

# Sepsis: what's new?

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# Sepsis: a global call to action

## Recognizing Sepsis as a Global Health Priority — A WHO Resolution

Konrad Reinhart, M.D., Ron Daniels, M.D., Niranjan Kissoon, M.D., Flavia R. Machado, M.D., Ph.D.,  
Raymond D. Schachter, L.L.B., and Simon Finfer, M.D.



Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

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



Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection

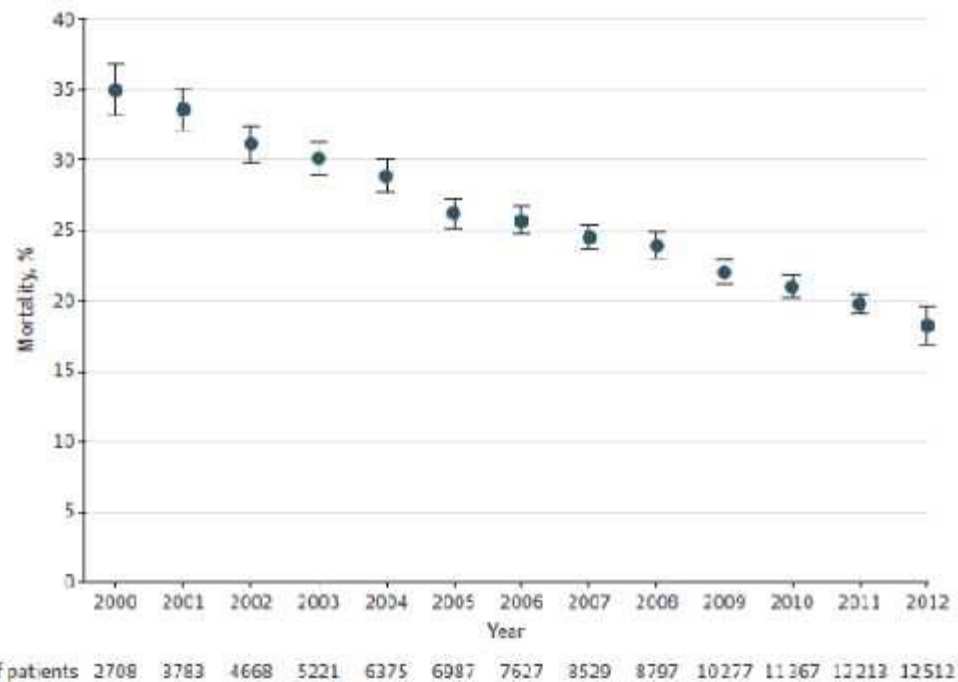
- Organ dysfunction: increase  $\geq 2$  total SOFA points
- Septic shock = vasopressor requirement to maintain MAP  $\geq 65$  mmHg and lactate  $> 2$  mmol/l in absence of other causes, e.g. hypovolemia
- QuickSOFA: Infected patients in non-ICU settings with poor outcomes identifiable by 3 variables: respiratory rate  $\geq 22$  breaths/min, altered mentation, systolic blood pressure  $\leq 100$  mmHg.

Research

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

## Mortality Related to Severe Sepsis and Septic Shock Among Critically Ill Patients in Australia and New Zealand, 2000-2012

Figure 1. Mean Annual Mortality in Patients With Severe Sepsis



n=101064 patients;  
171ICUs

Does this good news come with a price?

More longterm morbidity?

*Kaukonen, JAMA, 2014*

# Late sepsis morbidity and mortality

## Unplanned Readmissions After Hospitalization for Severe Sepsis at Academic Medical Center–Affiliated Hospitals\*

John P. Donnelly, MSPH<sup>1,2,3</sup>; Samuel F. Hohmann, PhD, MS-HSM<sup>4,5</sup>; Henry E. Wang, MD, MS<sup>1</sup>

One in five severe sepsis discharges readmitted within 30 days.

## Late mortality after sepsis: propensity matched cohort study

Hallie C Prescott,<sup>1, 2, 3, 4</sup> John J Osterholzer,<sup>1, 4</sup> Kenneth M Langa,<sup>1, 2, 3, 5</sup> Derek C Angus,<sup>6</sup> Theodore J Iwashyna<sup>1, 2, 3, 4, 5, 7</sup>

Over 1 in 5 patients who survives sepsis has a late death not explained by prior health status.

## Long-term Cognitive Impairment and Functional Disability Among Survivors of Severe Sepsis

Theodore J. Iwashyna, MD, PhD

Prevalence of cognitive impairment increases 10 percentage points among sepsis survivors.



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

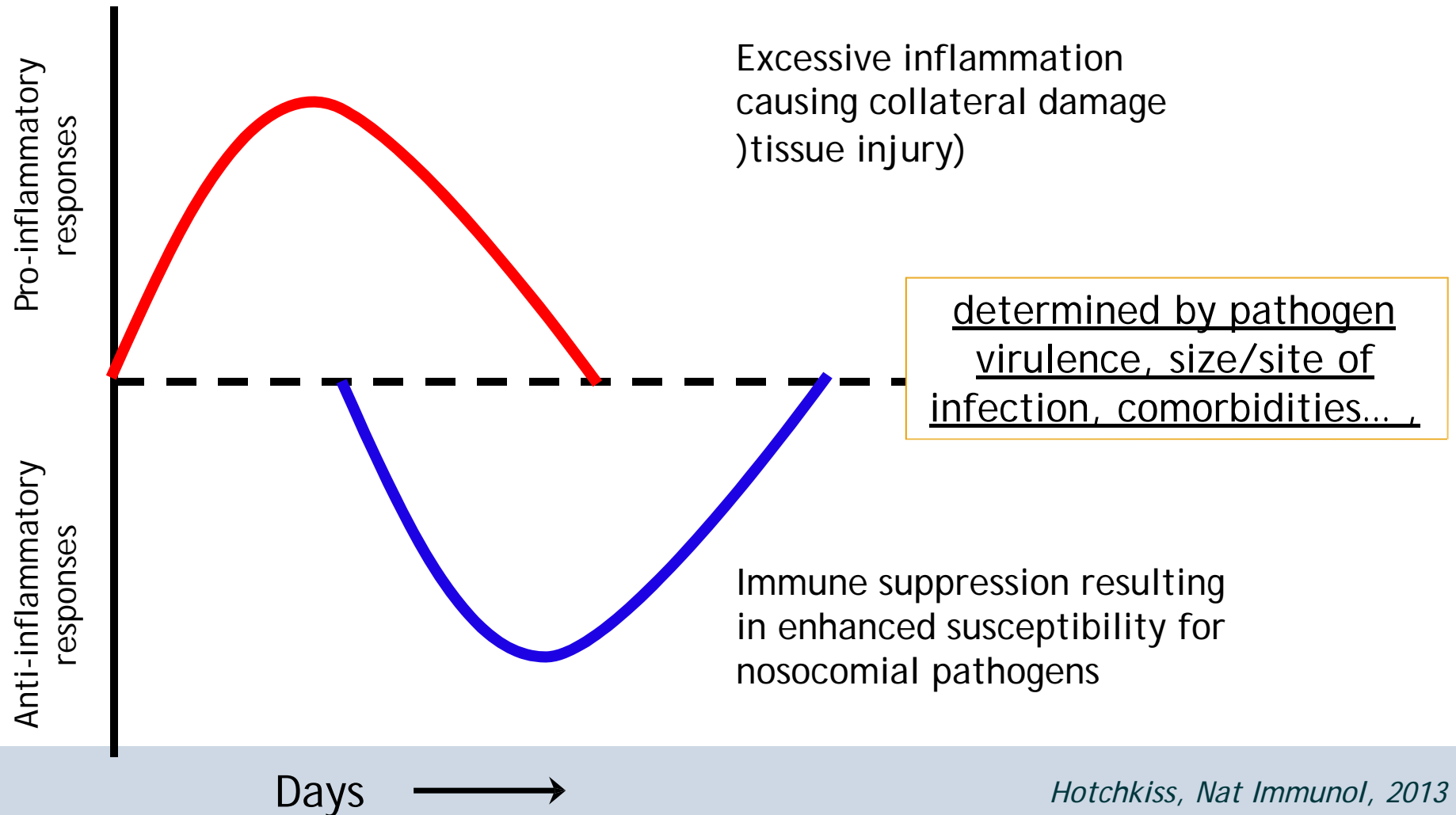
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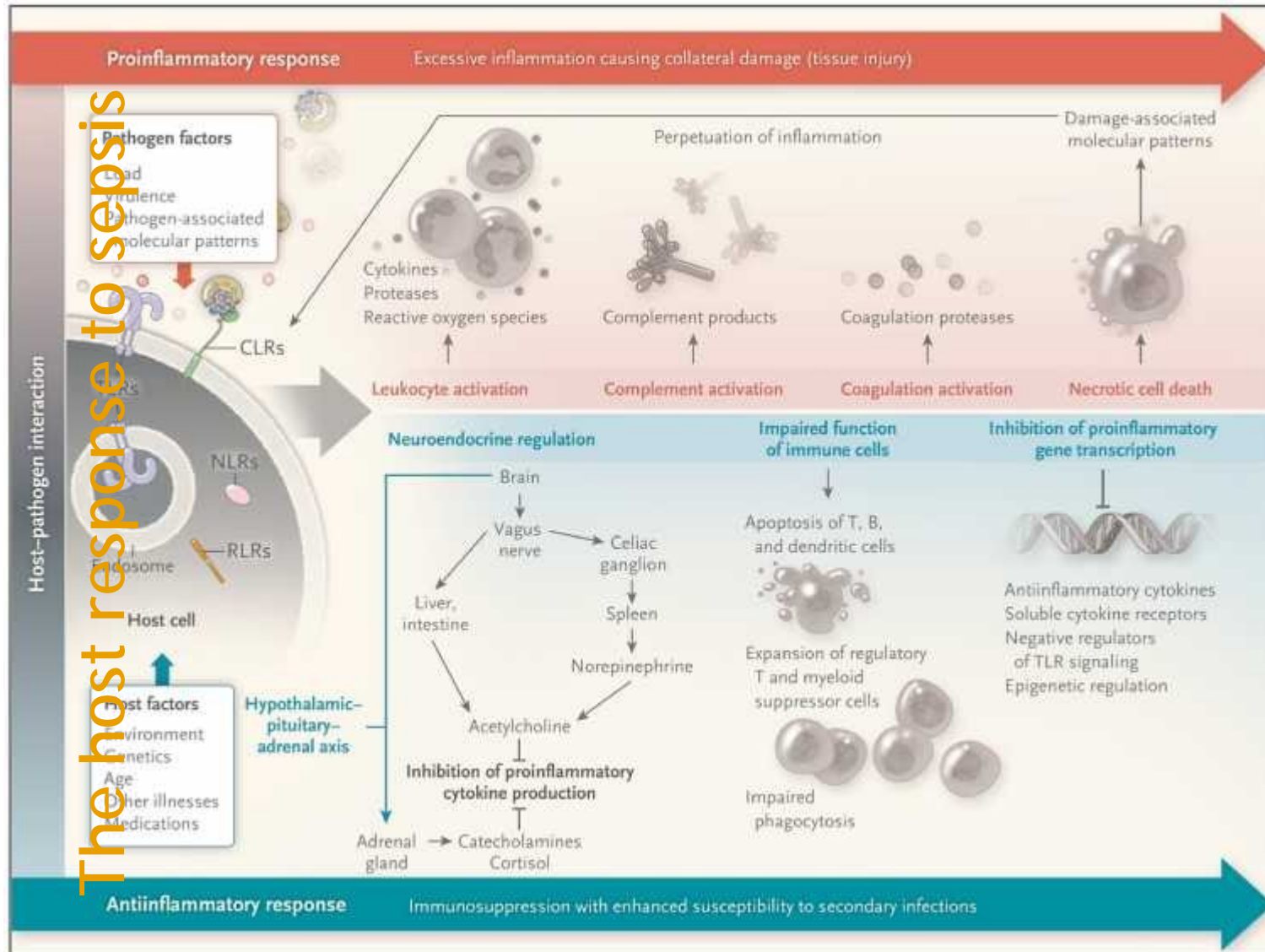


Sepsis is defined as life-threatening organ dysfunction caused by **a dysregulated host response** to infection

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# The host response to sepsis





The host response to sepsis





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CRITICALLY ILL PATIENT

**JAMA**<sup>®</sup>  
The Journal of the American Medical Association

# Immunosuppression in Patients Who Die of Sepsis and Multiple Organ Failure

Jonathan S. Boomer, PhD

Kathleen To, MD

Kathy C. Chang, PhD

Osamu Takasu, MD

Dale F. Osborne, BS

Andrew H. Walton, MS

Traci L. Bricker, BS

Stephen D. Jarman II, BSN, RN

Daniel Kreisel, MD, PhD

Alexander S. Krupnick, MD

Anil Srivastava, MD

Paul E. Swanson, MD

Jonathan M. Green, MD

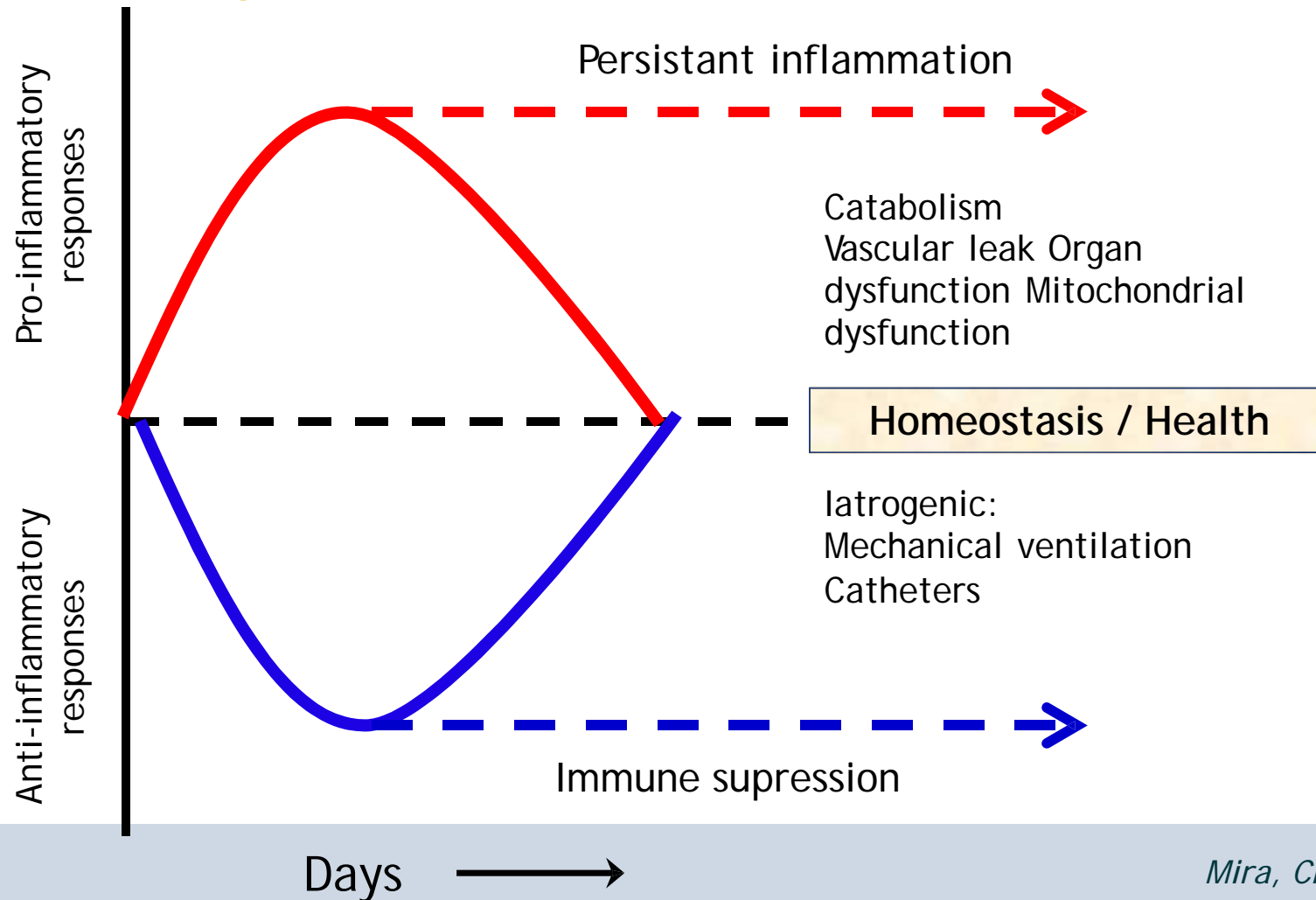
Richard S. Hotchkiss, MD

Another Perspective on Sepsis:

Postmortem studies of patients who die of sepsis show evidence of profound immunosuppression

*Boomer, JAMA, 2011*

# “Persistent Inflammation Immunosuppression and Catabolism Syndrome” (PICS)



# Towards novel treatments



# Treating sepsis: the latest evidence

**O** Antibiotics  
Early adm, n, strallofl

**O** Fluids  
SeYefa! hters  
10, tialty  
Collo, ds  
E: C, yst, 1llo1d  
O , (r, \*c,

**O** Goal oriented therapy

**O** EGDT  
Etrly goal directed therapy

**O** Vasopressors  
1--6 hours after  
C, Noreptnephnn"  
C, ]ponephrine  
C, Vnopr6sm  
O ( , , a n r

r

**O** Enteral feeding

**C**, Insulin therapy

**O** Deep sedation

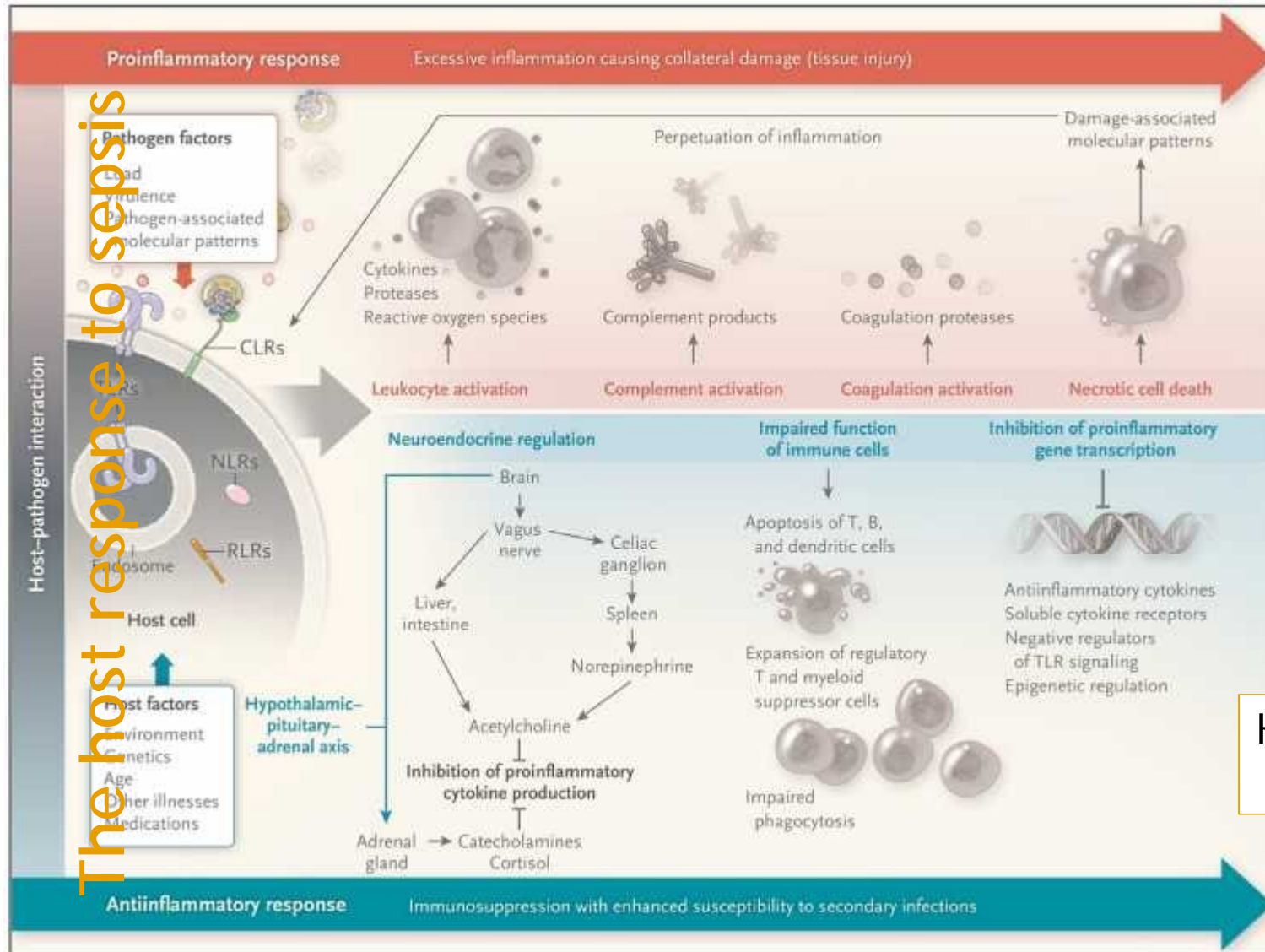
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@ Molecular targeted therapies

**O** Lung protective ventilation

**O** Urinary catheter

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Will St1hl-T1mmln1  
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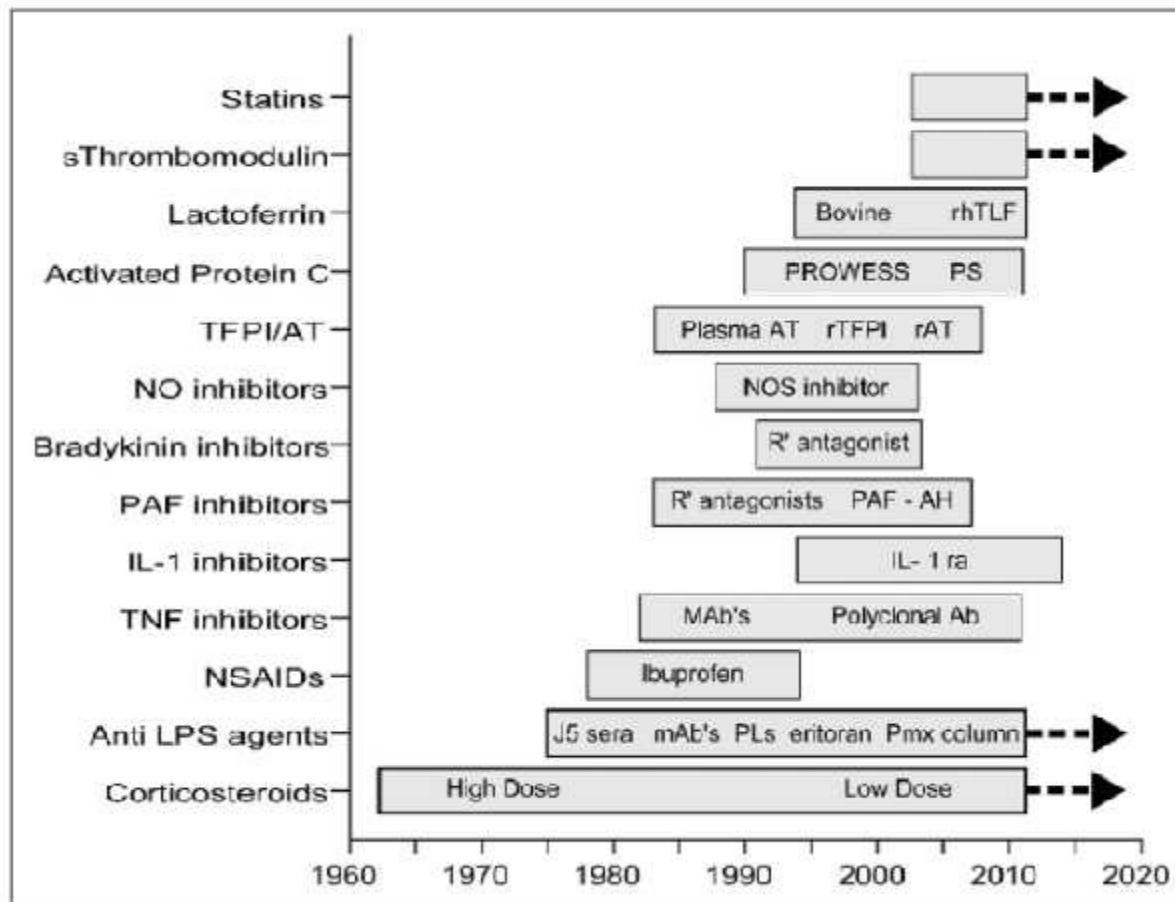


The host response to sepsis

How to target the host?



# The sepsis graveyard: over two decades of failed experimental agents tested in clinical trials



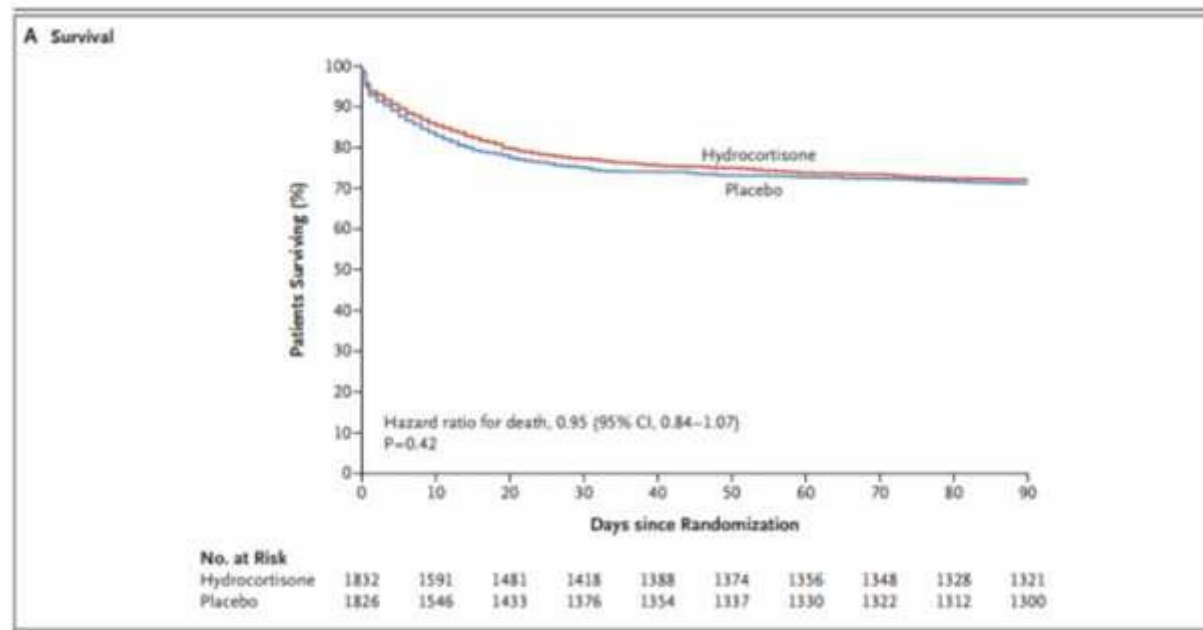
What have we done wrong?

# Bigger sample size?

The NEW ENGLAND JOURNAL of MEDICINE

## 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\*



n = 3800 patients with septic shock and mechanical ventilation receive 200 mg hydrocortisone per day or placebo for 7 days

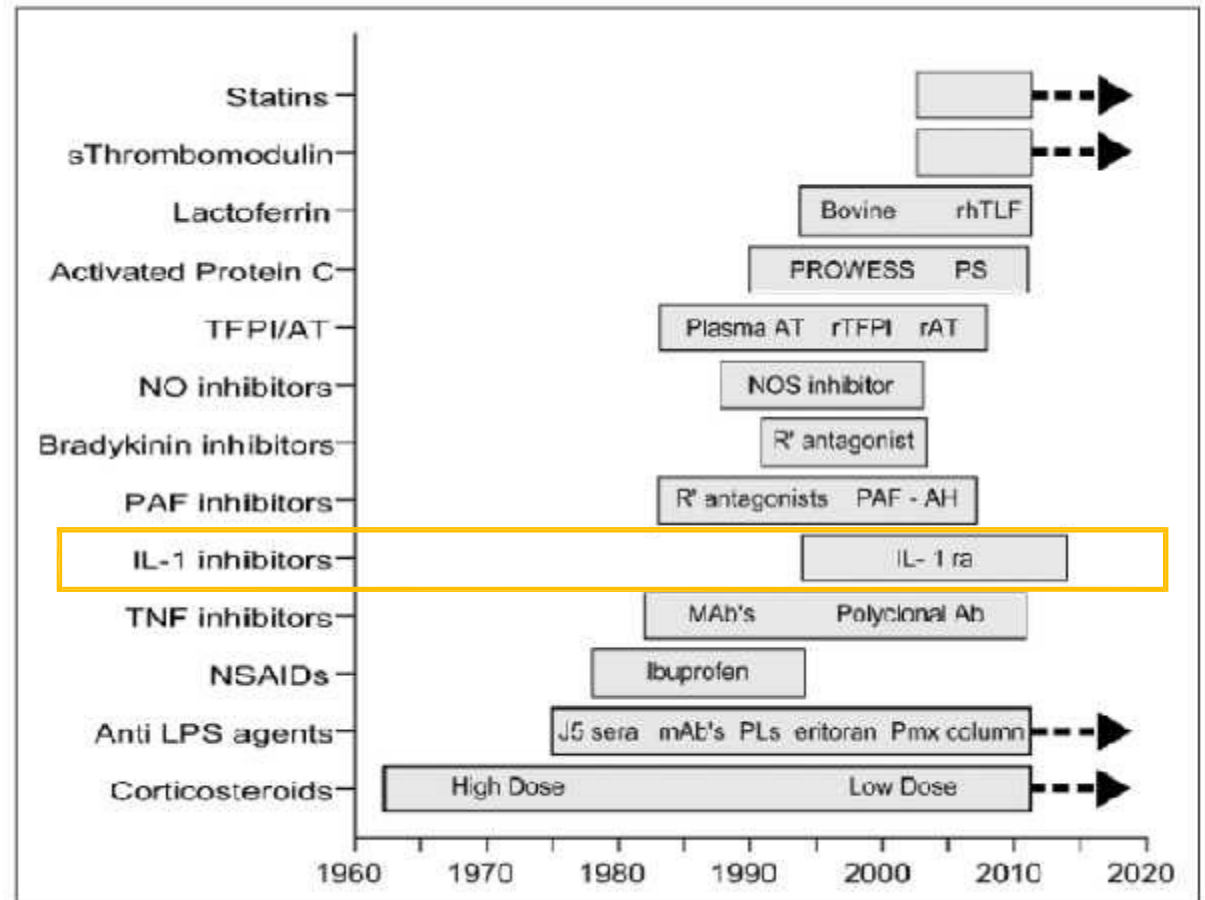
# The Search for Effective Therapy for Sepsis Back to the Drawing Board?

Derek C. Angus, MD, MPH

- 2 central misconceptions about sepsis
  - The host response is unhelpfully exuberant
  - The host response represents a final common pathway
- Not every sepsis is the same:
  - Different patients
  - Other bugs
  - Other phase of the septic response
- Let's focus on theranostics!

## Novel trial design: example

- Biomarker guided inclusion of patients
- Interleukin-1 receptor antagonist in patients with sepsis: overall intervention no effect
- Re-analysis subgroup of patients with signs of macrophage activation syndrome: improved survival



## Stratification of sepsis patients based on blood gene expression profiles

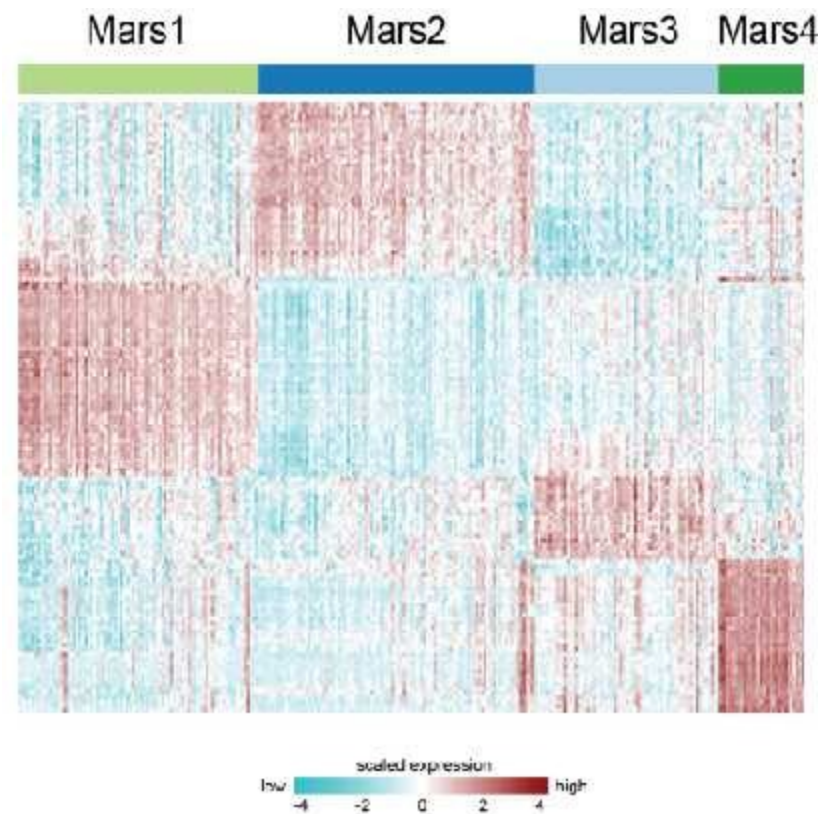
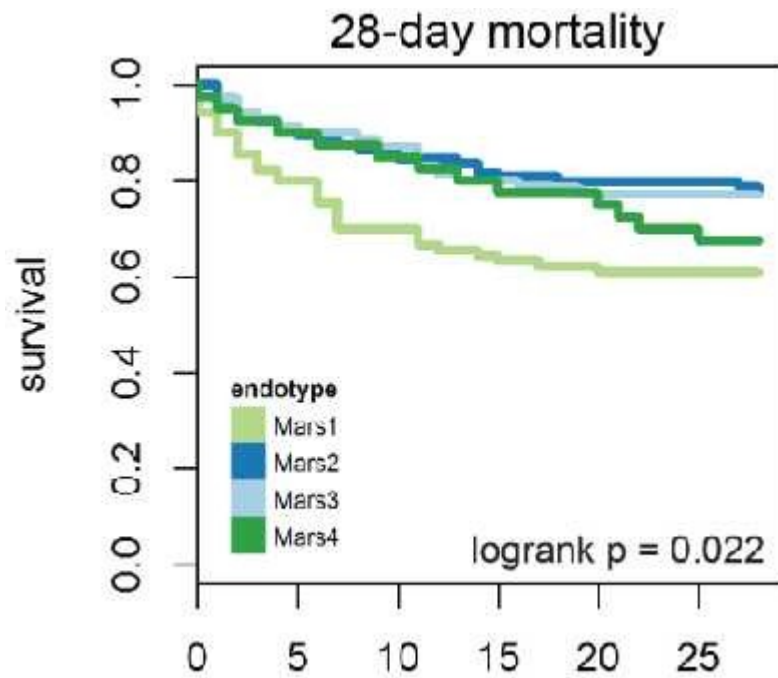


- ❖ Heterogeneous group
- ❖ Varied outcomes
- ❖ Therapy may benefit some, but harm others

- ❖ More homogeneous subgroups
- ❖ Better prognostication
- ❖ Personalized treatment



# Four sepsis endotypes with pathophysiologic and prognostic implications



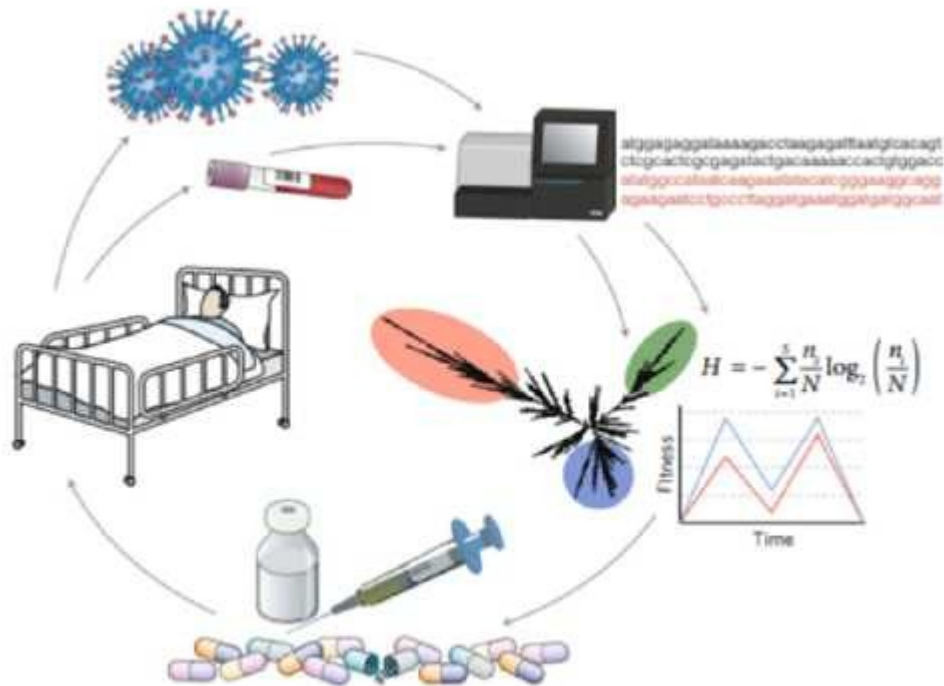
Validation in two independent cohorts



# Future perspective



# Future perspective



**Figure 1** | The patient loop. Genetic sequencing of pathogen and host-serum samples, combined with phenotype information, can be synthesized with evolutionary tools to design optimal treatment options.

## Infectious disease management must be evolutionary

Colin A. Russell and Menno D. de Jong

