27es JNI 2026 PARIS
et la région Île-de-France — Palais des Congrès
Journées Nationales d'infectiologie
du jeudi 18 juin au samedi 20 juin 2026
Journée Nationale de Formation des Paramédicaux en Infectiologie
Vendredi 19 juin 2026

Post-sepsis Immunosuppression

State of the art and clinical challenges

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Hôpital St-Antoine
Sorbonne Université

Déclaration d'intérêt de 2014 à 2025

- Intérêts financiers : none
- Liens durables ou permanents : none
- Interventions ponctuelles (consulting, symposium) : AOP pharma
- Intérêts indirects : none

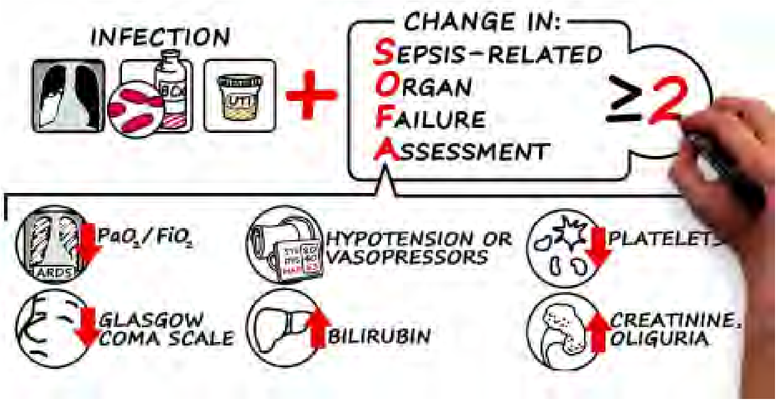
Aucun conflit d'intérêts réel ou potentiel en lien avec le contenu de cette présentation

Introduction

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

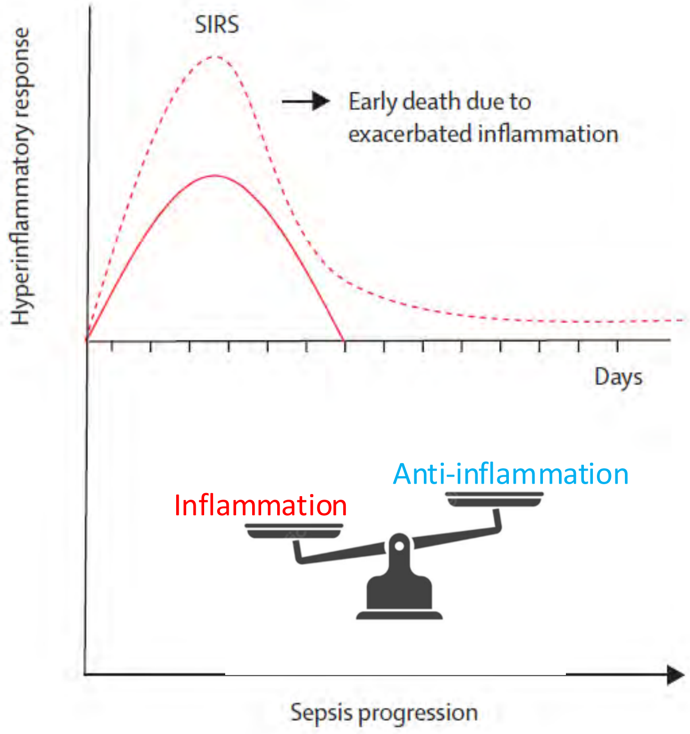
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Life-threatening organ dysfunction due to a *dysregulated host response* to infection



Singer, *JAMA*. 2016

"Old school" concept



Rubio, *Lancet Respir Med*. 2019

Introduction

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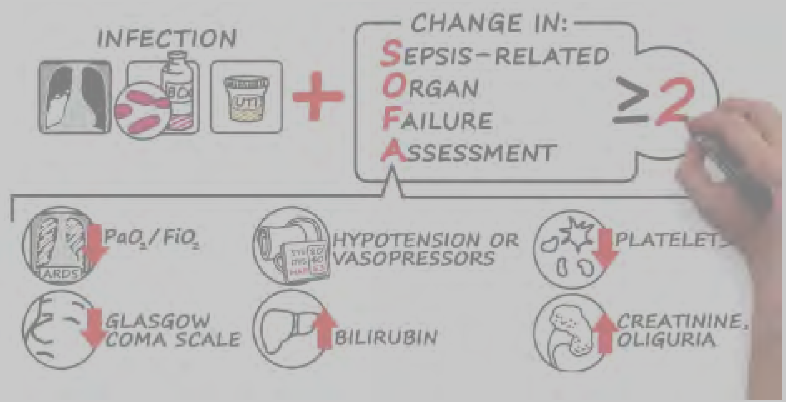
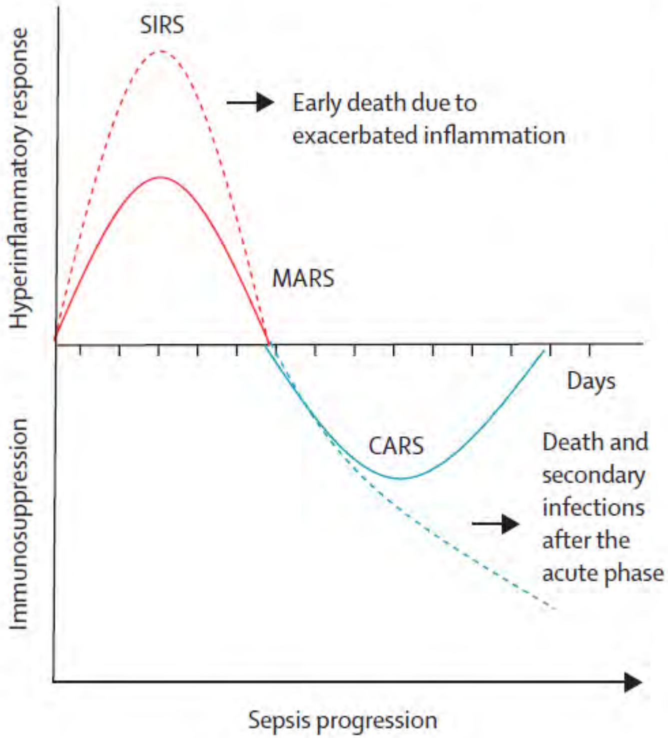


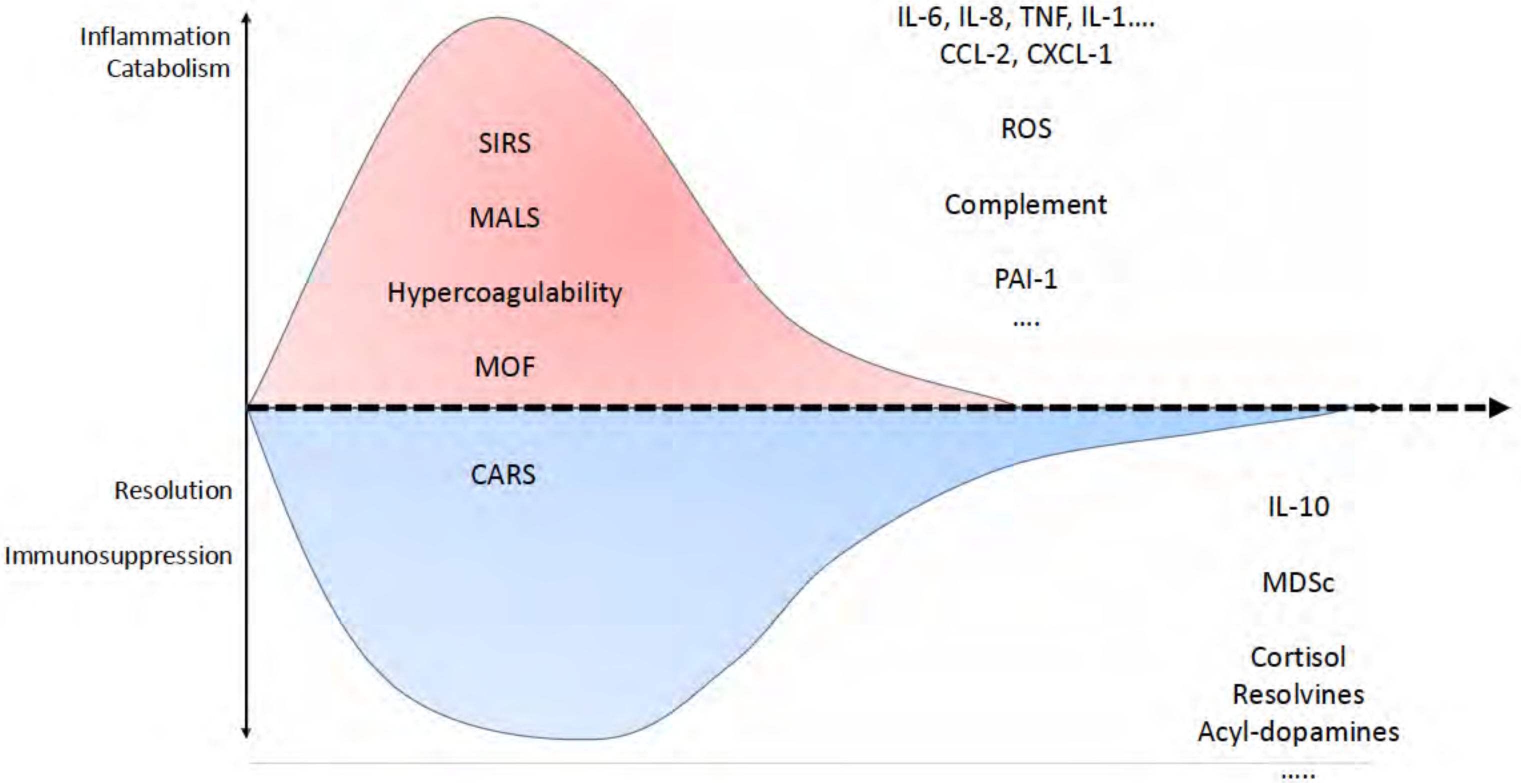
Singer, *JAMA*. 2016

2010 - 2015



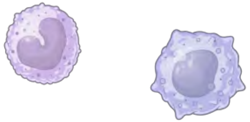
Rubio, *Lancet Respir Med.* 2019

« Modern » view of sepsis-associated dysregulated host response



Sepsis–induced immunosuppression: innate deficiency

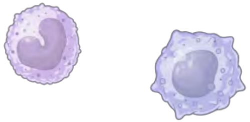
Innate


DCs	Monocytes / Macrophages	Neutrophils
↑ Apoptosis	Apoptosis → Mo-MDSCs	Apoptosis → Mo-MDSCs
↓ Ag presentation	↓ HLA-DR expression	↓ ROS / NOS
↓ Cytokines secretion	↓ Pro-infl. cytokines secretion	↓ Adhesion molecules
	↓ Pathogen killing	↑ Anti-infl. cytokines
	↑ Anti-infl. cytokines	

Adapted from Hotchkiss, *Nat. Rev. Immunol*. 2013

Innate immunosuppression: Mechanisms ?


Innate

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	↑ Anti-infl. cytokines	

Cell death

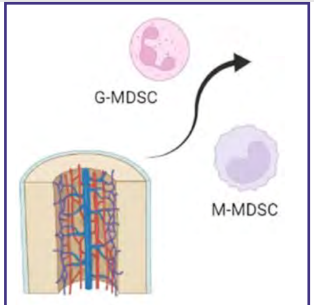
PAMPs
DAMPs
Activation-induced cell death (AICD)
Oxidative stress

Deactivation

IL-10
Resolvins
Neurolipids
Neuropeptids
….

MDSCs

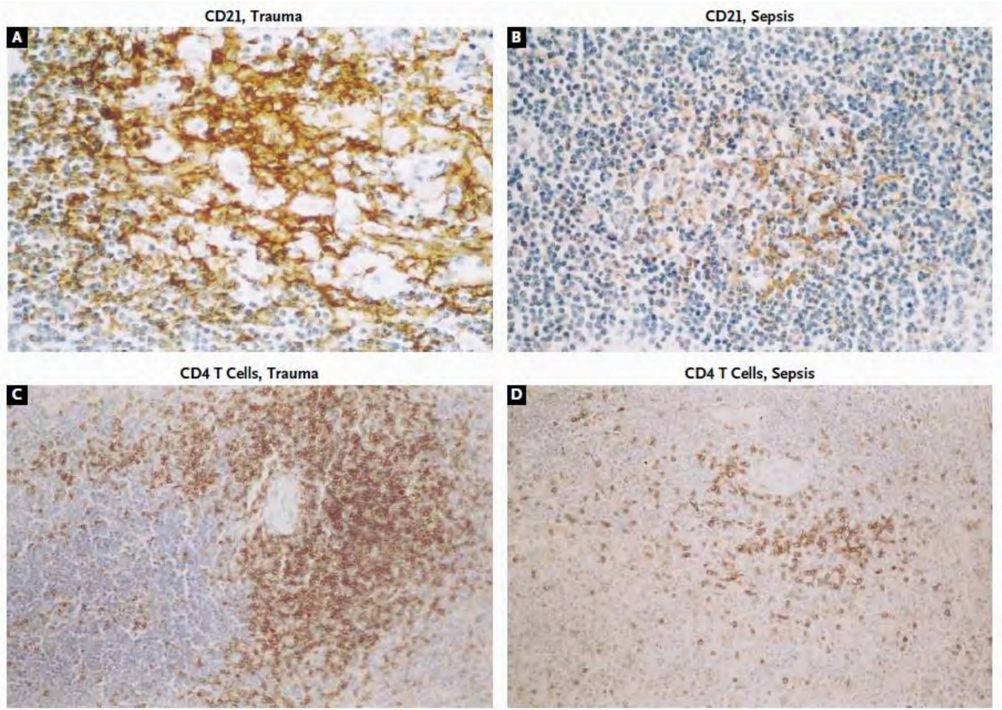
Emmergency myelopoiesis



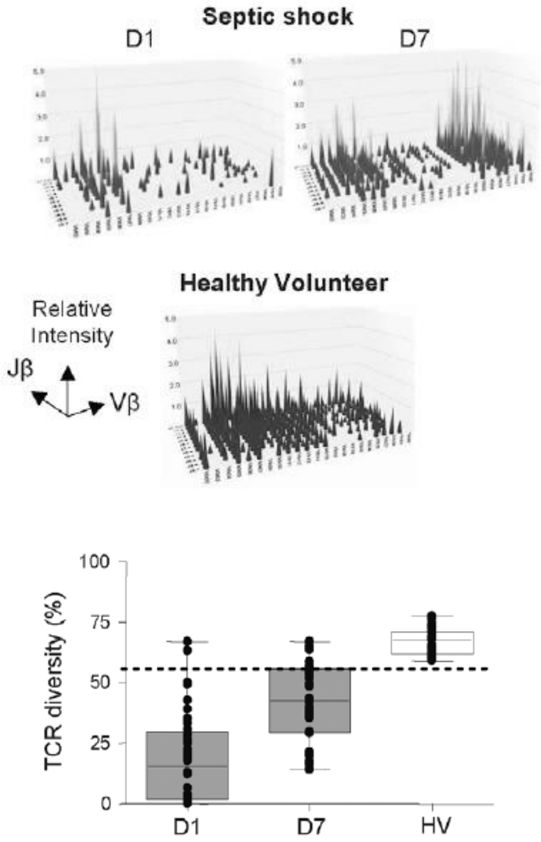
Extrinsic factors

Steroids?
Vasopressors?
…

Sepsis–induced immunosuppression: Lymphocyte deficiency



Hotchkiss, *NEJM*. 2003



Venet, *CCM*. 2003

Adaptive immunosuppression

Adaptive

CD4+ T cells	CD8+ T cells	T regs	B cells
↑ Apoptosis	↑ Apoptosis	↑ Resistance to apoptosis	↑ Apoptosis
↑ Th2 polarization	↓ Cytotoxic function	↑ Suppressive activities	↓ Ag specific Ab production
↓ Adhesion molecules	↓ Cytokines secretion		
↓ TCR diversity	↓ TCR diversity		
↓ CD28 expression			

Adapted from Hotchkiss, *Nat. Rev. Immunol*. 2013

Adaptive immunosuppression: Mechanisms?

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Cell death

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Oxidative stress

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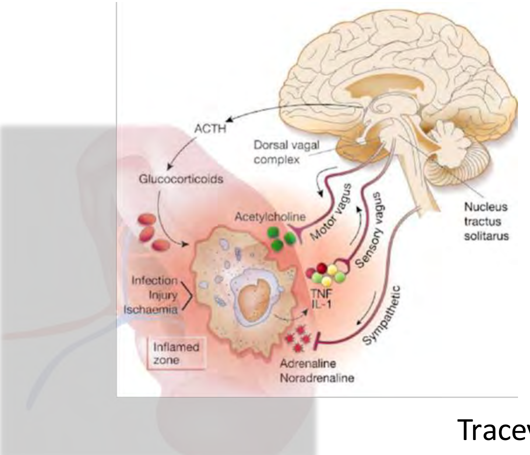
IL-10
Resolvins
....
Vago-splenic reflex



Tracey, *Nature.* 2002

Adaptive immunosuppression: Mechanisms?

Adaptive

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Cell death

PAMPs
DAMPs
Activation-induced cell death (AICD)
Oxidative stress

Deactivation

IL-10
Resolvins
....
Vago-splenic reflex

Tregs expansion

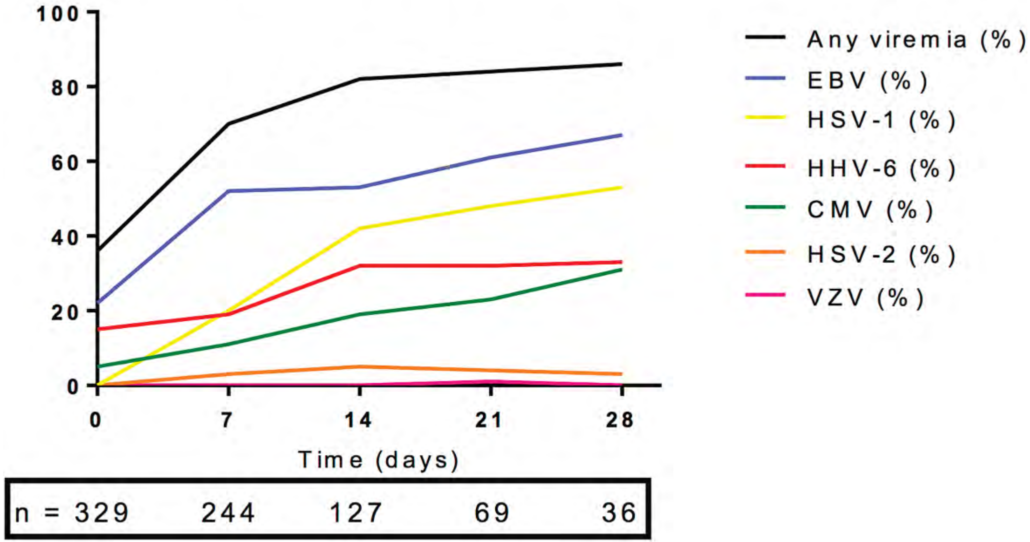
Suppressive activity

Extrinsic factors

Steroids?
Anti-IL-6?
....

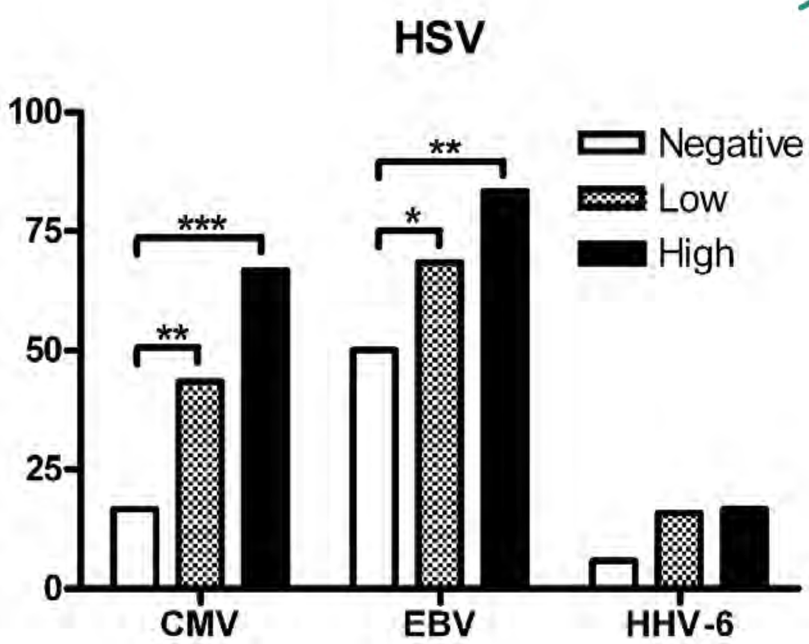
Adaptive immunosuppression => viral reactivation(s)

% of patients with viremia



Ong, *CID.* 2017

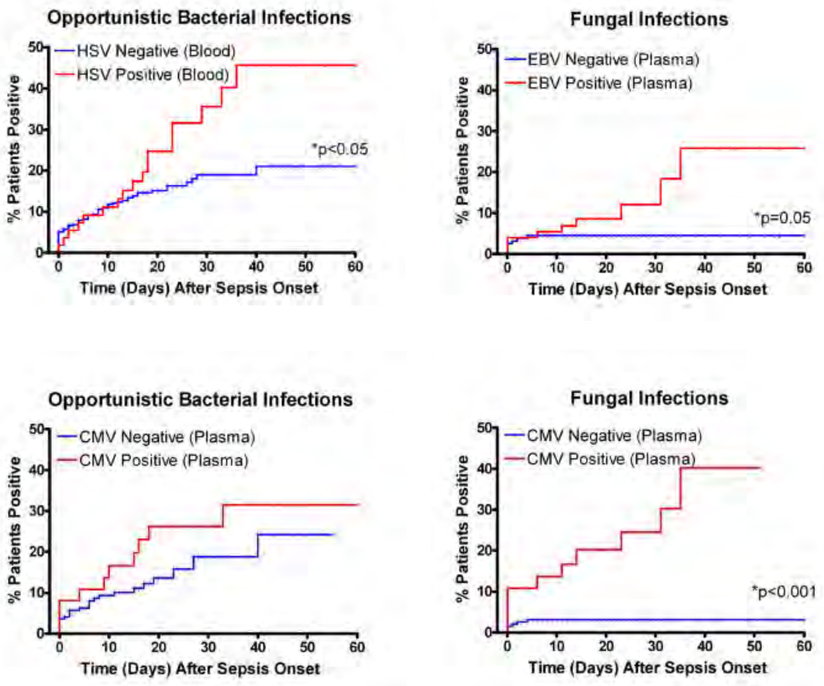
Adaptive immunosuppression => viral reactivation(s)



Walton, *Plos One.* 2014

Viral reactivation as markers of secondary infection and death

Viral reactivation and secondary infections



Walton, *Plos One.* 2014

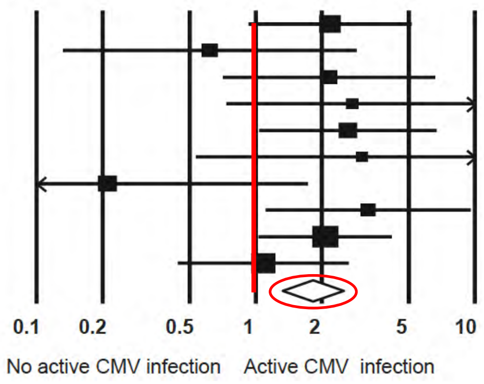
Viral reactivation and in-ICU mortality

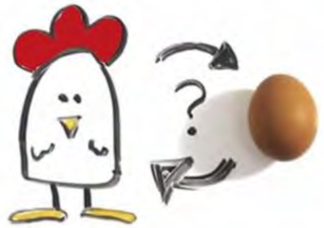
Active cytomegalovirus infection: all-cause mortality.

Study name	MHodds ratio	Lower limit	Upper limit
Domart Y 1990	2.18	0.93	5.13
Kutza A 1998	0.62	0.13	2.88
Heininger A 2001	2.16	0.71	6.58
Cook C 2003	2.76	0.74	10.35
Jaber S 2005	2.64	1.04	6.69
von Mueller L 2006	3.06	0.53	17.46
Limaye A 2008	0.21	0.03	1.72
Ziemann M 2008	3.26	1.11	9.54
Chiche L 2009	2.08	1.04	4.17
Heininger A 2011	1.08	0.44	2.65
	1.81	1.31	2.50

Statistics for each study

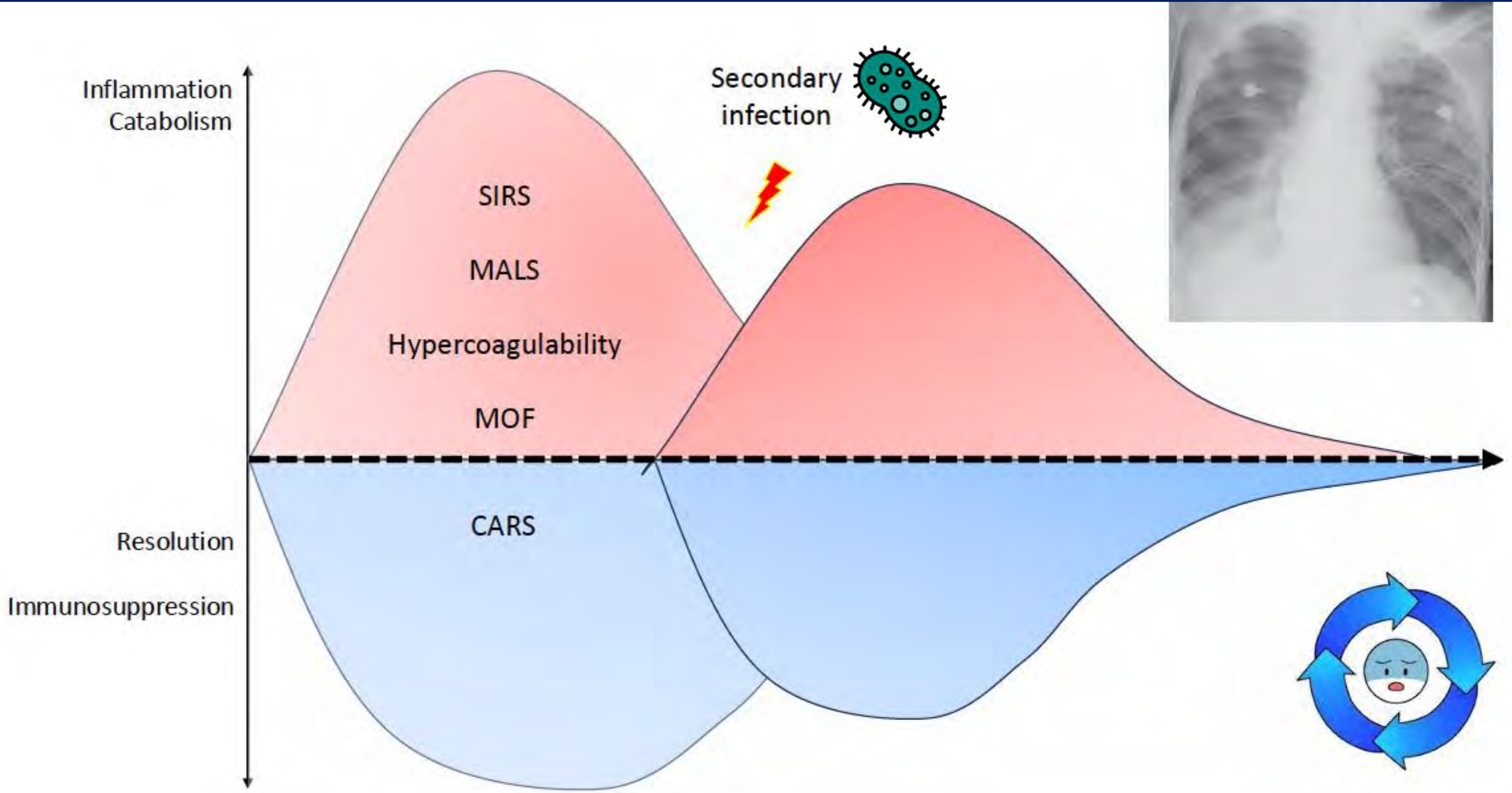
MH odds ratio and 95% CI



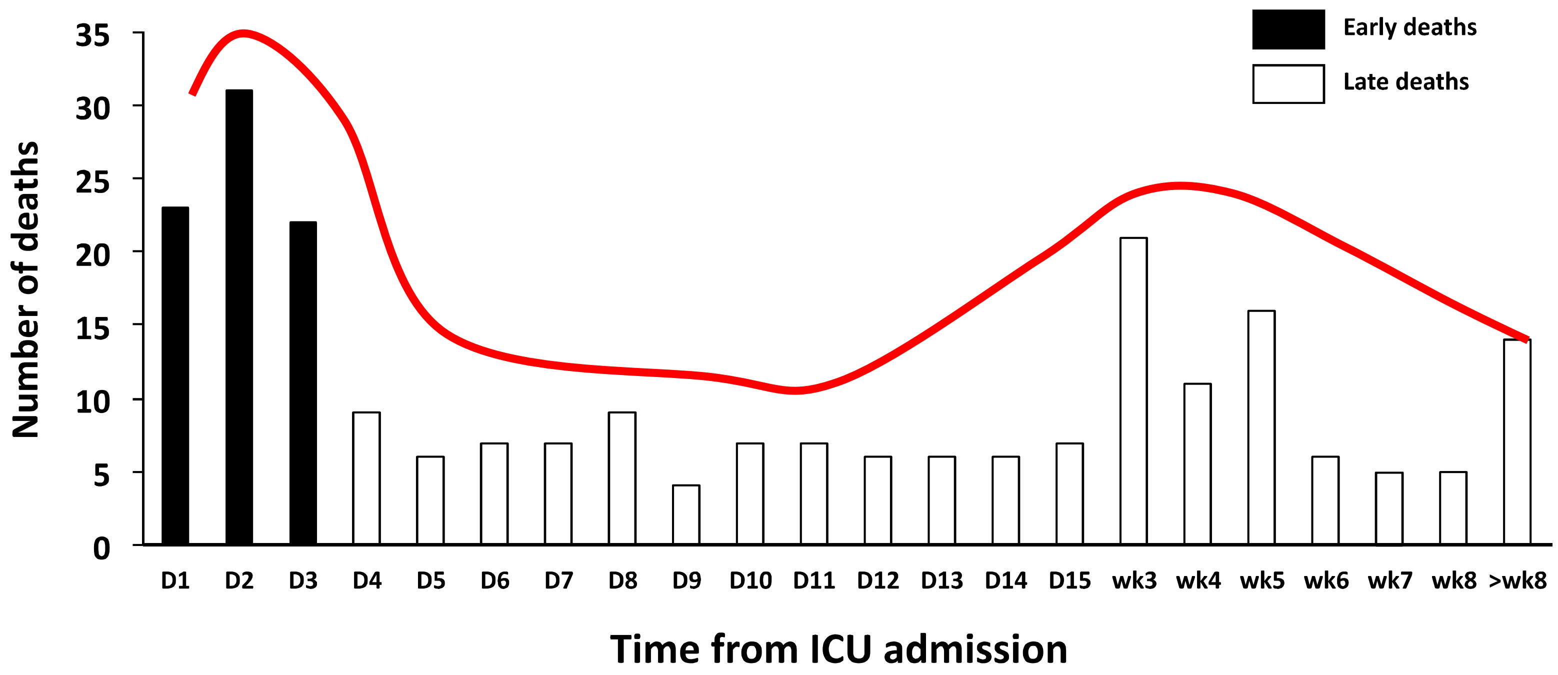


Kalil, *Crit. Care.* 2011

Sepsis-induced immunosuppression => secondary infection



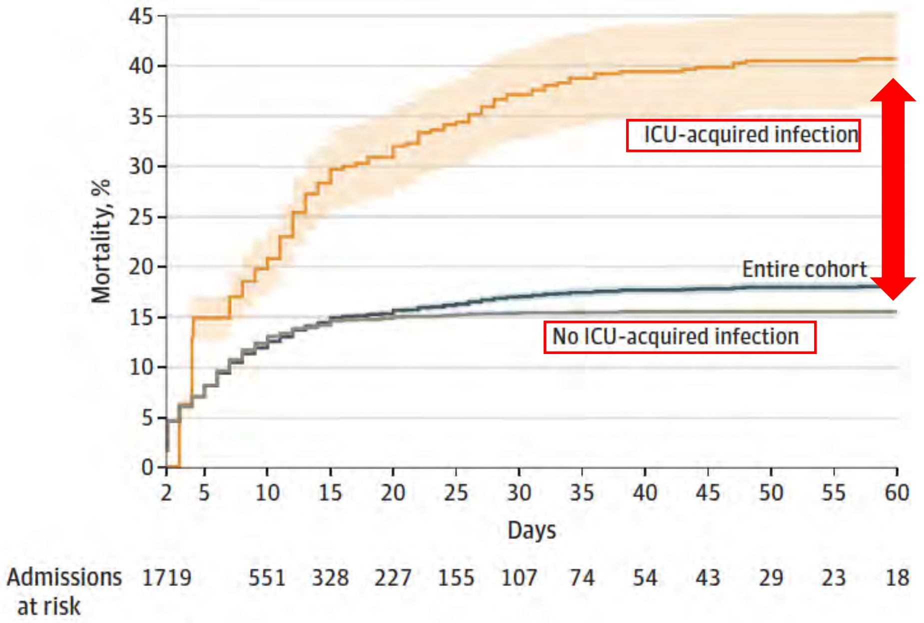
Secondary infection, chronic critical illlness and « late » death



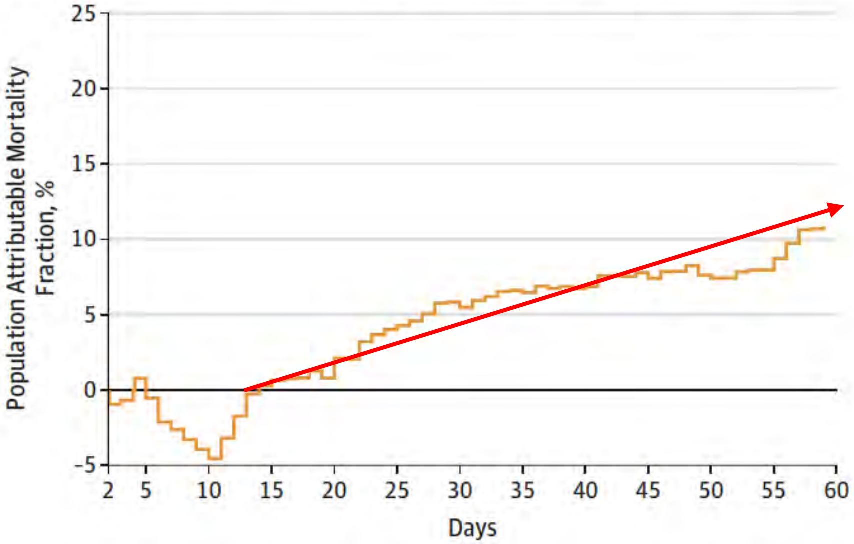
Daviaud, *AOIC.* 2015

Secondary infection, chronic critical illlness and « late » death

ICU mortality



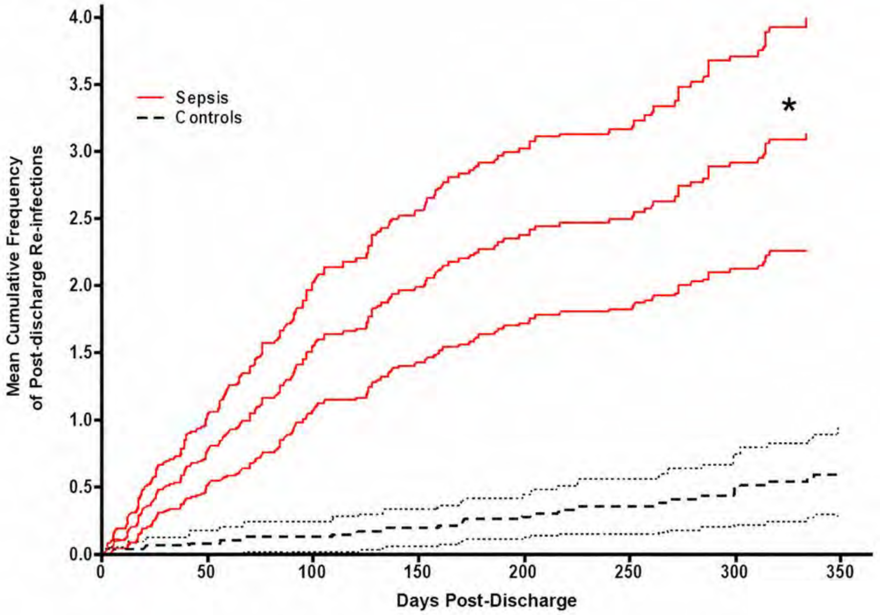
ICU-acquired infection attributable mortality



Van Vught, *JAMA*. 2016

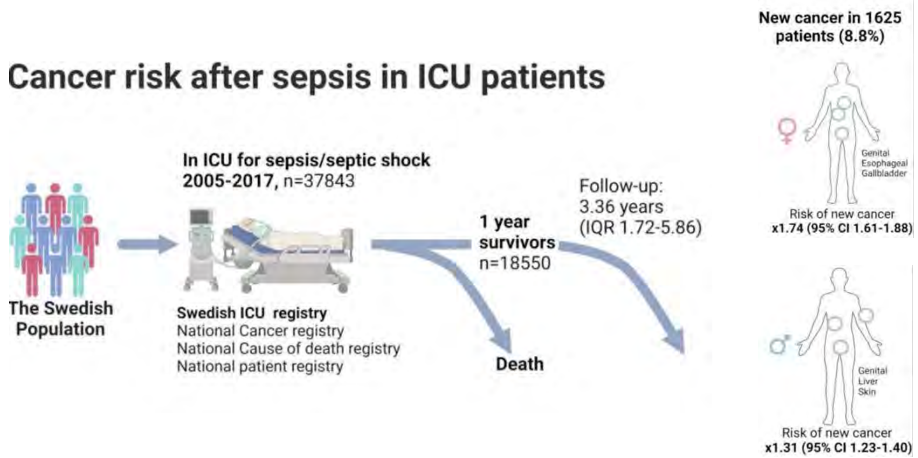
Long-term sepsis-induced immunosuppression ?

One year readmission for sepsis



Wang, *J. Crit .Care.* 2014

One year cancer diagnosis risk



Hästbacka, *Crit .Care.* 2023

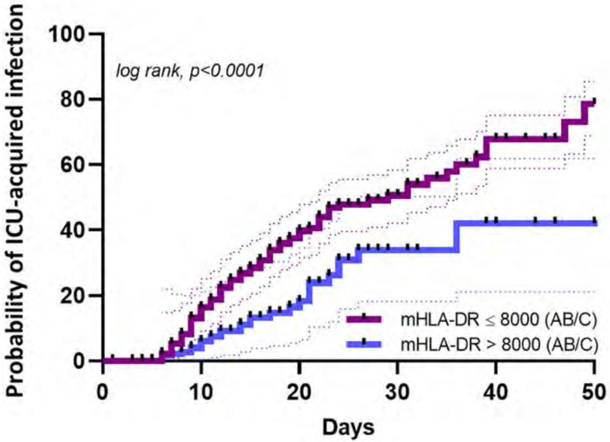
Sepsis-associated immunosuppression: clinical challenges

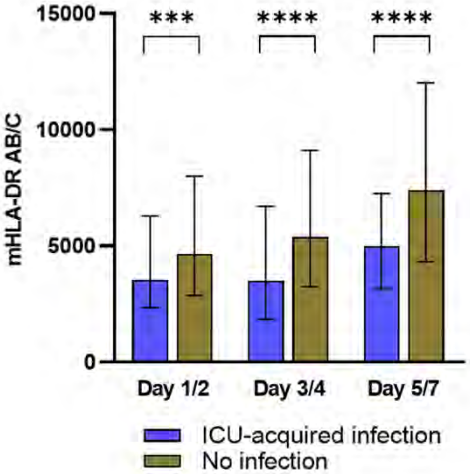
- Prevent ?

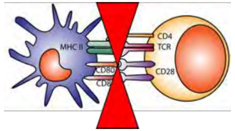
- Early identification of patients at risk ?

- Reverse ?

Low Mo HLA-DR is associated with secondary infection and death

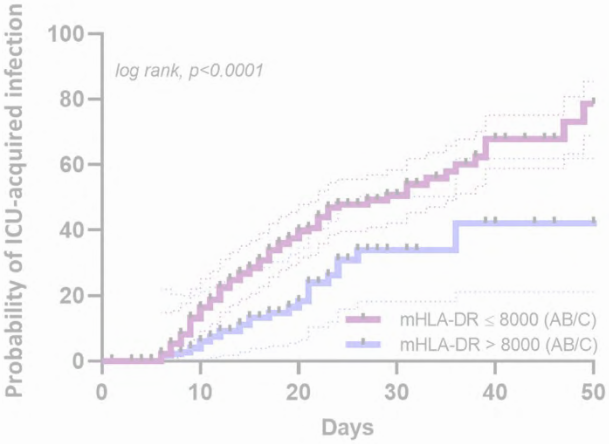


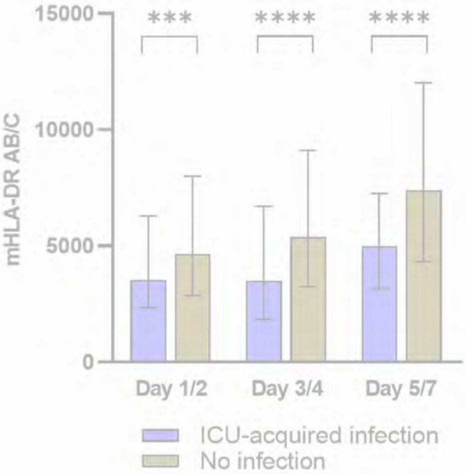


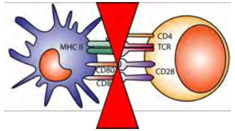


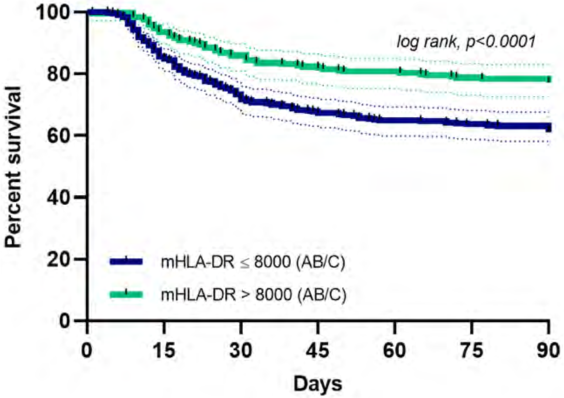
Monneret, *ICM*. 2025

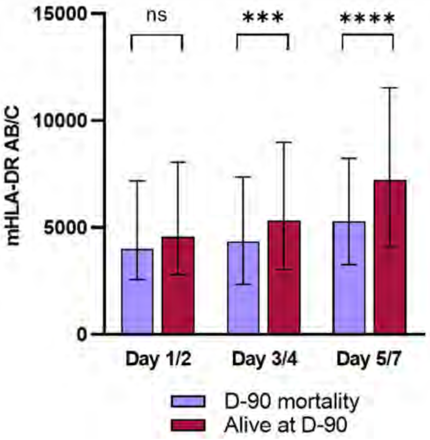
Low Mo HLA-DR is associated with secondary infection AND DEATH











Monneret, *ICM*. 2025

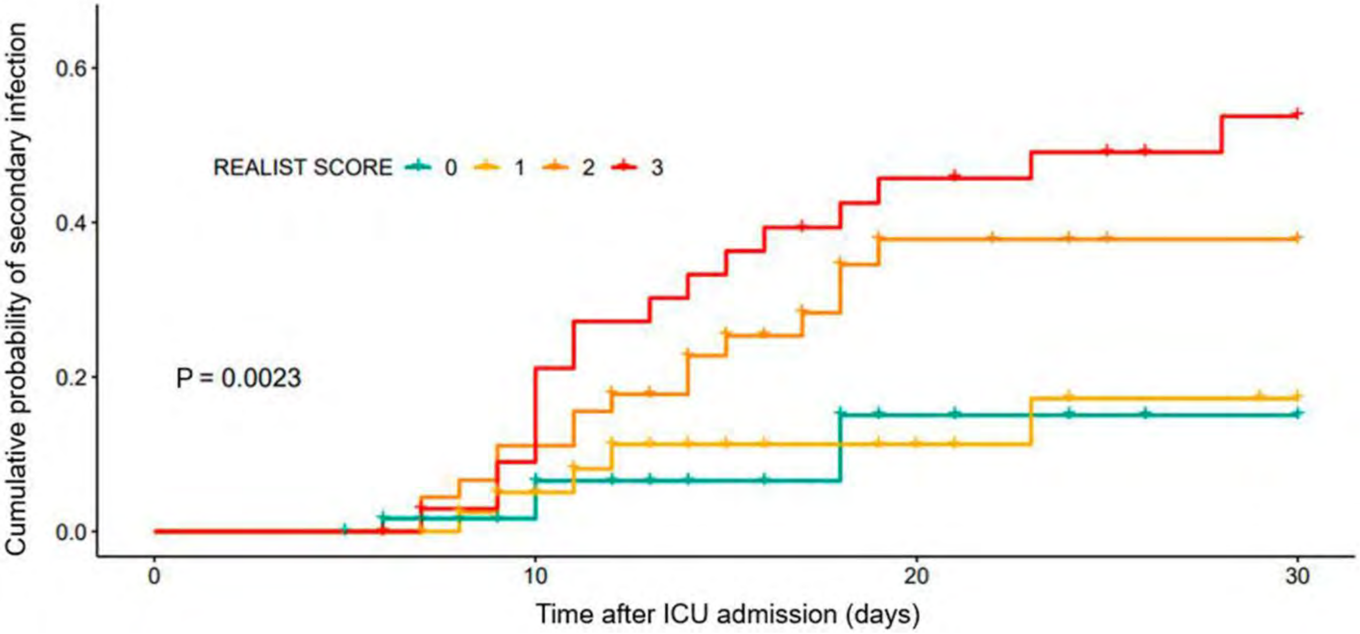
Immune markers associated with secondary infection

Three immune parameters measured at day 5-7

mHLA-DR ≤ 7627 Ab/cell

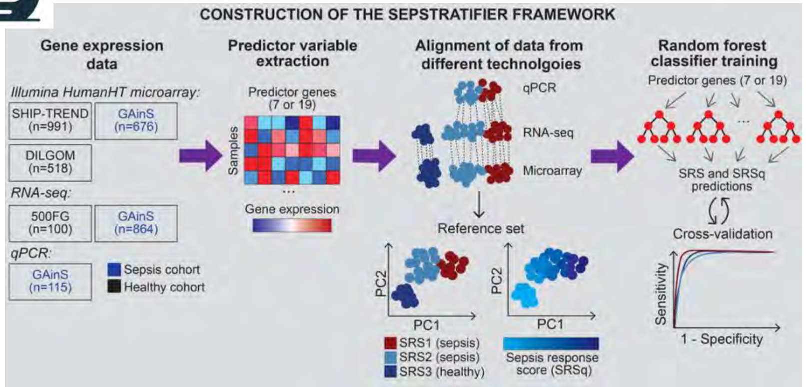
Immature neutrophils ≥ 23.5%

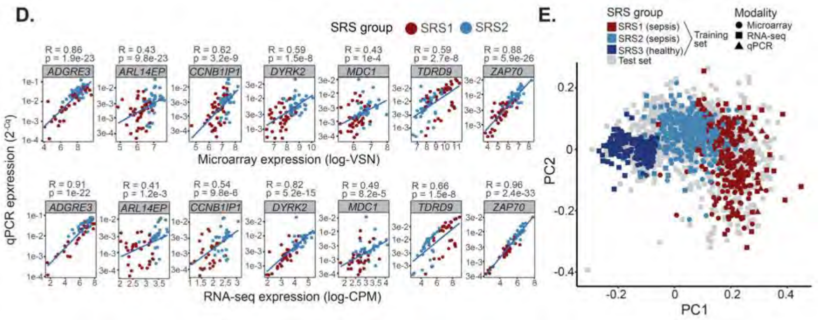
IL-10 ≥ 8.5 pg/mL



Tremblay, *AOIC. 2022*

Immune markers associated with secondary infection: Sophistication vs. simplification ?





Cano-Gamez , *Sci. Transl. Med.* 2022

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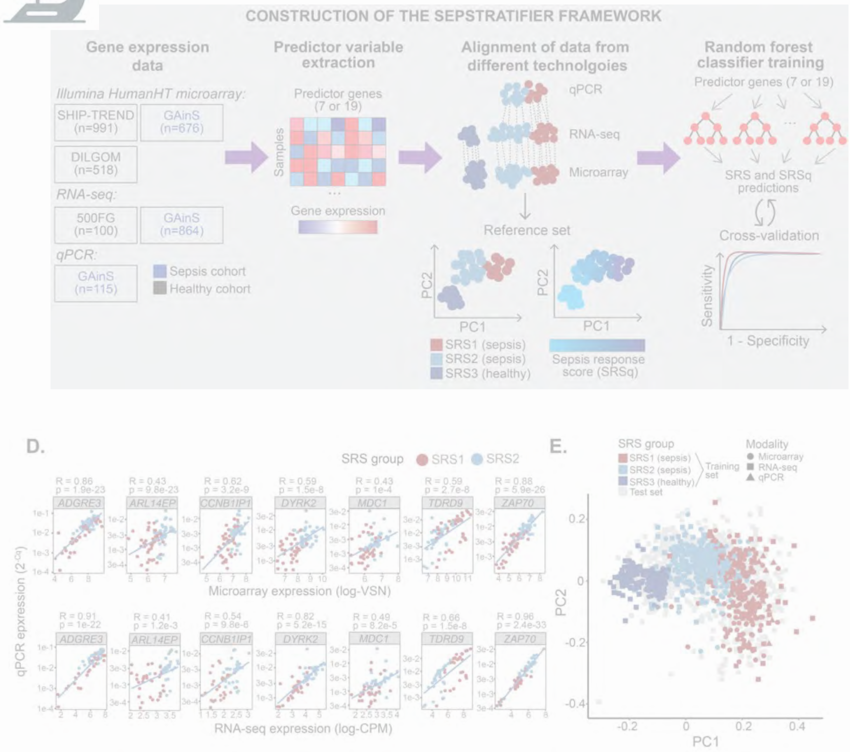
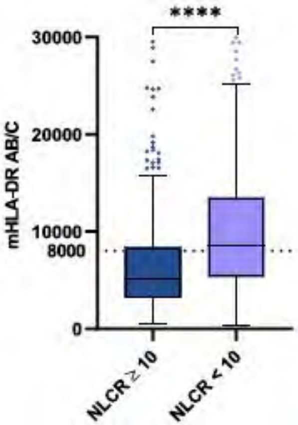
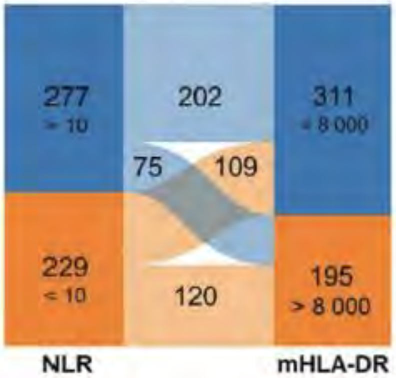


Cano-Gamez , *Sci. Transl. Med.* 2022

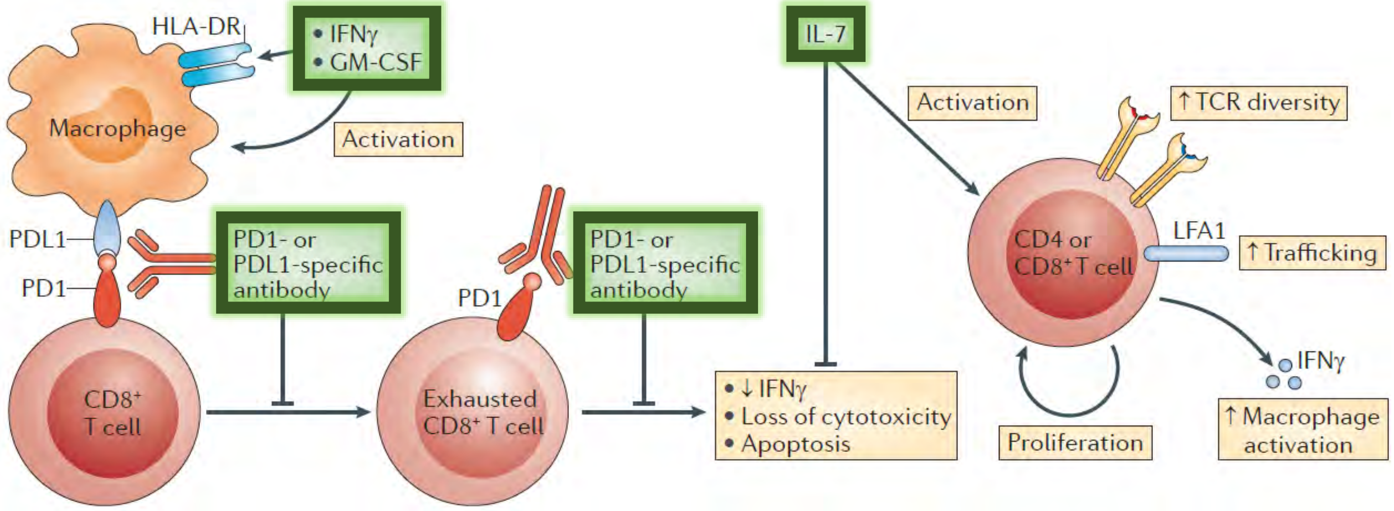
Neutrophil-to-lymphocyte ratio as a practical alternative to mHLA-DR measurement in delayed sepsis-induced immunosuppression





Lafon, *AOIC.* 2026

Reversing sepsis-induced immunosuppression: potential pathways ?

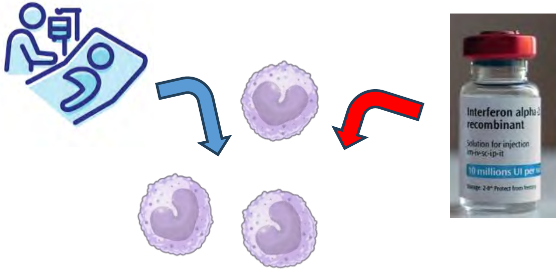


Hotchkiss, *Nat. Rev. Immunol.* 2013

Reversing sepsis-induced immunosuppression: IFNγ

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

Docke, *Nat. med.* 1997

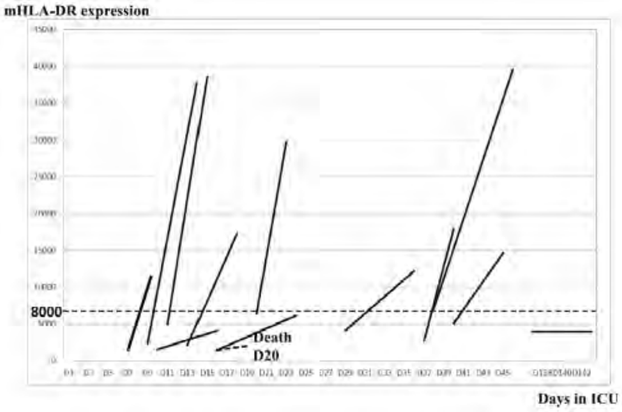


HLA-DR expression

LPS-induced IL-6 and TNF-α

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

Payen, *BMC inf. dis.* 2019



JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Precision Immunotherapy to Improve Sepsis Outcomes
The ImmunoSep Randomized Clinical Trial

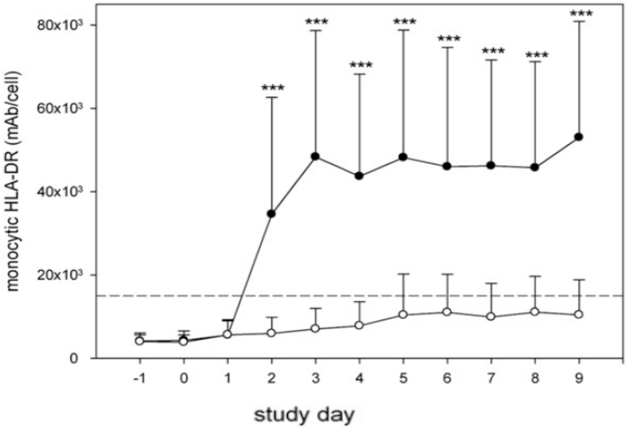
Giamarellos-Bourboulis, *JAMA.* 2025

% SOFA score > 1.4 by day 9

	Precision Immunotherapy	Placebo	p
MALS	48.0%	17.4%	0.04
Immuno paralysis	32.1%	18.0%	0.02

Reversing sepsis-induced immunosuppression: GM-CSF

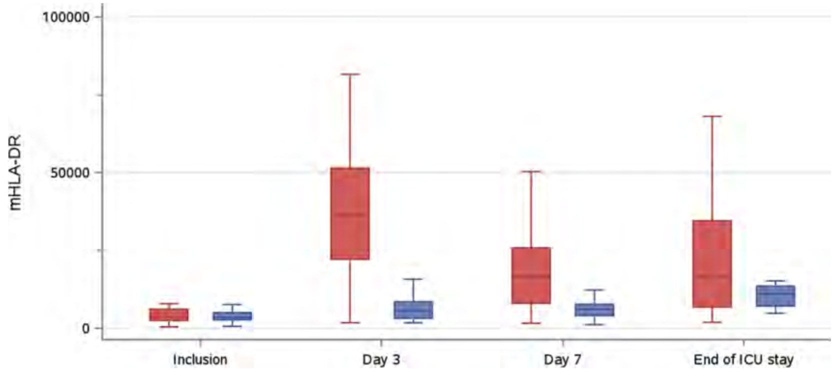
Granulocyte–Macrophage Colony-stimulating Factor to Reverse Sepsis-associated Immunosuppression
A Double-Blind, Randomized, Placebo-controlled Multicenter Trial



Characteristics	GM-CSF Group (*n* = 19)	Placebo Group (*n* = 19)	*P* Value
Mortality rate at study Day 28 (%)	3/19 (16)	4/19 (21)	NS[†]
Time on ventilator, Days 1–9, hours	147.9 ± 102.8	207.2 ± 57.5	0.037[*]

Meisel, *AJRCCM.* 2009

Granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients presenting sepsis-induced immunosuppression: The GRID randomized controlled trial



	Placebo (n = 44)	Intervention (n = 54)	P value
Number of ICU-acquired infections			1.000
0	39 (89)	48 (89)	
1	4 (9)	5 (9)	
2	1 (2)	1 (2)	
Mortality, n (%)	11 (25)	12 (22)	0.814
Length of hospital stay, days	29 [22–41]	32 [21–66]	0.294
Mortality, n (%)	6 (18)	5 (12)	0.525
28th day mortality	12 (27)	13 (24)	0.900
365th day mortality	18 (41)	18 (35)	0.672

Vacheron, *J. Crit. Care.* 2023

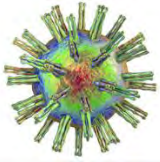
Treating viral reactivation to alleviate post-sepsis

Preemptive ganciclovir for mechanically ventilated patients with cytomegalovirus reactivation

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

Papazian, *AOIC.* 2021

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



Parameter	Study Group: Acyclovir (n = 119)	Study Group: Placebo (n = 119)	P Value
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

Luyt, *JAMA Int. Med*. 2020

Post-sepsis immunosuppression:
where do we stand, where do we go?

- **Clinical and biological rationale + meaningful short- and late-term impact !**

- **Stratification on relevant immune biomarkers: treatable traits or markers of severity?**

Post-sepsis immunosuppression:
where do we stand, where do we go?

- Clinical and biological rationale + meaningful short- and late-term impact !

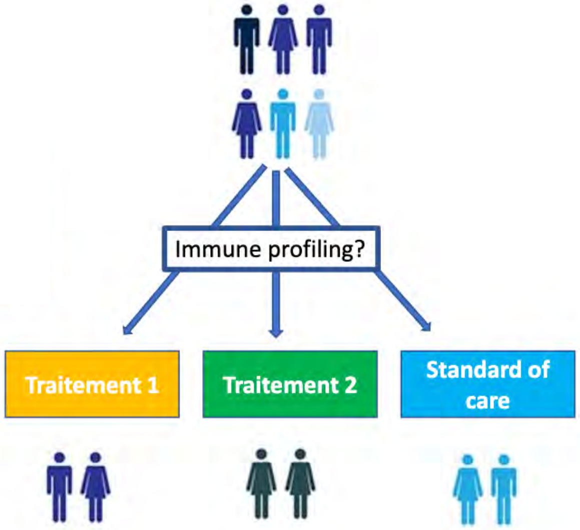
- Stratification on relevant immune biomarkers: treatable traits or markers of severity?

- **A case for personalized medicine !**

-> Patient selection: complexity versus do-able screening?

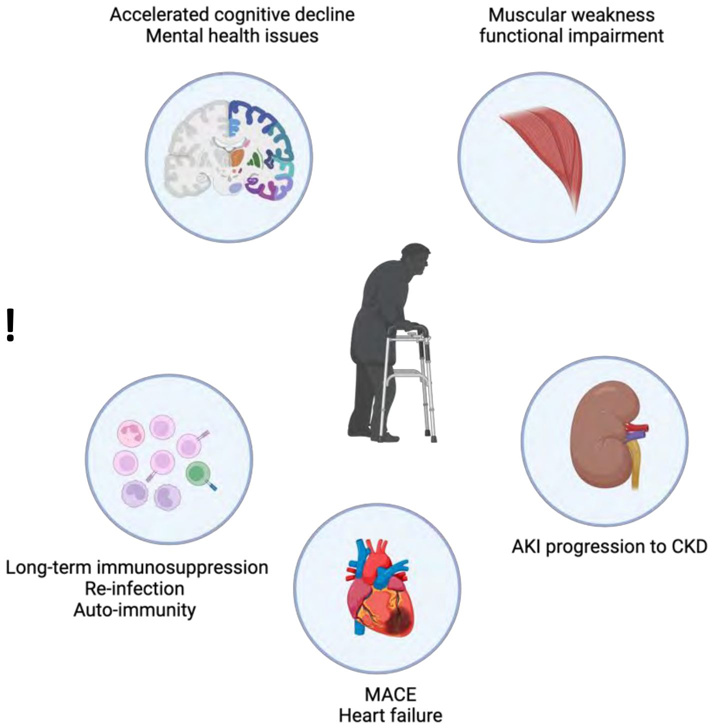
-> Multiple potential target: single vs combined therapy?

-> Strategy: Prophylaxy versus adjuvant therapy?



Post-sepsis immunosuppression: where do we stand, where do we go?

- Clinical and biological rationale + meaningful short- and late-term impact !
- Stratification on relevant immune biomarkers
- A case for personalized medicine !
- **Immunity beyond leukocytes and frailty beyond ICU!**



Thanks for your attention

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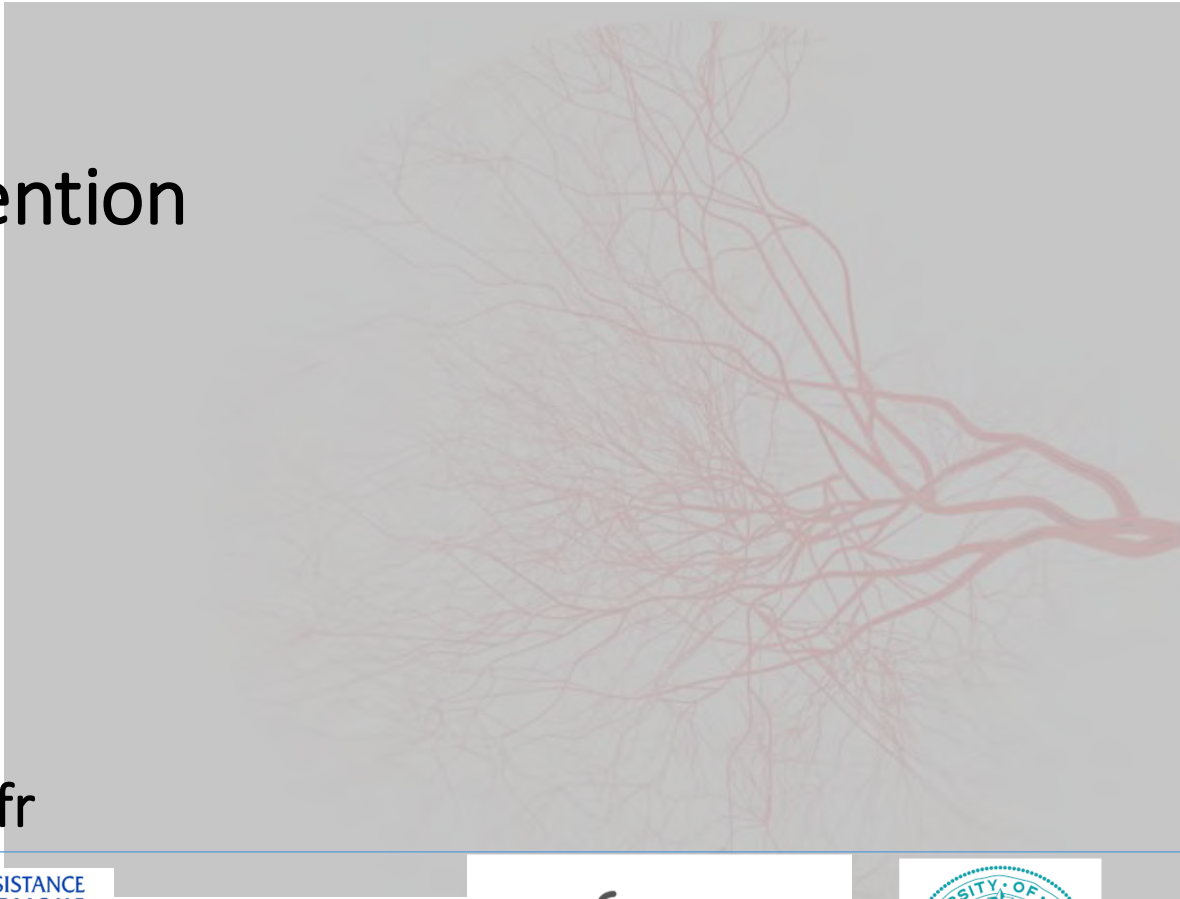
Q & A ?



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