Intensive Care Med (2020) 46:1425–1437
https://doi.org/10.1007/s00134-020-06109-z

ORIGINAL

Nangibotide in patients with septic shock: a Phase 2a randomized controlled clinical trial

Bruno François[1*], Xavier Wittebole[2], Ricard Ferrer[3], Jean-Paul Mira[4], Thierry Dugernier[5], Sébastien Gibot[6,7], Marc Derive[8], Aurélie Olivier[8], Valérie Cuvier[8], Stephan Witte[9], Peter Pickkers[10], François Vandenhende[11], Jean-Jacques Garaud[8], Miguel Sánchez[12], Margarita Salcedo-Magguilli[8] and Pierre-François Laterre[2]

Mortality As a Measure of Treatment Effect in Clinical Trials Recruiting Critically Ill Patients*

Jan O. Friedrich, MD, PhD[1,2]
Michael O. Harhay, PhD[3]
Derek C. Angus, MD, MPH[4]
Karen E. A. Burns, MD, MSc[1,2]
Deborah J. Cook, MD, MSc[5]
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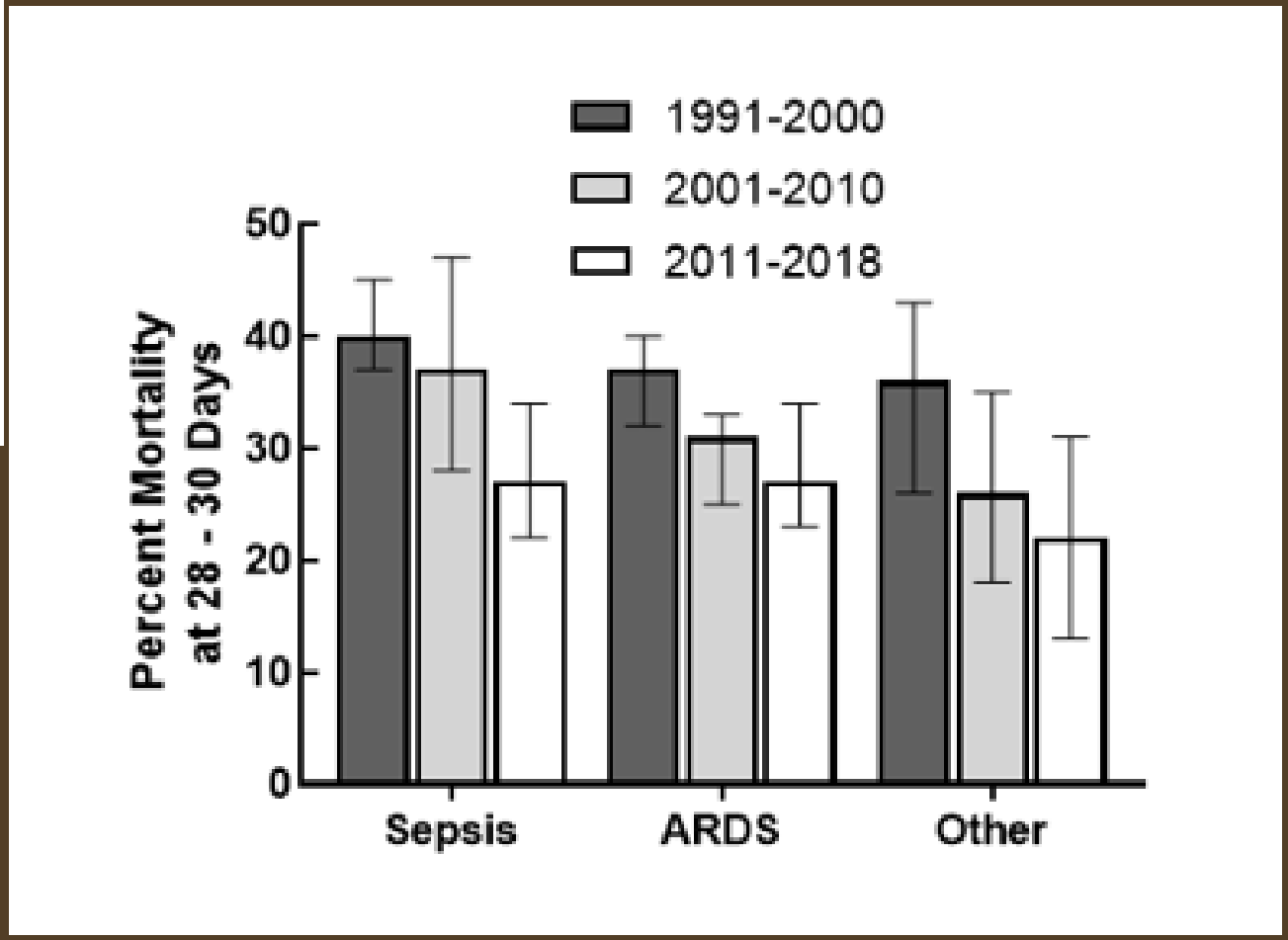
Simon Finfer, MD[7]
Paul Hébert, MD, MHSc[8]
Kathy Rowan, PhD[9]
Gordon Rubenfeld, MD, MSc[1,2,10]
John C. Marshall, MD[1,11]
in collaboration with the International Forum for Acute Care Trialists (InFACT)

Critical Care Medicine

Control group mortality over time

2018



343 clinical trials

Mortality As a Measure of Treatment Effect in Clinical Trials Recruiting Critically Ill Patients*

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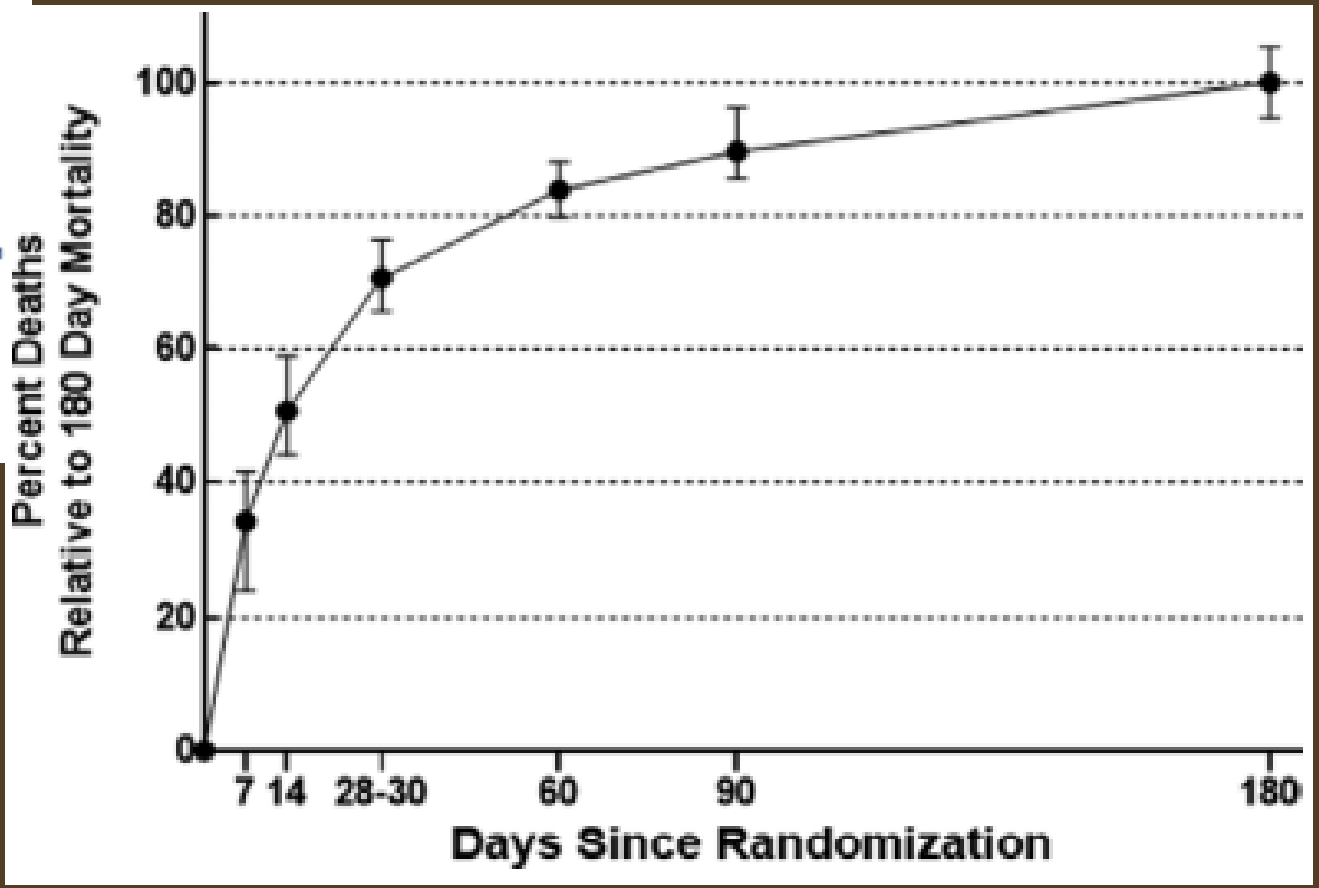
Critical Care Medicine

2018

Follow-up period



343 clinical trials

‘The secret in science is to ask the right question’

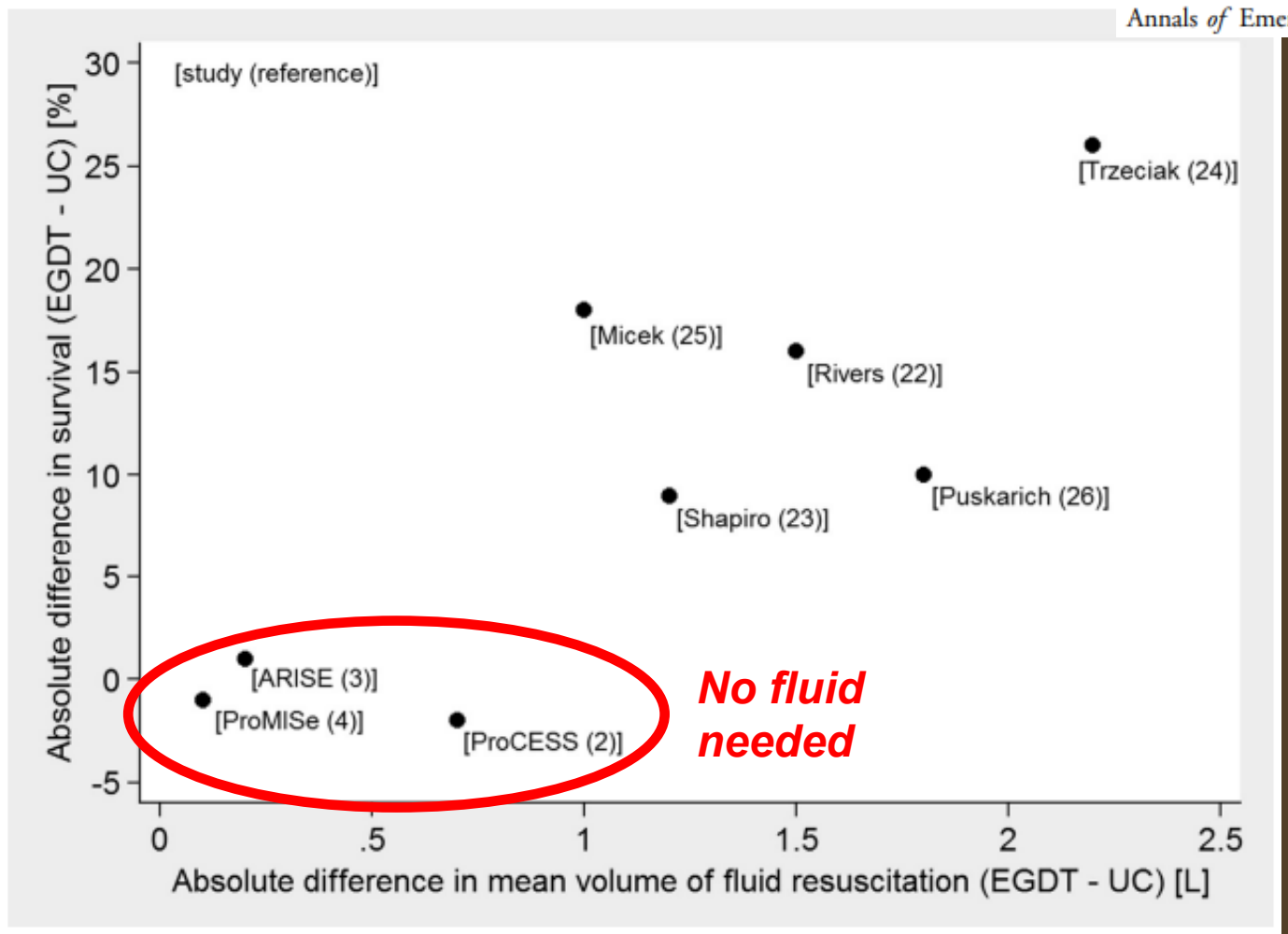
Sir Henry Tizard

(1885-1959)

Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial

2018

Wesley H. Self, MD, MPH*; Matthew W. Semler, MD, MSc; Rinaldo Bellomo, MBBS, MD; Samuel M. Brown, MD, MS; Bennett P. deBoisblanc, MD; Matthew C. Exline, MD; Adit A. Ginde, MD, MPH; Colin K. Grissom, MD; David R. Janz, MD, MSc; Alan E. Jones, MD; Kathleen D. Liu, MD; Stephen P. J. Macdonald, MB, ChB; Chadwick D. Miller, MD, MS; Pauline K. Park, MD; Lora A. Reineck, MD, MS; Todd W. Rice, MD, MSc; Jay S. Steingrub, MD; Daniel Talmor, MD; Donald M. Yealy, MD; Ivor S. Douglas, MD; Nathan I. Shapiro, MD, MPH; and the CLOVERS Protocol Committee and NHLBI Prevention and Early Treatment of Acute Lung Injury (PETAL) Network Investigators†



Intensive Care Med
DOI 10.1007/s00134-016-4482-5

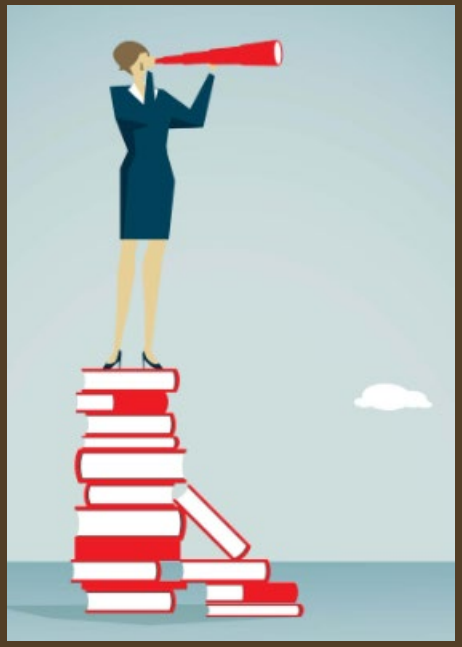
EDITORIAL

Improved survival in critically ill patients: are large RCTs more useful than personalized medicine? No

Jean-Louis Vincent*

2016 Nov;42(11):1778-1780

	Type of study/example	Hurdle(s)
Essential	New drug	Blinding sometimes difficult
	New technique	Blinding often impossible
	Fever control	Method used to lower body temperature (pharmacological, physical, etc)
	Glucose control	Monitoring technique (e.g., arterial blood vs. capillary sample)
	Blood transfusion	Decision not based only on hemoglobin levels
	Sepsis drugs	Great heterogeneity of patient populations
	Continuous vs intermittent RRT	Result different depending on the patient's condition
Avoidable	Two crystalloid solutions	Blood electrolytes should determine the choice of crystalloid fluids



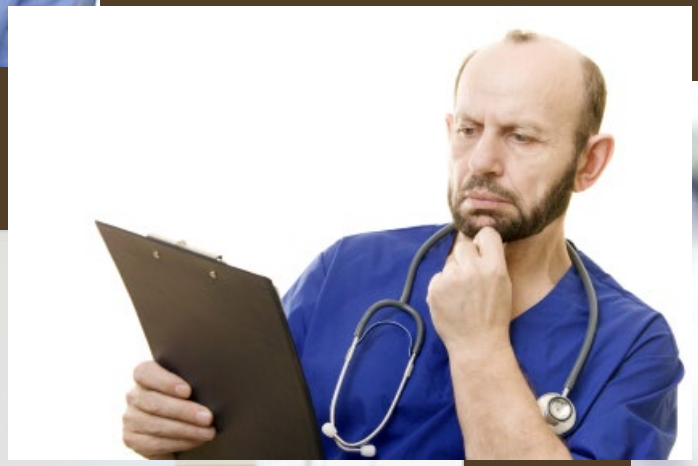
Hello !

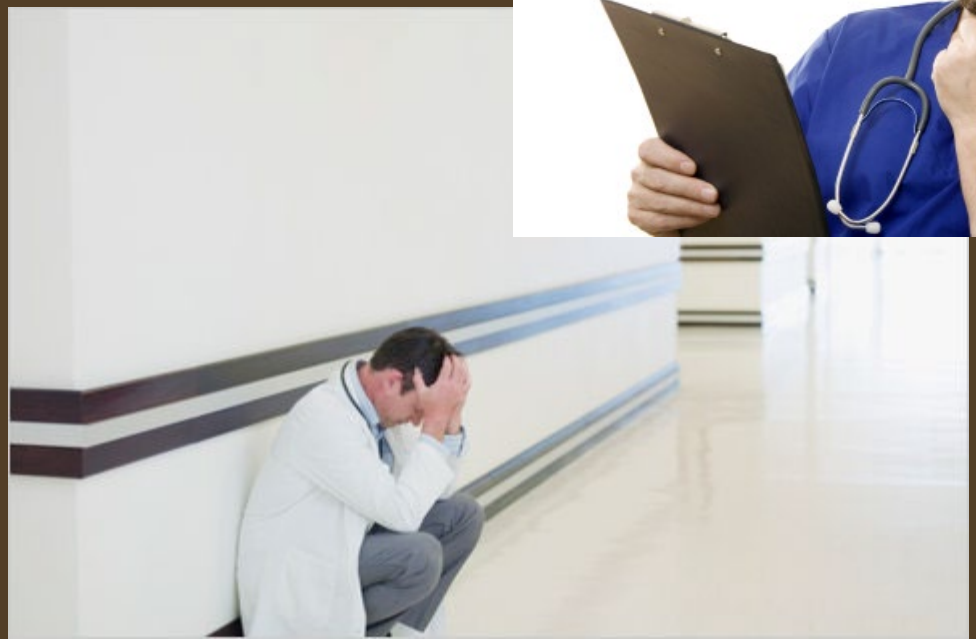
The future of clinical trials

Jean-Louis Vincent, MD, PhD
Professor of intensive care medicine
(University of Brussels)
Past-President, European Society of Intensive Care Medicine
Past-President, World Federation of Intensive and Critical Care Societies

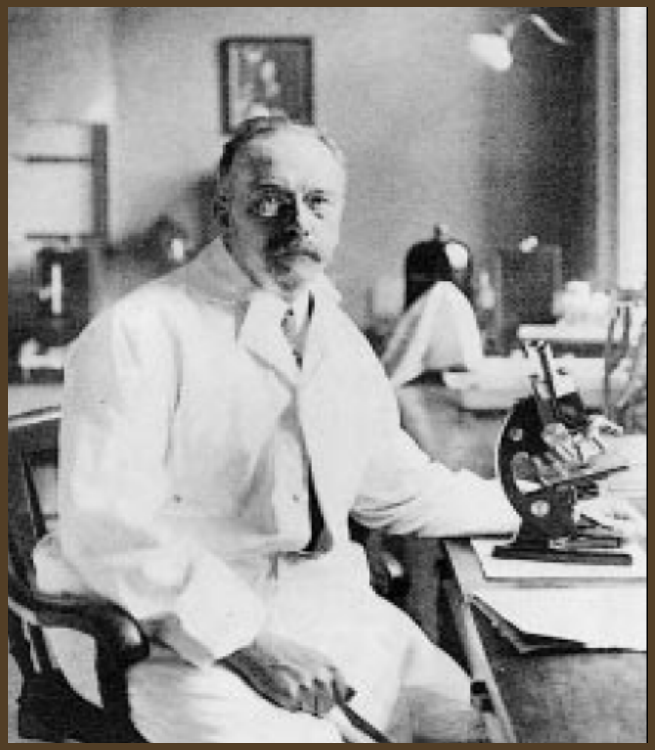
I KNOW HOW YOU FEEL …

depressed by all these negative prospective, randomized, controlled trials targeting mortality in critically ill patients





Serum treatment for diphteria



Johannes Fibiger (1867-1928)

Serum treatment for diphtheria, 1894

Fibiger J. Om Serumbehandling af Difteri.
Hospitalstidende 1898;6:309-25, 337-50.

Deaths

8/239

30/245

pseudo-randomisation
patients randomized according to the day of admission
no statistics

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor

TABLE II.—*Assessment of Radiological Appearance at Six Months as Compared with Appearance on Admission*

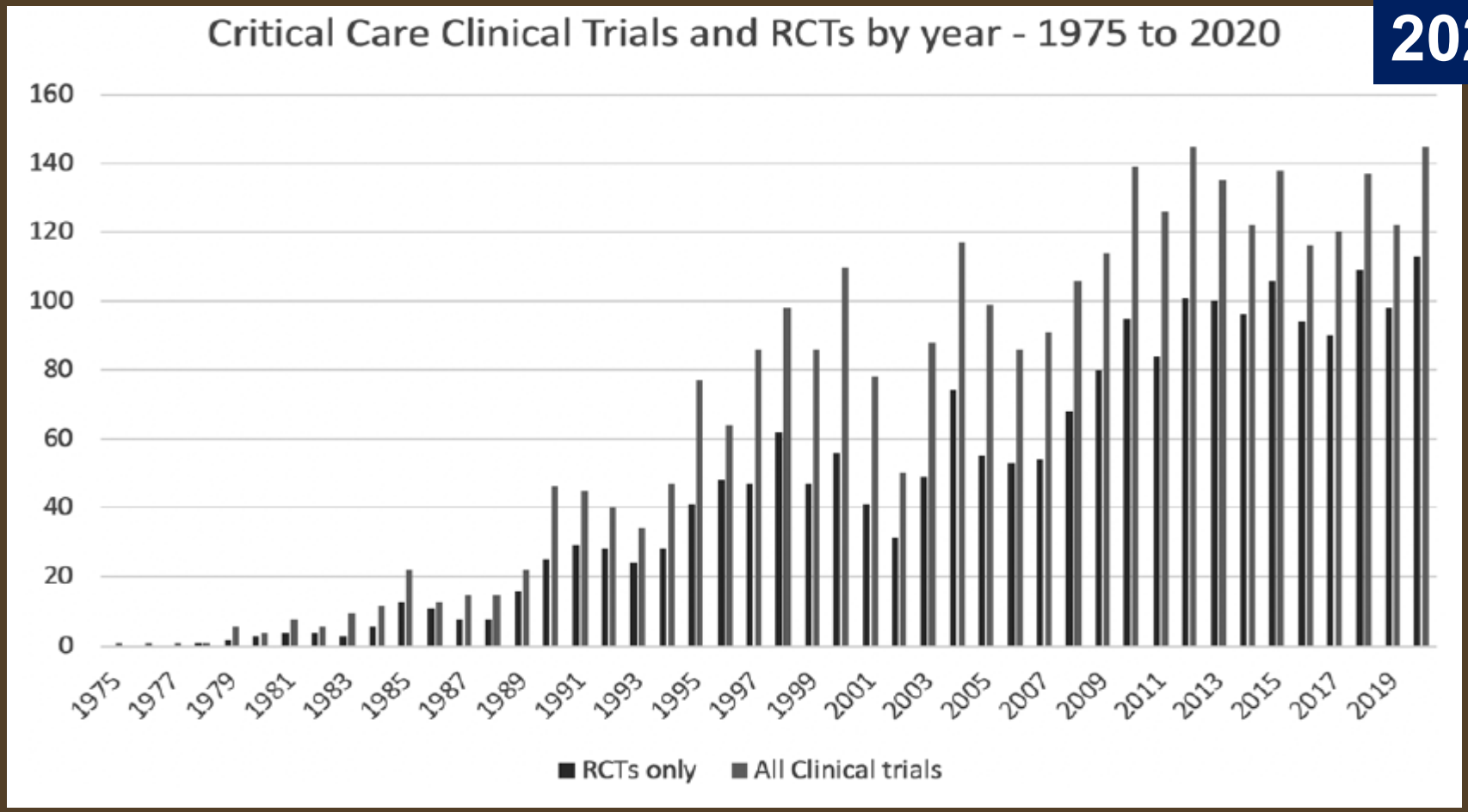
Radiological Assessment	Streptomycin Group		Control Group	
Considerable improvement ..	28	51%	4	8%
Moderate or slight improvement	10	18%	13	25%
No material change	2	4%	3	6%
Moderate or slight deterioration	5	9%	12	23%
Considerable deterioration ..	6	11%	6	11%
Deaths	4	7%	14	27%
Total	55	100%	52	100%

Clinical Research: From Case Reports to International Multicenter Clinical Trials

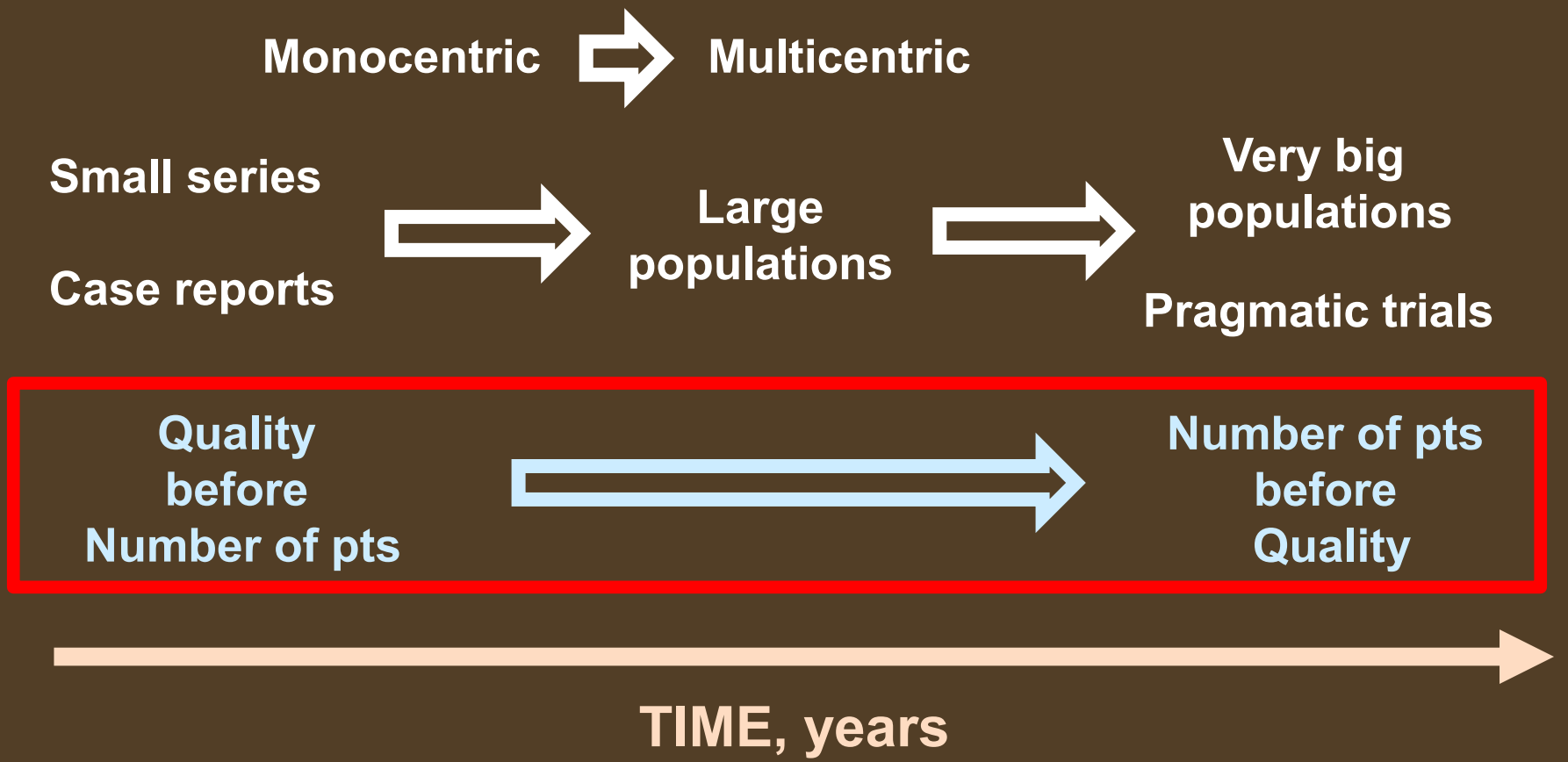
Critical Care Medicine

Simon Finfer, FRCP, FRCA, FCICM, FAHMS, DrMed[1,2]
Deborah Cook, MD[3,4]
Flavia R. Machado, MD, PhD[5]
Anders Perner, MD, PhD[6]

2021

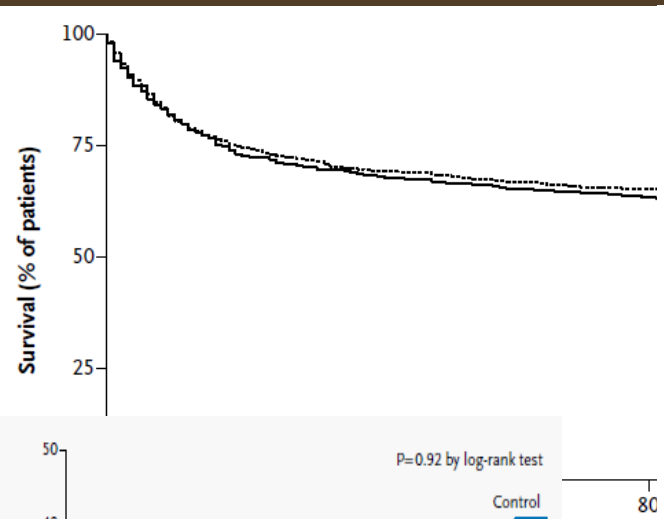


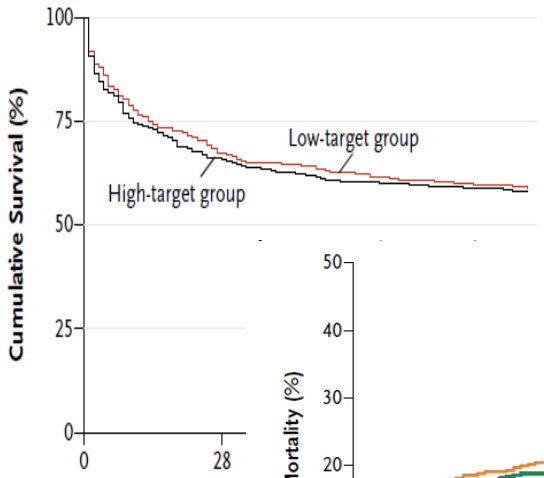
The evolution of our critical care trials

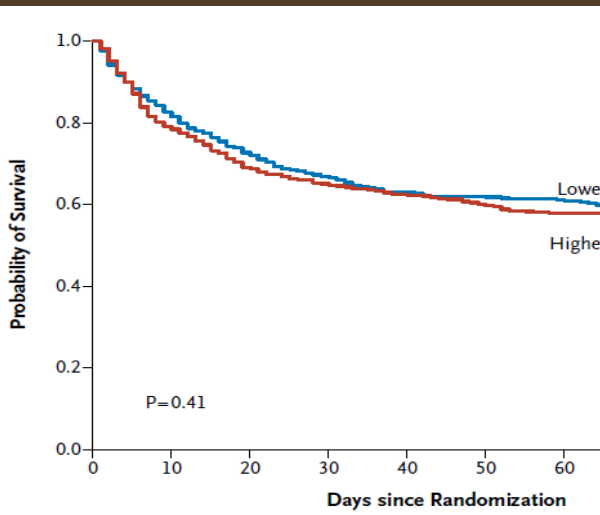


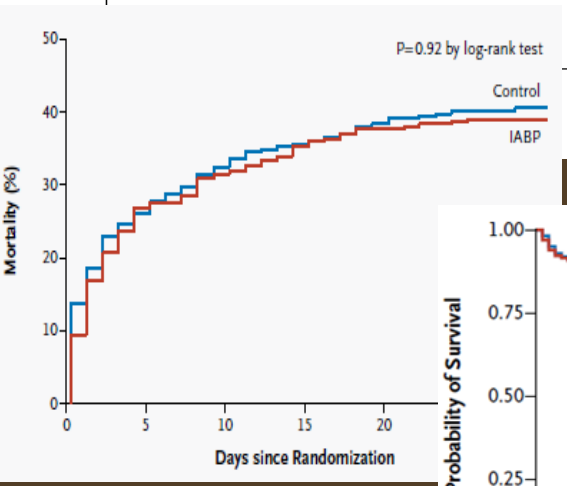
The NEW ENGLAND JOURNAL of MEDICINE

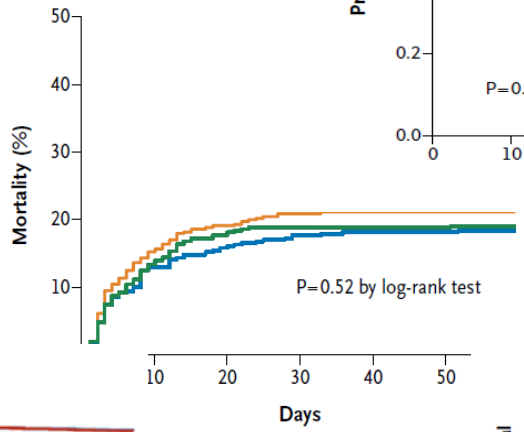
The typical ICU study on mortality

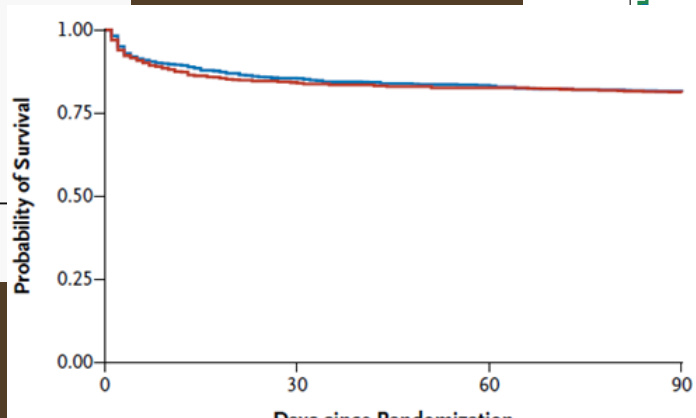


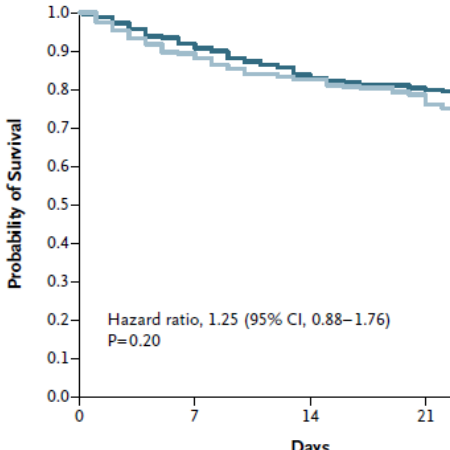












RCTs targeting mortality

Liberal vs. restrictive blood transfusions	No difference
Strict glucose control	No difference
Hypothermia in severe brain injury	No difference
The pulmonary artery catheter	No difference
Browth hormaon administration	No difference
Balloon counterpulsation in cardiogenic shock	No difference
Early goal-directed therapy	No difference
Early vs. late initiation of RRT	No difference
Glutamine administration	No difference
Craniectomy in severe brain injury	No difference
Early parenteral nutrition	No difference
Proton pump inhibitors administration	No difference
Dexmedetomidine administration	No difference
Bicarbonate administration	No difference
Higher vs. lower PEEP levels in ARDS	No difference
Minimal FiO2 for lung protection	No difference
Activated protein C in sepsis	No difference
Lactoferrin administration in sepsis	No difference
Statin administration in ARDS	No difference
TLR4 administration in sepsis	No difference
NOS inhibitor in septic shock	No difference
Hemglobin solution in severe polytrauma	No difference
High frequency oscillation in severe ARDS	No difference
Beta-stimulants in ARDS	No difference
Anti-oxidant supplementation	No difference
Albumin administration	No difference
Higher vs. lower arterial pressure in septic shock	No difference
ECMO in severe ARDS	No difference

multicentric **RCTs** targeting mortality in critically ill patients

Early goal directed therapy
Hemodynamic monitoring
Tight glucose control
Activated protein C in septic
Blood transfusions
Time of onset of re
Rate of renal re
TTM after c
Lower v ARDS
TLR4 inhi ock
Increased d imens
Statins admi ation in sepsis
Higher target blood pressure in septic shock
ECMO in ARDS
ECCO2 removal
….

NO DIFFERENCE IN MORTALITY

What else?

multicentric RCTs targeting mortality in critically ill patients

- Large tidal volumes are harmful
- Saline solutions may be harmful
- HES solutions may be harmful
- Hemoglobin solutions may be harmful
- Excessive sedation is harmful
- High frequency oscillation may be harmful
- Administration of growth hormone may be harmful
- Beta-2 stimulation in ARDS may be harmful
- Invasive mechanical ventilation is harmful (NIV is preferable)
- Too much fluid may be harmful
- Early parenteral nutrition may be harmful
- A TNF inhibitor in sepsis may be harmful
- High dose of vitamin C in sepsis may be harmful

Has it been shown to reduce mortality ?

Which Multicenter Randomized Controlled Trials in Critical Care Medicine Have Shown Reduced Mortality? A Systematic Review

Carlos A. Santacruz, MD[1]; Adriano J. Pereira, MD, PhD[2]; Edgar Celis, MD[1]; Jean-Louis Vincent, MD, PhD, FCCM[3]

2019

Any POSITIVE trial?

(showing a reduction in mortality in heterogeneous ICU populations?)

Which Multicenter Randomized Controlled Trials in Critical Care Medicine Have Shown Reduced Mortality? A Systematic Review

Carlos A. Santacruz, MD[1]; Adriano J. Pereira, MD, PhD[2]; Edgar Celis, MD[1]; Jean-Louis Vincent, MD, PhD, FCCM[3]

2019

TABLE 3. A Simple Overview of the Current Status of the Interventions Shown by Randomized Controlled Trial to Reduce Mortality in ICU Patients

Type of Intervention	Well Accepted	Still Debated[a]	Largely Unaccepted/ Disproved
Limiting iatrogenicity/respiratory support			
Limited tidal volume in ARDS	X		
NIV in hypercapnic respiratory failure	X		
NIV following extubation in complex cases	X		
Prone positioning in severe ARDS		X	
Muscle relaxants in severe ARDS			X
Monitoring systems			
Gastric tonometry			X
New therapeutic interventions			
Interleukin-1 receptor antagonist in sepsis			X
Drotrecogin alfa (activated) in sepsis			X
Talactoferrin in sepsis			X
Polymyxin B hemoperfusion in sepsis			X
Other strategies			
Selective digestive decontamination		X	
Corticosteroids in septic shock		X	
Early goal-directed therapy in acute kidney injury		X	

Avoiding iatrogenicity

Intensive Care Med
https://doi.org/10.1007/s00134-018-5220-y

EDITORIAL

Do trials that report a neutral or negative treatment effect improve the care of critically ill patients? No

Jean-Louis Vincent[1*], John J. Marini[2] and Antonio Pesenti[3,4]

2018

Box 1 Some perceived benefits that motivate clinicians to participate in large multicenter randomized controlled trials (RCTs)

Scientific (to address an important question)
Practical/pragmatic (benefit for patient care)
Financial (benefit for the department)
Political (benefit for the hospital/group)
Academic (for individual recognition/promotion)
Societal (benefit for society)


SEPSIS

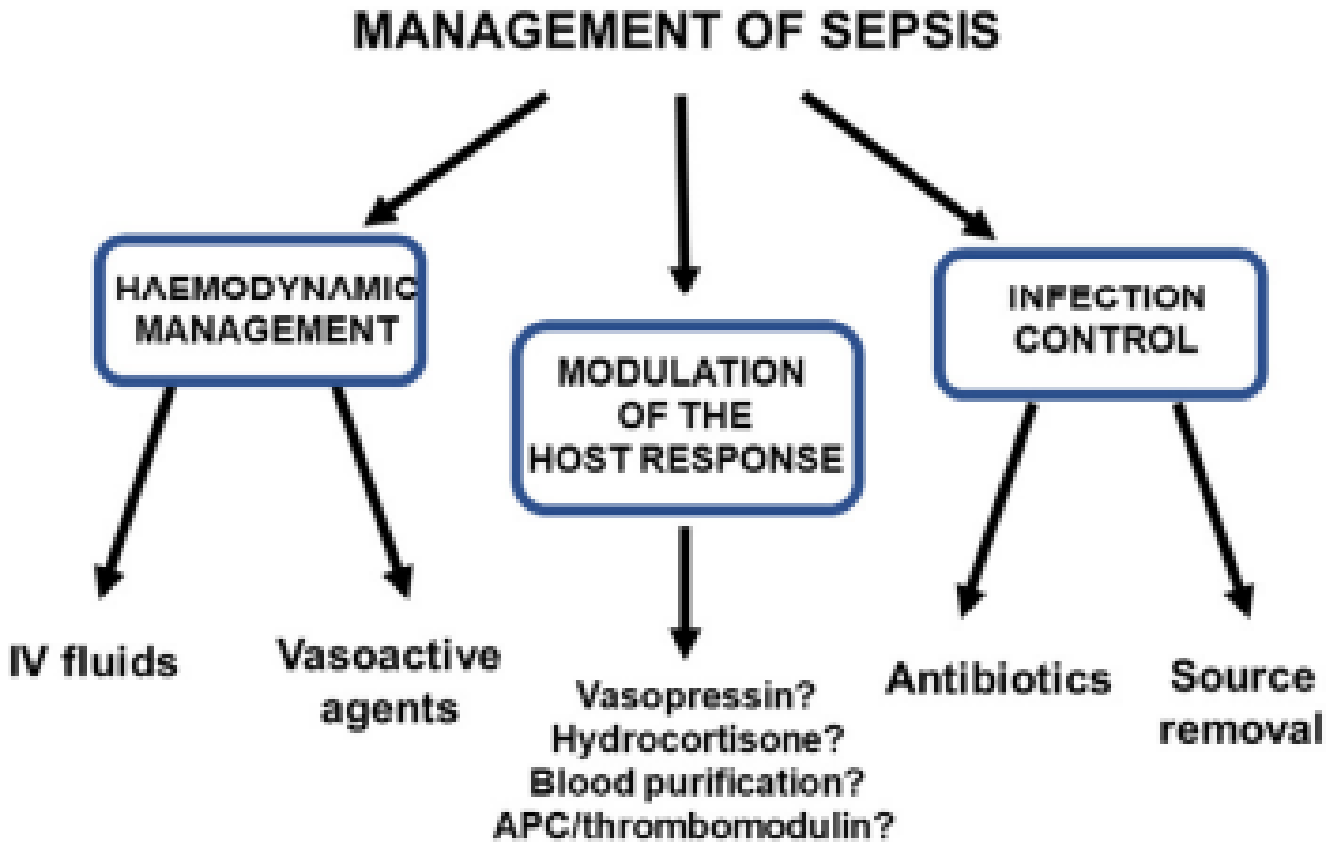
eBioMedicine

Current sepsis therapeutics

*Jean-Louis Vincent**

Department of Intensive Care, Erasme Hospital, Université libre de Bruxelles, Brussels, Belgium

2022



Hemodynamic Monitoring and Support

Strategy	References
In critically ill patients (in general)	
Higher vs lower mixed venous oxygen saturation targets in critically ill patients	Gattinoni et al (16)
Higher vs lower cardiac output in critically ill patients	Gattinoni et al (16)
Higher vs lower hemoglobin targets for blood transfusion	Hébert et al (50)
The pulmonary artery catheter	Sandham et al (48), Richard et al (51), Harvey et al (52)
Colloids vs crystalloids	Myburgh et al (53), Annane et al (54)
In septic patients (in particular)	
Vasopressin administration	Russell et al (55), Gordon et al (56)
Higher vs lower hemoglobin targets for blood transfusion	Holst et al (57)
Higher vs lower arterial pressure targets	Asfar et al (58)
Early goal-directed therapy	Yealy et al (18), Peake et al (19), Mouncey et al (20)
Levosimendan administration	Gordon et al (59)

Jean-Louis Vincent, MD, PhD, FCCM[1]

Alexandre Joosten, MD, PhD[2,3]

Bernd Saugel, MD[4]

Critical Care Medicine

2021

Some RCTs showing no reduction in mortality

ChatGPT

JL how much fluid should we give in sepsis?

The amount of fluid that should be given to a person with sepsis depends on a number of factors, including the severity of the condition, the underlying cause of the sepsis, and the person's overall health and medical history.

In general, people with sepsis may require fluid resuscitation to help restore and maintain adequate blood flow to vital organs and tissues. This may involve administering intravenous fluids, such as saline or lactated Ringer's solution, to increase the volume of fluid in the body and improve blood pressure.

The goal of fluid resuscitation in sepsis is to restore perfusion to vital organs and tissues and to prevent organ failure. The appropriate amount of fluid will depend on the individual needs of the person with sepsis and should be determined by a healthcare provider. It is important to monitor the person's vital signs and response to treatment and to adjust the fluid resuscitation plan as needed.

The NEW ENGLAND JOURNAL of MEDICINE

2023

ORIGINAL ARTICLE

Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension

The National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network*

Therapies	Restrictive Fluid Group (N=782)	Liberal Fluid Group (N=781)	Difference (95% CI)†
Median volume of IV fluid administered (IQR) — ml‡			
Over 6-hr period	500 (130 to 1097)	2300 (2000 to 3000)	−1800 (−1889 to −1711)
Over 24-hr period	1267 (555 to 2279)	3400 (2500 to 4495)	−2134 (−2318 to −1949)
Vasopressor administration during first 24-hr period — no./total no. (%)	460/780 (59.0)	290/779 (37.2)	21.7 (16.9 to 26.6)

NO DIFFERENCE

2 possible explanations

- **Fluids vs. vasopressors: it does not matter**

  (you do not need intelligence)

- **Treatment should be personalized**

  (you do need intelligence)

WHICH BLOOD PRESSURE TARGET?

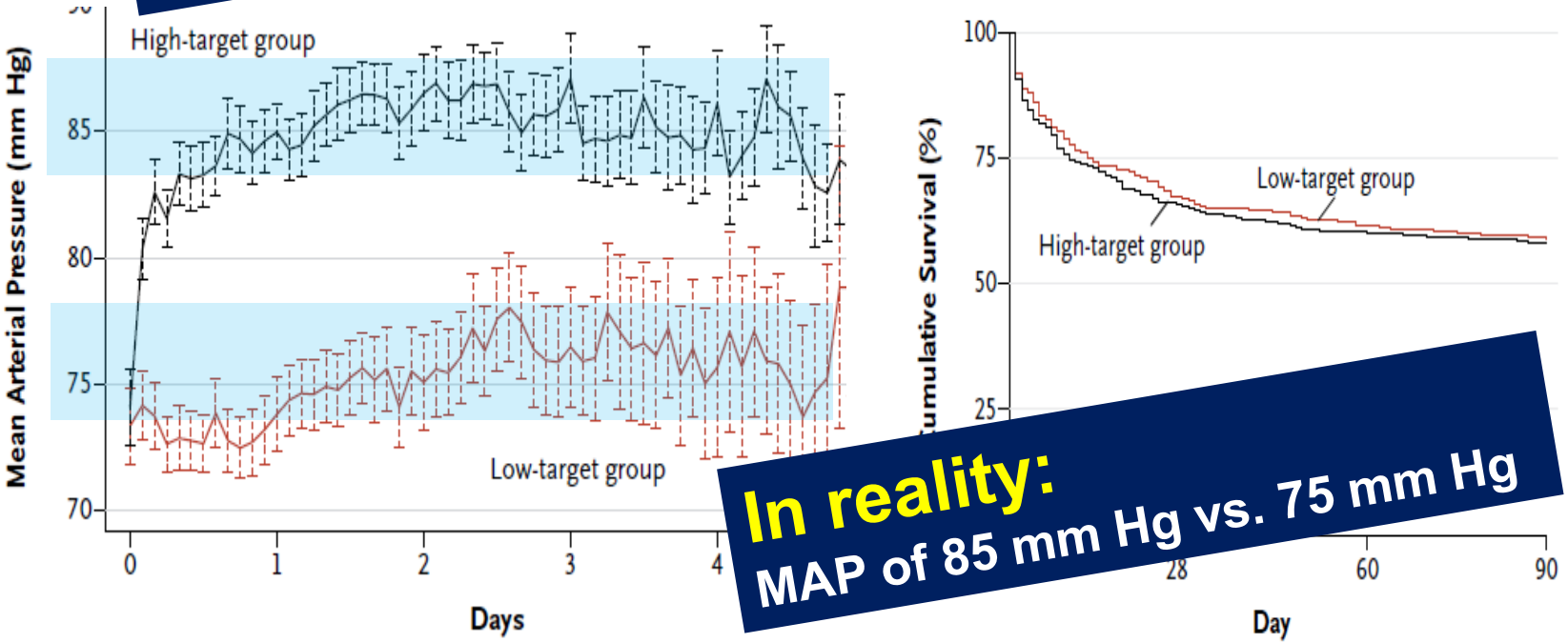
ORIGINAL ARTICLE

High versus Low Blood-Pressure Target in Patients with Septic Shock

2014

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., Yves Le Tulzo, M.D., Ph.D., Marie Con..., Frédéric Gonzalez..., Fabienne Tamion, M..., Thi..., D..., Alain..., R..., M.D., Ph.D. for the SEPSISPAM Investigators*

Target:
MAP of either 80 to 85 mm Hg (high-target group) or 65 to 70 mm Hg (low-target group).



In reality:
MAP of 85 mm Hg vs. 75 mm Hg

ORIGINAL ARTICLE

High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien Du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D. for the SEPSISPAM Investigators*

In patients with chronic arterial hypertension:

Variable	Low-Target Group (N=388)	High-Target Group (N=388)	P Value
Doubling of plasma creatinine			
	90/173 (52.0)	65/167 (38.9)	0.02
Renal-replacement therapy from day 1 to day 7			
	73/173 (42.2)	53/167 (31.7)	0.046

A MAP of 75 mm Hg is too low for some patients

THE MESSAGE

A MAP of 65 mmHg for all?

It can be the INITIAL target

A MAP > 75 mmHg

may be optimal in some patients

(history of hypertension)

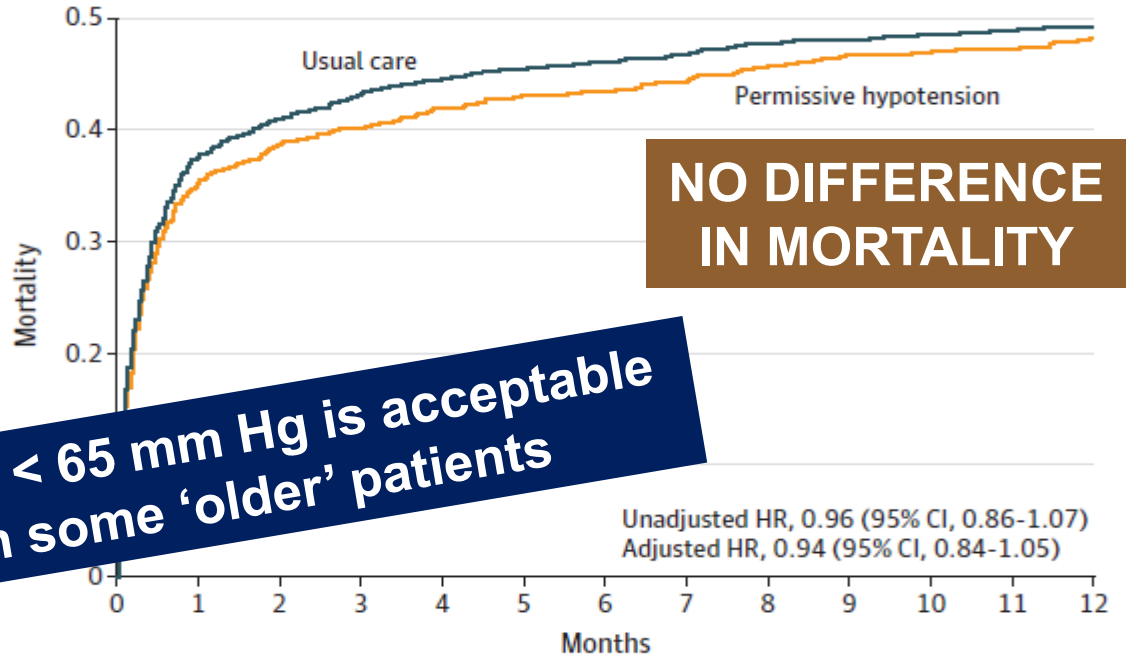
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension
A Randomized Clinical Trial

2020

François Lamontagne, MD; Alvin Richards-Belle, BSc; Karen Thomas, MSc; David A. Harrison, PhD; M. Zia Sadique, PhD; Richard D. Grieve, PhD; Julie Camsooksai, BSc; Robert Darnell, BA; Anthony C. Gordon, MD; Doreen Henry, MSc; Nicholas Hudson, BA; Alexina J. Mason, PhD; Michelle Saull, BSc; Chris Whitman, BSc; J. Duncan Young, DM; Kathryn M. Rowan, PhD; Paul R. Mouncey, MSc; for the 65 trial investigators

MAP target: ⇄ **60-65mmHg (permissive hypotension) (n = 1291) usual care (n = 1307).**



NO DIFFERENCE IN MORTALITY

A MAP < 65 mm Hg is acceptable in some 'older' patients

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Reduced Exposure to Vasopressors on 90-Day Mortality in Older Critically Ill Patients With Vasodilatory Hypotension
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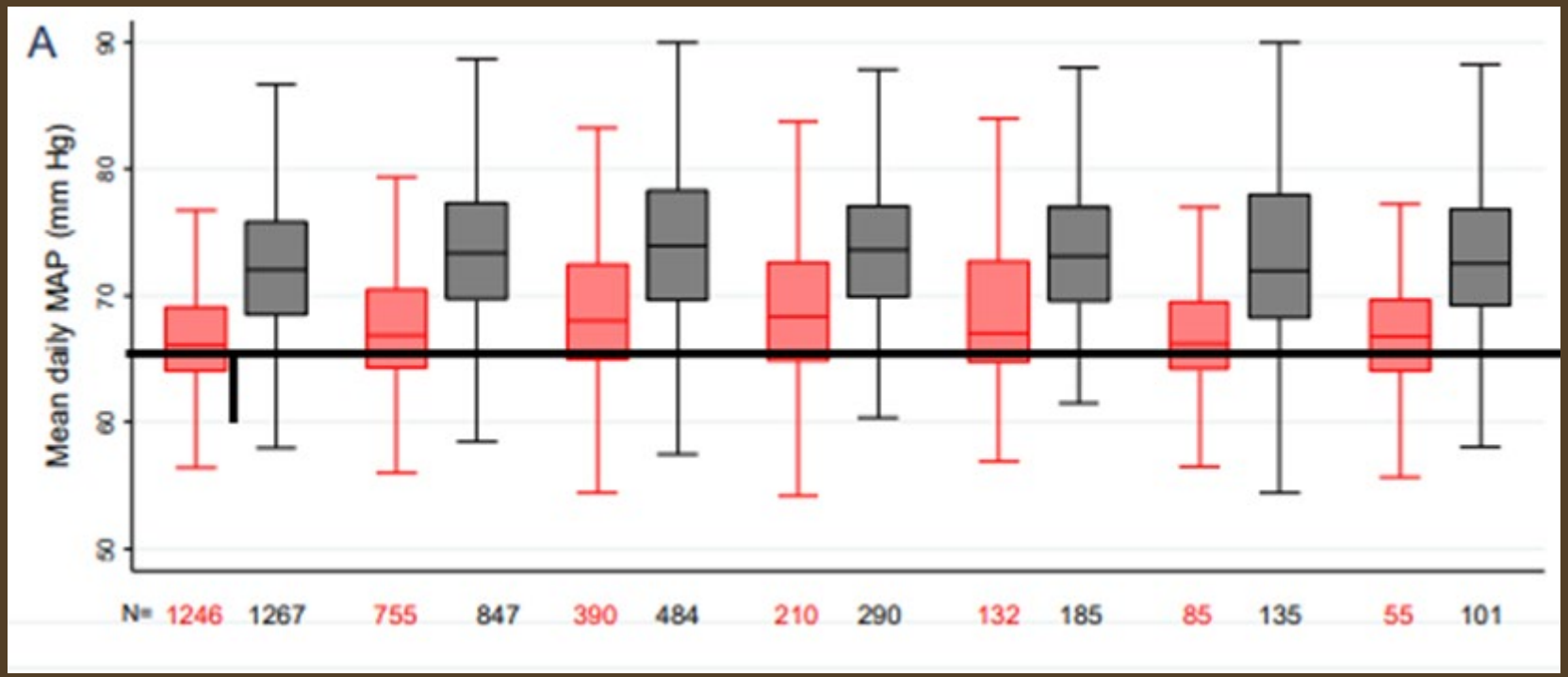


THE MESSAGE

A MAP of 65 mmHg for all?

It can be the INITIAL target

A MAP >75 mmHg

may be optimal in some patients

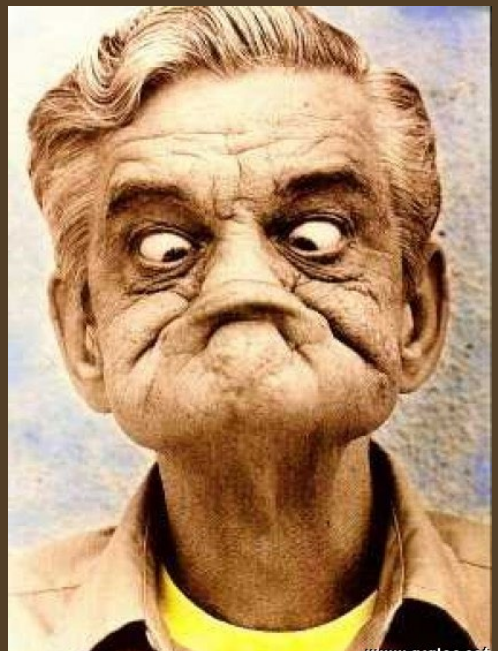
(history of hypertension)

A MAP <65 mmHg

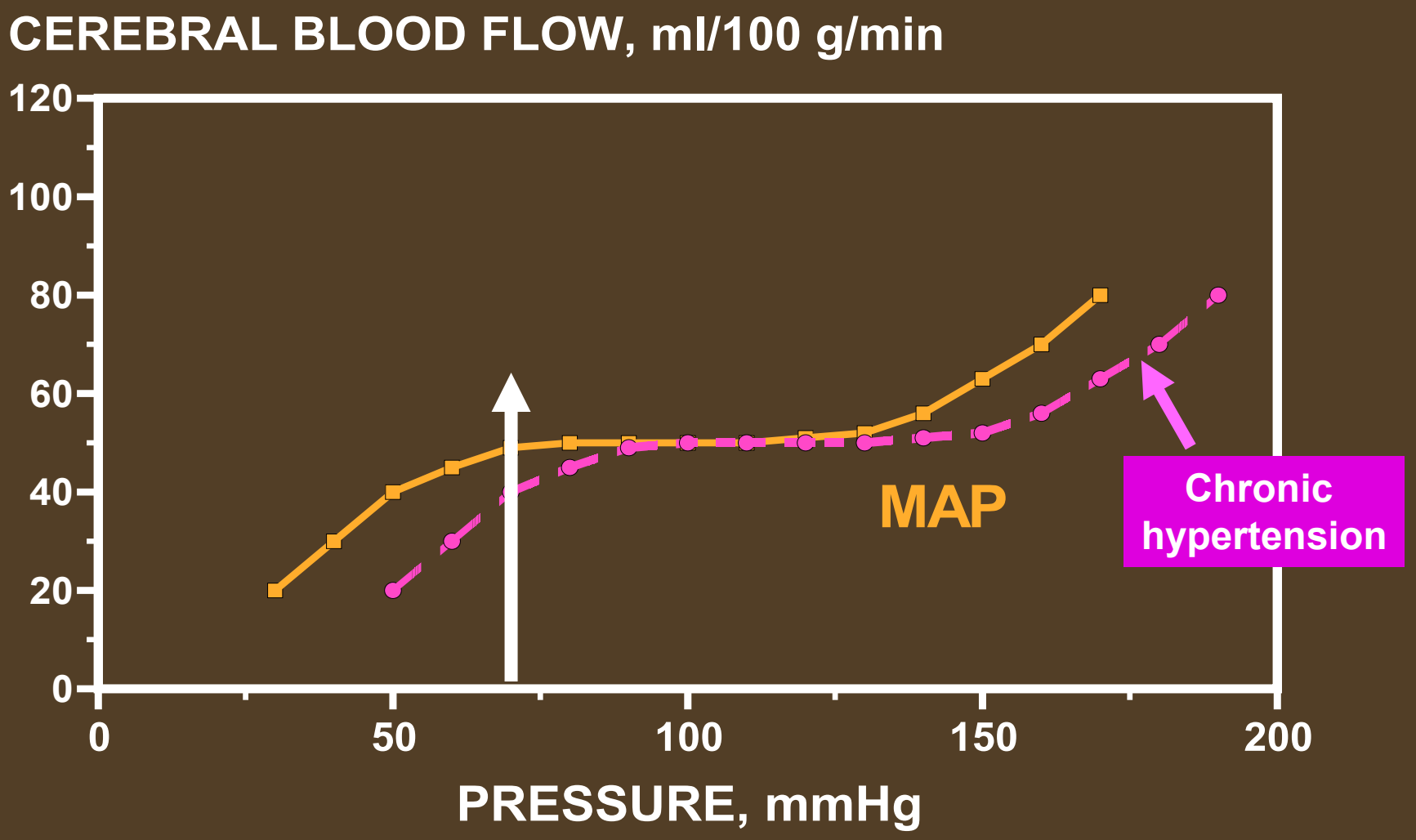
may be acceptable in some patients

(even if older than 65 years)

PHYSIOLOGY



AUTOREGULATION OF BLOOD FLOW



Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

2021

Vasopressor therapy

Mean arterial pressure

Recommendation
9. For adults with septic shock on vasopressors, we **recommend** an initial target mean arterial pressure (MAP) of 65 mm Hg over higher MAP targets
Strong recommendation, moderate-quality evidence

Quid thereafter?

SURVIVING **SEPSIS** CAMPAIGN

2016

VASOPRESSOR AGENTS

We recommend
an **initial** target mean arterial pressure (MAP) of 65 mm Hg
in patients with septic shock requiring vasopressors.

Grade 1 B

Remarks:

If initiated, vasopressor dosing should be titrated
to an end point reflecting perfusion…

Crit Care Med 2017
Intensive Care Med 2017

Vincent et al. Critical Care (2021) 25:397
https://doi.org/10.1186/s13054-021-03813-0

Critical Care

EDITORIAL Open Access

Equilibrating SSC guidelines with individualized care

2021

Jean-Louis Vincent[1*], Mervyn Singer[2], Sharon Einav[3], Rui Moreno[4], Julia Wendon[5], Jean-Louis Teboul[6], Jan Bakker[7,8,9,10], Glenn Hernandez[11], Djillali Annane[12], Angélique M. E. de Man[13], Xavier Monnet[14], V. Marco Ranieri[15], Olfa Hamzaoui[16], Jukka Takala[17], Nicole Juffermans[18,19], Jean-Daniel Chiche[20], Sheila N. Myatra[21] and Daniel De Backer[22]

We recommend individualizing arterial blood pressure levels.

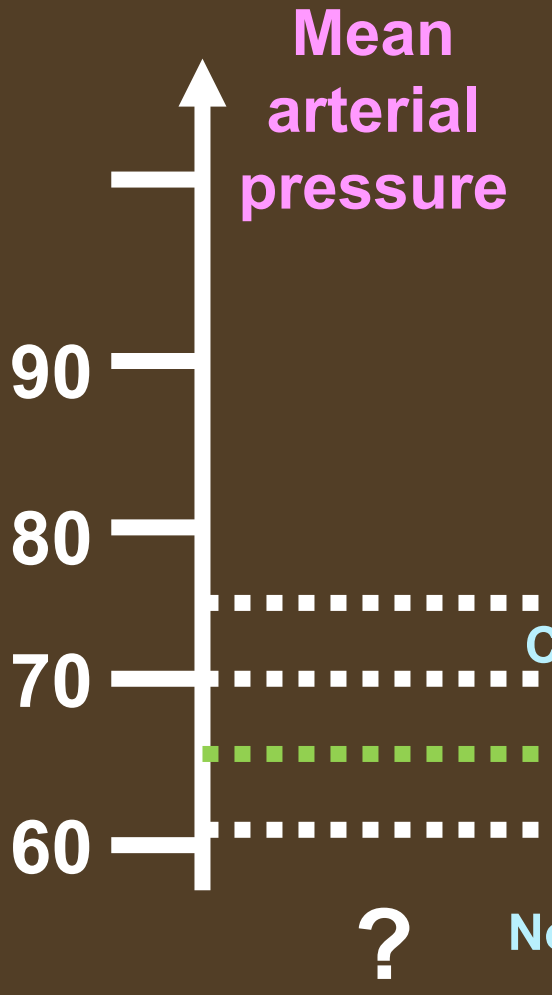
Although a mean value of 65 mmHg may be recommended as an initial goal, the optimal level may be higher in patients with a history of hypertension, atherosclerosis or chronic kidney disease.

Conversely it may be lower in younger patients without previous vascular problems, in those with chronically low arterial pressure, or in whom adequate tissue perfusion is maintained.

THE PROBLEM OF HYPOTENSION

INDIVIDUALIZE THE TARGETS

What is the target blood pressure in shock ?



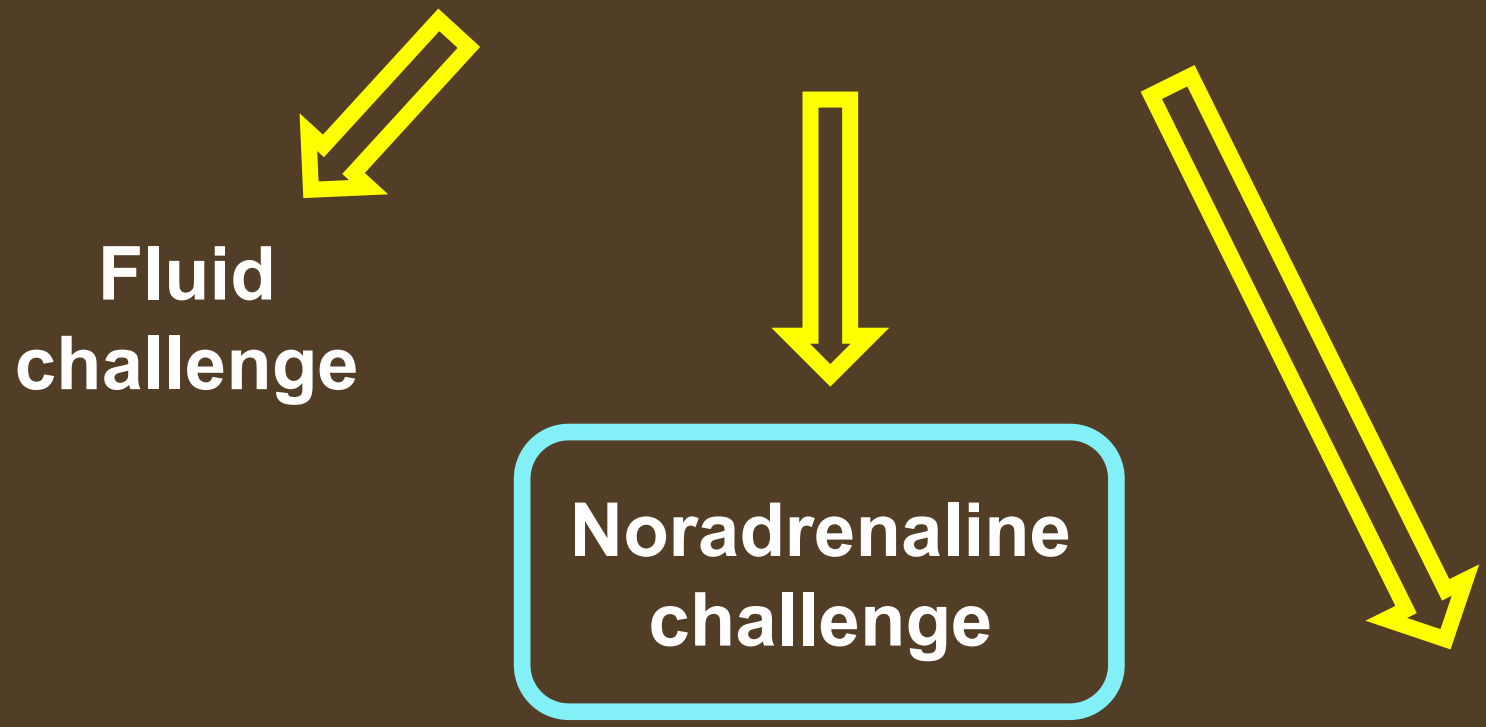
INITIAL target = 65 mmHg then REASSESS

Elderly
Atherosclerosis
Chronic hypertension

Young,
No atherosclerosis
No chronic hypertension

Diuresis ?
Consciousness ?
Skin perfusion ?
+
SvO2? Lactate?

THE CHALLENGES



De Backer et al. Critical Care (2022) 26:372
https://doi.org/10.1186/s13054-022-04255-y

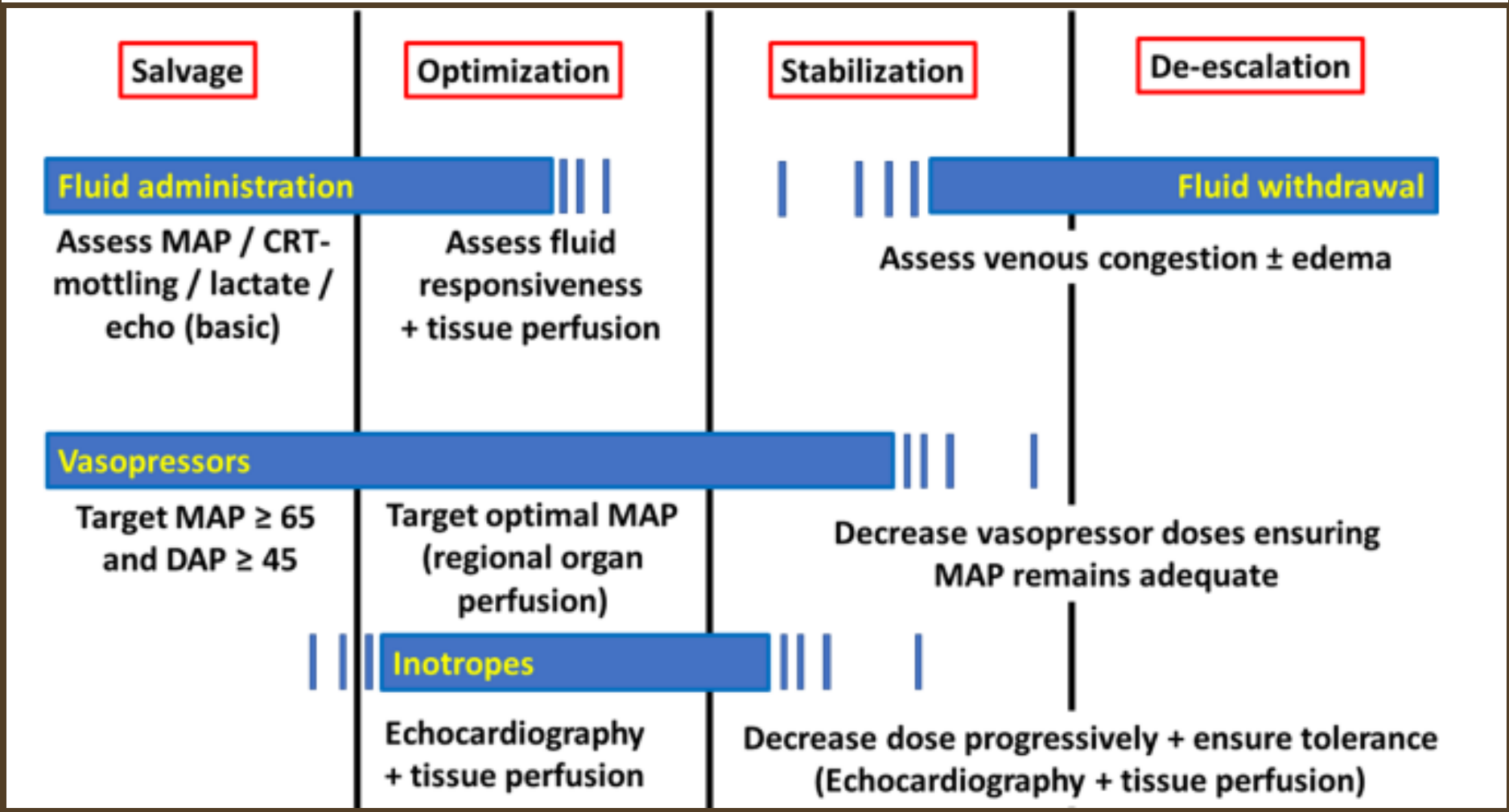
Critical Care

REVIEW Open Access

A plea for personalization of the hemodynamic management of septic shock

2022

Daniel De Backer[1*], Maurizio Cecconi[2,3], Michelle S. Chew[4], Ludhmila Hajjar[5], Xavier Monnet[6], Gustavo A. Ospina-Tascón[7,8], Marlies Ostermann[9], Michael R. Pinsky[10] and Jean-Louis Vincent[11]



- The large RCT targeting mortality in heterogeneous ICU patient populations

New therapeutic approaches

Not (only) mortality as an end-point

RCT

- The large RCT targeting mortality in heterogeneous ICU patient populations

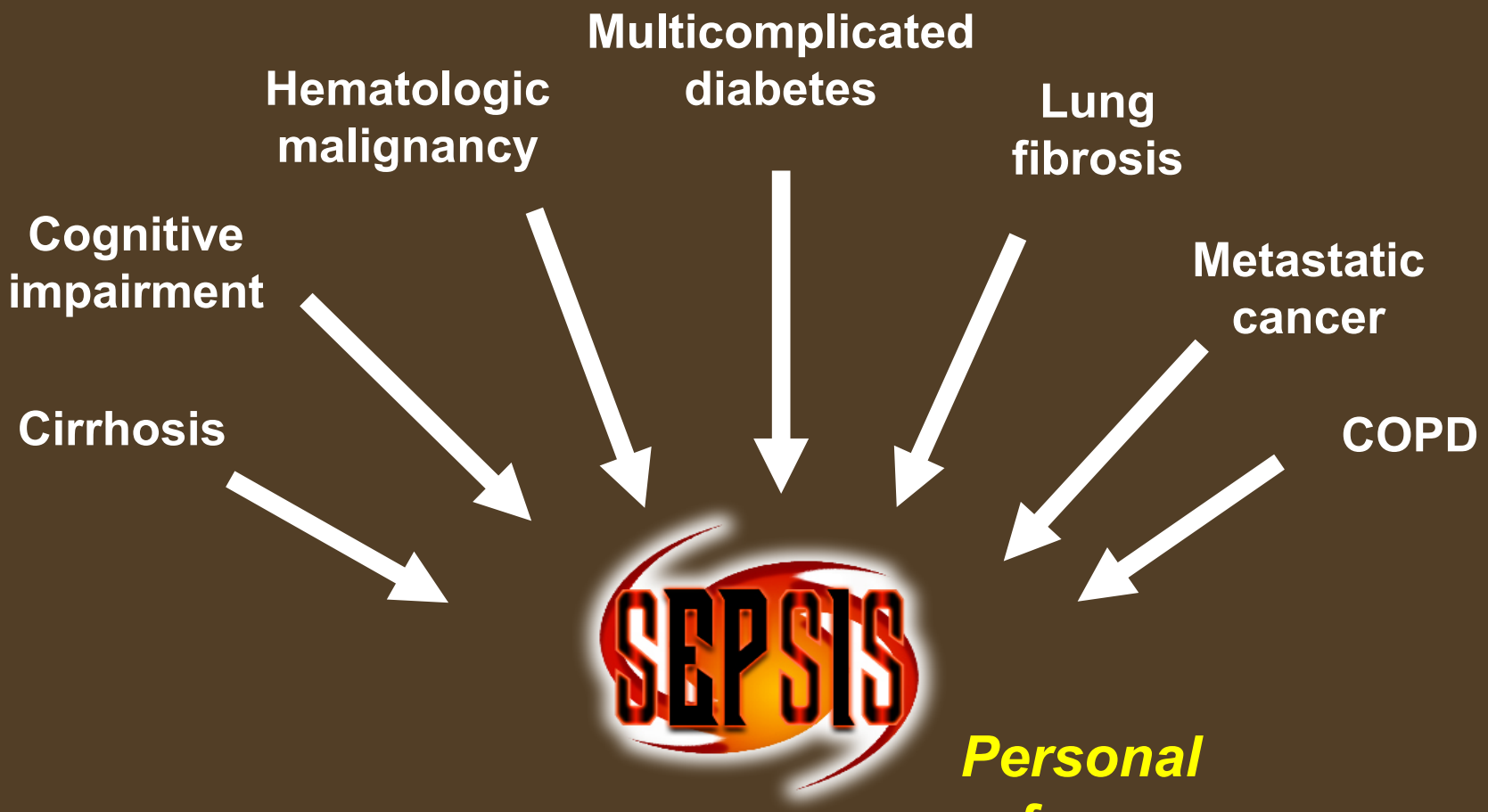
CLINICAL TRIALS

END-POINT

MORTALITY

THE IMPORTANCE OF THE UNDERLYING DISEASE and COMORBIDITIES

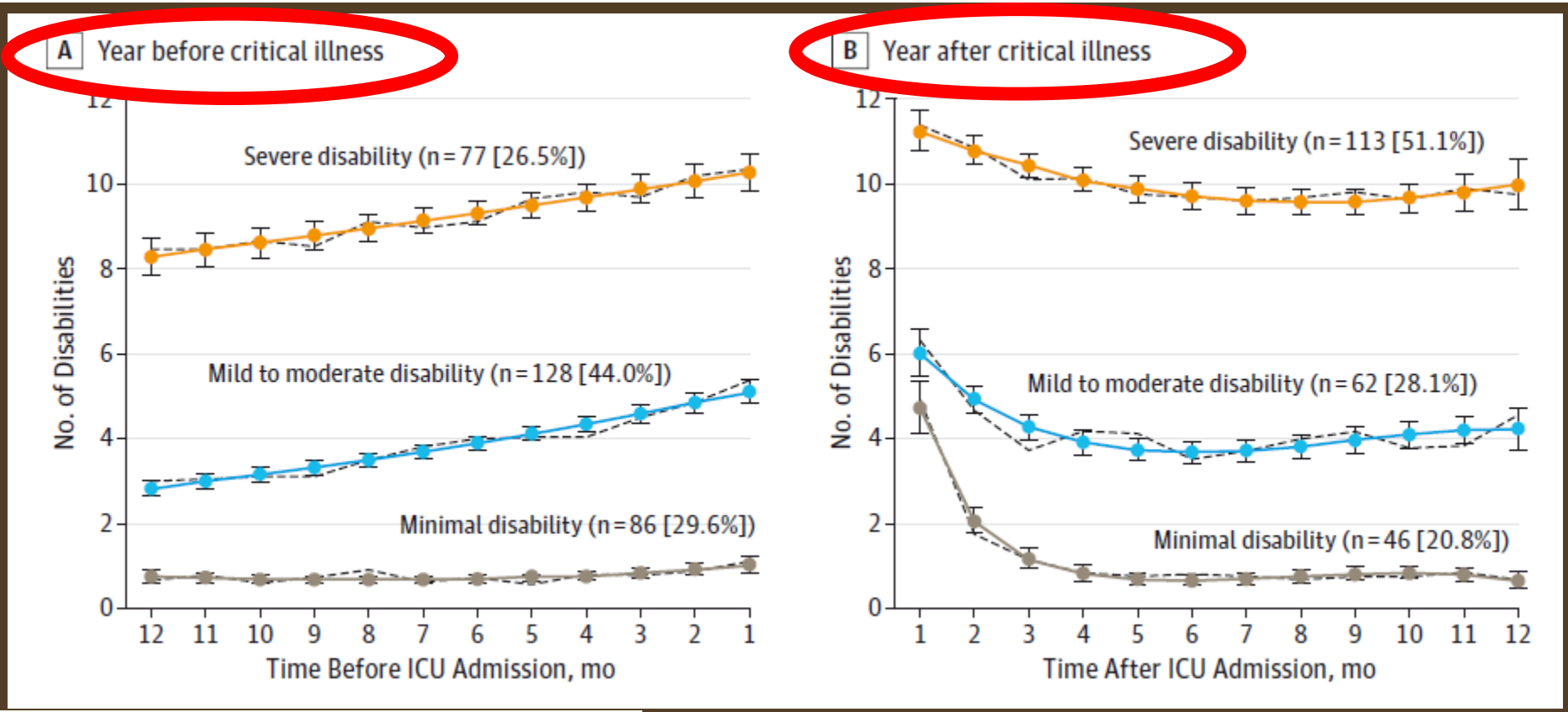
The importance of comorbidities



Original Investigation

Functional Trajectories Among Older Persons Before and After Critical Illness

Lauren E. Ferrante, MD; Margaret A. Pisani, MD, MPH; Terrence E. Murphy, PhD; Evelyne A. Gahbauer, MD, MPH; Linda S. Leo-Summers, MPH; Thomas M. Gill, MD

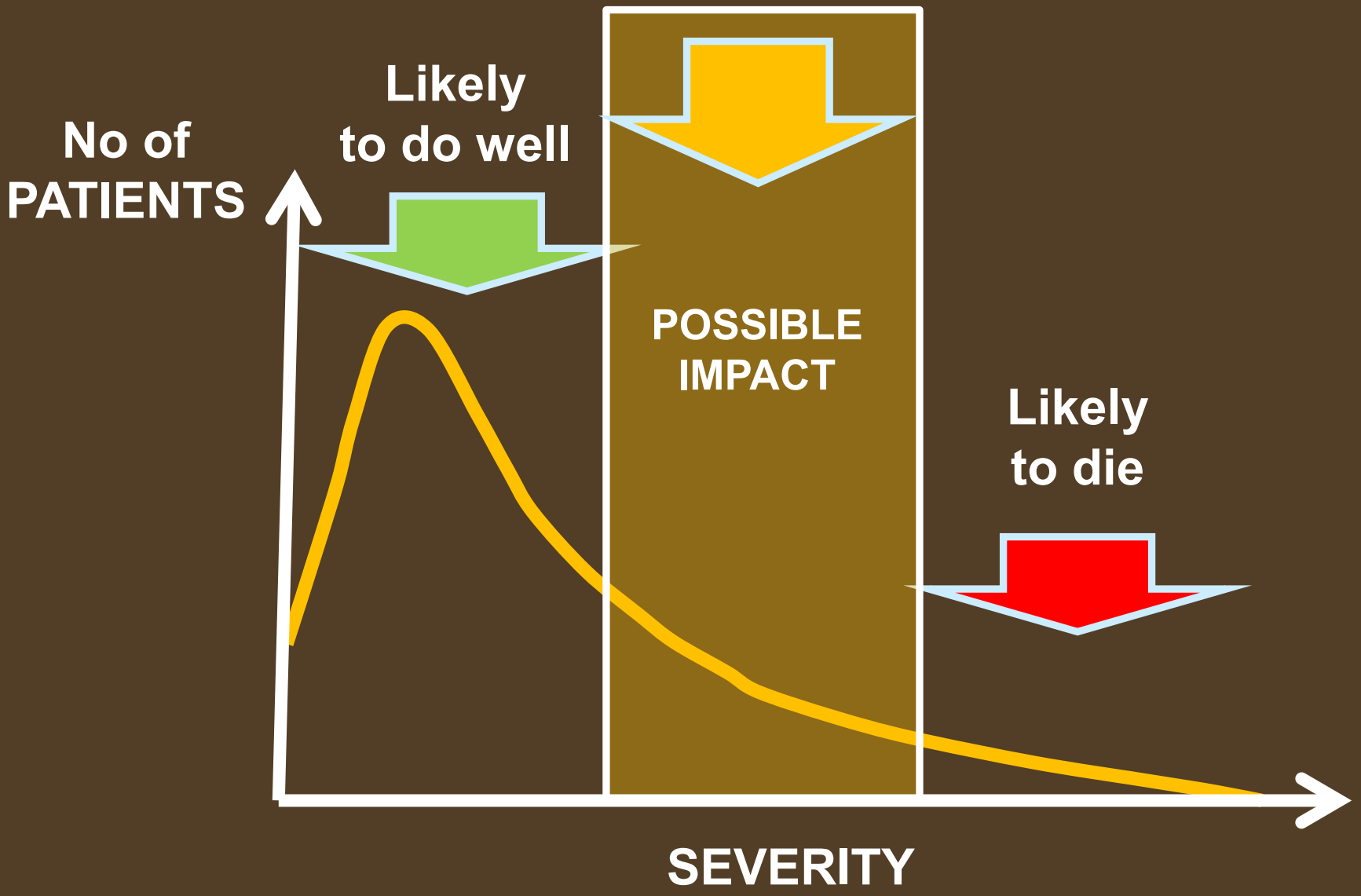


JAMA Intern Med. doi:10.1001/jamainternmed.2014.7889
Published online February 9, 2015.

> 70 years

In some cases,
death represents
the person's best interests...

THE EFFECTS OF OUR INTERVENTIONS



de Grooth *et al. Critical Care* (2017) 21:38
DOI 10.1186/s13054-017-1609-1

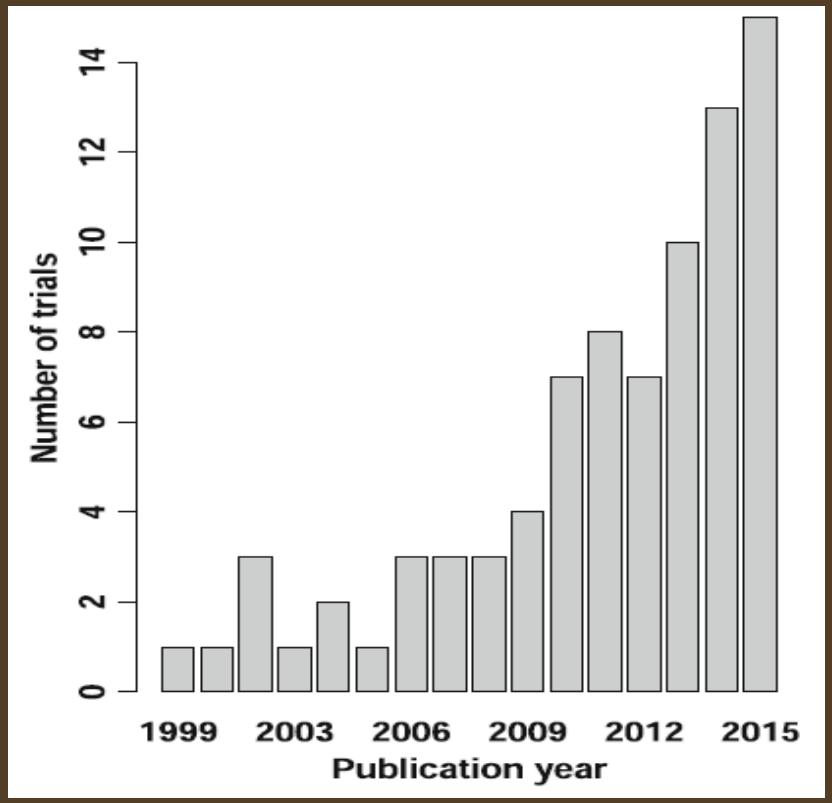
Critical Care

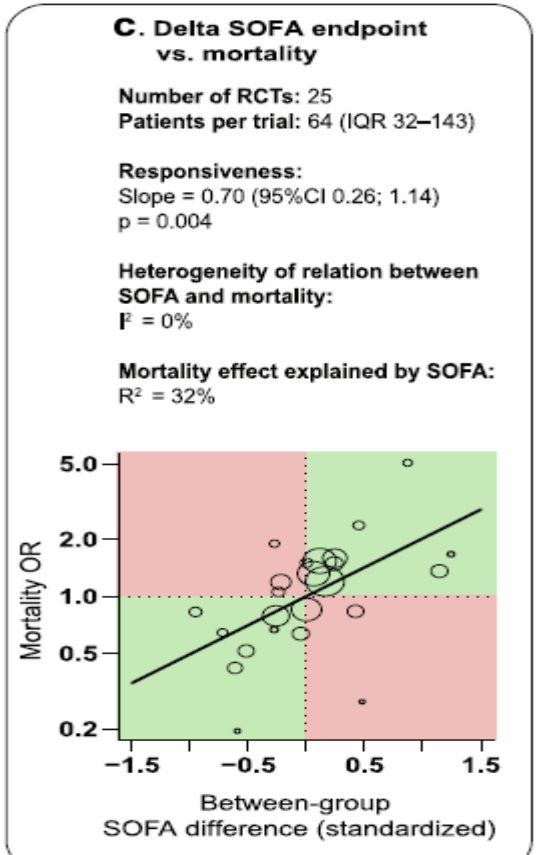
RESEARCH Open Access

SOFA and mortality endpoints in randomized controlled trials: a systematic review and meta-regression analysis

2017

Harm-Jan de Grooth[1*], Irma L. Geenen[1], Armand R. Girbes[1], Jean-Louis Vincent[2], Jean-Jacques Parienti[3,4] and Heleen M. Oudemans-van Straaten[1]





Karakike et al. Critical Care (2019) 23:387
https://doi.org/10.1186/s13054-019-2665-5

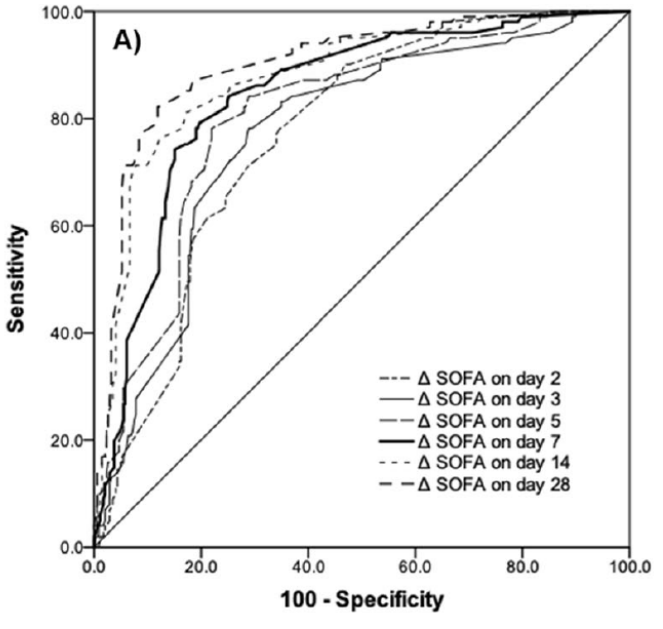
Critical Care

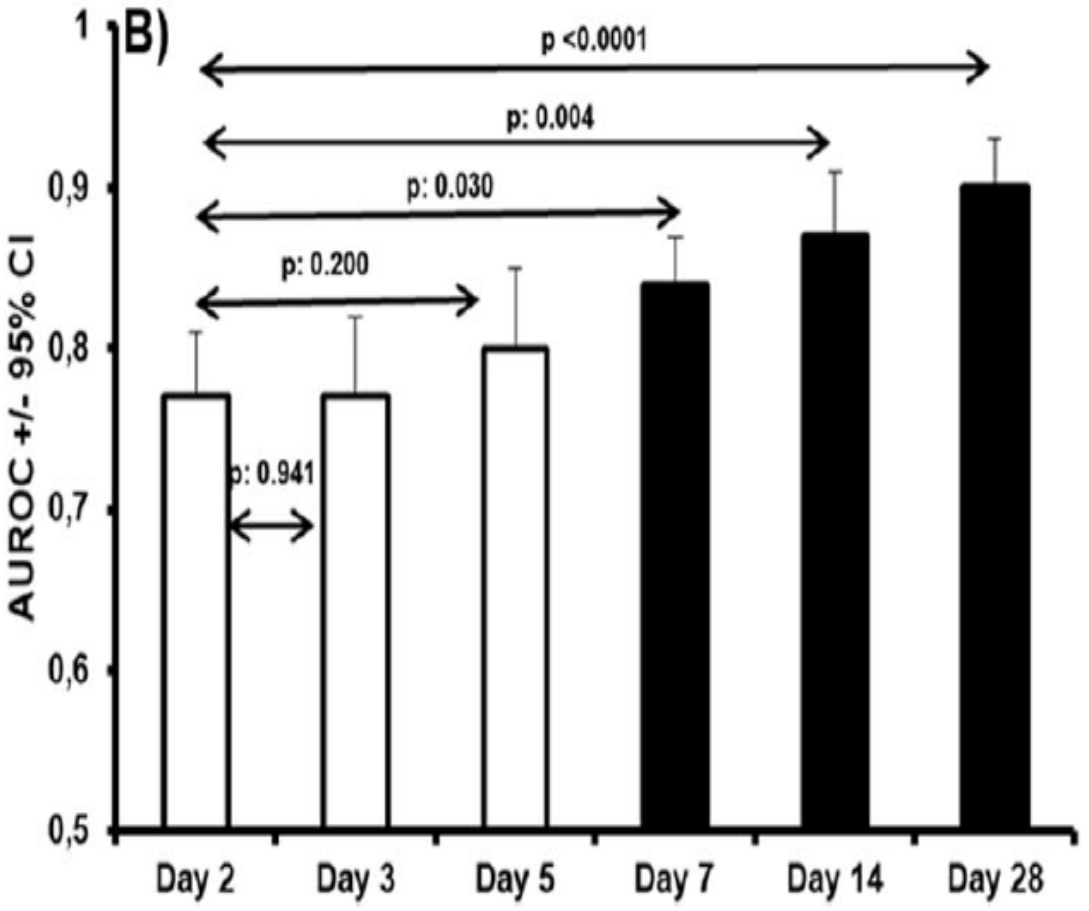
RESEARCH Open Access

The early change of SOFA score as a prognostic marker of 28-day sepsis mortality: analysis through a derivation and a validation cohort

2019

Eleni Karakike[1], Evdoxia Kyriazopoulou[1], Iraklis Tsangaris[2], Christina Routsi[3], Jean-Louis Vincent[4] and Evangelos J. Giamarellos-Bourboulis[1*]





Conclusions:

Δ_{SOFA} on day 7 is a useful early prognostic marker of 28-day mortality and could serve as an endpoint in future sepsis trials alongside mortality.

- The large RCT targeting mortality in heterogeneous ICU patient populations

New therapeutic approaches

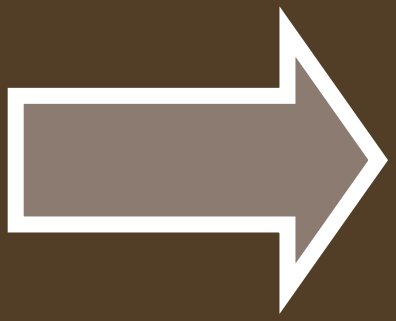
Better defined (less heterogeneous) populations

CLINICAL TRIALS IN THE ICU

ILLNESSES

Acute myocardial infarction
Stroke
Urinary tract infection

SYNDROMES



ARDS
Sepsis
SIRS
"critically ill"

30 Y/O
diabetes
urinary tract infection

57 Y/O
immunosuppressed
pneumonia
lung transplant

85 Y/O
recent CVA
peritonitis
ruptured colon Ca

+ organ dysfunction

Sepsis heterogeneity

SOURCE OF INFECTION

pneumonia
peritonitis
UTI
wound infection
...

SIGNS OF SEPSIS

fever
tachycardia
high CO - low SVR
tachypnea
high CRP/PCT
...

GENETIC FACTORS

TNF
NO, etc
gender
...

IMMUNOLOGIC STATUS

Monocyte function
(HLA-DR...)
Functional tests...

ORGAN DYSFUNCTION

PaO2/FiO2
platelet count
bilirubin
creatinine
GCS

CO-MORBIDITIES

diabetes
alcoholism
cancer...

MICROBIOLOGY

Gram + or -
mixed
fungi
...

SHOCK

hypotension
oliguria
altered mentation
lactic acidosis

MEDICATIONS

steroids
statins
β-adrenergic
agents…

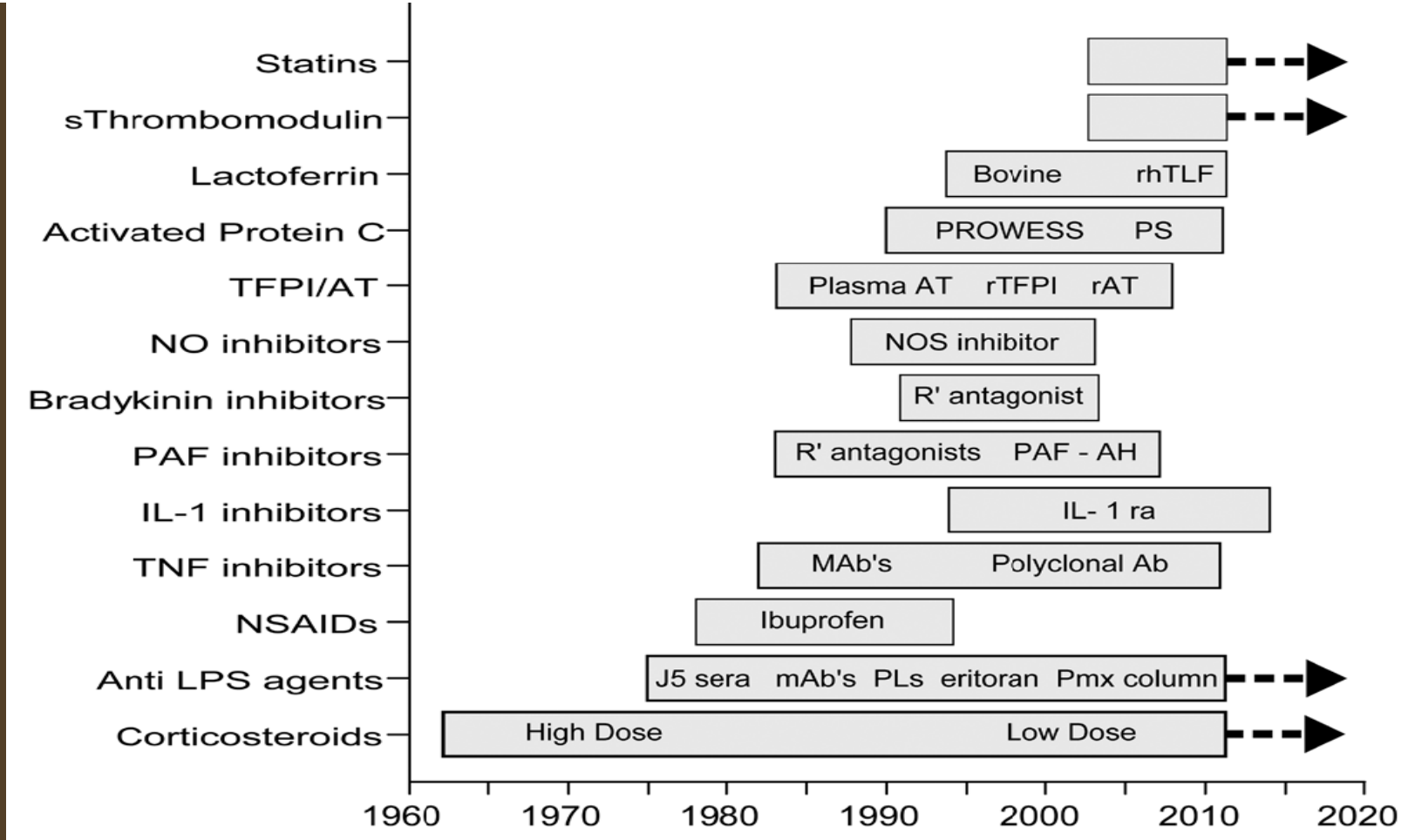
TIME

Special Article

Crit Care Med 2014; 42:1714–1721

The Next Generation of Sepsis Clinical Trial Designs: What Is Next After the Demise of Recombinant Human Activated Protein C?*

Steven M. Opal, MD[1]; R. Phillip Dellinger, MD[2]; Jean-Louis Vincent, MD, PhD[3]; Henry Masur, MD[4]; Derek C. Angus, MD, MPH[5]



biomedicines 2022

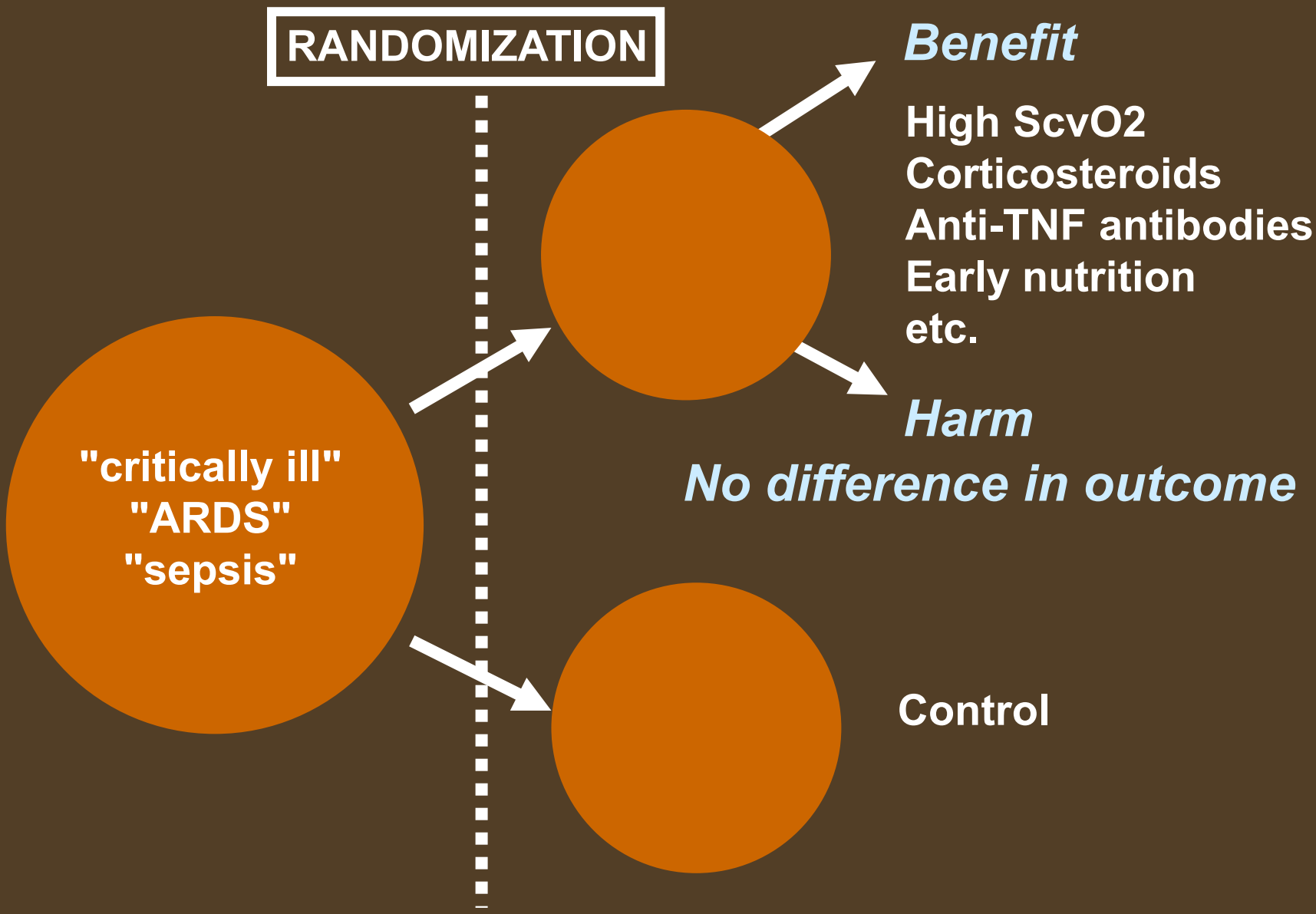
Review

The End of "One Size Fits All" Sepsis Therapies: Toward an Individualized Approach

Jean-Louis Vincent [1,*], Tom van der Poll [2,3] and John C. Marshall [4]

Intervention	Refs
Corticosteroids	[13–16]
Nonsteroidal anti-inflammatory agents (ibuprofen)	[18]
Anti-TNF (antibodies, receptors)	[5,23]
Anti-IL-1 (IL-1ra)	[6,27]
Anti-TLR4	[31,32]
Bradykinin inhibitors	[35]
Interferon	[37]
Anti-PAF	[7,39]
Nitric oxide inhibitors/scavengers	[41,42]
Antiendotoxin (antibodies, purification)	[44–48]
Alkaline phosphatase	[19,20]
Statins	[21,22]
Activated protein C/thrombomodulin	[24–26]
TFPI/antithrombin	[28–30]
Lactoferrin	[33,34]
Levocarnitine	[36]
Thymosin alfa 1	[38]
Antioxidants (N-acetylcysteine)	[40]
Vitamins	[43]
Traditional Chinese medicines (e.g., Xuebijing)	[49]

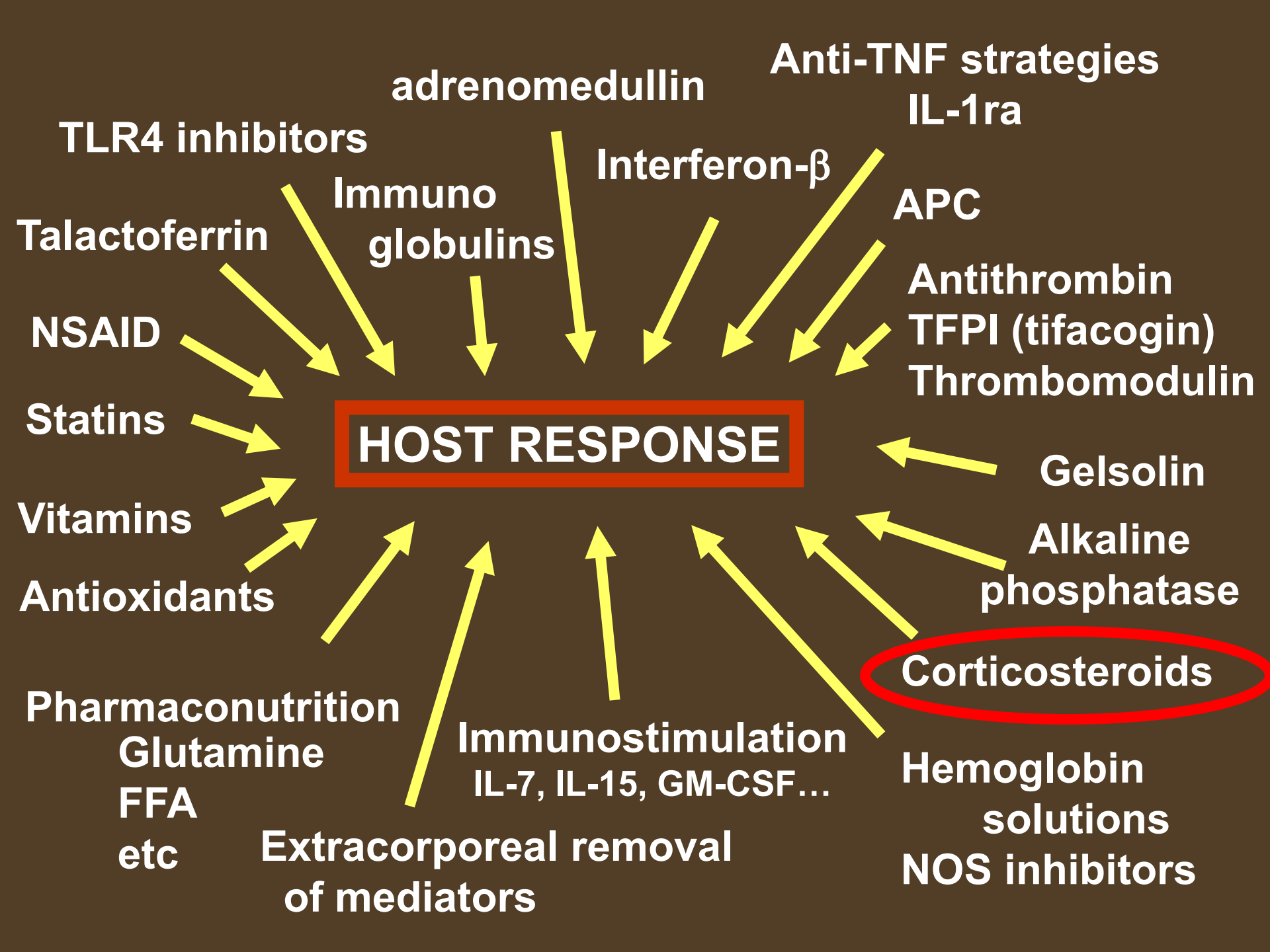
CLINICAL TRIALS IN THE ICU



WE HAVE A BIG PROBLEM

'critically ill'
Sepsis
ARDS
SIRS
AKI
...

HETEROGENEITY


Anti-TNF strategies
IL-1ra
adrenomedullin
TLR4 inhibitors
Interferon-β
Immuno
globulins
APC
Talactoferrin
Antithrombin
TFPI (tifacogin)
Thrombomodulin
NSAID
Statins
HOST RESPONSE
Gelsolin
Vitamins
Alkaline
phosphatase
Antioxidants
Corticosteroids
Pharmaconutrition
Glutamine
FFA
etc
Immunostimulation
IL-7, IL-15, GM-CSF…
Hemoglobin
solutions
NOS inhibitors
Extracorporeal removal
of mediators

The NEW ENGLAND JOURNAL of MEDICINE

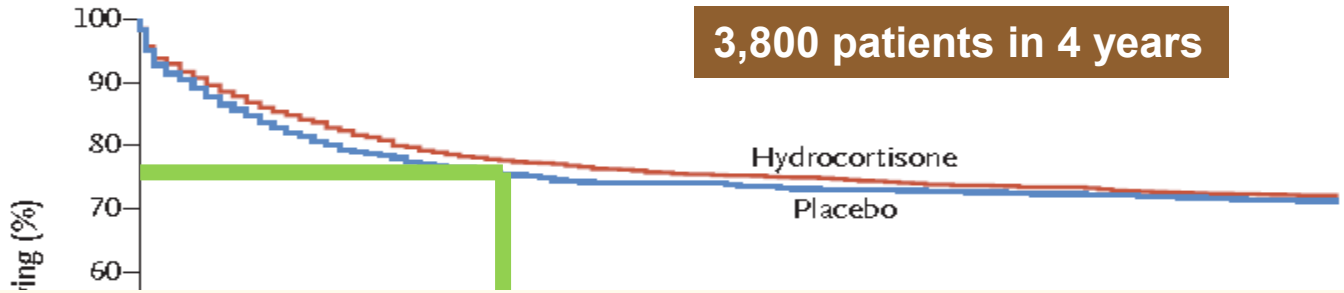
ORIGINAL ARTICLE

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

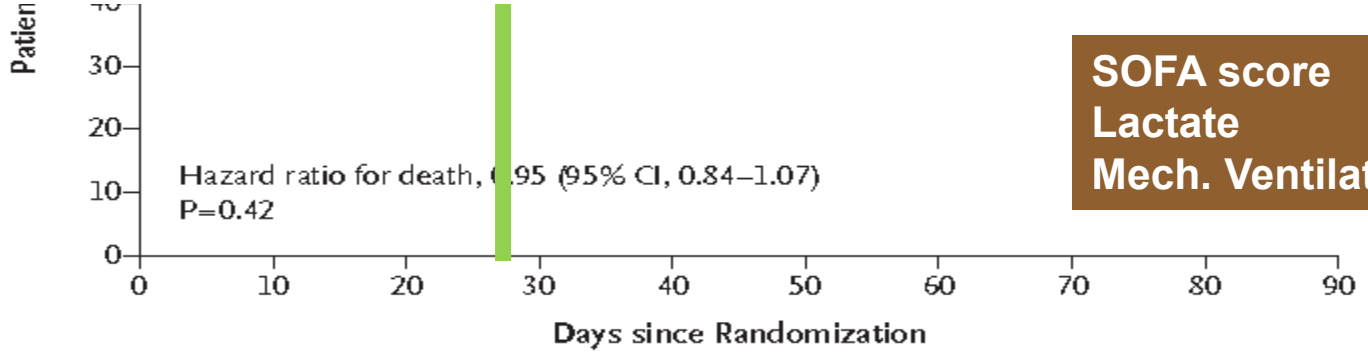
2018

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

3,800 patients in 4 years



Catecholamine dose >15 μg/min 981/1834 (53.5) 1013/1832 (55.3)



SOFA score ?
Lactate ?
Mech. Ventilation all

No. at Risk

Hydrocortisone	1832	1591	1481	1418	1388	1374	1356	1348	1328	1321
Placebo	1826	1546	1433	1376	1354	1337	1330	1322	1312	1300

The NEW ENGLAND JOURNAL of MEDICINE

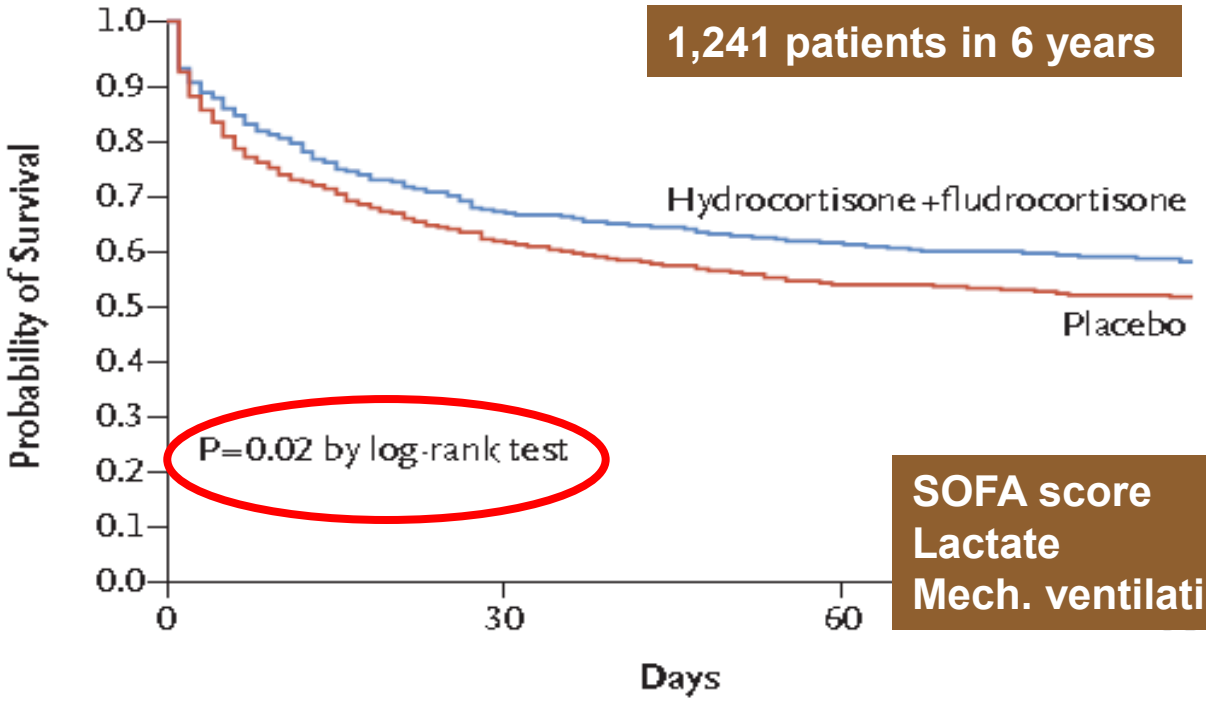
ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

2018

D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J.-P. Quenot, S. Siami, A. Cariou, X. Forceville, C. Schwebel, C. Martin, J.-F. Timsit, B. Misset, M. Ali Benali, G. Colin, B. Souweine, K. Asehnoune, E. Mercier, L. Chimot, C. Charpentier, B. François, T. Boulain, F. Petitpas, J.-M. Constantin, G. Dhonneur, F. Baudin, A. Combes, J. Bohé, J.-F. Loriferne, R. Amathieu, F. Cook, M. Slama, O. Leroy, G. Capellier, A. Dargent, T. Hissem, V. Maxime, and E. Bellissant, for the CRICS-TRIGGERSEP Network*

1,241 patients in 6 years



No. at Risk				
Hydrocortisone+ fludrocortisone	614	405	372	353
Placebo	627	381	333	319

SOFA score	**12**
Lactate	**4 .5 mMol/L**
Mech. ventilation	**92%**

The NEW ENGLAND JOURNAL of MEDICINE

2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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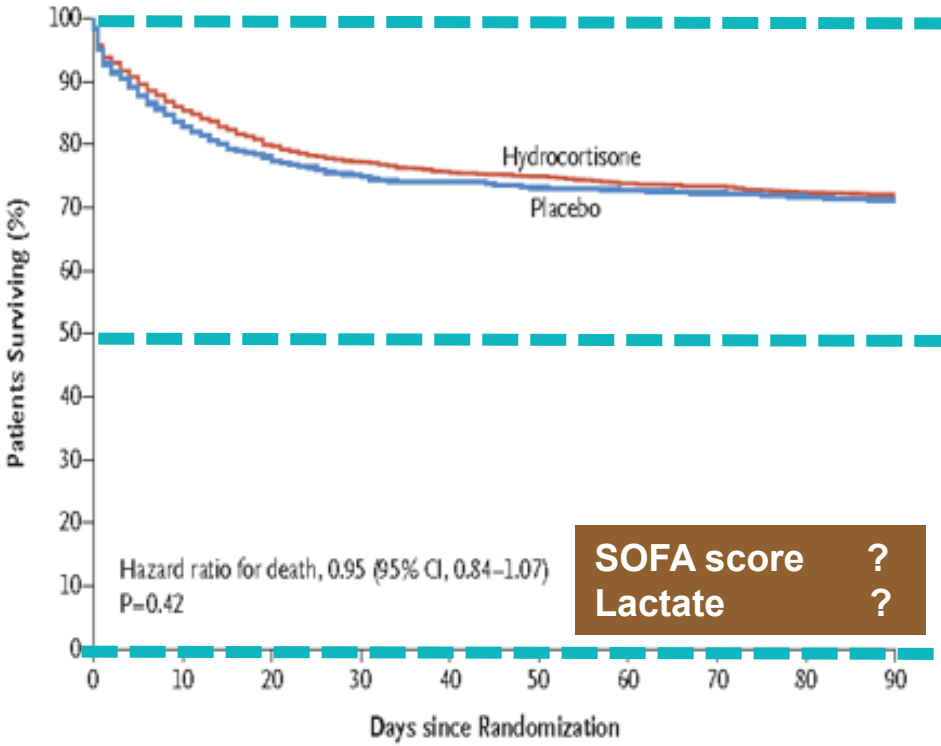
B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

Catechol dose > 15 mcg/min in 45% of patients
3800 patients in 4 years



SOFA score ?
Lactate ?

ORIGINAL ARTICLE

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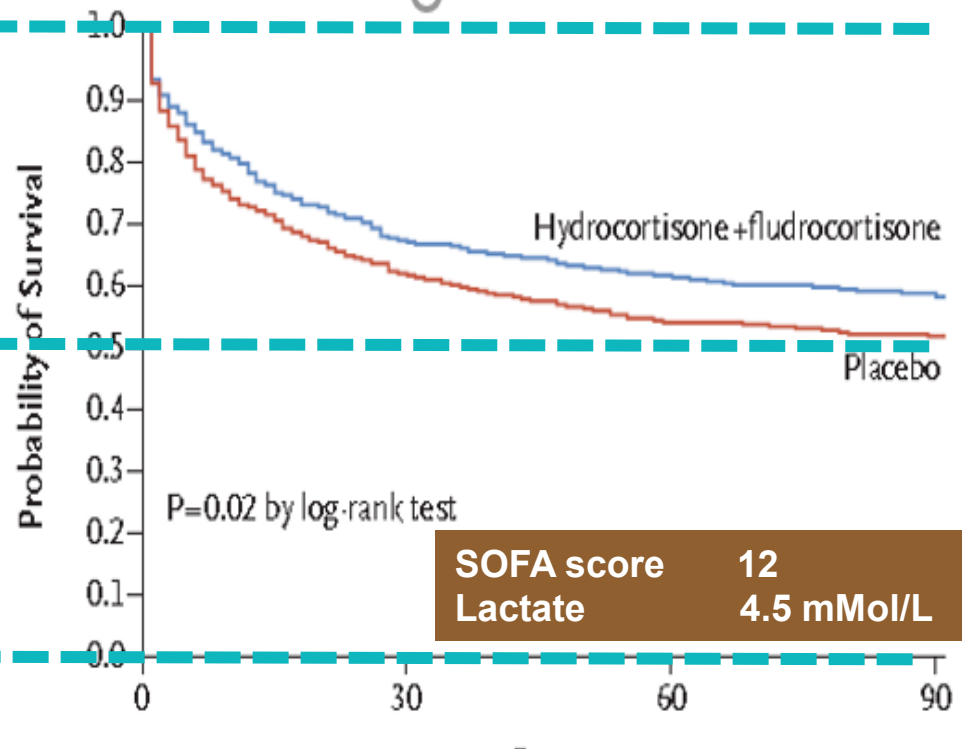
Norepi dose 1 mcg/kg/min
1033 patients in 7 years



SOFA score 12
Lactate 4.5 mMol/L

CRITICAL CARE MEDICINE

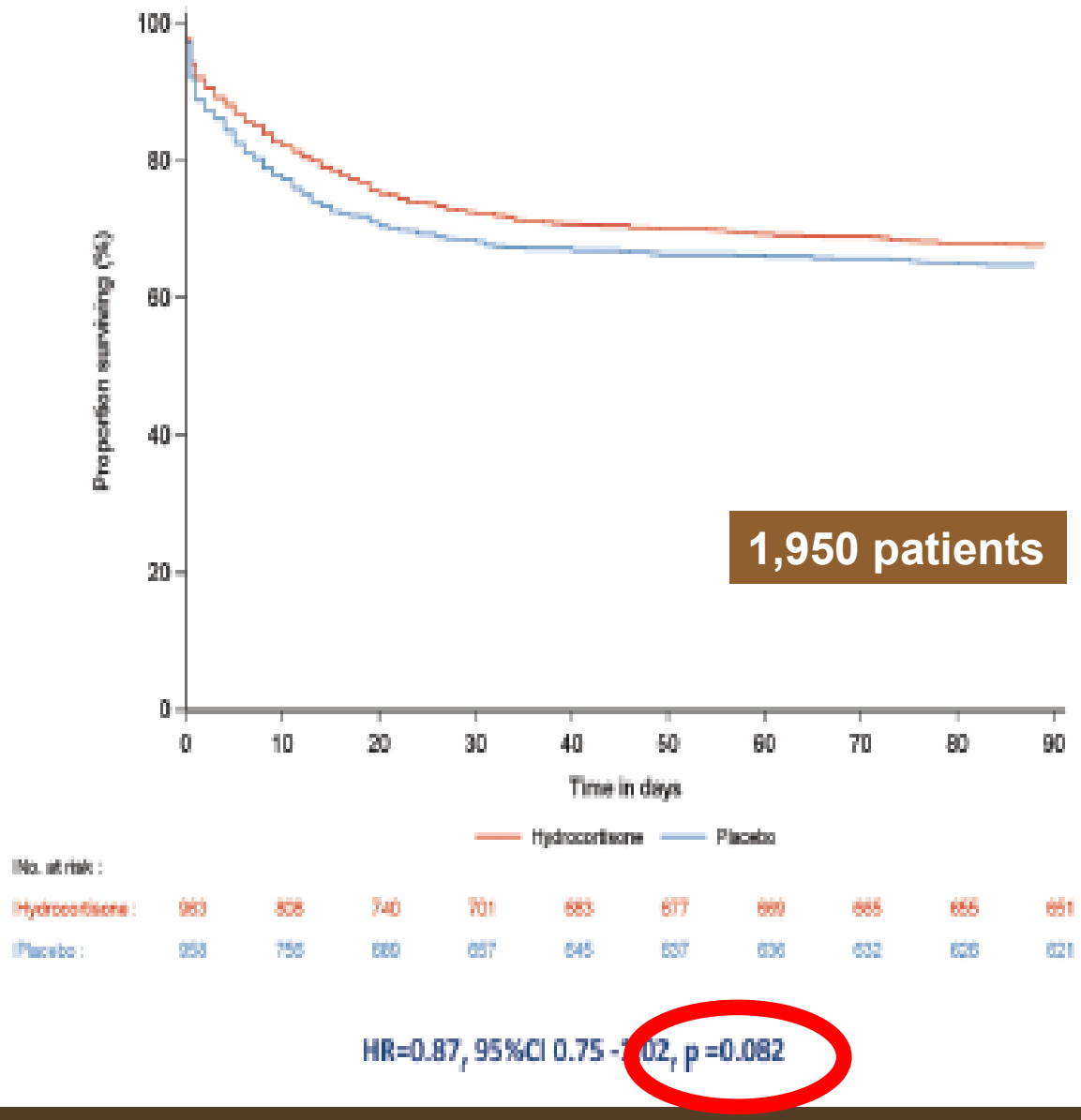
ANESTHESIOLOGY

Hydrocortisone Compared with Placebo in Patients with Septic Shock Satisfying the Sepsis-3 Diagnostic Criteria and APROCCHSS Study Inclusion Criteria

A *Post Hoc* Analysis of the ADRENAL Trial

Balasubramanian Venkatesh, M.D., Simon Finfer, M.D., Jeremy Cohen, M.D., Ph.D., Dorrilyn Rajbhandari, R.N., Yaseen Arabi, M.D., Rinaldo Bellomo, M.D., Laurent Billot, M.Sc., Parisa Glass, Ph.D., Christopher Joyce, M.D., Ph.D., Qiang Li, M.Biostat., Colin McArthur, M.D., Anders Perner, M.D., Ph.D., Andrew Rhodes, M.D., Kelly Thompson, R.N., M.P.H., Steve Webb, M.D., Ph.D., John Myburgh, M.D., Ph.D.

ANESTHESIOLOGY 2019; 131:1292–300



1,950 patients

Septic shock (including lactate > 2 mEq/L)

The NEW ENGLAND JOURNAL of MEDICINE

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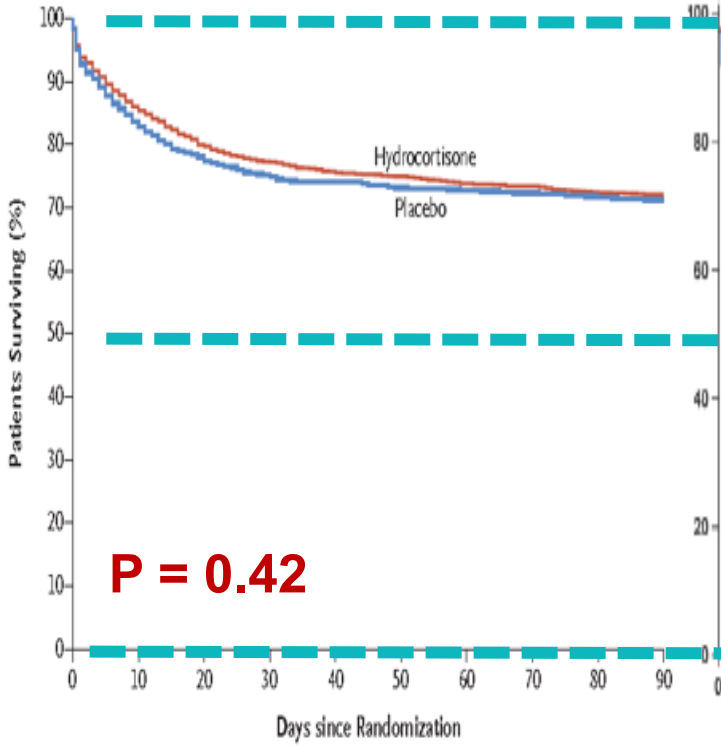
Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

norepi dose < 15 mcg/min in 55%
3800 patients in 4 years



ANESTHESIOLOGY

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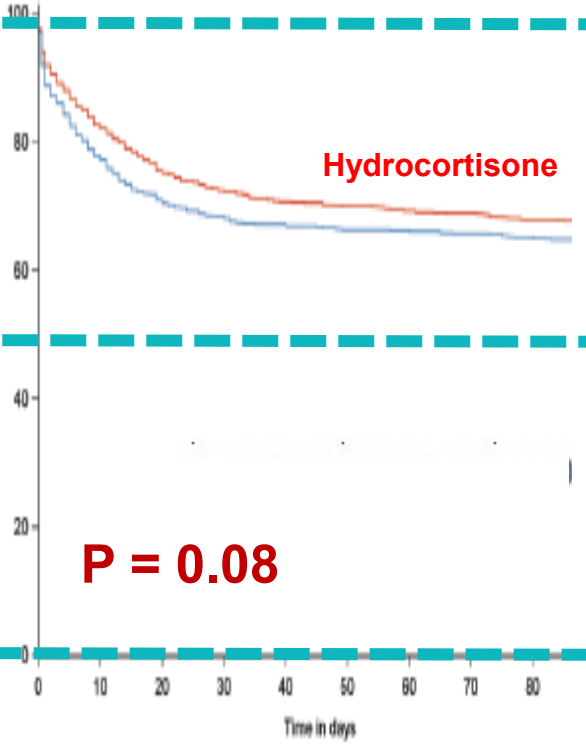

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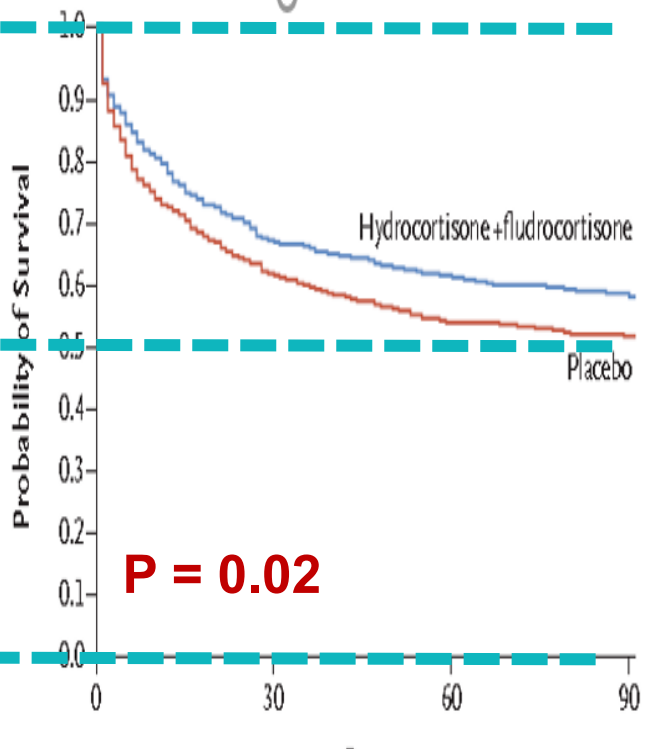
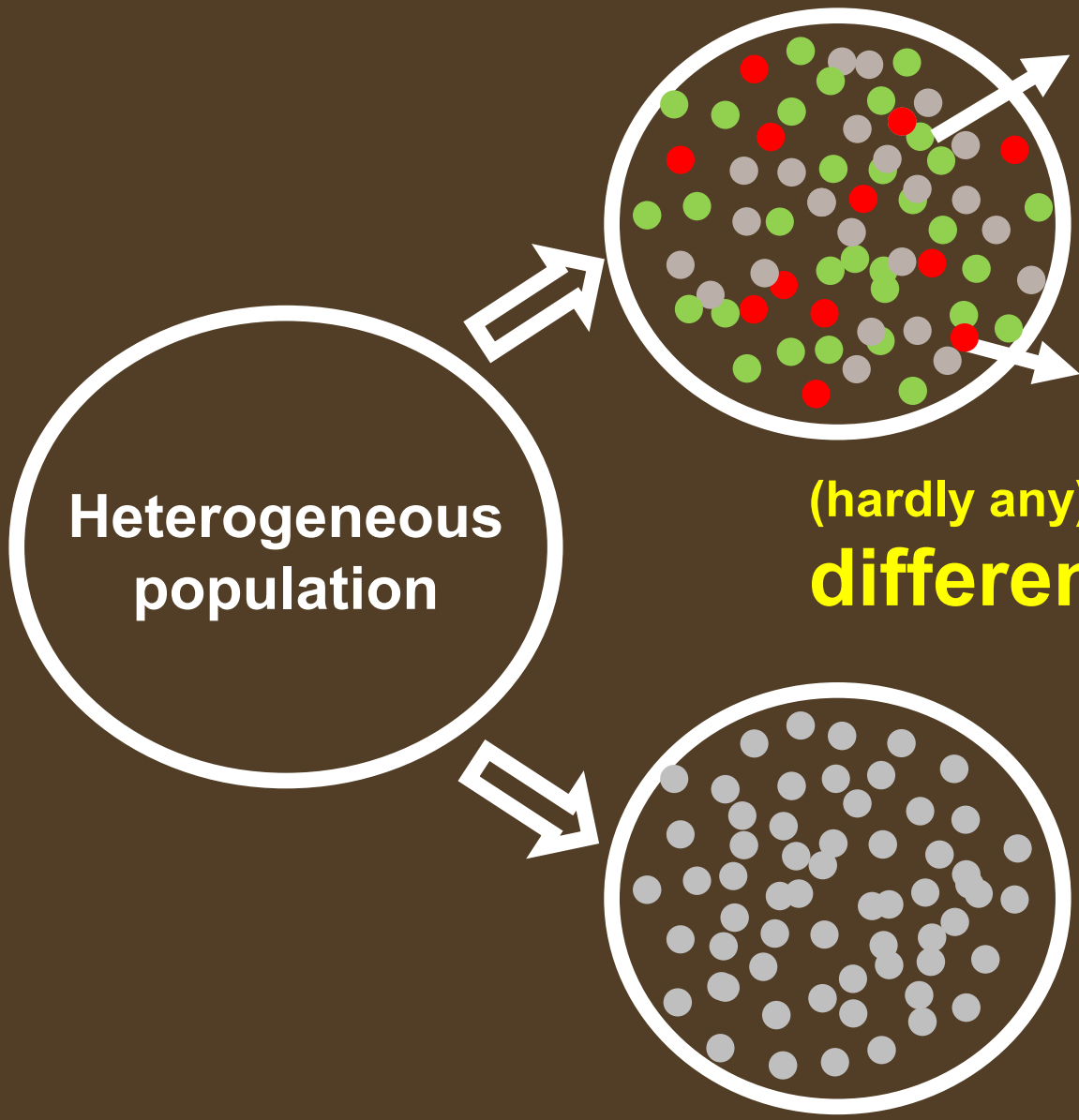
1033 patients in 7 years



RCT



Benefit > harm

Corticosteroids

Harm > benefit

(hardly any)

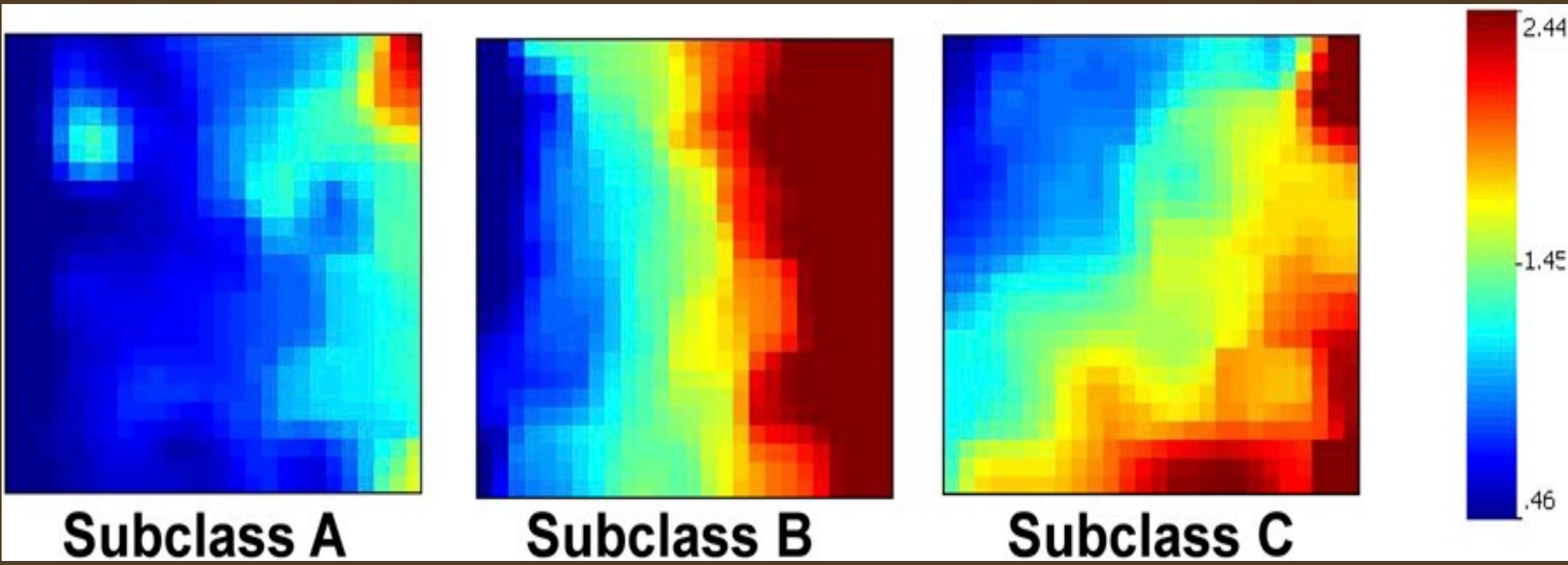
difference in outcome

Placebo

ORIGINAL ARTICLE

Developing a Clinically Feasible Personalized Medicine Approach to Pediatric Septic Shock

Hector R. Wong[1,2], Natalie Z. Cvijanovich[3], Nick Anas[4], Geoffrey L. Allen[5], Neal J. Thomas[6], Michael T. Bigham[7], Scott L. Weiss[8], Julie Fitzgerald[8], Paul A. Checchia[9], Keith Meyer[10], Thomas P. Shanley[11], Michael Quasney[11], Mark Hall[12], Rainer Gedeit[13], Robert J. Freishtat[14], Jeffrey Nowak[15], Raj S. Shekhar[16], Shira Gertz[17], Emily Dawson[18], Kelli Howard[1], Kelli Harmon[1], Eileen Beckman[1], Erin Frank[1], and Christopher J. Lindsell[19]



Worse outcome
Harmed by steroids

AJRCCM 2015 Feb 1;191(3):309-15.

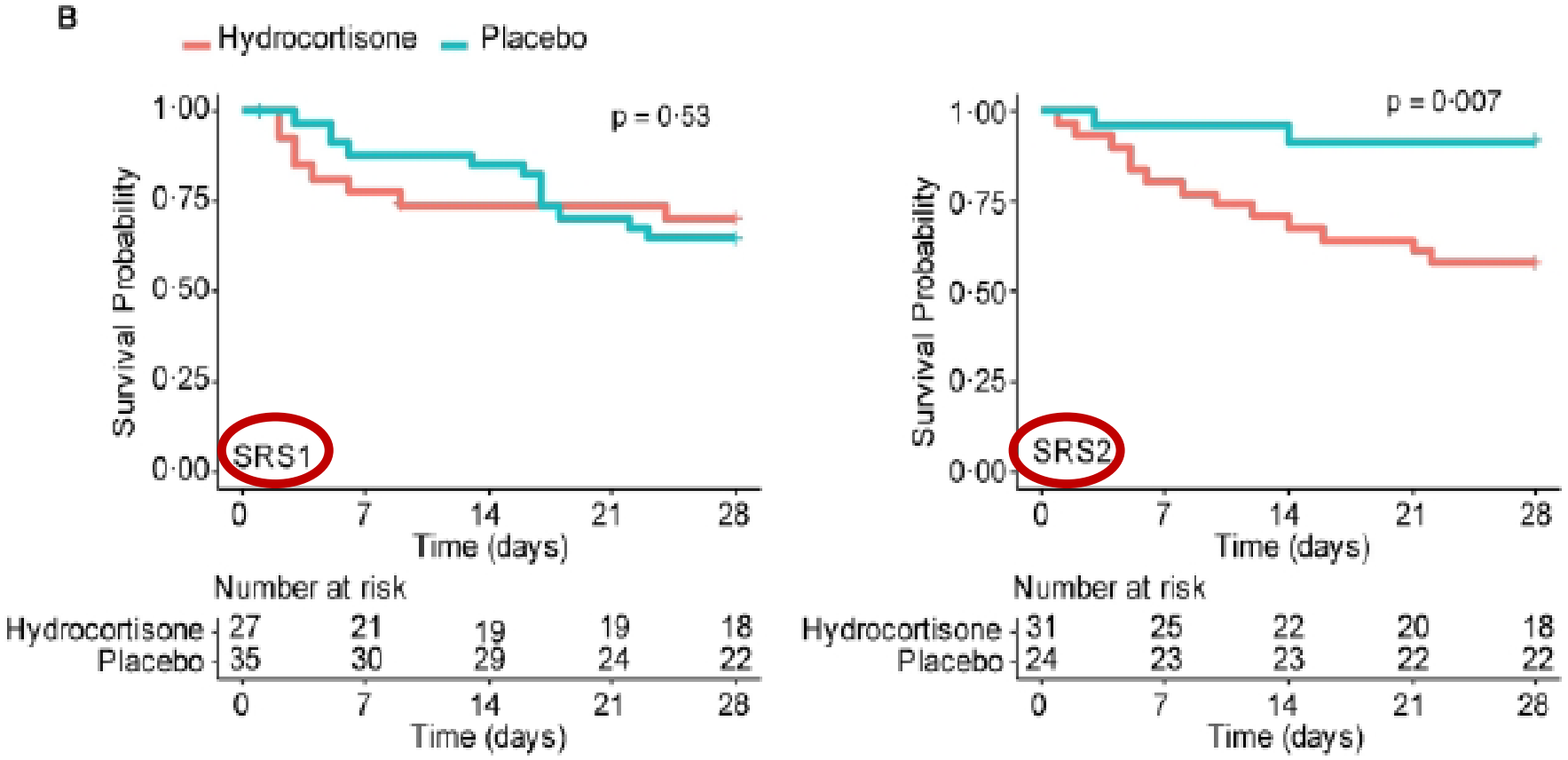
Transcriptomic Signatures in Sepsis and a Differential Response to Steroids

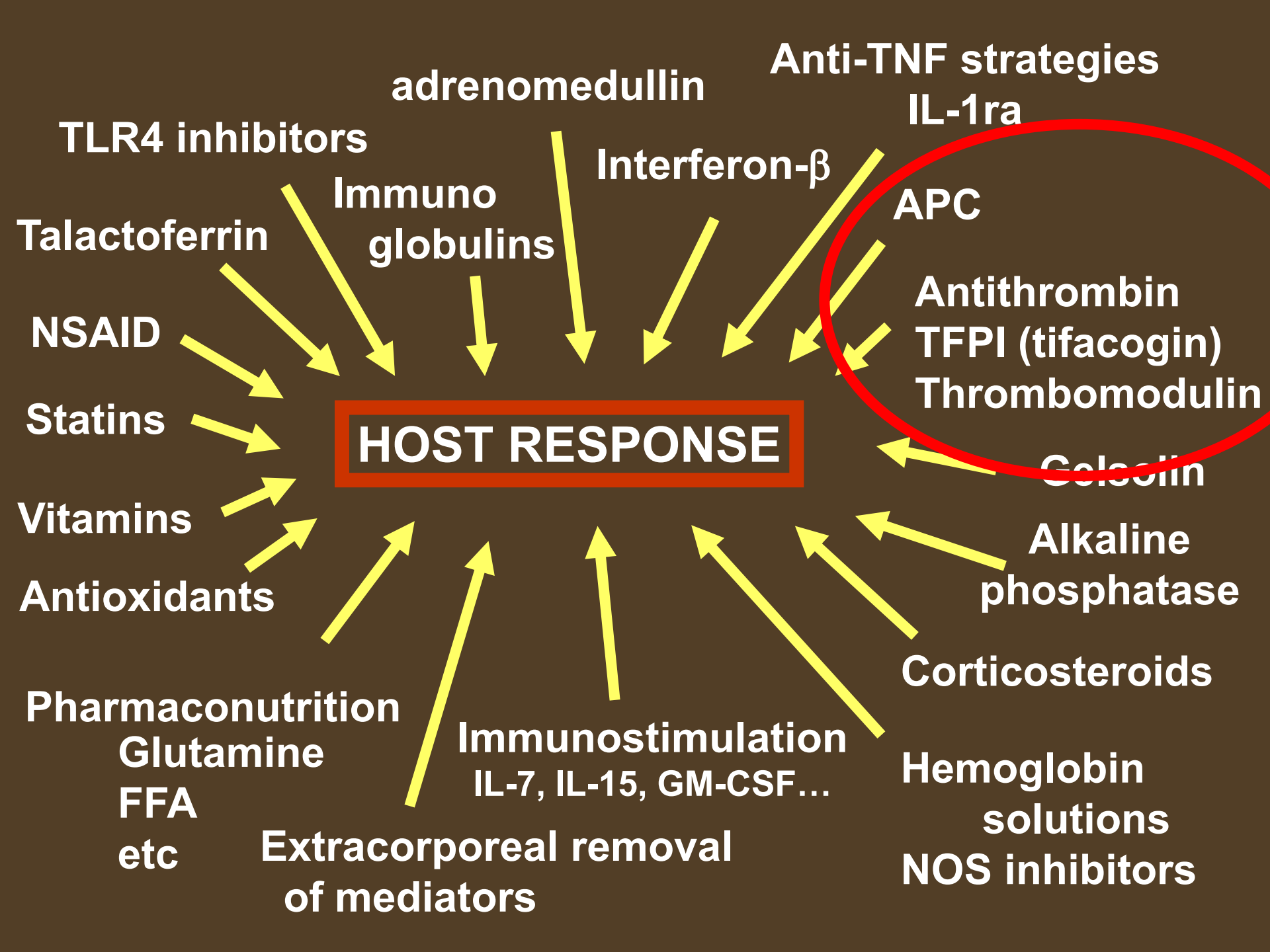
From the VANISH Randomized Trial

2019

David B. Antcliffe[1,2*], Katie L. Burnham[3*], Farah Al-Beidh[1], Shalini Santhakumaran[4], Stephen J. Brett[2], Charles J. Hinds[5], Deborah Ashby[4], Julian C. Knight[3], and Anthony C. Gordon[1,2]

[1]Section of Anaesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, United Kingdom; [2]Centre for Perioperative and Critical Care Research, Imperial College Healthcare National Health Service Trust, London, United Kingdom; [3]Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom; [4]Imperial Clinical Trials Unit, Faculty of Medicine, Imperial College London, London, United Kingdom; and [5]Intensive Care Unit, Barts and the London, Queen Mary School of Medicine, London, United Kingdom



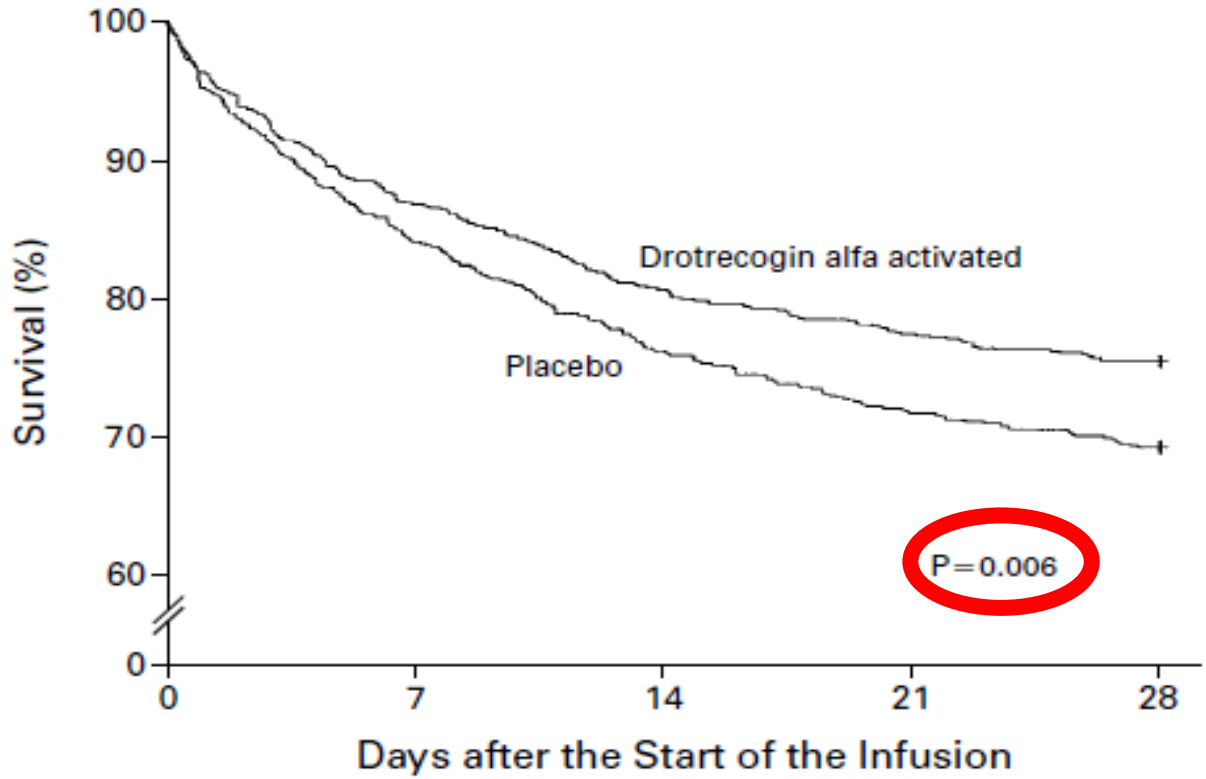

Anti-TNF strategies
IL-1ra
adrenomedullin
TLR4 inhibitors
Interferon-β
Immuno
globulins
APC
Talactoferrin
Antithrombin
TFPI (tifacogin)
Thrombomodulin
NSAID
Statins
HOST RESPONSE
Gelsolin
Vitamins
Alkaline
phosphatase
Antioxidants
Corticosteroids
Pharmaconutrition
Glutamine
FFA
etc
Immunostimulation
IL-7, IL-15, GM-CSF…
Hemoglobin
solutions
NOS inhibitors
Extracorporeal removal
of mediators

The New England
Journal of Medicine

VOLUME 344 MARCH 8, 2001 NUMBER 10

EFFICACY AND SAFETY OF RECOMBINANT HUMAN ACTIVATED PROTEIN C FOR SEVERE SEPSIS

GORDON R. BERNARD, M.D., JEAN-LOUIS VINCENT, M.D., PH.D., PIERRE-FRANCOIS LATERRE, M.D., STEVEN P. LAROSA, M.D., JEAN-FRANCOIS DHAINAUT, M.D., PH.D., ANGEL LOPEZ-RODRIGUEZ, M.D., JAY S. STEINGRUB, M.D., GARY E. GARBER, M.D., JEFFREY D. HELTERBRAND, PH.D., E. WESLEY ELY, M.D., M.P.H., AND CHARLES J. FISHER, JR., M.D., FOR THE RECOMBINANT HUMAN ACTIVATED PROTEIN C WORLDWIDE EVALUATION IN SEVERE SEPSIS (PROWESS) STUDY GROUP*



1690 patients
11 countries
164 sites

Let us do another clinical trial

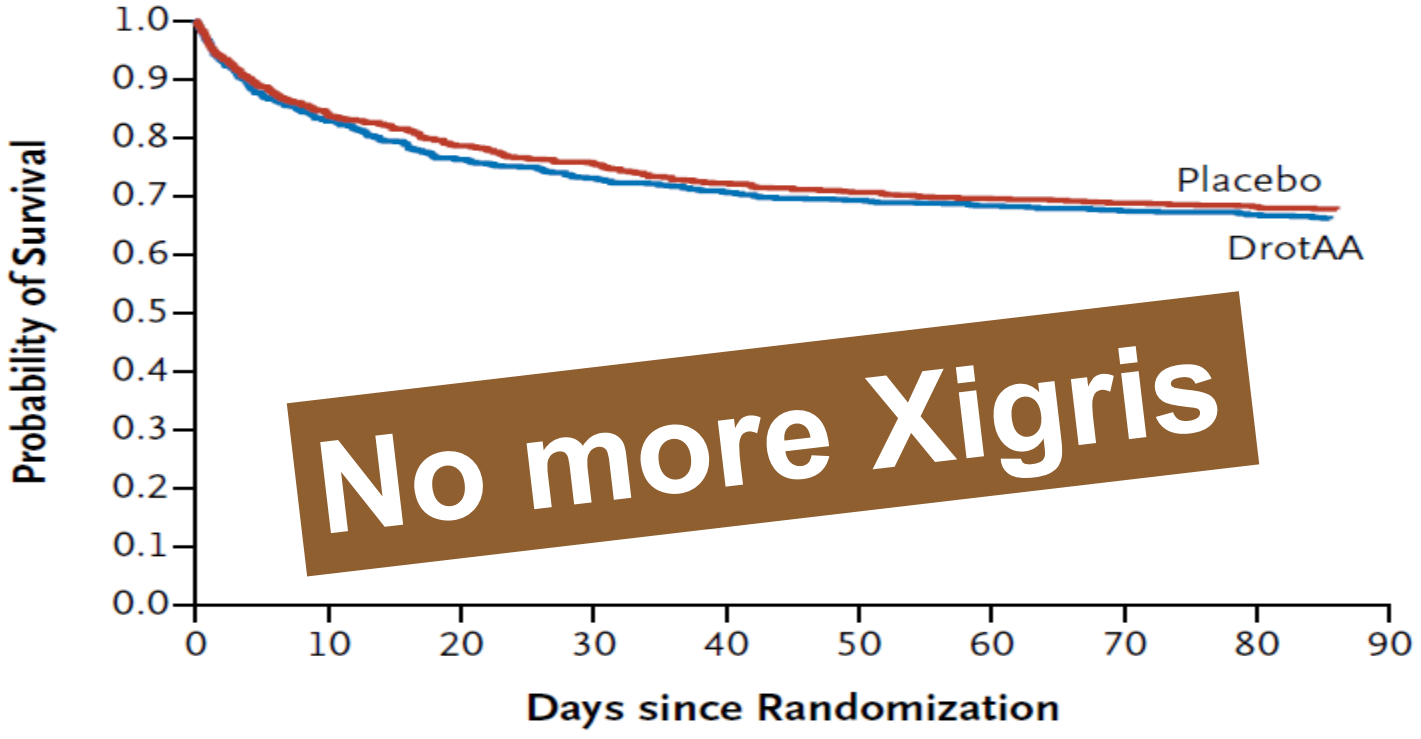
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PROWESS-SHOCK TRIAL

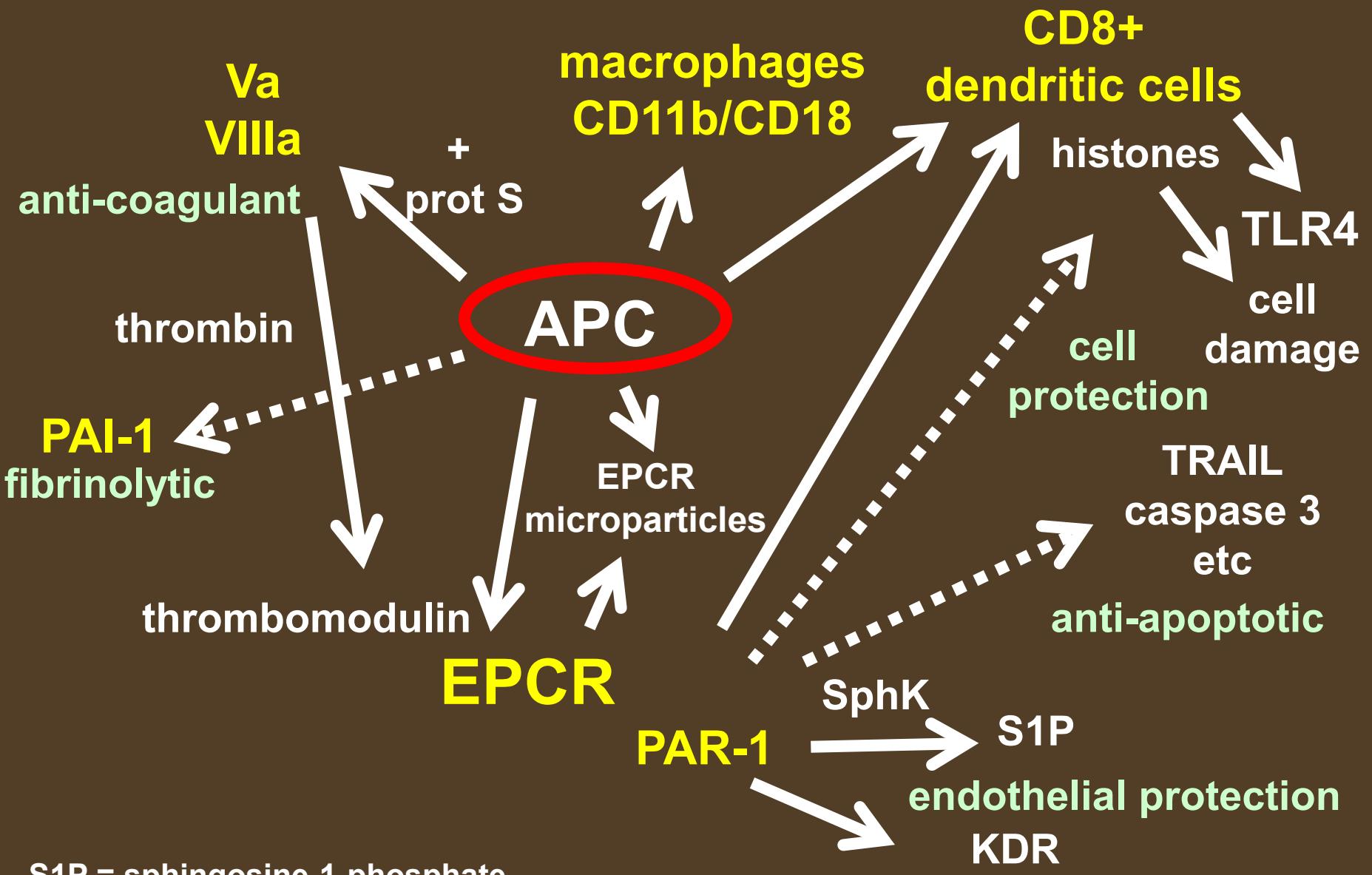
Drotrecogin Alfa (Activated) in Adults with Septic Shock

V. Marco Ranieri, M.D., B. Taylor Thompson, M.D., Philip S. Barie, M.D., M.B.A., Jean-François Dhainaut, M.D., Ivor S. Douglas, M.D., Simon Finfer, F.R.C.P., Bengt Gårdlund, M.D., John C. Marshall, M.D., Andrew Rhodes, M.D., Antonio Artigas, M.D., Ph.D., Didier Payen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D., Hussein R. Al-Khalidi, Ph.D., Vivian Thompson, M.P.H., Jonathan Janes, M.B., B.Ch., William L. Macias, M.D., Ph.D., Burkhard Vangerow, M.D., and Mark D. Williams, M.D., for the PROWESS-SHOCK Study Group*



No more Xigris

THE COMPLEX MODE OF ACTION OF APC



S1P = sphingosine-1-phosphate
KDR = kinase insert domain receptor

Thrombomodulin

ART-123

ARTISAN study

Phase IIb study

(N = 750)

Inclusion Criteria: DIC due to sepsis

Exclusion Criteria:

- Subjects < 18 years of age
- Known conditions that could confound the diagnosis of DIC due to sepsis
- Known conditions that increase the risk of bleeding
- Known medical condition associated with a hypercoagulable state
- Known or suspected severe liver disease
- History of solid organ (excluding uncomplicated kidney), bone marrow or stem cell transplantation
- Renal failure

741 patients

A Randomized, Double-Blind, Placebo-Controlled, Phase 2b Study to Evaluate the Safety and Efficacy of Recombinant Human Soluble Thrombomodulin, ART-123, in Patients With Sepsis and Suspected Disseminated Intravascular Coagulation*

Jean-Louis Vincent, MD, PhD, FCCM[1]; Mayakonda K. Ramesh, MS[2]; David Ernest, MBBS[3]; Steven P. LaRosa, MD[4]; Jan Pachl, MD, PhD[5]; Naoki Aikawa, MD, DMSc, FACS[6]; Eric Hoste, MD, PhD[7]; Howard Levy, MB, BCh, PhD[8]; Joe Hirman, PhD[9]; Marcel Levi, MD, PhD[10]; Mradul Daga, MD, FCCP[11]; Demetrios J. Kutsogiannis, MD, MHS[12]; Mark Crowther, MD, MSc, FRCPC[13]; Gordon R. Bernard, MD[14]; Jacques Devriendt, MD[15]; Joan Vidal Puigserver, MD[16]; Daniel U. Blanzaco, MD[17]; Charles T. Esmon, PhD[18]; Joseph E. Parrillo, MD[19]; Louis Guzzi, MD, FCCM[20]; Seton J. Henderson, MB, ChB[21]; Chaicharn Pothirat, MD, FCCP[22]; Parthiv Mehta, MD[23]; Jawed Fareed, PhD, FAHA[24]; Deepak Talwar, MD, DM, DNB[25]; Kazuhisa Tsuruta, PhD[26]; Kenneth J. Gorelick, MD, FCCP[27]; Yutaka Osawa, MPharm[26]; Inder Kaul, MD, MPH[26]

(*Crit Care Med* 2013; 41:2070–2079)

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- **ART-123 treatment effect most evident**
  - **Respiratory or cardiac dysfunction**
  - **INR > 1.40**
  - **Platelets 30 – 150K**

Survival Status	ART-123 n (%)	Placebo n (%)	Total n (%)
N	80	76	156
Dead	21 (26.3)	29 (38.2)	50 (32.1)
Alive	59 (73.8)	47 (61.8)	106 (67.9)

(*Crit Care Med* 2013; 41:2070–2079)

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Recombinant Human Soluble Thrombomodulin on Mortality in Patients With Sepsis-Associated Coagulopathy The SCARLET Randomized Clinical Trial

2019

Jean-Louis Vincent, MD, PhD; Bruno Francois, MD; Igor Zabolotskikh, MD, PhD; Mradul Kumar Daga, MD; Jean-Baptiste Lascarrou, MD; Mikhail Y. Kirov, MD; Ville Pettilä, MD; Xavier Wittebole, MD; Ferhat Meziani, MD, PhD; Emmanuelle Mercier, MD; Suzana M. Lobo, MD, PhD; Philip S. Barie, MD, MBA; Mark Crowther, MD; Charles T. Esmon, PhD; Jawed Fareed, PhD; Satoshi Gando, MD, PhD; Kenneth J. Gorelick, MD, PhD; Marcel Levi, MD, PhD; Jean-Paul Mira, MD, PhD; Steven M. Opal, MD; Joseph Parrillo, MD, PhD; James A. Russell, MD; Hidehiko Saito, MD, PhD; Kazuhisa Tsuruta, PhD; Takumi Sakai; David Fineberg, MD; for the SCARLET Trial Group

- **Randomized, double-blind, placebo-controlled, phase 3 study to assess the safety and efficacy of ART-123 in patients with sepsis and coagulopathy**

1º efficacy endpoint - 28 day mortality

- **Inclusion/Exclusion**
  - **Infection (febrile, known source controlled, WBC) AND**
  - **Organ dysfunction (CV or pulmonary) AND**
  - **Coagulopathy (INR >1.40 AND thrombocytopenia)**

SCARLET STUDY

N = 800 patients

Recomodulin

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Recombinant Human Soluble Thrombomodulin on Mortality in Patients With Sepsis-Associated Coagulopathy
The SCARLET Randomized Clinical Trial

2019

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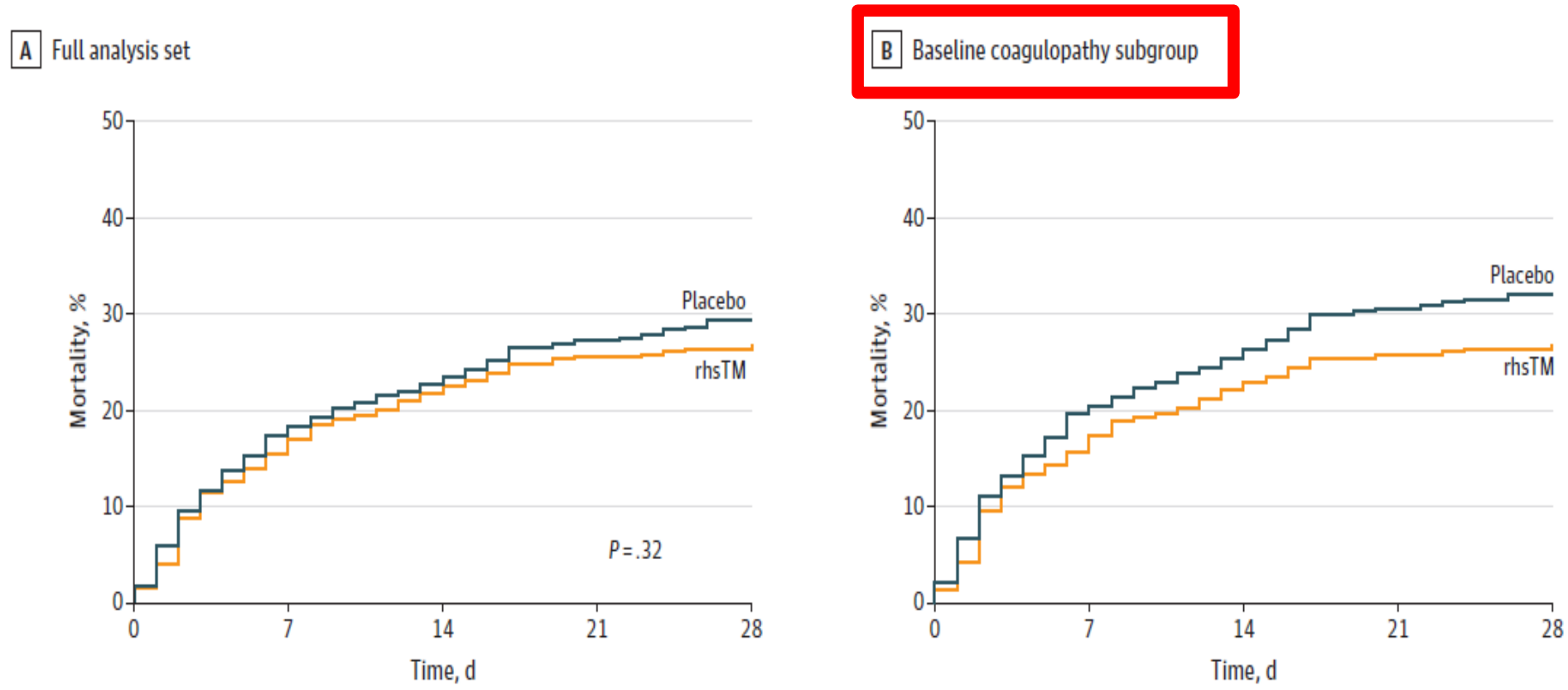
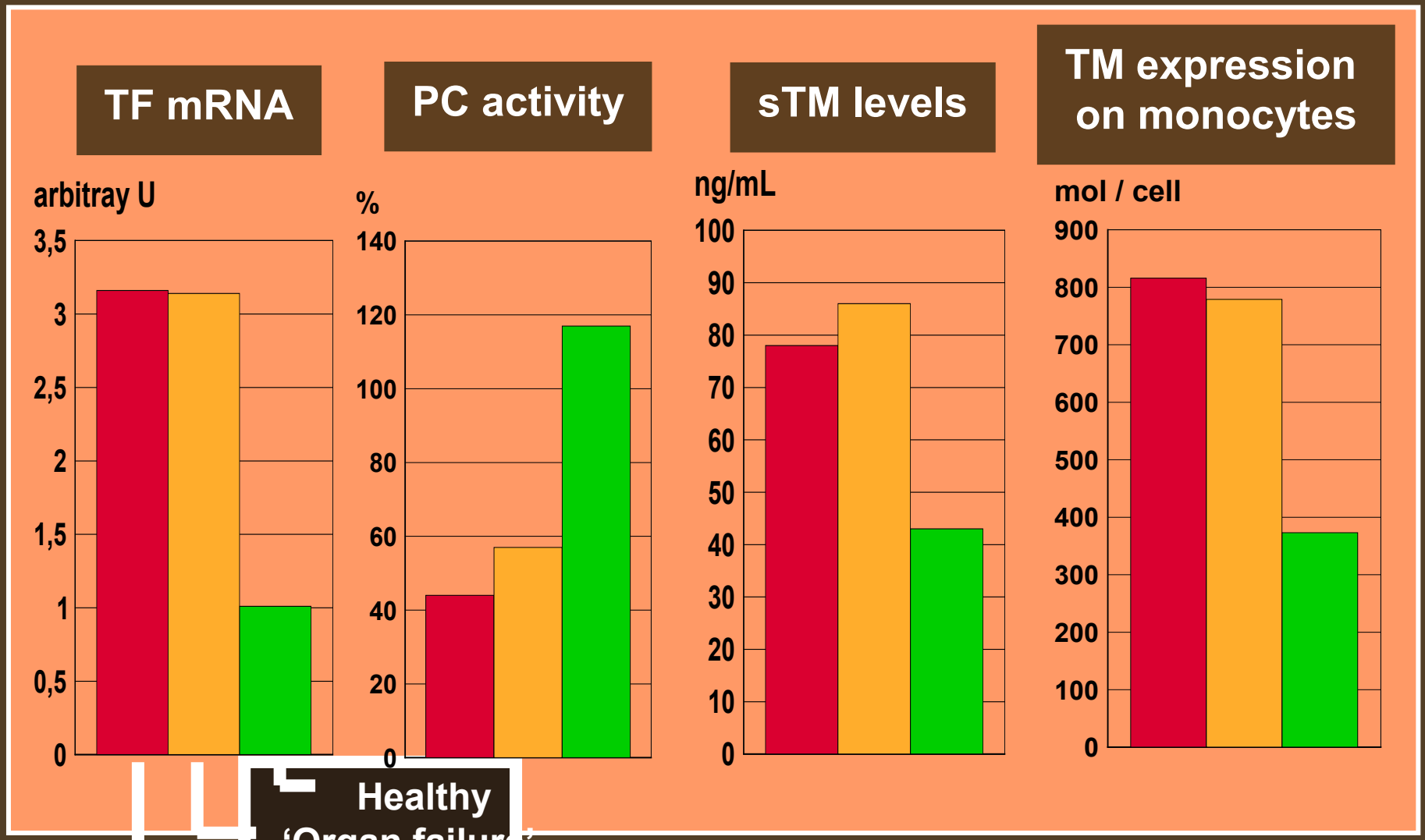


THE END OF ‘SEPSIS DRUGS’ ?

Protein C pathway in septic and non-septic patients with organ failure

Borgel et al, Am J Respir Crit Care Med 176: 878-85, 2007



Thrombomodulin

Patient population

ORGAN FAILURE

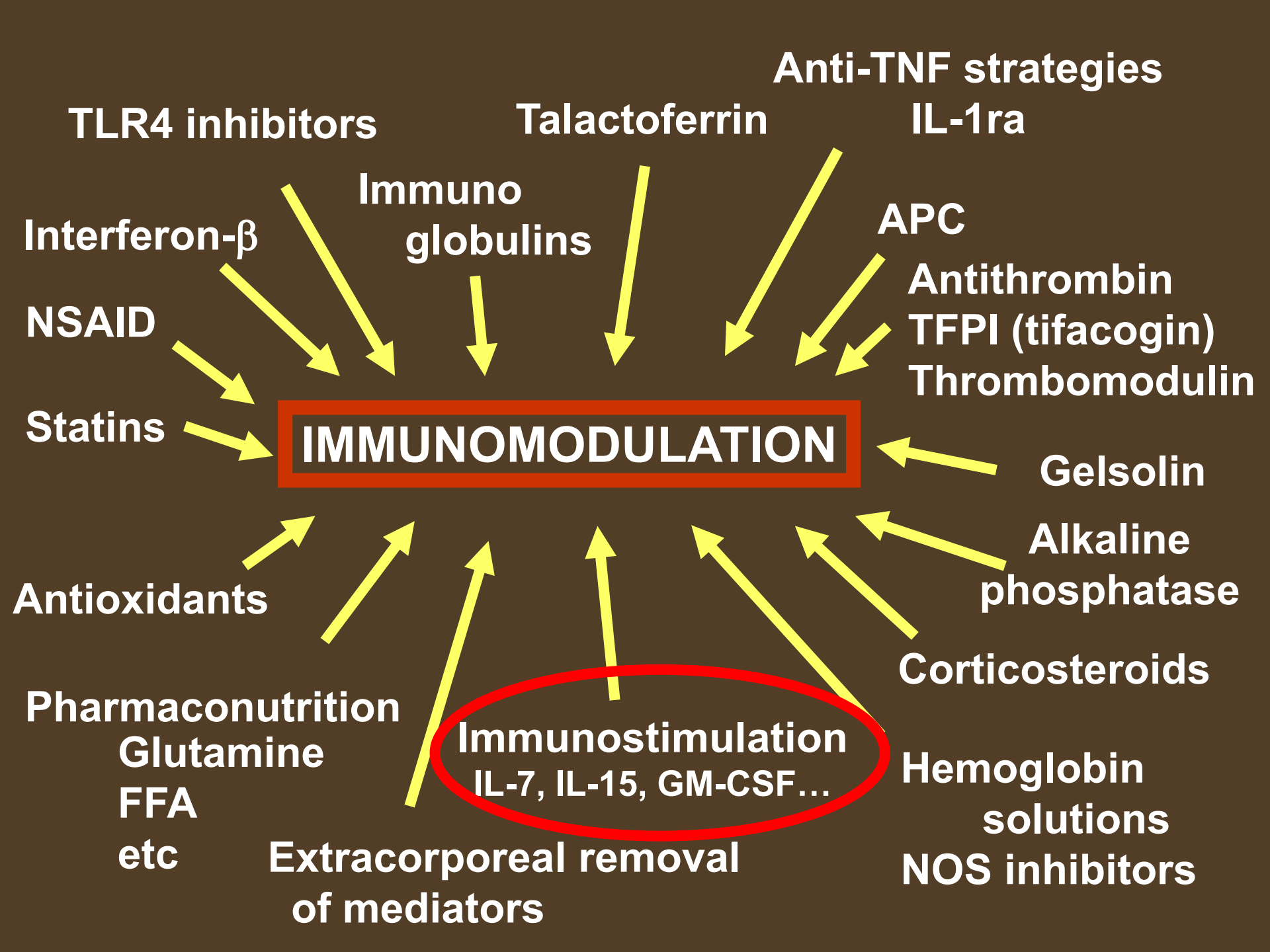
+

DIC

? **?**

ALARM SIGNAL

- ✓ Low platelet count
- ✓ Prolonged INR

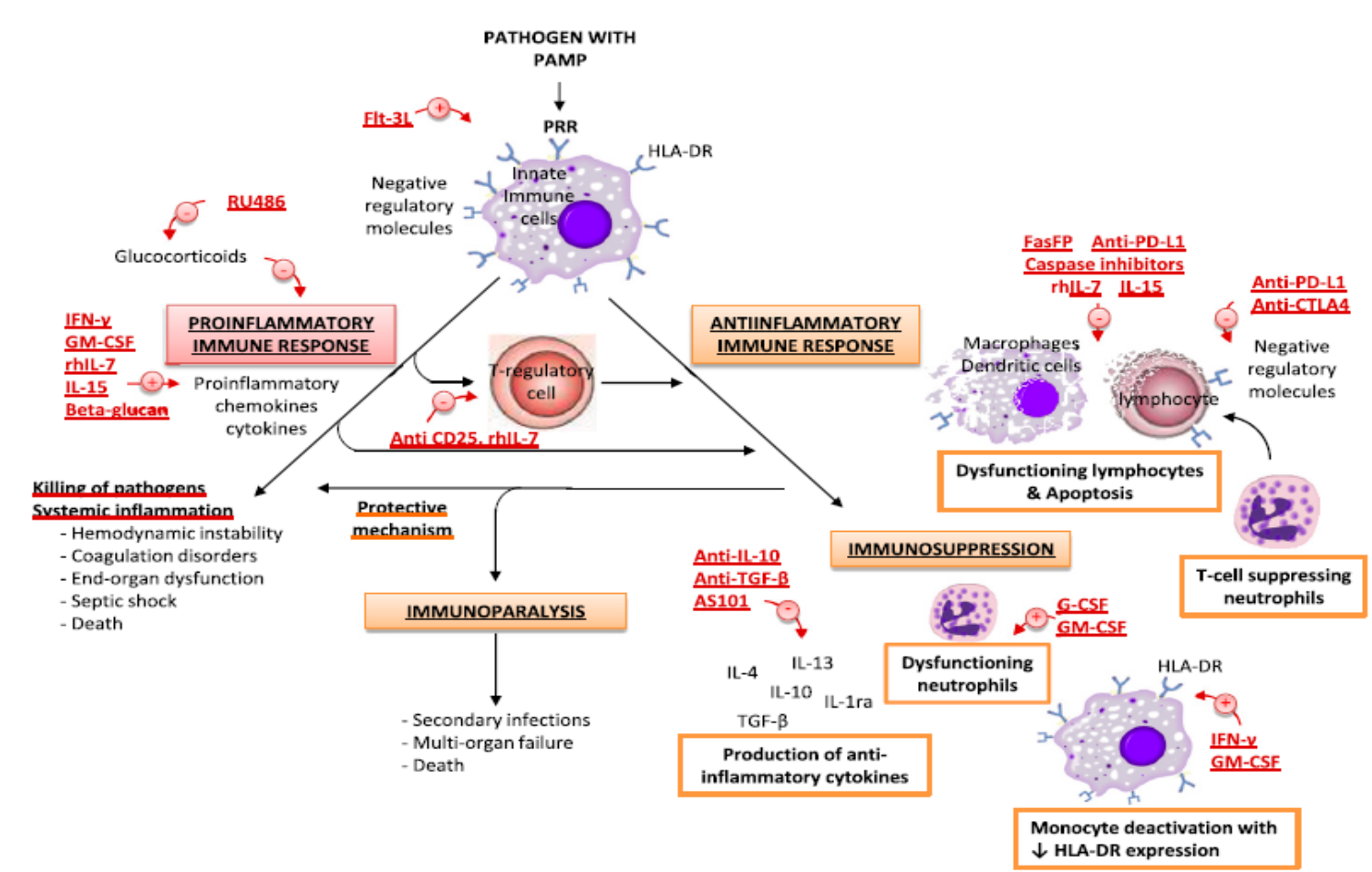

Anti-TNF strategies
IL-1ra
TLR4 inhibitors
Talactoferrin
Immuno
globulins
Interferon-β
APC
Antithrombin
TFPI (tifacogin)
Thrombomodulin
NSAID
Statins
IMMUNOMODULATION
Gelsolin
Alkaline
phosphatase
Antioxidants
Corticosteroids
Pharmaconutrition
Glutamine
FFA
etc
Immunostimulation
IL-7, IL-15, GM-CSF…
Hemoglobin
solutions
NOS inhibitors
Extracorporeal removal
of mediators

Immunotherapy for the Adjunctive Treatment of Sepsis: From Immunosuppression to Immunostimulation

Time for a Paradigm Change?

Jenneke Leentjens[1,2,3], Matthijs Kox[1,3,4], Johannes G. van der Hoeven[1,3], Mihai G. Netea[2,3], and Peter Pickkers[1,3]

[1]Department of Intensive Care Medicine, [2]Department of Internal Medicine, and [4]Department of Anesthesiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; and [3]Nijmegen Institute for Infection, Inflammation, and Immunity, Nijmegen, The Netherlands



Am J Respir Crit Care Med Vol 187, Iss. 12, pp 1287–1293, Jun 15, 2013


SEPSIS

SEPSIS THERAPIES

OPTION	PROBLEM
Blocking one mediator (e.g. TNF)	Can be bypassed (redundant systems) Neither ‘good’ nor ‘bad’

SEPSIS

is not just a **pro-inflammatory** response

but a ***dysregulated*** host response

Endotype Transitions During the Acute Phase of Pediatric Septic Shock Reflect Changing Risk and Treatment Response

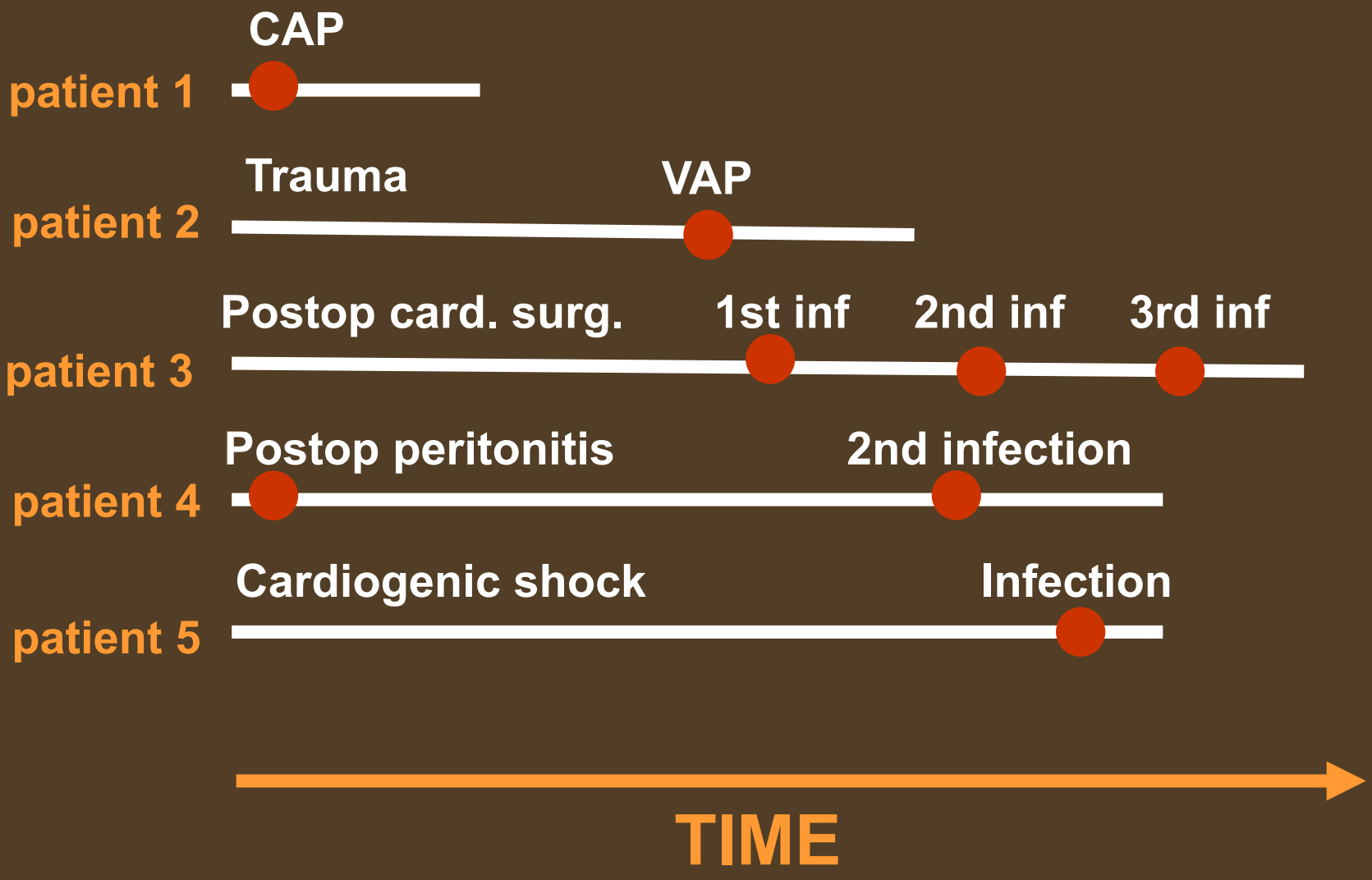
2018

Hector R. Wong, MD[1,2]; Natalie Z. Cvijanovich, MD[3]; Nick Anas, MD[4]; Geoffrey L. Allen, MD[5]; Neal J. Thomas, MD[6]; Michael T. Bigham, MD[7]; Scott L. Weiss, MD[8]; Julie C. Fitzgerald, MD, PhD[8]; Paul A. Checchia, MD[9]; Keith Meyer, MD[10]; Michael Quasney, MD, PhD[11]; Mark Hall, MD[12]; Rainer Gedeit, MD[13]; Robert J. Freishtat, MD[14]; Jeffrey Nowak, MD[15]; Riad Lutfi, MD[16]; Shira Gertz, MD[17]; Jocelyn R. Grunwell, MD, PhD[18]; Christopher J. Lindsell, PhD[19]

Crit Care Med

Change over time…

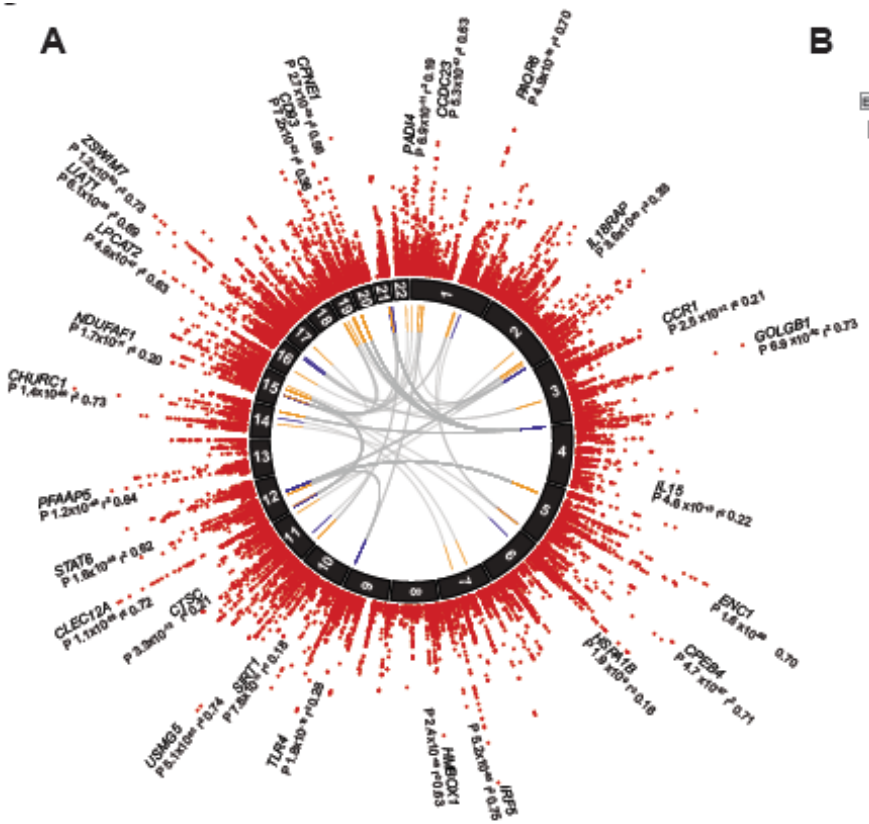
A POPULATION OF SEPTIC PATIENTS



2016

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

Emma E Davenport, Katie L Burnham, Jayachandran Radhakrishnan*, Peter Humburg, Paula Hutton, Tara C Mills, Anna Rautanen, Anthony C Gordon, Christopher Garrard, Adrian V S Hill, Charles J Hinds, Julian C Knight*



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Summary

Background Effective targeted therapy for sepsis requires an understanding of the heterogeneity in the individual host response to infection. We investigated this heterogeneity by defining interindividual variation in the transcriptome of patients with sepsis and related this to outcome and genetic diversity.

Methods We assayed peripheral blood leucocyte global gene expression for a prospective discovery cohort of 265 adult patients admitted to UK intensive care units with sepsis due to community-acquired pneumonia and evidence of

Lancet Respir Med 2016
Published Online
February 22, 2016
http://dx.doi.org/10.1016/S2213-2600(16)00046-1

*Contributed equally

Transcriptomic analysis of peripheral blood leucocytes

↓

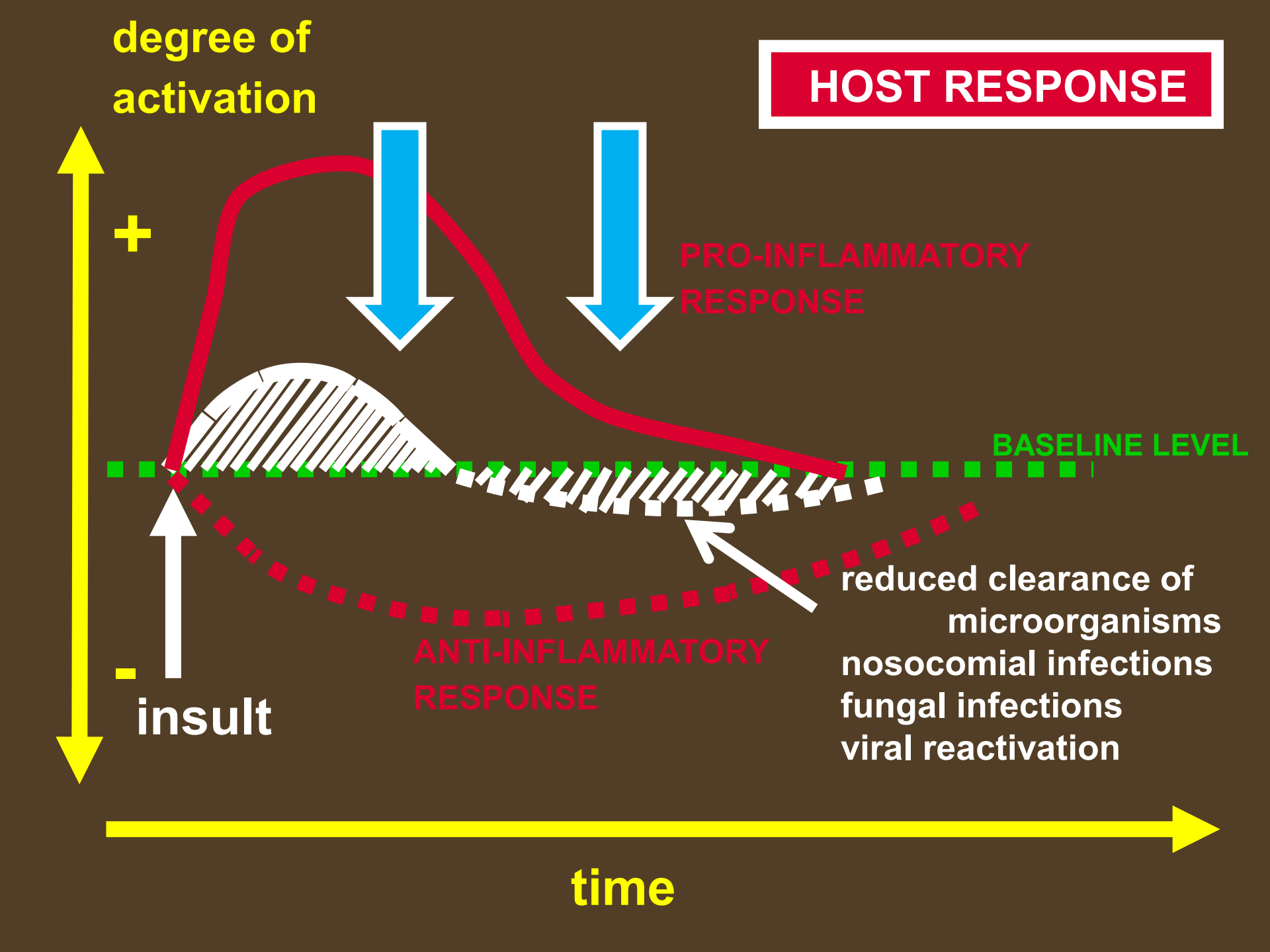
sepsis response signatures

↙ ↘

SRS1
Immunosuppressed phenotype

SRS2

41 % of patients
Increased mortality rate by about 2.5
No relation with timing since admission
Not suspected from clinical evaluation

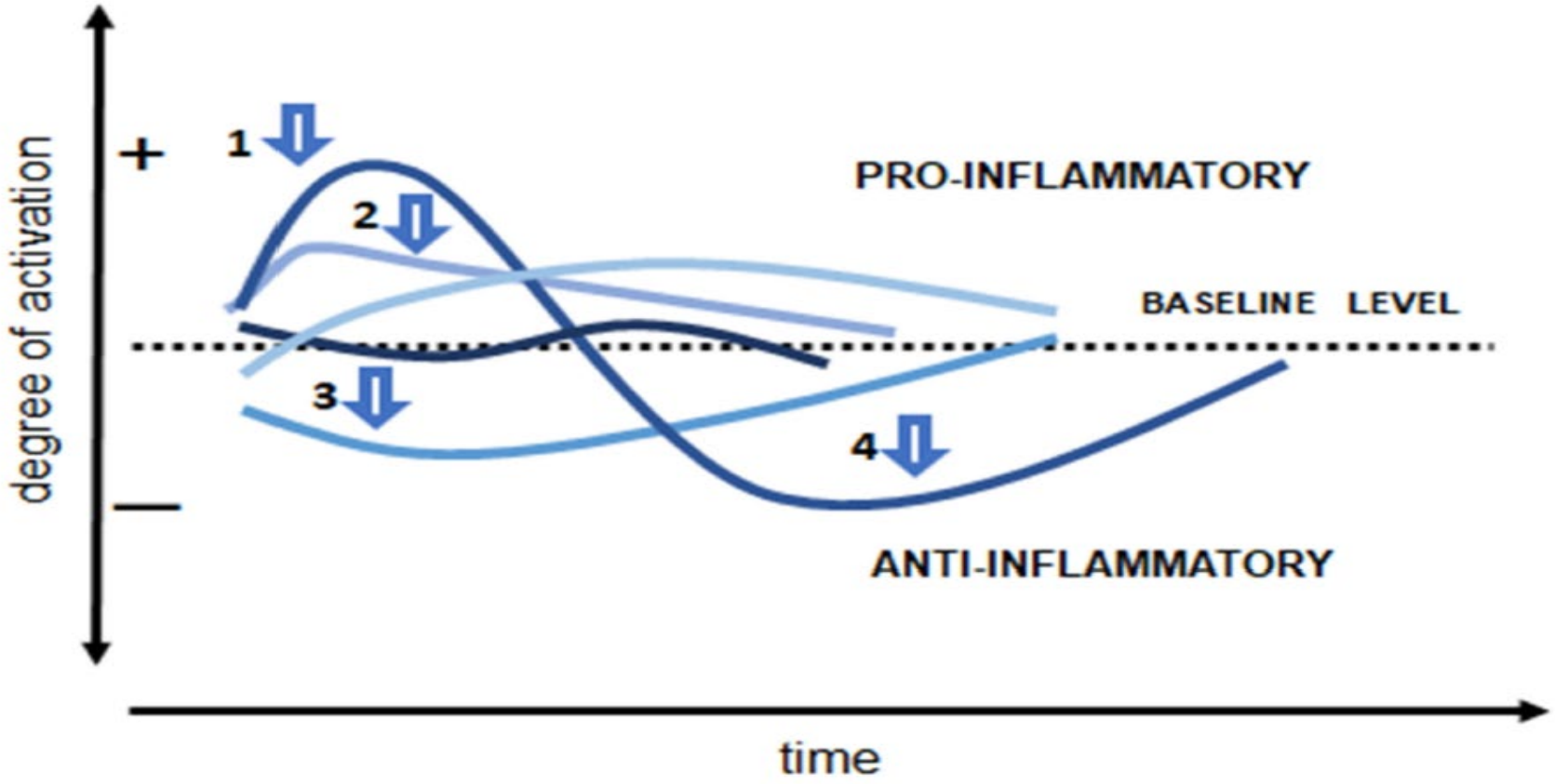

degree of activation
HOST RESPONSE
+
PRO-INFLAMMATORY RESPONSE
BASELINE LEVEL
ANTI-INFLAMMATORY RESPONSE
reduced clearance of microorganisms
nosocomial infections
fungal infections
viral reactivation
-
insult
time

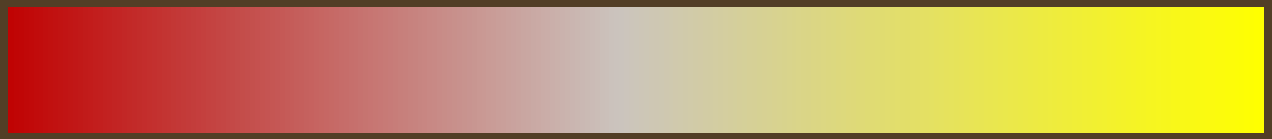
biomedicines 2022

Review

The End of "One Size Fits All" Sepsis Therapies: Toward an Individualized Approach

Jean-Louis Vincent [1,*], Tom van der Poll [2,3] and John C. Marshall [4]





Pro-inflammatory state

Acquired immunosuppression

Diagnosis

Very high CRP
High ferritin

Decreased HLA-DR expression
Low lymphocyte count

Some therapeutic options

Corticosteroids
Anti-TNF
IL-1ra

Interferon-γ
IL-7
GM-CSF
Anti-PD1

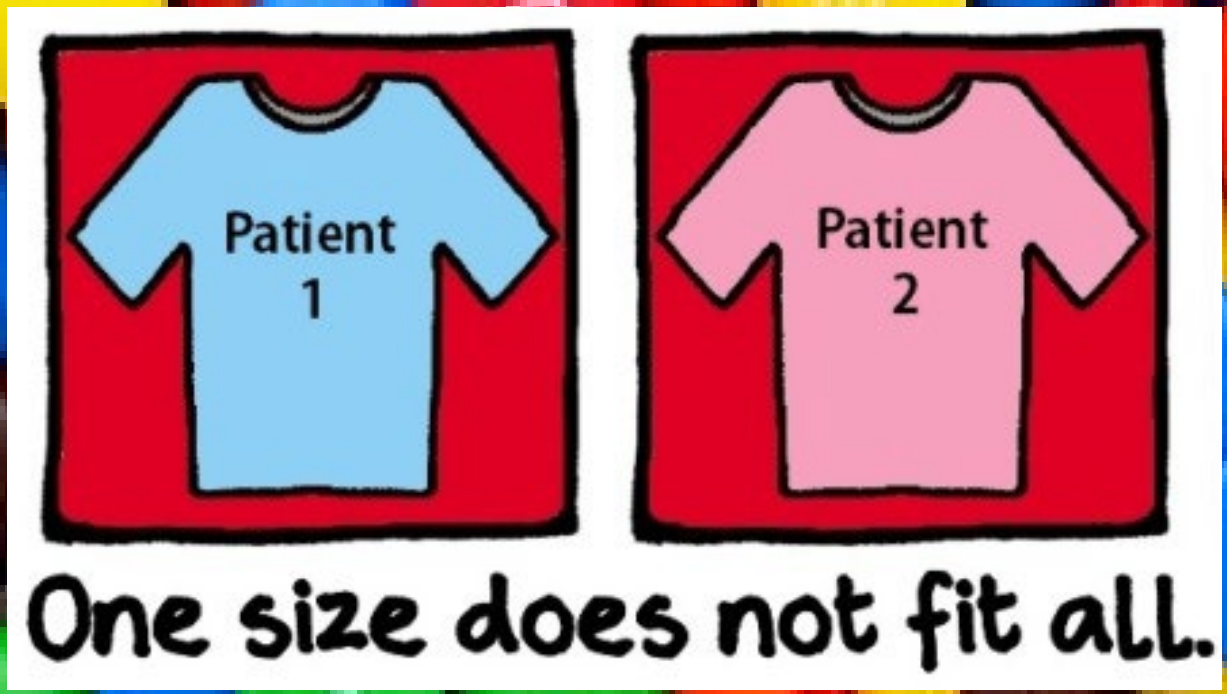
Immune monitoring in sepsis

The three hurdles

The characteristics can change rapidly over time

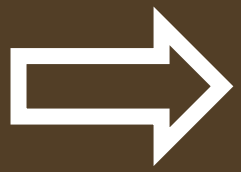
There can be mixed pro- and anti-inflammatory responses

Changes observed in the blood may not reflect changes in the tissues


Patient 1
Patient 2
One size does not fit all.

Sepsis therapies ??

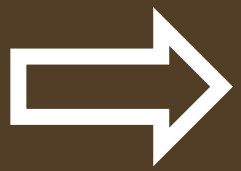
Sepsis



Sepsis drug

One size fits all

Particular phenotype



Specific drug

DIC
Specific type of organ dysfunction
Elevated biomarker level
Markers of immunosuppression

Individualized

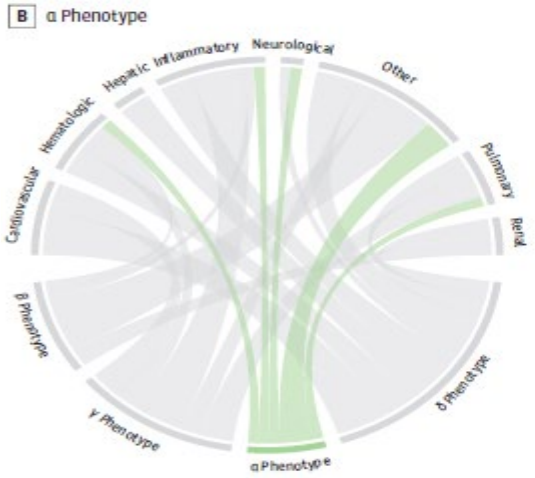
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

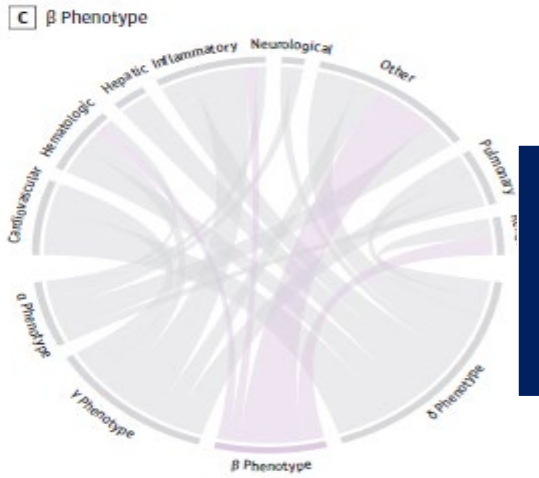
Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis

2019

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

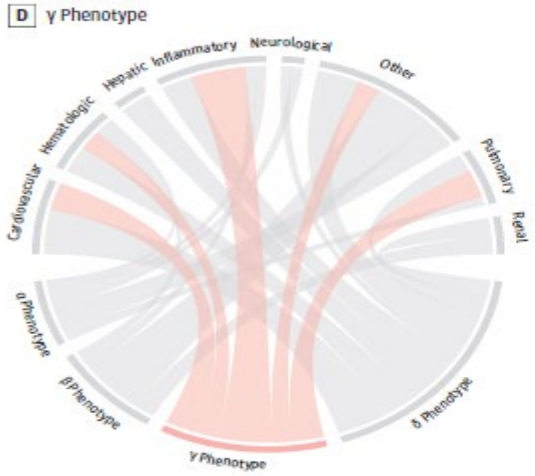
α 33%
Mortality 5%

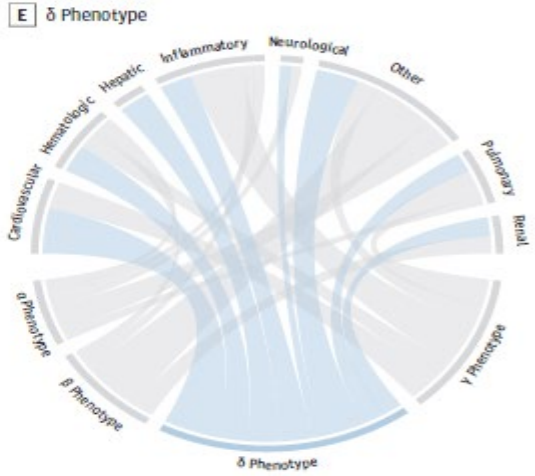




β 27%
Mortality 13%
Older
Chronic illness

γ 27%
Mortality 24%
Inflammation
Lung dysfunction



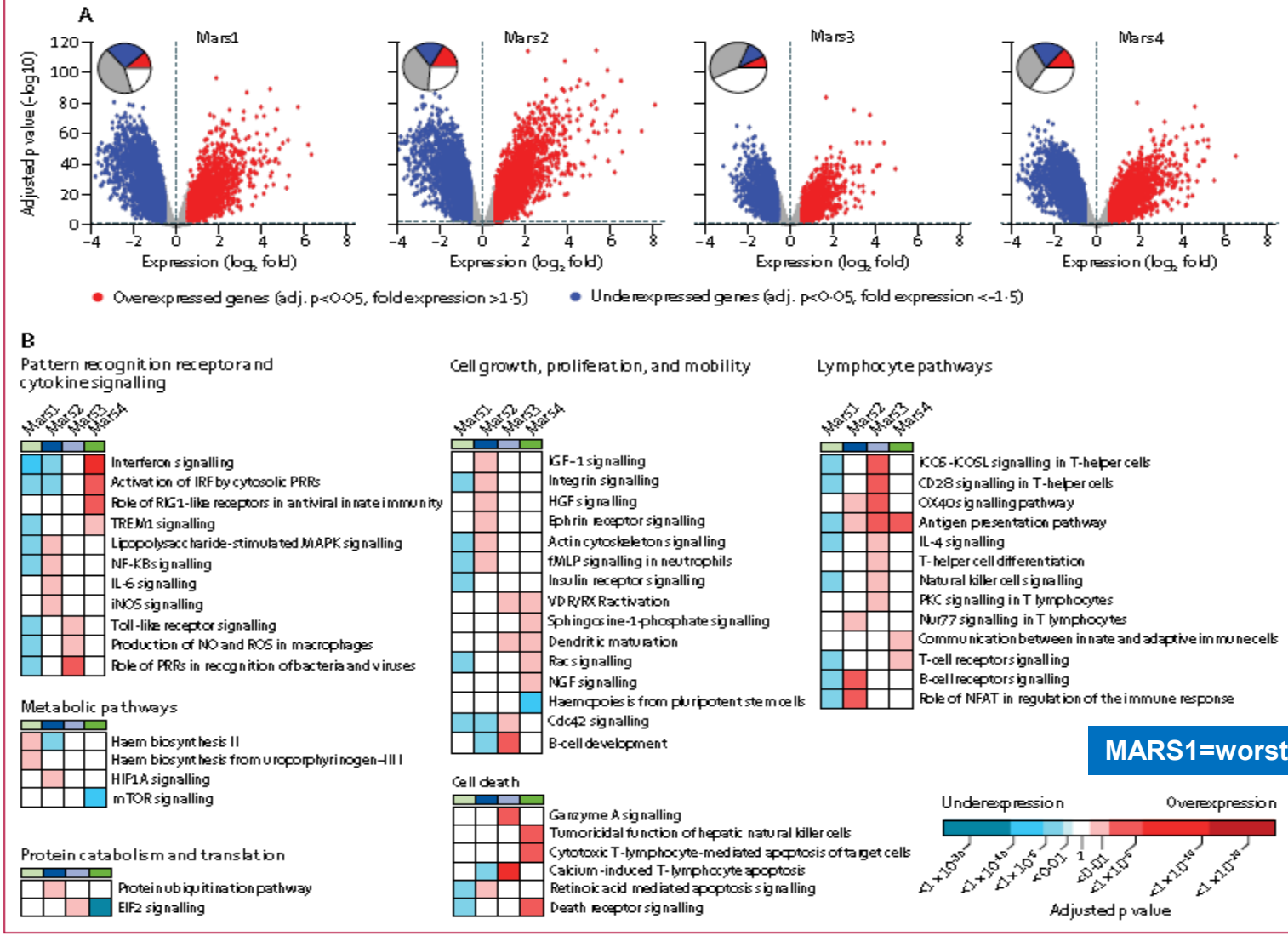


δ 13%
Mortality 40%
Liver alterations
Septic shock

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*

Lancet Respir Med 2017

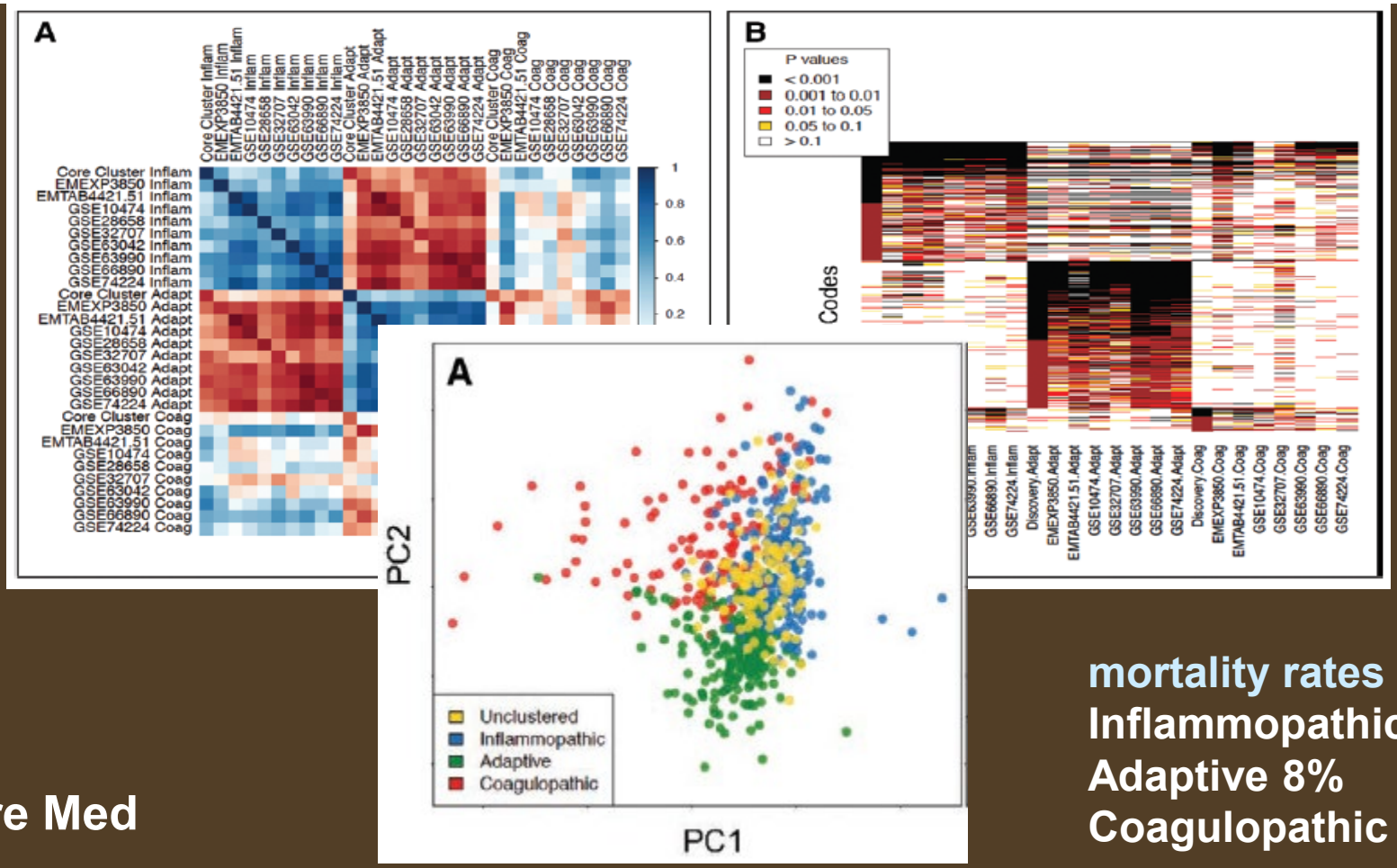


MARS1=worst outcome

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

2018

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]



Crit Care Med

mortality rates
Inflammopathic 30%
Adaptive 8%
Coagulopathic 25%

Ma et al. Crit Care (2021) 25:243
https://doi.org/10.1186/s13054-021-03682-7

Critical Care

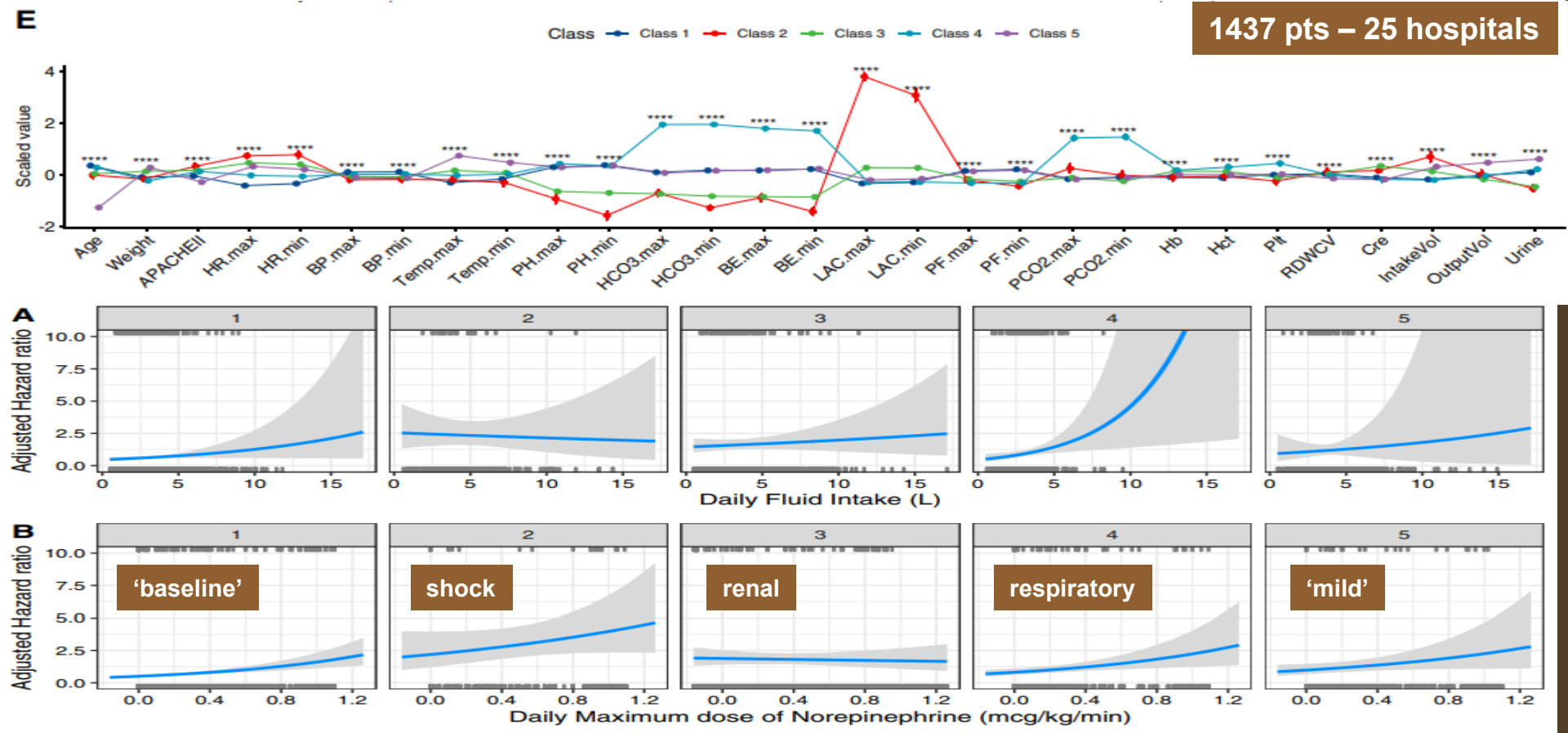
RESEARCH Open Access

2021

Individualized resuscitation strategy for septic shock formalized by finite mixture modeling and dynamic treatment regimen

Penglin Ma[1†], Jingtao Liu[2†], Feng Shen[3], Xuelian Liao[4], Ming Xiu[5], Heling Zhao[6], Mingyan Zhao[7], Jing Xie[8], Peng Wang[9], Man Huang[10], Tong Li[11], Meili Duan[12], Kejian Qian[13], Yue Peng[14], Feihu Zhou[15], Xin Xin[16], Xianyao Wan[17], ZongYu Wang[18], Shusheng Li[19], Jianwei Han[20], Zhenliang Li[21], Guolei Ding[22], Qun Deng[23], Jicheng Zhang[24], Yue Zhu[25], Wenjing Ma[26], Jingwen Wang[27], Yan Kang[28] and Zhongheng Zhang[29*]

1437 pts – 25 hospitals



A Data-Driven Approach to Predicting Septic Shock in the Intensive Care Unit

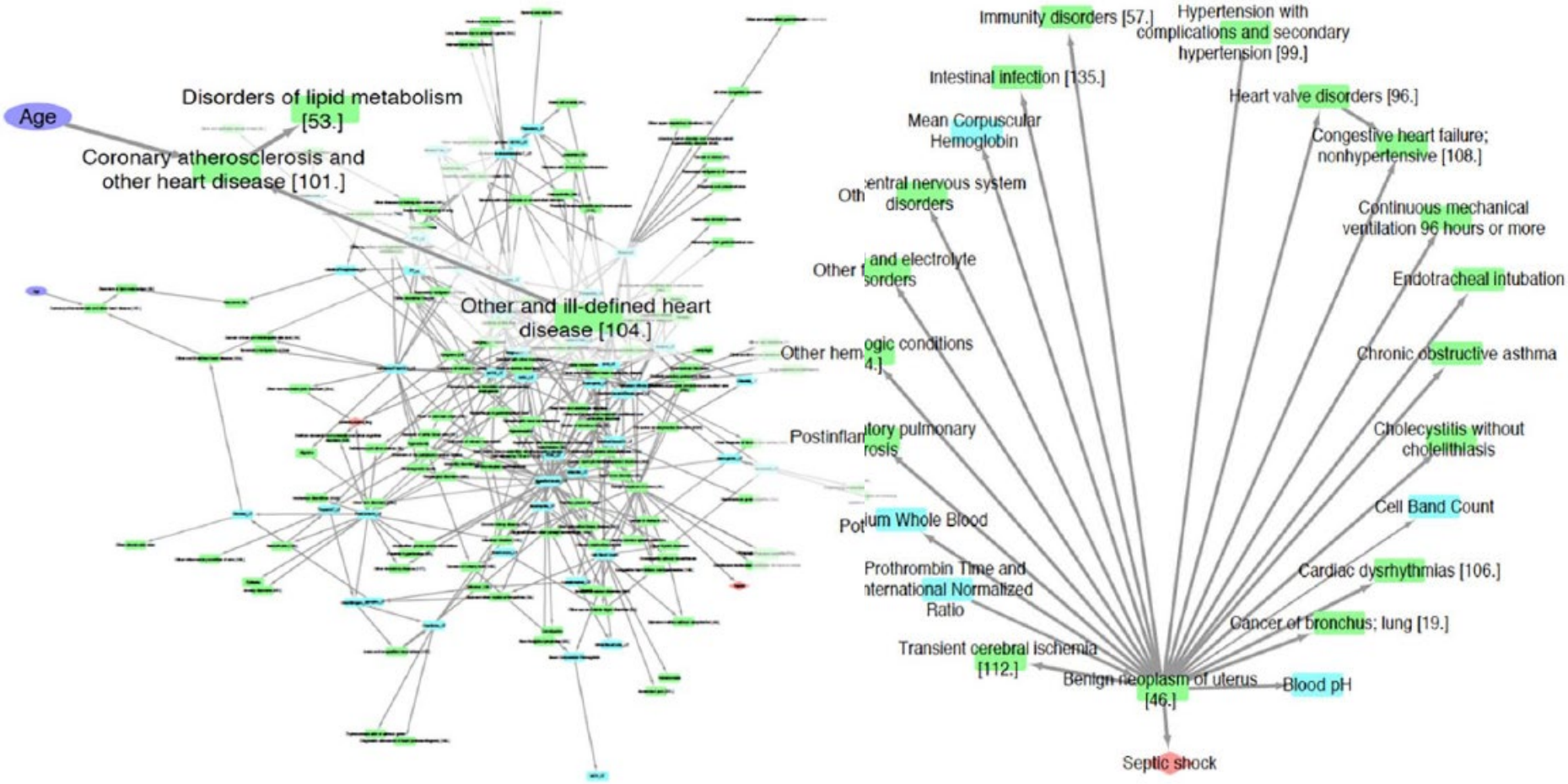
Christopher R Yee, Niven R Narain, Viatcheslav R Akmaev and Vijetha Vemulapalli

Berg LLC, Framingham, MA, USA.

Biomedical Informatics Insights
Volume 11: 1–9

DOI: 10.1177/1178222619885147

2019

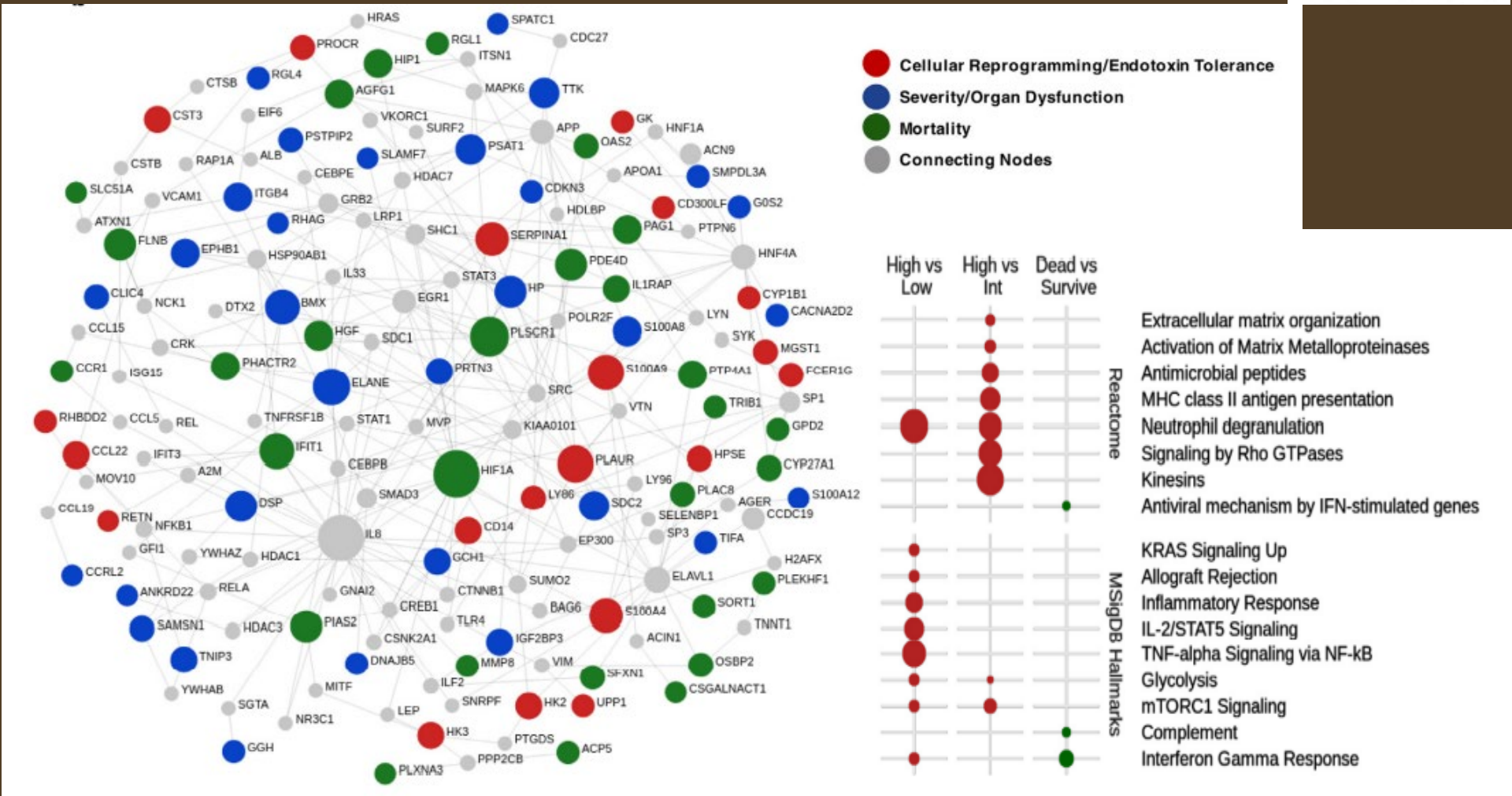


Predicting sepsis severity at first clinical presentation: The role of endotypes and mechanistic signatures

2021

Arjun Baghela,[a,b] Olga M. Pena,[a] Amy H. Lee,[c] Beverlie Baquir,[a] Reza Falsafi,[a] Andy An,[a] Susan W. Farmer,[a] Andrew Hurlburt,[d] Alvaro Mondragon-Cardona,[e,f] Juan Diego Rivera,[e,f] Andrew Baker,[g] Uriel Trahtemberg,[g] Maryam Shojaei,[h] Carlos Eduardo Jimenez-Canizales,[e,f] Claudia C. dos Santos,[g] Benjamin Tang,[h] Hjalmar R. Bouma,[i,j] Gabriela V. Cohen Freue,[k] and Robert E.W. Hancock[a]*

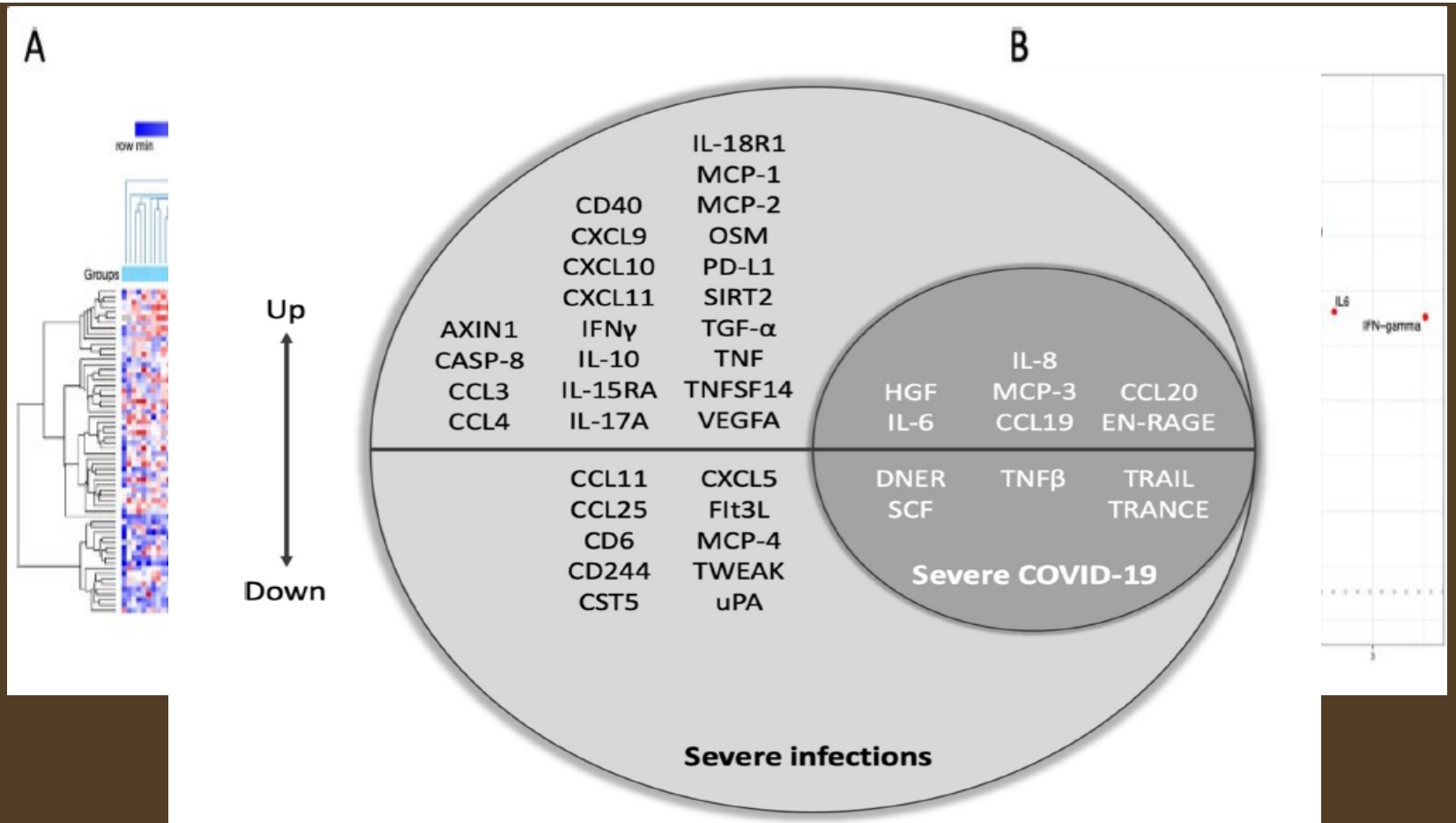
EBioMedicine



RESEARCH Open Access

Characterization of sepsis inflammatory endotypes using circulatory proteins in patients with severe infection: a prospective cohort study

Isis Ricaño-Ponce[1*†], Anca-Lelia Riza[1,2,3†], Aline H. de Nooijer[1†], Andrei Pirvu[2,3], Stefania Dorobantu[2,3], Adina Dragos[2,3], Ioana Streata[2,3], Mihaela Roskanovic[4,5], Inge Grondman[1], Florentina Dumitrescu[4,5], Vinod Kumar[1,6], Mihai G. Netea[1,7] and Mihai Ioana[2,3]

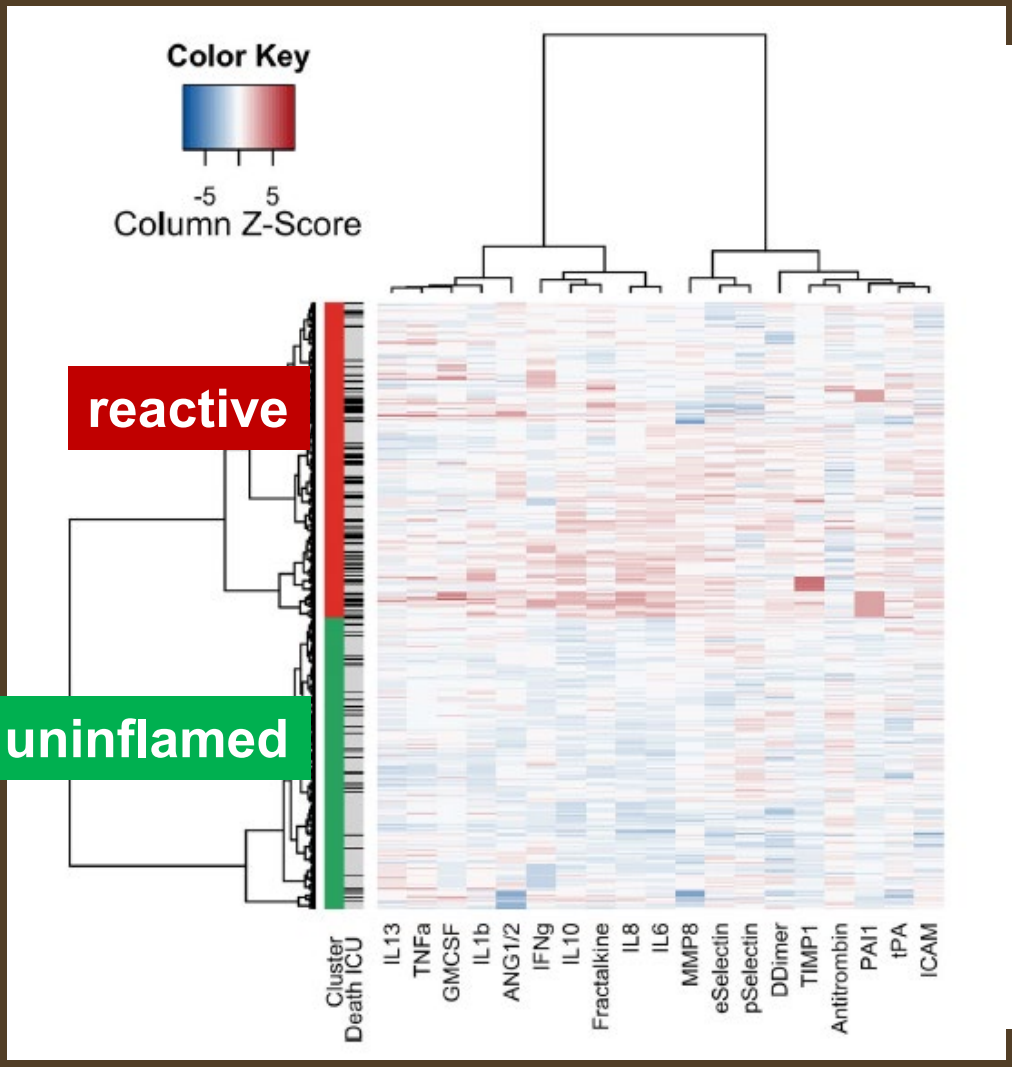


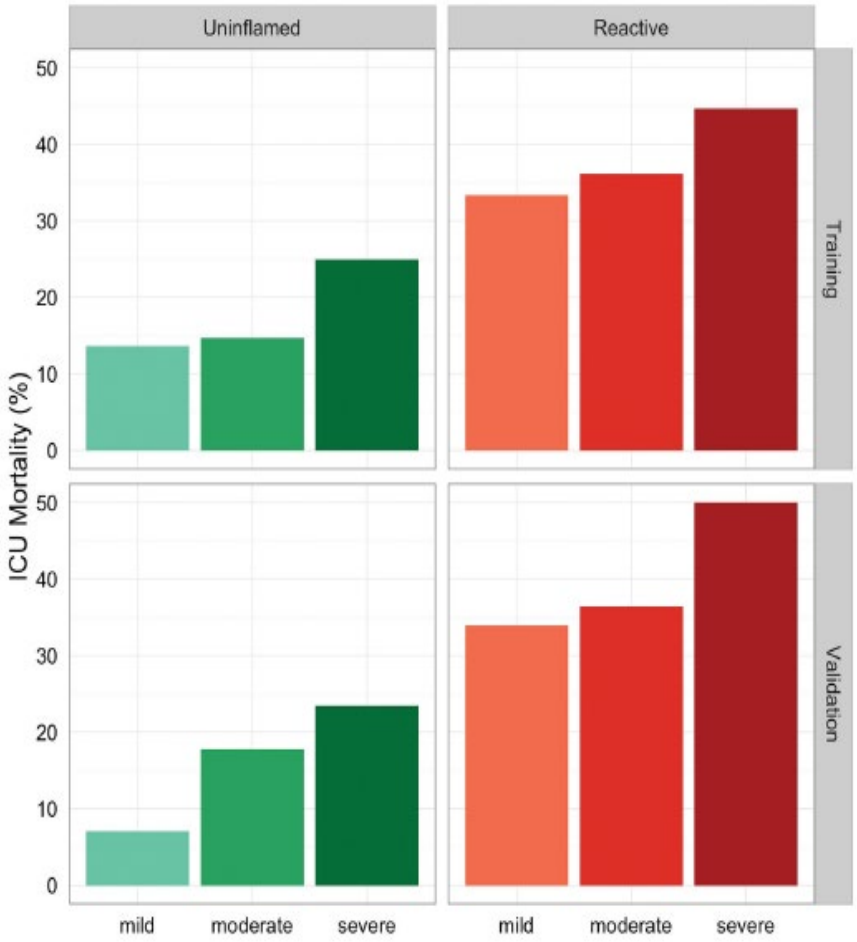
ARDS

Identification and validation of distinct biological phenotypes in patients with acute respiratory distress syndrome by cluster analysis

L.D. Bos[1,2,3], L.R. Schouten[1,3], L.A. van Vught[4], M.A. Wiewel[4], D. Ong[5,6], O. Cremer[6], A. Artigas[7], I. Martin-Loeches[8], A.J. Hoogendijk[4], T. van der Poll[4], J. Horn[1,3], N. Juffermans[1,3], C.S. Calfee[9], and M.J. Schultz[1,3] On behalf of the MARS consortium*

Thorax. 2017



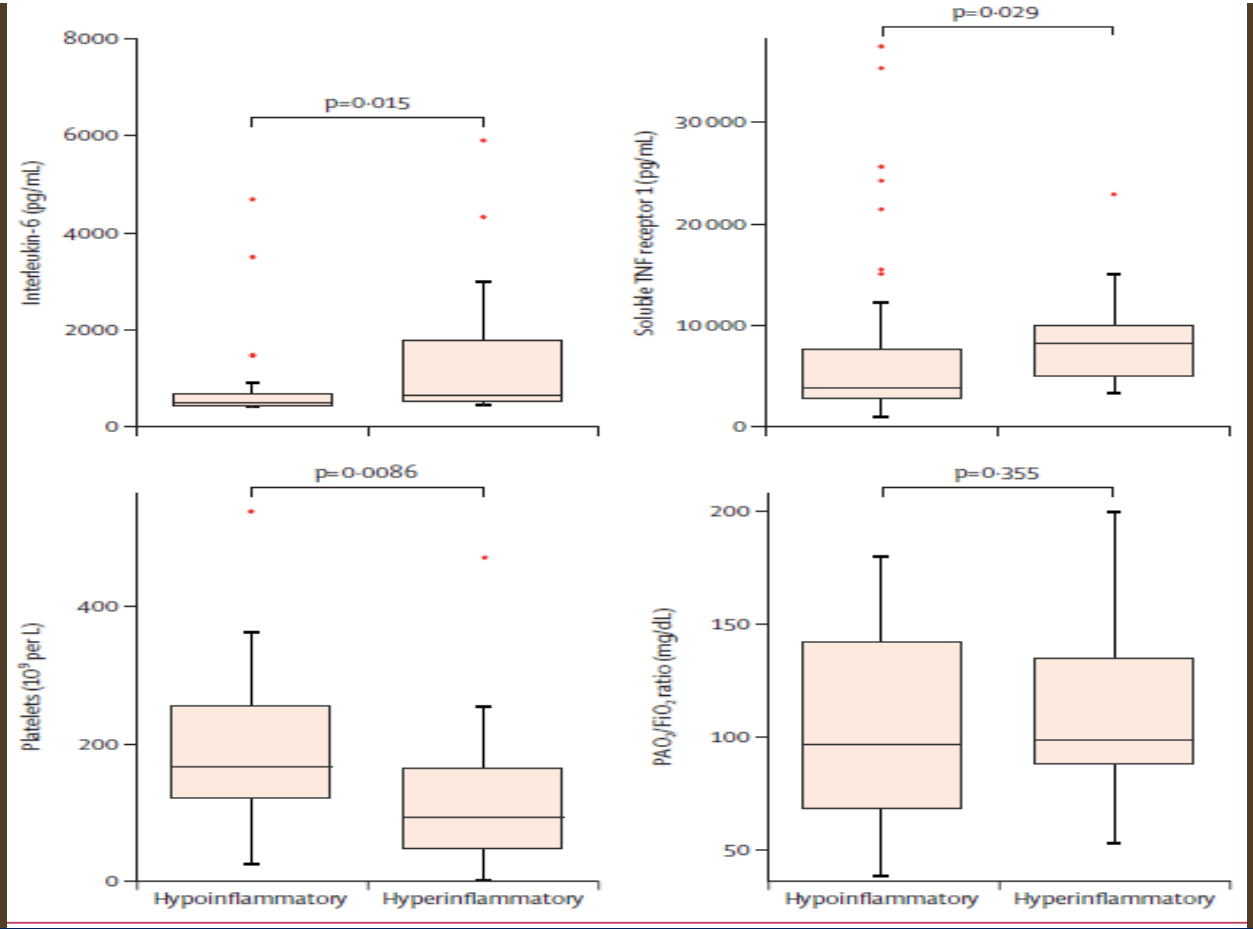


Development and validation of parsimonious algorithms to classify acute respiratory distress syndrome phenotypes: a secondary analysis of randomised controlled trials

Pratik Sinha, Kevin L Delucchi, Daniel F McAuley, Cecilia M O'Kane, Michael A Matthay, Carolyn S Calfee

2020

Lancet Respir Med



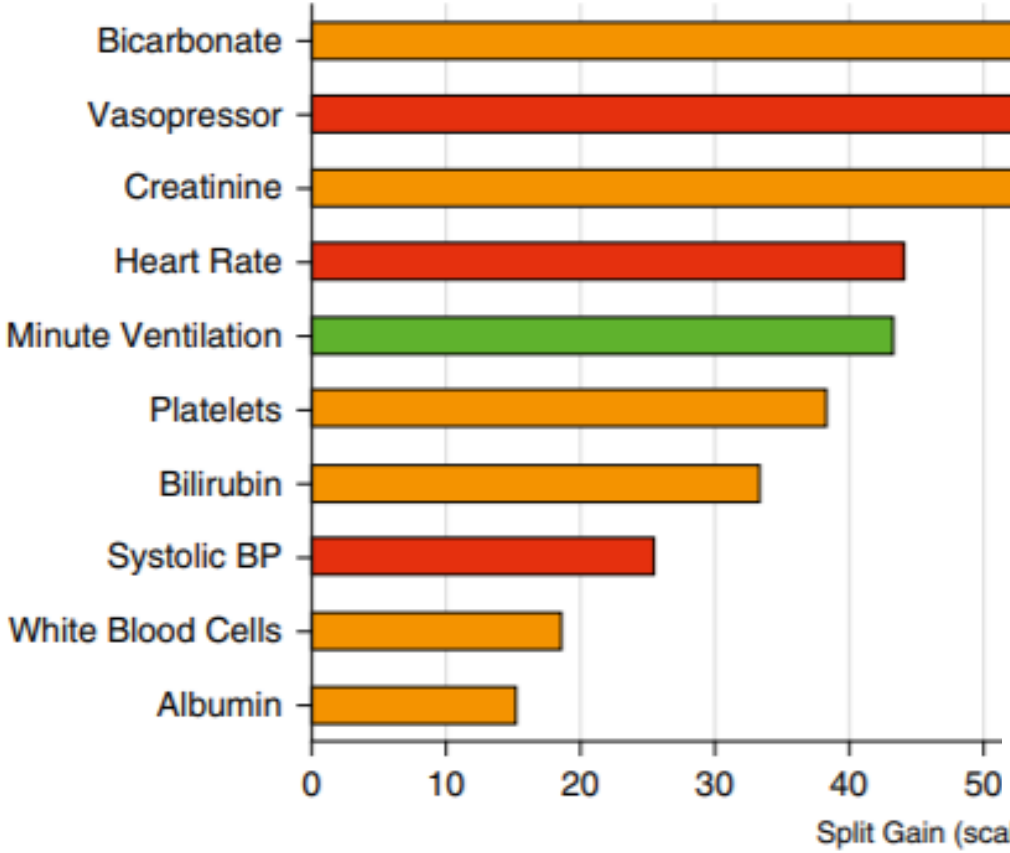
6 most important classifier variables:

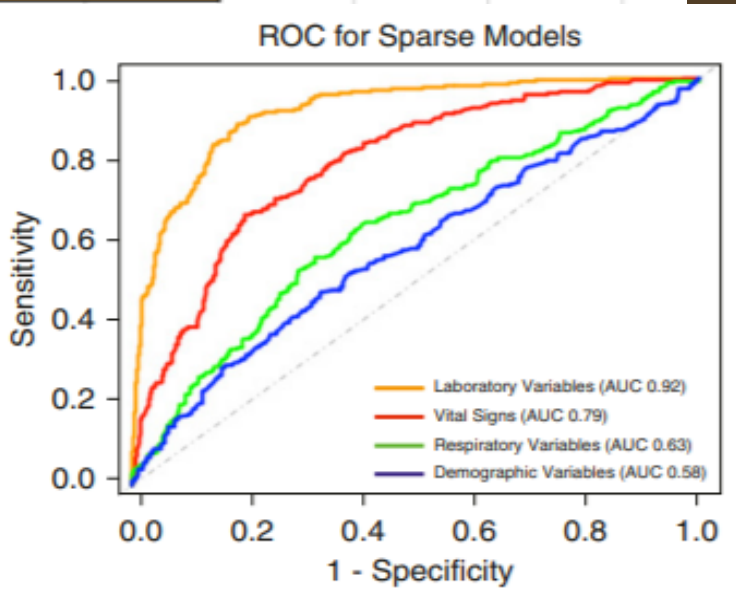
IL-8, IL-6, protein C, soluble TNFr 1, bicarbonate, vasopressor use.

Machine Learning Classifier Models Can Identify Acute Respiratory Distress Syndrome Phenotypes Using Readily Available Clinical Data

Pratik Sinha[1,2], Matthew M. Churpek[3], and Carolyn S. Calfee[1,2]

[1]Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Department of Medicine, and [2]Department of Anesthesia, University of California San Francisco, San Francisco, California; and [3]Department of Medicine, University of Wisconsin, Madison, Madison, Wisconsin





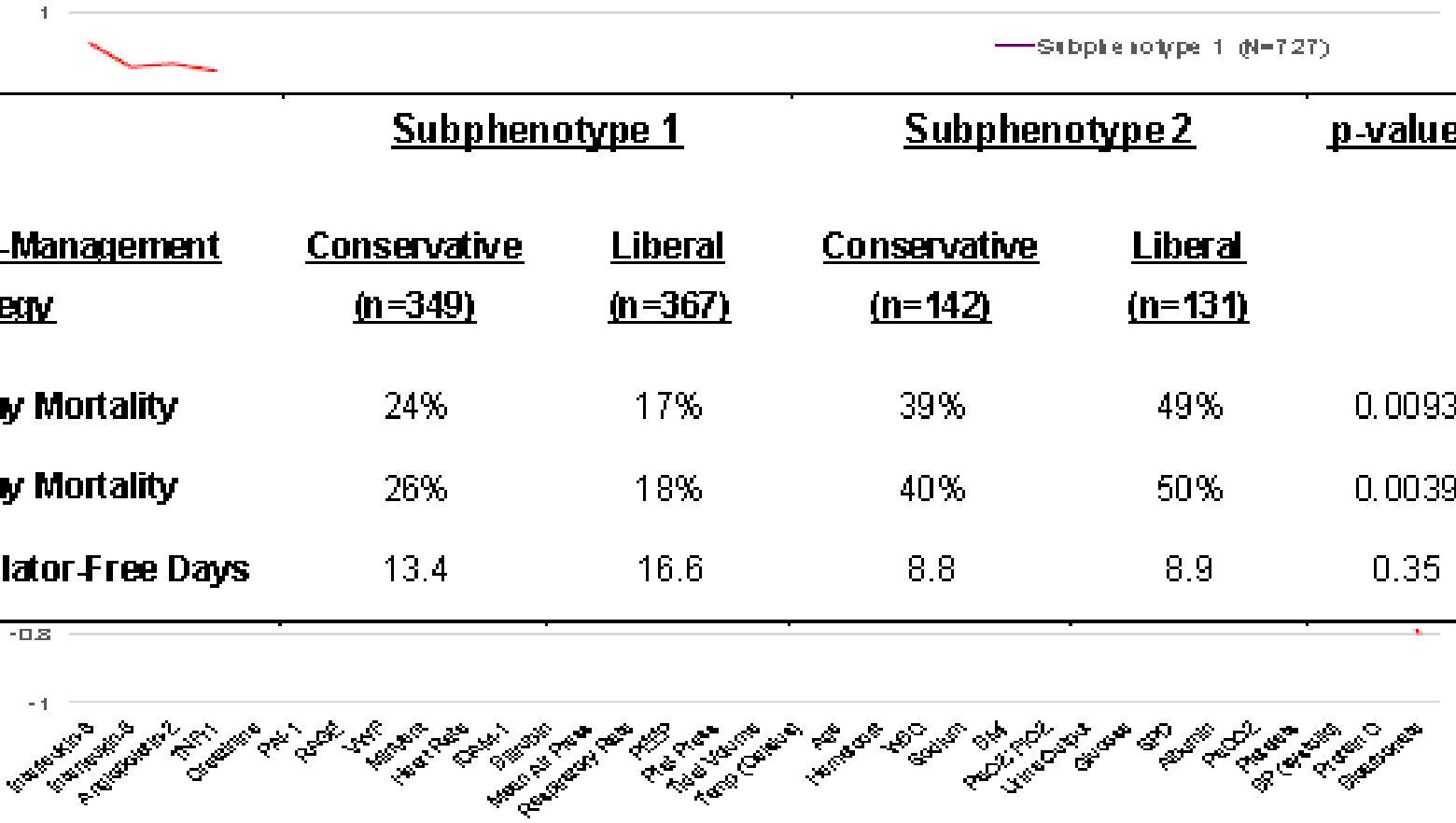
Acute Respiratory Distress Syndrome Subphenotypes Respond Differently to Randomized Fluid Management Strategy

2016

Katie R. Famous[1], Kevin Delucchi[2], Lorraine B. Ware[3,4], Kirsten N. Kangelaris[5], Kathleen D. Liu[6,7], B. Taylor Thompson[8], and Carolyn S. Calfee[1,7]; for the ARDS Network

[1]Division of Pulmonary and Critical Care Medicine, Department of Medicine, [2]Department of Psychiatry, [5]Division of Hospital Medicine, Department of Medicine, [6]Division of Nephrology, Department of Medicine, and [7]Department of Anesthesia, University of California San Francisco, San Francisco, California; [3]Department of Medicine, and [4]Department of Pathology, Microbiology, and Immunology, Vanderbilt University, Nashville, Tennessee; and [8]Division of Pulmonary and Critical Care, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

American Journal of Respiratory and Critical Care Medicine



	Subphenotype 1		Subphenotype 2		p-value
Fluid-Management Strategy	Conservative (n=349)	Liberal (n=367)	Conservative (n=142)	Liberal (n=131)	
60-day Mortality	24%	17%	39%	49%	0.0093
90-day Mortality	26%	18%	40%	50%	0.0039
Ventilator-Free Days	13.4	16.6	8.8	8.9	0.35

References

1. Wood ME, Stockwell RE, Johnson GR, Ramsay KA, Sherrard LJ, Jabbour N, *et al*. Face masks and cough etiquette reduce the cough aerosol concentration of *Pseudomonas aeruginosa* in people with cystic fibrosis. *Am J Respir Crit Care Med* 2018;197:348–355.
2. Saiman L, Siegel JD, LiPuma JJ, Brown RF, Bryson EA, Chambers MJ, *et al*.; Cystic Fibrosis Foundation; Society for Healthcare Epidemiology of America. Infection prevention and control guideline for cystic fibrosis: 2013 update. *Infect Control Hosp Epidemiol* 2014;35: S1–S67.
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7. Zuckerman JB, Clock SA, Prato BS, McDevitt JJ, Zhou JJ, Leclair LW, *et al*. Air contamination with bacteria in cystic fibrosis clinics: implications for prevention strategies. *Am J Respir Crit Care Med* 2015;191:598–601.
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Erratum: Acute Respiratory Distress Syndrome Subphenotypes Respond Differently to Randomized Fluid Management Strategy

The authors of an article published in the February 1, 2017, issue of the *Journal* have identified an error. In Famous and colleagues (1), the terms identifying two different therapies, *fluid-conservative* and *fluid-liberal*, have been inadvertently exchanged for one another. This error affects Table 4 in the Results, three sentences in the Discussion, and four words in the abstract, as well as Table E7 in the supplement. All other analyses for the publication were rechecked by the authors and determined by them to be correct. Because of the nature of the changes, the *Journal* is replacing the online version of the article with one that contains the corrections. For the convenience of our readers, we are also posting a copy of the original article with all corrections indicated in red (this may be found in the supplemental materials tab of the online article).

The authors have determined that this error does not affect the main conclusions of the paper, namely, that two acute respiratory distress syndrome subphenotypes were identified in the FACTT study, that these two subphenotypes were similar to those previously identified by the same authors in other trials, that these two subphenotypes had widely divergent clinical outcomes, and that the two subphenotypes responded differently to fluid therapy. The authors take full responsibility for this error and apologize to the readership of the *Journal*. ■

Reference

1. Famous KR, Delucchi K, Ware LB, Kangelaris KN, Liu KD, Thompson BT, Calfee CS; ARDS Network. Acute respiratory distress syndrome subphenotypes respond differently to randomized fluid management strategy. *Am J Respir Crit Care Med* 2017;195:331–338.

Acute Respiratory Distress Syndrome Subphenotypes Respond Differently to Randomized Fluid Management Strategy

2017

Katie R. Famous[1], Kevin Delucchi[2], Lorraine B. Ware[3,4], Kirsten N. Kangelaris[5], Kathleen D. Liu[6,7], B. Taylor Thompson[8], and Carolyn S. Calfee[1,7]; for the ARDS Network

[1]Division of Pulmonary and Critical Care Medicine, Department of Medicine, [2]Department of Psychiatry, [5]Division of Hospital Medicine, Department of Medicine, [6]Division of Nephrology, Department of Medicine, and [7]Department of Anesthesia, University of California San Francisco, San Francisco, California; [3]Department of Medicine, and [4]Department of Pathology, Microbiology, and Immunology, Vanderbilt University, Nashville, Tennessee; and [8]Division of Pulmonary and Critical Care, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts

American Journal of Respiratory and Critical Care Medicine

	Subphenotype 1		Subphenotype 2		p-value
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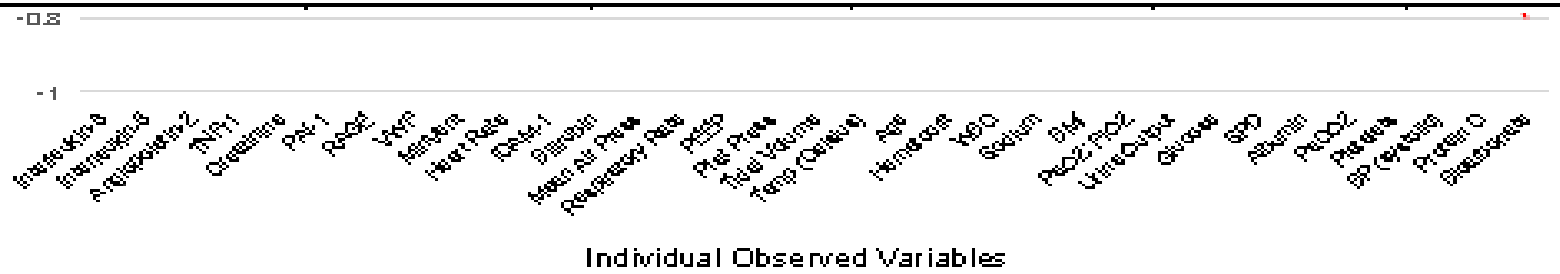


Machine Learning Classifier Models Can Identify Acute Respiratory Distress Syndrome Phenotypes Using Readily Available Clinical Data

Pratik Sinha[1,2], Matthew M. Churpek[3], and Carolyn S. Calfee[1,2]

[1]Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Department of Medicine, and [2]Department of Anesthesia, University of California San Francisco, San Francisco, California; and [3]Department of Medicine, University of Wisconsin, Madison, Madison, Wisconsin

Model	Mortality at Day 90 in the Hypoinflammatory Phenotype			Mortality at Day 90 in the Hyperinflammatory Phenotype			*P* Value
	Total [*n* (%)]	Liberal Fluid [*n* (%)]	Conservative Fluid [*n* (%)]	Total [*n* (%)]	Liberal Fluid [*n* (%)]	Conservative Fluid [*n* (%)]	
Clinical classifier	145/678 (21)	81/321 (25)	64/357 (18)	139/322 (43)	69/176 (39)	70/146 (48)	0.0072
Sparse combined	153/693 (22)	86/333 (26)	67/360 (19)	131/307 (43)	64/164 (42)	67/143 (51)	0.0124
LCA (8)	161/727 (22)	93/355 (26)	68/372 (18)	123/273 (45)	57/142 (40)	66/131 (50)	0.004

Model	Mortality at Day 90 in the Hypoinflammatory Phenotype			Mortality at Day 90 in the Hyperinflammatory Phenotype			*P* Value
	Total [*n* (%)]	Low PEEP [*n* (%)]	High PEEP [*n* (%)]	Total [*n* (%)]	Low PEEP [*n* (%)]	High PEEP [*n* (%)]	
Clinical classifier	73/372 (20)	27/184 (15)	46/188 (25)	75/177 (42)	42/89 (47)	33/88 (38)	0.0113
Sparse combined	85/402 (21)	35/200 (18)	50/202 (25)	63/147 (43)	34/73 (47)	29/74 (39)	0.0748
LCA (7)	81/404 (20)	33/202 (16)	48/202 (24)	67/145 (46)	36/71 (51)	31/74 (42)	0.049

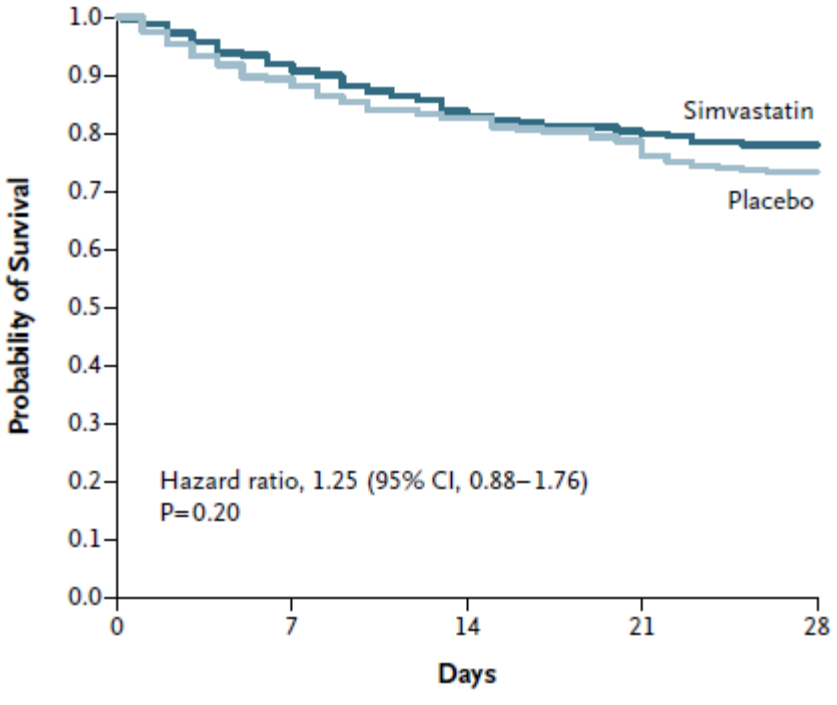
The NEW ENGLAND JOURNAL of MEDICINE

2014

ORIGINAL ARTICLE

Simvastatin in the Acute Respiratory Distress Syndrome

Daniel F. McAuley, M.D., John G. Laffey, M.D., Cecilia M. O'Kane, Ph.D., Gavin D. Perkins, M.D., Brian Mullan, M.B., T. John Trinder, M.D., Paul Johnston, M.B., Philip A. Hopkins, Ph.D., Andrew J. Johnston, M.D., Cliona McDowell, M.Sc., Christine McNally, B.A., and the HARP-2 Investigators, for the Irish Critical Care Trials Group*

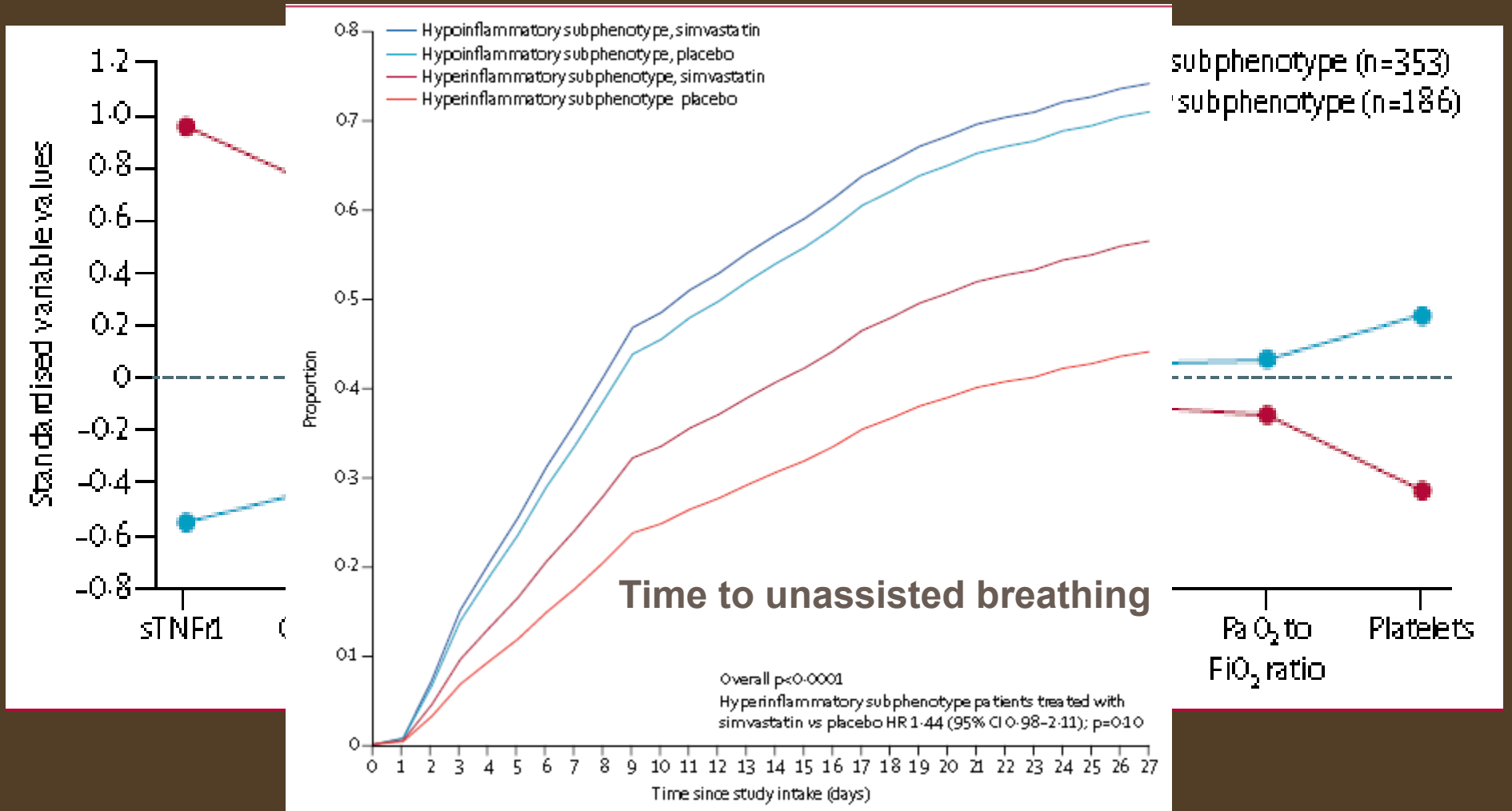


Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial

Carolyn S Calfee, Kevin L Delucchi, Pratik Sinha, Michael A Matthay, Jonathan Hackett, Manu Shankar-Hari, Cliona McDowell, John G Laffey, Cecilia M O'Kane, Daniel F McAuley, on behalf of the Irish Critical Care Trials Group

2018

THE LANCET
Respiratory Medicine



Boyle et al. Critical Care (2022) 26:164
https://doi.org/10.1186/s13054-022-04025-w

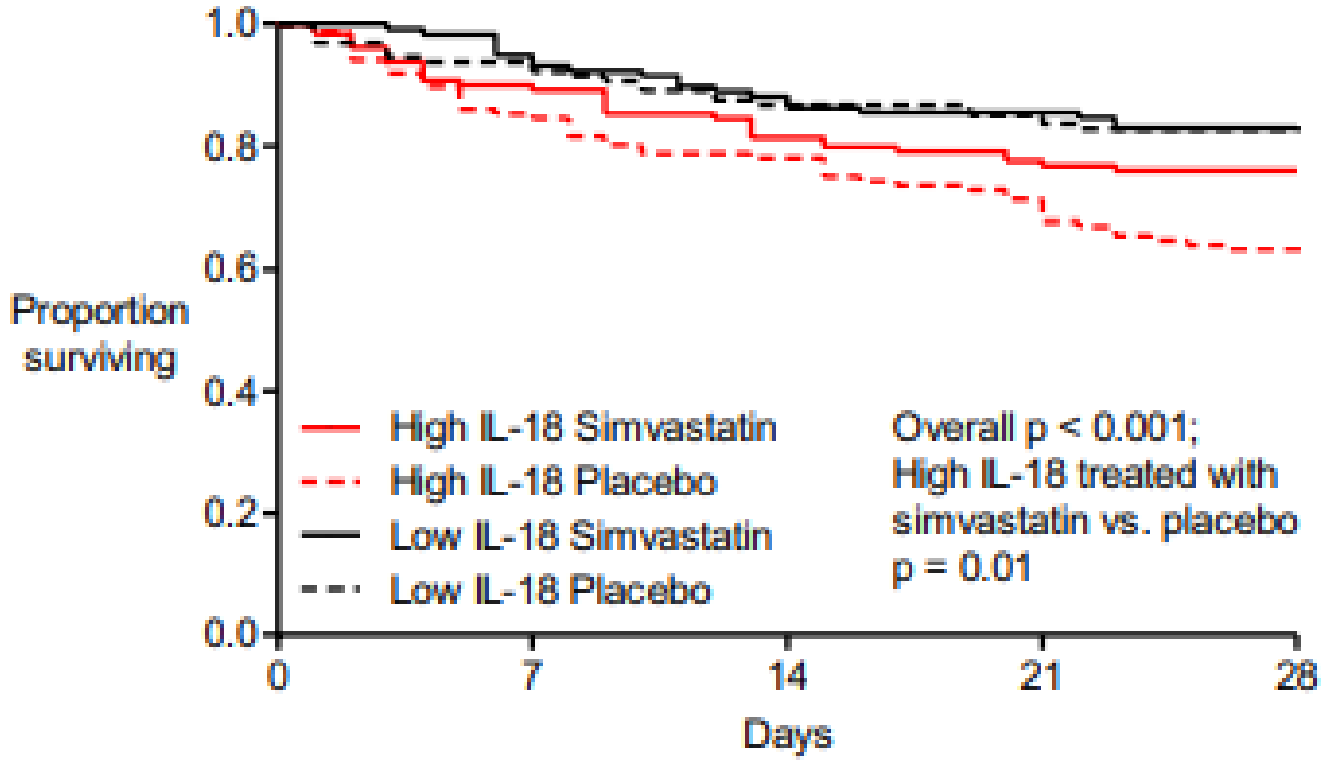
Critical Care

RESEARCH Open Access

2022

Baseline plasma IL-18 may predict simvastatin treatment response in patients with ARDS: a secondary analysis of the HARP-2 randomised clinical trial

Andrew James Boyle[1,2*†], Peter Ferris[1†], Ian Bradbury[3], John Conlon[1], Manu Shankar-Hari[4], Angela J. Rogers[5], Cecilia M. O'Kane[1] and Daniel F. McAuley[1,2]



High IL-18

simvastatin

placebo

Wick et al. Critical Care (2021) 25:404
https://doi.org/10.1186/s13054-021-03822-z

Critical Care

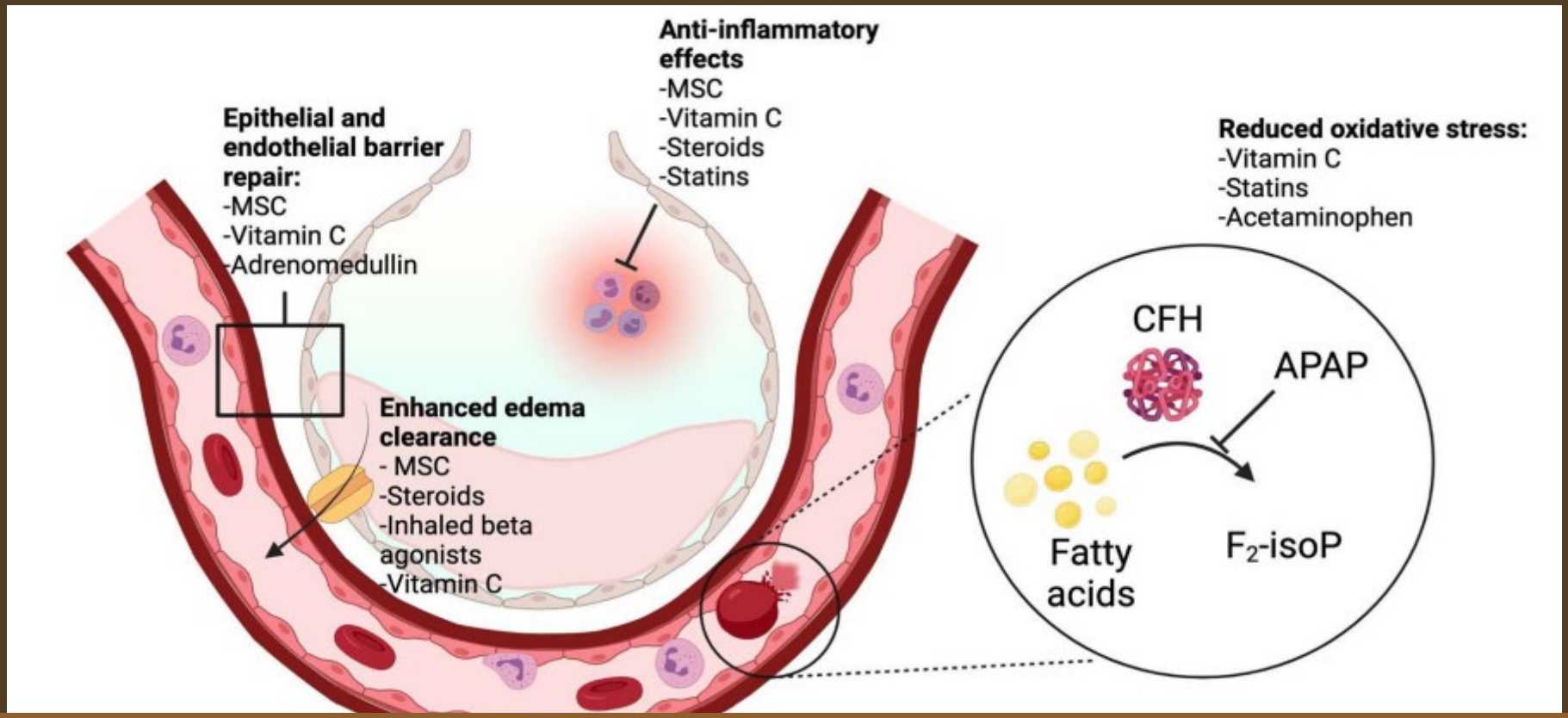
REVIEW Open Access

Promises and challenges of personalized medicine to guide ARDS therapy

2021

Katherine D. Wick[1*], Daniel F. McAuley[2], Joseph E. Levitt[3], Jeremy R. Beitler[4], Djillali Annane[5,6], Elisabeth D. Riviello[7], Carolyn S. Calfee[1,8] and Michael A. Matthay[1,8]

Biologic mechanisms in ARDS that may be targeted by various personalizable therapies.



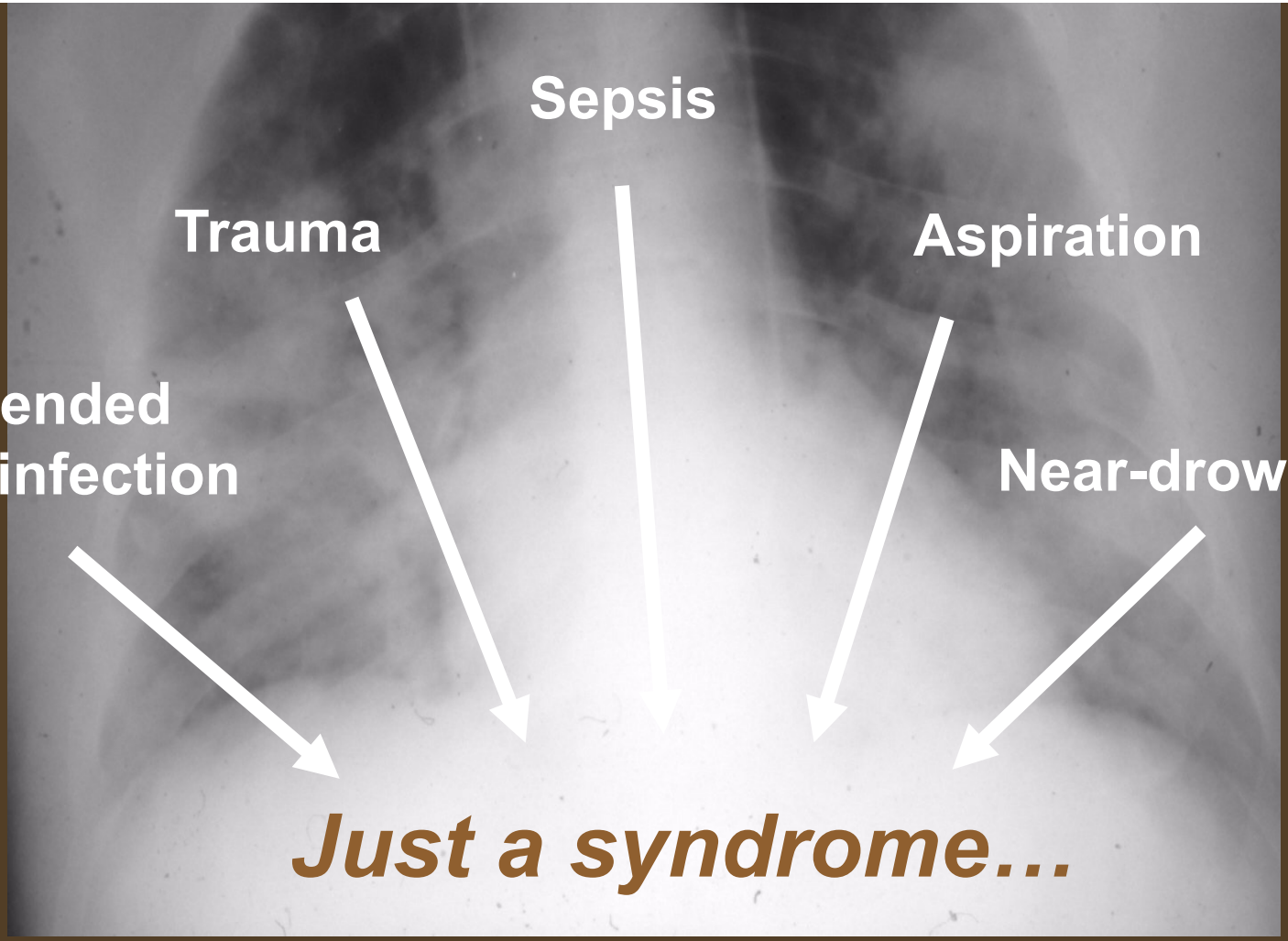
MSC mesenchymal stromal cells, CFH cell-free hemoglobin, F2-IsoP F2 isoprostanes, APAP acetaminophen

Intensive Care Med
DOI 10.1007/s00134-015-4120-7

EDITORIAL

Jean-Louis Vincent
Carlos Santacruz

Do we need ARDS?



Intensive Care Med
https://doi.org/10.1007/s00134-020-06255-4

2020

EDITORIAL

We've never seen a patient with ARDS!

Jean-Louis Vincent[1*] and Arthur S. Slutsky[2,3]

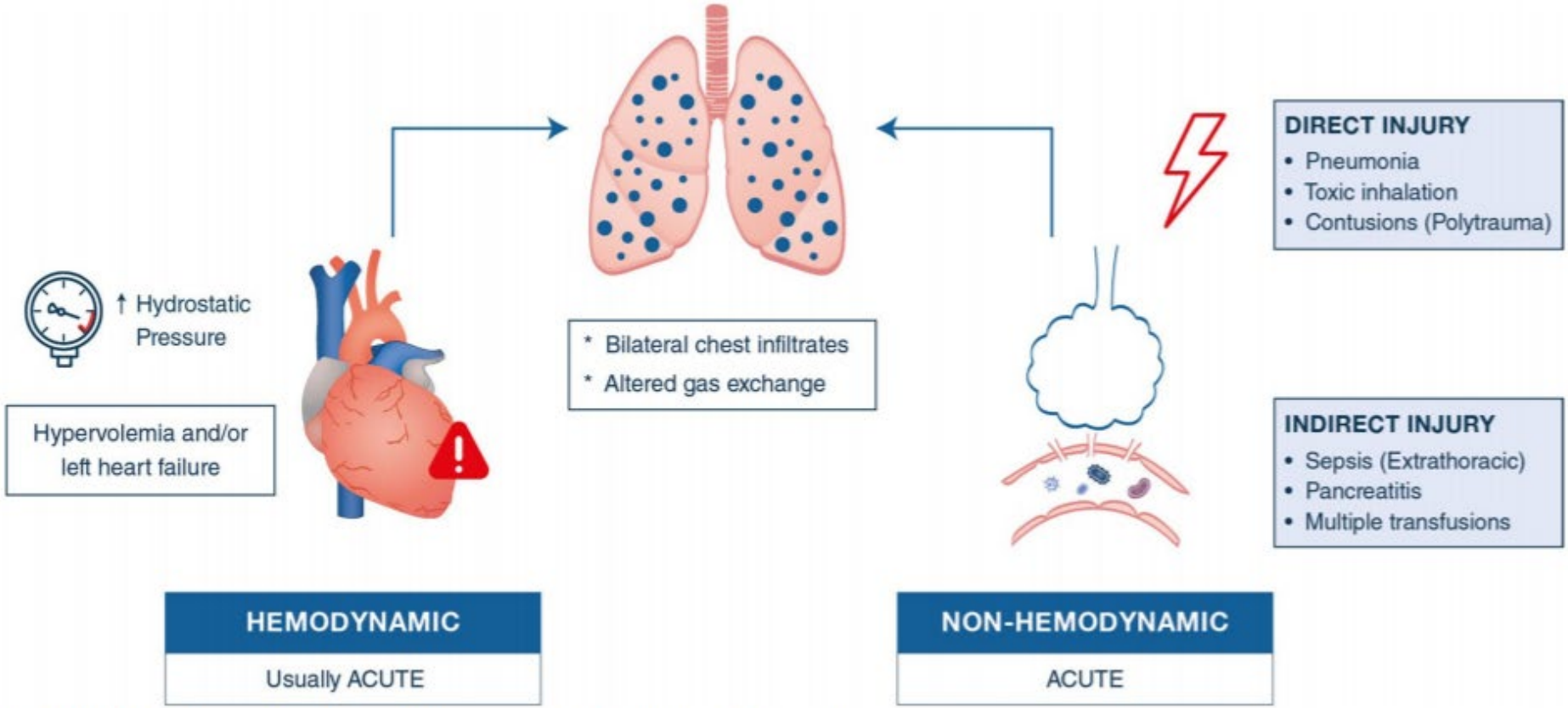


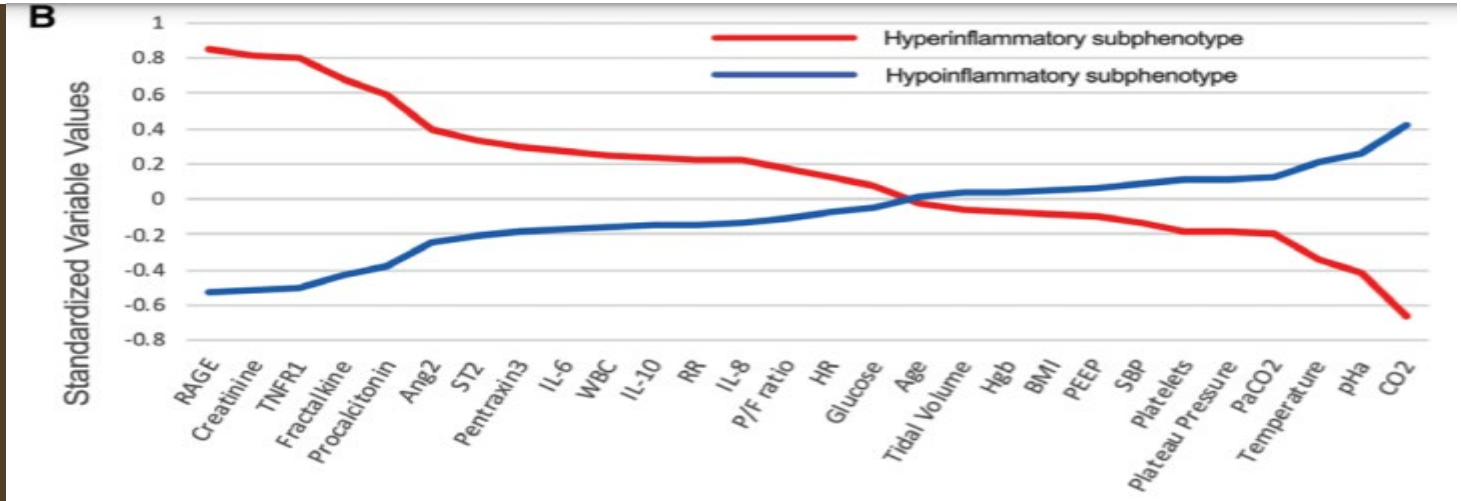
Fig. 1 The basic pathophysiologic approach to diffuse lung edema

Host-Response Subphenotypes Offer Prognostic Enrichment in Patients With or at Risk for Acute Respiratory Distress Syndrome*

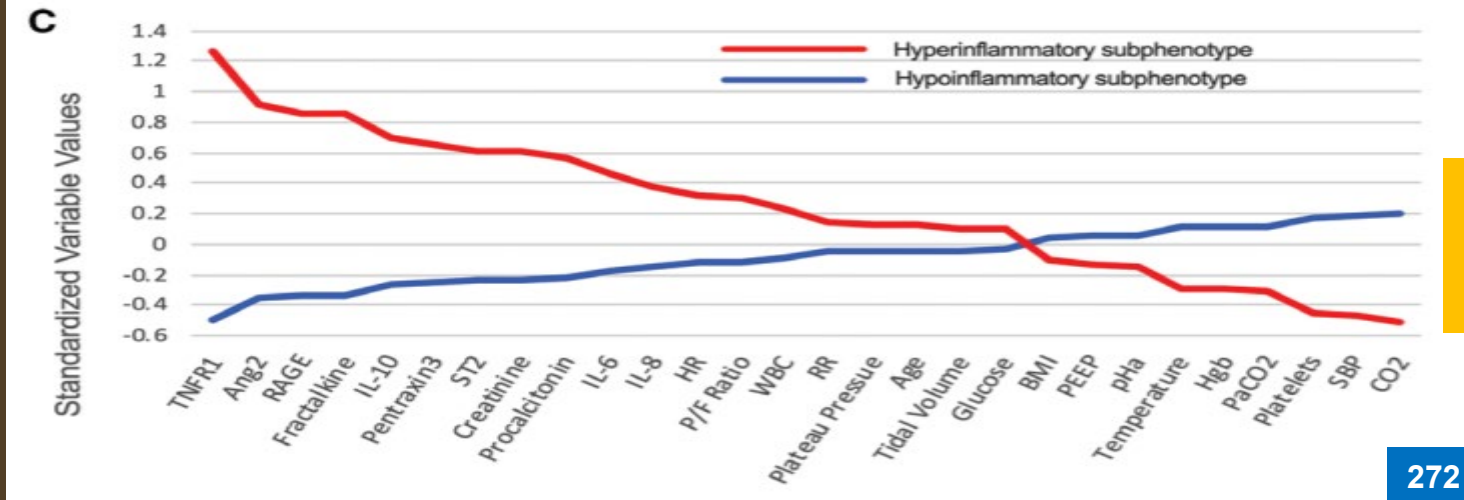
2019

Georgios D. Kitsios, MD, PhD[1,2]; Libing Yang, MDc[1]; Dimitris V. Manatakis, PhD[3]; Mehdi Nouraie, MD, PhD[1]; John Evankovich, MD[1]; William Bain, MD[1]; Daniel G. Dunlap, MD[1]; Faraaz Shah, MD, MPH[1]; Ian J. Barbash, MD, MS[1]; Sarah F. Rapport, BS, MPH[1]; Yingze Zhang, PhD[1]; Rebecca S. DeSensi, BA[1]; Nathaniel M. Weathington, MD, PhD[1]; Bill B. Chen, PhD[1]; Prabir Ray, PhD[1]; Rama K. Mallampalli, MD[1,4]; Panayiotis V. Benos, PhD[3]; Janet S. Lee, MD[1]; Alison Morris, MD, MS[1,2,5]; Bryan J. McVerry, MD[1,2]

Critical Care Medicine



with ARDS



at risk of ARDS

272 patients (Pittsburgh)

Host-Response Subphenotypes Offer Prognostic Enrichment in Patients With or at Risk for Acute Respiratory Distress Syndrome*

2019

Georgios D. Kitsios, MD, PhD[1,2]; Libing Yang, MDc[1]; Dimitris V. Manatakis, PhD[3]; Mehdi Nouraie, MD, PhD[1]; John Evankovich, MD[1]; William Bain, MD[1]; Daniel G. Dunlap, MD[1]; Faraaz Shah, MD, MPH[1]; Ian J. Barbash, MD, MS[1]; Sarah F. Rapport, BS, MPH[1]; Yingze Zhang, PhD[1]; Rebecca S. DeSensi, BA[1]; Nathaniel M. Weathington, MD, PhD[1]; Bill B. Chen, PhD[1]; Prabir Ray, PhD[1]; Rama K. Mallampalli, MD[1,4]; Panayiotis V. Benos, PhD[3]; Janet S. Lee, MD[1]; Alison Morris, MD, MS[1,2,5]; Bryan J. McVerry, MD[1,2]

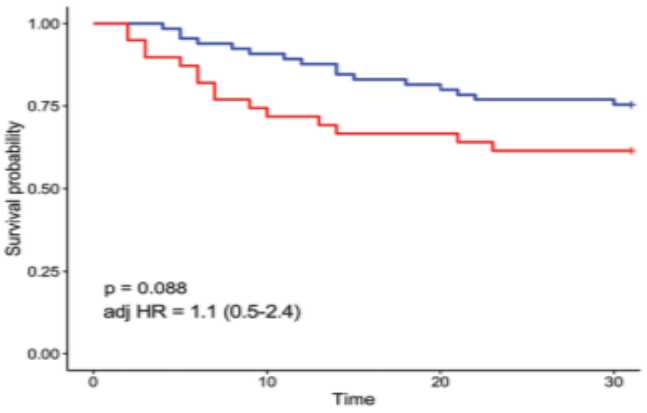
Critical Care Medicine

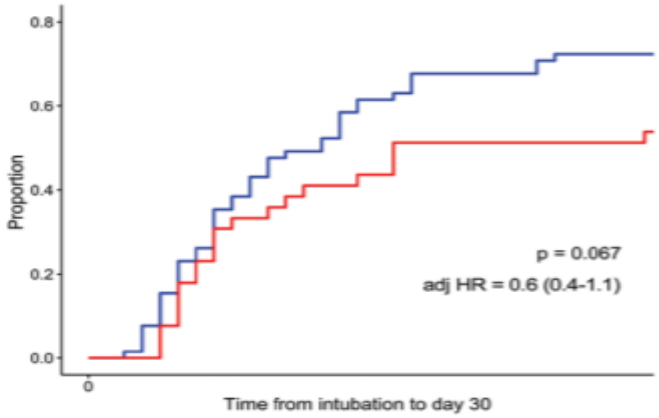
30 day survival

Time-to-liberation

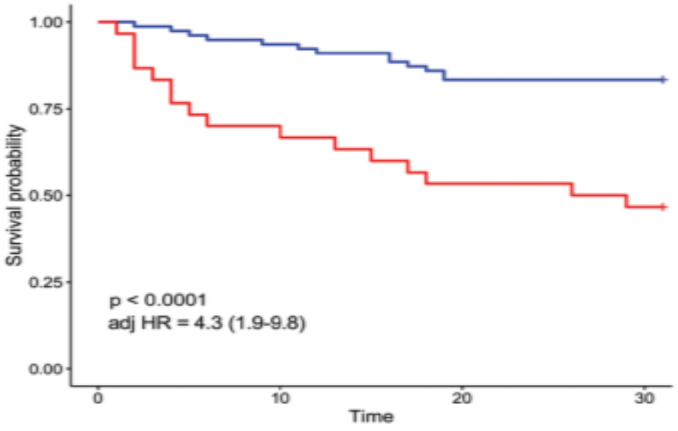
LCA subphenotype — Hyperinflammatory — Hypoinflammatory

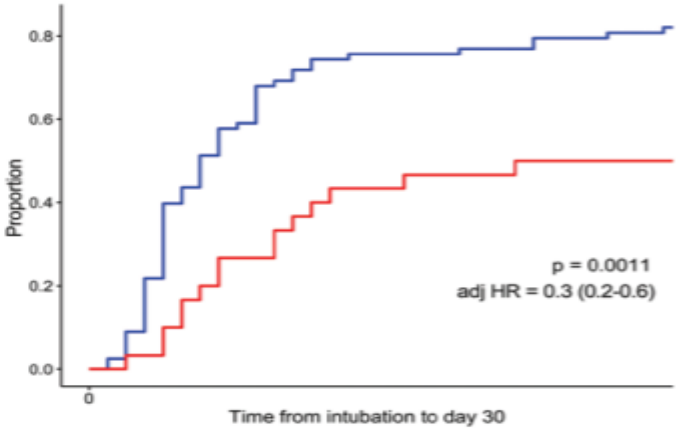
with ARDS





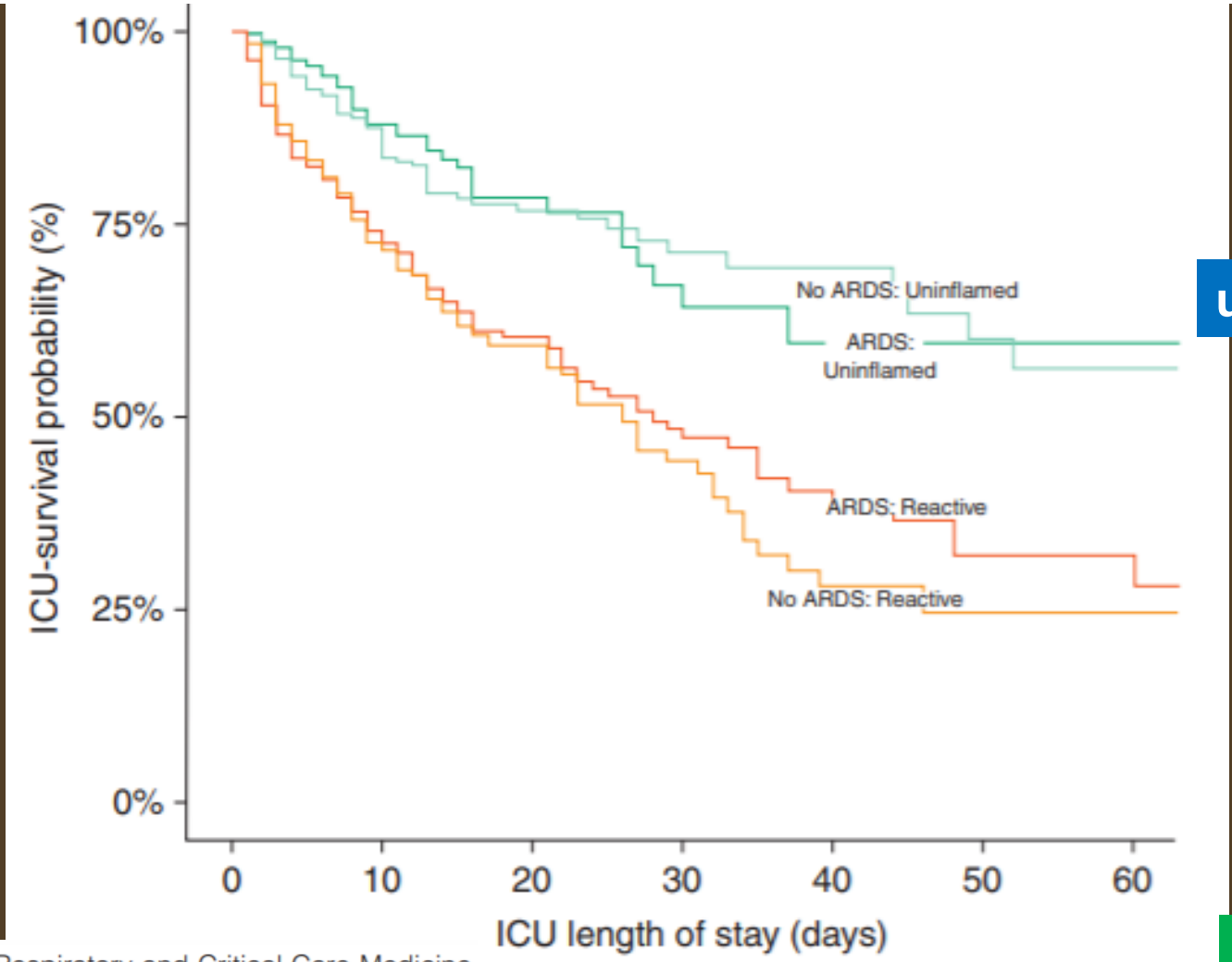
at risk of ARDS





Biological Subphenotypes of Acute Respiratory Distress Syndrome Show Prognostic Enrichment in Mechanically Ventilated Patients without Acute Respiratory Distress Syndrome

Nanon F. L. Heijnen[1], Laura A. Hagens[2], Marry R. Smit[2], Olaf L. Cremer[3], David S. Y. Ong[4,5], Tom van der Poll[6,7], Lonneke A. van Vught[2], Brendon P. Scicluna[6,8], Ronny M. Schnabel[1], Iwan C. C. van der Horst[1], Marcus J. Schultz[2,9,10,11], Dennis C. J. J. Bergmans[1], and Lieuwe D. J. Bos[2,12]; on behalf of the MARS Consortium



2021

uninflamed

reactive

2499 patients

American Journal of Respiratory and Critical Care Medicine

Gattinoni and Marini *Crit Care* (2021) 25:326
https://doi.org/10.1186/s13054-021-03748-6

Critical Care

COMMENTARY Open Access

Isn't it time to abandon ARDS? The COVID-19 lesson

2021

L. Gattinoni[1,2*] and J. J. Marini[1,2]

	Keep and modify ARDS definition	Abandon ARDS definition
Advantages	Easy patient categorization and labeling Facilitated enrollment in RCTs Standardized guidance of treatment	Recognizes need to personalize therapy Focuses on patient-relevant characteristics Encourages best responses to Δ's over time
Drawbacks	Non-uniformity encourages inappropriate Rx Promotes RCT enrollment of unqualified Pts May inform misleading treatment guidelines	Universal standards for Rx difficult to establish Precision inhibits RCT design and enrollment Often requires mastery of bedside physiology

It seems more logical simply to label the diseases as they are:
(pneumococcal, herpes, pancreatitis, etc.)
This de-lumping' approach would push our thinking towards truly personalized medicine, realizing that not only the etiological treatment but also the appropriate respiratory approach might well be different in different situations and at different stages of the disease process.

Intensive Care Med (2020) 46:2153–2156
https://doi.org/10.1007/s00134-020-06232-x

2020

NARRATIVE REVIEW

Designing an ARDS trial for 2020 and beyond: focus on enrichment strategies

Lorraine B. Ware[1*], Michael A. Matthay[2] and Alexandre Mebazaa[3]

Prognostic factor	Metric for enrichment	Outcome targeted by enrichment strategy	Used in published ARDS trials?
Strategies for prognostic enrichment			
Severity of hypoxemia	PaO_2/FiO_2	Death and/or prolonged mechanical ventilation	Yes
Presence of shock	Need for vasopressors	Death	No
Severity of pulmonary edema	RALE score	Prolonged mechanical ventilation	No
Biomarkers of poor prognosis	Model incorporating IL-8, Protein C, bicarbonate	Death and/or prolonged mechanical ventilation	No
Predictive factor	**Metric for enrichment**	**Mechanism targeted by enrichment strategy**	
Strategies for predictive enrichment			
Higher likelihood of fibroproliferative ARDS	BAL PCP III	Anti-fibroproliferative effects of corticosteroids	No, one trial is enrolling
Higher likelihood of oxidative injury from cell-free hemoglobin	Plasma cell-free hemoglobin	Hemoprotein-reductant effects of acetaminophen	Used in a pilot sepsis trial
Early lung injury more likely to respond	Enrollment prior to invasive ventilation	Anti-inflammatory effects of inhaled budesonide and formoterol	No, one trial is enrolling
Focal vs. diffuse ARDS	Chest CT distribution of infiltrates	Personalized ventilator strategy	Yes
Hyperinflammatory ARDS	Latent class analysis of clinical and biomarker features	Anti-inflammatory effects of simvastatin	No
Impaired vascular integrity	Plasma adrenomedullin	Vascular protective effects of adrecizumab	No, one trial is enrolling
Higher likelihood of ventilator-induced lung injury	Increased dead space fraction and lower compliance of the respiratory system	Identify group with highest predicted drop in driving pressure with extracorporeal CO_2 removal	No

A Research Agenda for Precision Medicine in Sepsis and Acute Respiratory Distress Syndrome

An Official American Thoracic Society Research Statement

2021

Faraaz Ali Shah*, Nuala J. Meyer*, Derek C. Angus, Rana Awdish, Élie Azoulay, Carolyn S. Calfee, Gilles Clermont, Anthony C. Gordon, Arthur Kwizera, Aleksandra Leligdowicz, John C. Marshall, Carmen Mikacenic, Pratik Sinha, Balasubramanian Venkatesh, Hector R. Wong, Fernando G. Zampieri, and Sachin Yende; on behalf of the American Thoracic Society Assembly on Critical Care

AMERICAN THORACIC SOCIETY DOCUMENTS

Developing precision medicine approaches will require reexamination of the conduct of observational studies and RCTs for sepsis and ARDS.

Recommendation 1
Create large richly phenotyped harmonized knowledge networks of clinical, imaging, and multianalyte molecular data from patients with sepsis and ARDS.

Recommendation 2
Implement novel trial designs to identify precision medicine strategies for sepsis and ARDS.

Recommendation 3
Advance data science and engineering approaches to facilitate precision medicine strategies for sepsis and ARDS.

Recommendation 4
Develop the tools necessary for the real-time application of precision medicine approaches.

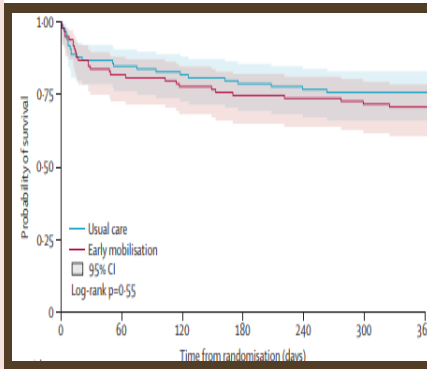
Am J Respir Crit Care Med

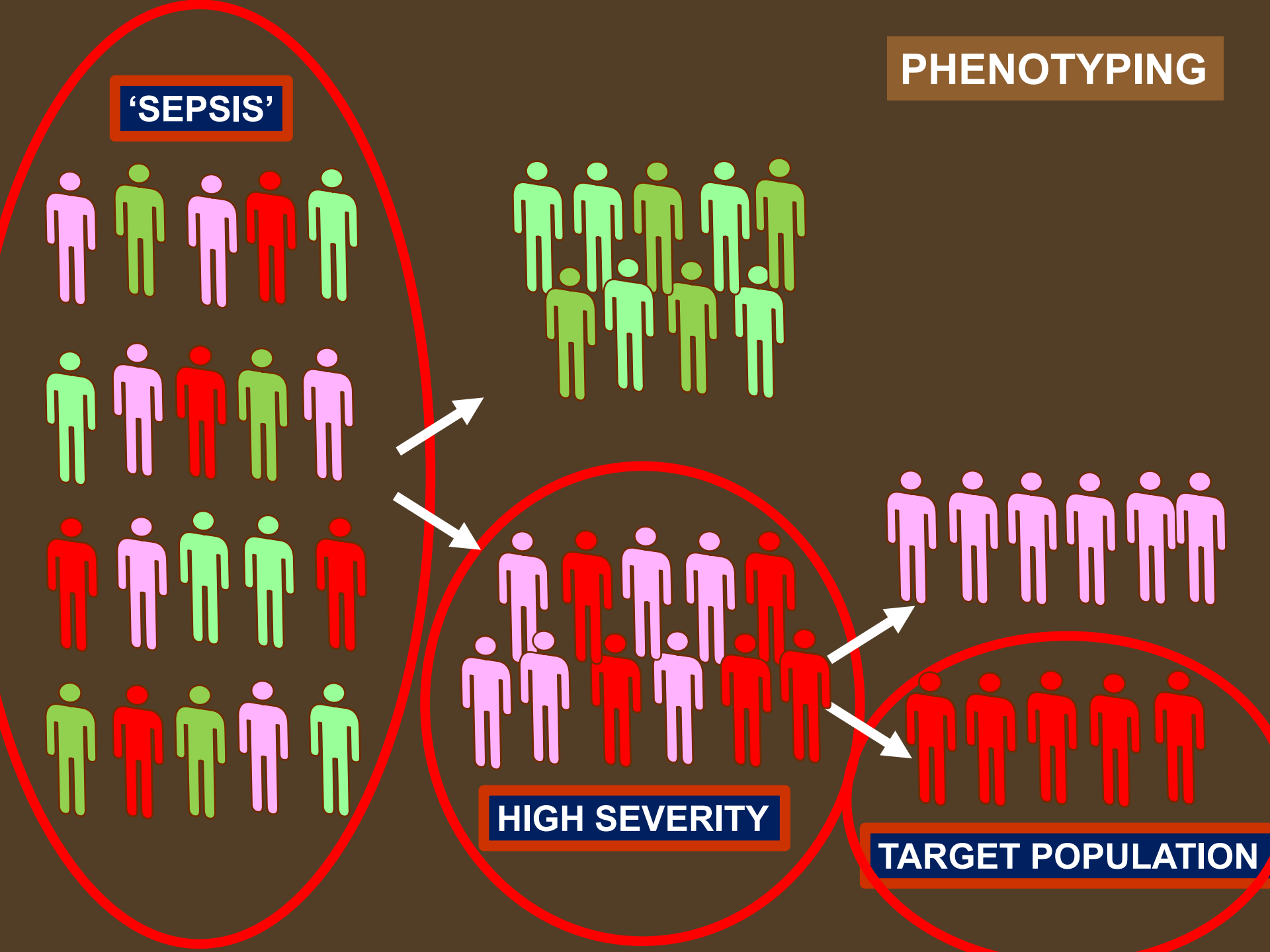
Effect of early mobilisation on long-term cognitive impairment in critical illness in the USA: a randomised controlled trial

2023

Bhakti K Patel, Krysta S Wolfe, Shruti B Patel, Karen C Dugan, Cheryl L Esbrook, Amy J Pawlik, Megan Stulberg, Crystal Kemple, Megan Teele, Erin Zeleny, Donald Hedeker, Anne S Pohlman, Vineet M Arora, Jesse B Hall, John P Kress

	Usual care group (n=99)	Intervention group (n=99)	Absolute difference	p value
Primary outcome				
Cognitive impairment at 1 year	43 (43%)	24 (24%)	−19·2%(−32·1 to −6.3)	0·0043
MoCA* score at 1 year	23 (21–26)	26 (24–28)	3 (1 to 4)	0·0001
Hospital discharge outcome				
Cognitive impairment	68 (69%)	53 (54%)	−15·2% (−28·6 to −1·7)	0·029
MoCA score	20 (16–23)	23 (19–27)	3 (2 to 5)	0·0004
ICU-acquired weakness†	38 (38%)	21 (21%)	−17·1% (−29·7 to −4·7)	0·0083
Total MRC score	49 (44–56)	56 (48–60)	7 (1 to 9)	0·0017
Functional independence	46 (47%)	66 (67%)	20·2% (6·7 to 33·7)	0·0041
Quality of life				
SF-36 physical component score	39·6 (31·8–48·5)	45·7 (29·7–55·6)	4·1 (−0·53 to 8·4)	0·081
Impaired physical health‡	39 (39%)	29 (29%)	−10·1% (−23·3 to 3·1)	0·13
SF-36 mental component score	47·6 (38·3–55·3)	53·3 (44·3–57·2)	5·7 (−0·16 to 6·9)	0·061
Impaired mental health	22 (22%)	13 (13%)	−9·1% (−19·6% to 1·5)	0·094
1-year follow-up				
ICU-acquired weakness	14 (14%)	0	−14·1% (−21·0 to −7·3)	0·0001
Total MRC score	56 (49–60)	58 (56–60)	2 (0 to 4)	0·0073
Functional independence	61 (62%)	64 (65%)	3·0% (−10·4 to 16·5)	0·66
Quality of life				
SF-36 physical component score	41·1 (31·8–49·4)	52·4 (45·3–56·8)	11·3 (6·3 to 13·8)	<0·0001
Impaired physical health	30 (30%)	8 (8%)	−22·2% (−32·7 to −11·7)	0·0001

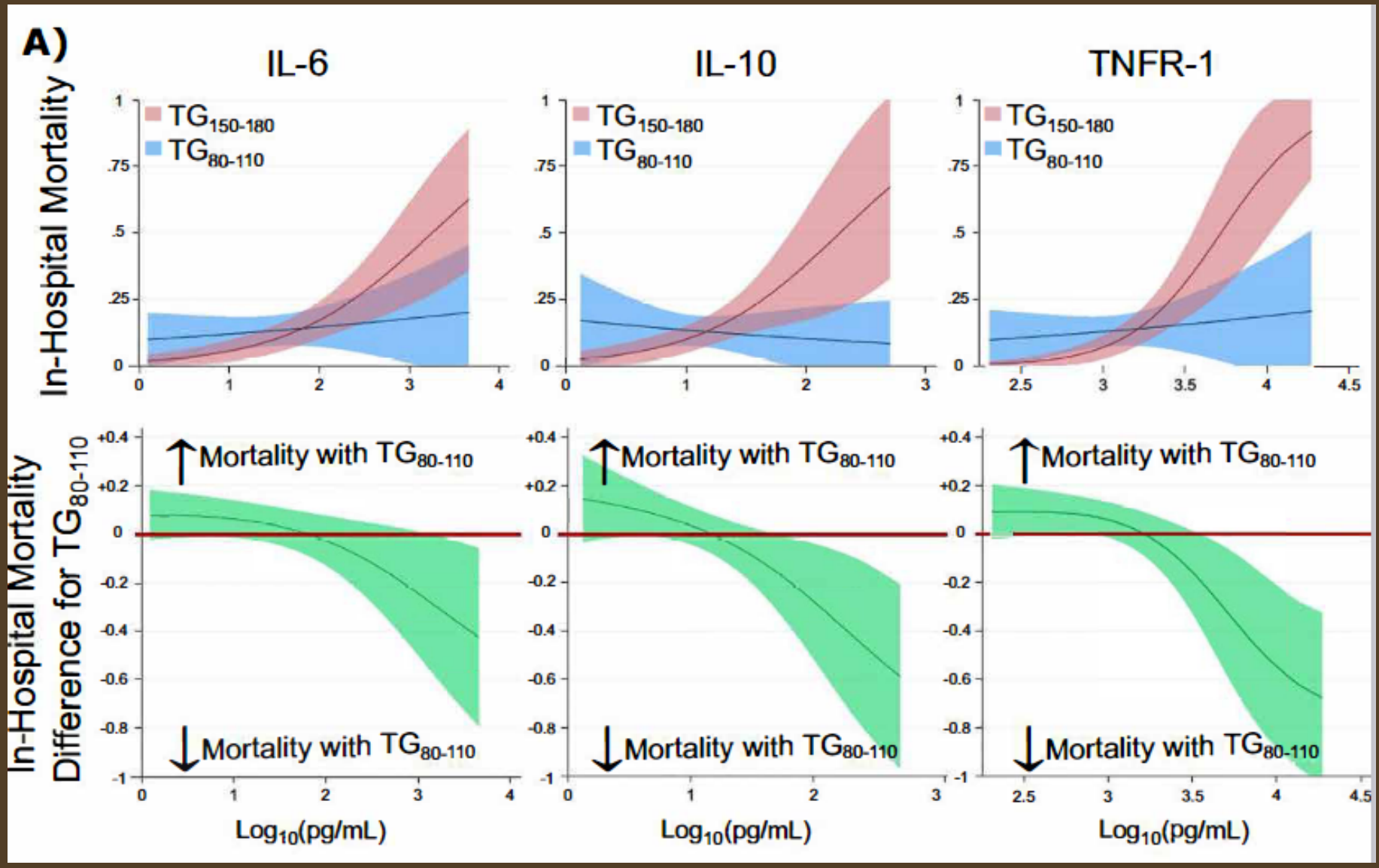



PHENOTYPING
'SEPSIS'
HIGH SEVERITY
TARGET POPULATION

Tight Glycemic Control, Inflammation, and the ICU:

Evidence for Heterogeneous Treatment Effects in 2 RCTs

MS. Zinter et al., AJRCCM 2023



Tight Glycemic Control, Inflammation, and the ICU:

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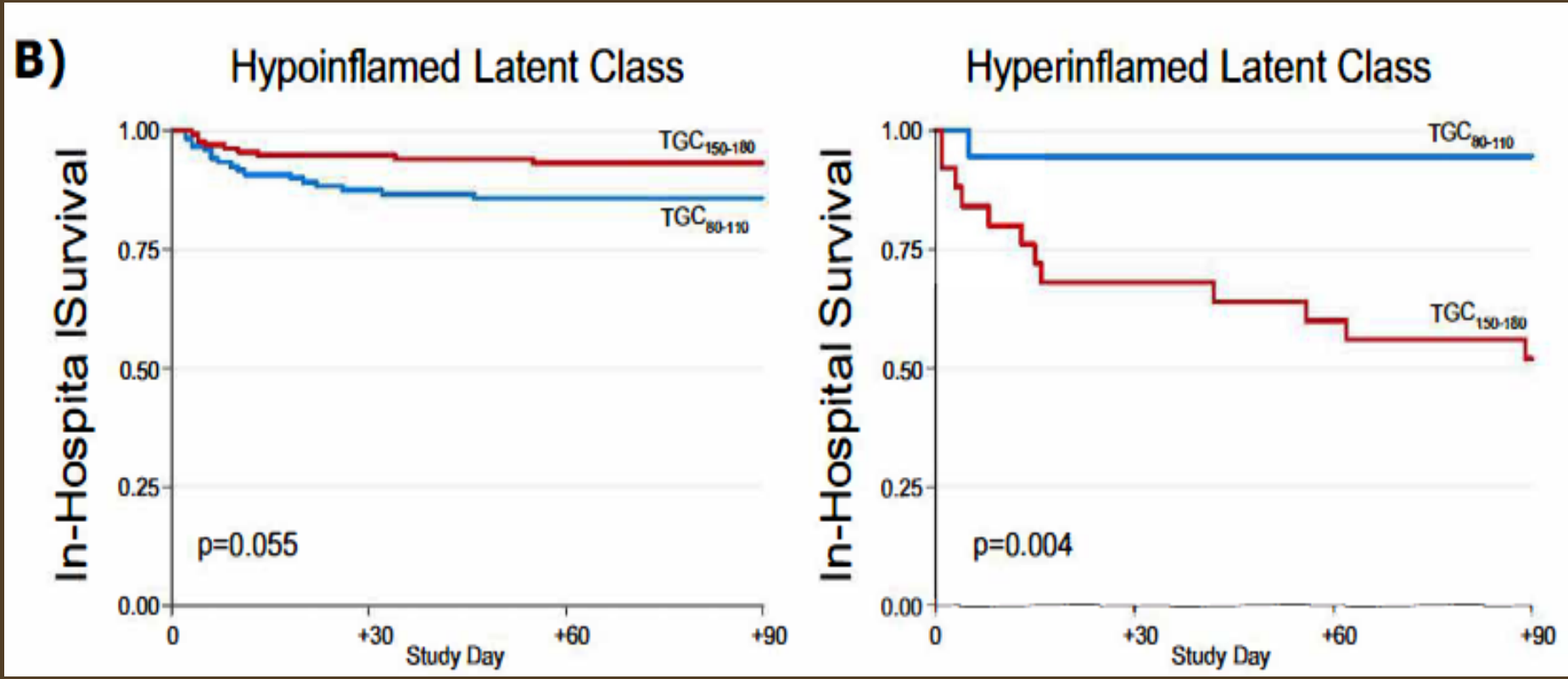


Qin et al. Critical Care (2022) 26:128
https://doi.org/10.1186/s13054-022-03977-3

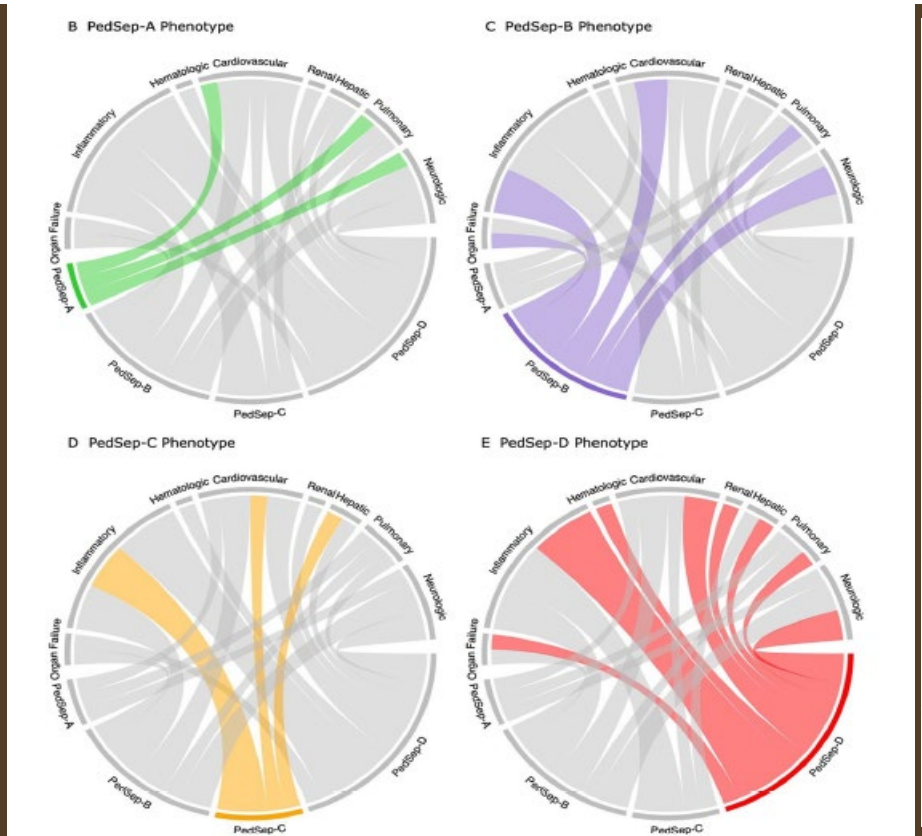
Critical Care

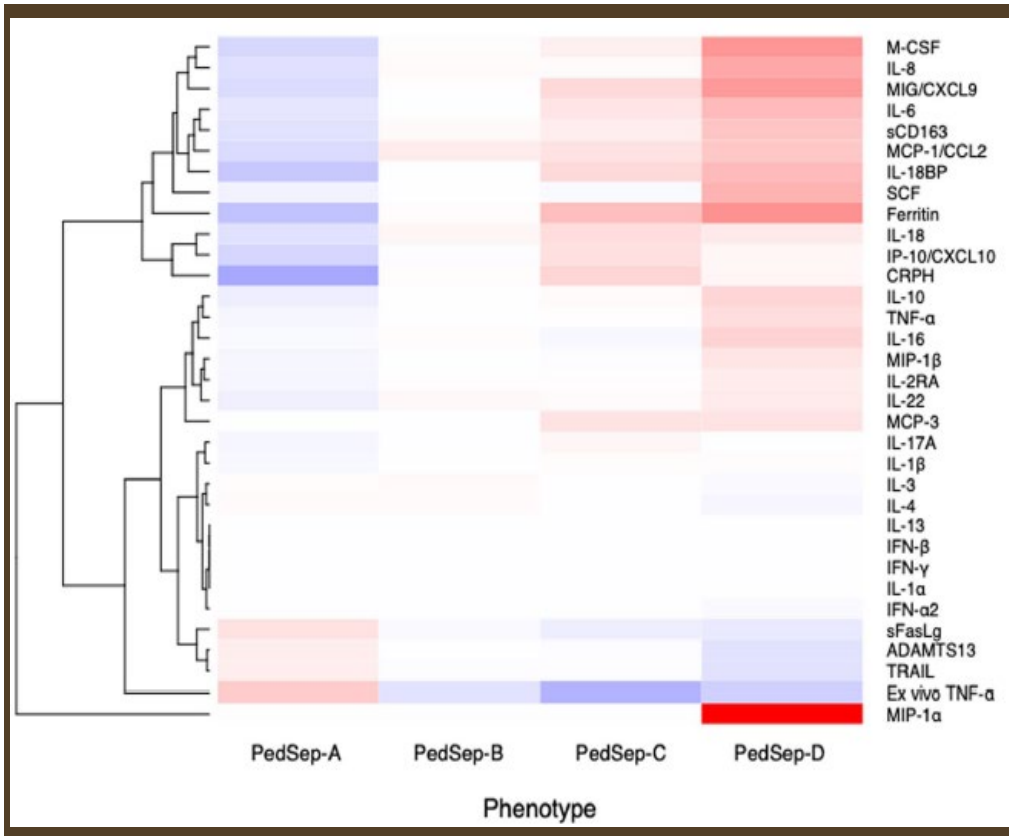
RESEARCH Open Access

2022

Machine learning derivation of four computable 24-h pediatric sepsis phenotypes to facilitate enrollment in early personalized anti-inflammatory clinical trials

Yidi Qin[1], Kate F. Kernan[2], Zhenjiang Fan[3], Hyun-Jung Park[1], Soyeon Kim[4], Scott W. Canna[4], John A. Kellum[2], Robert A. Berg[5], David Wessel[6], Murray M. Pollack[6], Kathleen Meert[7,8], Mark Hall[9], Christopher Newth[10], John C. Lin[11], Allan Doctor[11], Tom Shanley[13], Tim Cornell[14], Rick E. Harrison[12], Athena F. Zuppa[4], Russell Banks[13], Ron W. Reeder[13], Richard Holubkov[13], Daniel A. Notterman[14,15], J. Michael Dean[13] and Joseph A. Carcillo[2*]





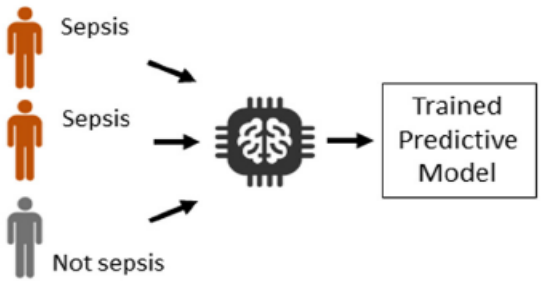
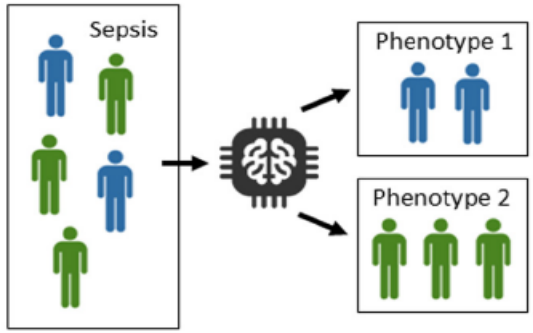
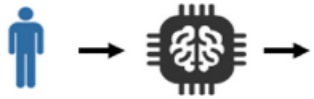
Sepsis biomarkers and diagnostic tools with a focus on machine learning

2022

Matthieu Komorowski,[a,*] Ashleigh Green,[a] Kate C. Tatham,[a,b] Christopher Seymour,[c] and David Antcliffe[a]

[a]Division of Anaesthetics, Pain Medicine, and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, SW7 2AZ, United Kingdom
[b]Anaesthetics, Perioperative Medicine and Pain Department, Royal Marsden NHS Foundation Trust, 203 Fulham Rd, London, SW3 6JJ, United Kingdom
[c]Department of Critical Care Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

eBioMedicine

	Supervised learning	Unsupervised learning
Objective	Learn the mapping between input data and labels	Learn the data structure or identify homogeneous subgroups
Model training		
Model use		
Examples of algorithms	• Logistic regression • Gradient boosting • Deep neural network	• K-means clustering • Latent class analysis • Dimensionality reduction
Examples of applications	• Sepsis prediction model • Transcriptomics sepsis signature	• Sepsis phenotypes from clinical/lab • HTE across phenotypes • Clustering of plasma metabolites

Round Table Conference

"ICU populations: from syndromes to phenotypes"

Brussels, March 21-24, 2023

Emphasizing the need to move towards personalized (and even precision) medicine

Chairpersons: Carolyn Calfee (San Francisco, USA) **& Antony Gordon** (London, UK)

Lieuwe Bos
(Amsterdam, Netherlands)
Carolyn Calfee
(San Francisco, USA)
Janet Diaz
(San Francisco, USA)
Simon Finfer
(Sydney, Australia)
Tomoko Fujii
(Tokyo, Japan)
Evangelos Giamarellos
(Athens, Greece)
Ewan Goligher
(Toronto, Canada)
Michelle Gong
(New York, USA)
Antony Gordon
(London, UK)

Vincent Liu
(Oakland, USA)
John Marshall
(Toronto, Canada)
David Menon
(Cambridge, UK)
Nuala Meyer
(Wynnewood, USA)
Sheila Myatra
(Mumbai, India)
Marlies Osterman
(London, UK)
Hallie Prescott
(Ann Arbor, USA)
Adrienne Randolph
(Boston, USA)

Edward Schenck
(New York, USA)
Chris Seymour
(Pittsburgh, USA)
Manu Shankar-Hari
(Edinburgh, UK)
Mervyn Singer
(London, UK)
Fabio S Taccone
(Brussels, Belgium)
B Taylor Thompson
(Boston, USA)
Tom van der Poll
(Amsterdam, Netherlands)
Jean-Louis Vincent
(Brussels, Belgium)
Fernando Zampieri
(Sao Paulo, Brazil)


THE
END IS
NEAR


We want
EBM !

Clinical trials

We must encourage clinical trials

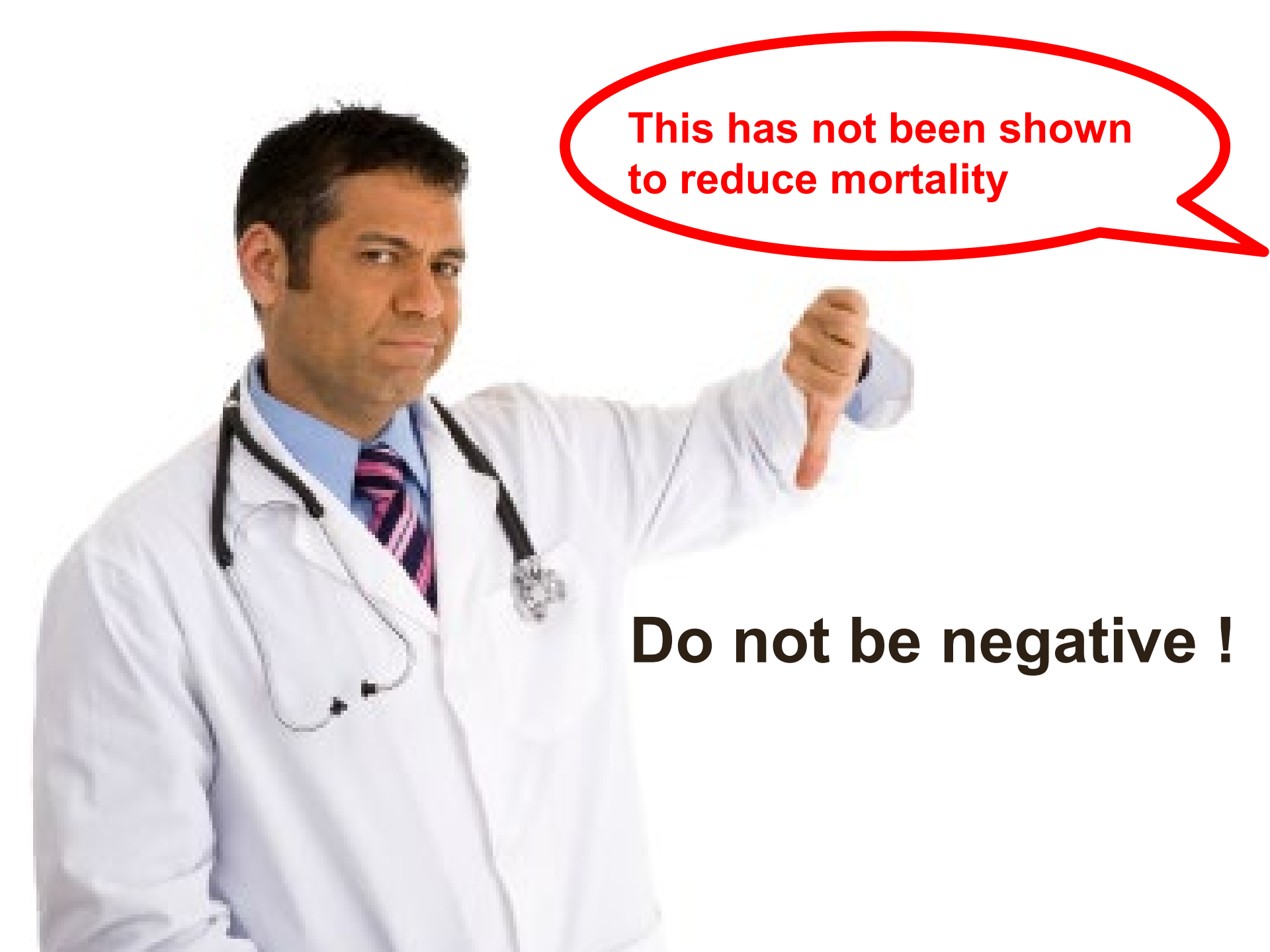
To improve management of future patients

To benefit the patients participating in the clinical trial

Through the Hawthorne effect
Through an overall improvement
of the quality of care

CLINICAL TRIALS IN THE ICU

- Syndromes vs specific disease
- Heterogeneous populations
- Rapidly changing physiology
- Treatments include multiple interventions


This has not been shown
to reduce mortality
Do not be negative !

The major problems with RCTs targeting mortality in heterogeneous populations

Targeting mortality → Other primary end-point than mortality

Organ function

In heterogeneous patient populations → Better defined population

Specific phenotype

Sepsis trials – some interventions

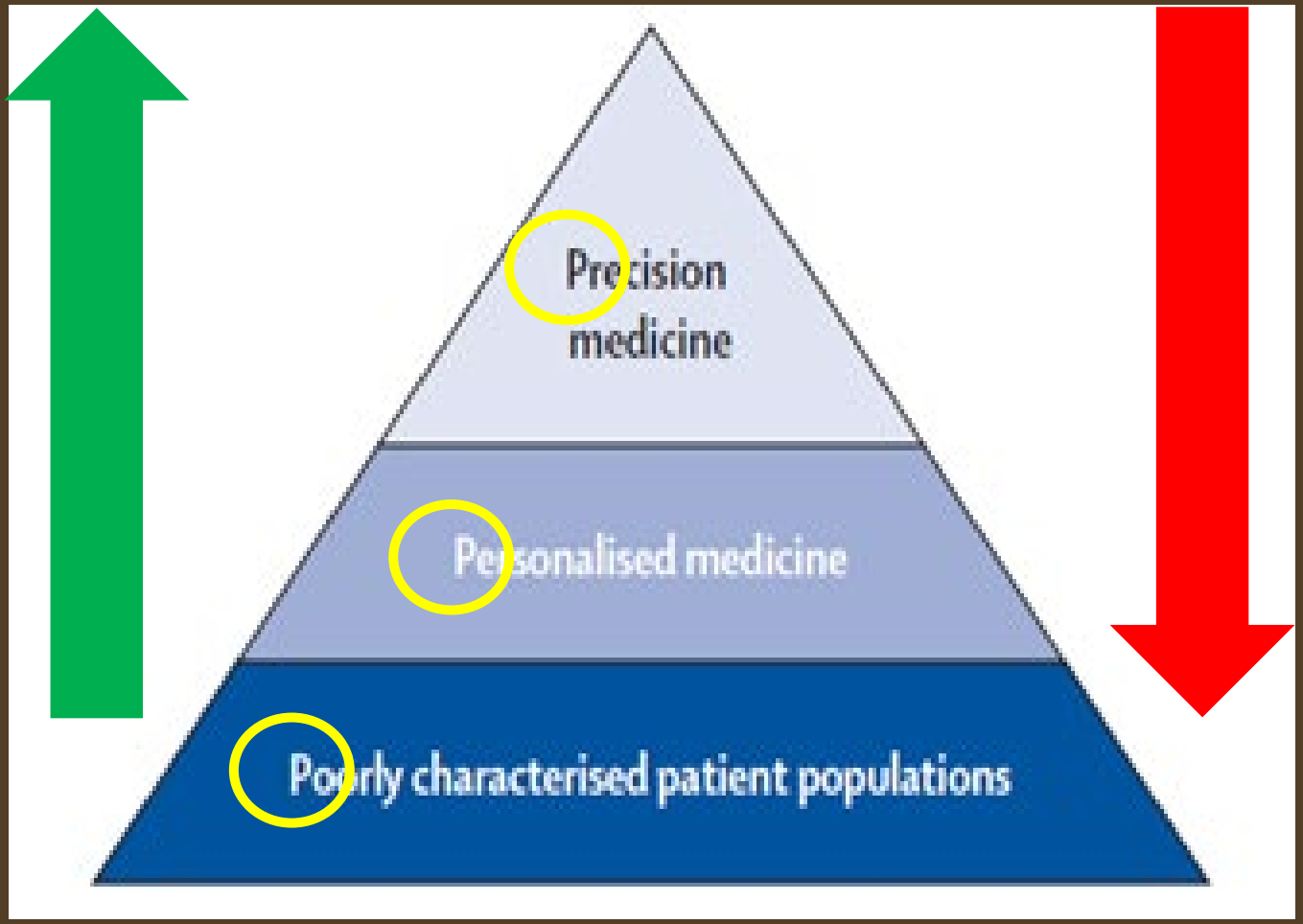
Corticosteroids
Non-steroid anti-inflammatory agents (ibuprofen)
Anti-TNF (antibodies, receptors)
Anti-IL-1 (IL-1ra)
Anti-TLR4
Bradykinin inhibitors
Interferon
Anti-PAF
Nitric oxide inhibitors
Antioxidants (N-acetylcysteine)
Anti-endotoxin (antibodies, purification)
Alkaline phosphatase
Statins
Activated protein C/Thrombomodulin
TFPI / antithrombin
Levocarnitine
Thymosin alfa 1
Epirubicin
Anti-histones
Traditional Chinese medicines (e.g. Xuebijing)
Vitamins

CLINICAL TRIALS

What is the aim?	Measure
Improve gas exchange	Gas exchange
Increase arterial pressure	Arterial pressure
Correct hypovitaminosis	Vitamin levels
Decrease inflammation	Inflammatory markers
Decrease endotoxin levels	Endotoxin levels
Antagonize adrenomedullin	Adrenomedullin levels
Correct endotheliopathy	Coagulation markers Microcirculatory variables


FUTURE
JUST AHEAD
BETTER PATIENT IDENTIFICATION

The 3 P letters of critical care medicine



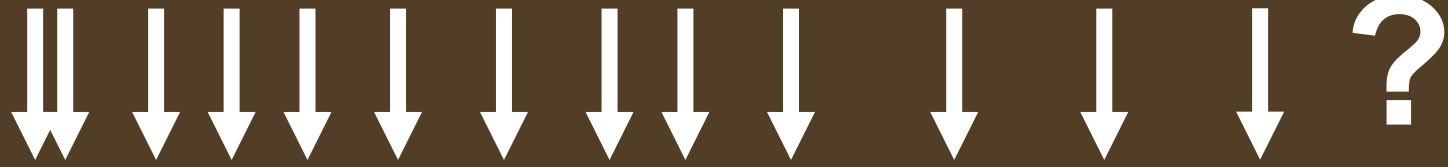
JL Vincent, Lancet Respir Med 2016

CLINICAL TRIALS IN THE ICU

We have enrolled 3000 patients !

(and our study is negative)

2020 2021 2022 2023 2024 2025 2026 2027



2020 2021 2022 2023 2024 2025 2026 2027

TIME

We cannot be too selective....

ENROLLMENT IN CLINICAL TRIALS ON NEW SEPSIS THERAPIES

NARROW CRITERIA
(homogeneity)

WIDE CRITERIA
(noise)

Slow enrollment
(limited number meeting the criteria)
Suboptimal enrollment
(missed opportunities)
Limited applicability
(marketing)

ARTIFICIAL INTELLIGENCE WILL HELP

THE FUTURE EVIDENCE

RCT on well selected patient populations targeting not only mortality

+

Big data

INDIVIDUALIZE therapy

The evolution of 'sepsis' trials

The past

Preclinical studies

Limited data on previously healthy animals made septic (e.g. CLP)

Limited information on the pathophysiologic process

Clinical studies

Patient selection :

Severe infection with some degree of organ failure

Treatment dose and duration

Arbitrarily defined

Primary end-point

28 day mortality

The future

Preclinical studies

Larger variety of animal studies

Better definition of the pathway of interest

More information on the pathophysiologic process

Development of a suitable biomarker

Clinical studies

Patient selection :

Based on the pathophysiologic process (ideally guided by a biomarker)

Infection may not be required

Treatment dose and duration

Individualized

(ideally guided by the biomarker)

Primary end-point

Morbidity (and mortality)

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
https://doi.org/10.1080/17512433.2019.1643235

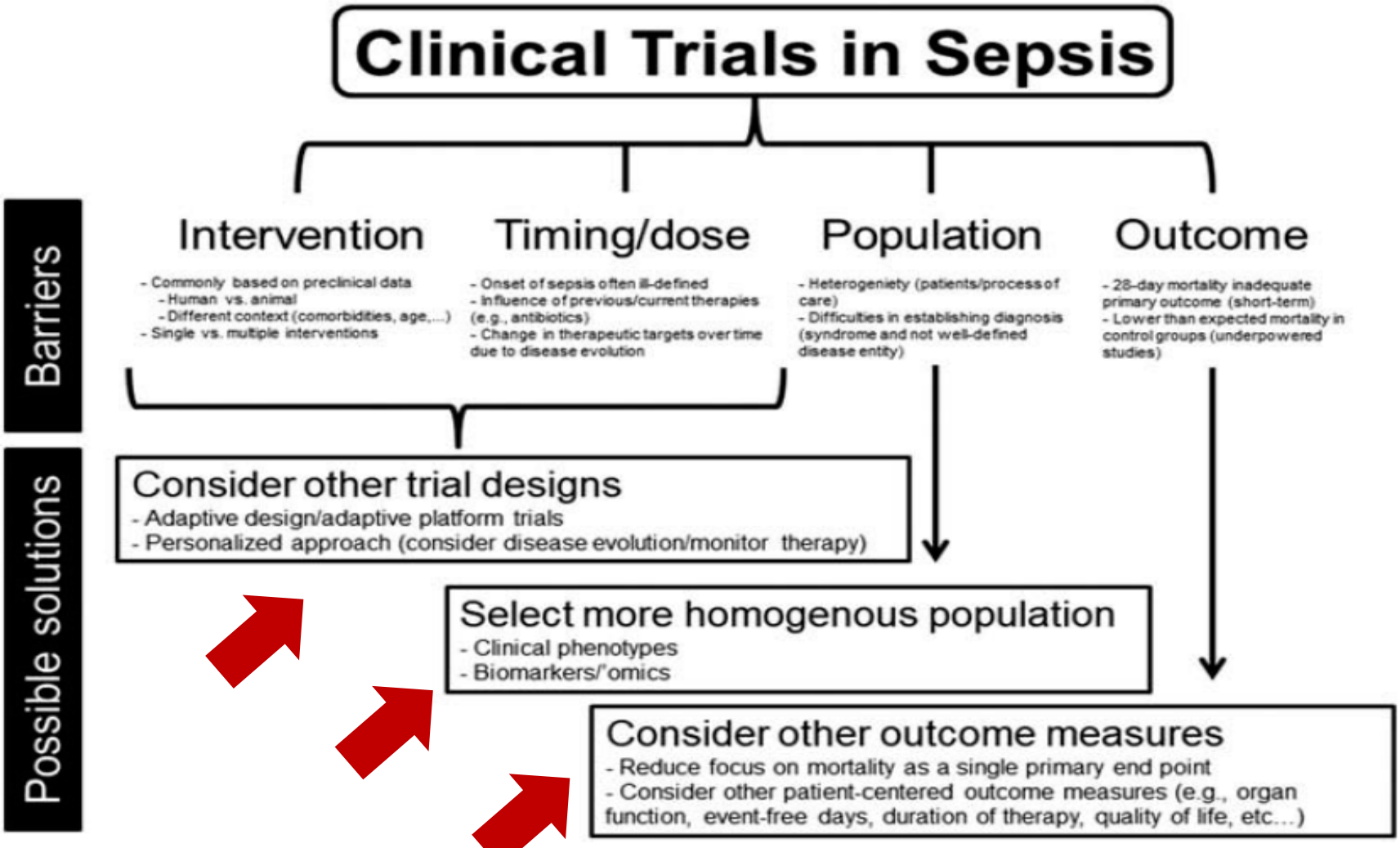
Taylor & Francis
Taylor & Francis Group

REVIEW

2019

Clinical trial design for unmet clinical needs: a spotlight on sepsis

Jean-Louis Vincent[a] and Yasser Sakr[b]



THANK YOU !