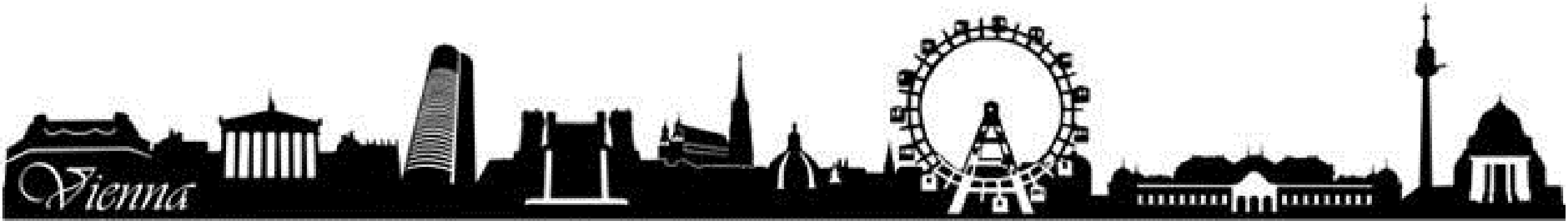


LUDWIG BOLTZMANN INSTITUTE Traumatology
The Research Center in Cooperation with AUVA

AUVA

Disclosures

1. No Conflict of Interest for this Talk
2. I REALLY like Kozel beer…



Intensive Care Med (2021) 47:733–736
https://doi.org/10.1007/s00134-021-06409-y

CONFERENCE REPORTS AND EXPERT PANEL

Reducing the global burden of sepsis: a positive legacy for the COVID-19 pandemic?

The European Society of Intensive Care Medicine (ESICM), The Global Sepsis Alliance (GSA)* and The Society of Critical Care Medicine (SCCM)

Recognition that sepsis caused by different pathogens and in different populations may respond to different treatment approaches

Fostering the understanding that increasing awareness of sepsis, education of the public and health care professionals on the prevention, early recognition, the need to manage sepsis as an emergency, and good training in supportive care will reduce sepsis mortality from all causes

Maintaining political and policymaker focus on public health measures that can reduce the global burden of sepsis and by following the requests of the WHO sepsis resolution to integrate sepsis in the national health strategies of all member states

Supporting with research funding and infrastructure to better understand the overall burden of sepsis and to characterize the heterogeneity of sepsis caused by different organisms in different populations and expanding the capacity of international platform trials embedded in routine clinical care

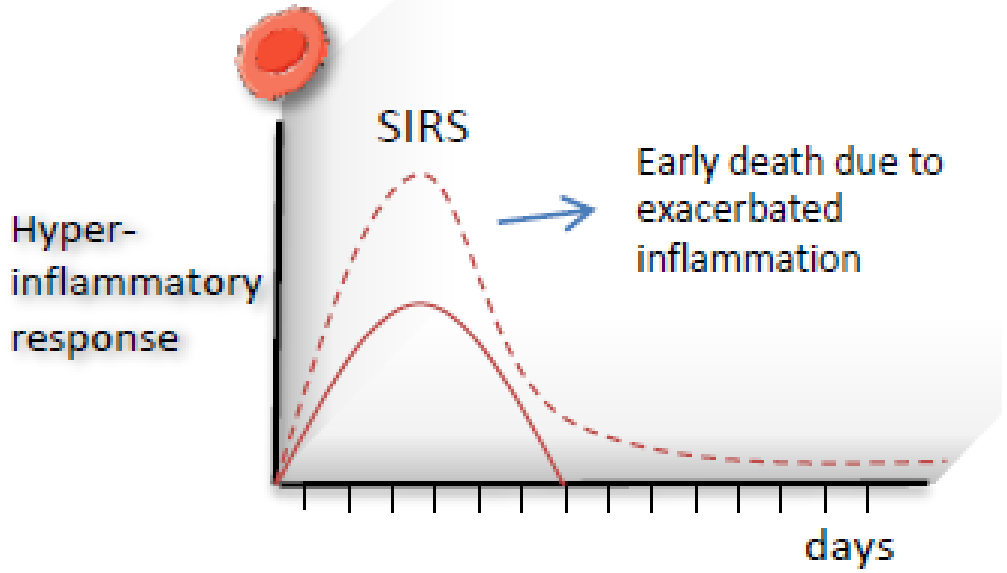
Misunderstanding the Disease…

A successful beginning of a pretty big failure

Conceptual evolution of the Immuno-Inflammatory Responses in Sepsis

I

Hyper-inflammatory response (SIRS) detectable in blood

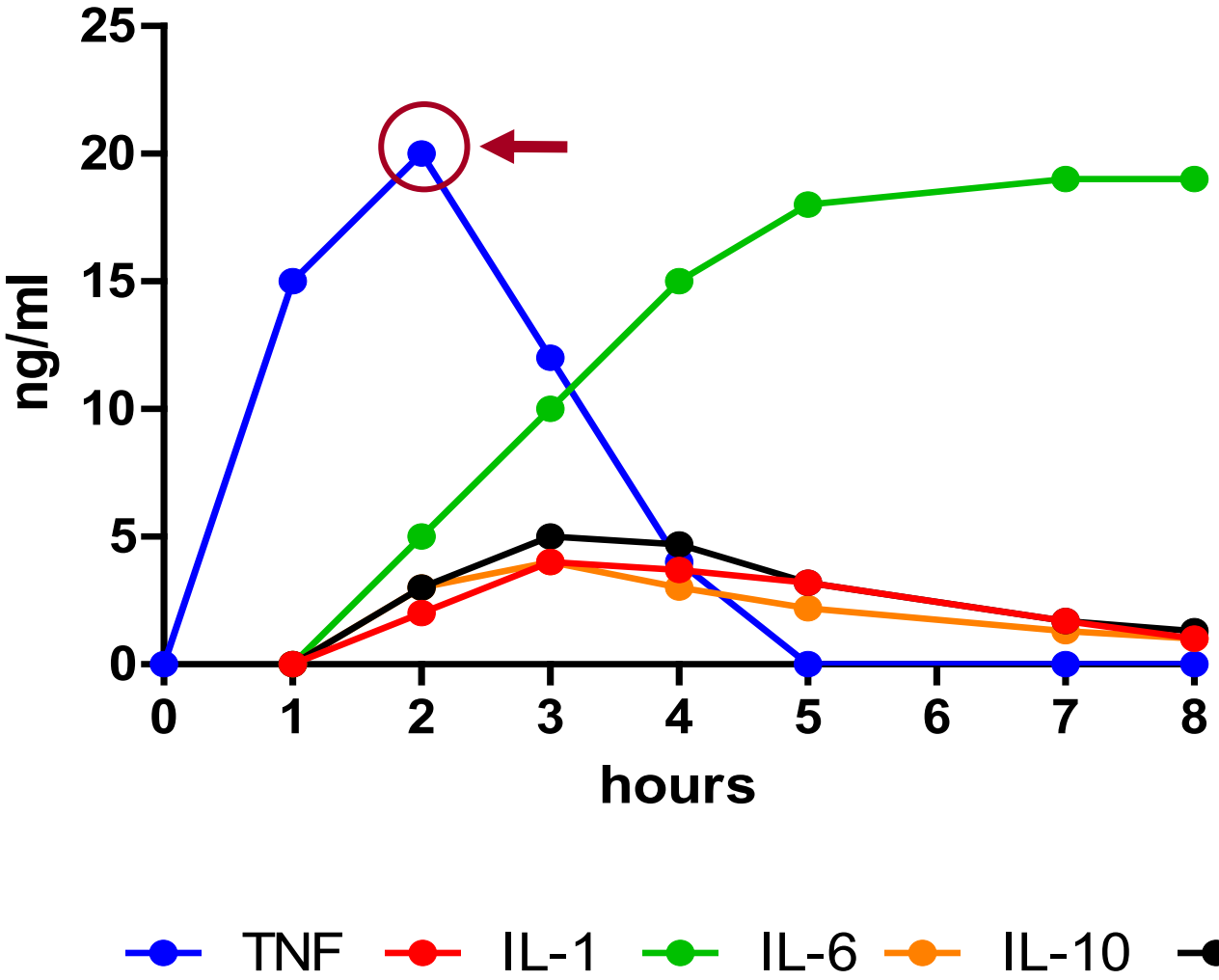


1992 – Roger Bone and team

> > Sepsis progression > >

Lancet Infect Dis 2019

General Schematic of Cytokine Release after lethal LPS/E.coli Bolus in Animals/Humans



dog/LPS Krausz et al. J. Clin. Invest. 1981 Apr;67(4):1118-25

mouse/LPS Beutler et al. Science 1985 Aug 30;229:869-71

rat/LPS Goto et al. 1991 Circ Shock. 35(1):60-4.

Rabbits/LPS Yamamoto et al. Eur J Pharmacol. 1997; 327:169-74.

Baboons/E.coli Hishaw et al. Circ Shock. 1990; 30(3):279-92.

Baboons/E.coli Tracey et al. Nature 1987,330(6149):662-4

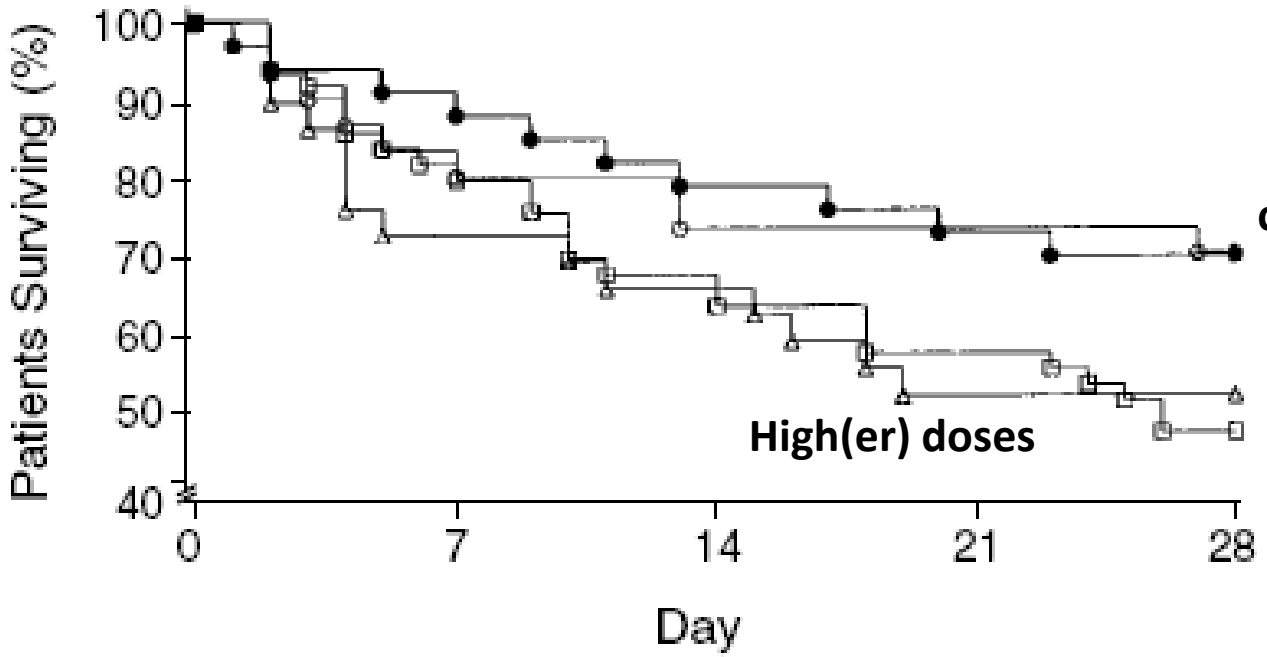
Baboons/S.aureus Hishaw et al. J Trauma. 1992 Oct;33(4):568-73.

Humans/LPS van der Poll T et al. J Immunol 1997;158:1490.

Humans/LPS van der Poll T et al. Blood 1997;89:3727-3734

The Spectacularly Lethal Failure –

The Soluble TNF Receptor Sepsis Study Group.



patients killed
by the treatment

Study Group	No. of Patients	No. of Deaths
Placebo (-●-)	33	10
0.15 mg/kg (-○-)	30	9
0.45 mg/kg (-△-)	29	14
1.5 mg/kg (-□-)	49	26

Figure 1. Kaplan–Meier Analysis of Survival in Patients with Sepsis Receiving Placebo or One of Three Doses of TNFR:Fc.

Fisher et al. N Engl J Med. 1996, 334(26):1697-702.

SHOCK, Vol. 4, No. 2, pp. 89–95, 1995

J Immunol May 1, 1992, 148 (9) 2724-2730

BLOCKADE OF TUMOR NECROSIS FACTOR REDUCES LIPOPOLYSACCHARIDE LETHALITY, BUT NOT THE LETHALITY OF CECAL LIGATION AND PUNCTURE

Daniel Remick*, Prerana Manohar*, Gerald Bolgos*, Jorge Rodriguez*, Lyle Moldawer‡ and Gordon Wollenberg*

*‡Department of Surgery, University of Florida, Gainesville, Florida 32610; and *Departments of Pathology and Surgery, University of Michigan, Ann Arbor, Michigan 48109-0602*

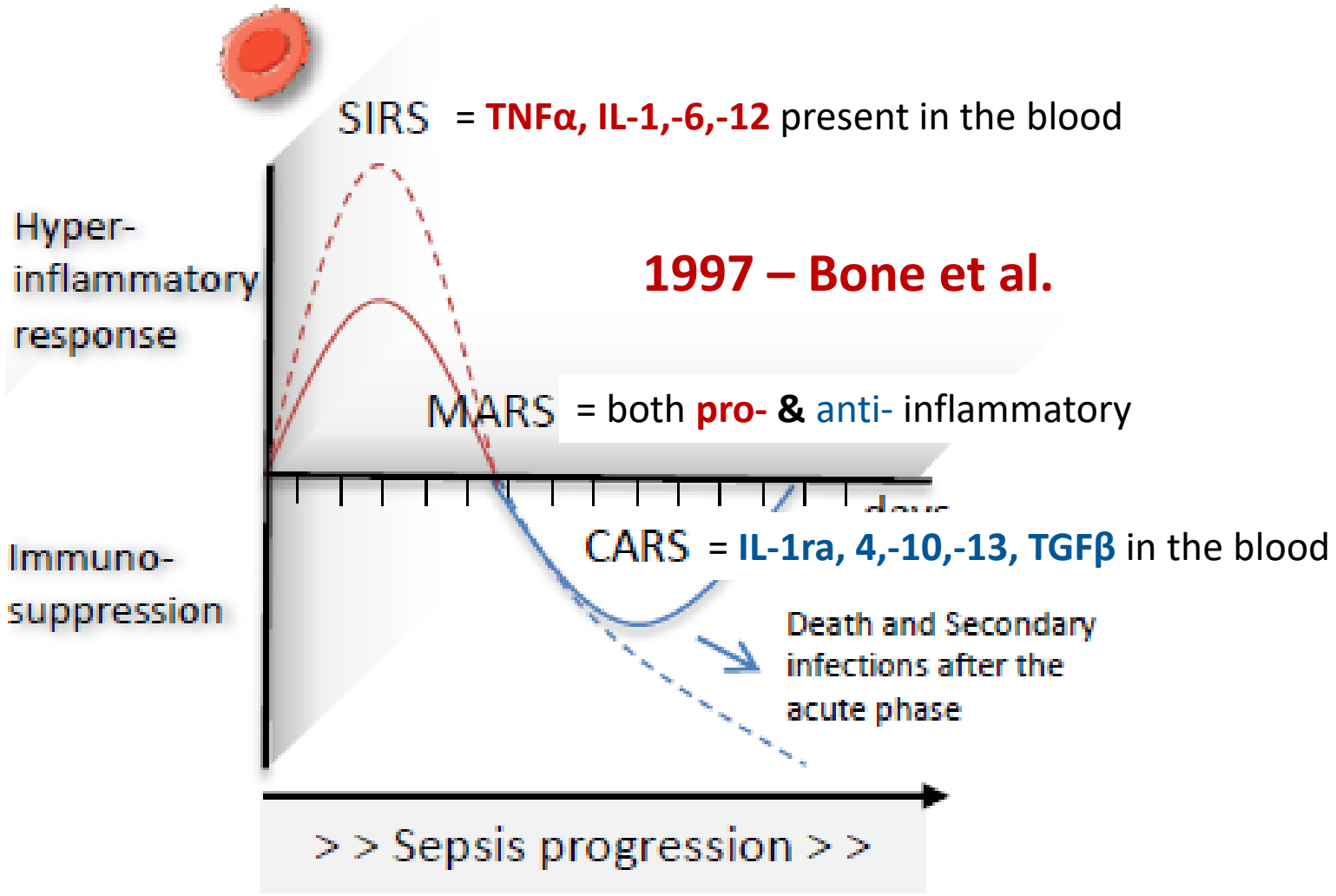
ABSTRACT—Inhibition of tumor necrosis factor (TNF) bioactivity has afforded protection in several animal models of sepsis. We examined whether inhibition of TNF could improve survival after lethal lipopolysaccharide (LPS) or cecal ligation and puncture (CLP) in CD-1 or BALB\c mice. Neutralizing rabbit anti-TNF antisera were evaluated in CD-1 mice by injecting the antisera 3 h before intravenous (i.v.) LPS (600 μg). Implantable radiotransmitters were used for continuous monitoring of temperature. No decrease in mor-

inhibition of TNF fails to reduce mortality in a more clinically relevant model of sepsis.

performed followed by administration of antibiotics. -TNF did not decrease pulmonary neutrophil sequestration, improve survival, or prevent the decrea in temperature observed as sepsis developed. CLP was performed in the BALB\c mice using antibio plus anti-TNF antisera, but no protection was observed. Our results demonstrate that anti-TNF treatm prevents LPS mortality only when using certain strains of mice and inhibition of TNF fails to reduce mortality in a more clinically relevant model of sepsis.

II

SIRS followed by Compensatory anti-inflammatory response (CARS) detectable in blood



SIRS = **TNFα, IL-1,-6,-12** present in the blood

1997 – Bone et al.

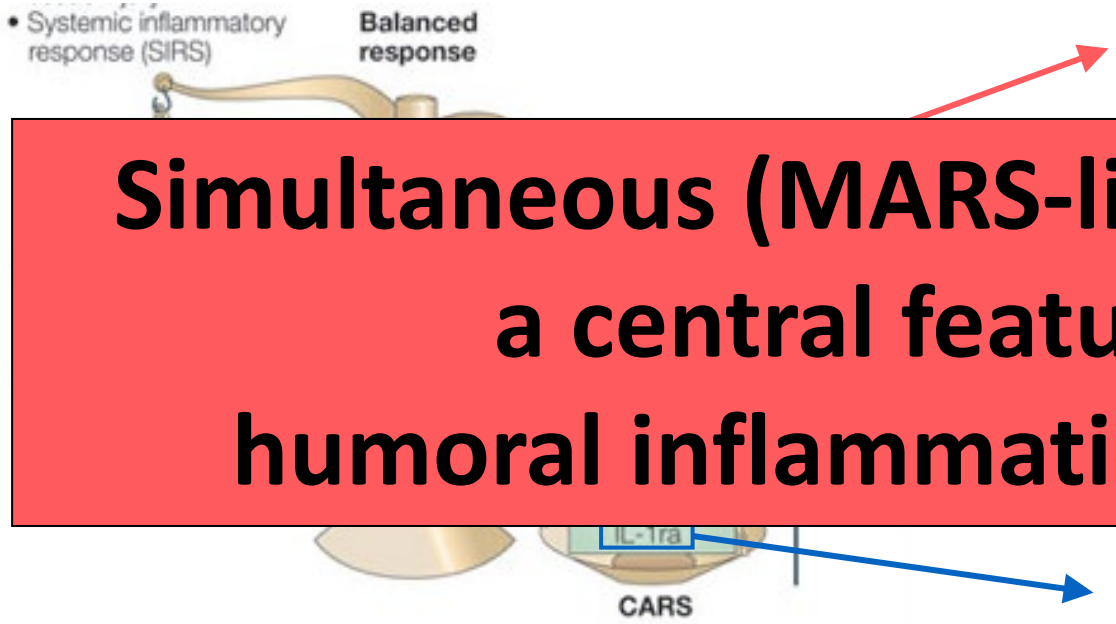
MARS = both **pro-** **&** anti- inflammatory

CARS = **IL-1ra, 4,-10,-13, TGFβ** in the blood

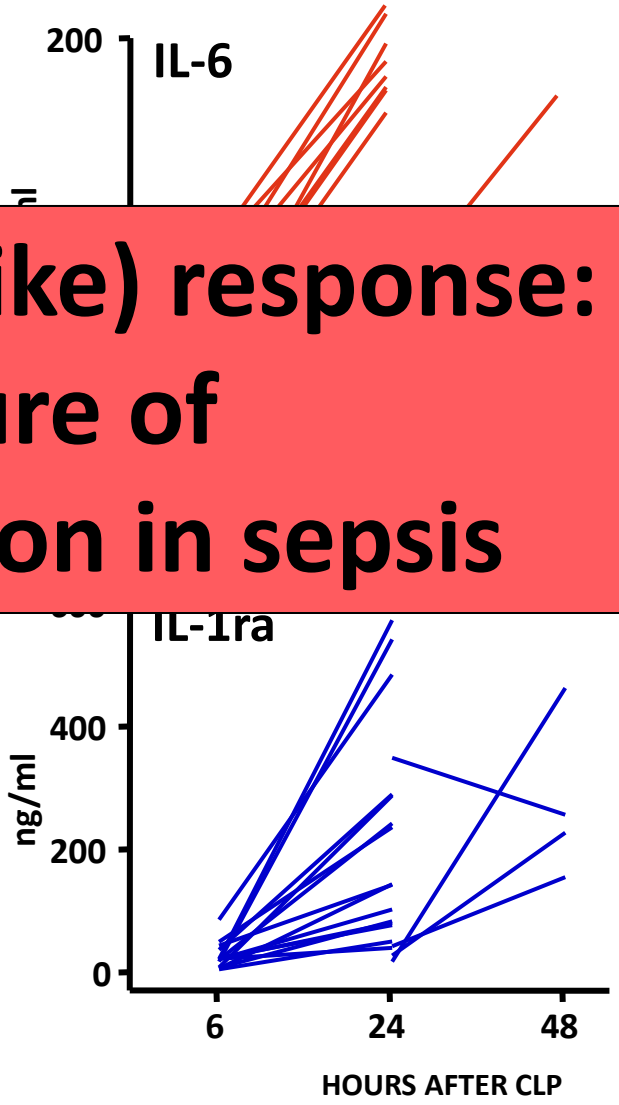
Lancet Infect Dis 2019

Bimodal SIRS-to-CARS Transition in Sepsis

Animal Models of sepsis: setting the stage
Jon A. Buras, Bernhard Holzmann & Michail Sitkovsky
2005 Nature Reviews Drug Discovery 4, 854-865



"Sepsis Always in MARS"



Osuchowski et al. J Immunol. 2006

Simultaneous (MARS-like) response: a central feature of humoral inflammation in sepsis

Diagnostic Criteria:

~~TNFα, IL-1,-6,-12 present in the blood = SIRS~~

~~IL-1ra, 4,-10,-13, TGFβ present in the blood = CARS~~

Too Simplistic to be Realistic!

Identical Patterns in Septic Patients

Eur. Cytokine Netw. Vol. 22 n° 2, *June 2011*

Pro- and anti-inflammatory responses are regulated simultaneously from the first moments of septic shock

Eduardo Tamayo[1,2,*], Ana Fernández[1,2,*], Raquel Almansa[2,3,*], Elena Carrasco[1,2], María Heredia[1,2], Carmen Lajo[1,2], Lisbeth Goncalves[2,3], Jose I. Gómez-Herreras[1,2], Raúl Ortiz de Lejarazu[2], Jesus F. Bermejo-Martin[23,4]

[1] Anesthesiology and Reanimation Service, Hospital Clínico Universitario de Valladolid,
[2] Investigación Médica en Infección e Inmunidad (IMI). Hospital Clínico Universitario de Valladolid-IECSCYL, Valladolid
[3] Servicio de Microbiología e Inmunología, Hospital Clínico Universitario de Valladolid
[4] Grupo Cooperativo de Investigación Biomédica en Inmunología (CIBI), Madrid, Spain

Immunobiology 217 (2012) 616–621

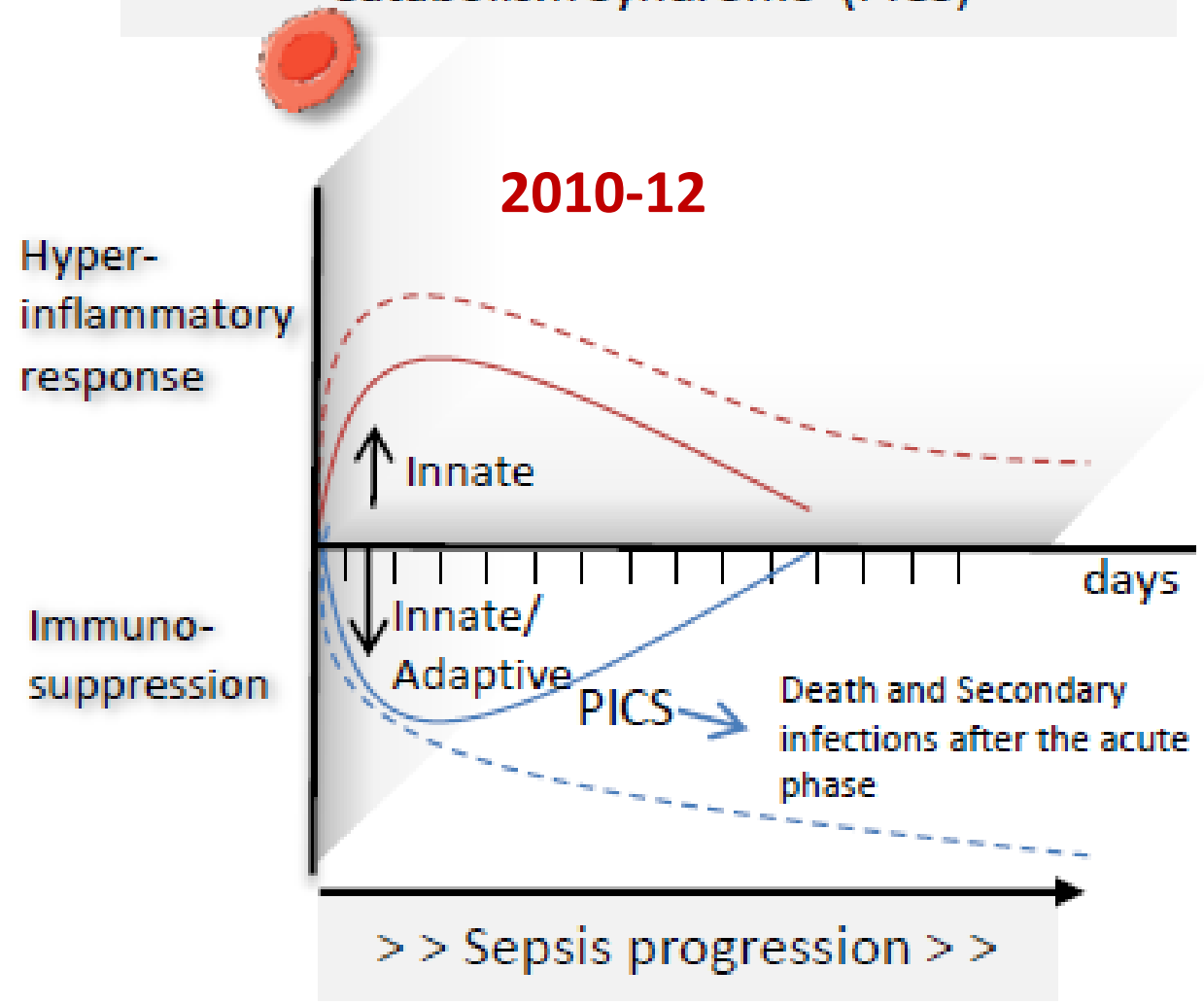
Mixed antagonist response and sepsis severity-dependent dysbalance of pro- and anti-inflammatory responses at the onset of postoperative sepsis

Alexander R. Novotny[a,*], Daniel Reim[a], Volker Assfalg[a], Felicitas Altmayr[a], Helmut M. Friess[a], Klaus Emmanuel[b,1], Bernhard Holzmann[a,1]

[a] *Department of Surgery, Klinikum rechts der Isar, Technische Universitaet Muenchen, Ismaninger Straße 22, 81675 Munich, Germany*
[b] *Department of Surgery, Salzburger Landeskliniken, University of Salzburg, Muellner Hauptstraße 48, 5020 Salzburg, Austria*

III

Simultaneous pro- and anti-inflammatory responses in blood ; Persistent Inflammation, Immunosuppression and Catabolism Syndrome (PICS)



Lancet Infect Dis 2019

MEDICAL PROGRESS

The Pathophysiology and Treatment of Sepsis

Richard S. Hotchkiss, M.D., and Irene E. Karl, Ph.D.

Table 1. Potential Mechanisms of Immune Suppression in Patients with Sepsis.*

Shift from an inflammatory (Th1) to an antiinflammatory (Th2) response
Anergy
Apoptosis-induced loss of CD4 T cells, B cells, and dendritic cells
Loss of macrophage expression of major-histocompatibility-complex class II and costimulatory molecules
Immunosuppressive effect of apoptotic cells

NEJM 2003

Immunosuppression in Patients Who Die of Sepsis and Multiple Organ Failure

Conclusions Patients who die in the ICU following sepsis compared with patients who die of nonsepsis etiologies have biochemical, flow cytometric, and immunohistochemical findings consistent with immunosuppression. Targeted immune-enhancing therapy may be a valid approach in selected patients with sepsis.

JAMA. 2011;306(23):2594-2605 www.jama.com

Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach

Richard S Hotchkiss, Guillaume Monneret, Didier Payen

www.thelancet.com/infection Vol 13 March 2013

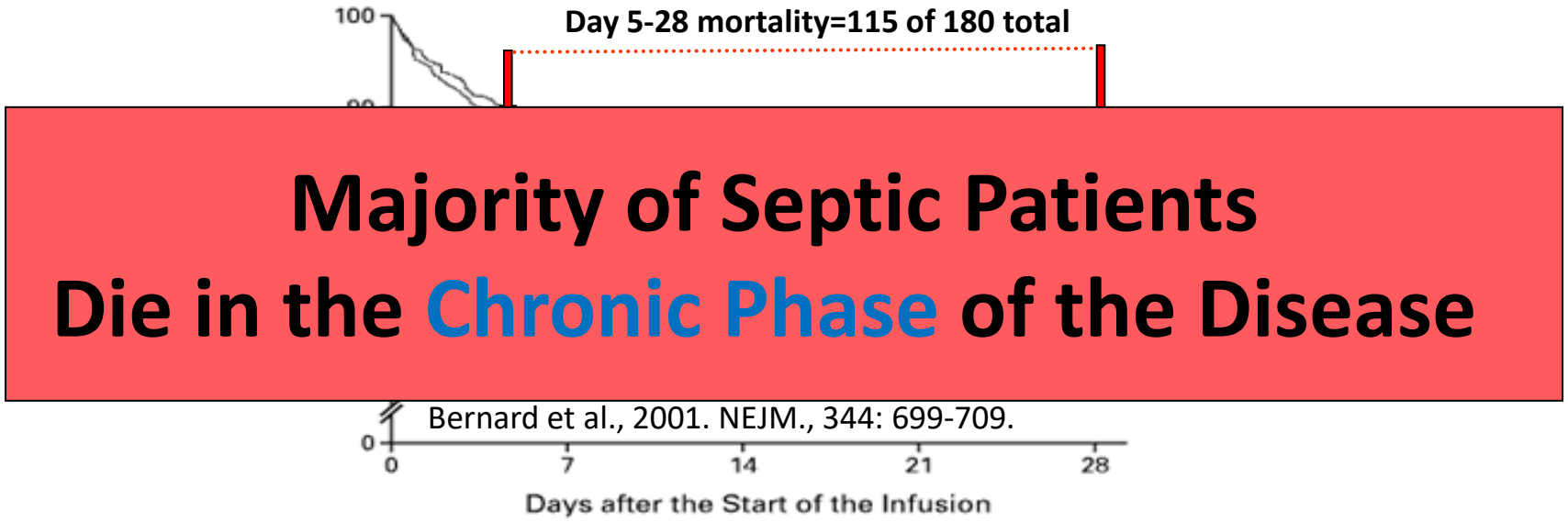
EXPERT REVIEW OF CLINICAL IMMUNOLOGY
https://doi.org/10.1080/1744666X.2019.1562336

New frontiers in precision medicine for sepsis-induced immunoparalysis

Niklas Bruse*, Guus P. Leijte*, Peter Pickkers and Matthijs Kox

Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, The Netherlands; Radboud Center for Infectious Diseases, Radboud University Medical Center, Nijmegen, The Netherlands

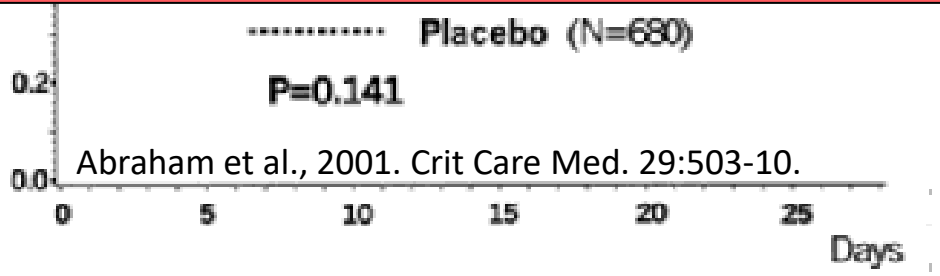
Chronic/Late Phase Sepsis – Clinical Reality



Majority of Septic Patients Die in the Chronic Phase of the Disease

Bernard et al., 2001. NEJM., 344: 699-709.

IS the Majority of Those Who Die in Chronic Sepsis "Immunoparalyzed"?



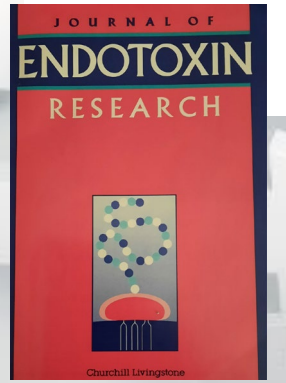
Abraham et al., 2001. Crit Care Med. 29:503-10.

Journal of Endotoxin Research, Vol. 7, No. 2, 2001

Immunodepression in sepsis and SIRS assessed by *ex vivo* cytokine production is not a generalized phenomenon: a review

Jean-Marc Cavaillon, Minou Adib-Conquy, Isabelle Cloëz-Tayarani, Catherine Fitting

Department of Physiopathology, Institut Pasteur, Paris, France



of

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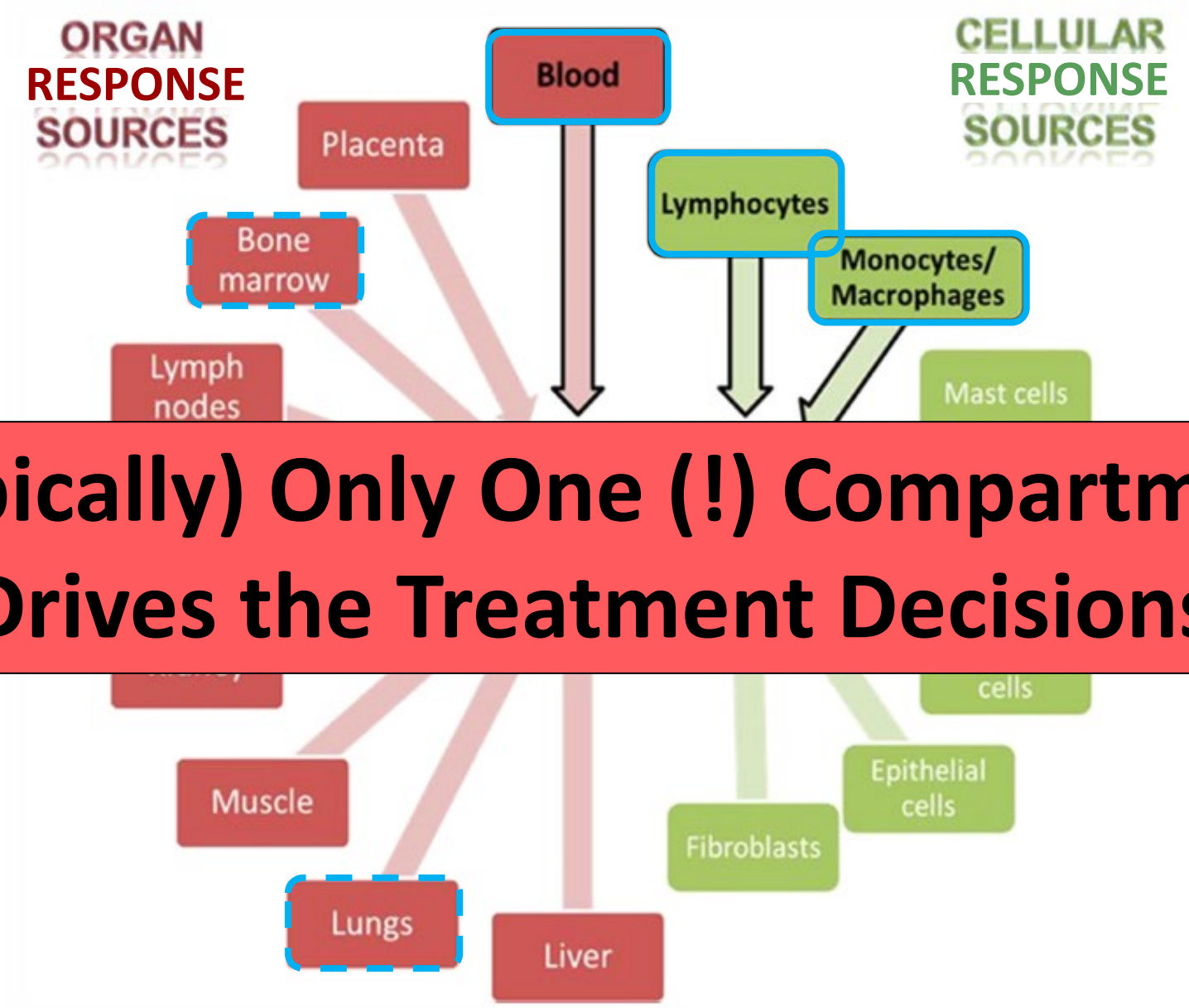
in sepsis

Be Aware! It is not BLACK & WHITE

Leukocytes	Reduced ↓	Increased ↑	Unchanged ↔
Lymphocytes	Proliferation to mitogens	Apoptosis	
	Cytokine production		
Monocytes	Surface expression of:	Surface expression of:	Surface expression of:
	HLA-DR	Fcγ R I (CD64)	C5a R
	TNF R p75	TNF R p55	
	CD14	CD40; CD48; CD80	
	Transferrin receptor (CD71)	Fcα R I (CD89)	
	Co-activation marker (CD86)	TLR4	
	GM-CSF	TREM-I	
	CX3CR	Tissue factor	
	IL-1β, IL-6, IL-8, IL-12, TNF production in response to LPS	IL-1Ra, MIF production in response to LPS	Cytokine response to whole bacteria
Neutrophils	Surface expression of:	Surface expression of:	Surface expression of:
	TLR2	Fcγ R I (CD64)	CD11b, CD11c
	TNF & IL-1 receptors	fMLP-Receptor	CXCR1
	CXCR2	CD66b	
		IL-10R1	
	Apoptosis	PEBF production	
	Response to chemoattractant	Expression of cytosolic phospholipase A2	IL-1Ra production in response to *S. aureus*
	Phagocytosis	Elastase release	

Adib-Conquy, Cavaillon: Systemic inflammation and immune status **Thromb Haemost 2009; 101: 36–47**

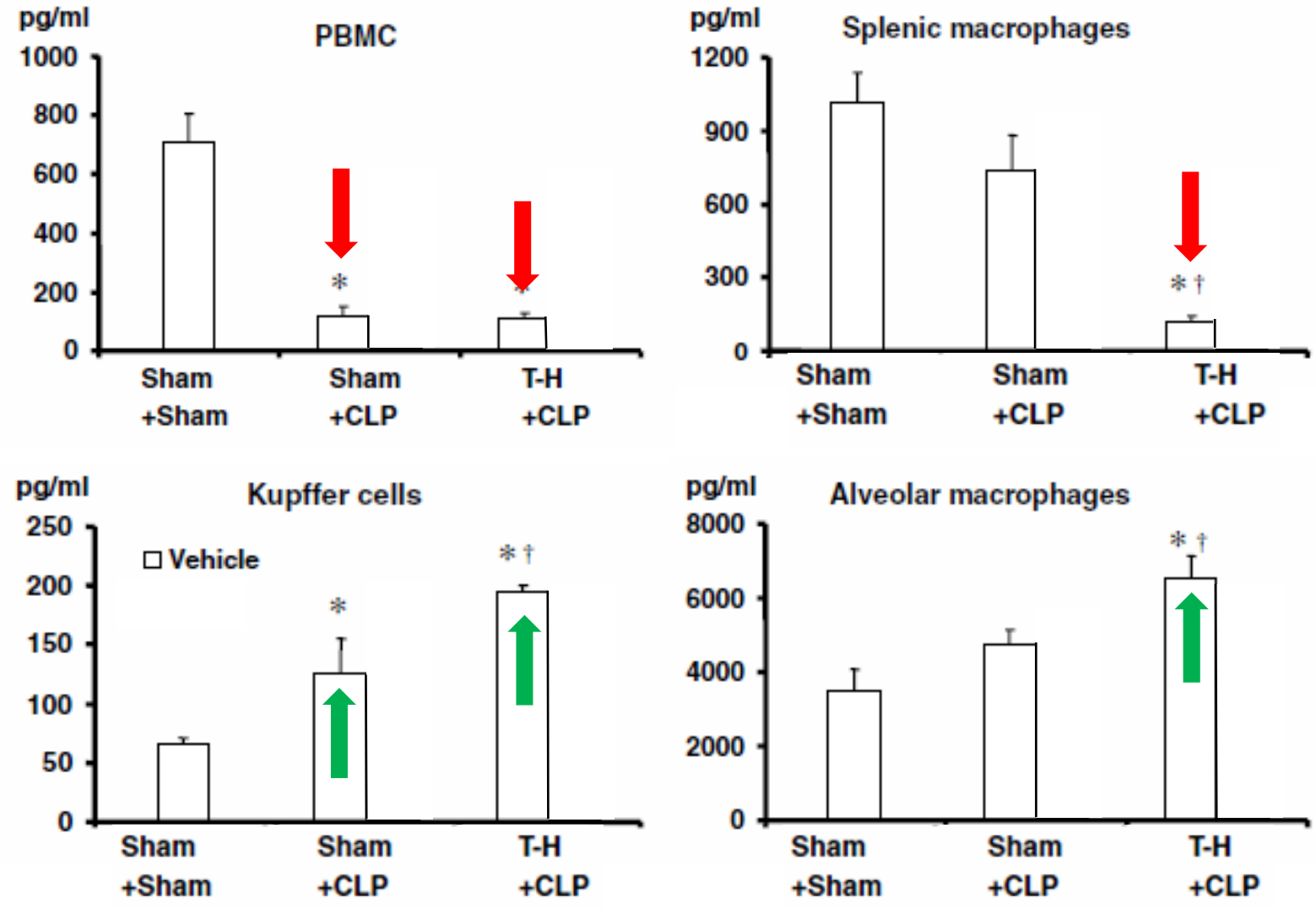


(Typically) Only One (!) Compartment Drives the Treatment Decisions

SHOCK, Vol. 41, No. 6, pp. 463–475, 2014

Macrophages:
TNFα Response Depends on the Body Compartment

Irshad Chaudry

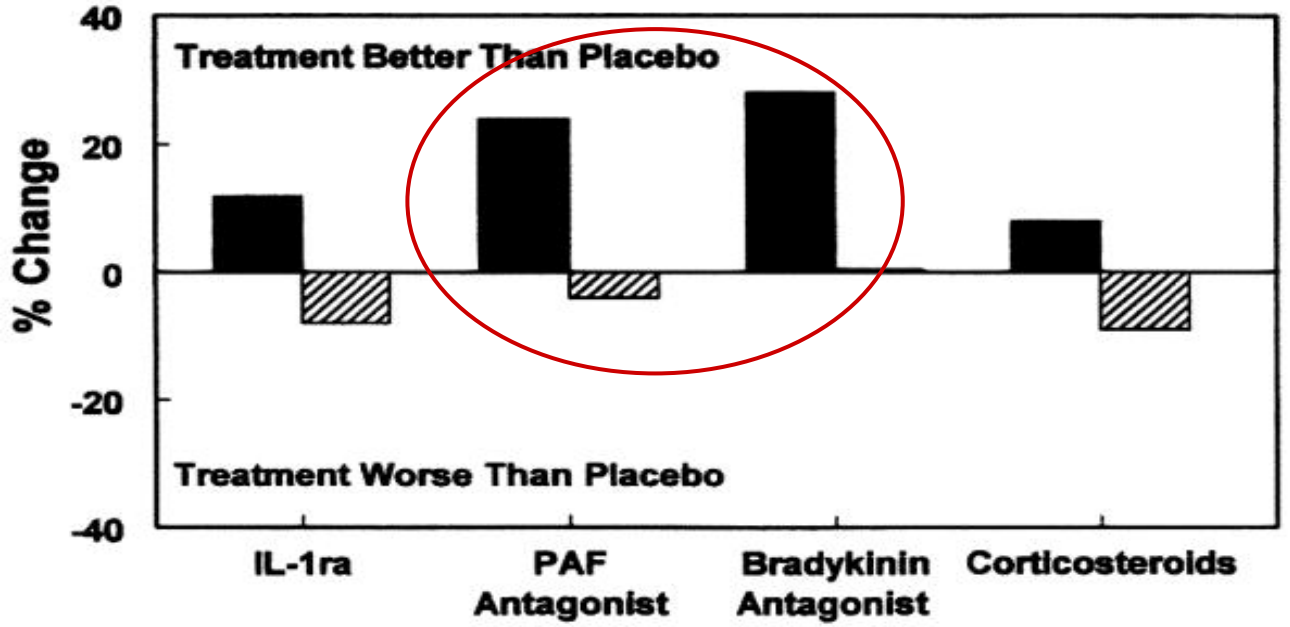


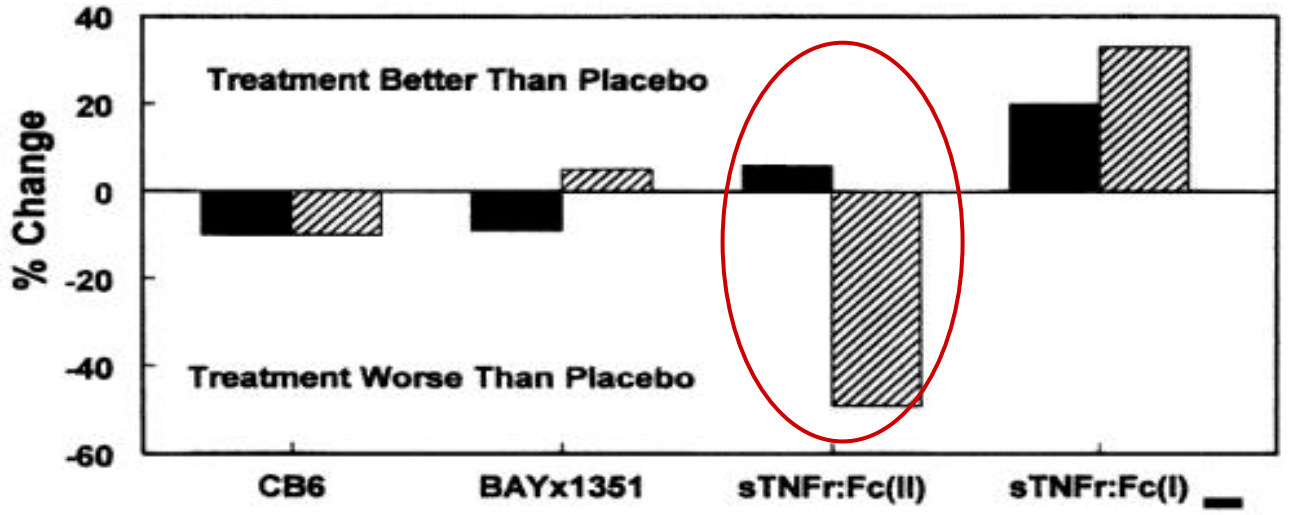
Irshad Chaudry's lab Cytokine 34 (2006) 76–84

Different ways to reduce heterogeneity by focusing on:

- Type of infecting microorganism (e.g., G-pos. vs. G-neg. vs. fungus)
- Presence/absence of specific comorbidities (e.g. diabetes, cancer)
- Immuno-inflammatory status (i.e. robust response vs. immunosuppression)
- Sepsis severity/risk of death (high vs. low)
- Infectious source (e.g. abdominal vs. pneumonia)

Focusing on Pathogens: Types Define Outcome?





Gram (+)

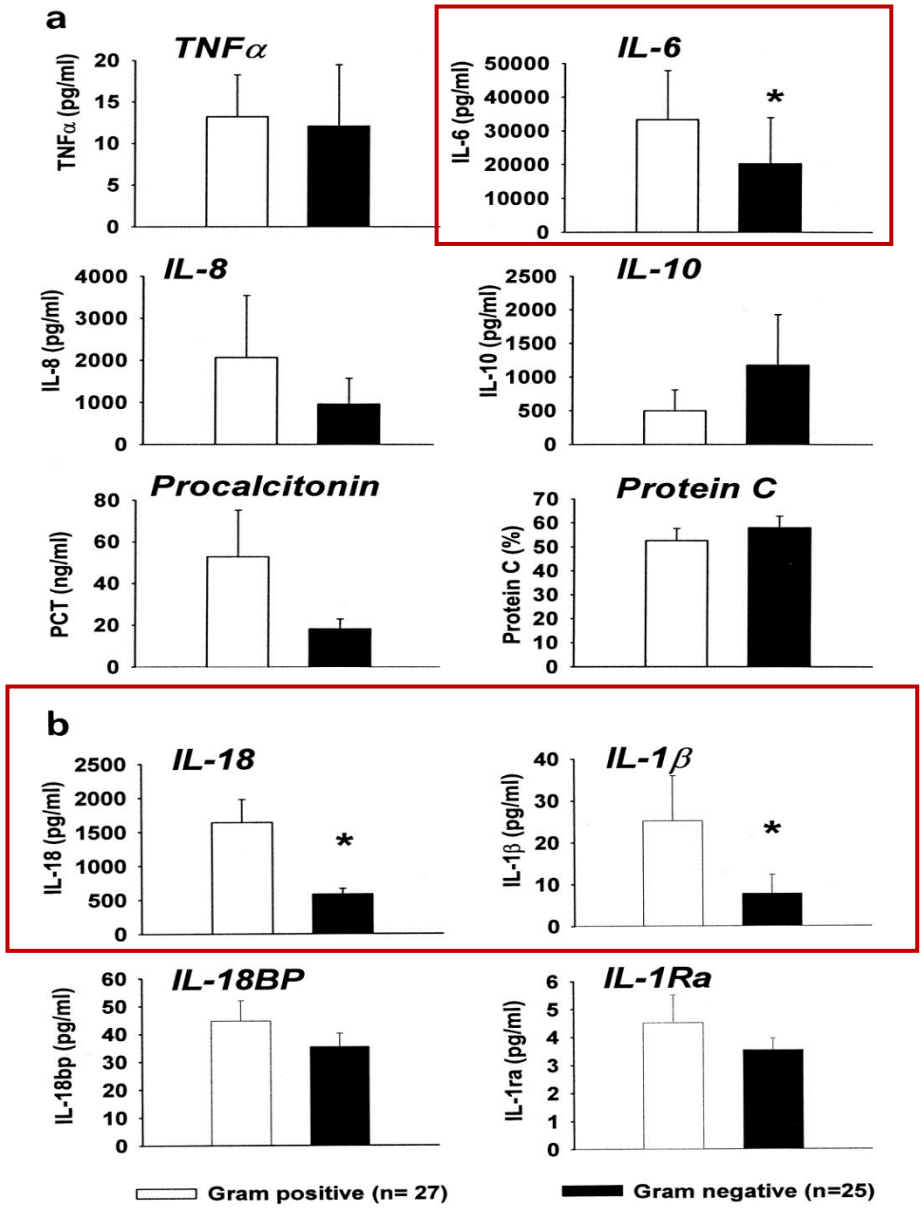
Gram (-)

PAF: platellet activating factor

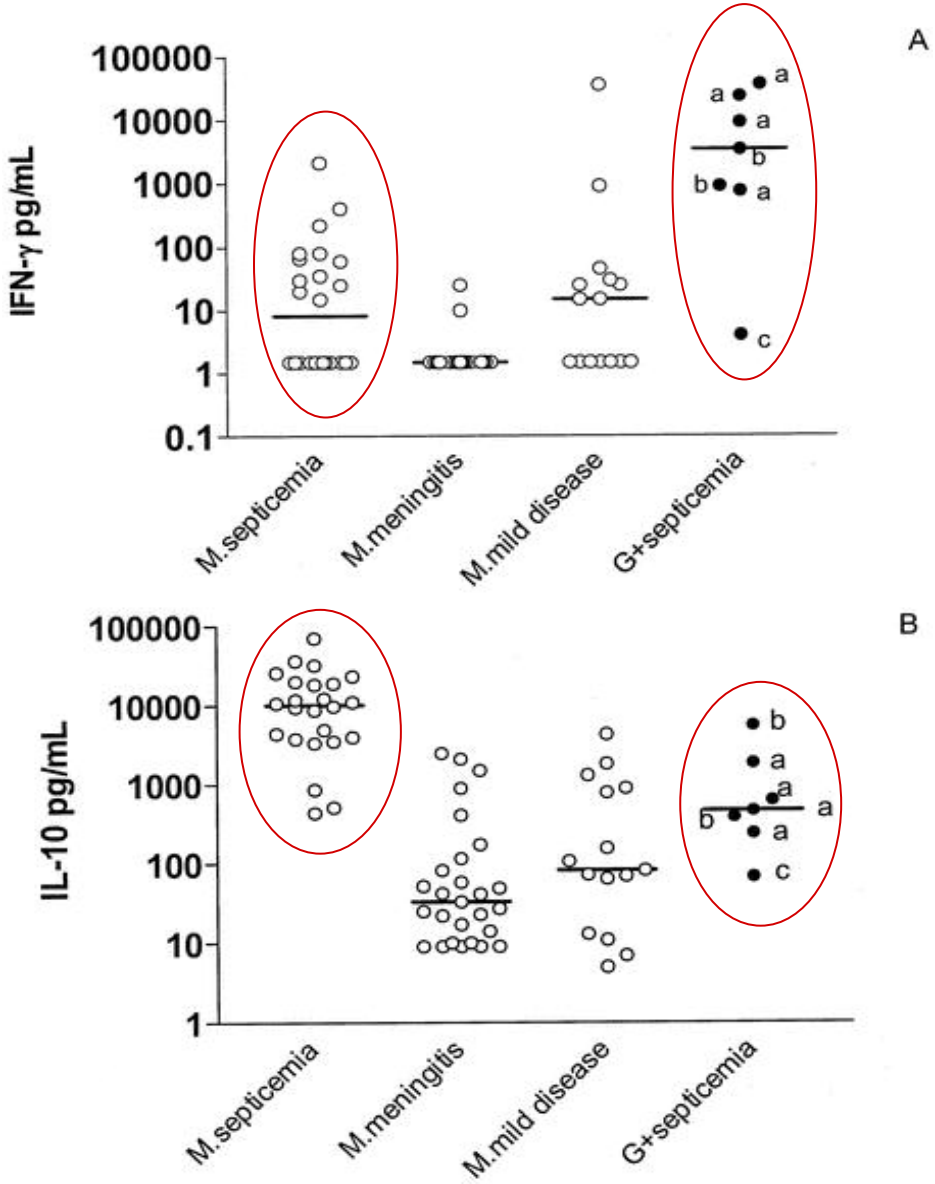
Anti-TNF treatments

Opal et al., 1999 CCM.26; 8:38.

Diverse reactions in patients with G+ vs. G- sepsis



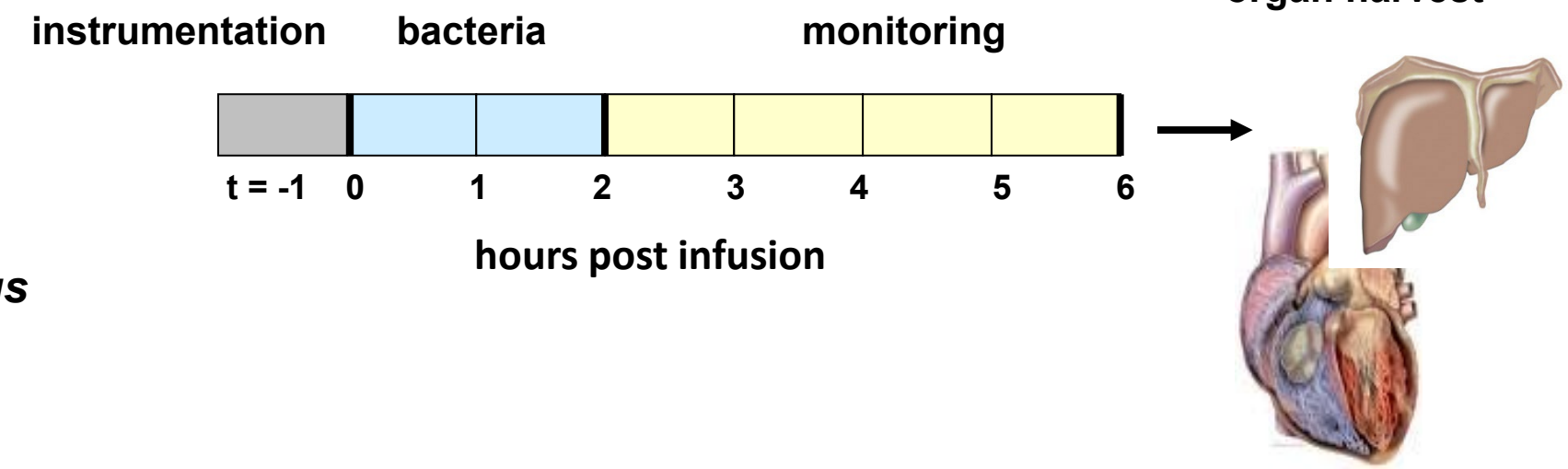
Feezor et al., 2003 *Infect Immun.* .71: 5803-13.



Bjerre et al., 2004 *Crit Care Med.* 32: 433-8

Baboon Study: checking genetic diversity

male, adult
papio ursinus

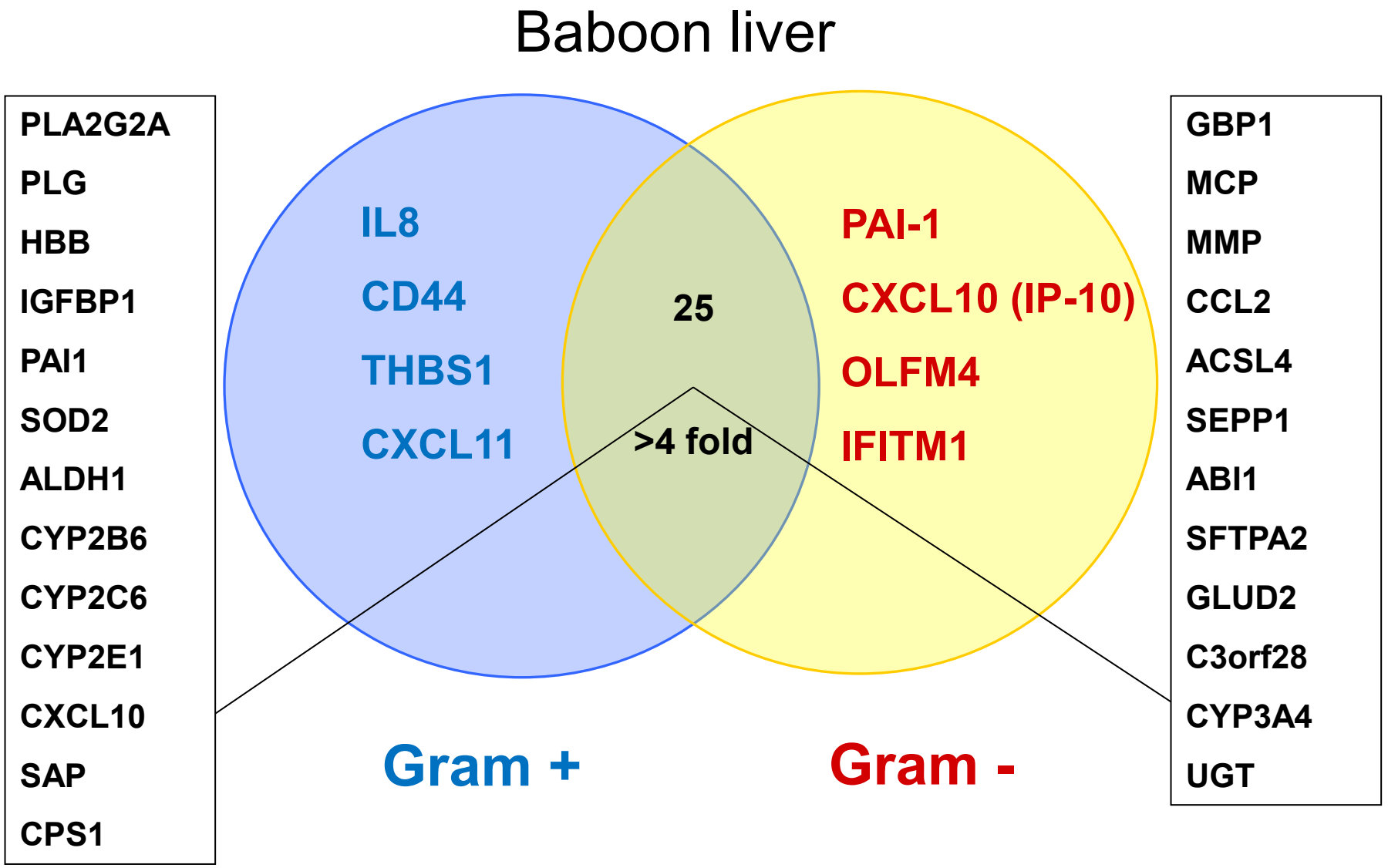


Sham group: - NaCl 0.9%

Gram-positive group: - *S.pyogenes* (~ 2.5×10^8 cfu / kg BW in 200ml saline/h)

Gram-negative group: - *E.coli* (~ 0.2×10^8 cfu / kg BW in 200ml saline/h)

Differentially expressed genes



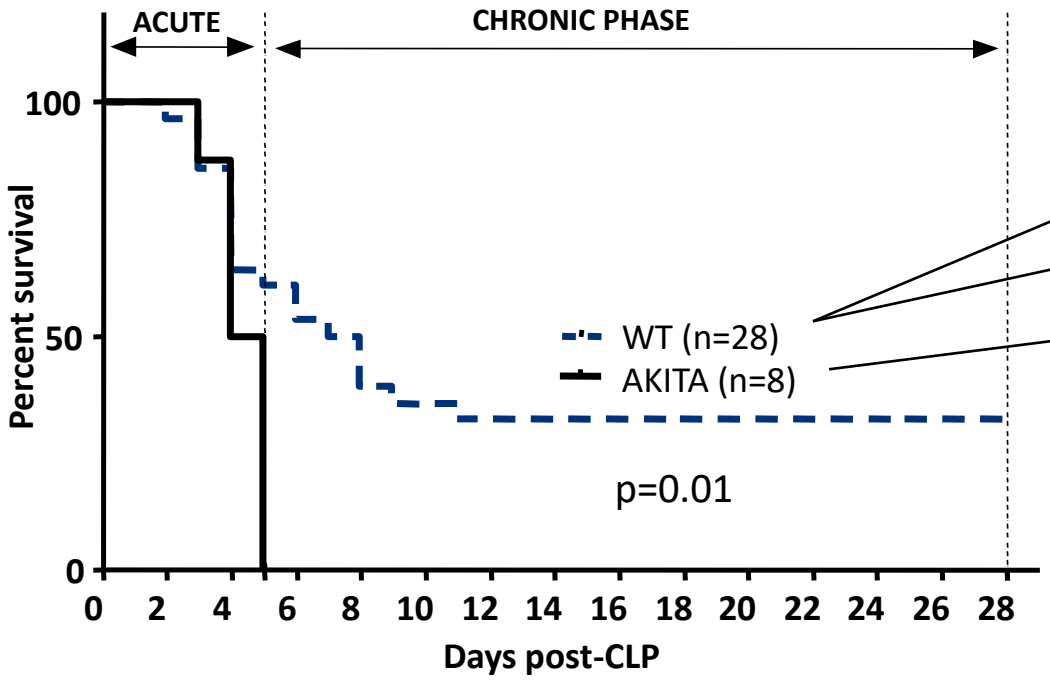
Focusing on Comorbidities: Impact on Immuno-Inflammatory Endpoints?

Table 3. *Effects of comorbid conditions in sepsis and their relative incidences among septic patients*

Co-Morbid Condition	Effect in Sepsis	Incidence Among Sepsis Patients, % (232, 254)
Diabetes mellitus	Increased risk of acute renal failure but decreased risk of acute respiratory failure (102)	23
Cancer	Chemotherapy-induced neutropenia (296)	16
Cirrhosis	Complement deficiency, impaired neutrophil function, and spontaneous bacterial peritonitis (145)	7
Chronic obstructive pulmonary disease	Significant impairment of phagocytosis in pulmonary macrophages (340)	17
End-stage renal disease	Uremia impairs innate and adaptive immune function (152)	11
HIV/AIDS	Enhanced susceptibility to bacterial pneumonia (333)	10.3

Physiol Rev 93: 1247–1288, 2013
doi:10.1152/physrev.00037.2012

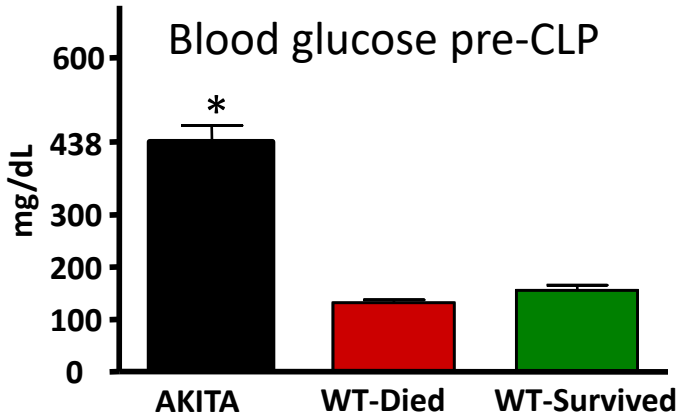
Untreated Type 1 Diabetes and Early Cytokine Response



WT-Survived (alive within days 1-5)

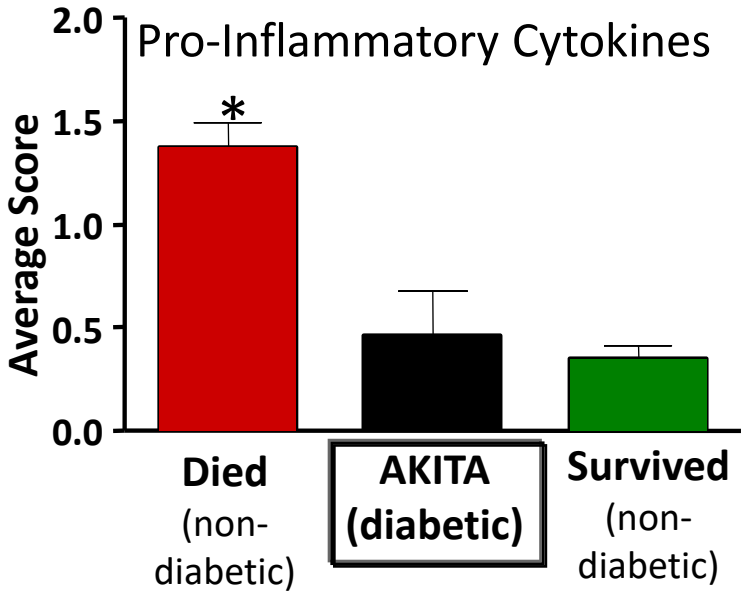
WT-Died (dead by day 5)

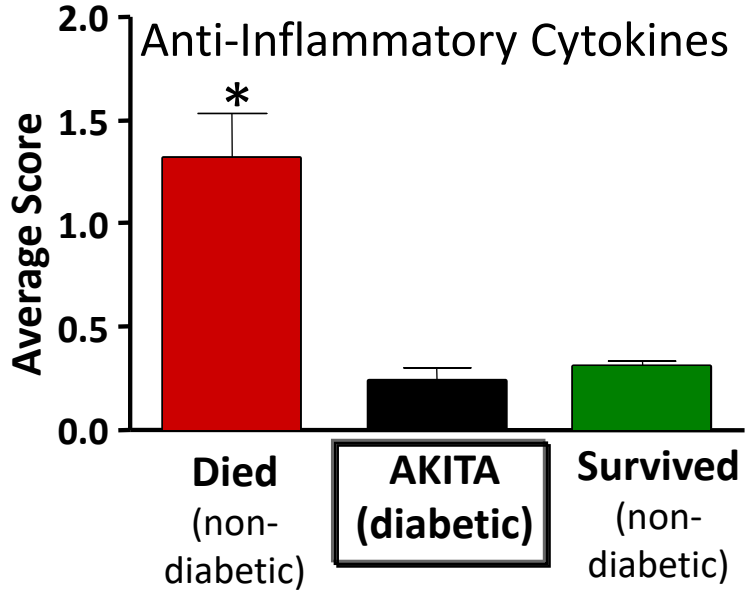
Diabetes - AKITA (dead by day 5)



SHOCK, Vol. 34, No. 4, pp. 369–376, 2010

UNTREATED TYPE 1 DIABETES INCREASES SEPSIS-INDUCED MORTALITY WITHOUT INDUCING A PRELETHAL CYTOKINE RESPONSE





PRO-inflammatory block:

IL-1β	IFNγ
IL-2	ICAM-1
IL-5	MIP-1α
Il-6	MIP-2
IL-12	MCP-1
IL-17	Eotaxin
TNFα	EOX-2

ANTI-inflammatory block

IL-1ra
IL-4
IL-10
Il-13
TNF srI
TNF srII

SHOCK, Vol. 34, No. 4, pp. 369–376, 2010

Few Words about:
Phenotyping/Personalizing Trials

Out of 69 Anti-sepsis Ph2/3 Human Trials listed…

2 used advanced (IL-6-based) treatment targeting

Table 1. Summary of clinical trials of pharmacological interventions for the adjuvant treatment of sepsis, which have been reported since 1982

1st Author	Year	Patients (sample size)	Trial Acronym	Experimental agent	Effect on mortality[a]	References
Ziegler	1982	Septic shock (212)		Human antiserum to mutant *E. coli*	Benefit[b]	2
Ziegler		Sepsis and presumed or proven Gram-negative infection (543)		HA-1A, a human mAb that binds the lipid A domain of LPS	Benefit	67
McCloskey	1994	Septic shock and Gram-negative bacteremia (621)	CHESS	HA-1A, a human mAb that binds the lipid A domain of LPS	No effect[c]	5
Greenman,	1991	Gram-negative sepsis (486)		E5, a murine mAb that binds the lipid A domain of LPS	No effect	68
Bone	1995	Gram-negative sepsis with organ dysfunction (847)		E5, a murine mAb that binds the lipid A domain of LPS	No effect	69
Fisher	1996	Septic shock (141)		Etanercept, a recombinant fusion protein that is a dimer of the extracellular portion of the human p75 TNF receptor [illegible] Fc portion of IgG1; it binds and [illegible] TNF	Harm	20
Abraham	1995	Sepsis (994)	NORASEPT I	BAY x 1351, a m[illegible]i-TNF mAb	No effect	75
Cohen	1996	Sepsis (564)	INTERSEPT	BAY x 135[illegible]e anti-TNF mAb	No effect	76
Abraham	1998	Septic shock (1878)	NORASEPT II	BAY [illegible] murine anti-TNF mAb	No effect	77
Rice	2006	Severe sepsis or septic shock (81)		C[illegible](ab) fragments of an ovine polyclonal antibody to TNF	No effect	78
Reinhart	1996	Severe sepsis or septic shock (122)		Afelimomab, the F(ab')2 fragment of a murine anti-TNF mAb	No effect	79
Reinhart	2001	Severe sepsis and high serum concentration of IL-6 (446)	RAMSES	Afelimomab, the F(ab')2 fragment of a murine anti-TNF mAb	No effect	80
Panacek	2004	Severe sepsis and high serum concentration of IL-6 (998)	MONARCS	Afelimomab, the F(ab')2 fragment of a murine anti-TNF mAb	Benefit	9
Dhainaut	1995	Septic shock (42)		CDP571, a humanized anti-TNF mAb	No effect	81
Fisher	1993	Severe sepsis or septic shock (80)		CB0006, a murine anti-TNF mAb	No effect	82
Dhainaut	1994	Sepsis (262)		BN 52021, a small molecule PAF receptor antagonist	No effect	83
Dhainaut	1998	Severe sepsis suspected to be caused by Gram-negative infection (609)		BN 52021, a small molecule PAF receptor antagonist	No effect	84
Vincent	2000	Clinical suspicion of infection and APACHE II score between 15 and 35 (152)		BB-882, a small molecule PAF receptor antagonist	No effect	85

Experimental agent	Effect on mortality[a]	References
BB-882, a small molecule PAF receptor antagonist	No effect	86
TCV-309, a small molecule PAF receptor antagonist	No effect	87
TCV-309, a small molecule PAF receptor antagonist	No effect	88
[illegible]fase, recombinant human platelet activat-	Benefit	10
[illegible]rin		
GR270773, a phospholipids emulsion	No effect	93
[illegible]facogin, recombinant human tissue factor pathway inhibitor	No effect	61
[illegible]facogin, recombinant human tissue factor pathway inhibitor	No effect	60
[illegible]facogin, recombinant human tissue factor pathway inhibitor	No effect	62
[illegible]nakinra, recombinant human interleukin-1 receptor antagonist	Benefit	6
[illegible]nakinra, recombinant human interleukin-1 receptor antagonist	No effect	7
[illegible]nakinra, recombinant human interleukin-1 receptor antagonist	No effect	8
[illegible]P-0127, a small molecule bradykinin receptor antagonist	No effect	94
[illegible]P-0127, a small molecule bradykinin receptor antagonist	No effect	
[illegible]rotrecogin alfa, recombinant human activated protein C	Benefit	14
[illegible]rotrecogin alfa, recombinant human activated protein C	No effect	16
[illegible]rotrecogin alfa, recombinant human activated protein C	No effect	15

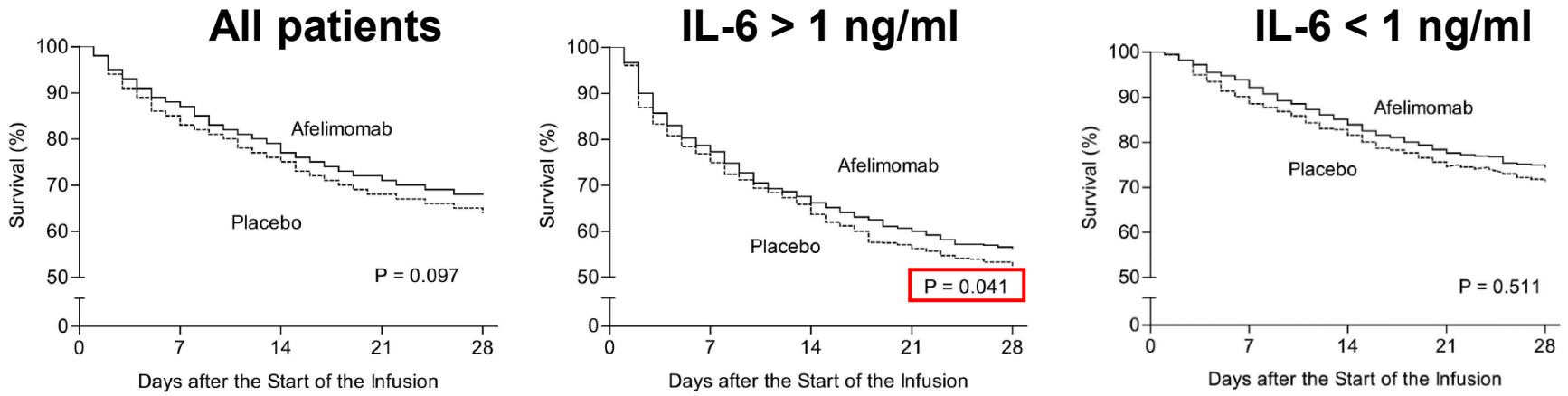
Experimental agent	Effect on mortality[a]	References
[illegible]cogin alfa, recombinant human activated protein C	No effect	17
[illegible]en, small molecule isoform unselective cyclooxygenase inhibitor	No effect	95
Hydrocortisone	No effect	103
Hydrocortisone	No effect	104
[illegible]rocortisone and fludrocortisone	Benefit	18
Hydrocortisone	No effect	19
Hydrocortisone	No effect	105
Hydrocortisone	No effect	106
[illegible]m, recombinant human granulocyte colony stimulating factor	No effect	107
[illegible]nostim, recombinant human granule macrophage colony stimulating factor	No effect	108
[illegible]nostim, recombinant human granule macrophage colony stimulating factor	No effect	109
[illegible]nostim, recombinant human granule macrophage colony stimulating factor	No effect	110
Unfractionated heparin	No effect	111
Pentoxifylline	No effect	112
[illegible], small molecule isoform unselective [illegible]itric oxide synthase inhibitor	No effect	113
[illegible], small molecule isoform unselective [illegible]itric oxide synthase inhibitor	Harm	21

Reinhart	2001	Severe sepsis and high serum concentration of IL-6 (446)	RAMSES	Afelimomab, the F(ab')2 fragment of a murine anti-TNF mAb	No effect
Panacek	2004	Severe sepsis and high serum concentration of IL-6 (998)	MONARCS	Afelimomab, the F(ab')2 fragment of a murine anti-TNF mAb	Benefit

Fink MP., Virulence **2014**

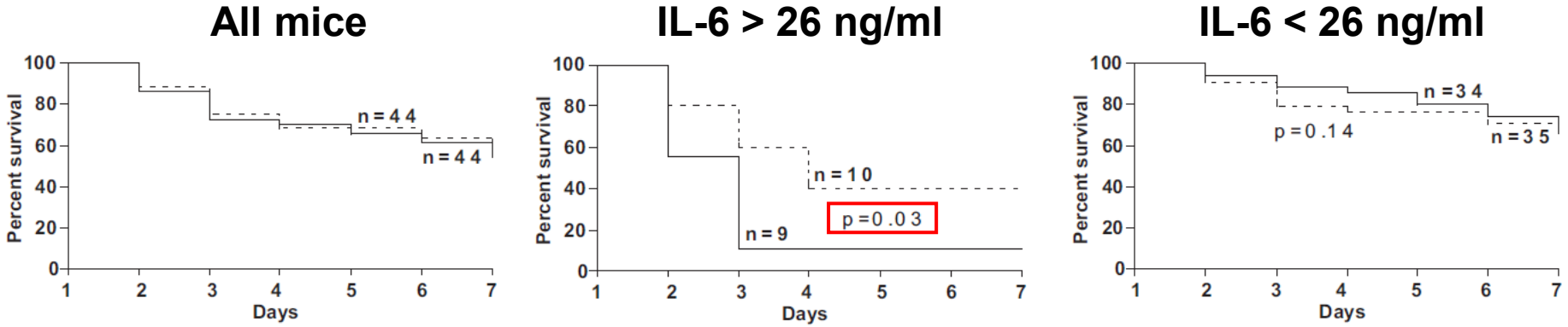
IL-6 – based Risk-Stratification for Sepsis Treatment

Clinical: anti-TNF (afelimomab) in severly septic patients



Panacek *et al.* Crit Care Med. 2004

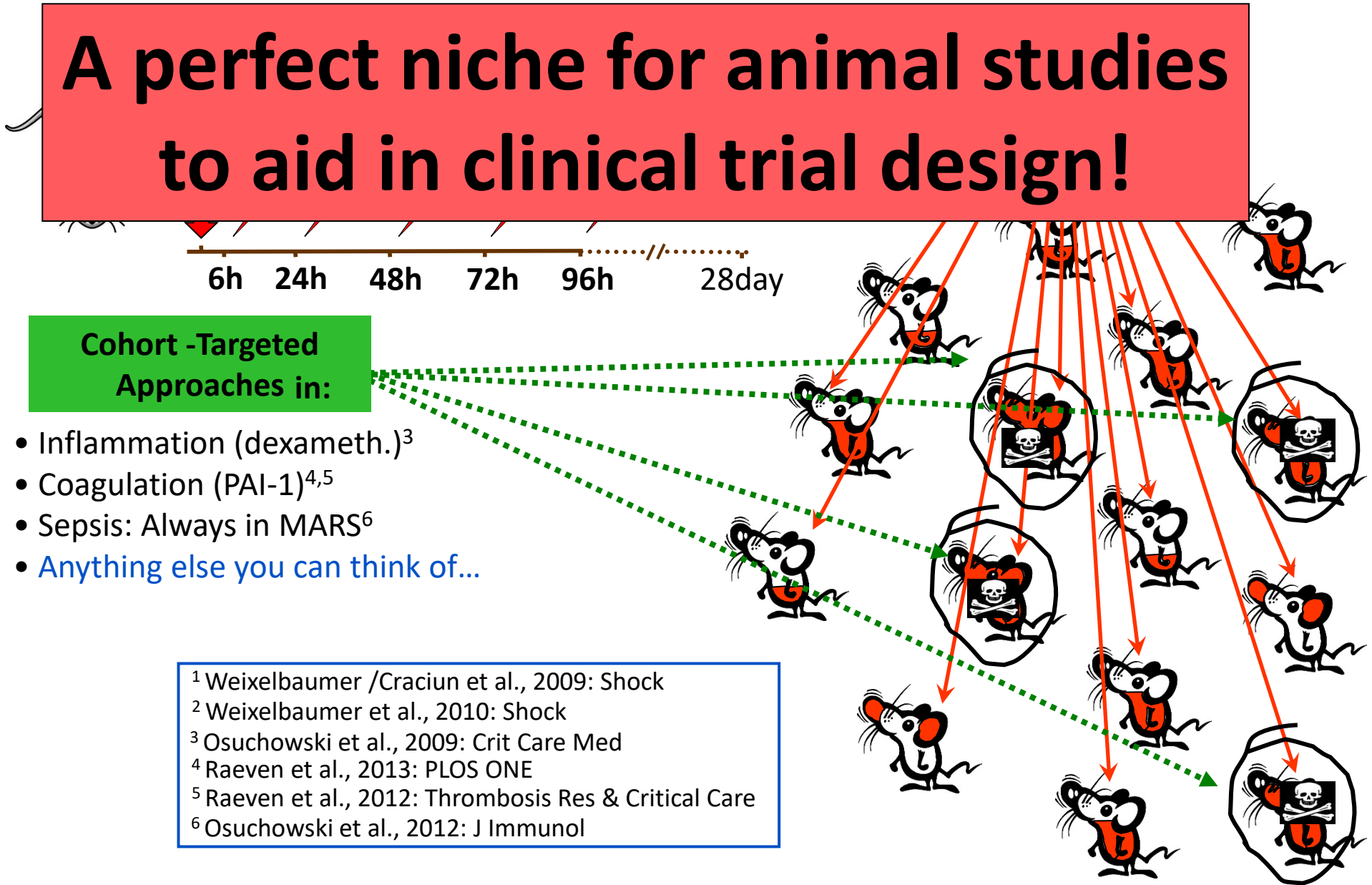
Preclinical: corticosteroids (dexamethasone) in stratified septic mice



Osuchowski *et al.* Crit Care Med. 2009

Reducing Heterogeneity by Predicting Outcome

A perfect niche for animal studies to aid in clinical trial design!



Cohort -Targeted Approaches in:

- Inflammation (dexameth.)[3]
- Coagulation (PAI-1)[4,5]
- Sepsis: Always in MARS[6]
- Anything else you can think of…

[1] Weixelbaumer /Craciun et al., 2009: Shock
[2] Weixelbaumer et al., 2010: Shock
[3] Osuchowski et al., 2009: Crit Care Med
[4] Raeven et al., 2013: PLOS ONE
[5] Raeven et al., 2012: Thrombosis Res & Critical Care
[6] Osuchowski et al., 2012: J Immunol

Reducing Heterogeneity by Predicting Outcome

Research

JAMA. doi:10.1001/jama.2019.5791
Published online May 19, 2019.

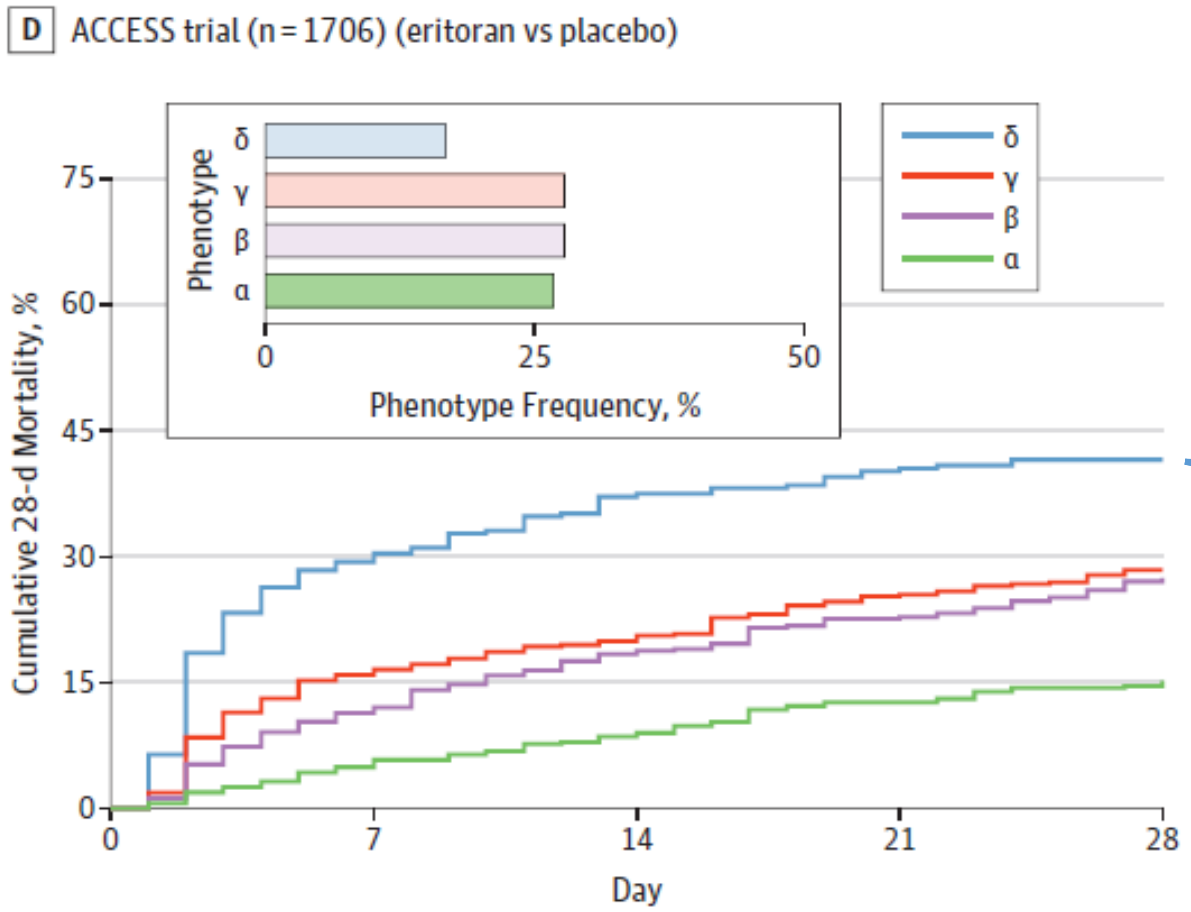
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

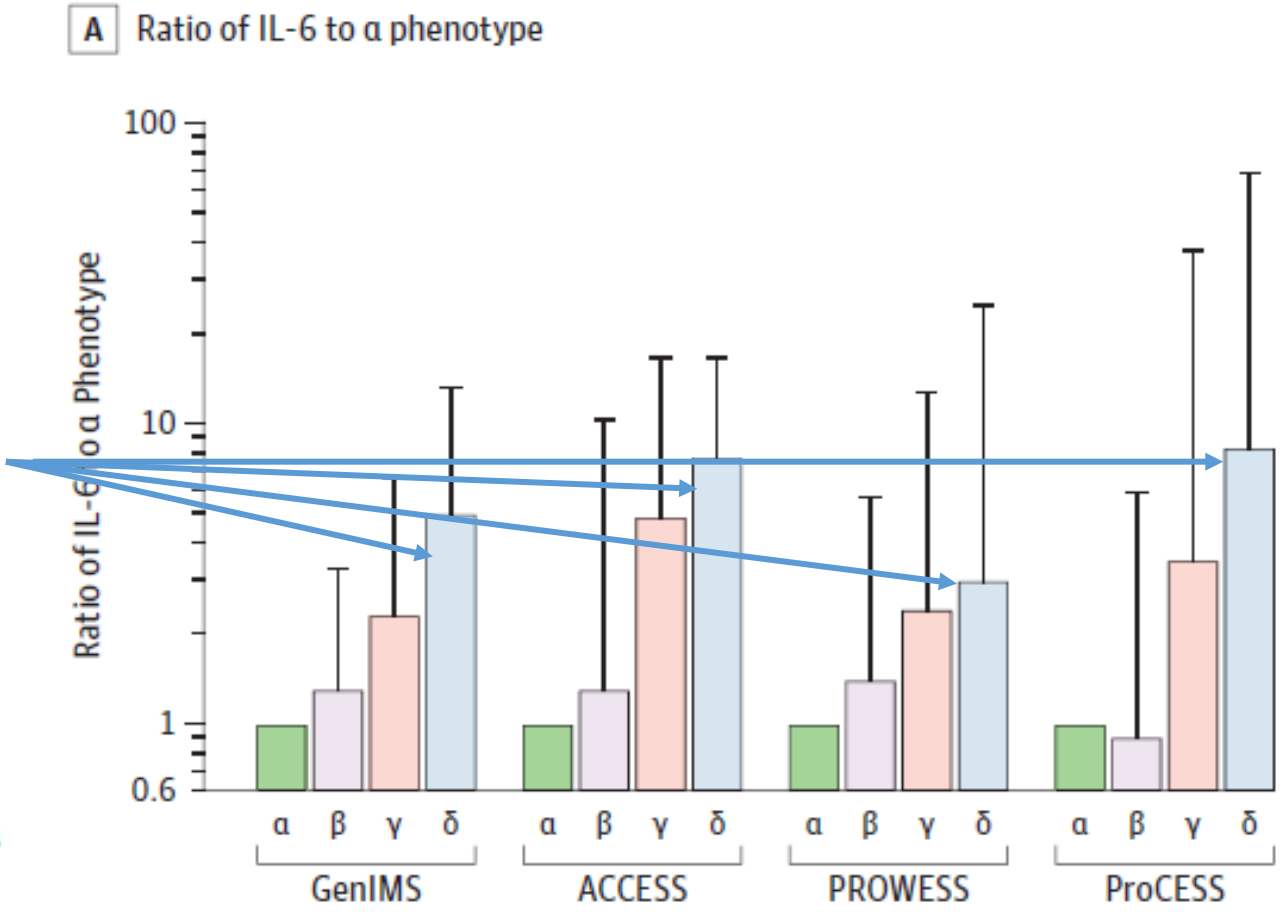
Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis

Christopher W. Seymour, MD, MSc; Jason N. Kennedy, MS; Shu Wang, MS; Chung-Chou H. Chang, PhD; Corrine F. Elliott, MS; Zhongying Xu, MS; Scott Berry, PhD; Gilles Clermont, MD, MSc; Gregory Cooper, MD, PhD; Hernando Gomez, MD, MPH; David T. Huang, MD, MPH; John A. Kellum, MD, FACP, MCCM; Qi Mi, PhD; Steven M. Opal, MD; Victor Talisa, MS; Tom van der Poll, MD, PhD; Shyam Visweswaran, MD, PhD; Yoram Vodovotz, PhD; Jeremy C. Weiss, MD, PhD; Donald M. Yealy, MD, FACEP; Sachin Yende, MD, MS; Derek C. Angus, MD, MPH

4 sepsis phenotypes identified: α, β, γ, δ.

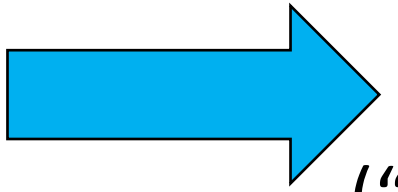
Higher Circulating IL-6 Correlates with Higher Mortality





What has been changing in Trials??

Blocking
(Hyperinflammation)



Boosting
("Immunosuppression")

All Patients

All & Selected Patients

Classical RCT

Adaptive RCT

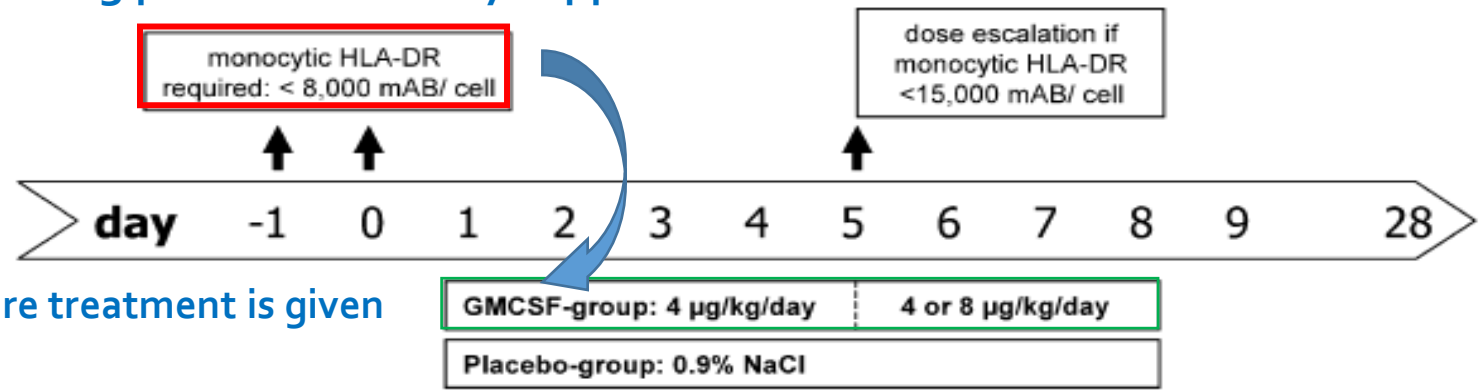
The first biomarker-based immuno-stimulatory trial (2009)

Granulocyte–Macrophage Colony-stimulating Factor to Reverse Sepsis-associated Immunosuppression

A Double-Blind, Randomized, Placebo-controlled Multicenter Trial

Christian Meisel[1]*, Joerg C. Schefold[2]*, Rene Pschowski[2], Tycho Baumann[1], Katrin Hetzger[1], Jan Gregor[3], Steffen Weber-Carstens[4], Dietrich Hasper[2], Didier Keh[4], Heidrun Zuckermann[3], Petra Reinke[2,5], and Hans-Dieter Volk[1,5]

confirming patients are really suppressed



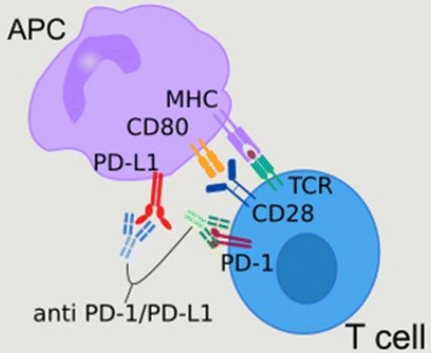
Treatment restored monocytic immunocompetence & improved clinical endpoints (ventilation-free days, APACHE II)

Biomarker-guided Treatment Sepsis Trials

Immune cells	Markers and cut-off value	Intervention	Number of patients (to be enrolled)	Reference /Clinicaltrials.gov identifier
Monocytes	HLA-DR expression < 8000 ABs/cell	GM-CSF	38	[97]
	HLA-DR expression < 8000 ABs/cell at day 3	GM-CSF	166 *	NCT02361528
	HLA-DR MFI < 150 for 48 hours	GM-CSF	9	[96]
	HLA-DR positive monocytes < 30%	IFNγ	9 278 *	[92] NCT03332225
	LPS-stimulated TNFα production < 160 pg/mL	GM-CSF	14	[98]
Lymphocytes	< 0.9 *10^9 lymphocytes/L	IL-7	27	[104]
Neutrophils	Phagocytic capacity < 50%	GM-CSF	64 *	NCT01653665

Niklas Bruse, Guus P. Leijte, Peter Pickkers & Matthijs Kox (2018) EXPERT REVIEW OF CLINICAL IMMUNOLOGY

Blocking wth Nivolumab/BMS-936559



T cell exhaustion reversed*

↓

Immunosuppression reduced

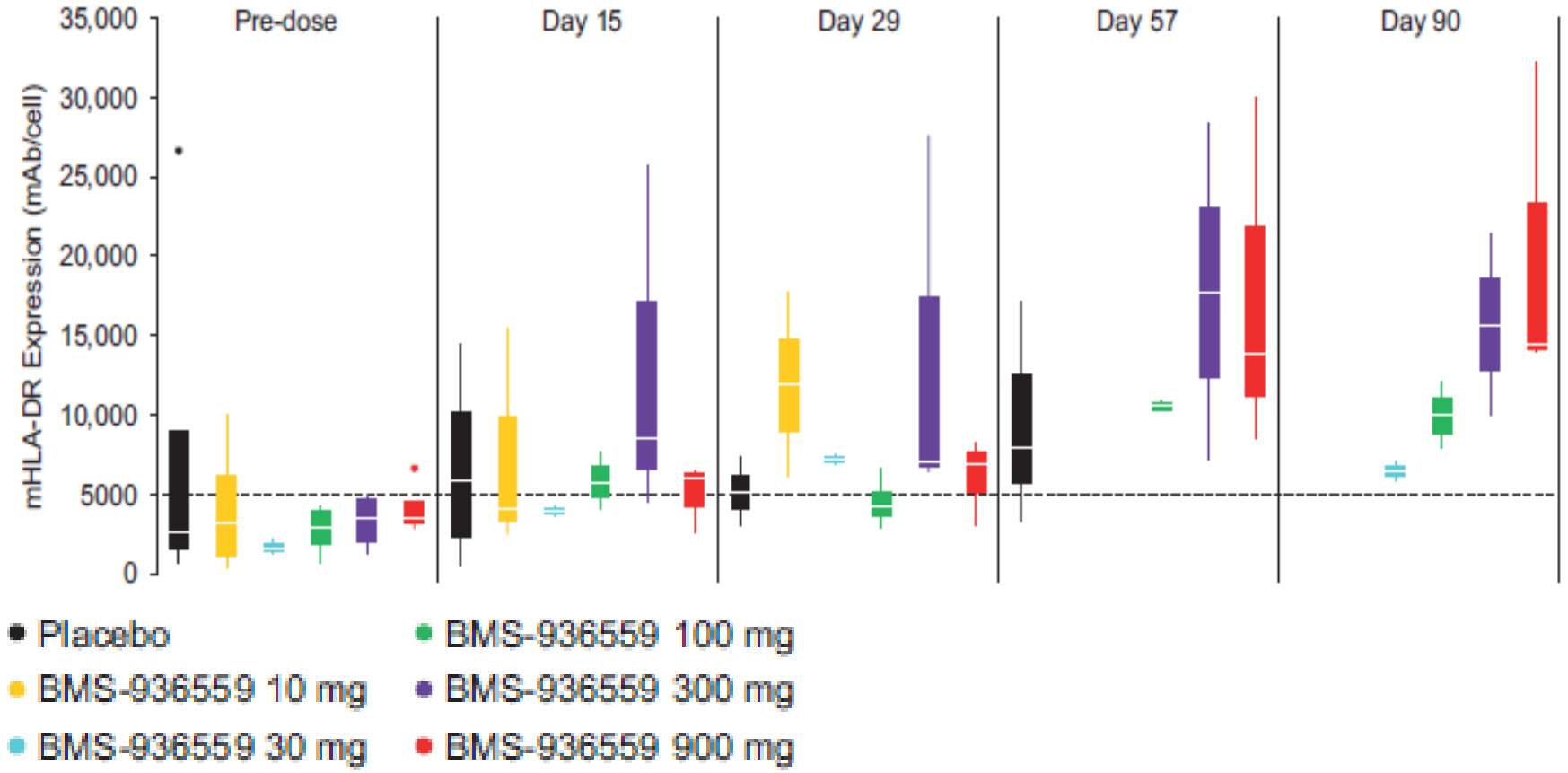
↓

Outcome?

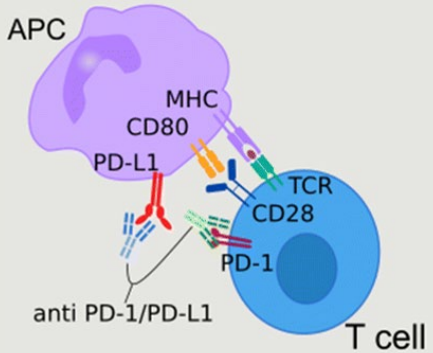
Immune Checkpoint Inhibition in Sepsis: A Phase 1b Randomized, Placebo-Controlled, Single Ascending Dose Study of Antiprogrammed Cell Death-Ligand 1 (BMS-936559)

Crit Care Med. 2019

Richard S. Hotchkiss, MD[1]; Elizabeth Colston, MD, PhD[2]; Sachin Yende, MD[3,4]; Derek C. Angus, MD, MPH[4]; Lyle L. Moldawer, PhD[5]; Elliott D. Crouser, MD[6]; Greg S. Martin, MD, MSc, FCCM[7]; Craig M. Coopersmith, MD[8]; Scott Brakenridge, MD, MSCS[5]; Florian B. Mayr, MD, MPH[3,4]; Pauline K. Park, MD[9]; June Ye, PhD[2]; Ian M. Catlett, PhD[2]; Ihab G. Girgis, PhD[2]; Dennis M. Grasela, PharmD, PhD[2]



Blocking wth Nivolumab/BMS-936559



T cell exhaustion reversed*

↓

Immunosuppression reduced

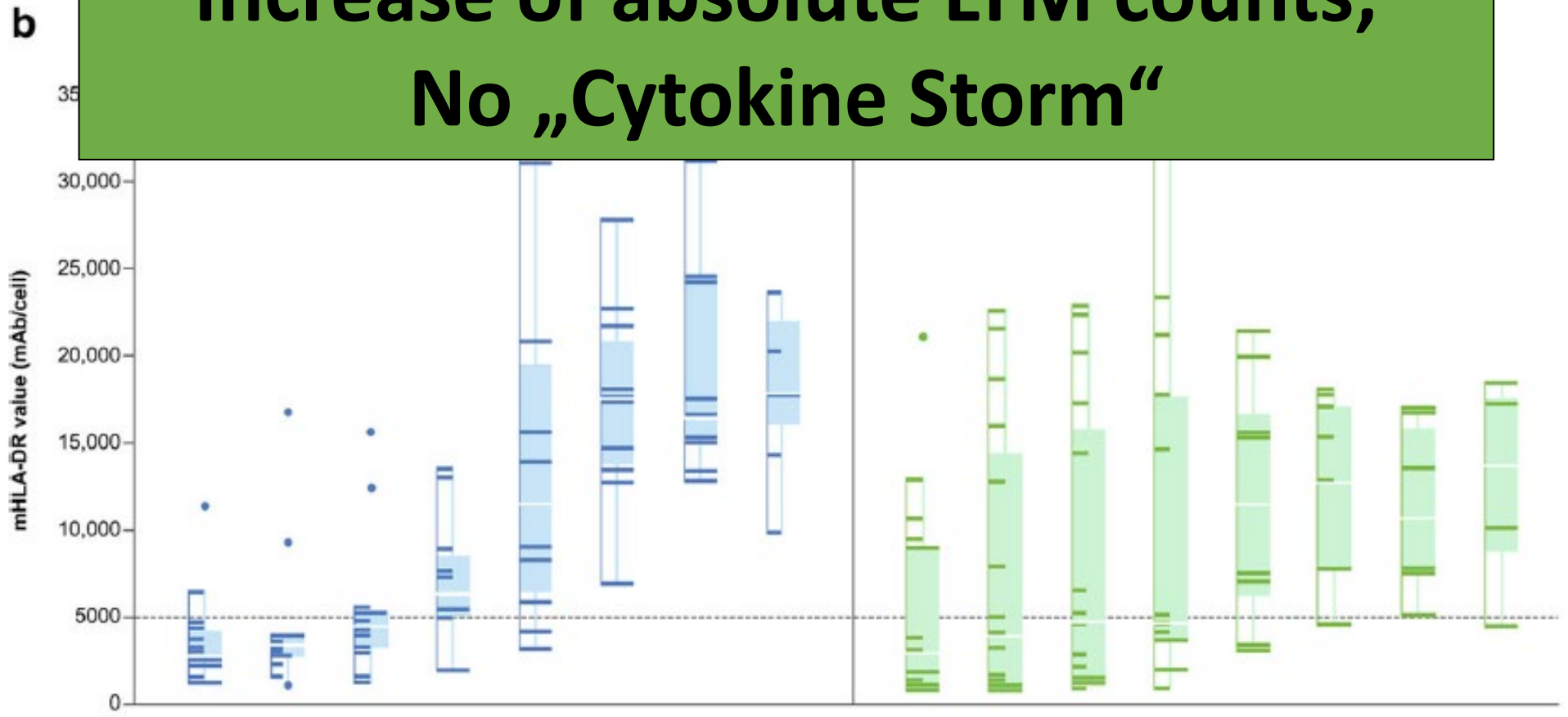
↓

Outcome?

Intensive Care Med. 2019 October ; 45(10): 1360–1371. doi:10.1007/s00134-019-05704-z.

Immune checkpoint inhibition in sepsis: a Phase 1b randomized study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of nivolumab

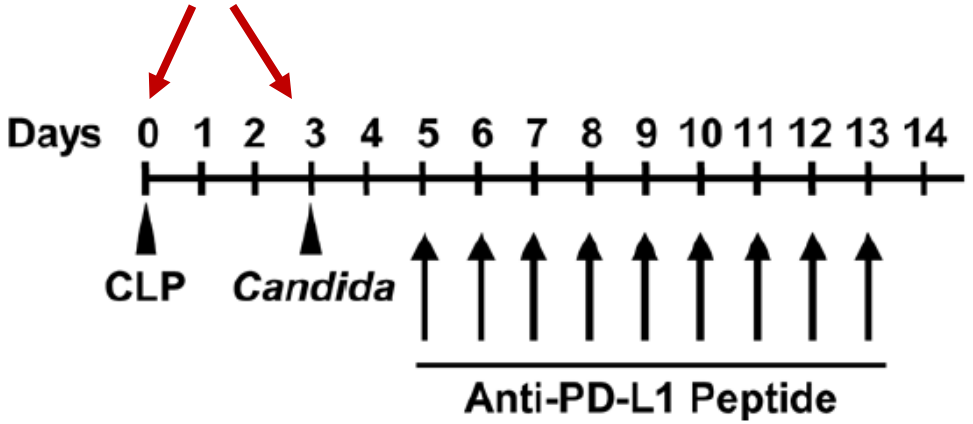
Restoration of HLA-DR on Monocytes;
Increase of absolute LYM counts;
No „Cytokine Storm“

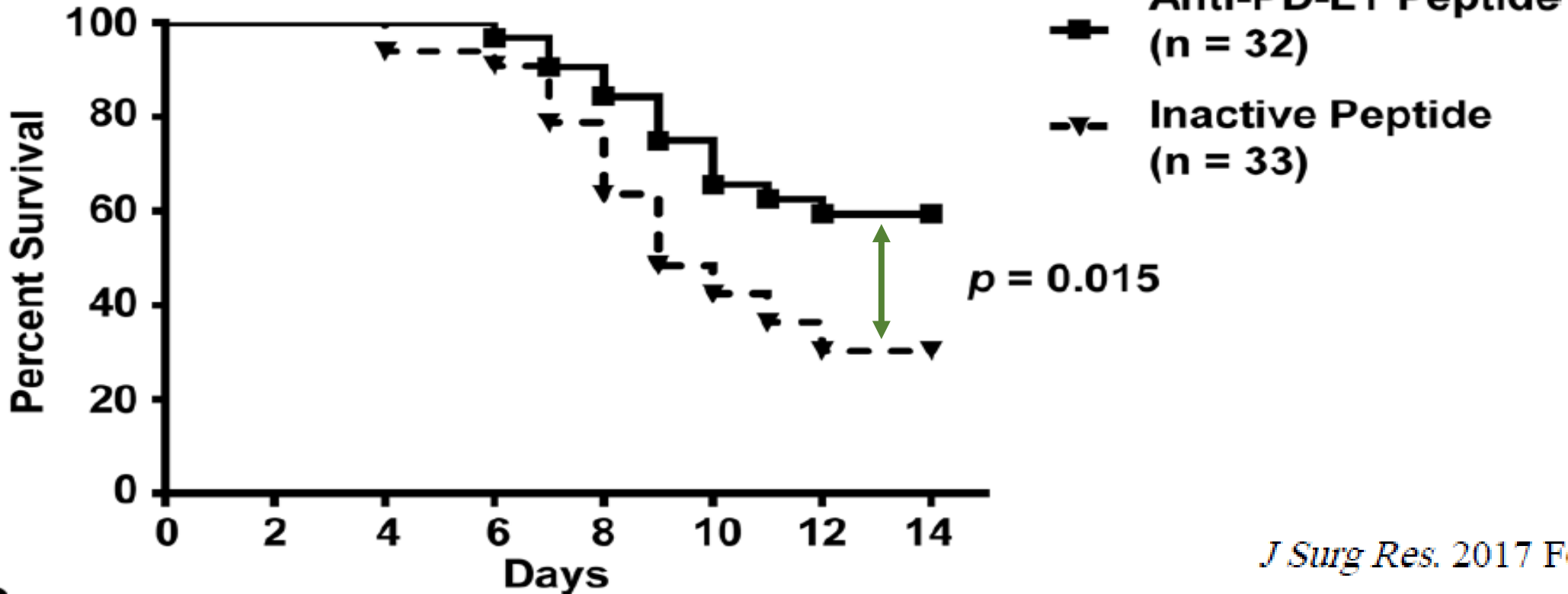


Double-hit Sepsis Model

Anti-Programed Cell Death Ligand 1 Peptide Improves Survival in Sepsis

Yuichiro Shindo, MD[1,2,3], Jacquelyn S. McDonough, B.S.[1], Katherine C. Chang, PhD[1], Murali Ramachandra, PhD[4], Pottayil G. Sasikumar, PhD[4], and Richard S. Hotchkiss, MD[5]

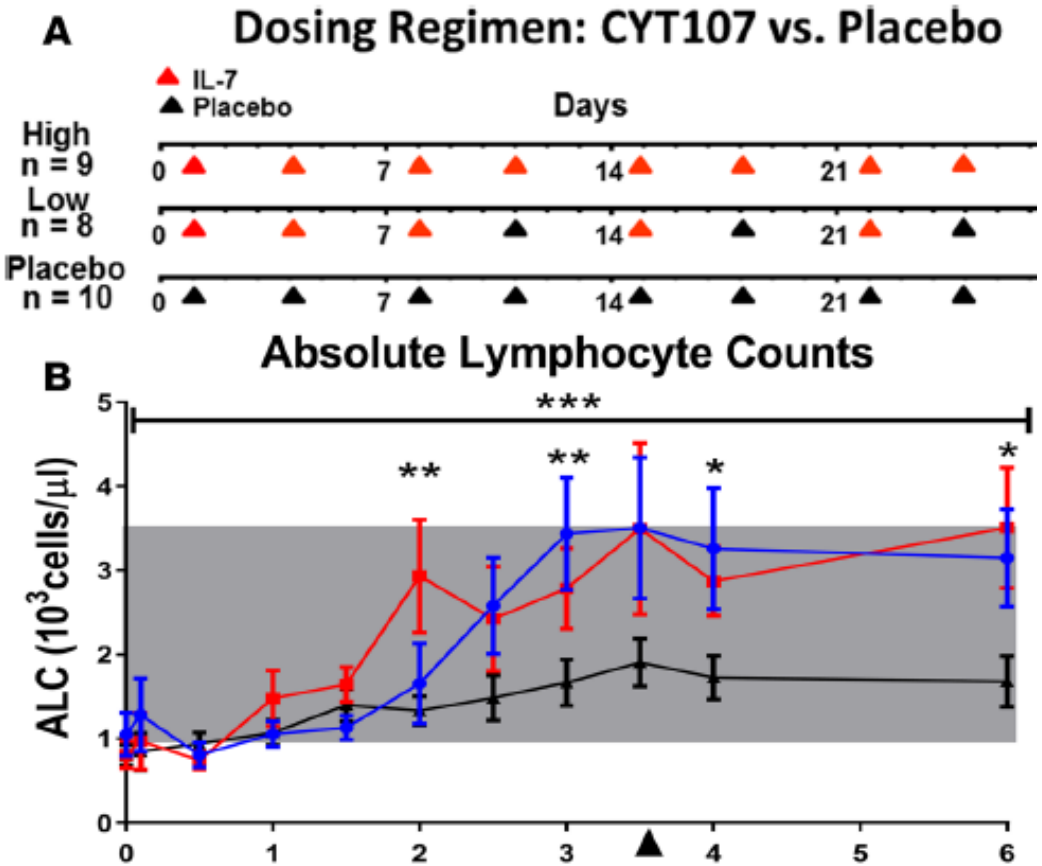


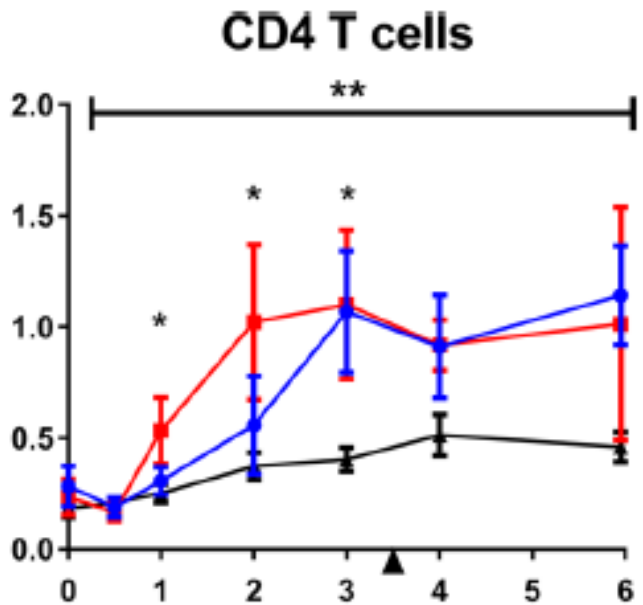


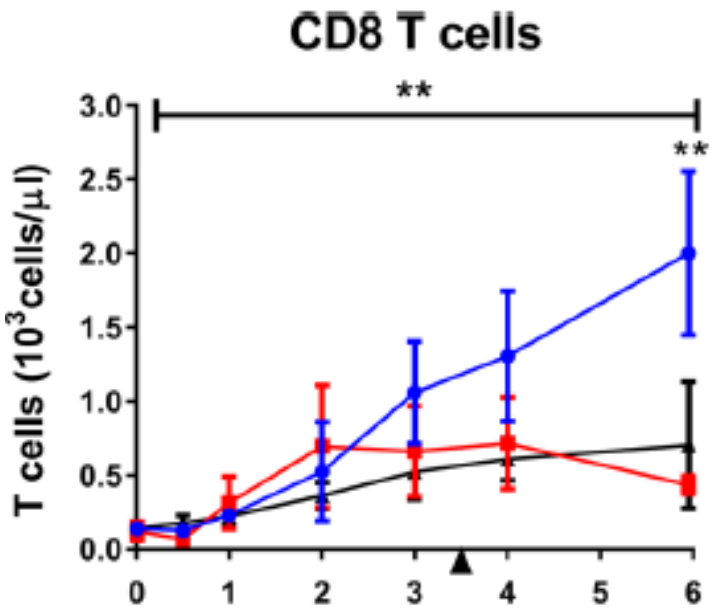
J Surg Res. 2017 February ; 208: 33–39.

Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial

Bruno Francois,[1,2,3] Robin Jeannet,[2] Thomas Daix,[1,2] Andrew H. Walton,[4] Matthew S. Shotwell,[5] Jacqueline Unsinger,[4] Guillaume Monneret,[6,7] Thomas Rimmelé,[7,8] Teresa Blood,[4] Michel Morre,[9] Anne Gregoire,[9] Gail A. Mayo,[10] Jane Blood,[4] Scott K. Durum,[11] Edward R. Sherwood,[10,12] and Richard S. Hotchkiss[4,13,14]



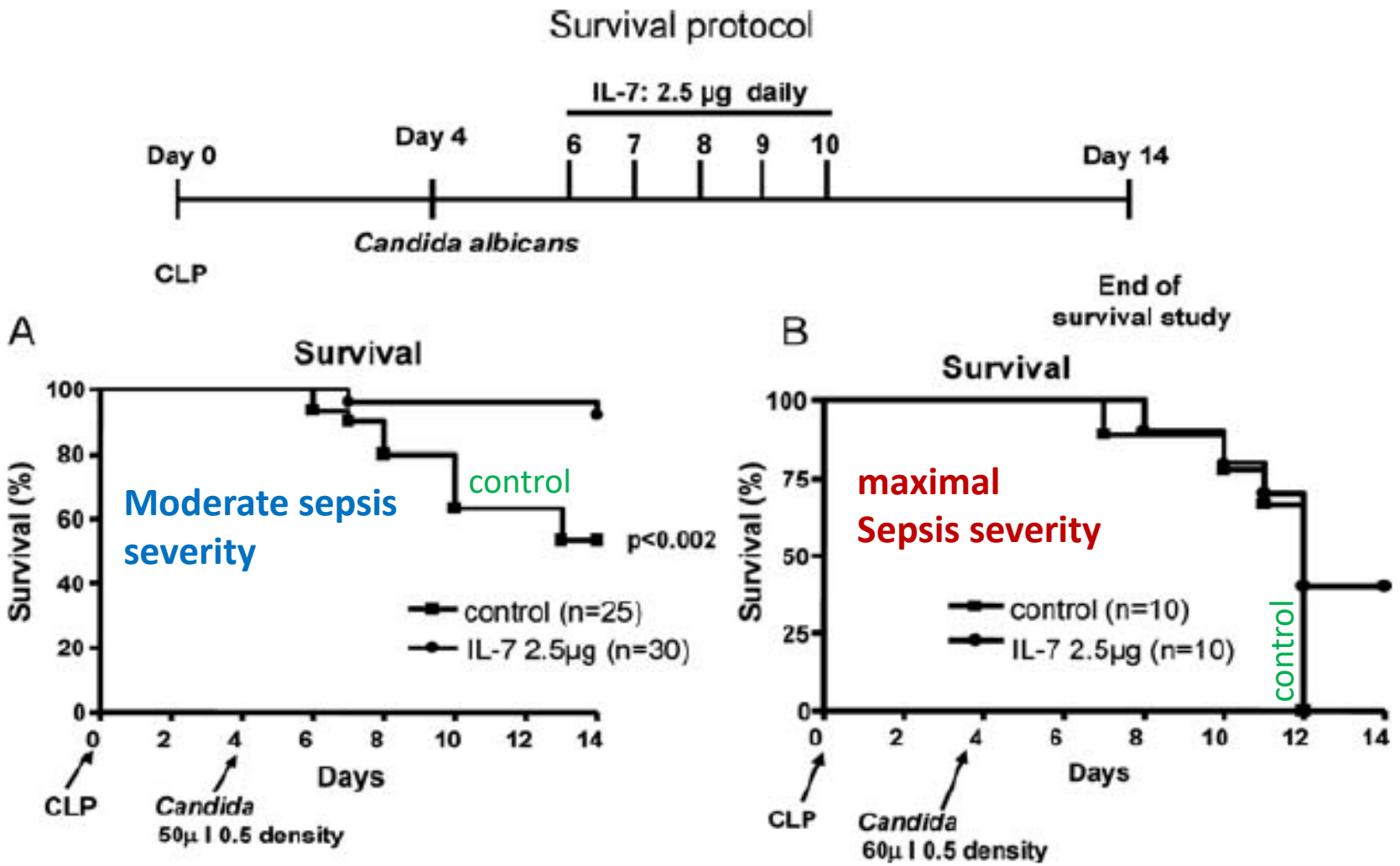




JCI Insight. 2018;3(5):e98960.

Interleukin-7 Ameliorates Immune Dysfunction and Improves Survival in a 2-Hit Model of Fungal Sepsis

Jacqueline Unsinger,[1] Carey-Ann D. Burnham,[2] Jacquelyn McDonough,[1] Michel Morre,[3] Priya S. Prakash,[4] Charles C. Caldwell,[4] W. Michael Dunne, Jr.,[2] and Richard S. Hotchkiss[1,5,6]



EudraCT number 2017-002171-26
ClinicalTrials.gov NCT03332225

A PERSONALIZED RANDOMIZED TRIAL OF VALIDATION AND RESTORATION OF IMMUNE DYSFUNCTION IN SEVERE INFECTIONS AND SEPSIS
THE PROVIDE STUDY: DECEMBER 2017-

PATIENT TO BE ENROLLED

Identification/allocation based on:
↑Circulating ferritin & ↓HLA-DR expression (on CD14 monocytes)

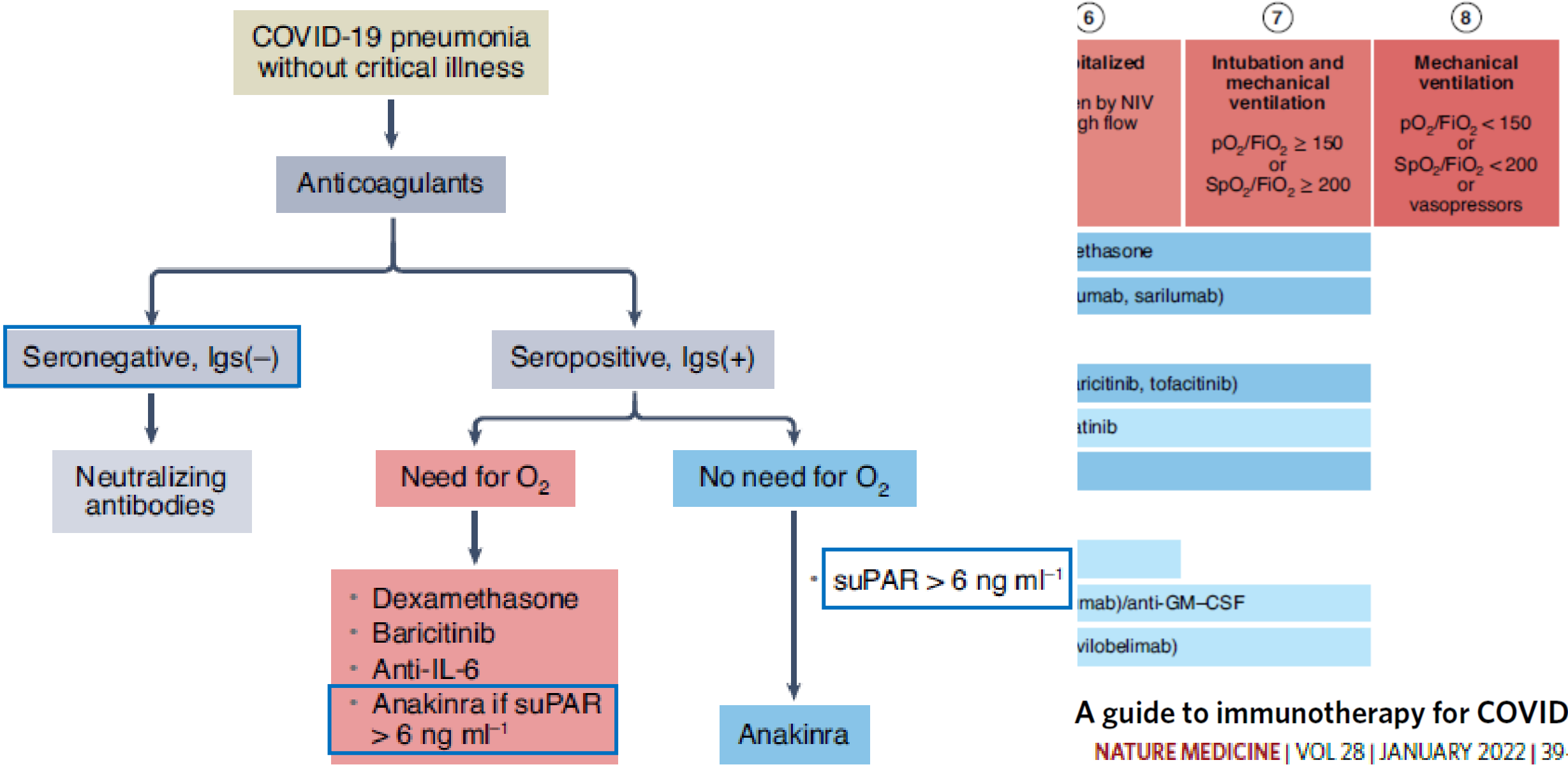
MACROPHAGE-ACTIVATION LIKE SYNDROME

Anakinra iv

HYPOINFLAMMATION

rhIFNγ sc

Immunomodulatory treatment options according to WHO Clinical Progression Score



A guide to immunotherapy for COVID-19

NATURE MEDICINE | VOL 28 | JANUARY 2022 | 39–50 |

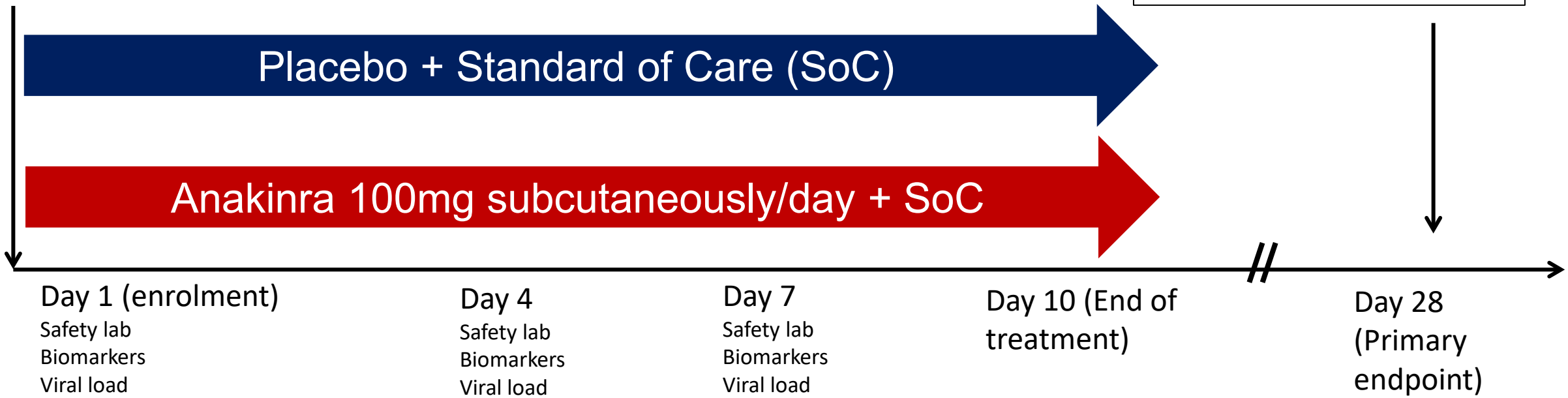
THE SAVE-MORE, PIVOTAL RCT

(Kyriazopoulou E, et al. *Nature Medicine* 2021; 27: 1752)

Inclusion criteria

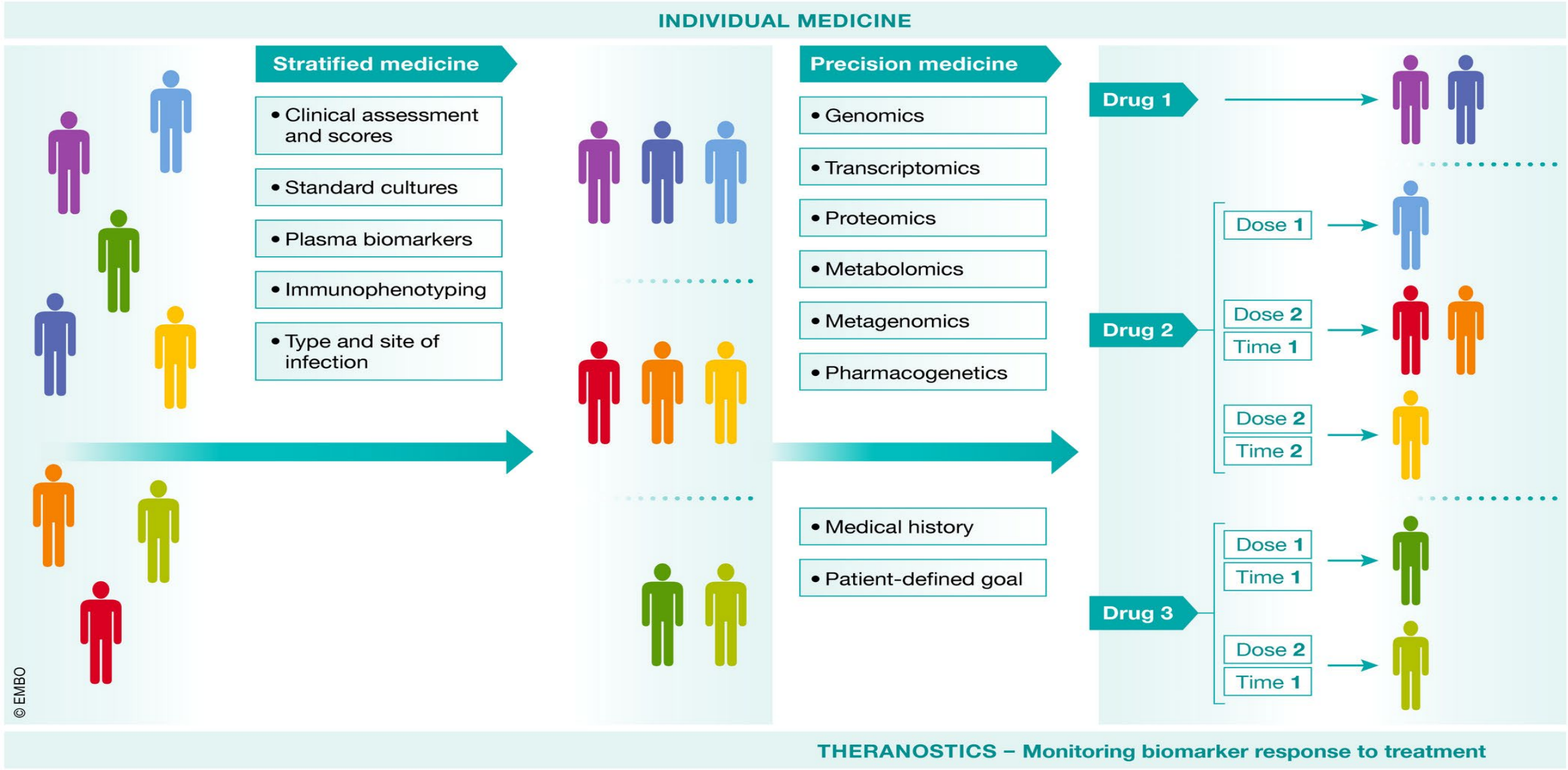
- Age ≥18 years, both genders, ICF
- Confirmed SARS-CoV-2 infection
- LRTI: positive chest-X-ray or CT
- **Plasma suPAR ≥6ng/ml**

PRIMARY ENDPOINT
11-point WHO ordinal scale



CT: computed tomography
ICF: written informed consent form
LRTI: lower respiratory tract infection
SOC: standard-of-care
suPAR: soluble urokinase Plasminogen Activator Receptor

Sepsis therapies: learning from 30 years of failure of translational research to propose new… leads



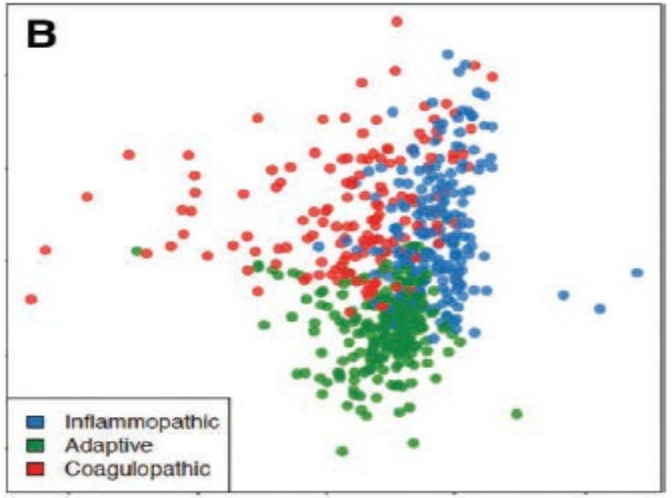
EMBO Mol Med, Volume: 12, Issue: 4, First published: 16 March 2020, DOI: (10.15252/emmm.201810128)

Critical Care Medicine 2018

Unsupervised Analysis of Transcriptomics in Bacterial Sepsis Across Multiple Datasets Reveals Three Robust Clusters

Timothy E. Sweeney, MD, PhD[1,2]; Tej D. Azad[1,2]; Michele Donato, PhD[1,2]; Winston A. Haynes[1,2]; Thanneer M. Perumal, PhD[3]; Ricardo Henao, PhD[4,5]; Jesús F. Bermejo-Martin, MD, PhD[6]; Raquel Almansa, PhD[6]; Eduardo Tamayo, MD, PhD[6]; Judith A. Howrylak, MD[7]; Augustine Choi, MD[8]; Grant P. Parnell, PhD[9]; Benjamin Tang, MD[9–12]; Marshall Nichols, MS[4]; Christopher W. Woods, MD[4,13,14]; Geoffrey S. Ginsburg, MD, PhD[4]; Stephen F. Kingsmore, MD, DSc[15]; Larsson Omberg, PhD[3]; Lara M. Mangravite, PhD[3]; Hector R. Wong, MD[16,17]; Ephraim L. Tsalik, MD[4,13,14]; Raymond J. Langley, PhD[18]; Purvesh Khatri, PhD[1,2]

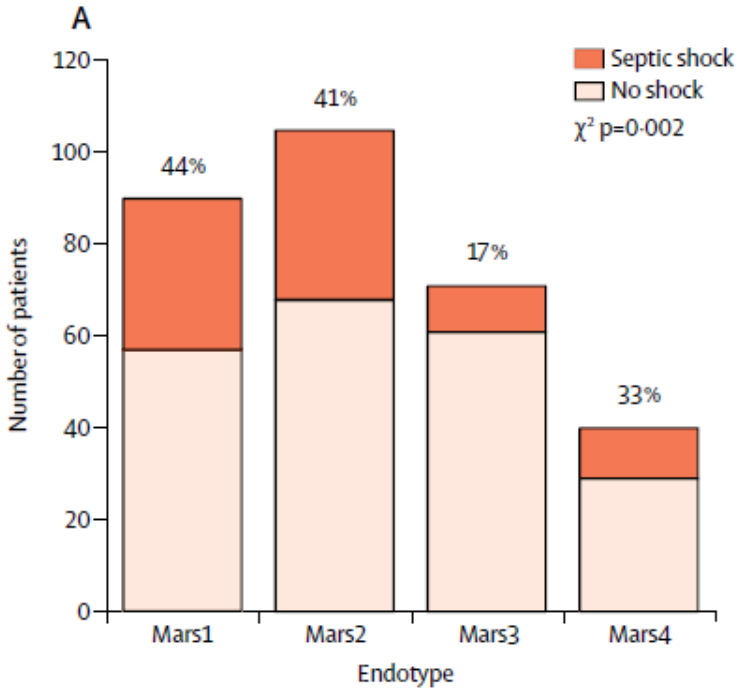
3 clusters identified



Lancet Respir Med 2017

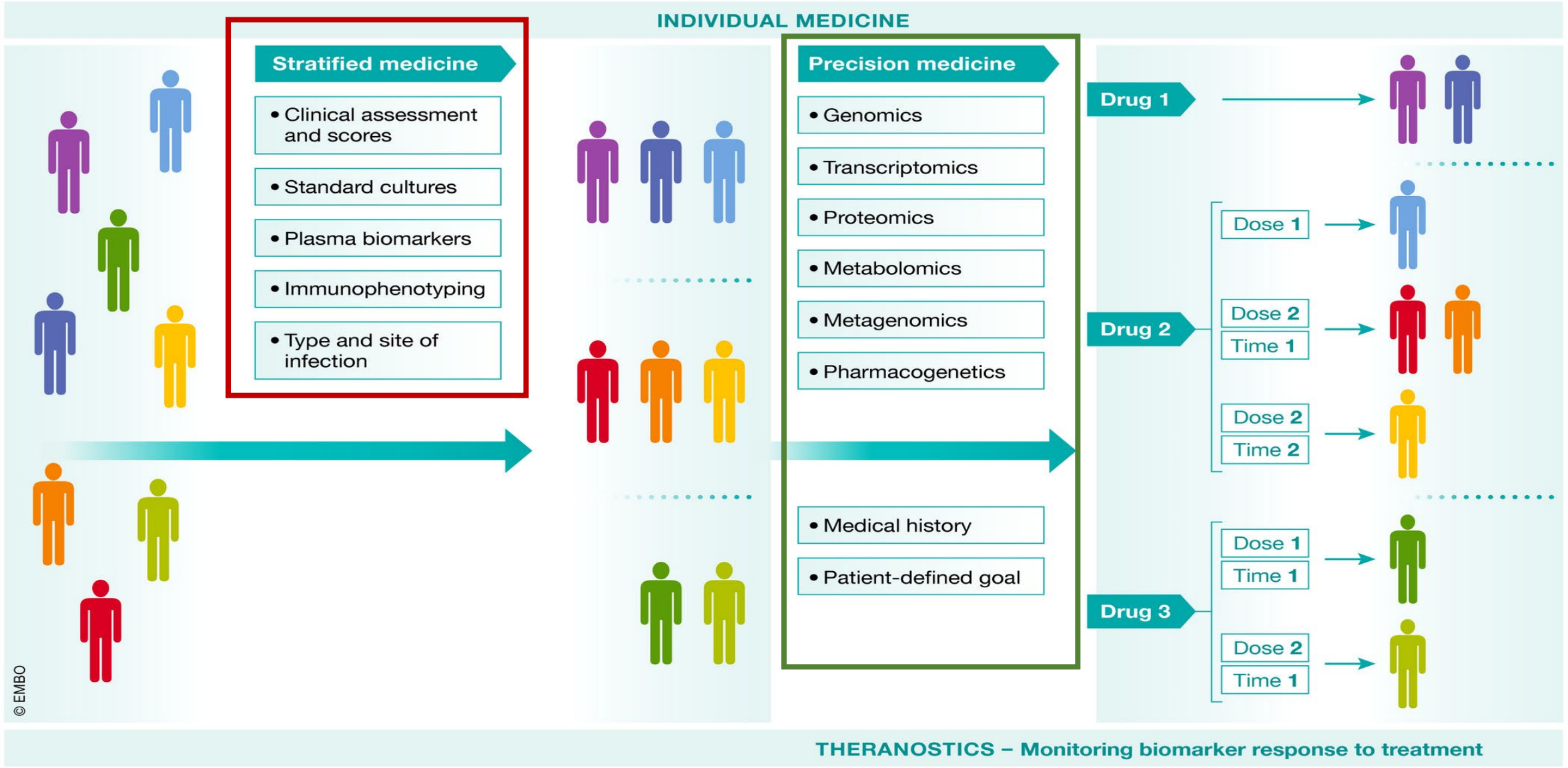
Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study

*Brendon P Scicluna, Lonneke A van Vught, Aeilko H Zwinderman, Maryse A Wiewel, Emma E Davenport, Katie L Burnham, Peter Nürnberg, Marcus J Schultz, Janneke Horn, Olaf L Cremer, Marc J Bonten, Charles J Hinds, Hector R Wong, Julian C Knight, Tom van der Poll, on behalf of the MARS consortium**



4 endotypes identified

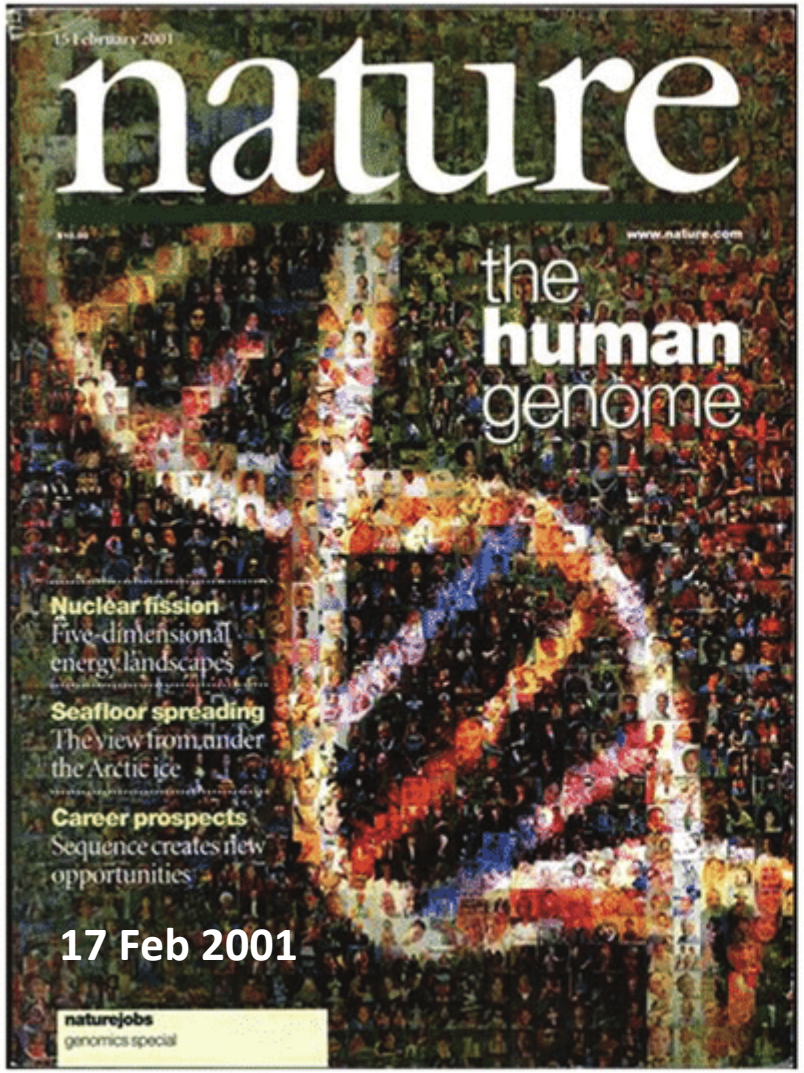
Sepsis therapies: learning from 30 years of failure of translational research to propose new… leads

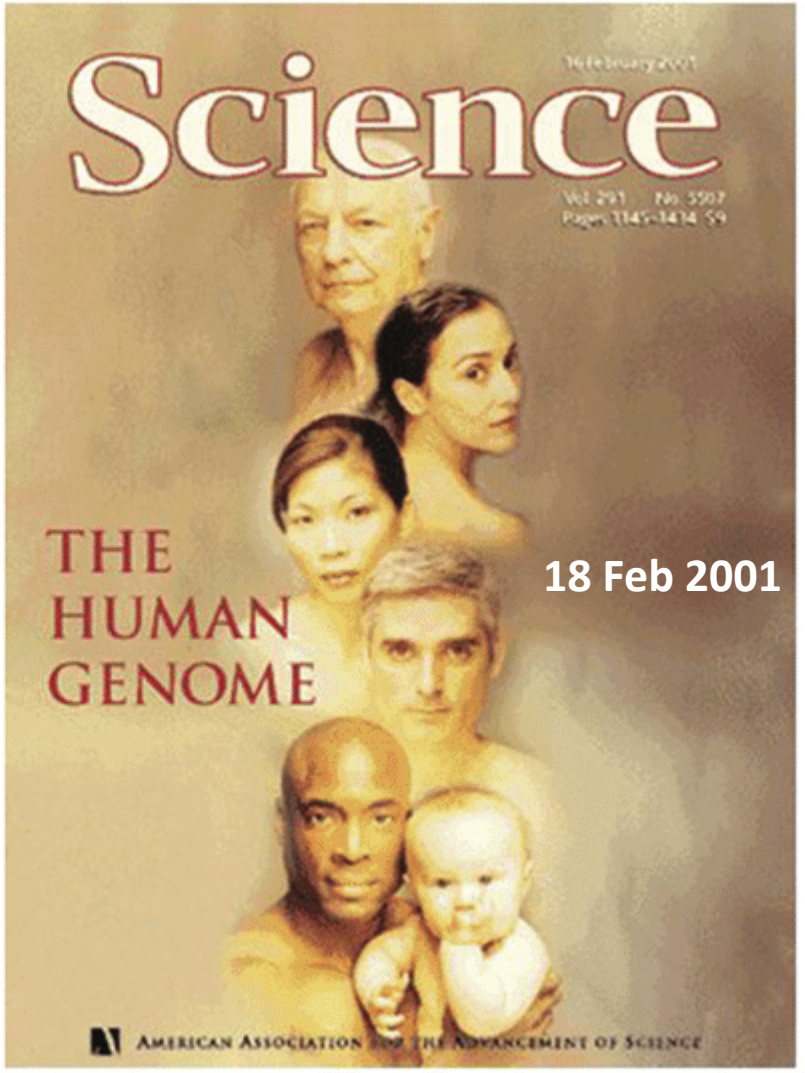


EMBO Mol Med, Volume: 12, Issue: 4, First published: 16 March 2020, DOI: (10.15252/emmm.201810128)

Human Genome Project

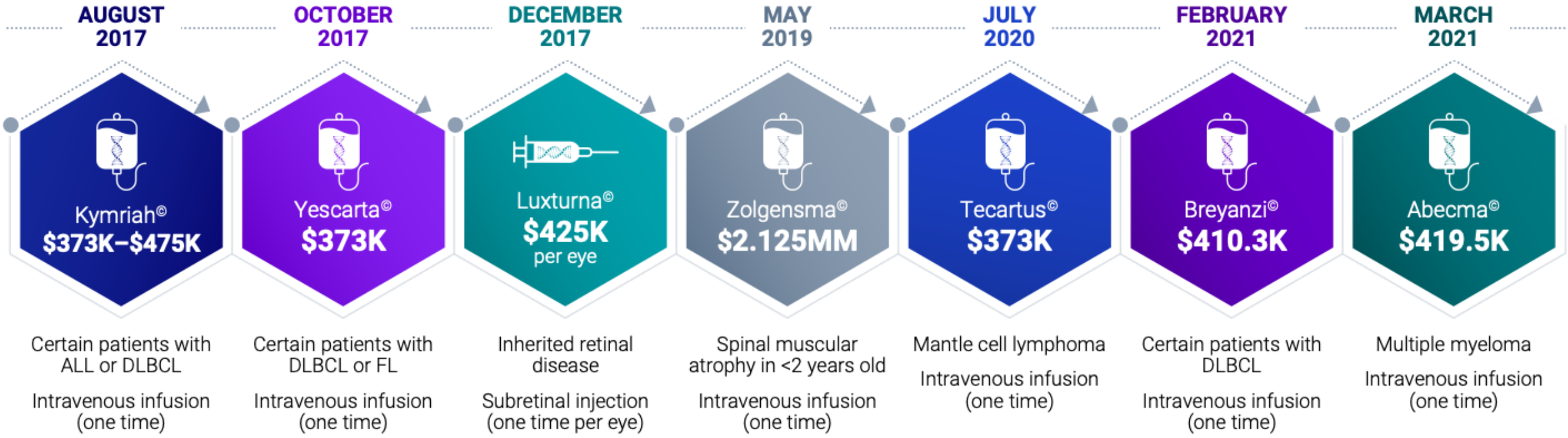
- initial analysis of the human genome sequence published in February 2001
- Successful completion announced on April 14, 2003





20 Years Later…

Current FDA approved gene therapies.



ALL: acute lymphoblastic leukemia; **DLBCL:** Diffuse large B-cell lymphoma; **FL:** Follicular lymphoma;

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

truveris

Treating Sepsis:
A very narrow road into the Unknown…

30 Years Later…
No specific anti-septic therapies


Thanks
Thanks
Thanks
Thanks

LUDWIG BOLTZMANN INSTITUT
Traumatologie
Das Forschungszentrum in Kooperation mit der AUVA

AUVA

LUDWIG BOLTZMANN GESELLSCHAFT

2021 WEB - CONFERENCE OF THE EUROPEAN SHOCK SOCIETY

XIXth Congress of ESS

FRIDAY 5 & SATURDAY 6 NOVEMBER 2021

www.ESSwebconference2021.com

Past ESS President

Evangelos J. Giamarellos-Bourboulis

New ESS President

Marcin Osuchowski


EUROPEAN SHOCK SOCIETY
ESS
1983
20th
Congress
September 21-23, 2023
STUDII SAPIENTIAE VIENNENSIS
University of Vienna

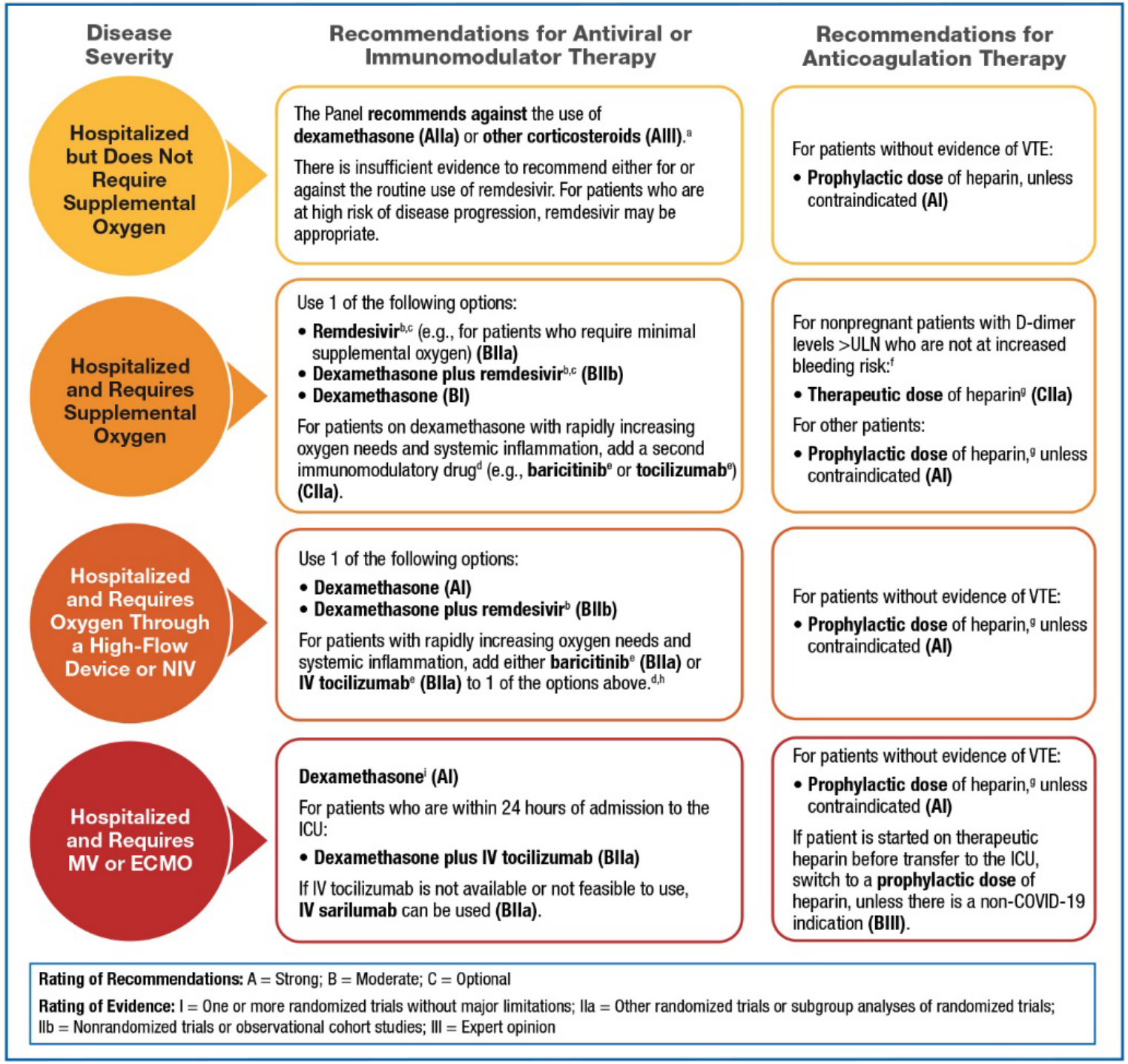


Figure 2. Therapeutic M
COVID-19 Based on Dis

Safety and Efficacy of Polymyxin B Hemoperfusion (PMX) for Septic Shock (EUPHRATES) – started 2010

(removal of endotoxin from circulation)

ClinicalTrials.gov Identifier:
NCT01046669
Sponsor:
Spectral Diagnostics (US) Inc.

Inclusion Criteria:
Hypotension requiring vasopressor support
The subject must have received intravenous fluid resuscitation
Documented or suspected infection
Endotoxin Activity Assay ≥ 0.60 EAA units
Evidence of at least 1 new onset organ dysfunction

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level

The EUPHRATES Randomized Clinical Trial

, MD, MBA;

Key Points

Question Does polymyxin B hemoperfusion improve survival in patients with septic shock and high levels of endotoxin in the blood?

Findings In this multicenter, randomized, clinical trial that included 450 adults with septic shock and high circulating endotoxin activity, polymyxin B hemoperfusion compared with sham hemoperfusion did not significantly decrease 28-day mortality, 37.7% vs 34.5%, respectively.

Meaning Polymyxin B hemoperfusion was not effective in reducing mortality in septic shock.

NATURE COMMUNICATIONS | (2018)9:694 | DOI: 10.1038/s41467-018-03078-2 | www.nature.com/naturecommunications

A community approach to mortality prediction in sepsis via gene expression analysis

Timothy E. Sweeney[1,2,25], Thanneer M. Perumal[3], Ricardo Henao[4,5], Marshall Nichols[4], Judith A. Howrylak[6], Augustine M. Choi[7], Jesús F. Bermejo-Martin[8], Raquel Almansa[8], Eduardo Tamayo[8], Emma E. Davenport[9,10,11], Katie L. Burnham[12], Charles J. Hinds[13], Julian C. Knight[12], Christopher W. Woods[4,14,15], Stephen F. Kingsmore[16], Geoffrey S. Ginsburg[4], Hector R. Wong[17,18], Grant P. Parnell[19], Benjamin Tang[19,20,21,22], Lyle L. Moldawer[23], Frederick E. Moore[23], Larsson Omberg[3], Purvesh Khatri[1,2], Ephraim L. Tsalik[4,14,15], Lara M. Mangravite[3] & Raymond J. Langley[24]

Lancet Respir Med 2016;

Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study

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Are mice really so bad?! Should we just quit it?!?

Table 1. Selected mouse-to-human translantional examples (26 listed)

No.	Translational phenomenon/response	Specific comments: mouse	Specific comments: human
1	Antibodies to TNF given indiscriminately fail to reduce sepsis mortality	BALB/c mice were pretreated with antibodies to TNF prior to CLP sepsis. The murine studies were published 3 y before the failed human trials (101, 116)	Anti-TNF antibodies failed to be an effective treatment strategy in a general population of septic patients (117, 118)
2	Pretreatment with an anti-TNF strategy prevents early systemic inflammatory response syndrome	Passive immunization with the antiserum to TNF-α in BALB/c mice protected them against the lethal hyperinflammation by *Escherichia coli* LPS (98)	Anti–TNF-α therapy was effective in humans with louse-borne relapsing fever when given as a pretreatment against Jarisch-Herxheimer reactions (119)
3	Low-dose steroid therapy is associated with decreased mortality in septic mice and humans	Demonstrated in C57BL/6 male mice subjected to CLP and treated with different corticoid concentrations; low but not high-dose steroids improved 21-d survival (120)	Early initiation of low-dose corticosteroid therapy decreased mortality in septic shock patients (121)
4	Regulation of chemotactic behavior of mouse and human neutrophils via purinergic signaling	Human and mouse neutrophils rely on same purinergic receptor subtypes (P2Y2, A3, and A2a receptors) for autocrine signaling (122–124)	Demonstrated *in vitro* and *in vivo*; mice are suitable to study chemotaxis in inflammation, trauma, and sepsis (122–124; NCT01180361*)
5	Human and mouse neutrophils rely on similar signaling mechanisms for their activation during bacteria-induced acute lung injury	Increased nuclear activation of NF-κB in pulmonary neutrophils of mice after *in vivo* administration with endotoxin (125, 126)	Increased nuclear accumulation of NF-κB in peripheral or pulmonary neutrophils of human volunteers after *in vitro* or *in vivo* stimulation with endotoxin (127) or in peripheral neutrophils of patients with sepsis (128)
6	Sepsis always in MARS: simultaneous systemic release of both proinflammatory and anti-inflammatory cytokines in sepsis	Demonstrated in ICR/CD-1 (outbred) female mice subjected to CLP sepsis (129, 130)	Demonstrated in septic shock patients (131) and patients with postoperative abdominal sepsis (132)
7	IL-6 serves as a biomarker for sepsis mortality	IL-6 measured 6 h after the onset of CLP sepsis in BALB/c (133) and CD-1 mice (129) accurately predicts survival	Patients with high levels of IL-6 are at increased risk of dying of sepsis (134, 135)
8	Role of nicotinic receptors in inflammatory responses after endotoxemia is similar in mice and humans	Demonstrated in C57BL/6 mice and α7 nicotinic receptor–deficient mice; endotoxin-induced response was abrogated via activation of anti-inflammatory cholinergic pathway (vagus nerve stimulation) (136)	Human volunteers were administered endotoxin and GTS-21 (α7nAChR agonist) or placebo to study anti-inflammatory effects of cholinergic pathway (137; NCT00783068*)
9	Similar mode of pathogen-associated molecular patterns detection via Toll-like receptors (TLRs) in mice and humans	TLR-4 was identified as the receptor that senses LPS in experiments with congenic sensitive (C3H/HeN; C57BL/10ScSn) and resistant (C3H/HeJ and C57BL/10ScCr) mice (138); TLR-4 expression level determines the degree of LPS-susceptibility in mice (139)	Human volunteers administered with LPS demonstrated altered TLR-induced genes expression (140). TLR-signaling pathways are strongly modulated in septic patients (141)
10	Sepsis induces profound apoptosis of immune and gastrointestinal epithelial (GIE) cells	Demonstrated in CLP female ND4 mice (142) and *Pseudomonas aeruginosa* pneumonia-induced septic FVB/N mice (143); apoptosis in B and T lymphocytes and dendritic cells. GIE cell apoptosis in large and small intestine	Demonstrated in patients who died of sepsis and sepsis and MODS; data obtained by retrospective (rapid autopsy) and prospective (tissue resection) examination (144–146)

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International Expert Consensus for Pre-Clinical Sepsis Studies

MINIMUM QUALITY THRESHOLD IN PRE-CLINICAL SEPSIS STUDIES (MQTiPSS): AN INTERNATIONAL EXPERT CONSENSUS INITIATIVE FOR IMPROVEMENT OF ANIMAL MODELING IN SEPSIS

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EXPERT OPINION

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