

Sepsis: quelle place pour l'immunothérapie à l'avenir?

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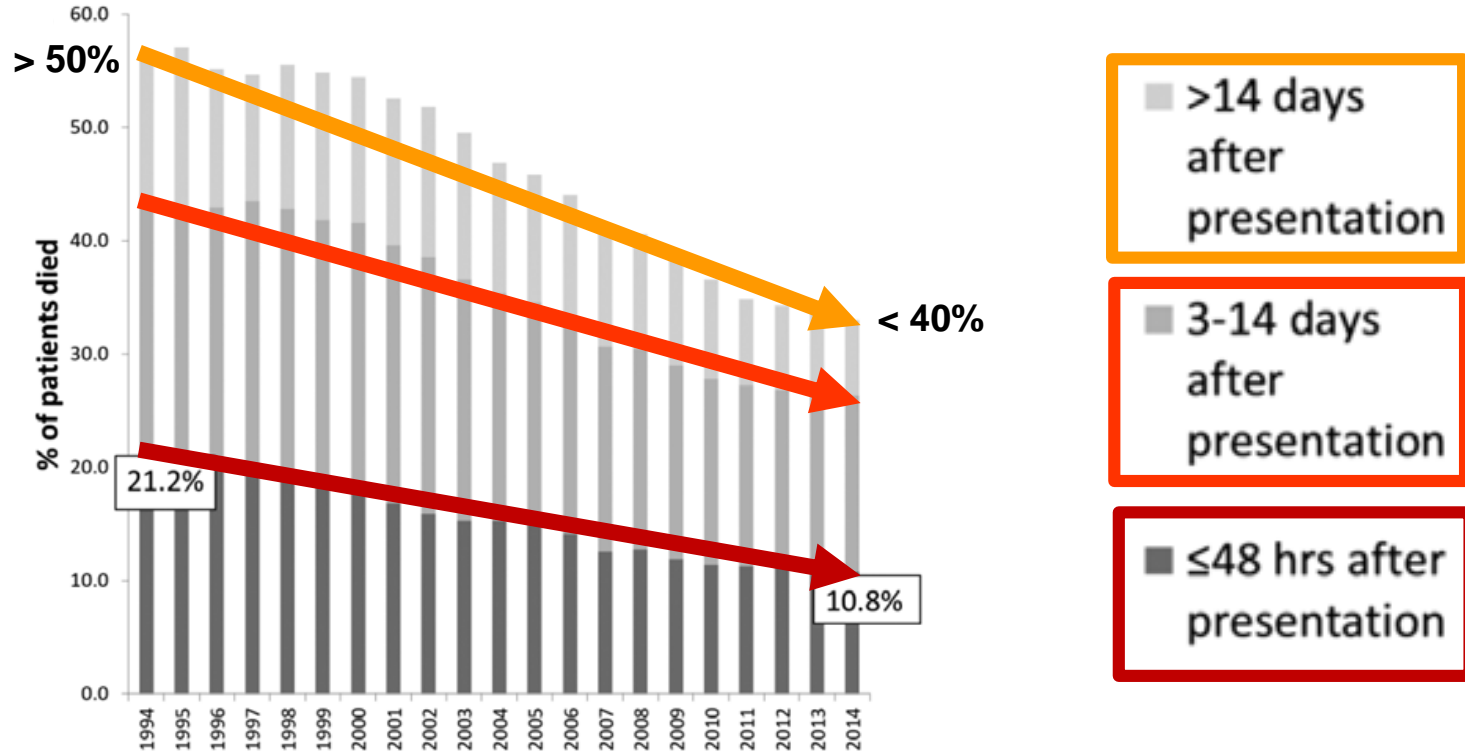


Déclaration de liens d'intérêt

GILEAD (personal lecture fees, congress)

National Trends in Timing of Death Among Patients With Septic Shock, 1994–2014

Anica C. Law, MD^{1,2}; Jennifer P. Stevens, MD, MS^{1,2}; Allan J. Walkey, MD, MS^{3,4,5}



Host response to pathogens: a finely tuned balance

**Clearing
pathogens**



**Avoiding
Immunopathological
damage**

Current gaps in sepsis immunology: new opportunities for translational research

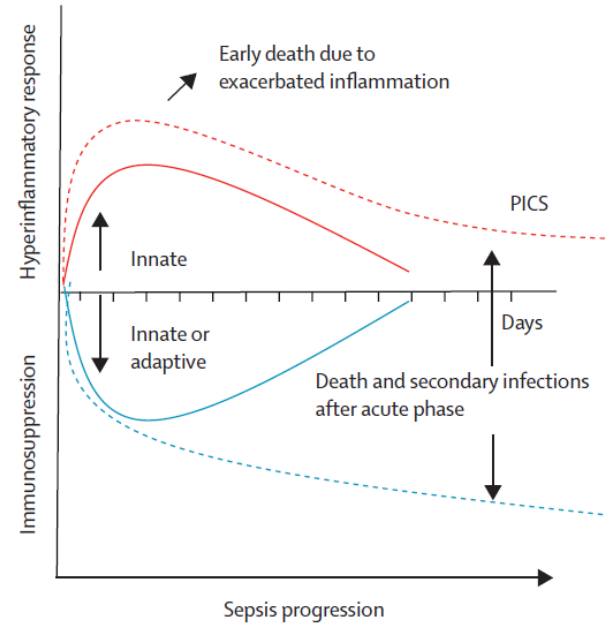
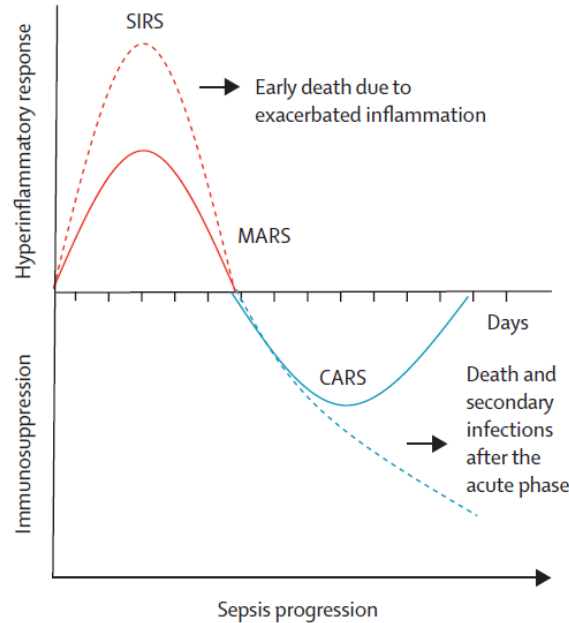
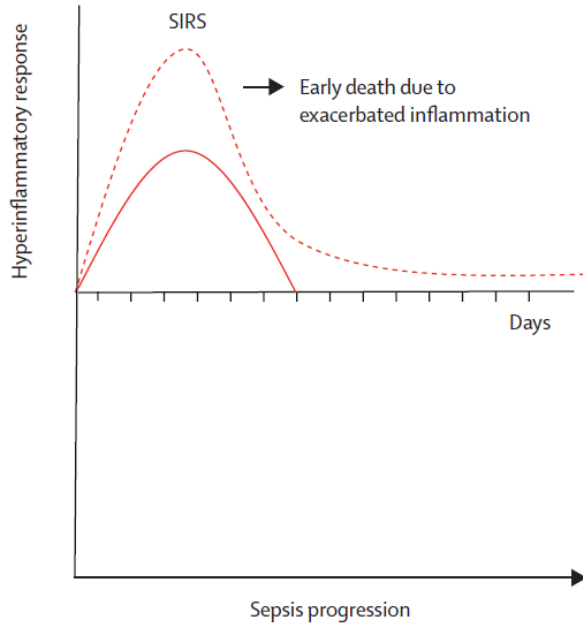
Lancet Respir Med 2019

Ignacio Rubio, Marcin F Osuchowski, Manu Shankar-Hari, Tomasz Skirecki, Martin Sebastian Winkler, Gunnar Lachmann, Paul La Rosée, Guillaume Monneret, Fabienne Venet, Michael Bauer, Frank M Brunkhorst, Matthijs Kox, Jean-Marc Cavailon, Florian Uhle, Markus A Weigand, Stefanie B Flohé, W Joost Wiersinga, Marta Martin-Fernandez, Raquel Almansa, Ignacio Martin-Loeches, Antoni Torres, Evangelos J Giamarellos-Bourboulis, Massimo Girardis, Andrea Cossarizza, Mihai G Netea, Tom van der Poll, André Scherag, Christian Meisel, Joerg C Schefold, Jesús F Bermejo-Martín

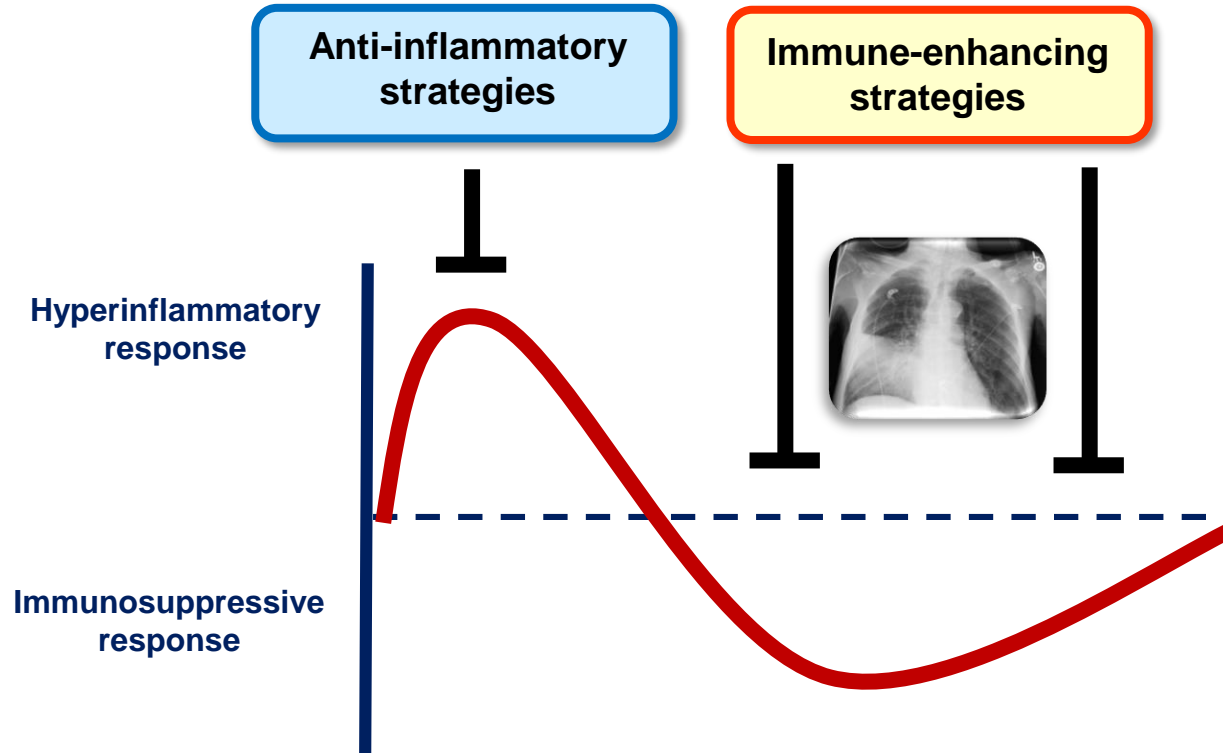
SIRS detectable in blood

SIRS followed by CARS detectable in blood

Simultaneous pro-inflammatory and anti-inflammatory responses in blood



When and how to treat ?



Immunomodulatory candidates in sepsis

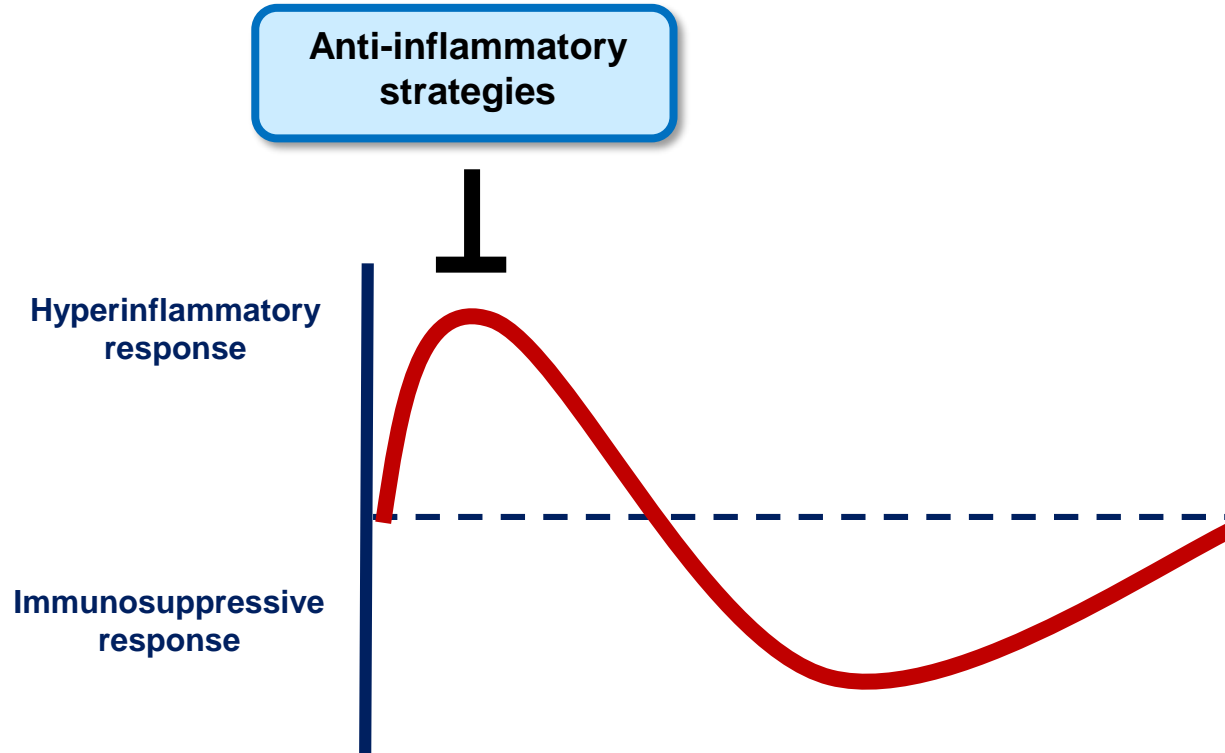
Anti-inflammatory

- Cytokine/chemokine inhibitors
- Corticosteroids
- IV Ig
- TLR inhibition
- Cell therapy ?

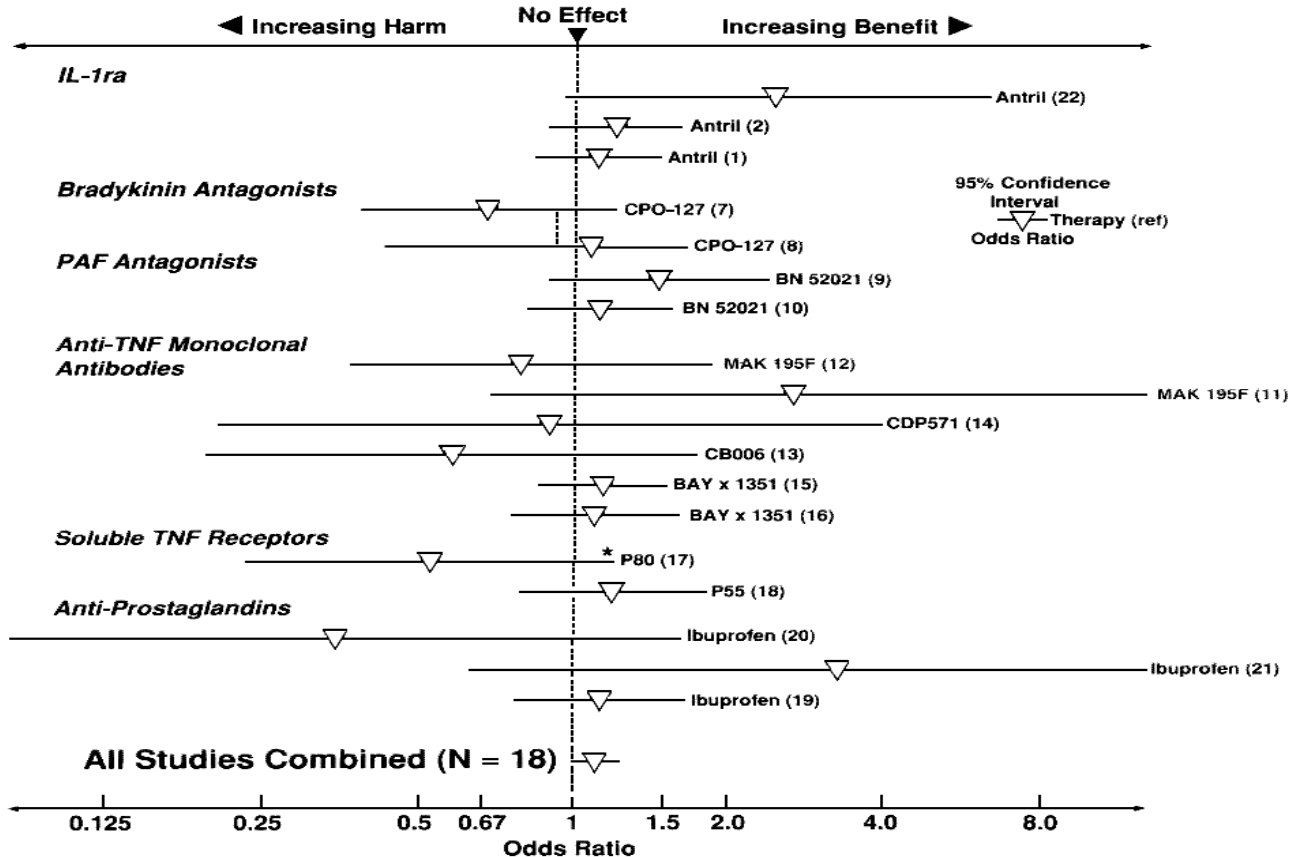
Immune-enhancing

- Cytokines
- Hematopoietic growth factors
- Immune checkpoint inhibitors
- Antiviral treatment
- Cell therapy ?

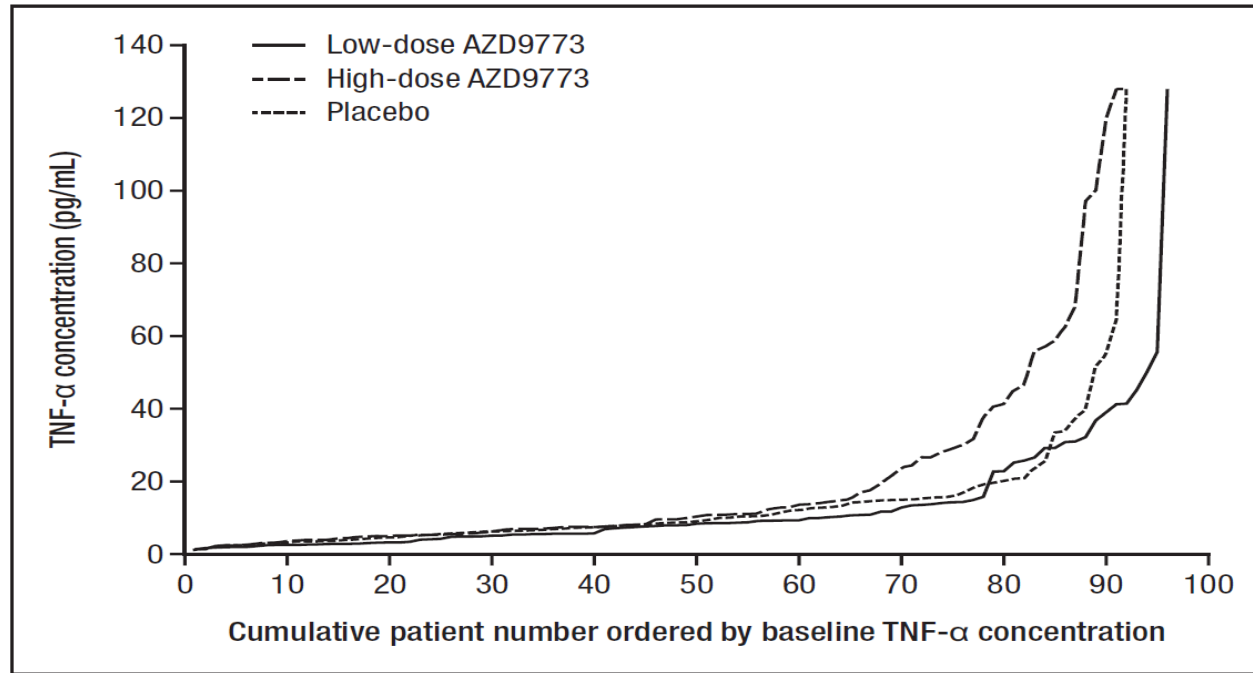
When and how to treat ?



Anti-inflammatory strategies

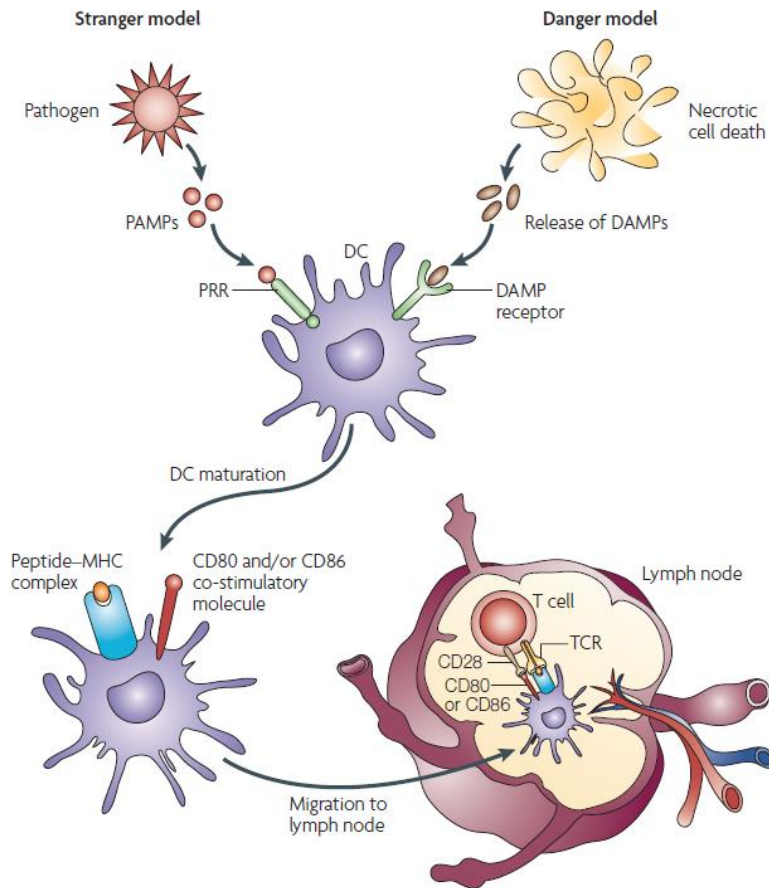


Evaluating the Efficacy and Safety of Two Doses of the Polyclonal Anti-Tumor Necrosis Factor- α Fragment Antibody AZD9773 in Adult Patients With Severe Sepsis and/or Septic Shock: Randomized, Double-Blind, Placebo-Controlled Phase IIb Study



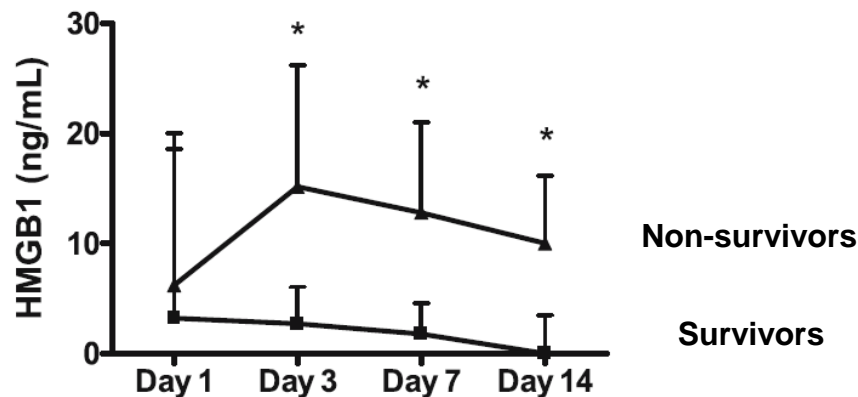
How dying cells alert the immune system to danger

Hajime Kono and Kenneth L. Rock



Sébastien Gibot
Frédéric Massin
Aurélie Cravoisy
Damien Barraud
Lionel Nace
Brune Levy
Pierre-Edouard Bollaert

High-mobility group box 1 protein plasma concentrations during septic shock



number of patients	Day 1	Day 3	Day 7	Day 14
Survivors	23	23	10	8
Non Survivors	19	16	11	9

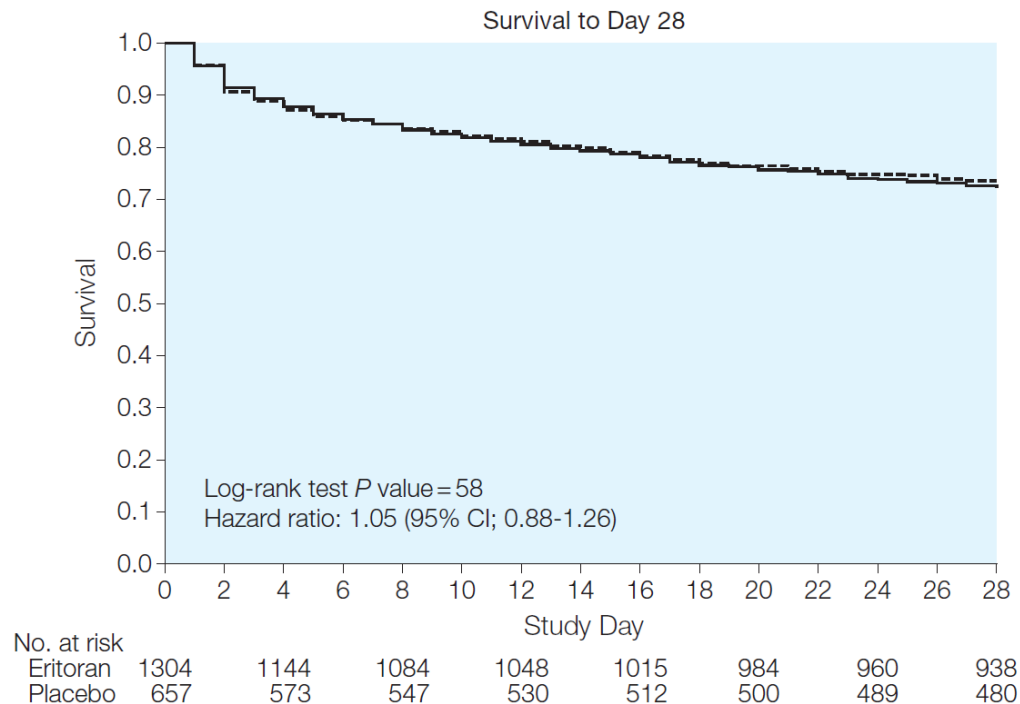
Fig. 2 Time course of median (interquartile range) HMGB1 plasma concentrations in survivors (*squares*) and nonsurvivors (*triangles*).
* $p < 0.02$

Effect of Eritoran, an Antagonist of MD2-TLR4, on Mortality in Patients With Severe Sepsis

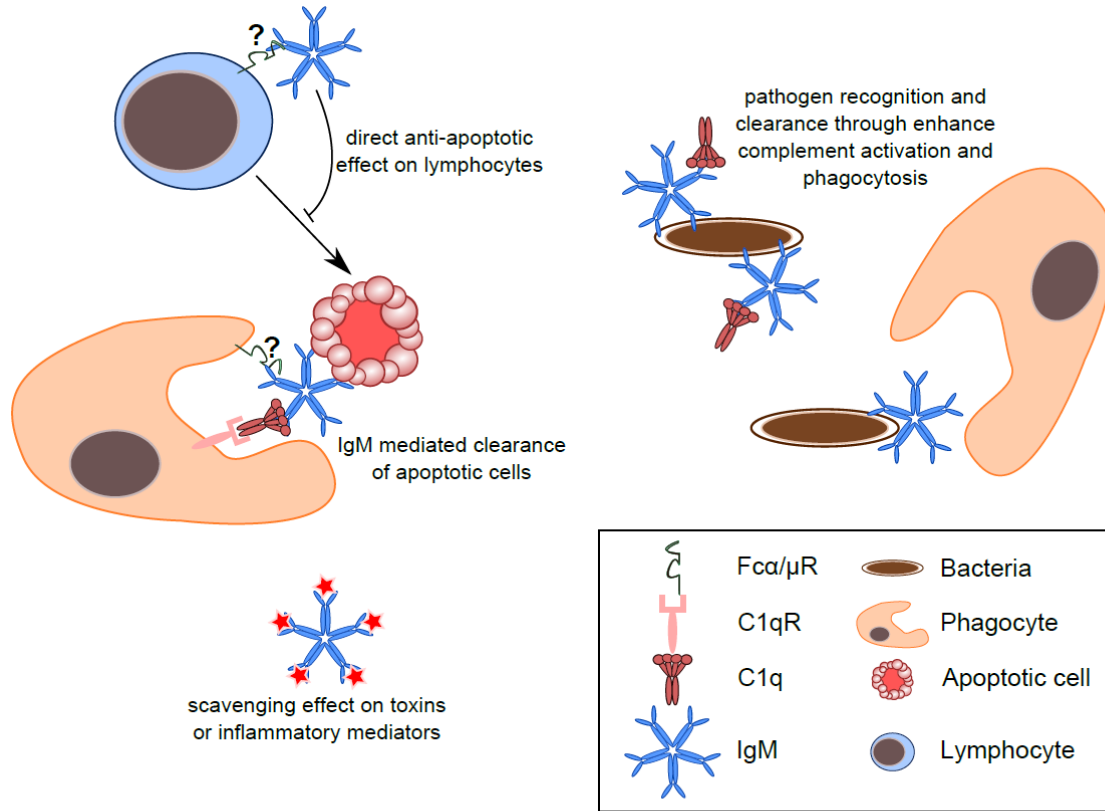
The ACCESS Randomized Trial

S. Opal and coll.

JAMA, March 20, 2013—Vol 309, No. 11
Corrected on March 19, 2013

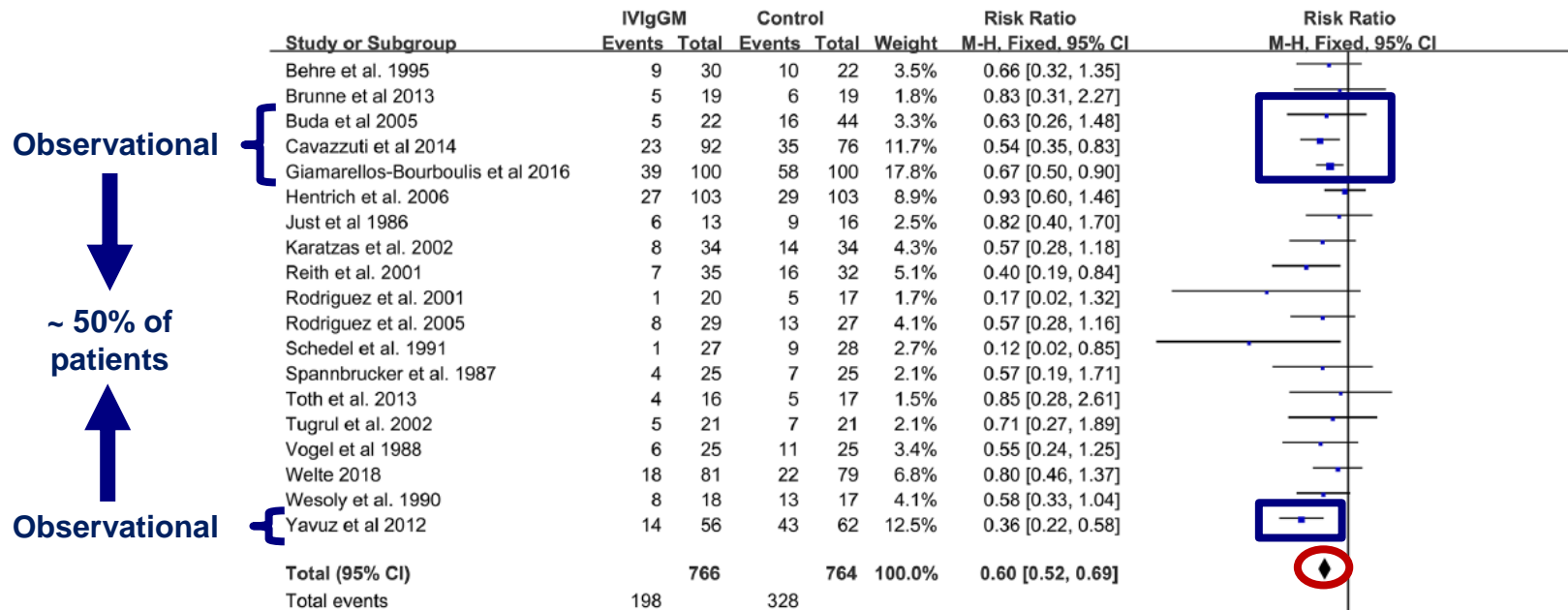


Alleged mechanisms of action of Ig in sepsis



The clinical efficacy of intravenous IgM-enriched immunoglobulin (pentaglobin) in sepsis or septic shock: a meta-analysis with trial sequential analysis

Jie Cui^{1††}, Xuxia Wei^{3††}, Haijin Lv^{3††}, Yuntao Li⁵, Ping Li⁶, Zhen Chen^{4*} and Genglong Liu^{2*}



Observational

~ 50% of patients

Observational



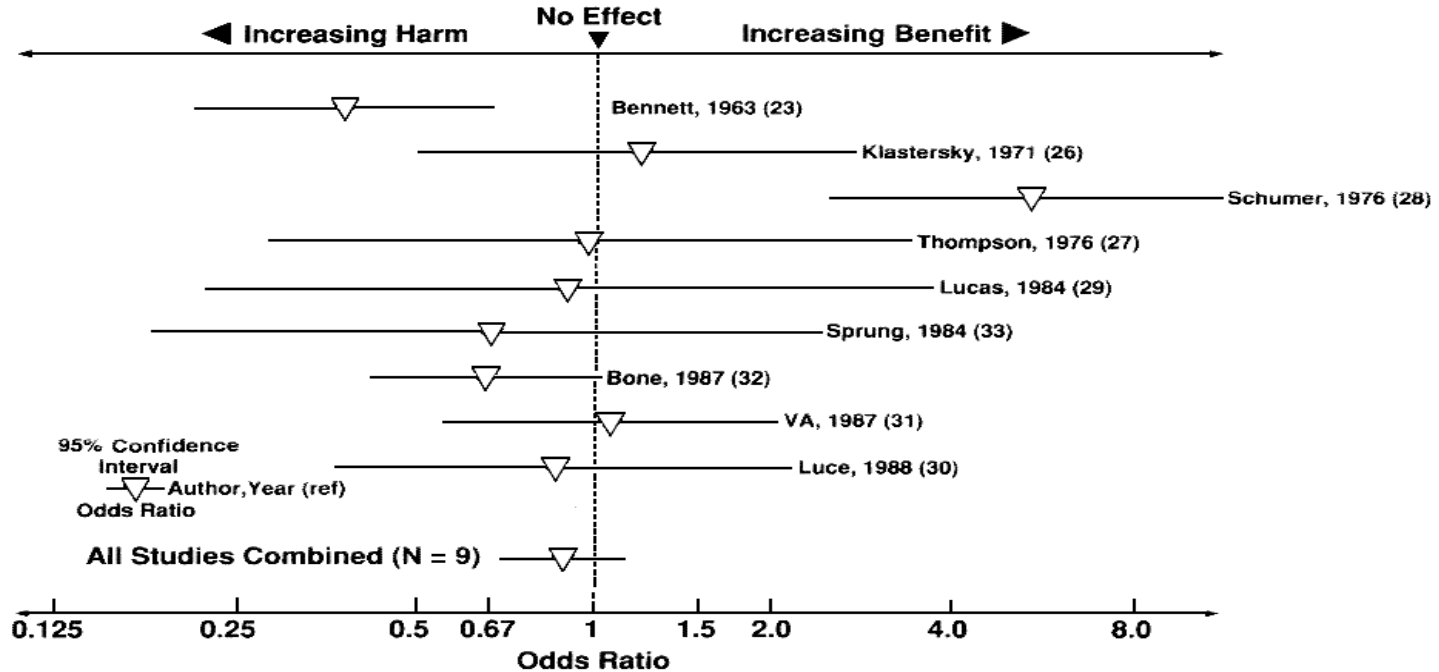
LOW

62

For adults with sepsis or septic shock we **suggest against** using intravenous immunoglobulins

Surviving Sepsis Campaign 2021

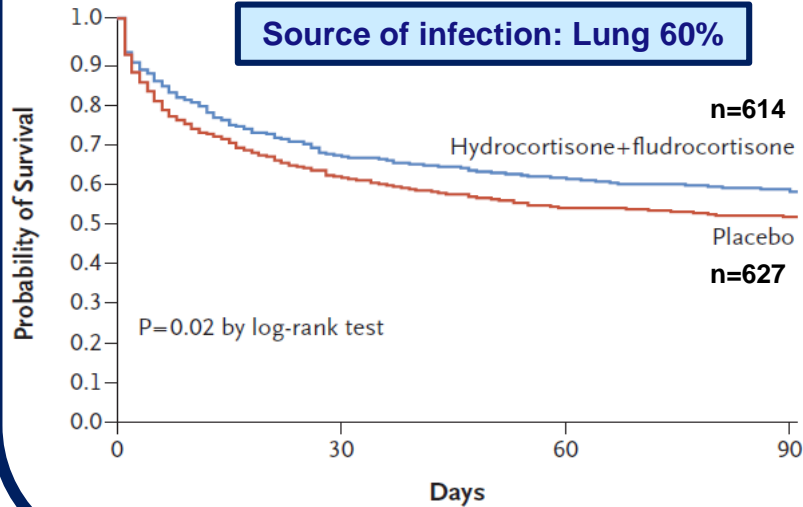
High-dose steroids in septic shock



Low-dose corticosteroids, winner by points

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

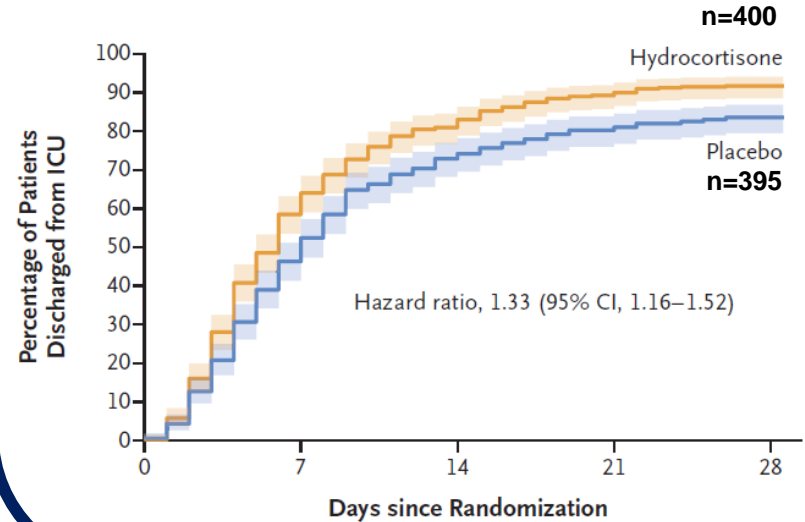
D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J.-P. Quenot, S. Siami,



Annane, NEJM 2018

Hydrocortisone in Severe Community-Acquired Pneumonia

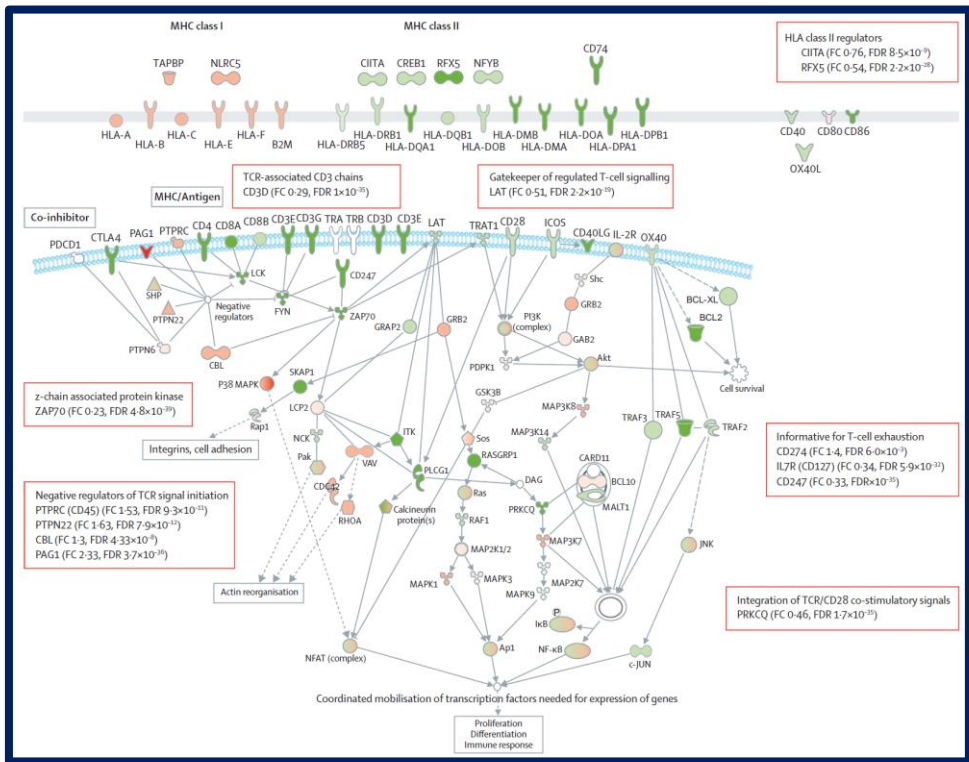
P.-F. Dequin, F. Meziani, J.-P. Quenot, T. Kamel, J.-D. Ricard, J. Badie, J. Reignier,



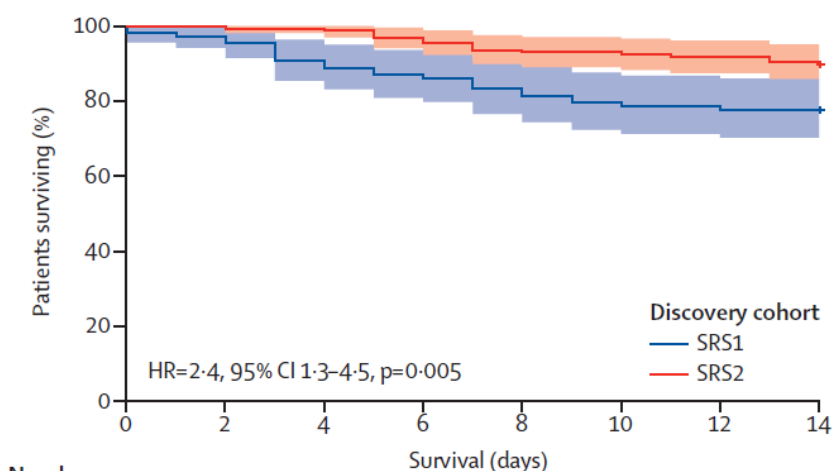
Dequin, NEJM 2023

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

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

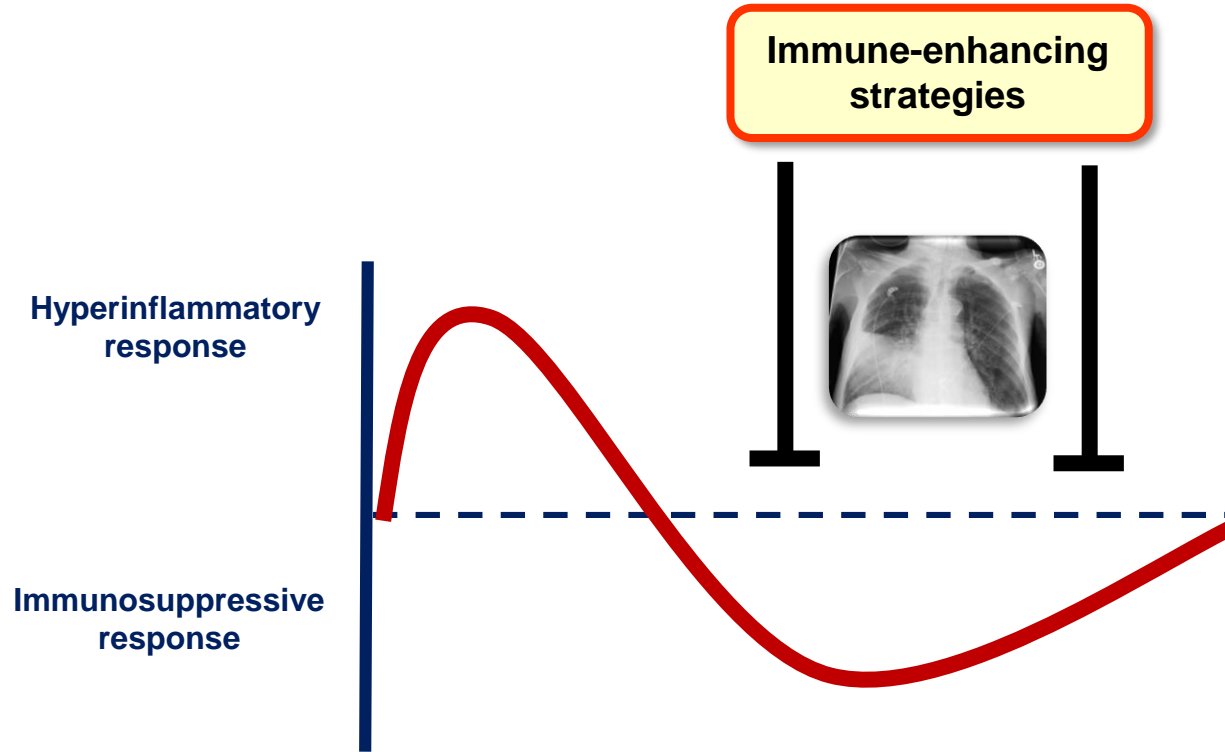


Immunosuppressed SRS1
Endotoxin tolerance
T-cell exhaustion
Dowregulation of MHCII



Number at risk	0	2	4	6	8	10	12	14
SRS1	106	103	96	93	88	85	84	84
SRS2	157	156	155	150	146	145	144	141

When and how to treat ?



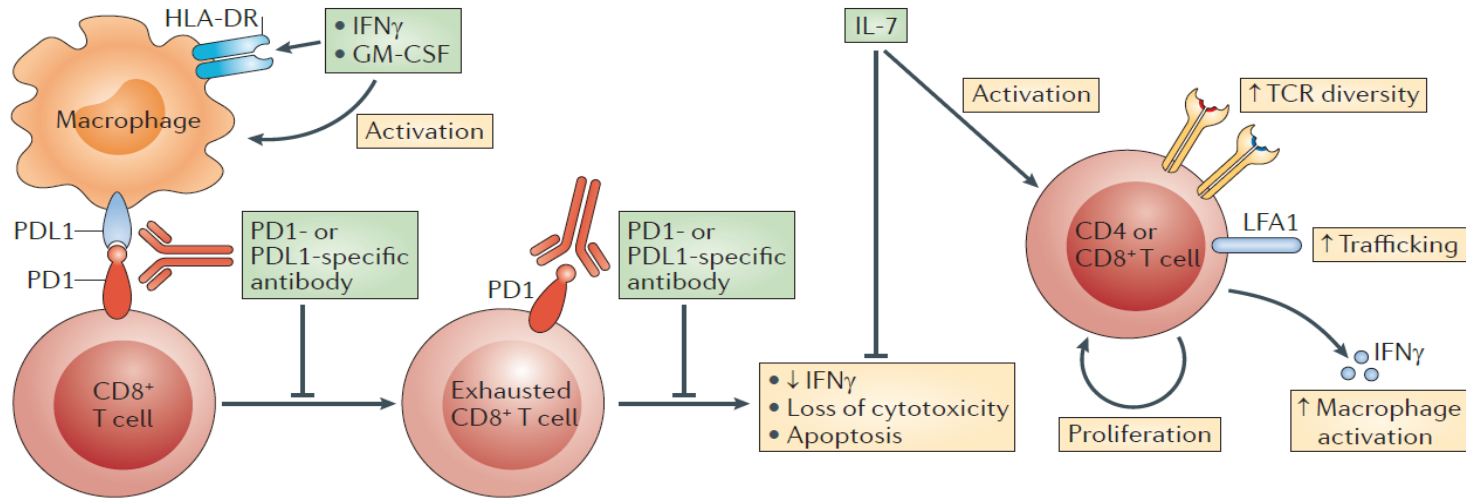
Immuno-inflammatory Response in Sepsis



Patient population	Healthy, young or middle-aged	Elderly (immunosenescence), malnourished, comorbidities (e.g. chronic renal or liver failure, cancer)
Pathogen characteristics	Often virulent, toxin-producing, (<i>N. meningitidis</i> , <i>S. pyogenes</i> , <i>S. aureus</i>), pneumococcal sepsis in asplenic hosts	May be weakly virulent or opportunistic (<i>Acinetobacter</i> , <i>Stenotrophomonas</i> , <i>Enterococcus</i> , fungi)
Clinical presentation	High fever, shock, vascular leak, ARDS, hypercatabolism, community acquired infection	More blunted response with subtle findings: altered mental status, hypothermia, nosocomial infections
Laboratory findings	Marked increase or dramatic fall in absolute granulocyte count, severe lactic acidosis	Low absolute lymphocyte count persisting beyond 3-4 days

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss¹, Guillaume Monneret² and Didier Payen³





A stratification strategy to predict secondary infection in critical illness-induced immune dysfunction: the REALIST score

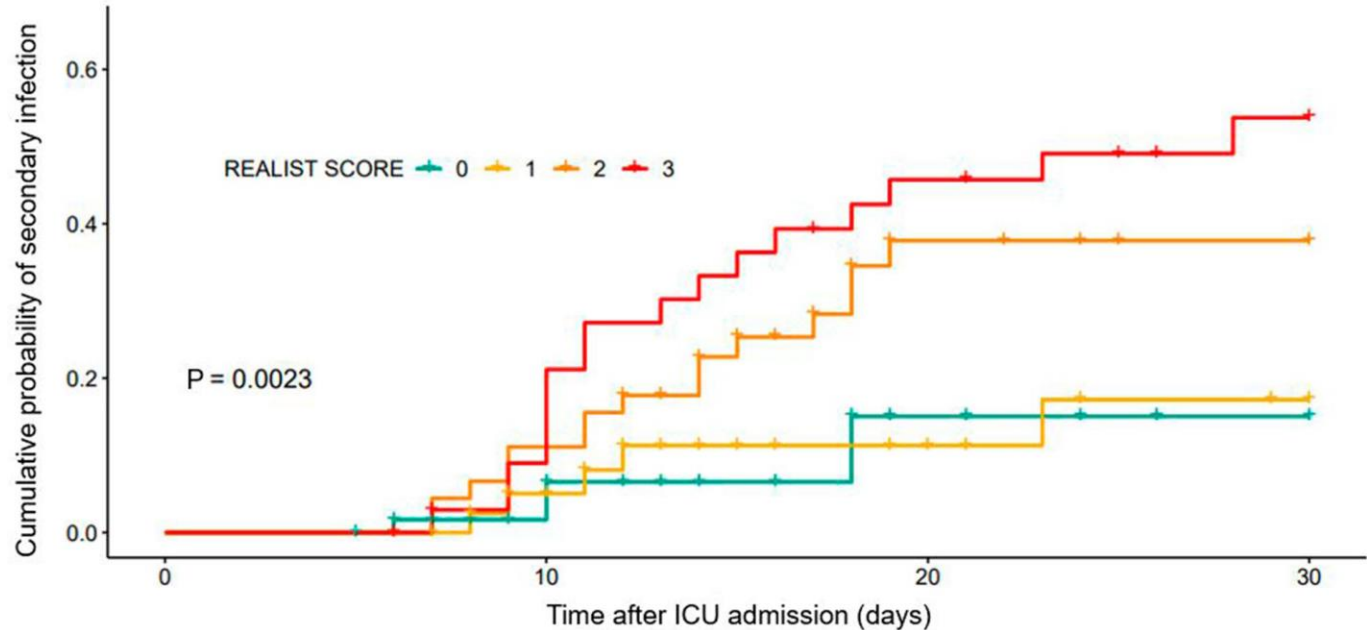
Jan-Alexis Tremblay^{1,2*}, Florian Peron¹, Louis Kreitmann¹, Julien Textoris¹, Karen Brengel-Pesce¹, Anne-Claire Lukaszewicz^{1,3}, Laurence Quemeneur⁴, Christophe Vadrine⁵, Lionel K. Tan⁶, Fabienne Venet^{7,8}, Thomas Rimmelé^{1,3}, Guillaume Monneret^{1,7} and the REALISM study group

Three immune parameters measured at day 5-7

mHLA-DR ≤ 7627 Ab/cell

Immature neutrophils $\geq 23.5\%$

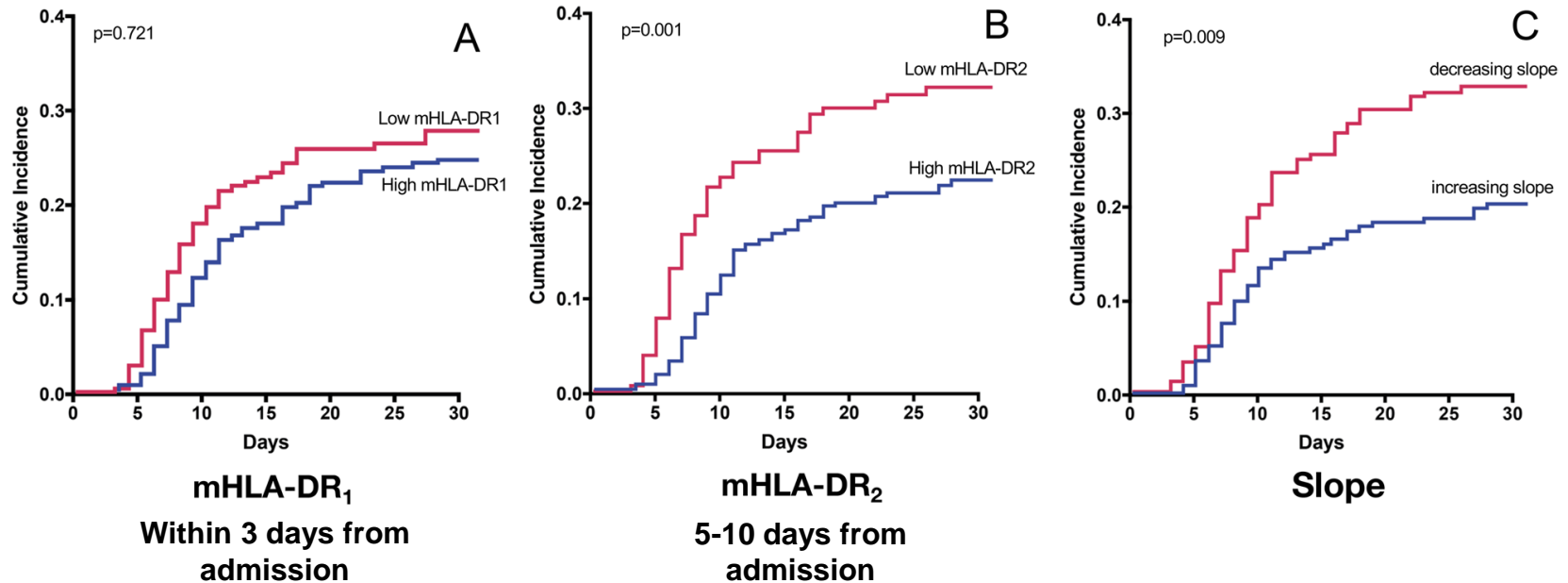
IL-10 ≥ 8.5 pg/mL



Monitoring of circulating monocyte HLA-DR expression in a large cohort of intensive care patients: relation with secondary infections

C. de Roquetaillade^{1,7*†}, C. Dupuis², V. Faivre³, A. C. Lukaszewicz⁴, C. Brumpt⁵ and D. Payen^{6†}

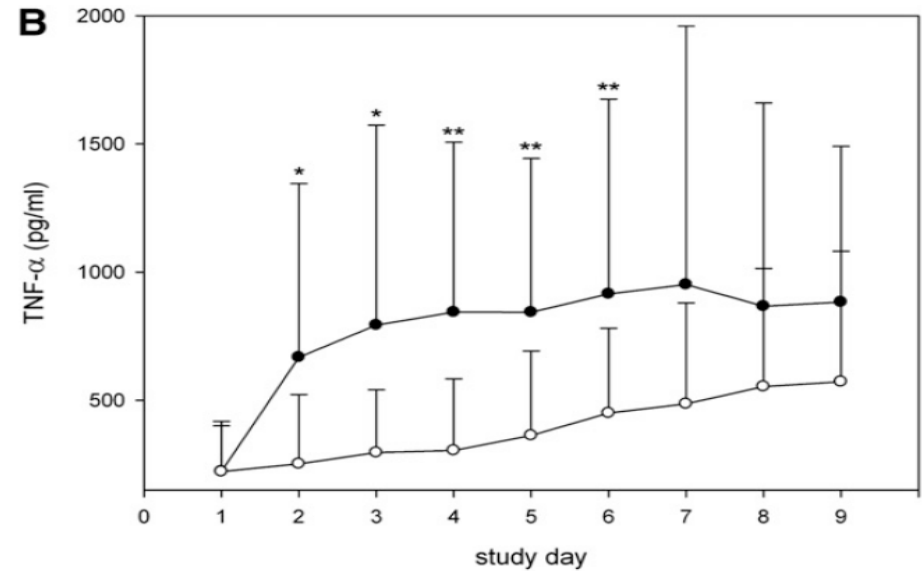
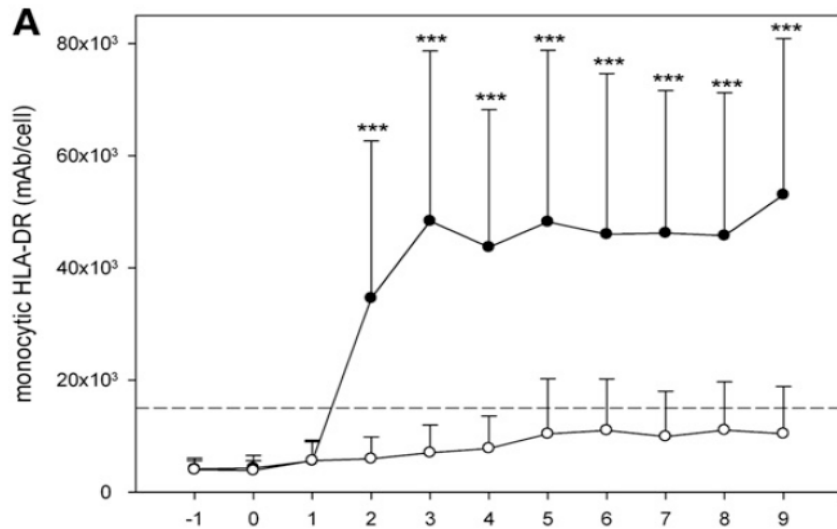
Incidence in ICU-acquired infections



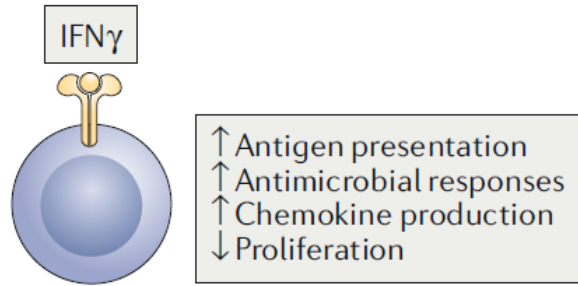
Granulocyte–Macrophage Colony-stimulating Factor to Reverse Sepsis-associated Immunosuppression

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

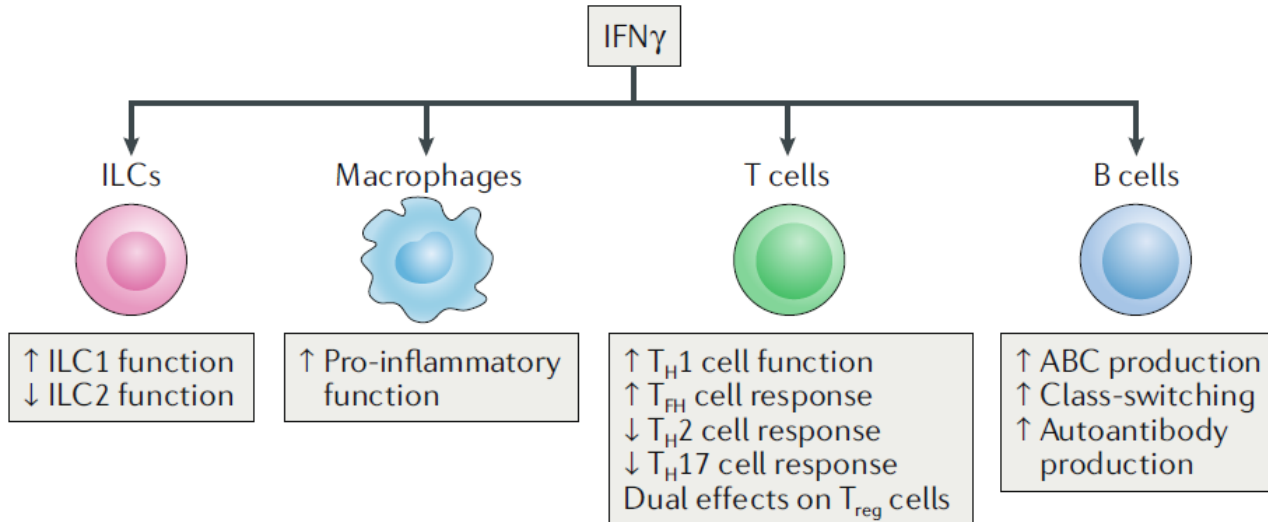
Christian Meisel^{1*}, Joerg C. Schefold^{2*}, Rene Psochowski², Tycho Baumann¹, Katrin Hetzger¹, Jan Gregor³, Steffen Weber-Carstens⁴, Dietrich Hasper², Didier Keh⁴, Heidrun Zuckermann³, Petra Reinke^{2,5}, and Hans-Dieter Volk^{1,5}



Characteristics	GM-CSF Group (n = 19)	Placebo Group (n = 19)	P Value
Age, years	64.0 ± 13.6	63.3 ± 14.2	NS*
Sex, male (%)	16/19 (84)	15/19 (79)	NS†
Body mass index	27.4 ± 6.3	26.5 ± 4.8	NS*
Septic shock at baseline (%)	11/19 (58)	10/19 (53)	NS†
Major source of sepsis at baseline (%)			
Pneumonia	11/19 (58)	10/19 (52)	NS†
Peritonitis	6/19 (32)	5/19 (26)	NS†
Other	2/19 (11)	4/19 (21)	NS†
Mortality rate at study Day 28 (%)	3/19 (16)	4/19 (21)	NS†
Days on ICU until study inclusion	6.0 ± 3.3	8.47 ± 8.9	NS*
Length of ICU stay, days	40.9 ± 26.1	52.1 ± 39.6	NS*
Total intrahospital stay, days	58.8 ± 32.6	68.9 ± 45.6	NS*
Need for RRT			
ARF at baseline (%)	12/19 (63)	11/19 (58)	NS†
Days on RRT	14.4 ± 10.2	11.5 ± 10.2	NS*
Time on ventilator, Days 1–9, hours	147.9 ± 102.8	207.2 ± 57.5	0.037*



Immune cells



Monocyte deactivation in septic patients: Restoration by IFN- γ treatment

NATURE MEDICINE • VOLUME 3 • NUMBER 6 • JUNE 1997

WOLF-DIETRICH DÖCKE¹, FELIX RANDOW¹, UTA SYRBE¹, DIETMAR KRAUSCH², KHUSRU ASADULLAH¹, PETRA REINKE³, HANS-DIETER VOLK¹, WOLFGANG KOX²

Interferon Gamma-1b in the Treatment of Compensatory Anti-inflammatory Response Syndrome

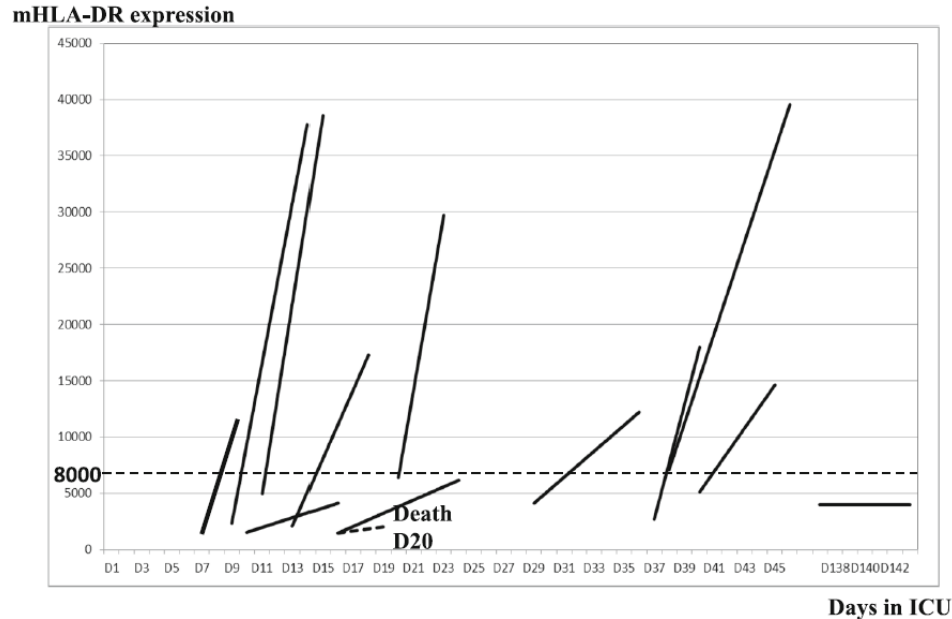
A New Approach: Proof of Principle

Wolfgang J. Kox, MD, PhD; Roger C. Bone, MD; Dietmar Krausch, MD; Wolf-Dietrich Döcke, MD; S. Nilden Kox, PhD; Helmar Wauer, MD; Karl Egerer, MD; Susanne Querner, PhD; Khusru Asadullah, MD; Rüdiger von Baehr, MD; Hans-Dieter Volk, MD

Arch Intern Med. 1997;157:389-393

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 Leentjens⁵, Caren Brumpt⁶, Pierre Tissières^{3,4}, Claire Dupuis¹, Peter Pickkers^{7,1} and Anne Claire Lukaszewicz^{1,2†}



17 patients

**Uncontrolled / ICU-
acquired infection**

mHLA-DR < 8000 Ab/cell

**9-134 days post ICU
admission**

3-5 days of treatment

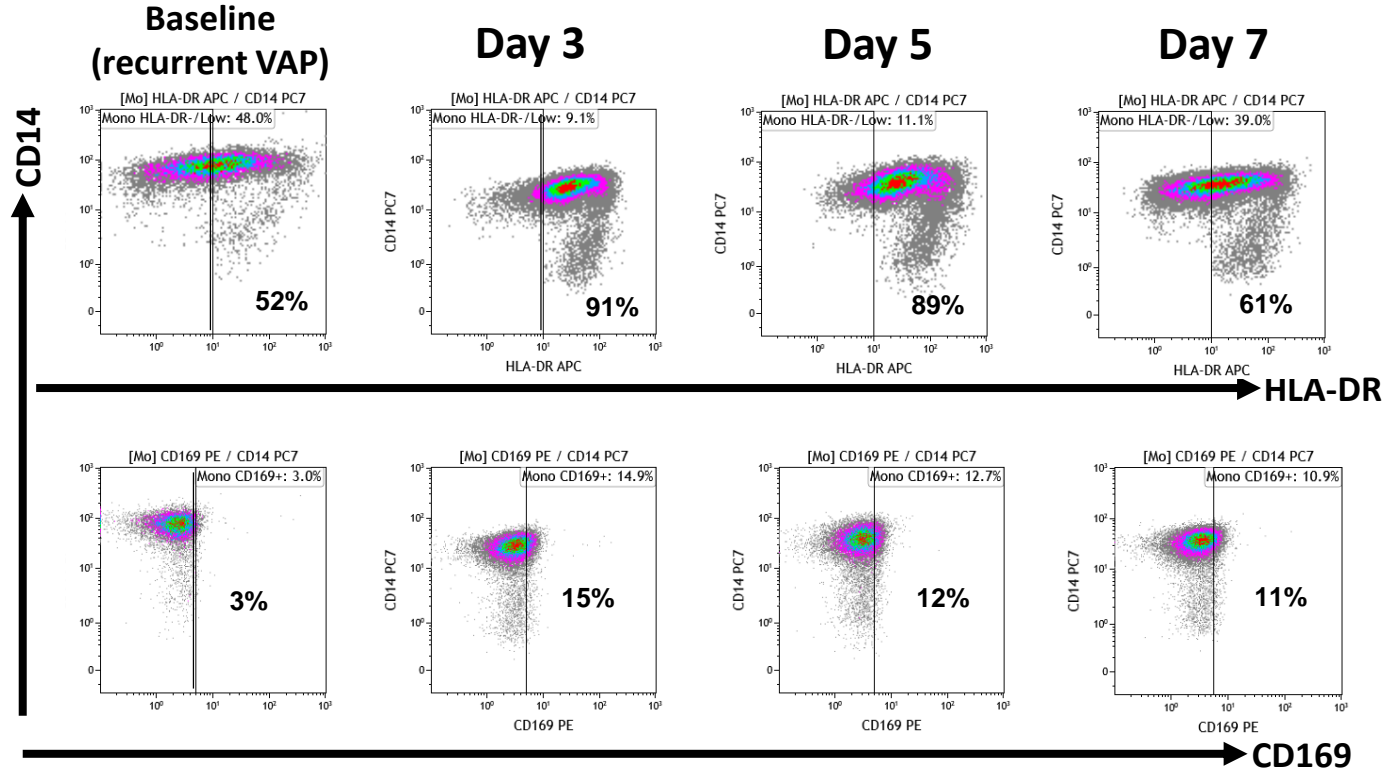
49 y.o. patient
ARDS COVID19

Prolonged mechanical
ventilation (day 25)

3rd episode of Gram-
negative ventilator-
acquired pneumonia
(VAP)

Clinical failure

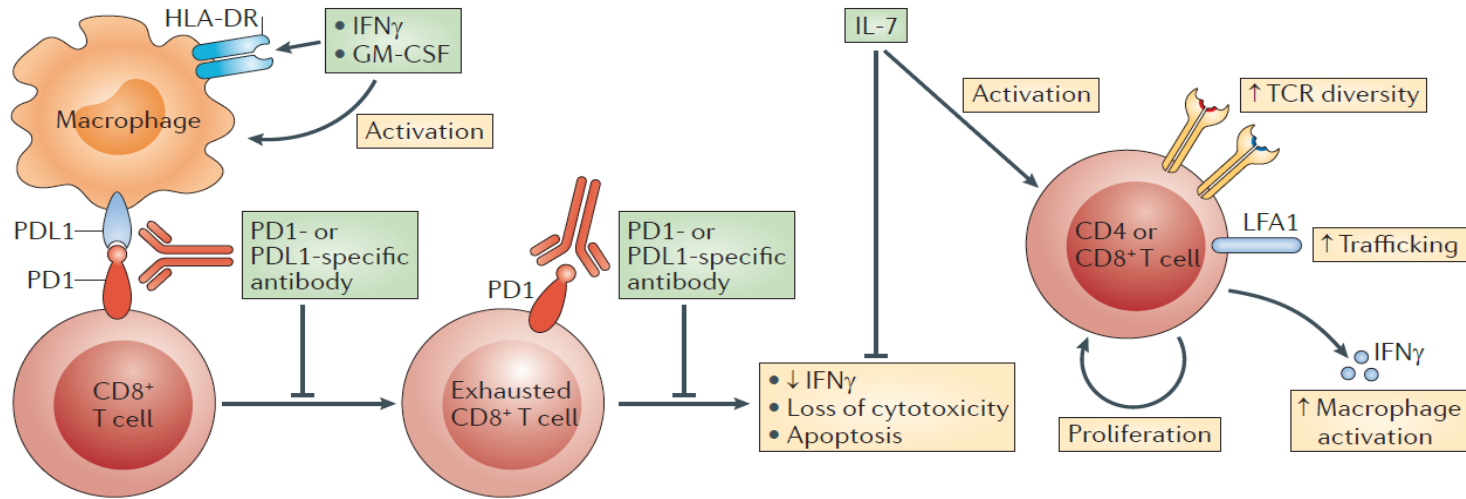
Adjuvant treatment?



5-day treatment with IFN γ (100 μ g/d)

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss¹, Guillaume Monneret² and Didier Payen³

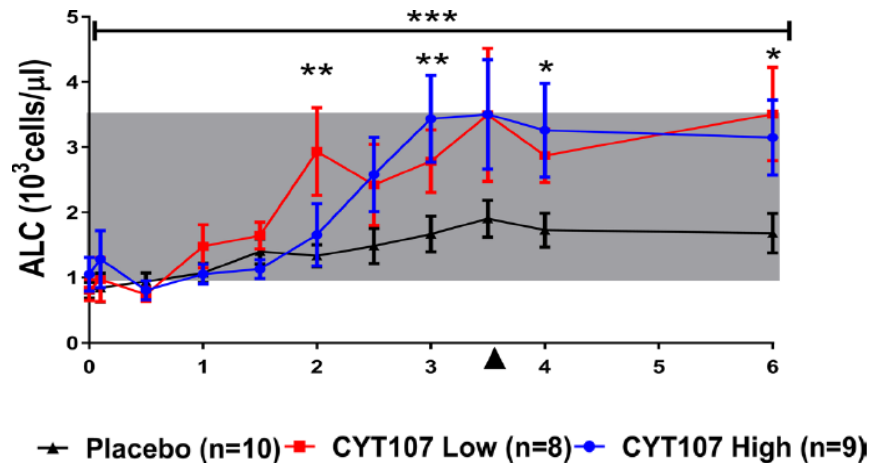


Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial

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

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

Absolute lymphocyte count

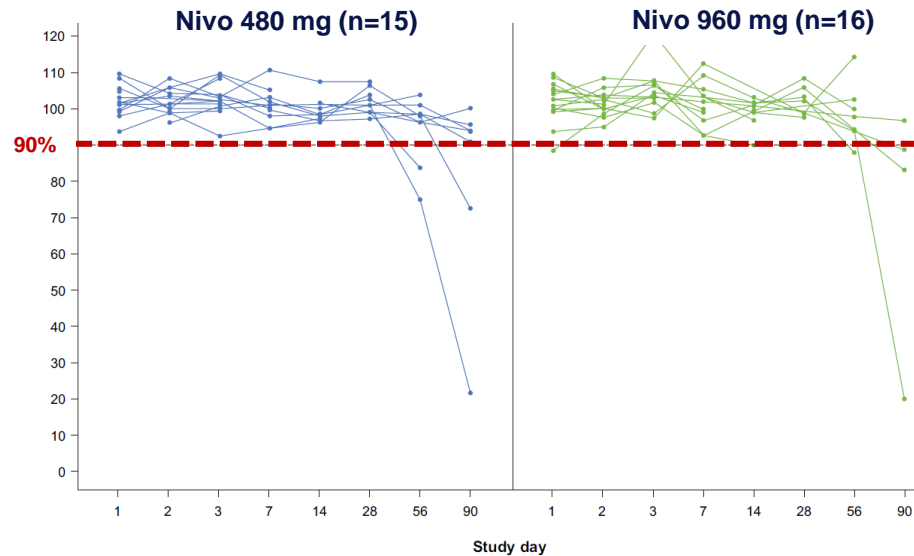


Immune checkpoint inhibition in sepsis: a Phase 1b randomized study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of nivolumab

Richard S. Hotchkiss^{1*}, Elizabeth Colston², Sachin Yende^{3,4}, Elliott D. Crouser⁵, Greg S. Martin⁶, Timothy Albertson^{7,8}, Raquel R. Bartz⁹, Scott C. Brakenridge¹⁰, Matthew J. Delano¹¹, Pauline K. Park¹¹, Michael W. Donnino¹², Mark Tidswell¹³, Florian B. Mayr^{3,4}, Derek C. Angus⁴, Craig M. Coopersmith¹⁴, Lyle L. Moldawer¹⁰, Ian M. Catlett², Ihab G. Girgis², June Ye² and Dennis M. Grasela²

Intensive Care Med (2019) 45:1360–1371

Receptor occupancy





David Grimaldi, Olivier Pradier,
Richard S Hotchkiss,
*Jean-Louis Vincent

Nivolumab plus interferon- γ in the treatment of intractable mucormycosis

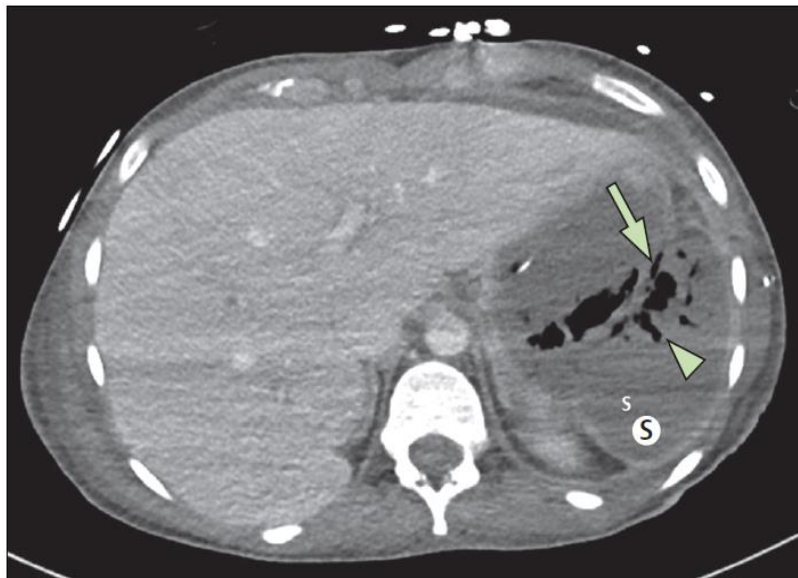
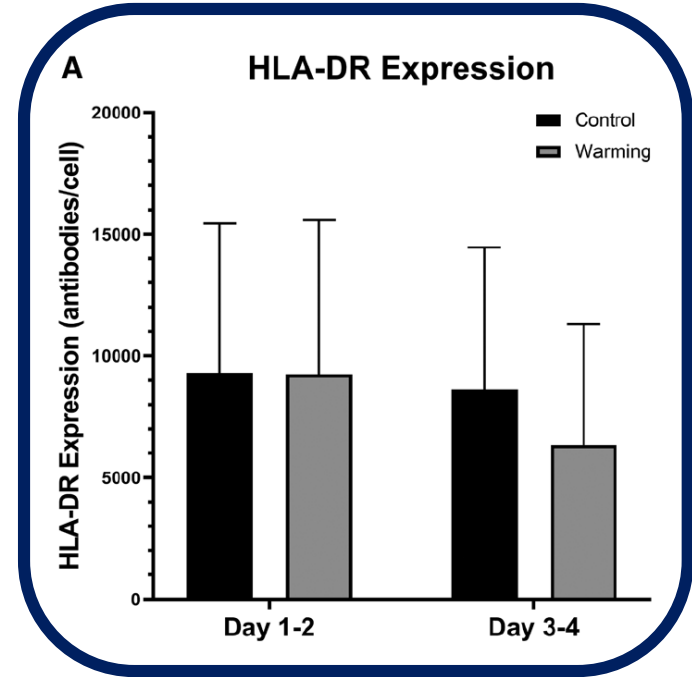
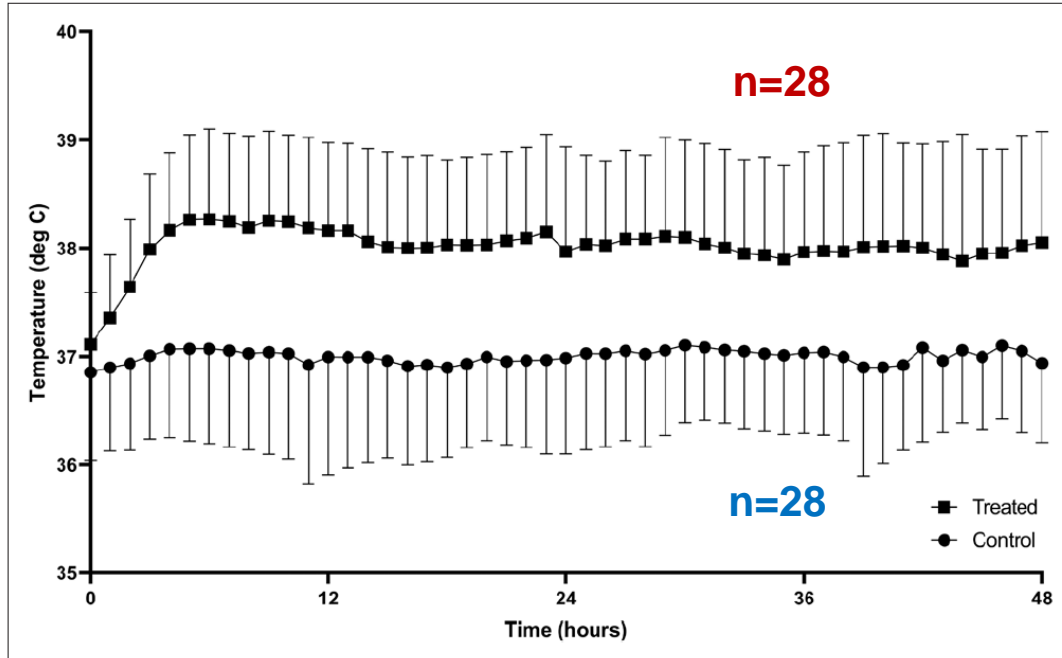


Figure: Abdominal CT scan

CT scan with contrast, showing a lack of enhancement of splenic parenchyma (S), gas in the splenic parenchyma (arrowhead), and gastric intramural gas (arrow).

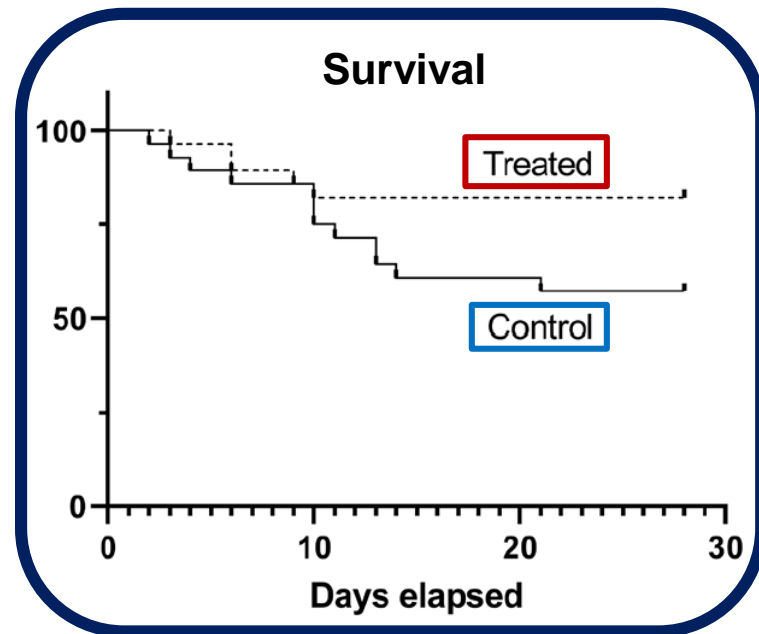
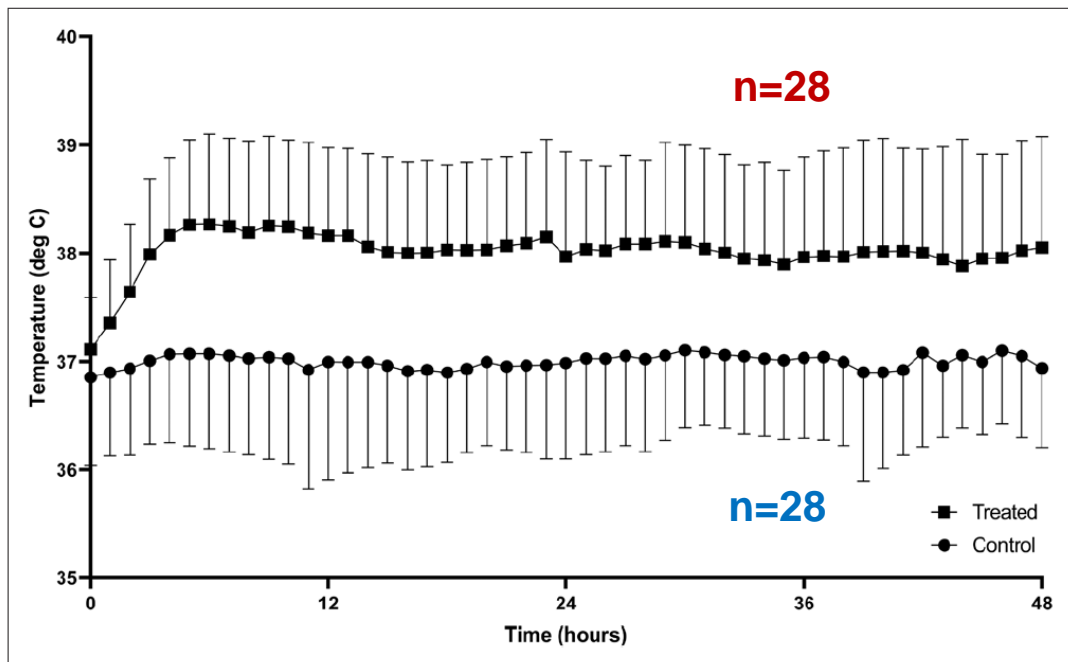
Therapeutic Hyperthermia Is Associated With Improved Survival in Afebrile Critically Ill Patients With Sepsis: A Pilot Randomized Trial

Drewry, Crit Care Med 2022



Therapeutic Hyperthermia Is Associated With Improved Survival in Afebrile Critically Ill Patients With Sepsis: A Pilot Randomized Trial

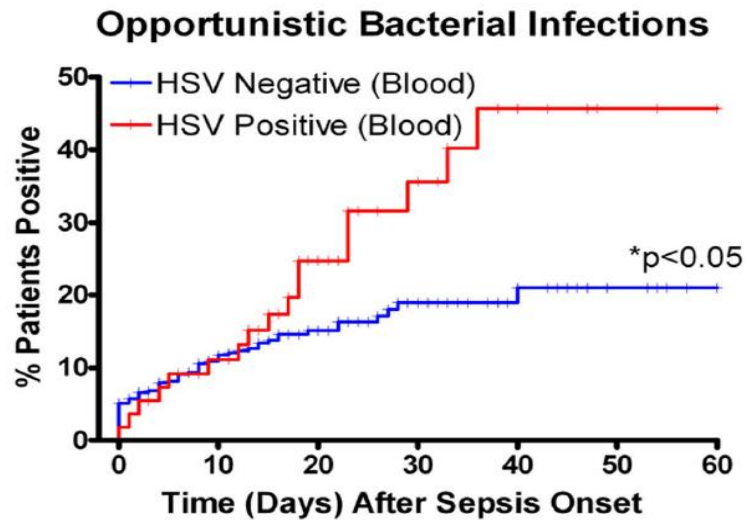
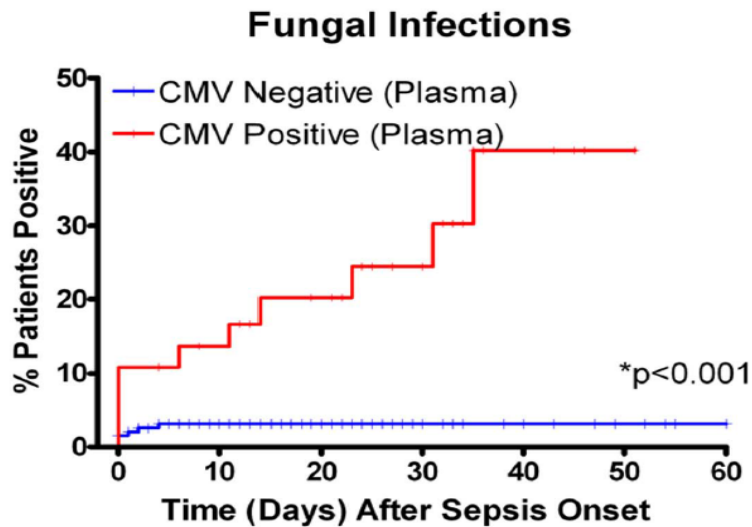
Drewry, Crit Care Med 2022




30-day ICU-acquired infections
9 vs 8 episodes

Reactivation of Multiple Viruses in Patients with Sepsis

Andrew H. Walton¹, Jared T. Muenzer², David Rasche¹, Jonathan S. Boomer³, Bryan Sato⁴, Bernard H. Brownstein¹, Alexandre Pachot⁵, Terrence L. Brooks³, Elena Deych³, William D. Shannon³, Jonathan M. Green³, Gregory A. Storch², Richard S. Hotchkiss^{1*}



Preemptive ganciclovir for mechanically ventilated patients with cytomegalovirus reactivation

Laurent Papazian^{1*}, Samir Jaber², Sami Hraiech¹, Karine Baumstarck³, Sophie Cayot-Constantin⁴,

Parameters	Placebo group (N = 37)	Ganciclovir group (N = 39)	P Value
Primary outcome			
Ventilator-free days on day 60	0 (0–43)	10 (0–51)	0.459
Secondary outcomes (post-randomization)			
Day-60 mortality, no. (%)	16 (43.2)	16 (41.0)	0.845
Duration of MV	20 (7–40)	12 (6–29)	0.246
ICU length of stay (from admission)	44.0 (21.0–66.5)	36.0 (24.0–51.0)	0.377
ICU length of stay (from randomization)	26.0 (11.0–50.0)	17.0 (8.0–34.0)	0.318
Hospitalization length (from admission)	60.0 (33.0–75.5)	65.0 (28.0–78.0)	0.988
Hospitalization length (from randomization)	42.0 (18.5–60.0)	38.0 (13.0–60.0)	0.945
HSV bronchopneumonitis, no. (%)	1 (2.7)	0 (0)	0.487
Cytomegalovirus infection, no. (%)	5 (13.5)	1 (2.6)	0.103
Ventilator-associated pneumonia, no. (%)	15 (40.5)	13 (33.3)	0.515
Secondary bacteremia or fungemia, no. (%)	8 (21.6)	7 (17.9)	0.688

Acyclovir for Mechanically Ventilated Patients With Herpes Simplex Virus Oropharyngeal Reactivation A Randomized Clinical Trial

Charles-Edouard Luyt, MD, PhD; Jean-Marie Forel, MD, PhD; David Hajage, MD, PhD; Samir Jaber, MD, PhD;

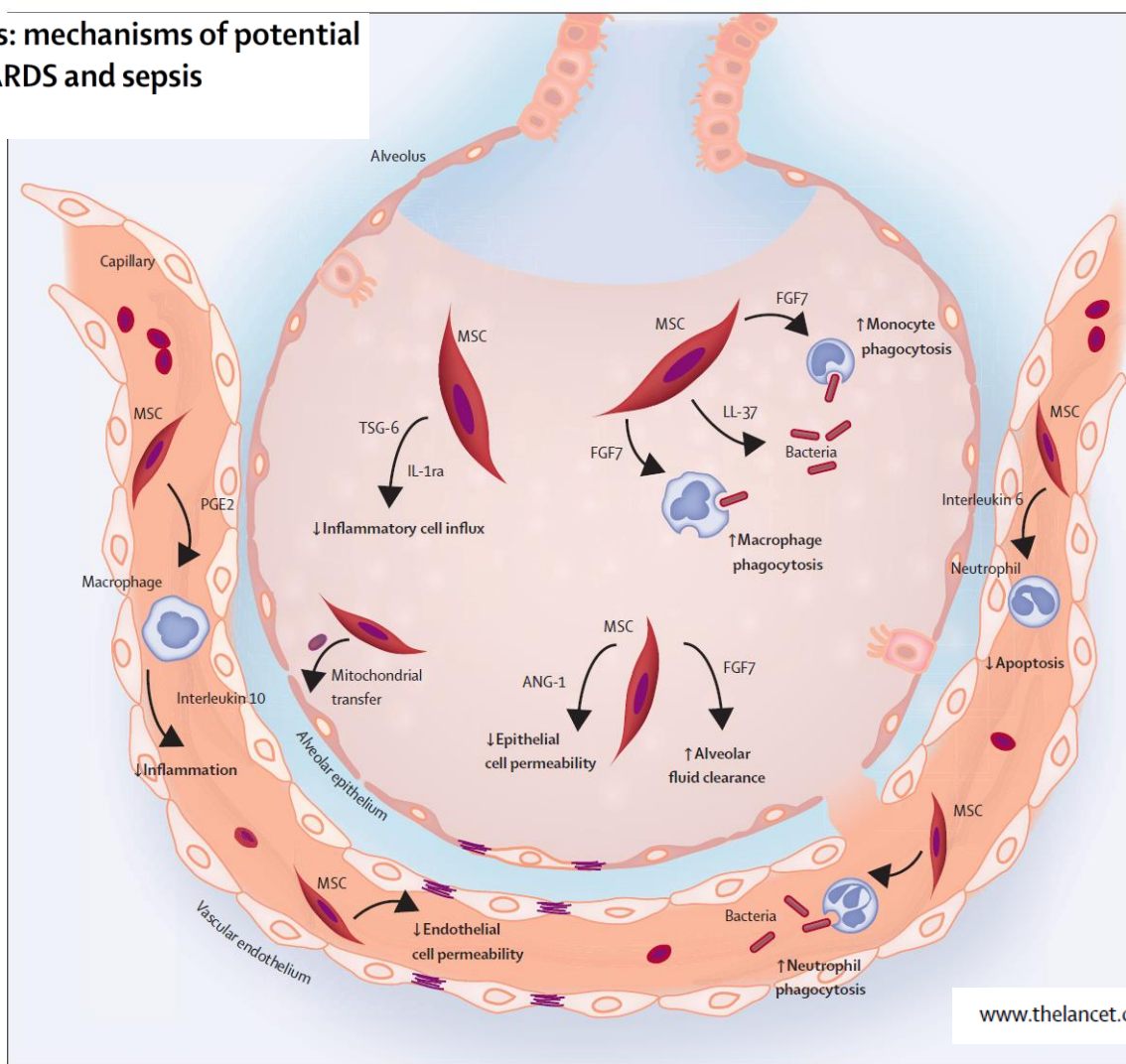
Parameter	Study Group		P Value
	Acyclovir (n = 119)	Placebo (n = 119)	
Primary outcome			
Ventilator-free days at day 60, median (IQR)	35 (0-53)	36 (0-50)	.17
Secondary outcomes post randomization			
Day 60 mortality, No. (%)	26 (22)	39 (33)	.06
Duration of MV, median (IQR)	17 (7-30)	13 (7-23)	.41
Probability of more favorable outcome, % ^a	50.78	40.48	.16
ICU length of stay, median (IQR)	20 (12-41)	17 (11-31)	.10
HSV bronchopneumonitis, No. (%)	1 (1)	4 (3)	.37
Cytomegalovirus infection, No. (%)	1 (1)	5 (4)	.21
Hospital-acquired bacterial pneumonia, No. (%)	58 (49)	53 (45)	.52
Secondary bacteremia or fungemia, No. (%)	29 (24)	27 (23)	.75

Ongoing and future studies of interest

Name	Number / recruiting	Country	Drug	Enrollment criteria	Main endpoints
GRID	466 / stopped	France	GM-CSF (5 days)	Sepsis mHLA-DR < 8000 AB/C	28-day ICU-acquired infection
PREV-HAP	200 / yes	France, Greece, Spain	IFN- γ (10 days)	Mechanically ventilated patients	28-day all cause mortality and/or hospital-acquired pneumonia
IGNORANT	132 / not yet	France	IFN- γ (5 days)	First episode of VAP mHLA-DR < 8000 AB/C	28-day ventilator-free days
INFINITY	180 / not yet	France	IFN- γ (3 days)	Mechanical ventilation SOFA admission \geq 6 mHLA-DR < 8000 AB/C	28-day ventilator-free days

Mesenchymal stem cells: mechanisms of potential therapeutic benefit in ARDS and sepsis

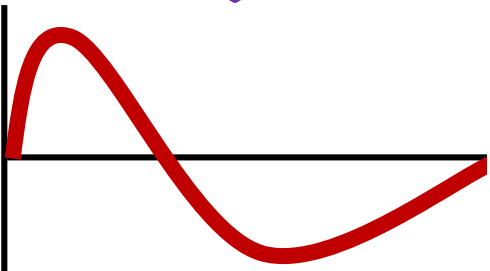
James Walter, Lorraine B Ware, Michael A Matthay



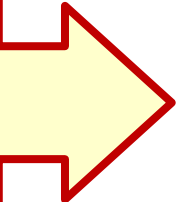
Immunotherapy in sepsis: where do we stand, where do we go?

- **Anti-inflammatory strategies: corticosteroids**
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Age
Underlying conditions



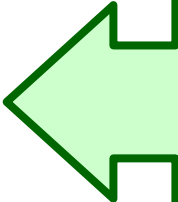
Organ failure supports
Steroids
Transfusions



Source of insult
Severity



HSV
?
CMV



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