30 ans de Réanimation: le choc septique

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THE PRINCIPLES AND PRACTICE OF MEDICINE

DESIGNED FOR THE USE OF PRACTITIONERS AND STUDENTS OF MEDICINE

BY

THE LATE SIR WILLIAM OSLER, BT., M.

FELLOW OF THE ROYAL COLLEGE OF PHYSICIANS, LONDON; REGIUS PROFESSOR OF MEDICINE, OXFORD UNIVERSITY; HONORARY PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE; FORMERLY PROFESSOR OF THE INSTITUTES OF MEDICINE, McGILL UNIVERSITY, MONTREAL, AND PROFESSOR OF CLINICAL MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA

NEW YORK AND LONDON
D. APPLETON AND COMPANY
1921

Immunity.

Not all exposed to-the infection take the disease.

Some families seem more susceptible than others;

The **blood-serum of persons suffering from advanced chronic disease** was found to **be less destructive to the *staphylococci aureus* than normal human serum**

En 30 ans, que s'est-il passé?

- **Sepsis definition** more or less **stable from 1991 (Bone) → 2016 → Sepsis 3 based on OF**
- **Epidemiology → incidence increase**
  - **incidence, age, comorbidities↗**
  - **Big data → large cohort → AI for Dg & Pn**
- **Better education**, **faster diagnosis**, **reasonable recommendations (SSC x 3)**
- **Huge techno-biolological progresses**: **genotyping**; **transcriptomic**; **proteomic**; **metabolomic**…
- **Dynamic aspects** of the **immuno-inflammatory processes**
- **Reasonable supportive therapy: Fluid amount**; **pressors**; **ventilation**; **RRT**; **ECorp Circ…**

En 30 ans, qu'en ai-je tiré?

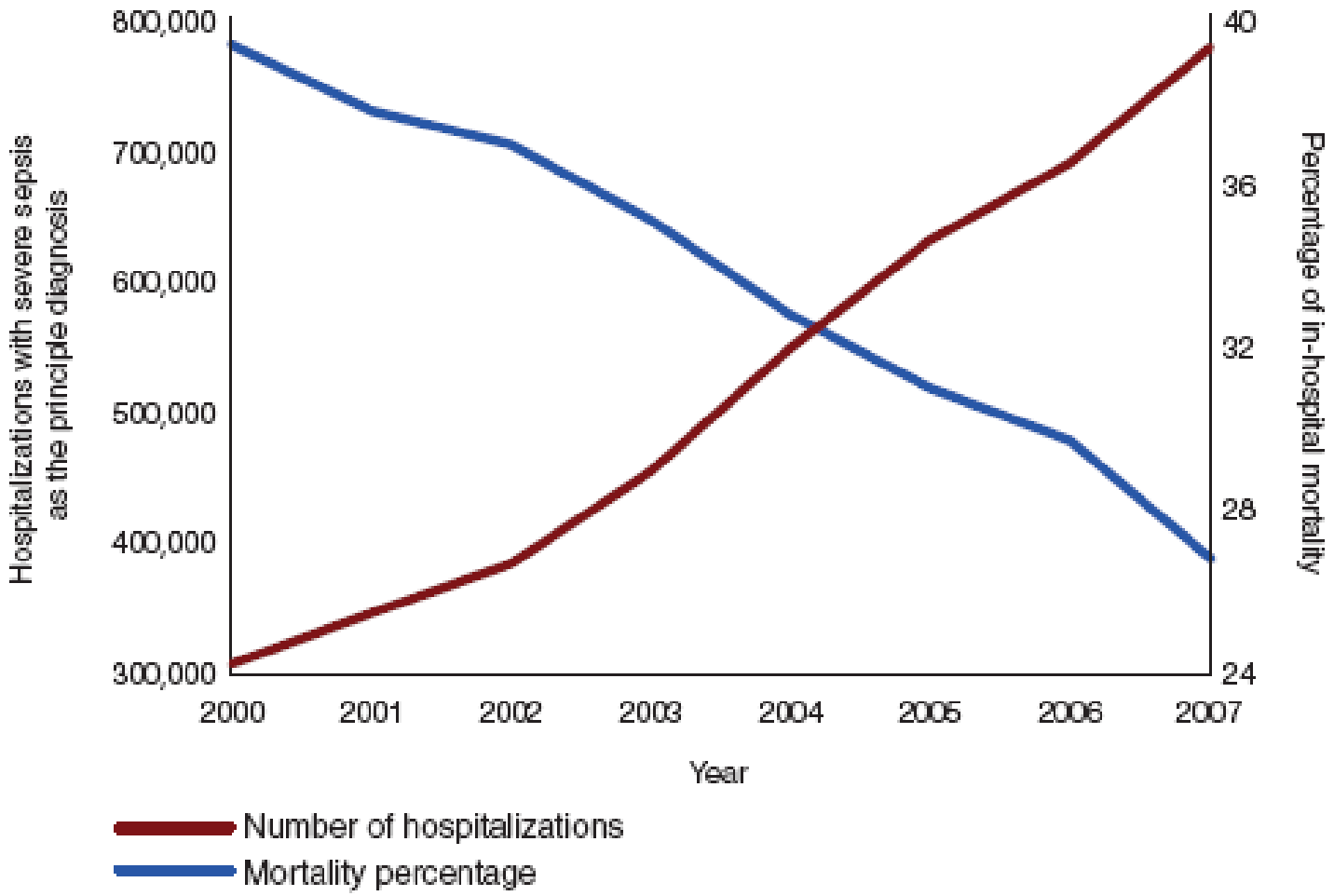
- **Over simplistic view** leads to **mistakes**: → **RCTs always failed** despite **solid basic science background**
- **Infection does not kill by itself but by host response**
  - **Concept of septic phases**
  - **Inflammation BMarkers; organ damage BM, etc…**
- **Delay for infection treatment is crucial (SSC x 3)**
  - **Golden hours; early AB administration; fluid is necessary but not too much! Pressors YES but for what BP level?**
- **Huge techno-biological progresses**:
  - **genotyping**; **transcriptomic**; **proteomic**; **metabolomic**…
  - **More rapid detection of pathogens**
- **Elderly patients SHOULD be treated**.
- **Exp models** are **not easily transposable to human beings**

Le Sepsis: un pb de Santé Publique Mondial (OMS)…

A democratic syndrome!

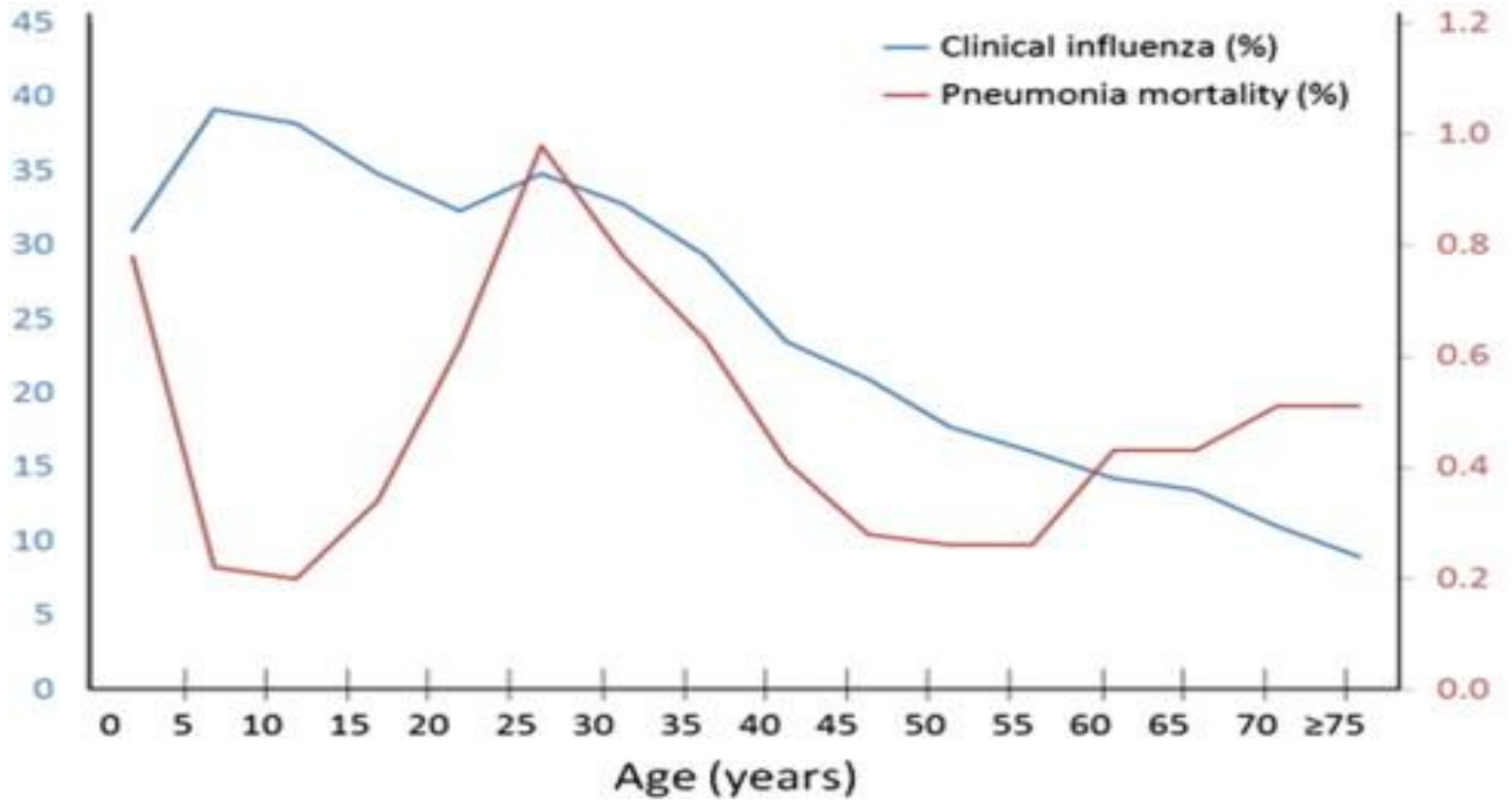
All can die!

Despite improving hospital care, one in 1,200 Americans will die of severe sepsis this year.



Chest **140**, 1223–1231 (2011).

Budget 1% of US PIB



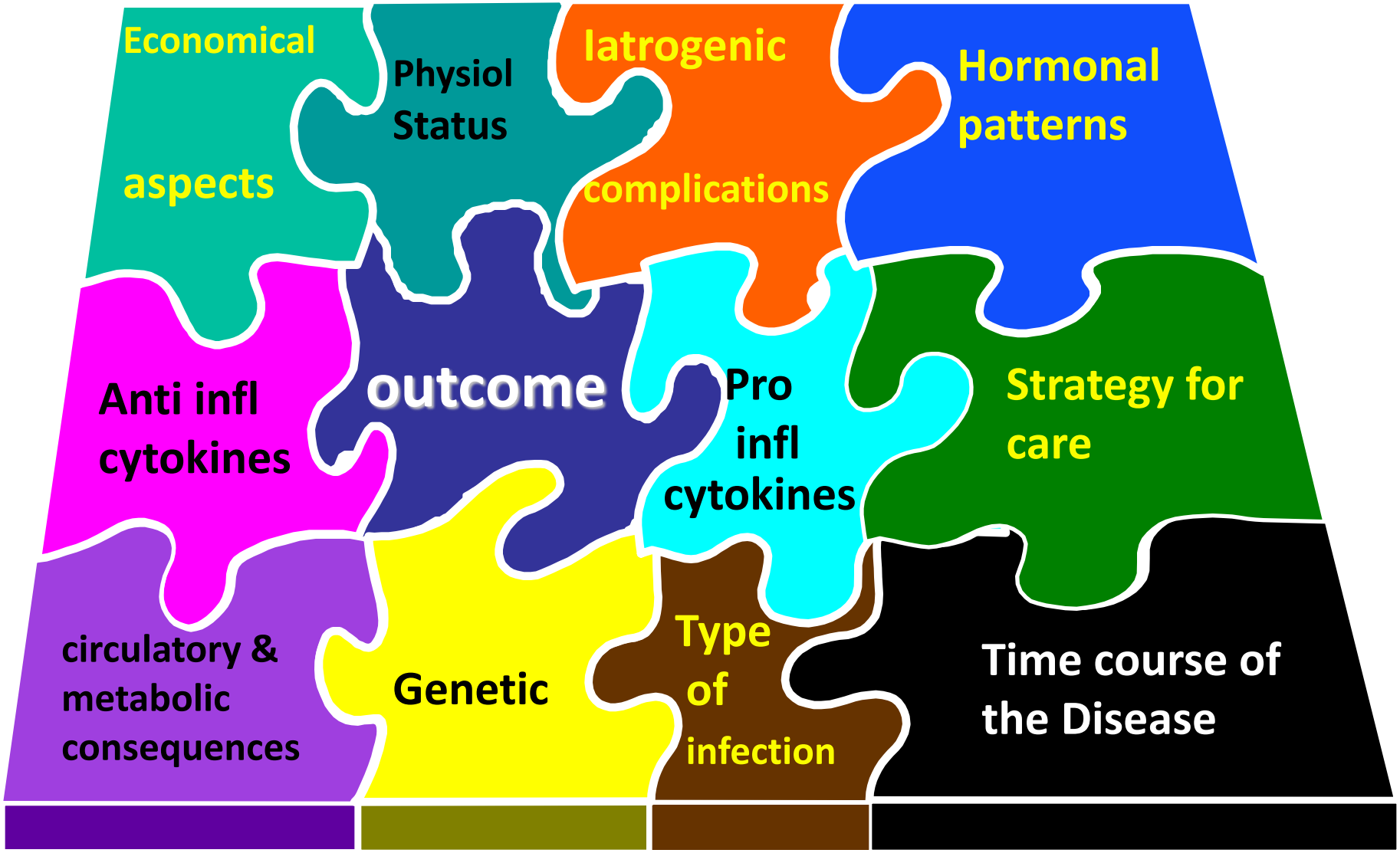
The W-shaped mortality curve seen in the 1918 influenza pandemic curves for incidence of clinical illness vs. fatality rate markedly differ

Same age-dependent mortality pattern is seen for TB, pneumococcal infection, trauma, Yellow fever, malaria, streptococcal Toxic shock, etc. ➔ What accounts for this difference?

Fedson D. Antiviral Research 2013; 99,(3), 417- 435

Sepsis: a syndrome with multiple facets… multiple determinants for outcome

Sepsis Puzzle



Vocabulary

- **Antigen**
  - Is an **internal** or **external** « **substance** » of the body that **stimulates** the **immune system** to produce **Abodies against this substance**.
- **Antibodies**
  - **Specific** proteins (**immunogloblins**) produced by the **B Lymphocytes triggered** by **foreign substances**. **AB identify and neutralize their targets.**
- **Innate Immunity** **(genetically determined)**
  - **Early** response **quite immediate**
- **Adaptive Immunity** **(acquired)**
  - **Later** response but **more specific.**

Vocabulary (2nd)

- **Tolerance:** Capacity of the **immune system to determine the « friends or foe »**
- **Apoptosis :** programmed cell death
- **PAMPs :** Pathogen Associated Molecular Patterns
- **DAMPs :** Damage Associated Molecular Patterns (sterile inflammation)
- **Lymphatic System**

- **Phagocytose**

Major concepts

- **This is inflammation that kills the patient more than infection itself (*proof: COVID-19*)**
- **Host response (inflammation) is self limited ➔ phases of inflammation**
- ***Inflammation concerns*: immunity; coagulation; cell metabolism**
- **Inflammation is induced by pathogens and/or by tissue damage**

The actors of the immune response

- **Innate response**: **monocytes macrophages dendritic cells**
  - ***Cellular plasticity***: **dendritic cells monocytes macrophage (APC)**
  - ***Immune memory :*** **epigenetic "Trained Immunity" +++ for BCG**
  - ***APCells to*** **Lymphocytes (HLA class I; II)**
- **Adaptive response**: "**naïves"** cells**; specific cells Ex: SARS-Cov-2**
  - ***T Lymphocyte***: **T4, T8, T_{reg}**
  - ***NK cells***
  - ***B Lymphocyte*** → **Specific Antibodies « neutralising» +++ Vaccine**
- **Mediators:**
  - ***Cytokines*** **pro- anti inflammatory**
  - ***Lymphokines; chemokines***

Time response for immune response related to infection

- **Innate Immunity** **0 - 4 hours**
  - ***Recognition***; ***pre-fixed response***, **non-specific** mechanisms
  - **Early response** **4 – 96 hours**
  - Pathogens recognition by ***highly conserved microbial motifs***
  - ***Starting*** and ***amplifying*** the inflammatory response
- **Adaptative immune response** **> 96 heures**
  - ***Transportation towards Lymphoïd tissue***
  - ***Specific identification of the pathogen***
  - ***B & T Lymphocytes Response*** ➔ **Specific ABodies or effective cells**

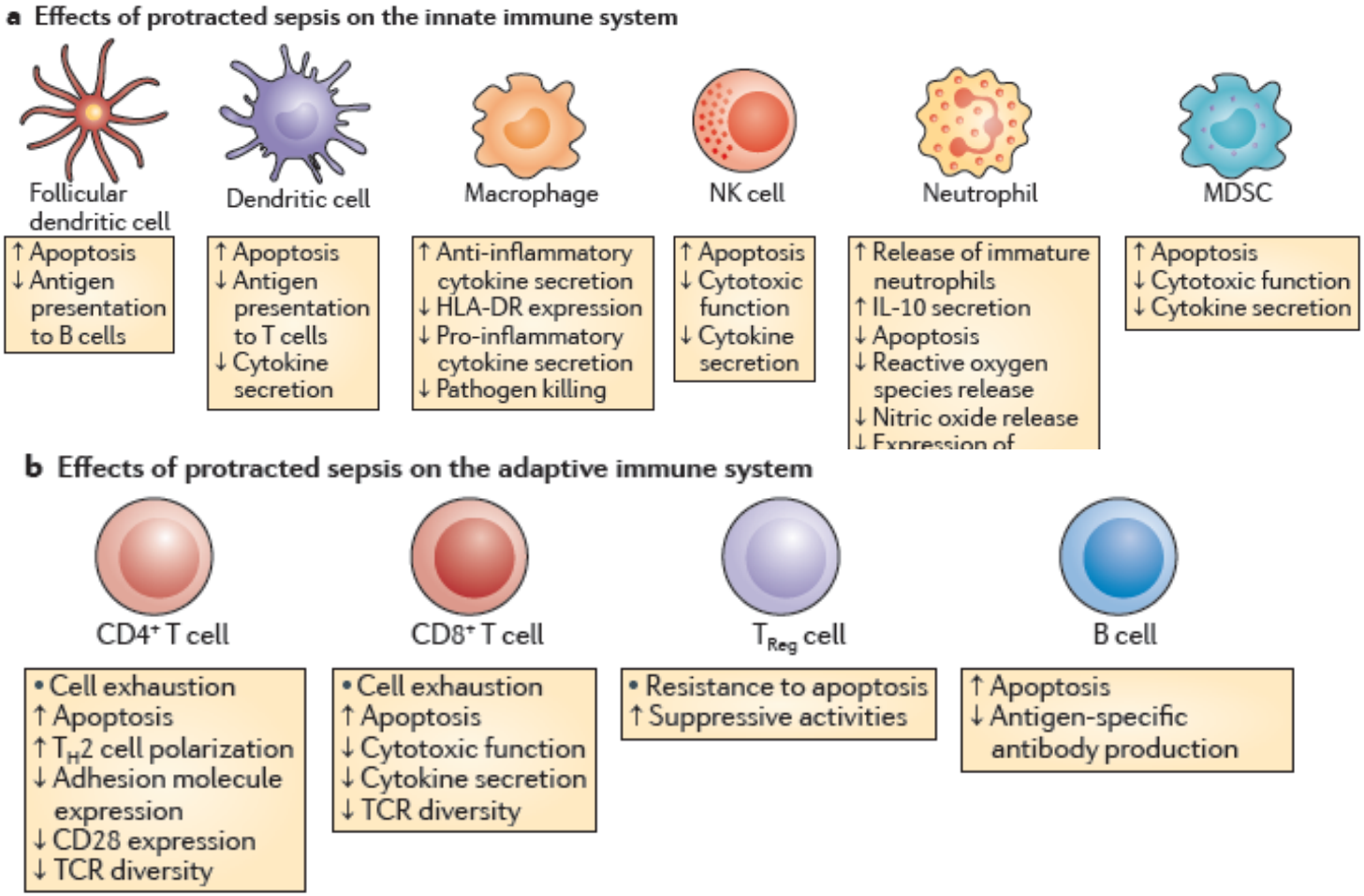
Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

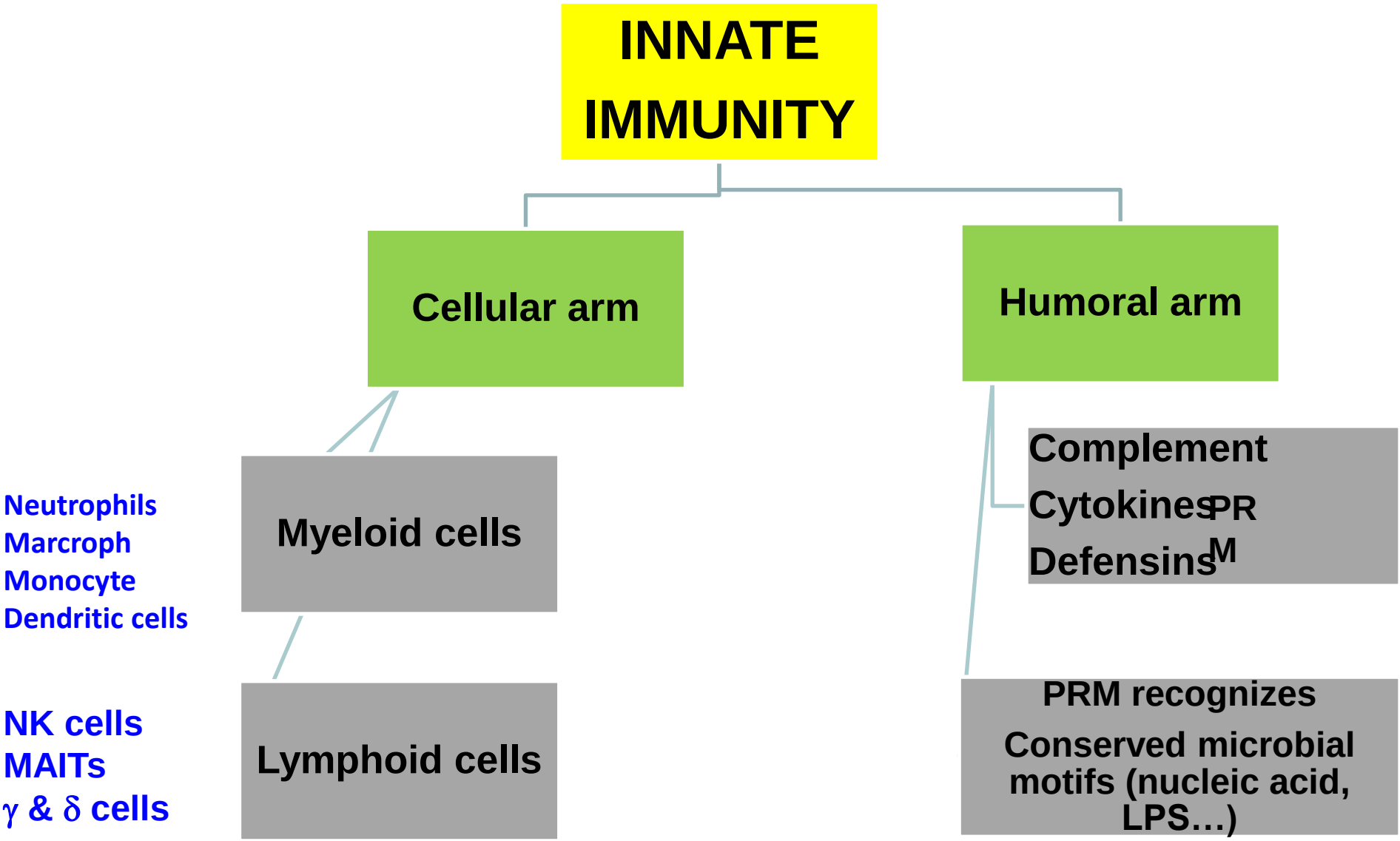
NATURE REVIEWS | IMMUNOLOGY

15 November 2013; doi:10.1038/nri3552

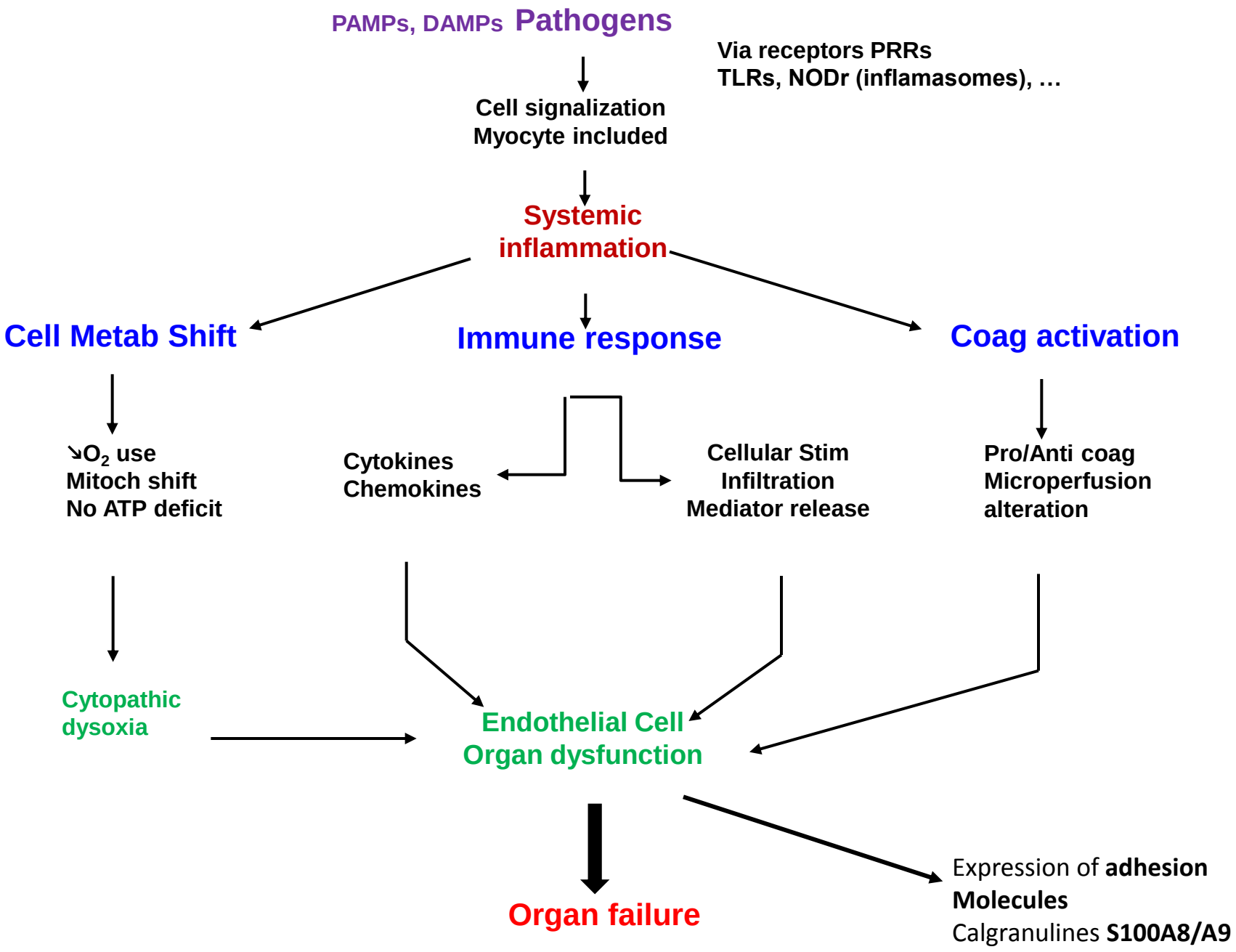
Richard S. Hotchkiss[1], Guillaume Monneret[2] and Didier Payen[3]

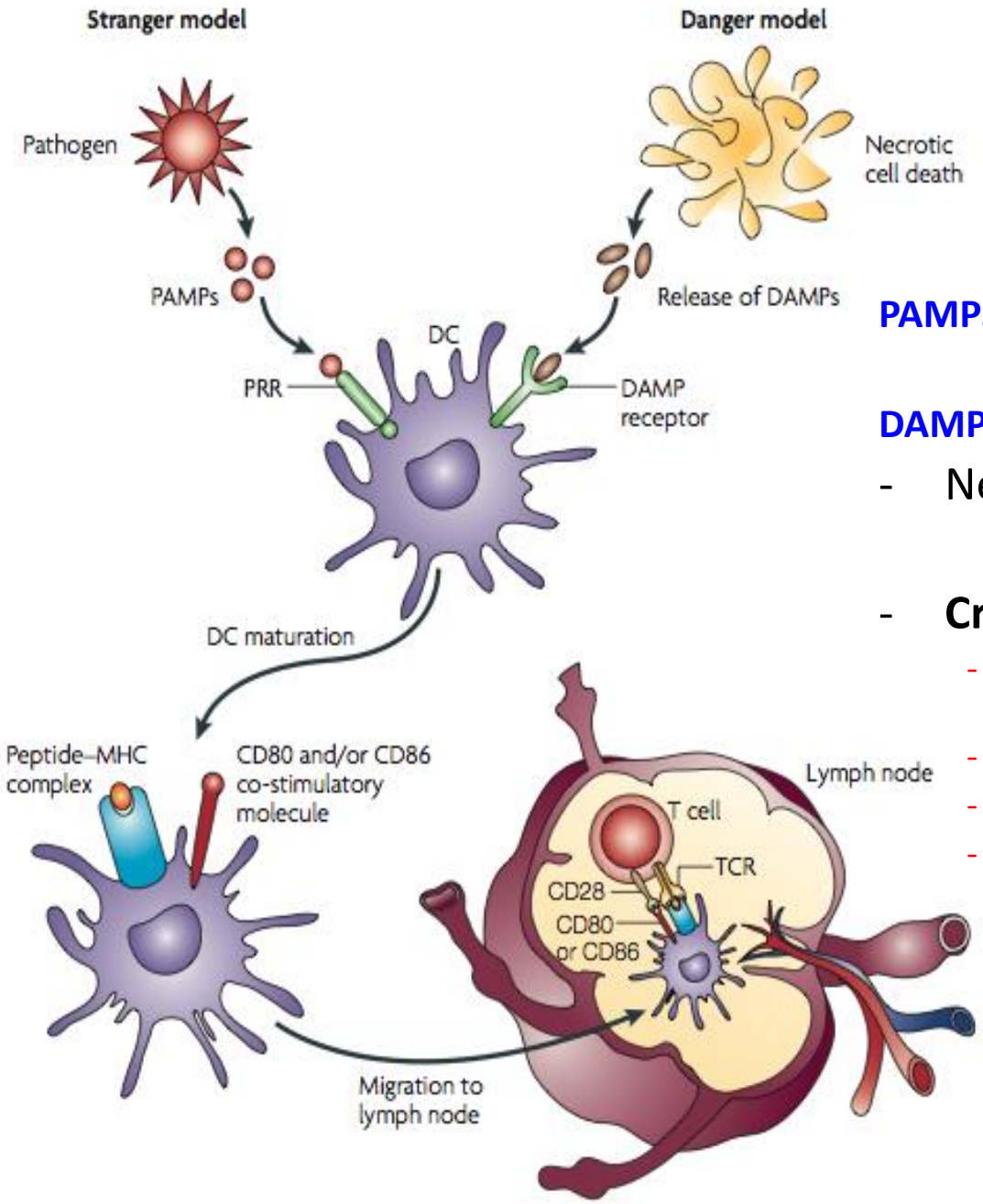
Impact of sepsis on innate and adaptive immune cells





This system is the only that control microbial infections in the 1st days following contact during 1ary infection


PAMPs, DAMPs
Pathogens
Via receptors PRRs
TLRs, NODr (inflamasomes), …
Cell signalization
Myocyte included
Systemic inflammation
Cell Metab Shift
Immune response
Coag activation
↘O2 use
Mitoch shift
No ATP deficit
Cytokines
Chemokines
Cellular Stim
Infiltration
Mediator release
Pro/Anti coag
Microperfusion
alteration
Cytopathic dysoxia
Endothelial Cell
Organ dysfunction
Organ failure
Expression of adhesion Molecules
Calgranulines S100A8/A9



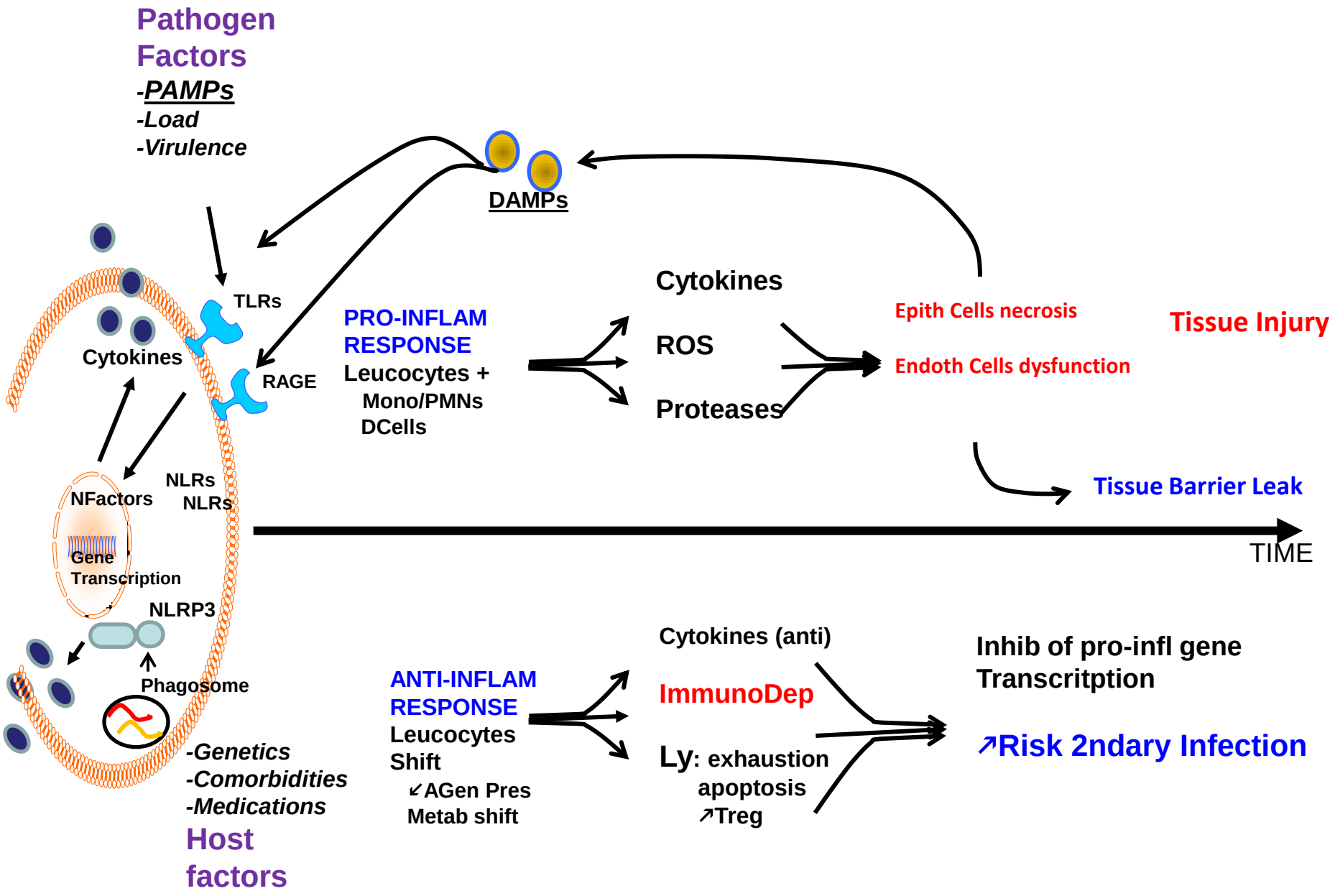
PAMPS → mutiple; PRR

DAMPS → multiple; DAMP rec

- Necrotic cells → **DAMPs**

- **Criteria for DAMPs**
  - **Alone → biological response** without contamination (PAMPs = 0)
  - **Being efficient at physiological [ ]**
  - **Their blockade → inhibates their action**
  - **Examples: HMGB1; Calgranulines…**

From Matzinger theory

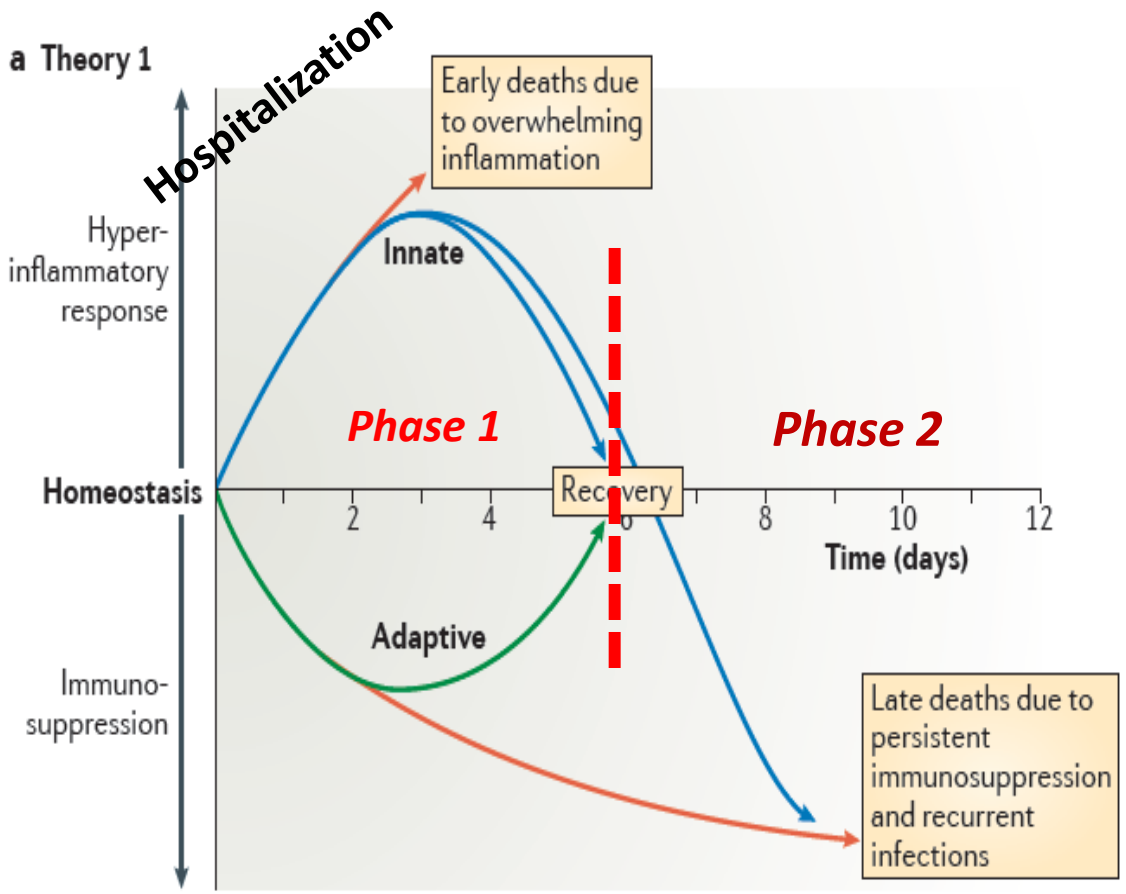

Pathogen Factors
-PAMPs
-Load
-Virulence
DAMPs
TLRs
RAGE
Cytokines
NFactors
NLRs
NLRs
Gene Transcription
NLRP3
Phagosome
-Genetics
-Comorbidities
-Medications
Host factors
PRO-INFLAM RESPONSE
Leucocytes +
Mono/PMNs
DCells
Cytokines
ROS
Proteases
Epith Cells necrosis
Endoth Cells dysfunction
Tissue Injury
Tissue Barrier Leak
TIME
ANTI-INFLAM RESPONSE
Leucocytes Shift
↙AGen Pres
Metab shift
Cytokines (anti)
ImmunoDep
Ly: exhaustion
apoptosis
↗Treg
Inhib of pro-infl gene Transcritption
↗Risk 2ndary Infection

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

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

Nature Reviews Immunology | AOP, published online 15 November 2013; doi:10.1038/nri3552

Acquired Immuno-Depression (AID) Syndrome



Is it present in the inflamed lung?

Probably Yes

Phase 3

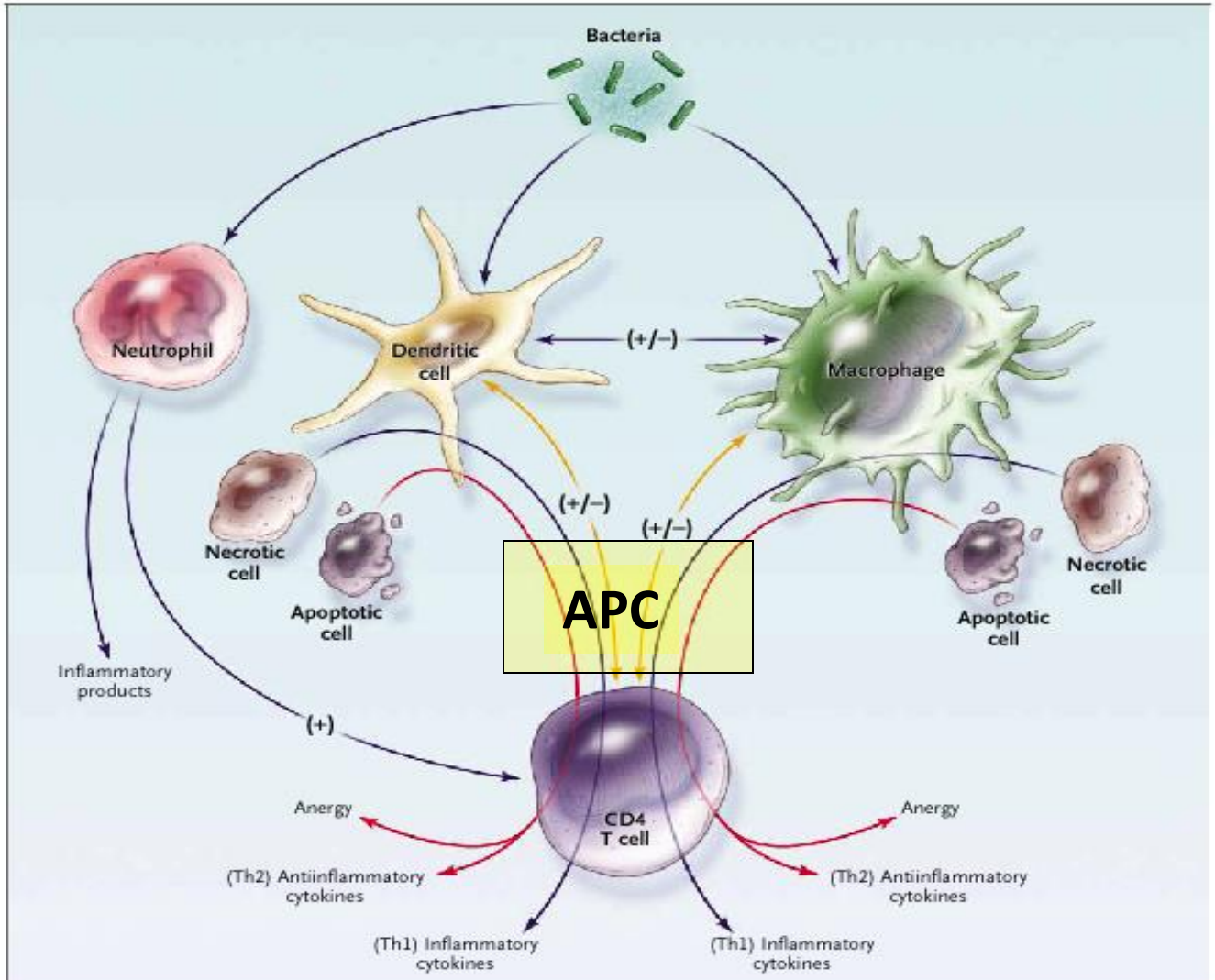
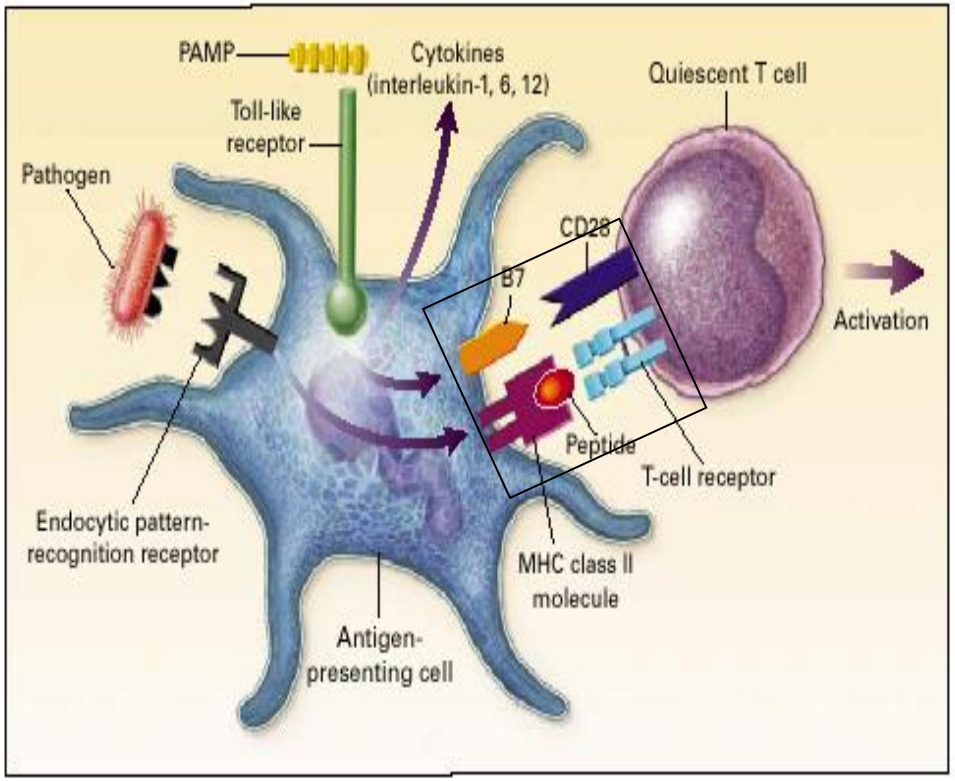


Figure 1. The Response to Pathogens, Involving "Cross-Talk" among Many Immune Cells, Including Macrophages, Dendritic Cells, and CD4 T Cells.

Macrophages and dendritic cells are activated by the ingestion of bacteria and by stimulation through cytokines (e.g., interferon-γ) secreted by CD4 T cells. Alternatively, CD4 T cells that have an antiinflammatory profile (type 2 helper T cells [Th2]) secrete interleukin-10, which suppresses macrophage activation. CD4 T cells become activated by stimulation through macrophages or dendritic cells. For example, macrophages and dendritic cells secrete interleukin-12, which activates CD4 T cells to secrete inflammatory (type 1 helper T-cell [Th1]) cytokines. Depending on numerous factors (e.g., the type of organism and the site of infection), macrophages and dendritic cells will respond by inducing either inflammatory or antiinflammatory cytokines or causing a global reduction in cytokine production (anergy). Macrophages or dendritic cells that have previously ingested necrotic cells will induce an inflammatory cytokine profile (Th1). Ingestion of apoptotic cells can induce either an antiinflammatory cytokine profile or anergy. A plus sign indicates up-regulation, and a minus sign indicates down-regulation; in cases where both a plus sign and a minus sign appear, either up-regulation or down-regulation may occur, depending on a variety of factors.

APC = ANTIGEN PRESENTING CELLS



- **PAMP:** Proteins from pathogens are processed in the lysosomes to generate **antigenic peptides**, which form a **complex** with **MHC class II** on the surface of **APC**, recognized by **T cell receptors (TCR)**

How dying cells alert the immune system to danger

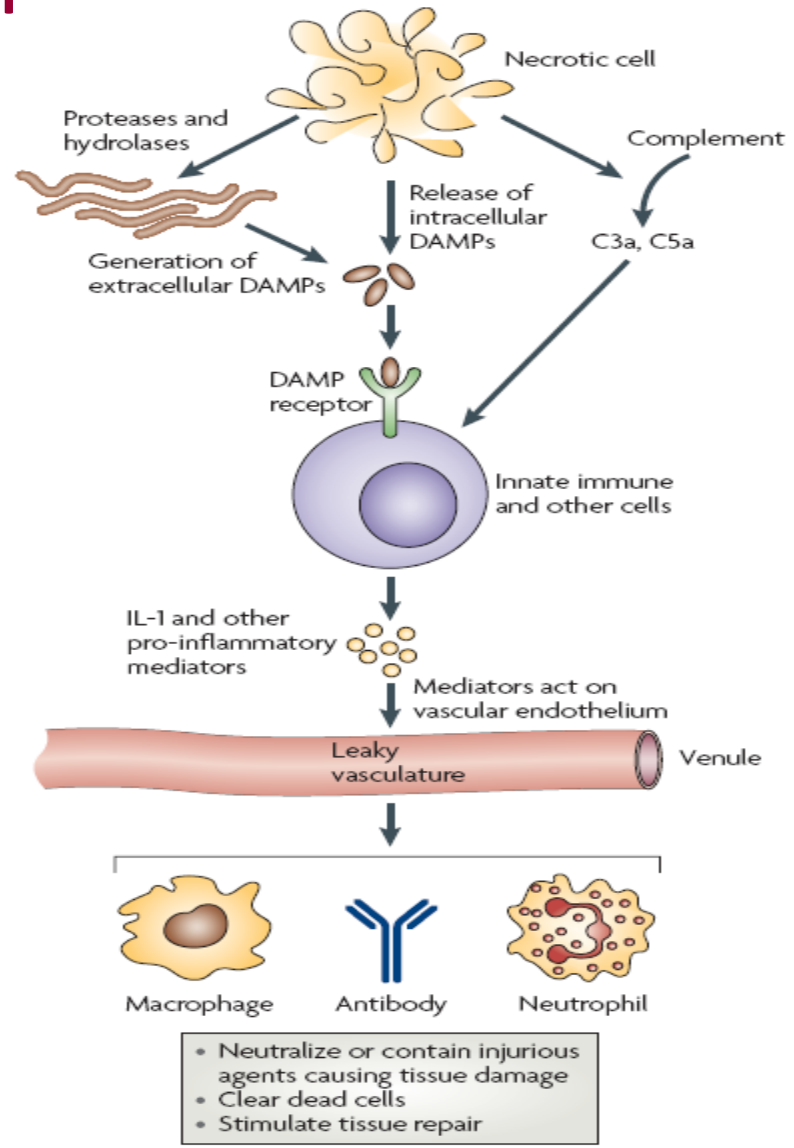
Hajime Kono and Kenneth L. Rock

e-mails: hajime.kono@umassmed.edu; kenneth.rock@umassmed.edu

NATURE REVIEWS | IMMUNOLOGY VOLUME 8 | APRIL 2008 | 279

From Cell death to inflammation and OF

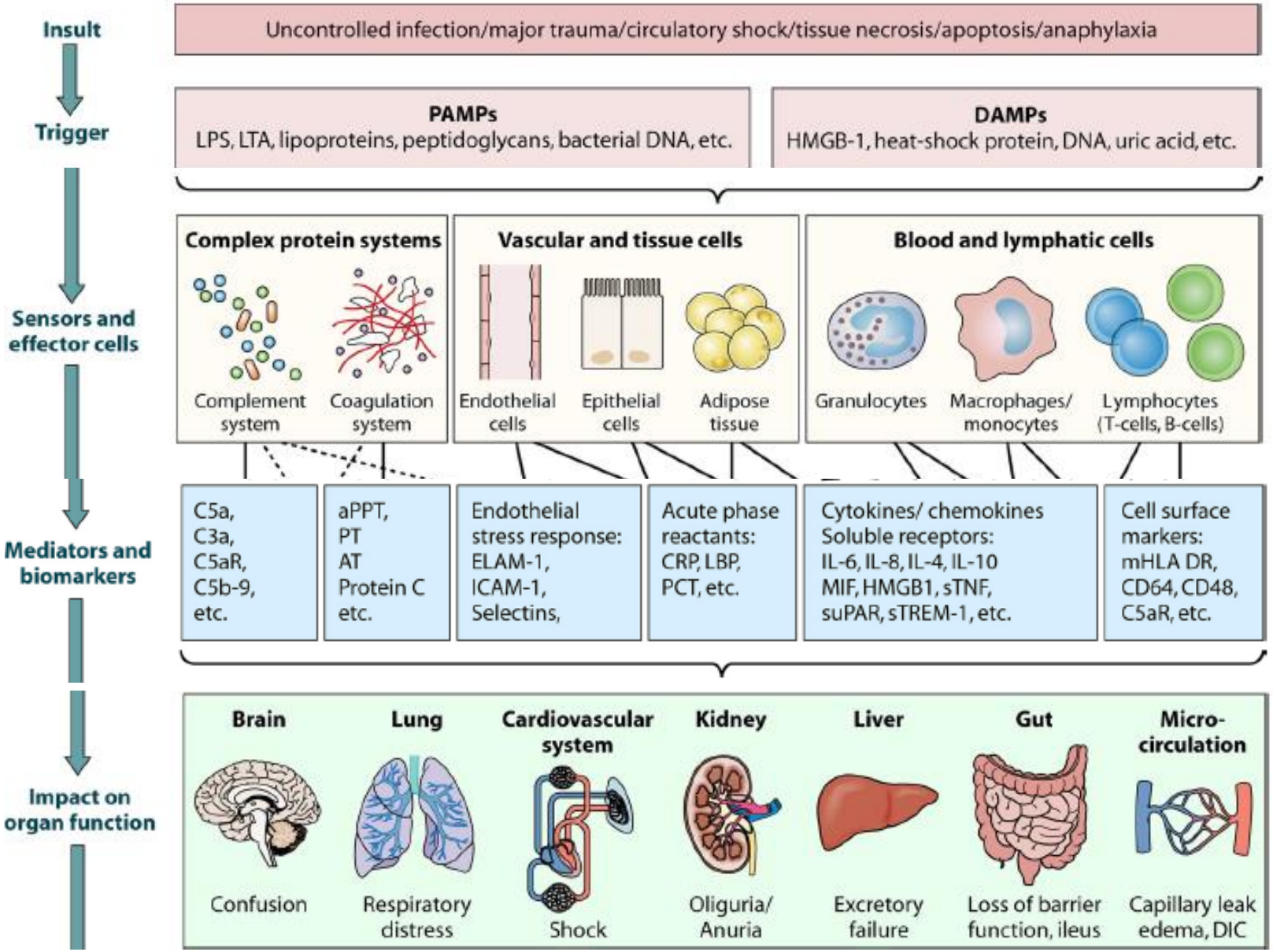
- **Necrotic cell death** ➔ **DAMPs** ➔ receptors ➔+ **prod of inflam cytokines** (IL-1).
- **Other molecules proteases**; **hydrolases** act on **EC components** ➔ + **mediators** (complement fragments) or **DAMPs** ➔ prod of **inflam cytokines** by host cells.
- **Pro-inflam mediators** ➔ **local vascular endothelium lesions** ➔ **'leaky', attracts neutrophils** and **monocytes/macrophages** ➔ **soluble (antibody) and cellular defences in the tissue (cell infiltration) neutralize or contain pathogens**



New Approaches to Sepsis: Molecular Diagnostics and Biomarkers

Konrad Reinhart,[a] Michael Bauer,[a,b] Niels C. Riedemann,[a] and Christiane S. Hartog[a,b]

Clinical Microbiology Reviews October 2012 Volume 25

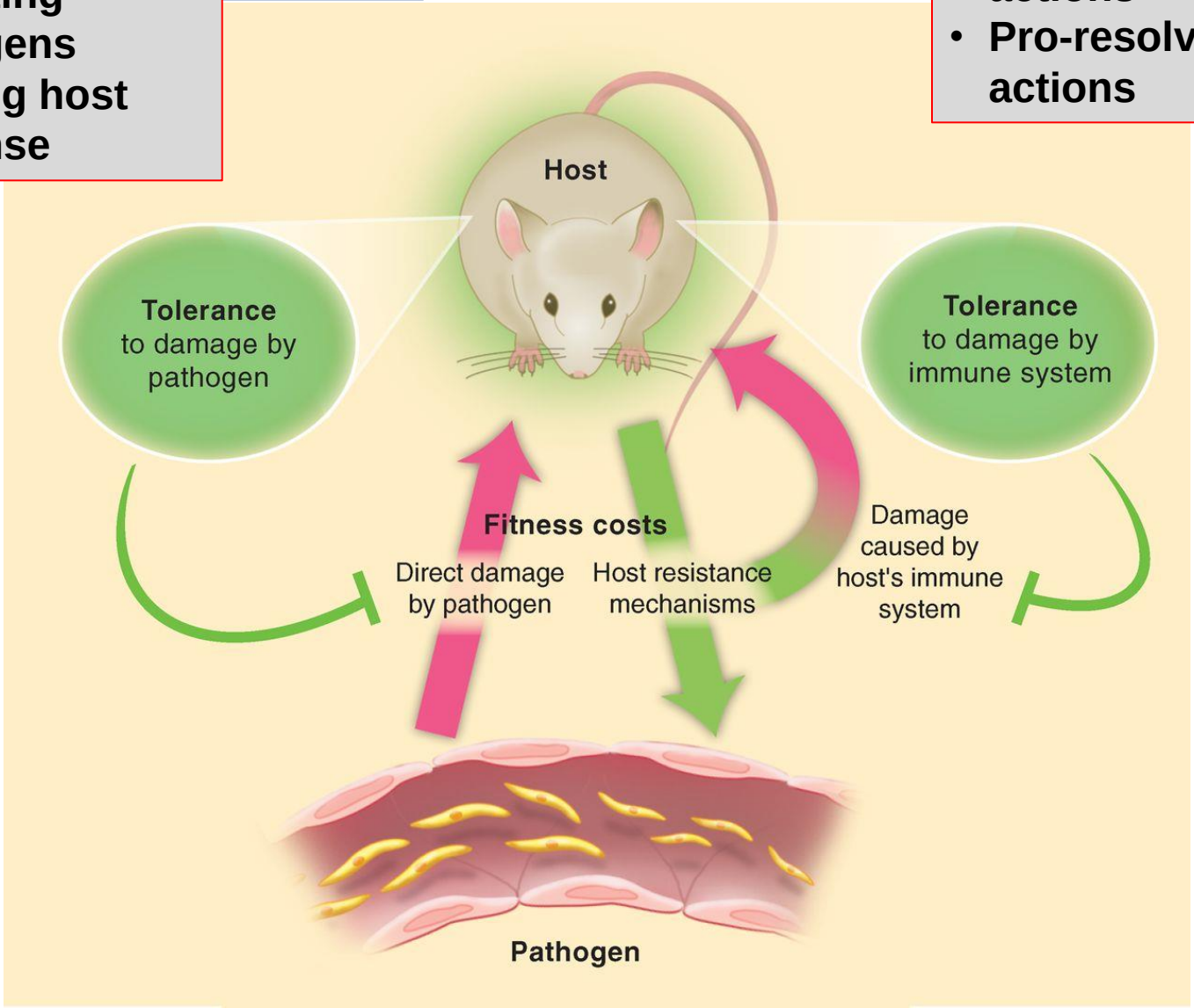



It's Not Stress That Kills Us
It is our reaction to it
Hans Selye
We learnt that we can
Modulate host response
ACQYR.COM

- "Threat" vs. non-threat
- Tolerating pathogens
- Limiting host response

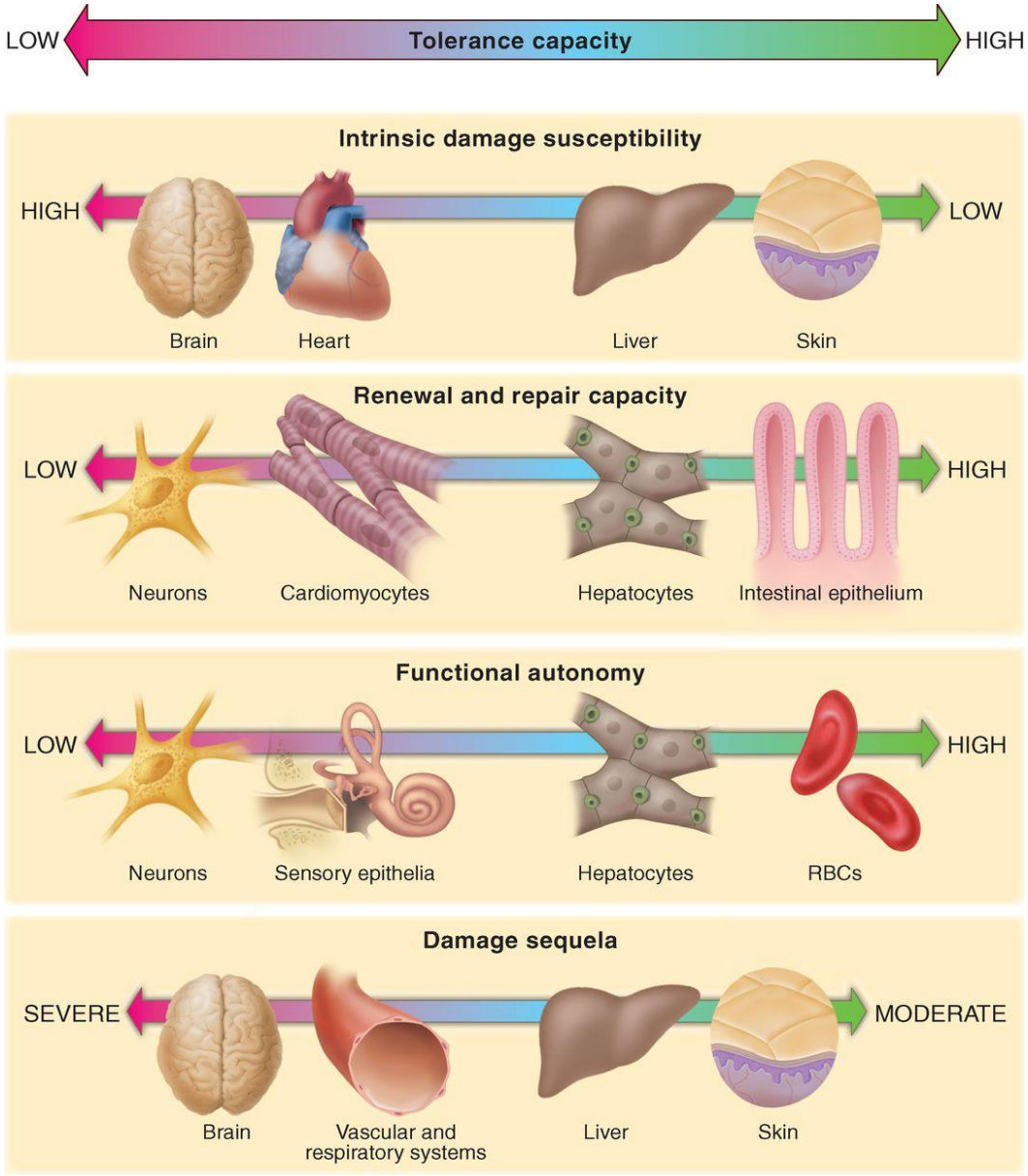
Disease Tolerance as a Defense
Ruslan Medzhitov *et al.*
Science **335**, 936 (2012);
DOI: 10.1126/science.1214935

- Stress hormones
- Anti-inflammatory actions
- Pro-resolving actions



Medzhitov et al. Science 2012; 355:936-41

Organ-specific tolerance capacity to pathogen- or immune-induced pathology



Organs largely differ in term of :

- **Susceptibility**
- **Repair capabilities**
- **Functional autonomy**
- **sequela**

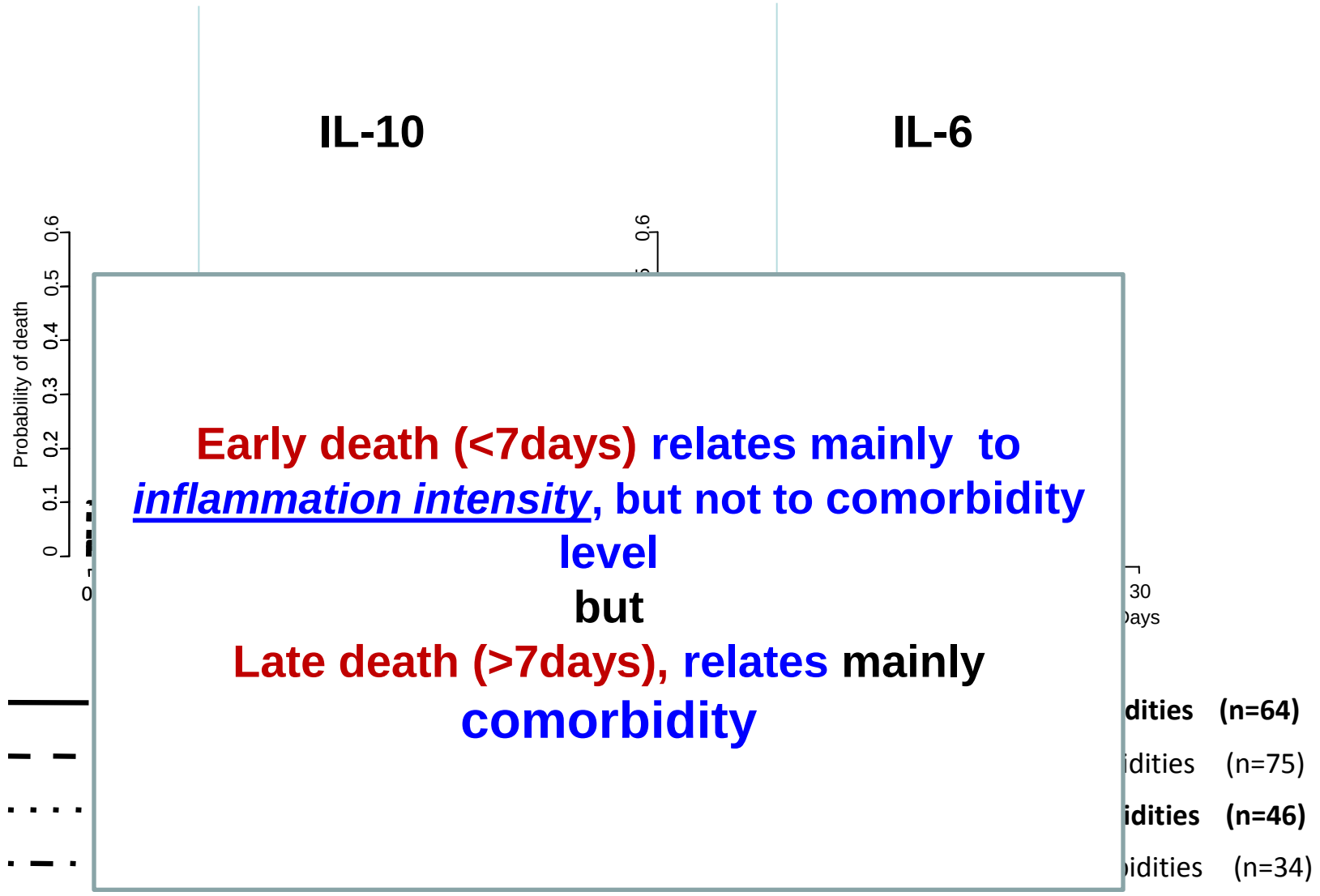
Medzhitov et al. Science 2012; 355:936-41

Mortality

- Is early mortality (1st Wk) similar to late mortality?
- Is inflammation changing along time?

- What is sepsis-induced mortality?
  - *Crude mortality?*
  - *Attributable mortality?*

202 SS Patients (multicentric)



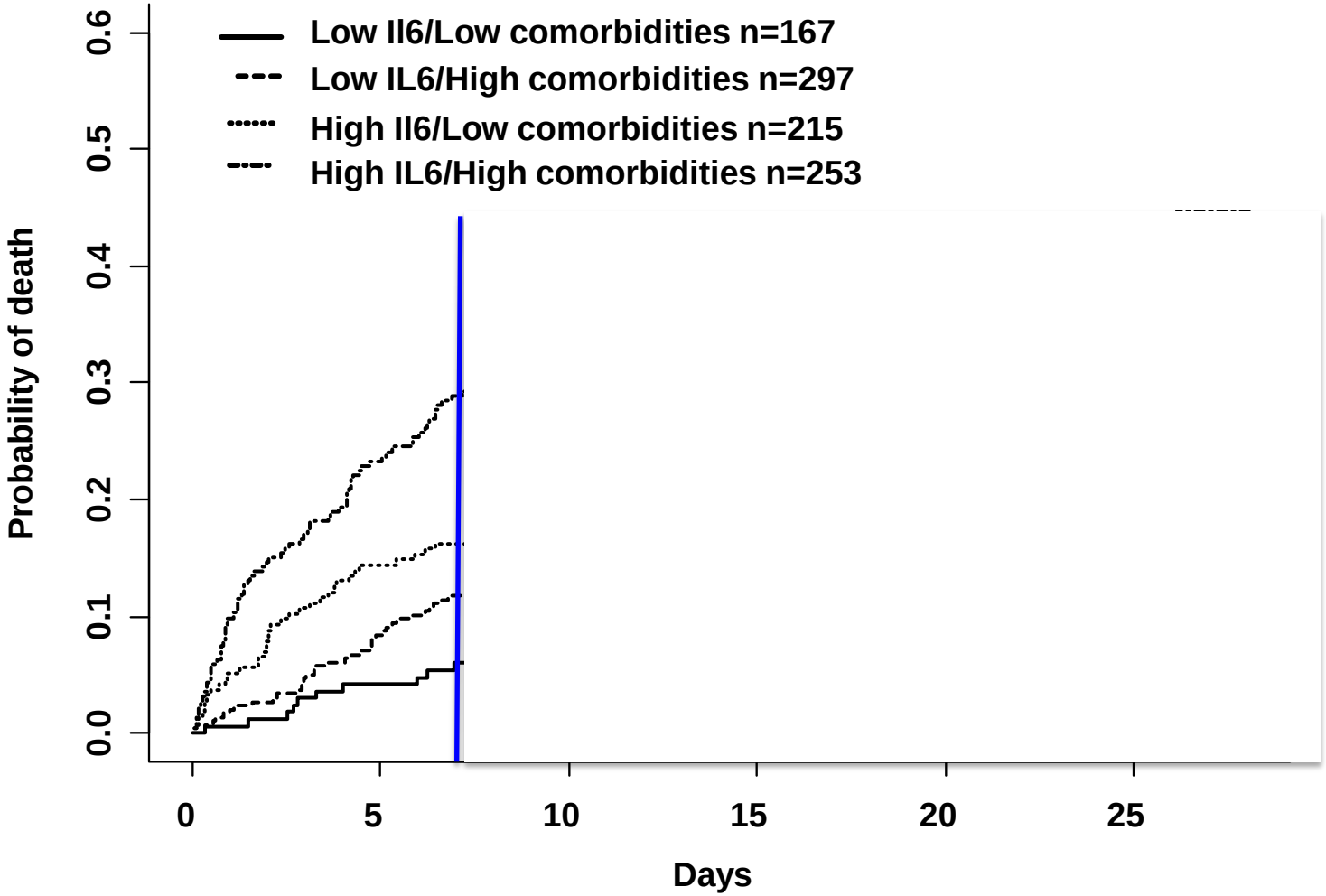
Early death (<7days) relates mainly to *inflammation intensity*, but not to comorbidity level

but

Late death (>7days), relates mainly comorbidity

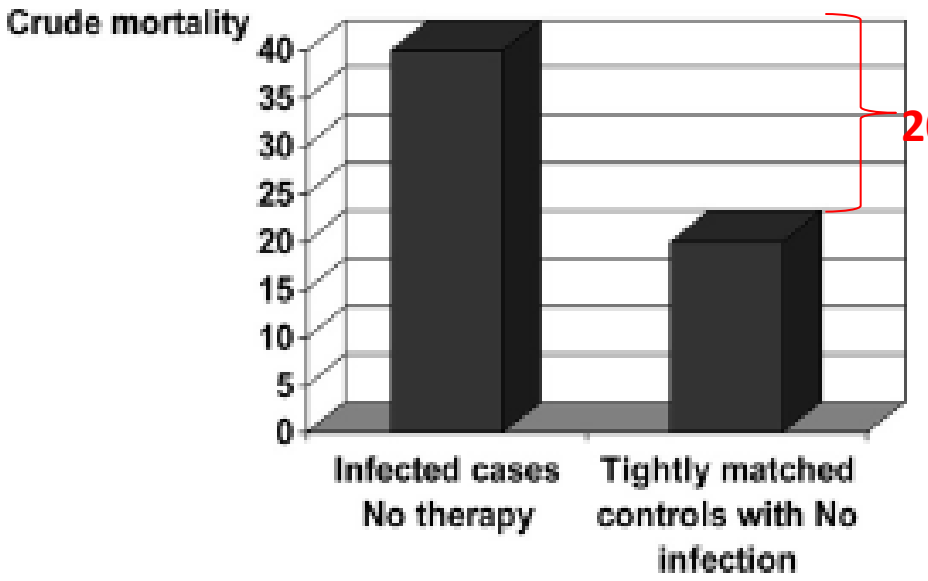
This concept obtained from a training cohort (202 pts) was tested in large testing cohort N = 989 SS patients from Prowess data base

N = 989 patients in septic shock



Residual Attributable Mortality, a New Concept for Understanding the Value of Antibiotics in Treating Life-Threatening Acute Infections▽

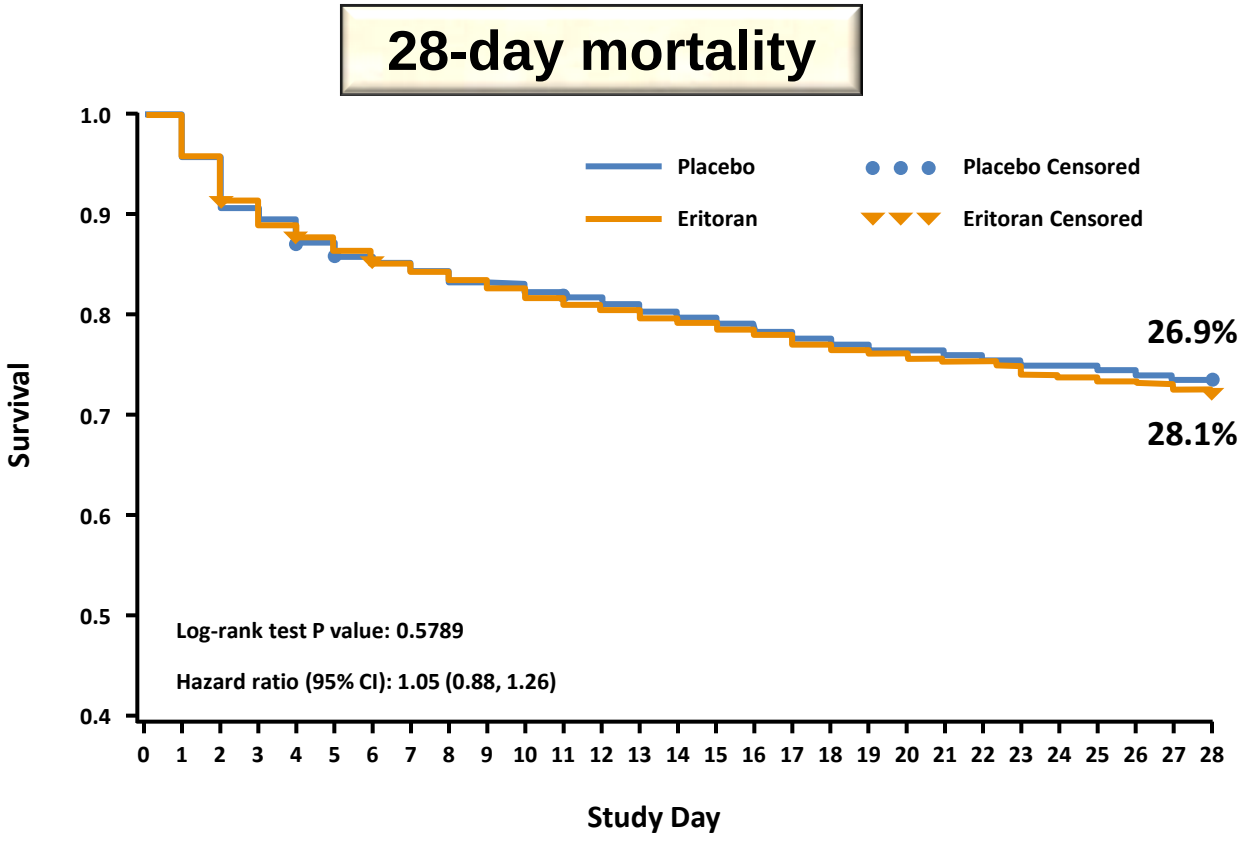
Richard P. Wenzel[1]* and Chris Gennings[2]



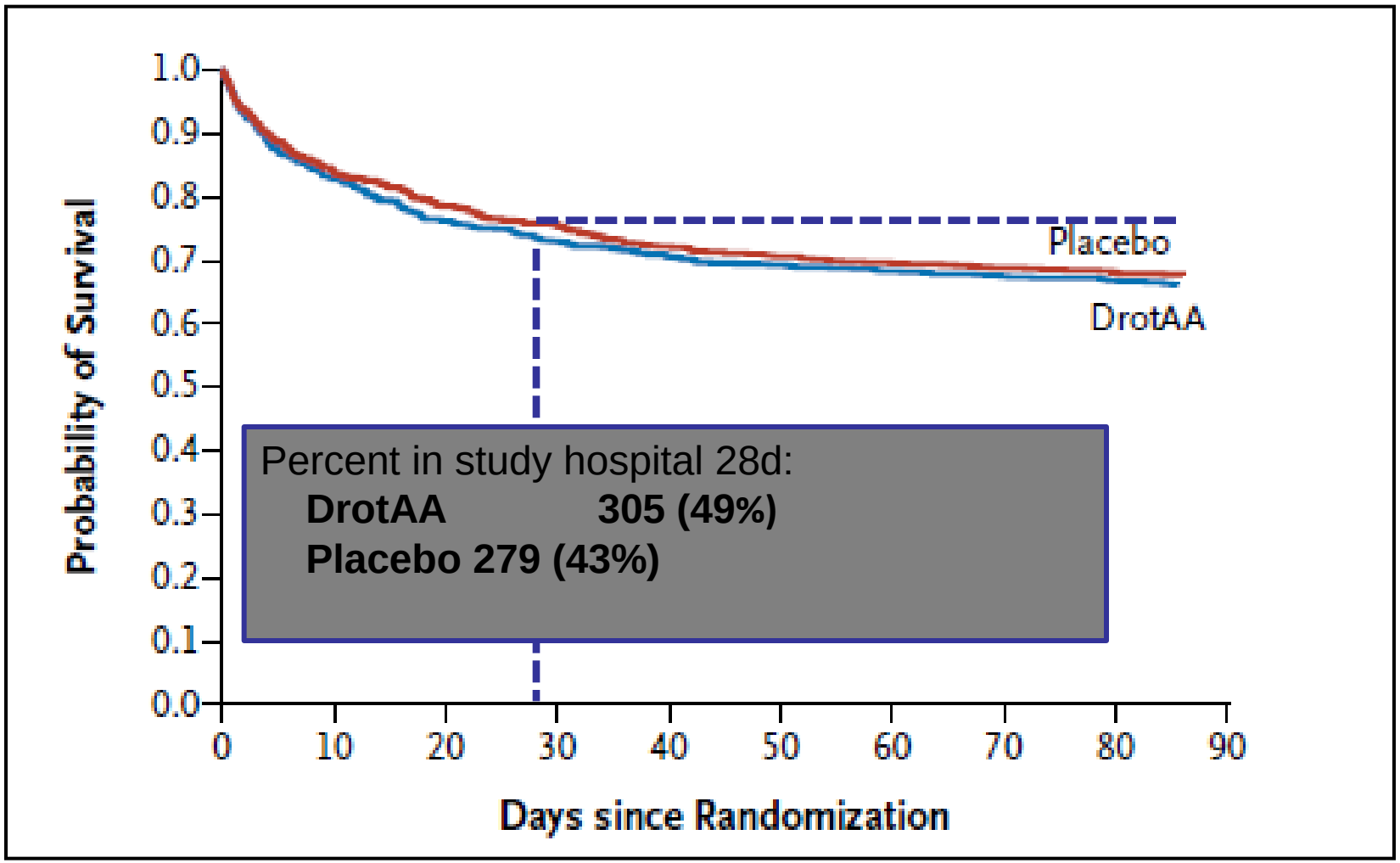
Theoretical **crude mortality of 40% in the absence of therapy.**
Since ***matched controls*** had a **crude mortality of 20%,**
➔the estimate **of attributable mortality is 20% (40% -20%).**
➔The **best ttmt can reduce mortality about max 20% but cannot reduce the mortality due to the underlying diseases.**

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2010, p. 4956–4960
0066-4804/10/$12.00 doi:10.1128/AAC.00438-10

ACCESS trial: TLR4/MD2 inhibition in severe sepsis



PROWESS-SHOCK (*NEJM 2012*)



Ranieri *et al* NEJM 2012

Swiss Med Wkly. 2016;146:w14276

Swiss Medical Weekly

Sepsis: the need for tolerance not complacency

Tiago R. Velho[a], Isa Santos[a], Pedro Póvoa[b,c], Luís Ferreira Moita[a]

Anthracyclines Induce DNA Damage Response-Mediated Protection against Severe Sepsis

Immunity
Article

cecal lig … nbed within 4

- **epir… again 2** signific…
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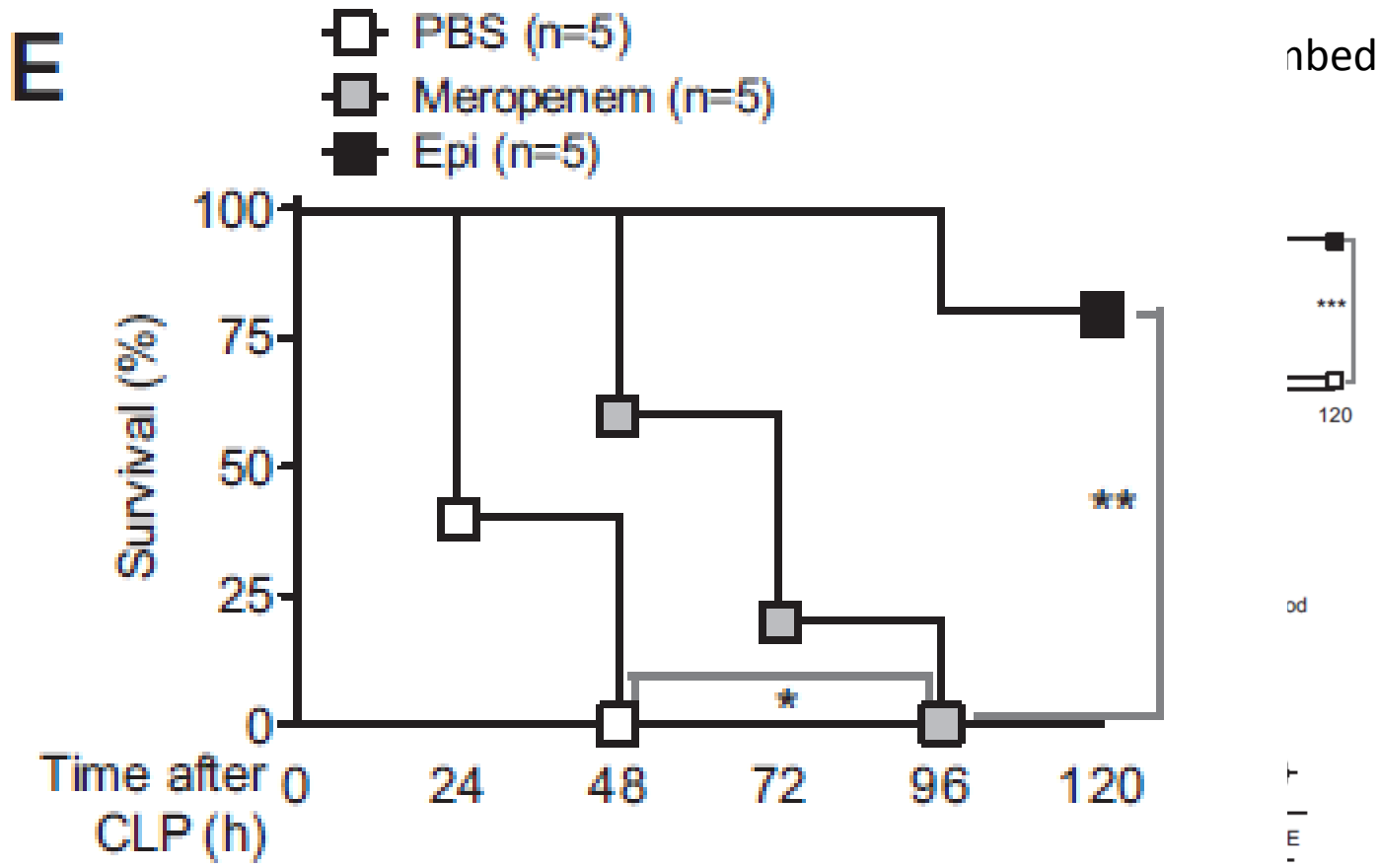
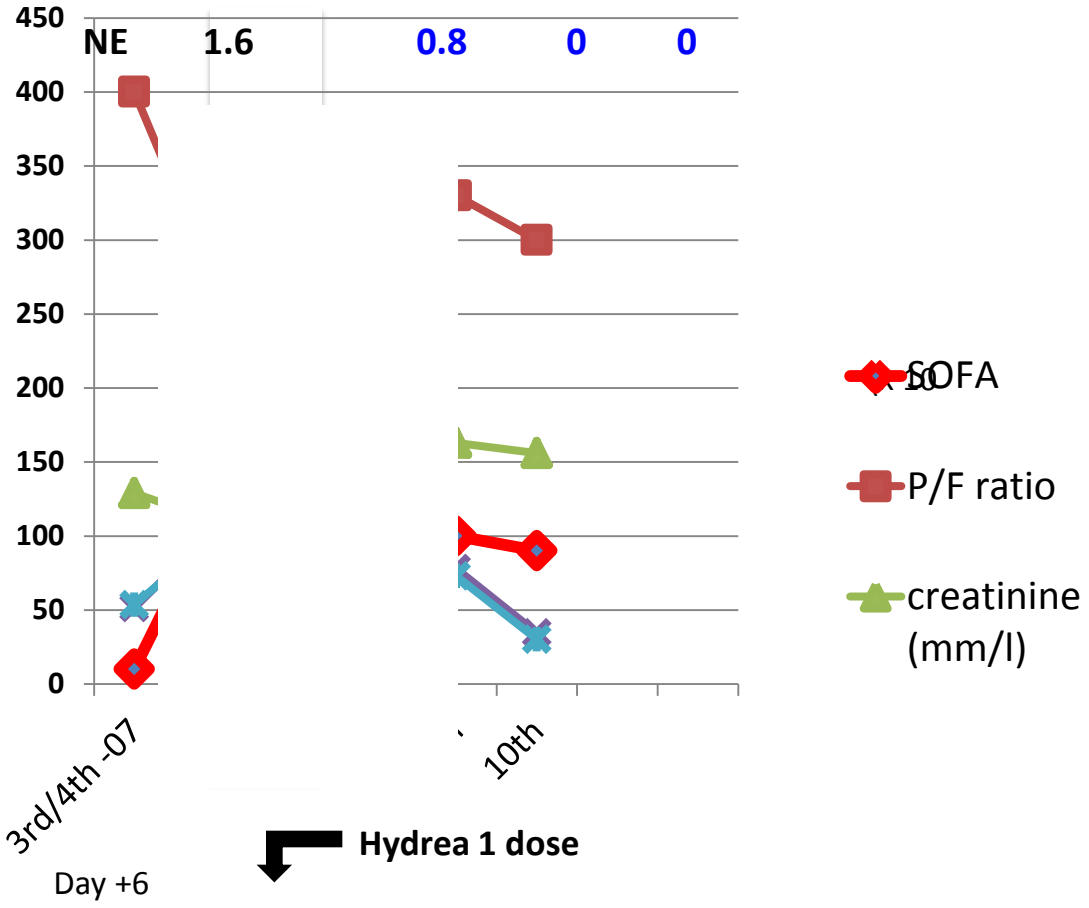
  to perit…
- **epir…** bact… post…
- a sul… inflamm… HMGB1…



Immunity 39, 874–884,

Let's see the results of immune monitoring… and modulation!

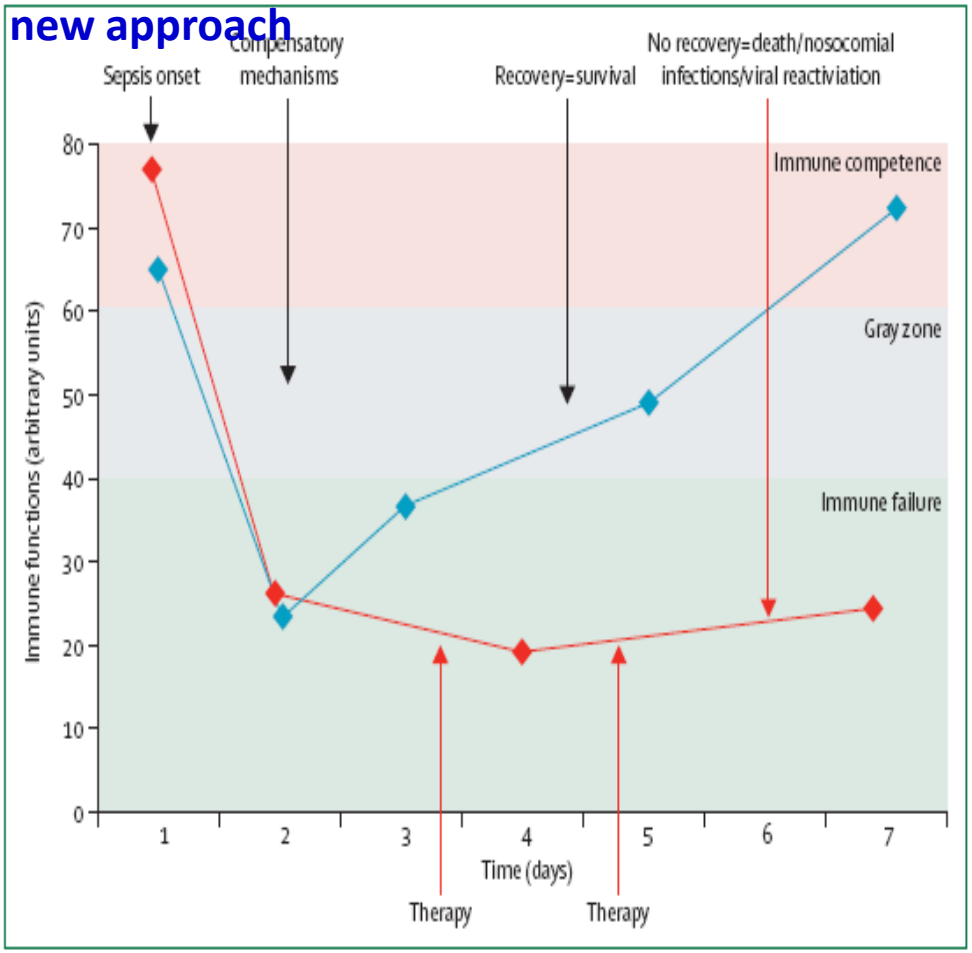


HYDROXYCARBAMIDE 1 dose 500 mg

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

Richard S Hotchkiss, Guillaume Monneret, Didier Payen

Immunostimulation therapy in sepsis: a new approach



THELANCETID-D-12-00762R2 February 2013

Monitoring the immune response in sepsis: a rational approach to administration of immunoadjuvant therapies

Fabienne Venet[1], Anne-Claire Lukaszewicz[2], Didier Payen[2], Richard Hotchkiss[3] and Guillaume Monneret[1]

25 YEARS Current Opinion in Immunology

Current Opinion in Immunology 2013, 25:477–483

Sepsis-induced immune dysfunctions: pathophysiology at a glance

Mechanisms	Features of sepsis-induced immune alterations
Endotoxin tolerance	↓ pro-inflammatory ↑ anti-inflammatory cytokine production ↓ Ag presentation capacity
Apoptosis	↓ cell number Cell anergy
Energetic failure	Cell anergy Apoptosis Mitochondrial dysfunction
Anti-inflammatory mediators	↓ activating co-receptor expressions ↑ inhibitory co-receptor expressions Cell anergy Endotoxin tolerance
Epigenetic regulation	↓ pro-inflammatory gene expressions Cellular reprogramming
Central and endocrine Regulations	↓ pro-inflammatory cytokine production

Monitoring innate immune alterations in sepsis and related therapies

Recent clinical studies evaluating mHLA-DR predictive value regarding outcome in injured patients

1st author, Journal, Year	No. of patients	Pathology
Monneret, Intensive Care Med, 2006	93	Septic shock
Venet, Crit Care Med, 2007	14	Severe burns
Lukaszewicz, Crit Care Med, 2009	283	ICU patients
Berres, Liver Int, 2009	38	Decompensated liver cirrhosis
Landelle, Intensive Care Med, 2010	209	Septic shock
Lin, Blood, 2011	40	B cell non-Hodgkin lymphoma
Chéron, Crit Care, 2010	105	Trauma
Wu, Crit Care, 2011	79	Severe sepsis
Wu, Crit Care, 2011	35	Severe sepsis
Zhang, Eur J Neurol, 2011	53	Neurologic patients
Berry, Intensive Care Med, 2011	100	Cirrhosis
Gouel-Chéron, PLoS One, 2012	100	Trauma
Trimmel, Shock, 2012	413	ICU patients

at least 1500 patients

Multicentric experience with interferon gamma therapy in sepsis induced immunosuppression. A case series

Didier Payen[1,2*], Valerie Faivre[1,2], Jordi Miatello[3,4], Jenneke Leentjens[5], Caren Brumpt[6], Pierre Tissières[3,4], Claire Dupuis[1], Peter Pickkers[7†] and Anne Claire Lukaszewicz[1,2†]

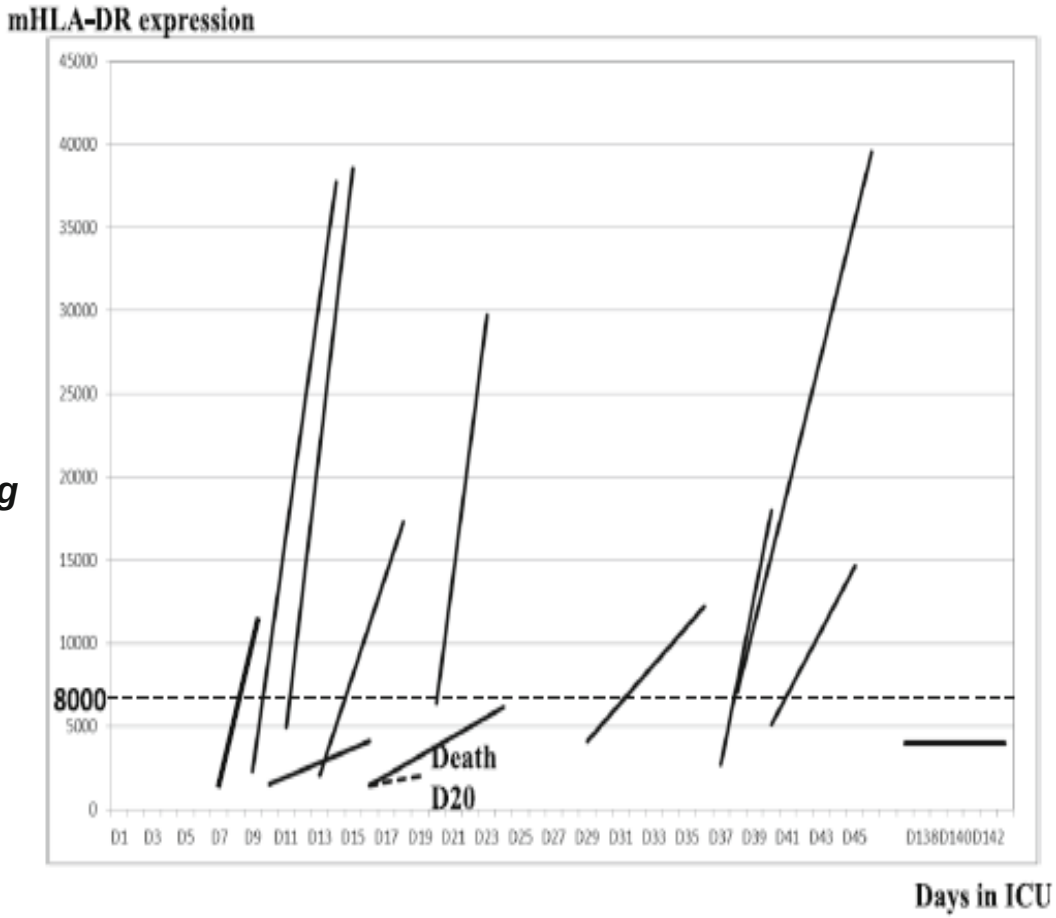
Payen et al. BMC Infectious Diseases (2019) 19:931
https://doi.org/10.1186/s12879-019-4526-x

Individual data of mHLA-DR expression before and 24 h after stopping IFNγ treatment

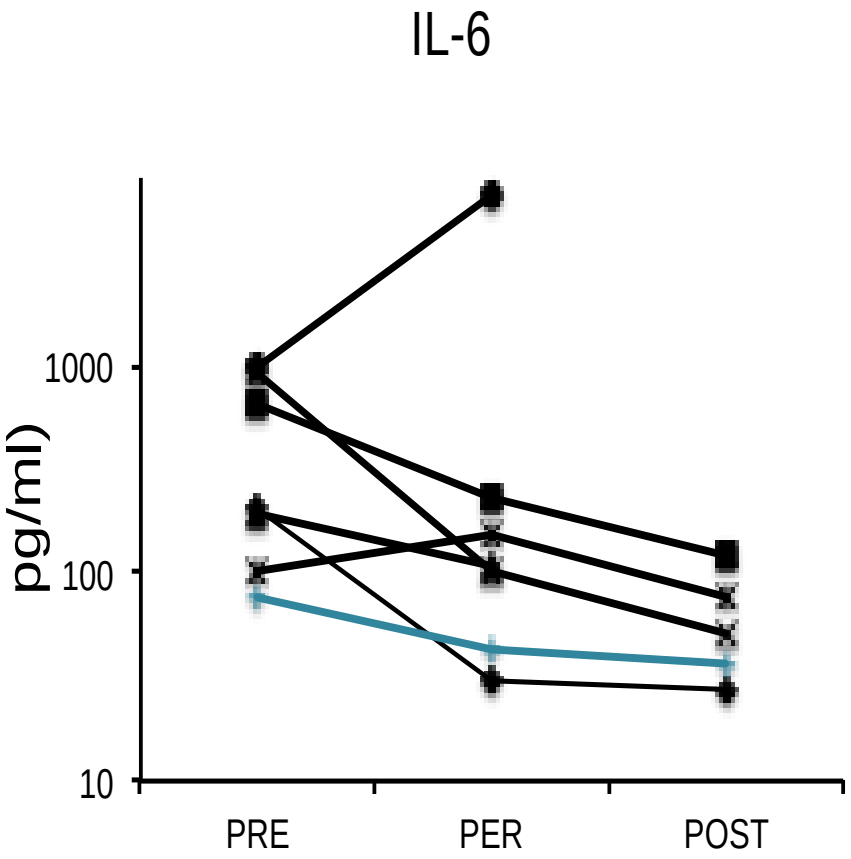
X axis: real delay from admission to be treated.
Y axis represents the quantitative AB/C values of mHLA-DR expression

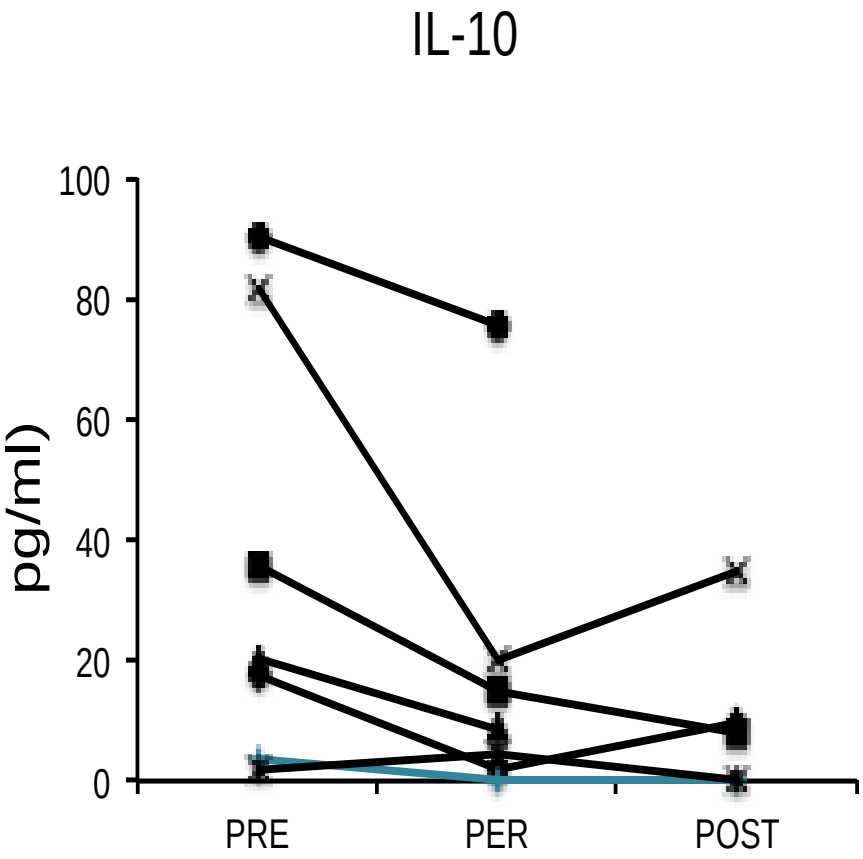
Dotted line: threshold for immunodepression Dg

Among the 13 patients, 4 ↗HLA-DR expression but did not reach the defined threshold.

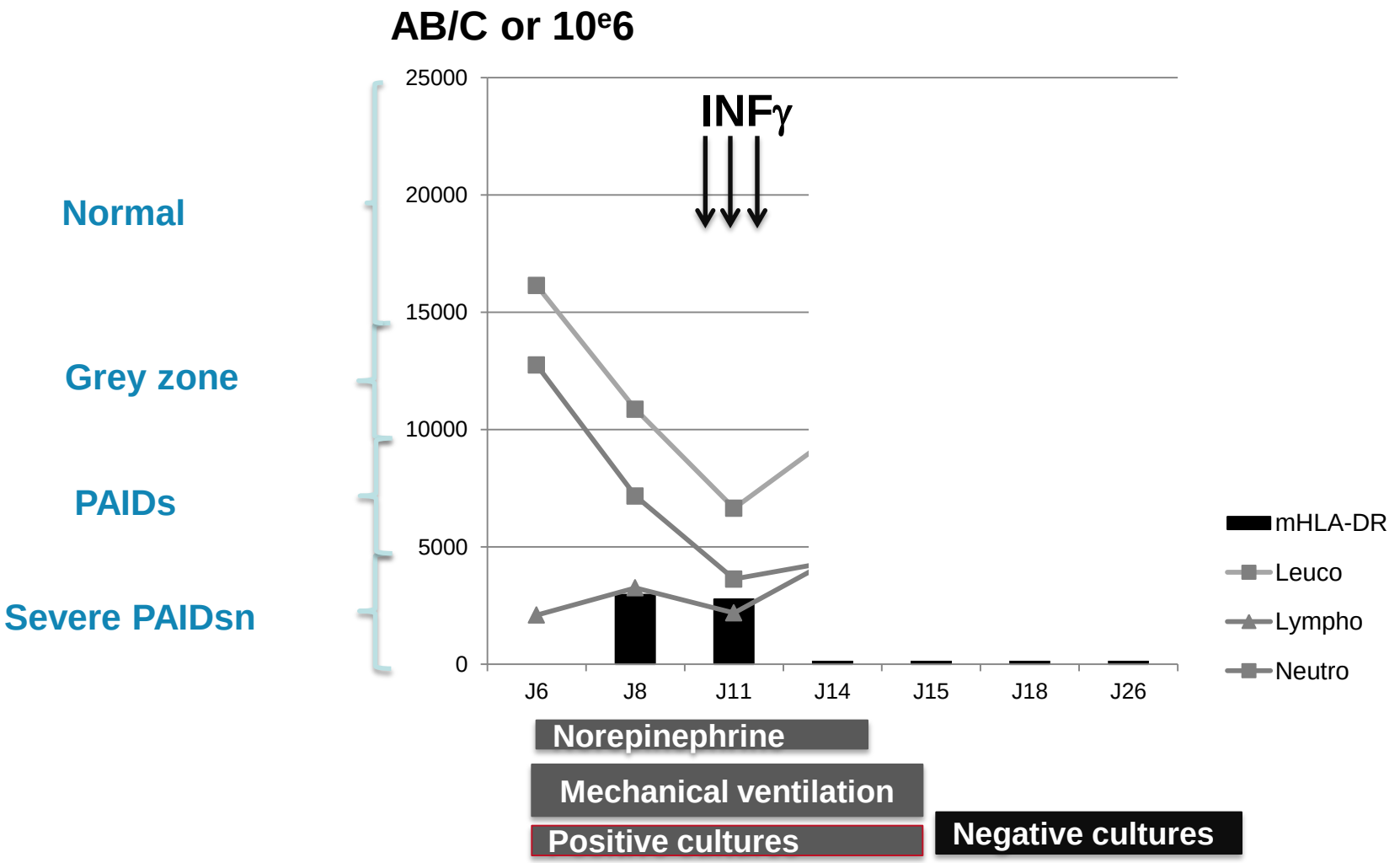


Evolution on IL-6 and IL-10 plasma levels



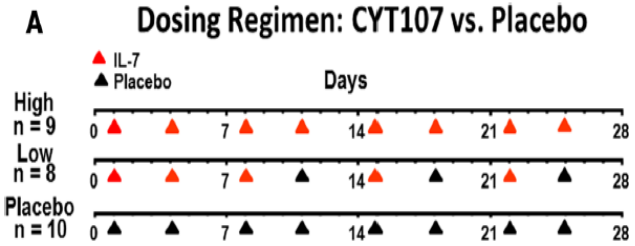


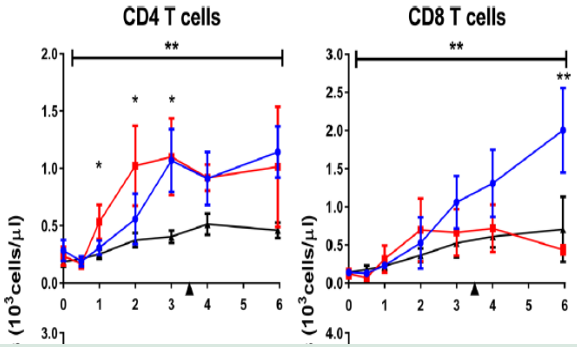
TotoR *Pseudomonas aeruginosa* septic shock – severe ARDS – peritonitis in a 15 months post-LT child

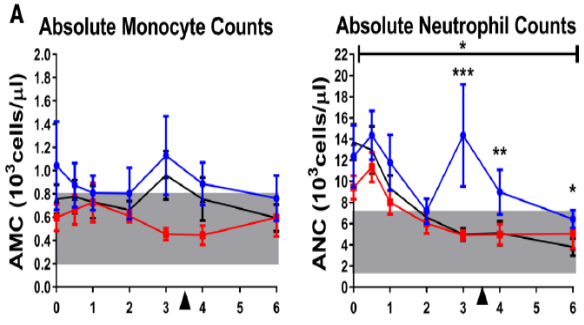


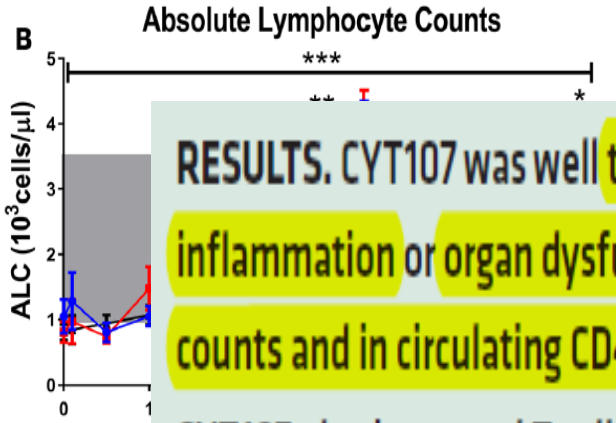
Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial

JCI insight

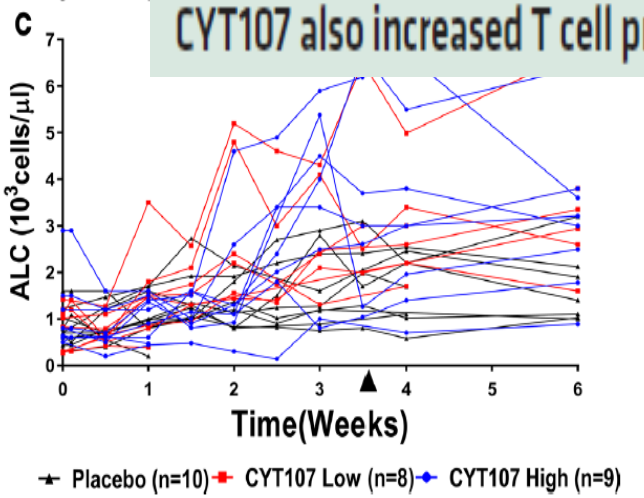








RESULTS. CYT107 was well tolerated without evidence of inducing cytokine storm or worsening inflammation or organ dysfunction. CYT107 caused a 3- to 4-fold increase in absolute lymphocyte counts and in circulating CD4⁺ and CD8⁺ T cells that persisted for weeks after drug administration. CYT107 also increased T cell proliferation and activation.

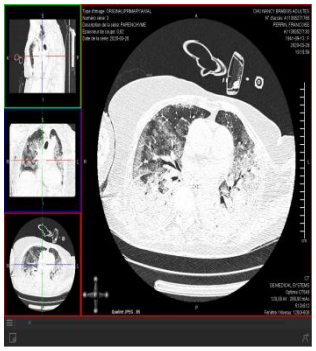


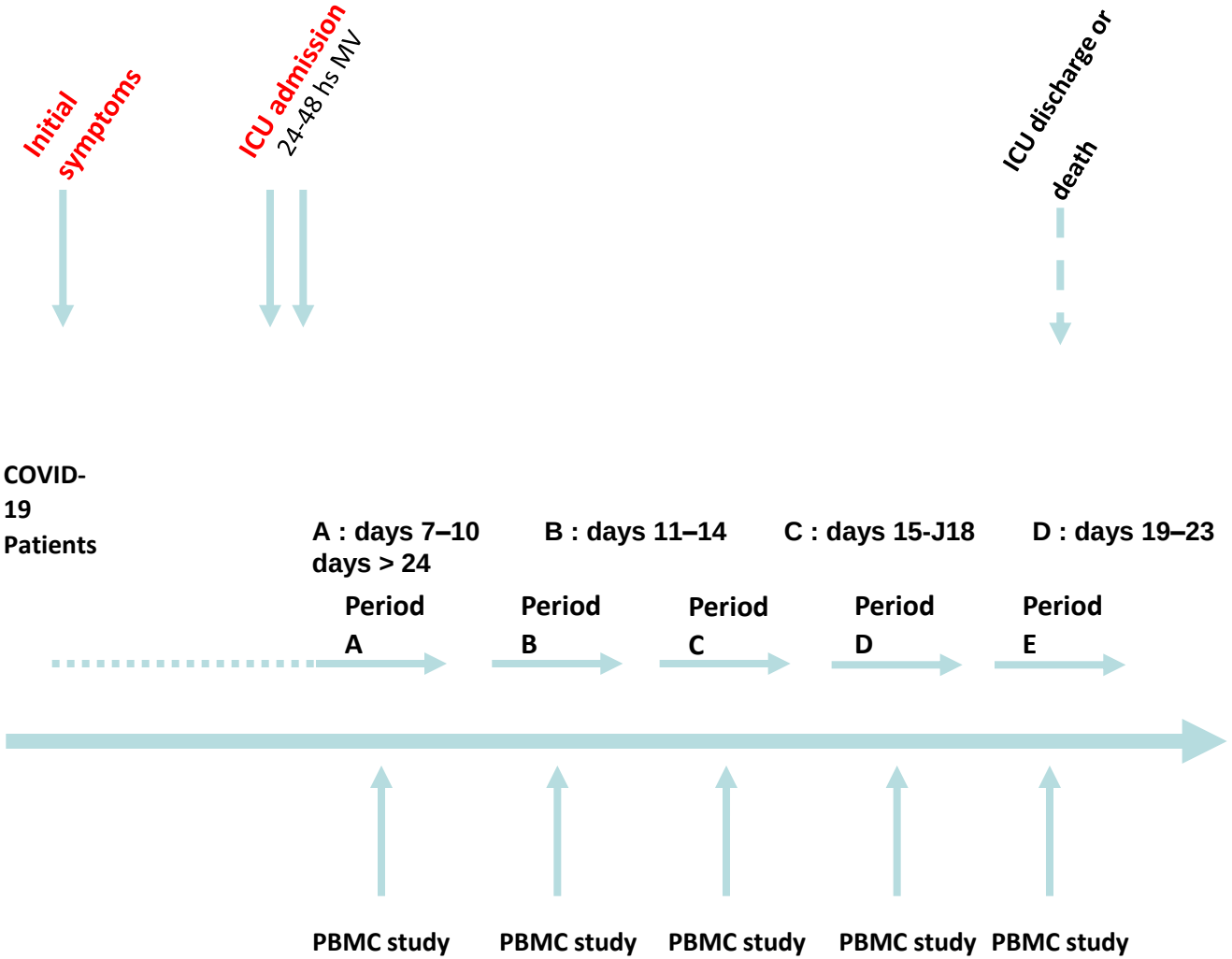
frontiers in Immunology

A Longitudinal Study of Immune Cells in Severe COVID-19 Patients

Didier Payen[1], Maxime Cravat[2], Hadil Maadadi[3], Carole Didelot[4], Lydia Prosic[4], Claire Dupuis[5], Marie-Reine Losser[3,6†] and Marcelo De Carvalho Bittencourt[2,4,7†]*

ORIGINAL RESEARCH
published: 23 October 2020
doi: 10.3389/fimmu.2020.580250





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ORIGINAL RESEARCH
published: 23 October 2020
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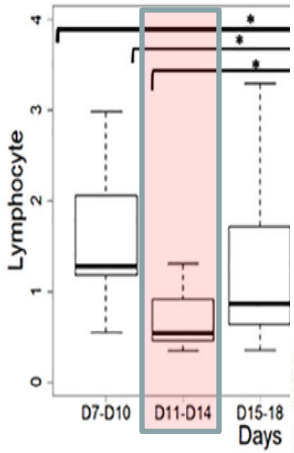
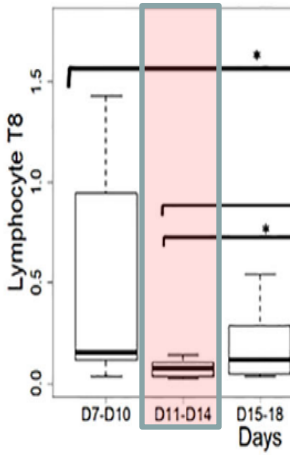
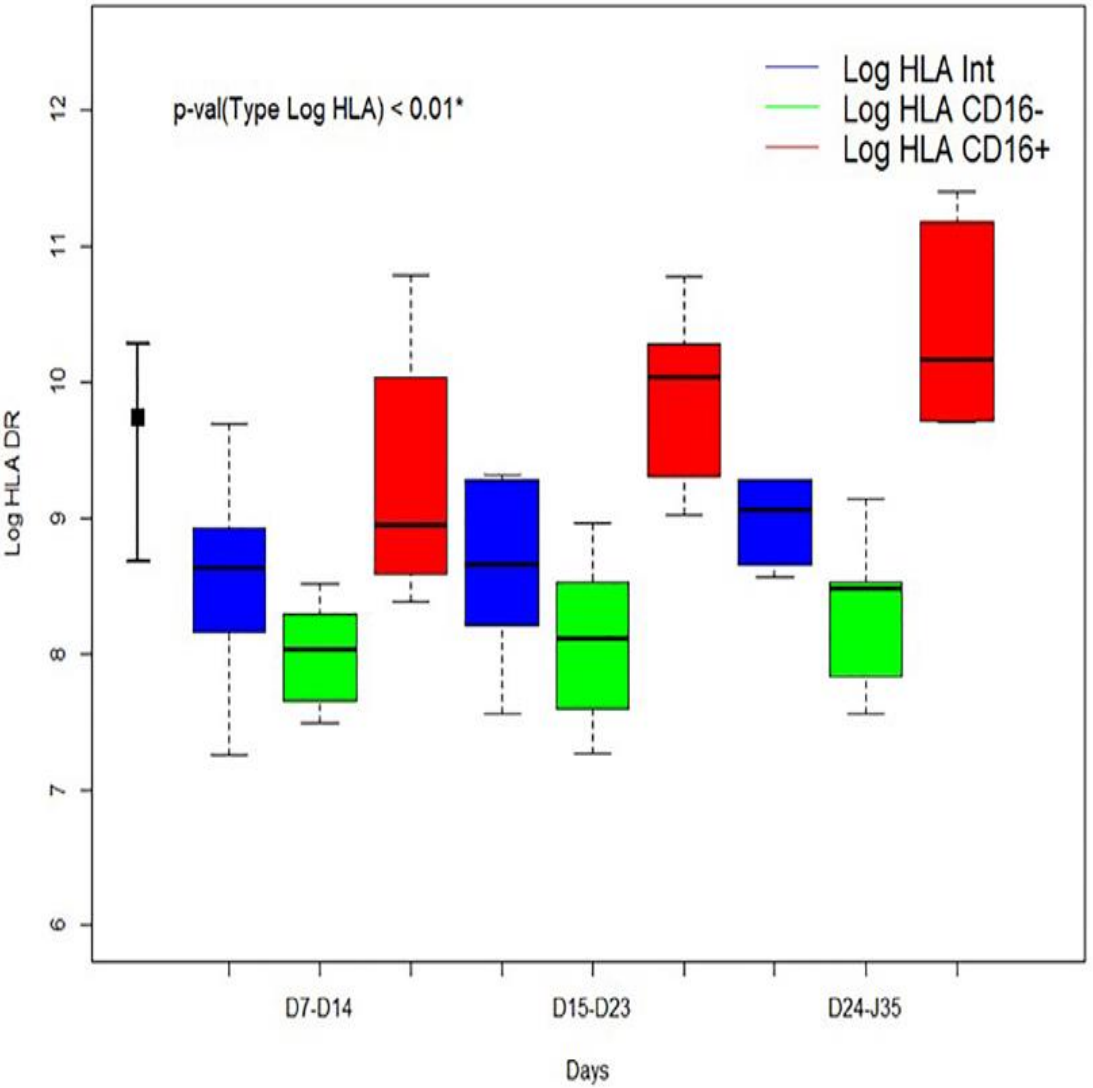
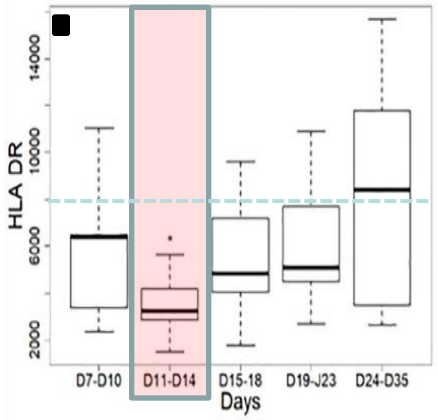
Time evolution of sub-populations of immune cells and HLA-DR expres







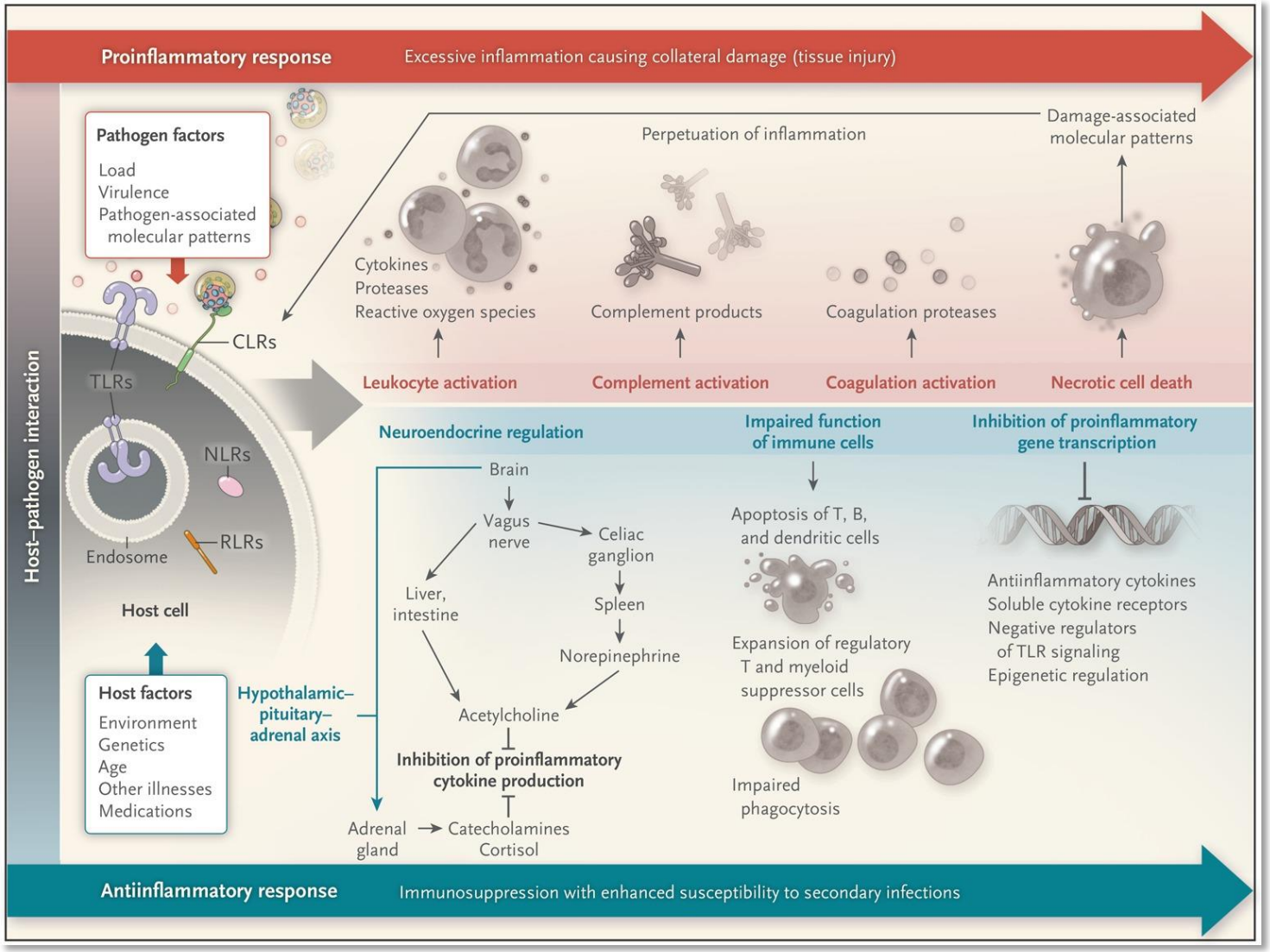
NI Exp



Conclusion

- ✓ **Sepsis is moved from strict infection to *systemic inflammation***
- ✓ **Septic shock moved from *HD analysis to coagulation, metabolism and immunity***
- ✓ ***Genetic susceptibility* and *gene transcription* are key**
- ✓ **Inflammation is *DYNAMIC process***
- ✓ ***Phases of sepsis* are of major impact to explain the RCTs failures**
- ✓ ***Personalized care based on AI*?**

To summarize: The Host Response to Sepsis canbe seen as

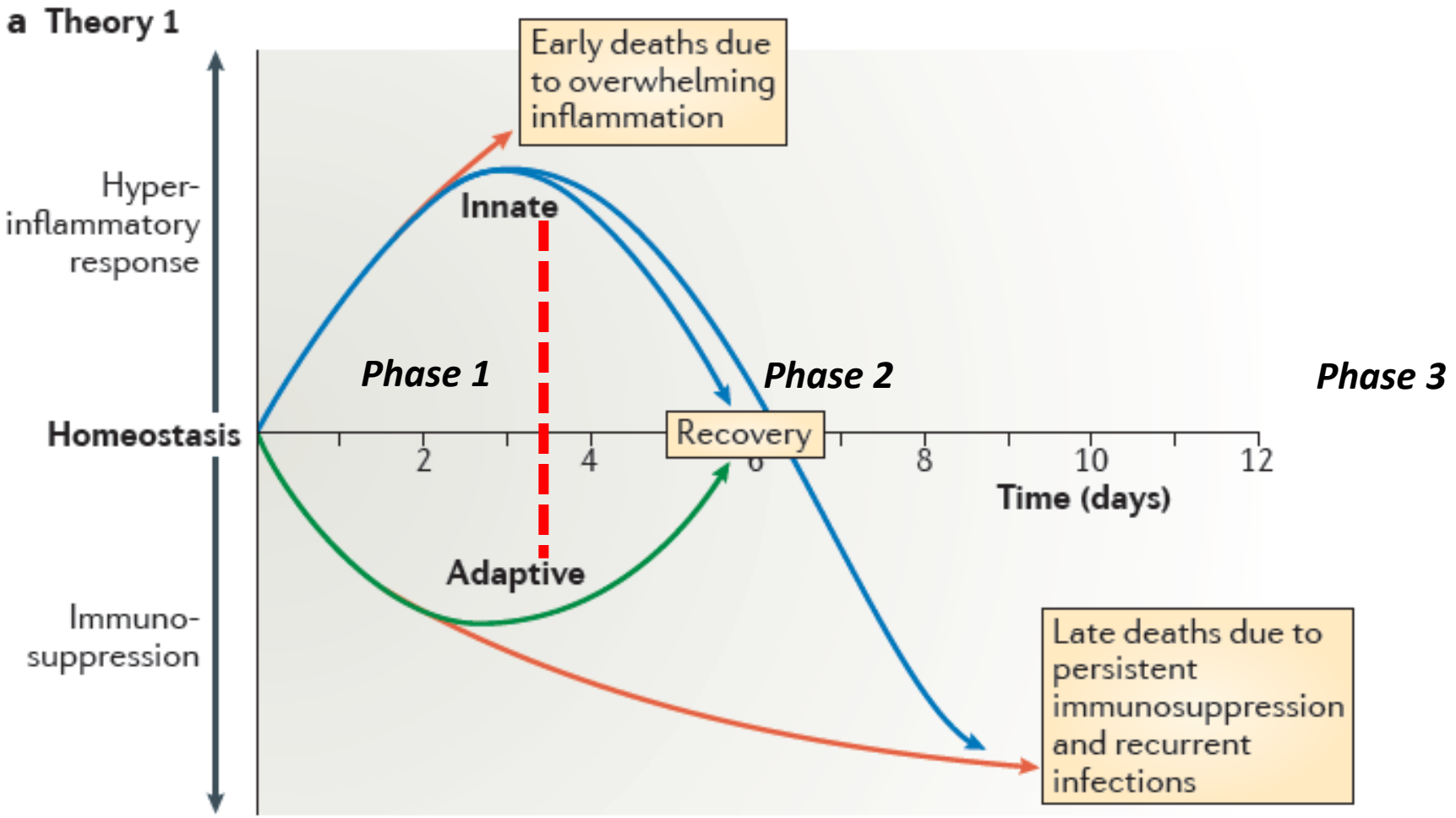


NEJM 2013; 369: 840

The time phases of sepsis

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

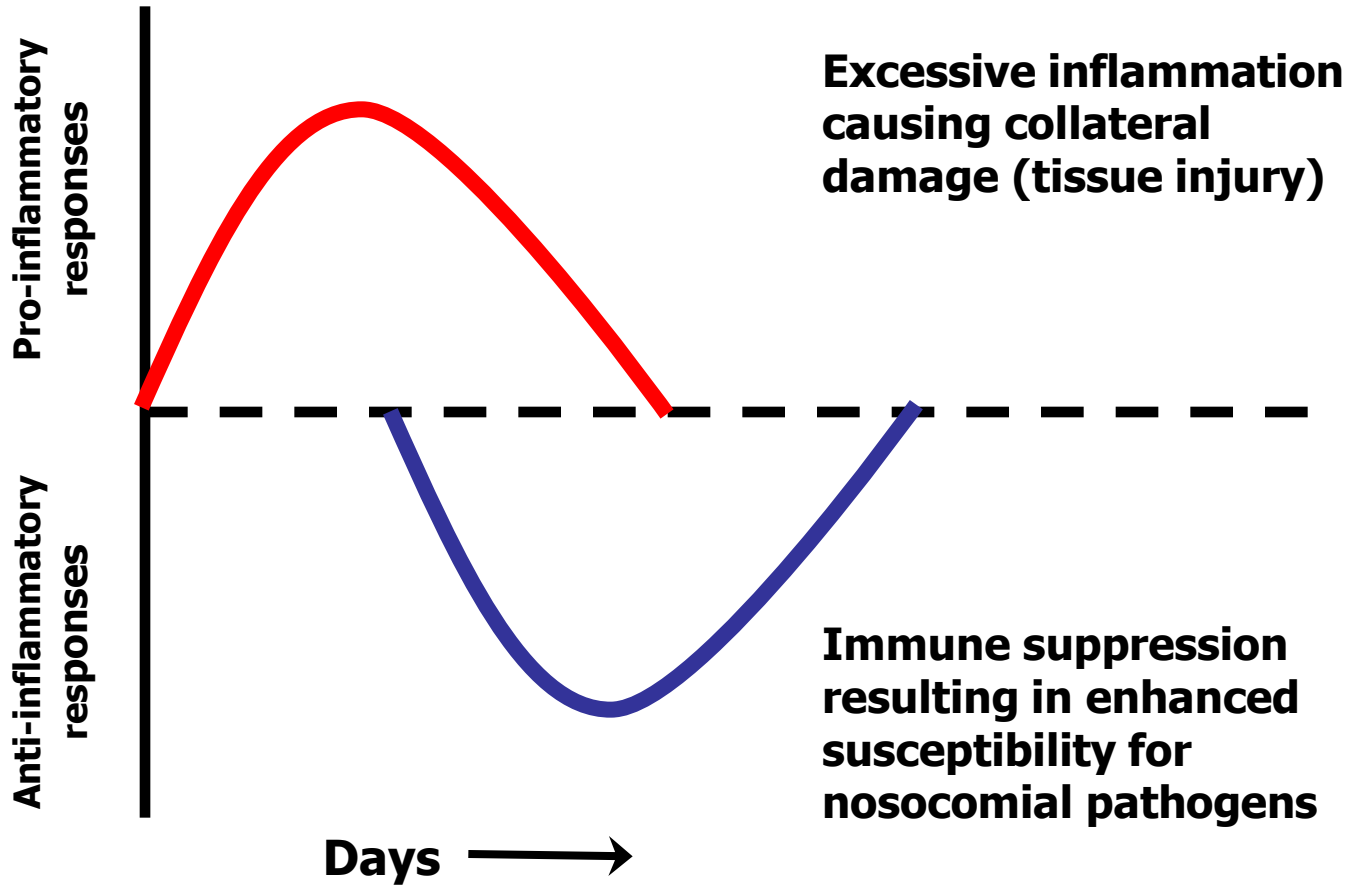
Richard S. Hotchkiss[1], Guillaume Monneret[2] and Didier Payen[3]



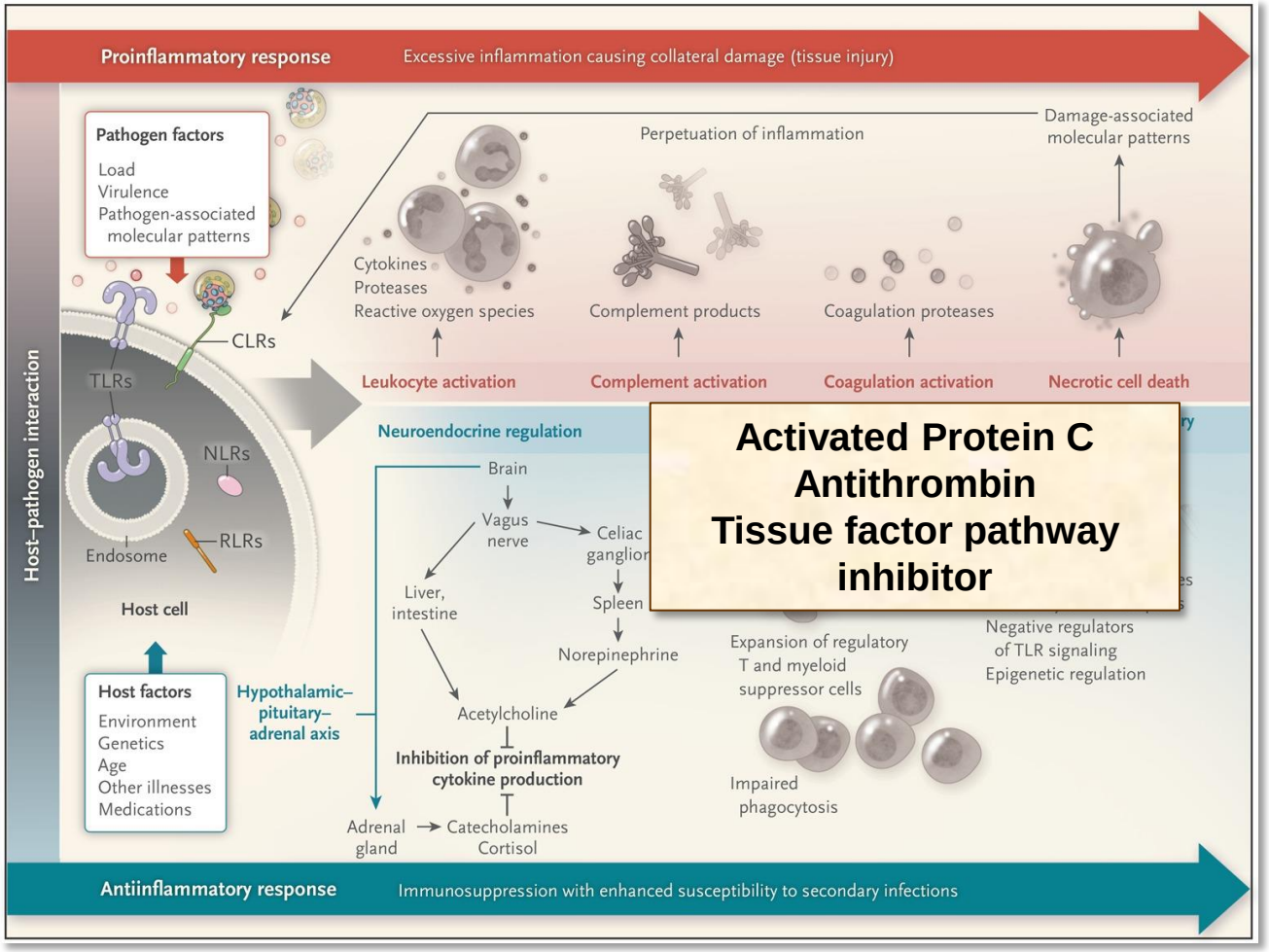
Nature Reviews Immunology | AOP, published online 15 November 2013; doi:10.1038/nri3552

Phase 1

The host response to sepsis



The Host Response to Sepsis



Early phase is challenging because of:

- fast track process (short windows: hrs…)

- multi interactive processes

- lack of validated BM to rapidly characterize host reponse

Why not being inspired by cancer strategies?

NATURE|Vol 444|14 December 2006|doi:10.1038/nature05485

Inflammation and metabolic disorders

Gökhan S. Hotamisligil[1]

Metabolic and immune systems are among the most fundamental requirements for survival. Many metabolic and immune response pathways or nutrient- and pathogen-sensing systems have been evolutionarily conserved throughout species. As a result, immune response and metabolic regulation are highly integrated and the proper function of each is dependent on the other. This interface can be viewed as a central homeostatic mechanism, dysfunction of which can lead to a cluster of chronic metabolic disorders, particularly obesity, type 2 diabetes and cardiovascular disease. Collectively, these diseases constitute the greatest current threat to global human health and welfare.

PHASE 2

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

Lancet Infect Dis 2013; 13: 260–68

Richard S Hotchkiss, Guillaume Monneret, Didier Payen

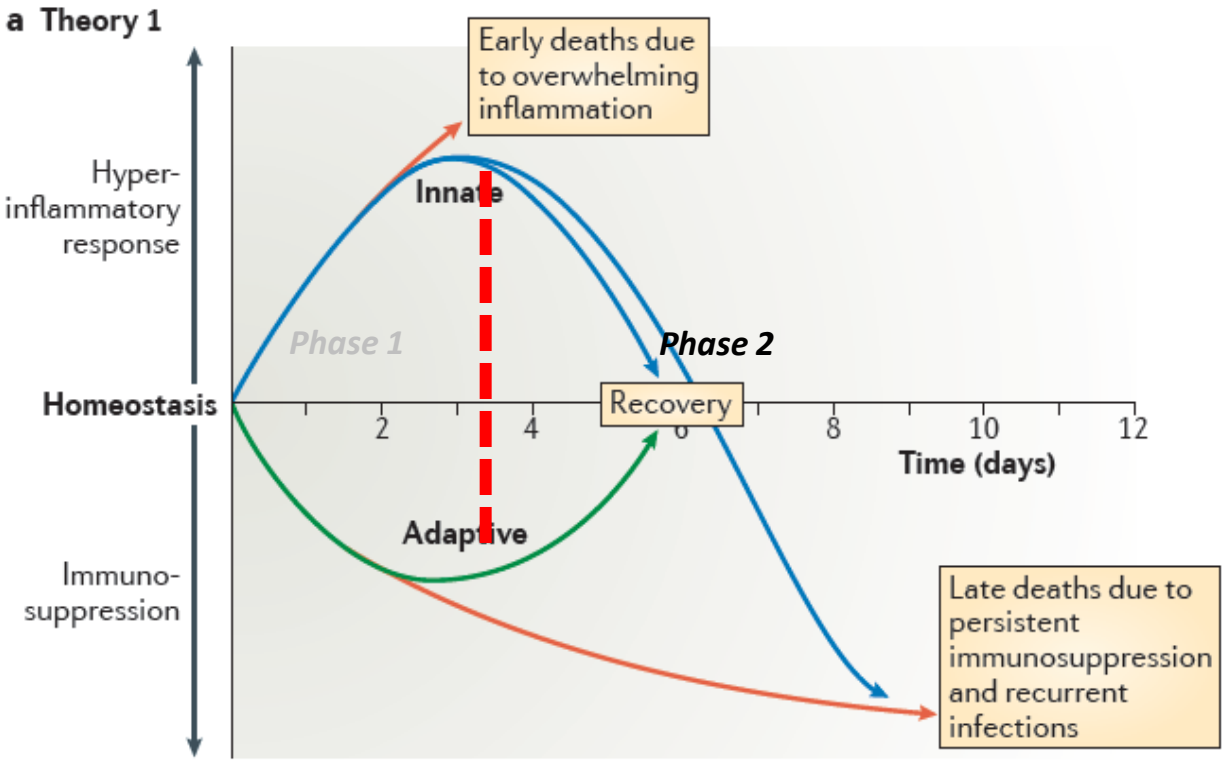
Clinical or laboratory evidence for sepsis being an immunosuppressive disorder

- **Loss of delayed type hypersensitivity response** to common recall antigens
- **Apoptosis-induced depletion of immune effector cells, loss of CD4, CD8, B, and dendritic cells**
- **Reactivation of latent viruses (CMV; herpes** virus in roughly 25–35% of patients with sepsis)
- **autopsy → most patients admitted to *ICUs* for treatment of sepsis had unresolved septic foci at post mortem,**
  →patients unable to eradicate invading pathogens and were more susceptible to nosocomial organisms, or both
- **Blood studies** with and without sepsis → **decreased**

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

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

Post-Agressive Immuno-Depression (PAID) Syndrome



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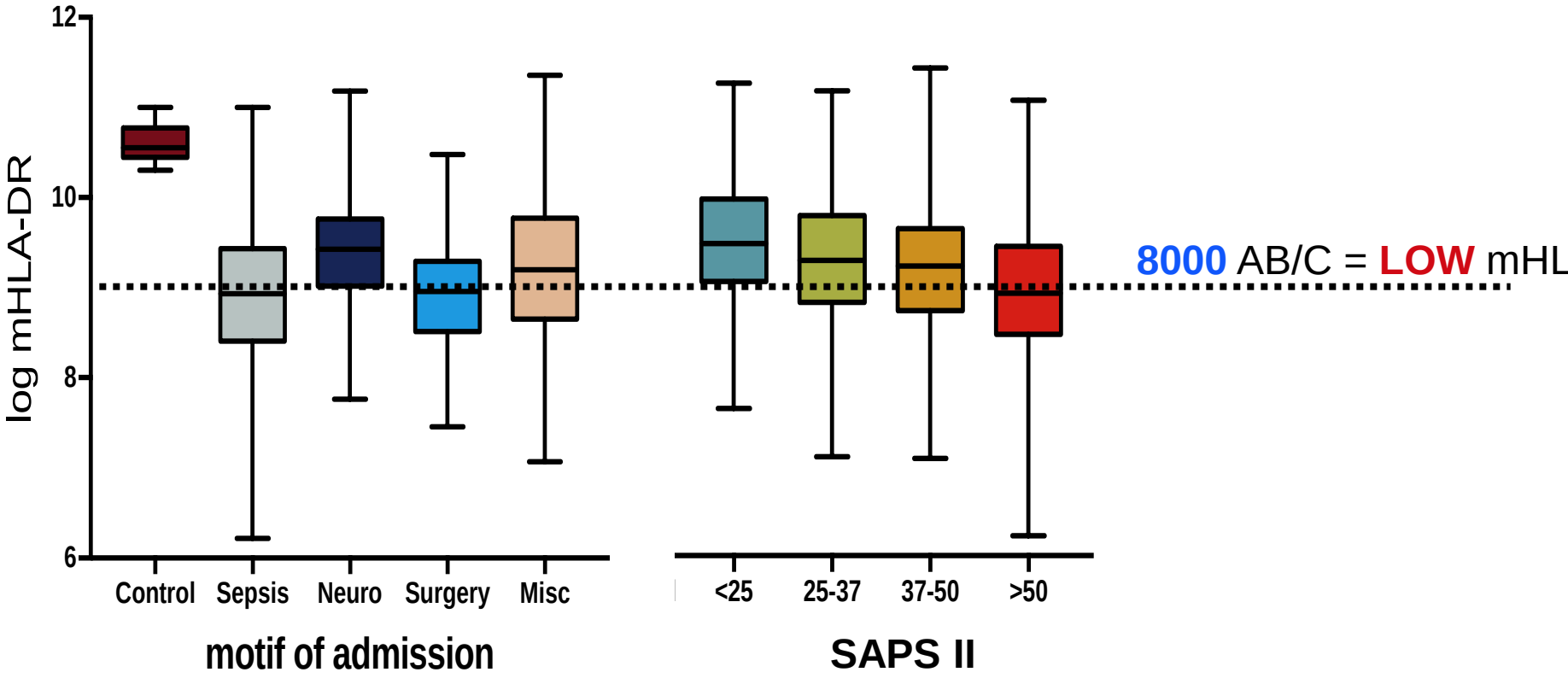
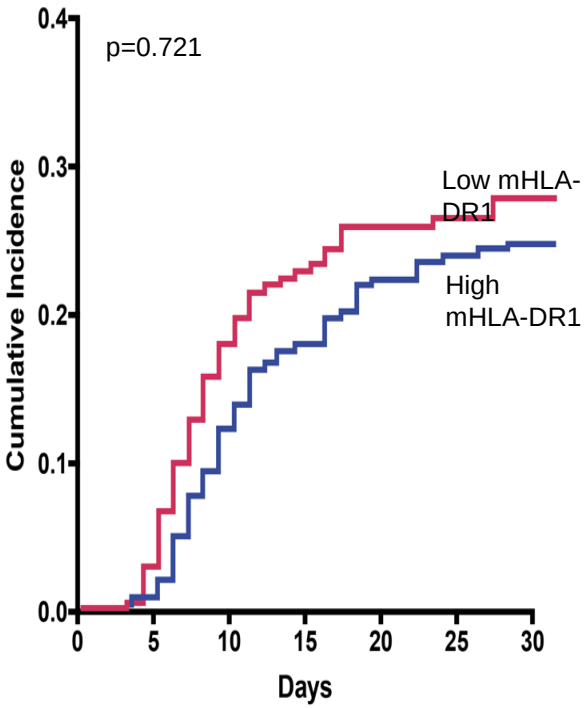
- **Reactivation of latent viruses (CMV; herpes** virus in roughly 25–35% of patients with sepsis)
- **autopsy ➔ most patients admitted to *ICUs* for treatment of sepsis had unresolved septic foci at post mortem, ➔patients unable to eradicate invading pathogens and were more susceptible to nosocomial organisms, or both**
- **Blood studies** from patients with and without sepsis show **decreased production of proinflammatory cytokines, decreased monocyte HLA-DR expression, increased numbers of regulatory T cells (Treg Fox P3), increased production of PD-1 or PD-L1**

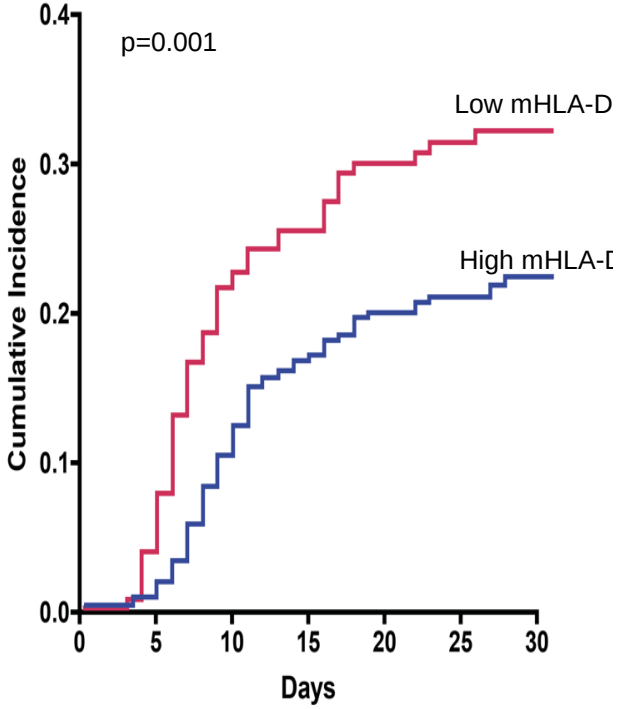
mHLA-DR expression



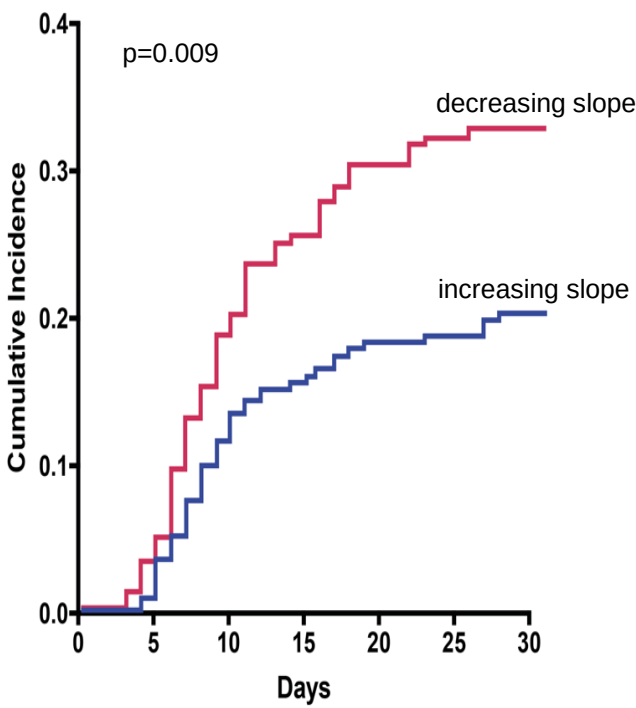
ICU-acquired infection



mHLA-DR$_1$



mHLA-DR$_2$



Slope

Can We treat this immunosuppression?

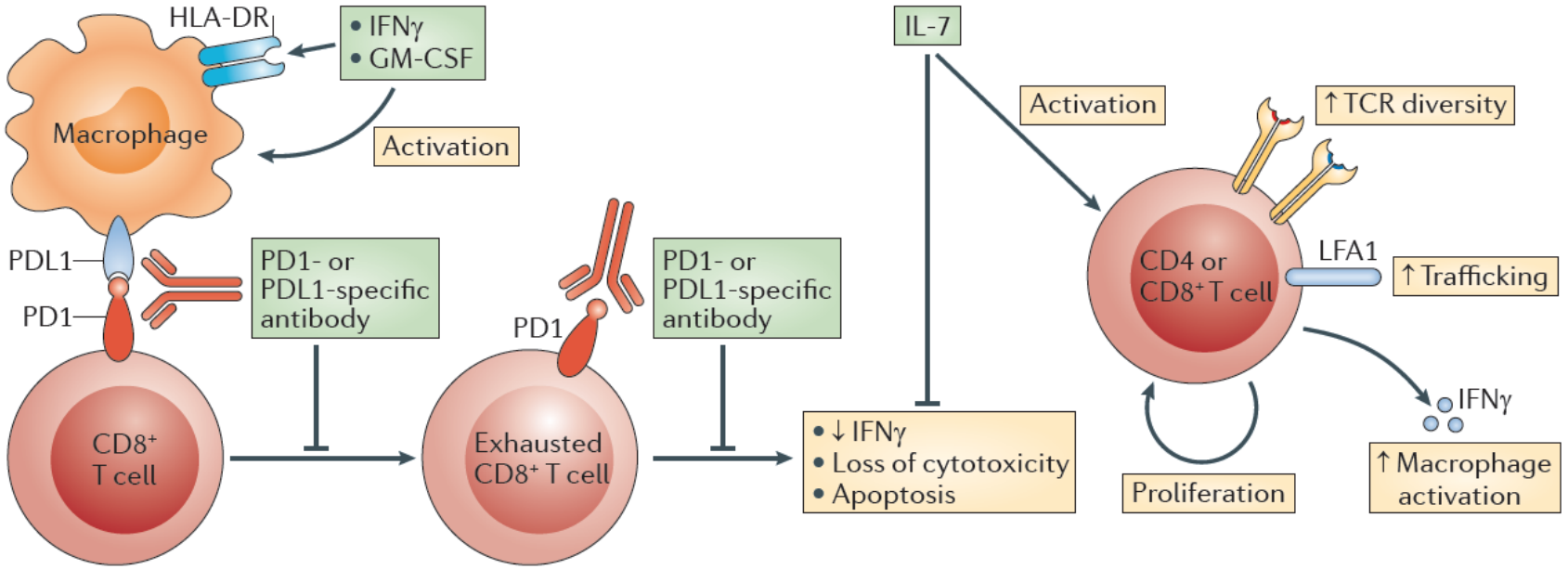
Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

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

Fct Mono
Phagocytose

PMN, Mono
phagocytose
mHLA-DR
TNFα

Prolif. Tcell
IFNγ
Anti-apoptose
↓PD-1, ↑ molec adhesion
↓Treg
Diversité récepteurs TCR

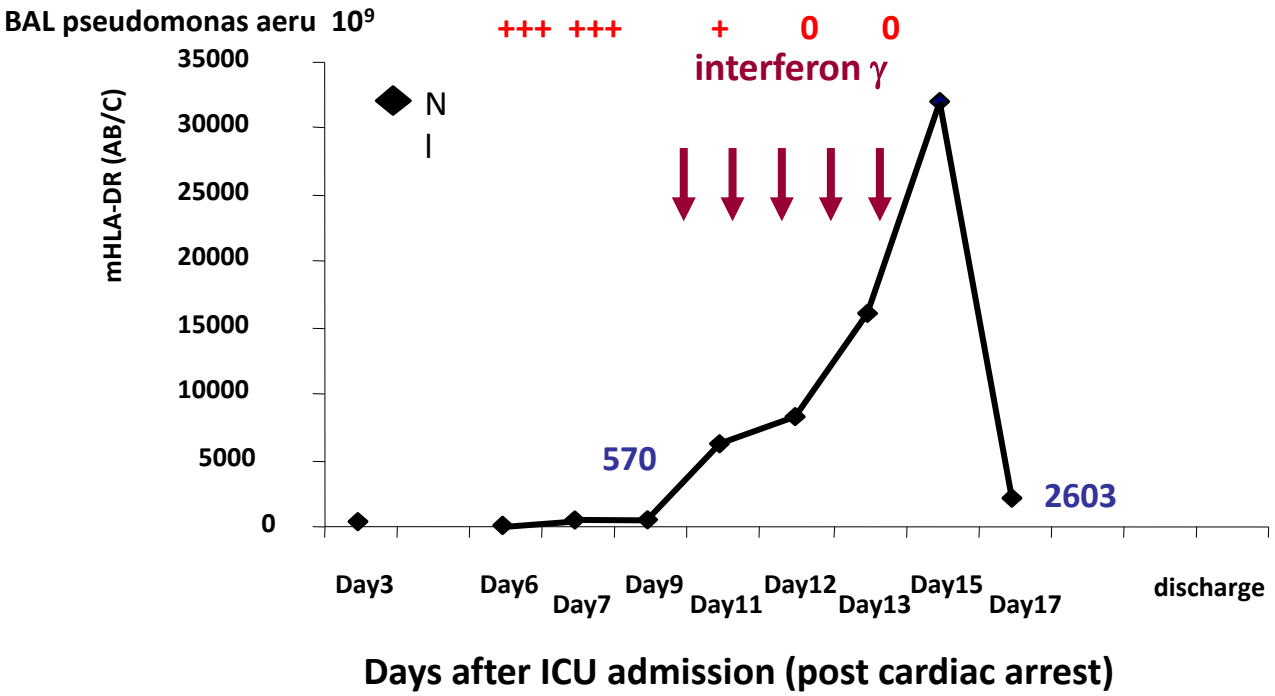


To conclude

- **PAIDs** is a fact that concerns **all acute situations**, particularly **severe sepsis is always present after 1 or 2 days post injury**
- **IMMUNOSCOPE**
  - **Blood measurements: WBC (fractions), NCLRatio; semi-quantitative cytokine level**
  - **Flowcytometry: HLA-DR; Ly sub-populations**
- **➔ IMMUNOSCOPE! ➔ Personalized therapy**
- **HLA-DR is a good candidate** and is **cheap** and **fast** to be measured with **semi-quantitative IL-6, IL-10**.
- **Immuno-stimulation can be proposed** on **solid criteria**
- **RCT are on going** testing **different targets and molecules (INFγ, GM-CSF; IL-7…)**

Monocytic HLA-DR expression in intensive care patients: Interest for prognosis and secondary infection prediction*

Anne-Claire Lukaszewicz, MD; Marion Grienay, MD; Matthieu Resche-Rigon, MD, PhD; Romain Pirracchio, MD; Valérie Faivre, PhD; Bernadette Boval, MD; Didier Payen, MD, PhD



Lukaszewicz et al.Crit Care Med 2009; 37: 2746–2752

Cytokine storm

- Term used around the 90s
- **“uncontrolled” systemic inflammatory reaction** triggered by a **variety of factors**
- Equivalent to **Cytokine Release Syndrome (CRS)**
- **Different phenotypes** ➔ different cytokines responses in relation to the etiologies…
- ➔ **vague term and really nonspecific**!
- Let’s see **the COVID-19 related**

Is a "Cytokine Storm" Relevant to COVID-19?

JAMA Internal Medicine September 2020 Volume 180, Number 9

Pratik Sinha, MB, ChB, PhD; Michael A. Matthay, MD; Carolyn S. Calfee, MD, MAS

EDITORIAL

Plasma Levels of Interleukin-6 Reported in COVID-19 Compared With Levels Previously Reported in ARDS

	Severe disease	
COVID-19	No.	IL-6 levels, pg/mL
Zhou et al[4]	54[b]	11 (8-14)
Wu et al[1]	84[c]	7 (6-11)
Mo et al[5]	85[d]	64 (31-165)
Qin et al[2]	286[e]	25 (10-55)
Cummings et al[6]	237[f]	26 (11-69)
ARDS	Hyperinflammatory	
	No.	IL-6 levels, pg/mL
ALVEOLI[7]	135	1525 (584-3802)
FACTT[8]	246	578 (181-2621)
SAILS[9]	269	1618 (517-3205)

ARDS Network are approximately **10- to 40-fold higher,** even when only patients with **severe COVID-19 are considered**.

In patients with the **hyperinflammatory phenotype of ARDS IL-6** are **10- to 200-fold higher than levels** in **severe**

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Pratik Sinha, MB, ChB, PhD; Michael A. Matthay, MD; Carolyn S. Calfee, MD, MAS

EDITORIAL

Widespread acceptance of the term *cytokine storm* in COVID-19 has motivated the use of potent immunomodulatory therapies both in clinical trials and on a compassionate basis as **IL-6 inhibitors** and **high dose CSt blocking pathways critical to host immune responses**.

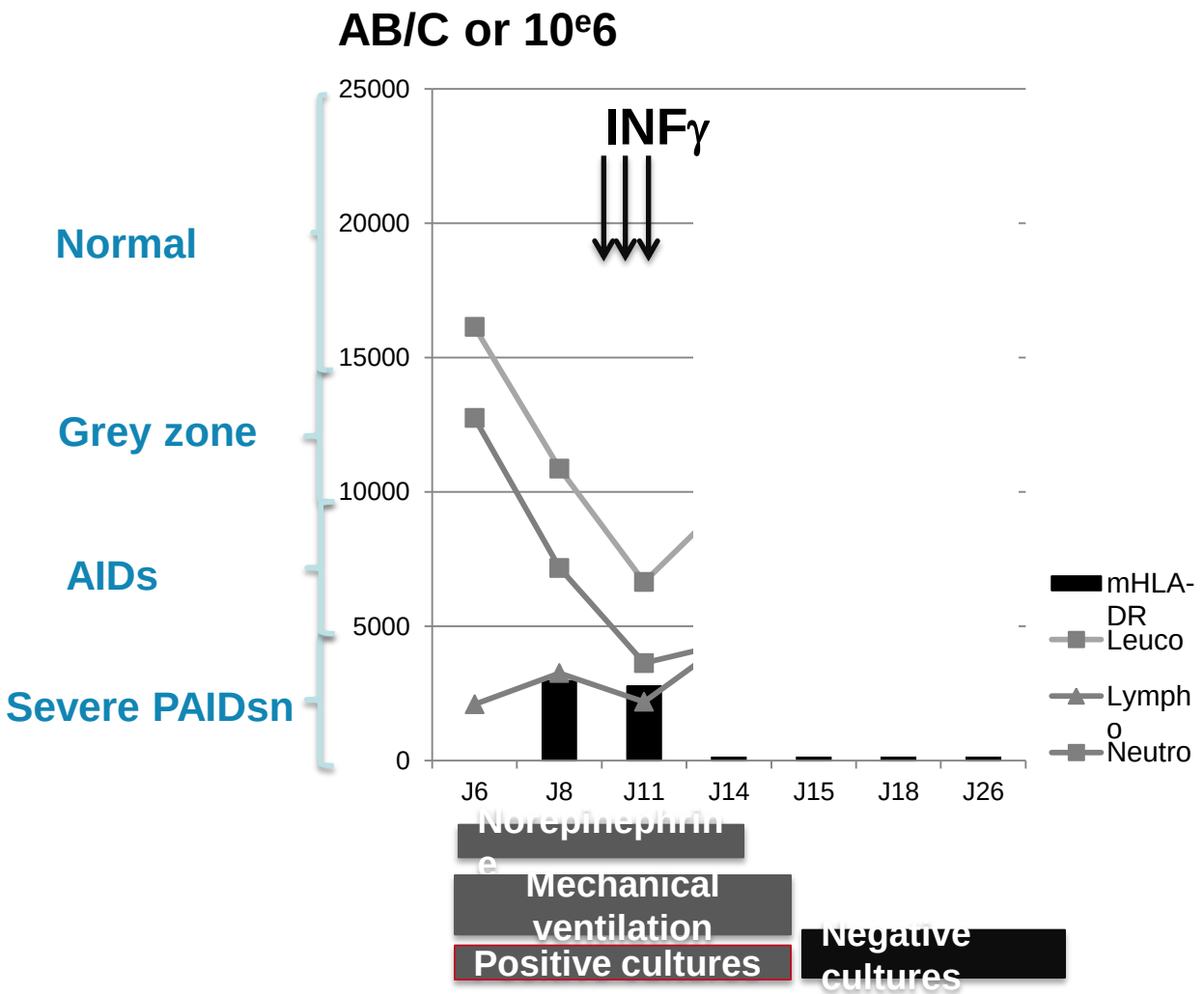
The term ***cytokine storm* may be misleading in COVID-19 ARDS**.

Although the **term *cytokine storm*** **conjures up dramatic imagery** and ***has captured the attention of the main stream and scientific media***, the **current data do not support its use**.

Until new data establish otherwise, the **linkage of cytokine storm to COVID-19 may be nothing more than a tempest in a teapot**

Can We treat this immunosuppression?

TotoR *Pseudomonas aeruginosa* septic shock – severe ARDS – peritonitis in a 15 months post-LT child



Multicentric experience with interferon gamma therapy in sepsis induced immunosuppression. A case series

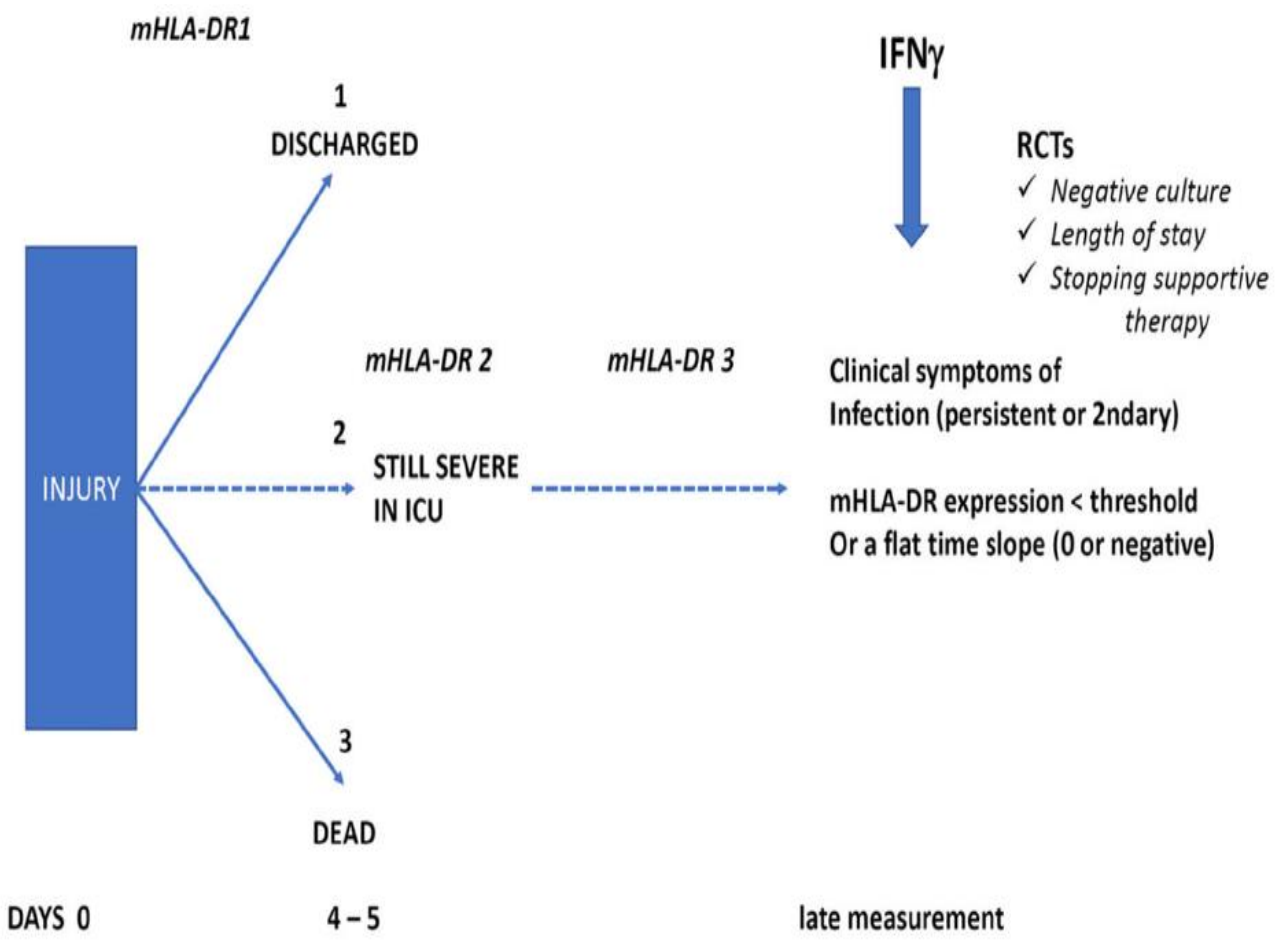
Didier Payen[1,2*], Valerie Faivre[1,2], Jordi Miatello[3,4], Jenneke Leentjens[5], Caren Brumpt[6], Pierre Tissières[3,4], Claire Dupuis[1], Peter Pickkers[7†] and Anne Claire Lukaszewicz[1,2†]

Payen *et al. BMC Infectious Diseases* (2019) 19:931
https://doi.org/10.1186/s12879-019-4526-x

Table 1 Clinical and infection characteristics of patients treated with IFNγ for cohort 1 and Cohort 2. AB/C = antibodies per cell. MFI = Mean Fluorescence Intensity

Cohort 1

	Age	Diagnosis a admission
1	30	Cardiac arr
2	83	Postop cardiogenic shock
3	73	Cardiogeni shock
4	63	Peritonitis
5	42	Peritonitis
6	64	Peritonitis
7	65	Postoparati pneumonia
8	56	Pneumonia
9	34	Pneumonia
10	56	Cervical cellulitis septicemia
11	60	Fasciitis
12	74	Keto-acido
13	82	Rectal Fistu & fasciitis



(7 days)

Conclusion

- Almost **all life threatening situations involve mainly INFLAMMATION**
- Inflammation concerns **coagulation, immunity, and cell metabolism**
- **Cytokines = cell microenvironment** ➔ cell functions
- **Phases** ➔ longitudinal monitoring ➔ potential use of **immunomodulating drugs**
- **Cytosorbent use may then change the cell microvironment**

  ➔ **functional and recovery of tissue fitness**
- **Immune monitoring** is then **essential to make the decision**

A Longitudinal Study of Immune Cells in Severe COVID-19 Patients

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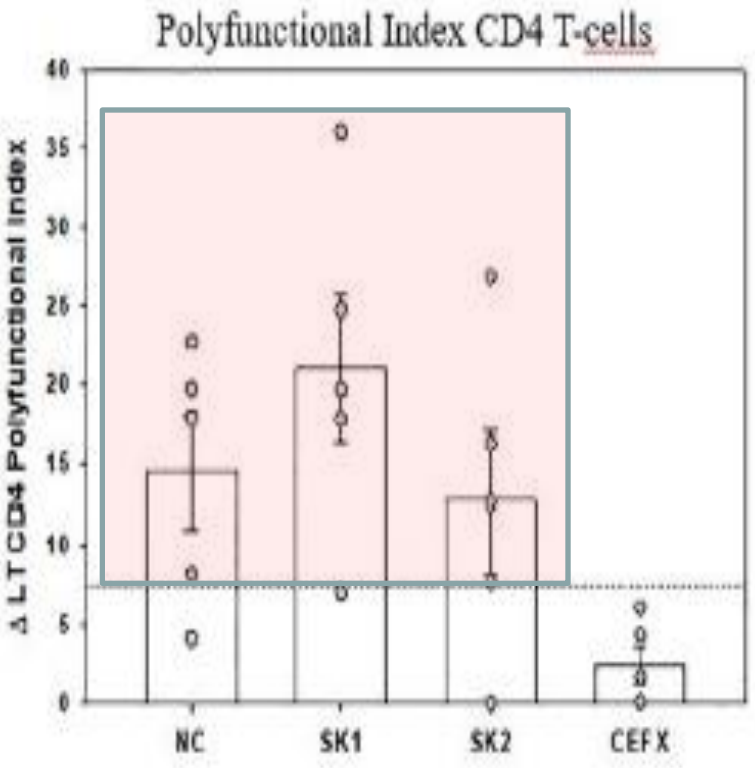
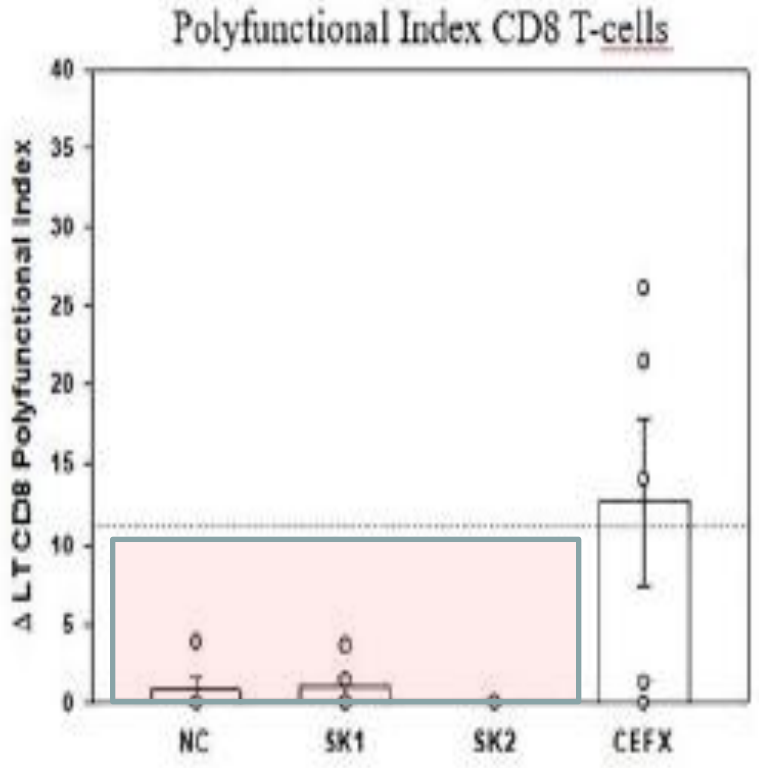
Frontiers in Immunology | October 2020 | Volume 11 | Article 580250

Neutrophil





Lessons Learned Comparing Immune System Alterations of Bacterial Sepsis and SARS-CoV-2 Sepsis

Xijie Dong, Chuntao Wang, Xinghua Liu, Wei Gao, Xiangjun Bai and Zhanfei Li**

Frontiers in Immunology November 2020 | Volume 11 | Article 598404

Cytokine levels in bacterial **sepsis always >> to COVID-19**.