

Physiopathologie de l'immunodépression post-septique: up to date "de la physiopathologie aux perspectives thérapeutiques"

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UR 7426 – Immunodépression induite par les inflammations systémiques - U. Lyon 1



Conflict of interest disclosure

Roche DF, Volition, Beckman

Conference invitation to scientific congresses: fees paid to the research credits of the team

BioMérieux

Inventor of common patents (n = 15, transcriptomics)



Périmètre du cours

Sujets non traités

Phase précoce

Sepsis/choc septique : up to date "de la physiopathologie au traitement des premières heures" : Pr. Hafid Ait-Oufella

Immunodépression sous-jacente préalable à l'admission en réanimation

Back to definitions and pathophysiology

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

2016

Sepsis

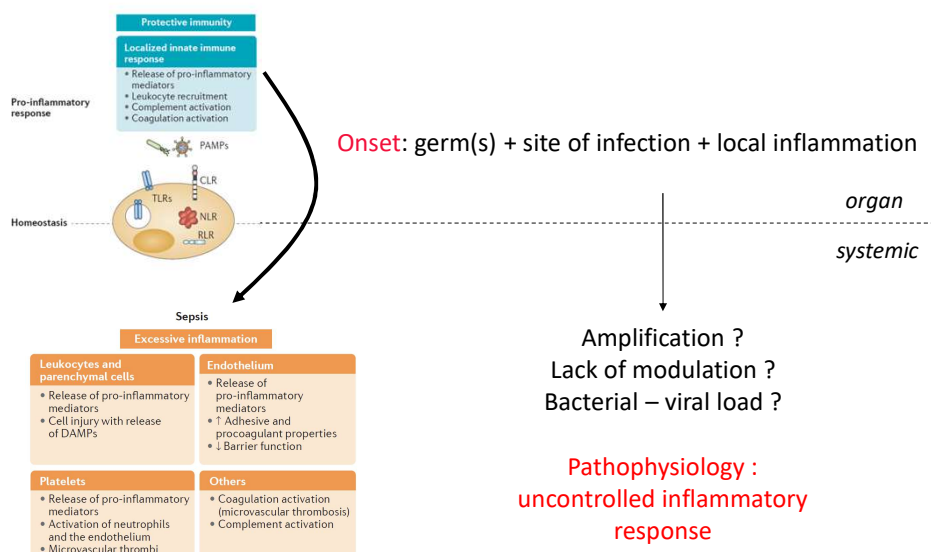
Life threatening organ dysfunction caused by a dysregulated host response to infection (*i.e.*, one infection + one organ failure)

Septic shock

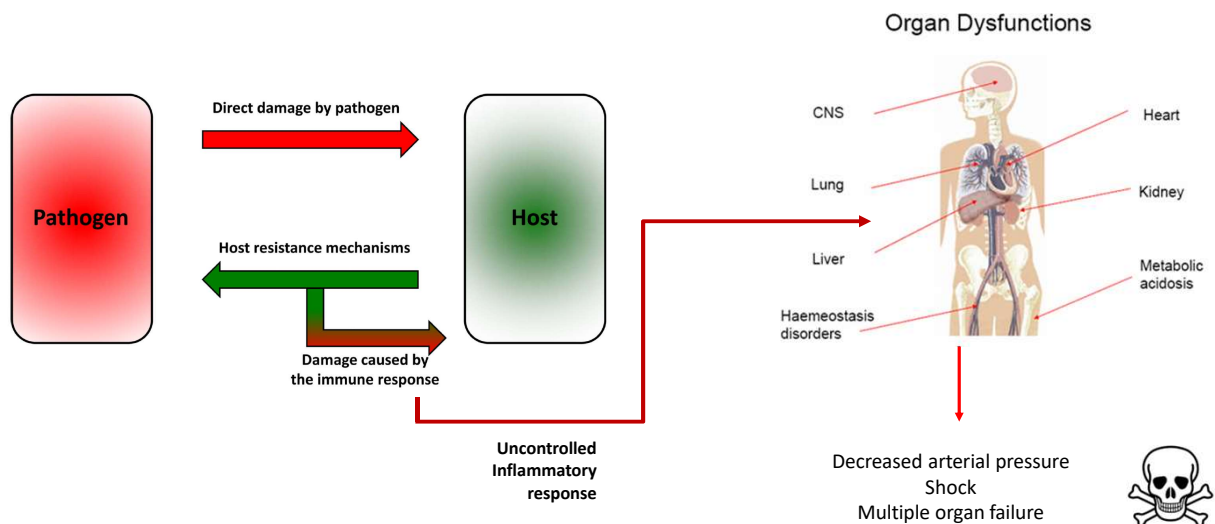
Sepsis + vasopressor therapy needed (*i.e.*, cardiovascular failure) + Lactate > 2mmol/L

Singer et al., JAMA 2016

Pathophysiology - Inflammation is a balancing act: neither too much nor too little is desirable

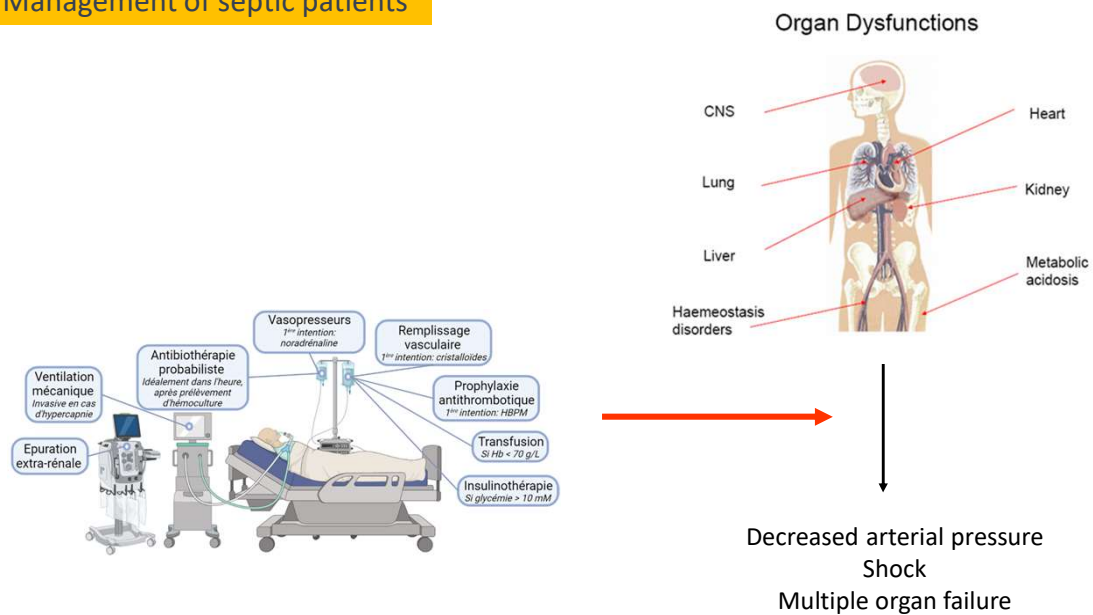


Old paradigm for sepsis pathophysiology

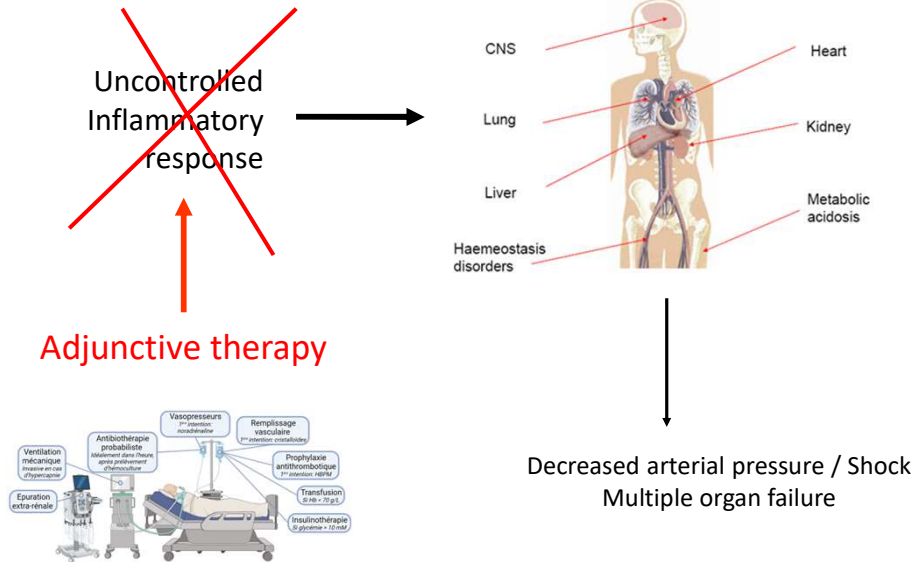


Adapted from Medzhitov et al., Science 2012

Management of septic patients



Management of septic patients



40 years of failure in anti-inflammatory therapies

Meta-analysis

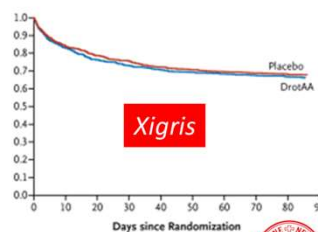
Drug	Number of studies	Number of patients	Mortality (%)	
			Placebo	Drug
Anti-endotoxine	4	2010	35	35
Anti-bradykinine	2	755	36	39
Anti-PAF	2	870	50	45
Anti-TNF	8	4132	41	40
R solubles TNF	2	688	38	40
AINS	3	514	40	37
Steroids	9	1267	35	39
...	...	...	...	...
Total	33	12034	38	38

Critical Care Medicine

Zeni et al., 1997

The NEW ENGLAND JOURNAL of MEDICINE

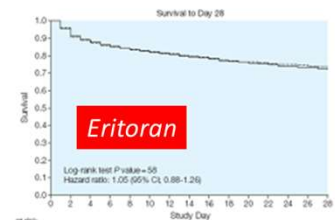
Drotrecogin Alfa (Activated) in Adults with Septic Shock



Ranieri et al. 2012

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

The ACCESS Randomized Trial

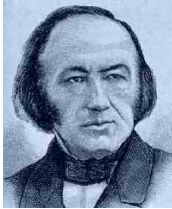


JAMA The Journal of the American Medical Association

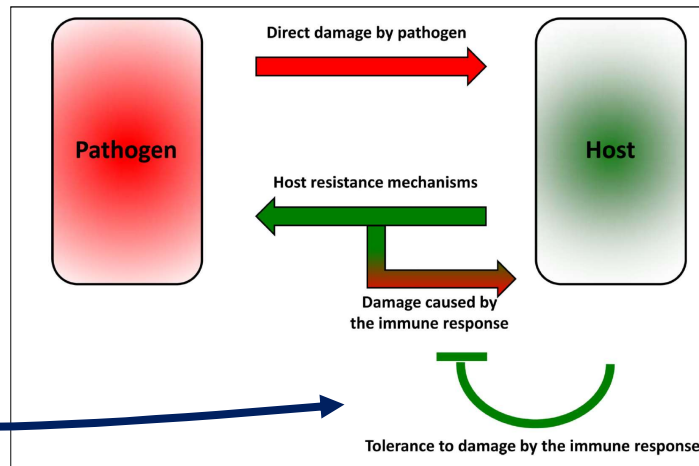
Opal et al. 2013

Reasons for the failure of anti-inflammatory strategy => Neglecting the principle of homeostasis

« Only homeostasis matters »

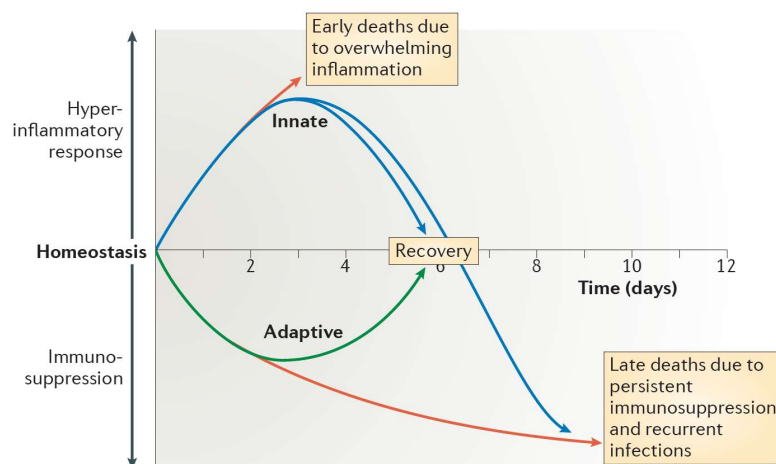


Claude Bernard (1813 – 1878)



Adapted from Medzhitov et al., Science 2012

Rethinking immuno-inflammatory dysregulation in sepsis: a novel vision



nature
REVIEWS
IMMUNOLOGY

Hotchkiss and friends, Nature Rev Immunol 2013

Marked alterations in skin testing

1977

Delayed Hypersensitivity:

Indicator of Acquired Failure of Host Defenses in Sepsis and Trauma

JONATHAN L. MEAKINS, M.D., D.Sc., FRCSC; JOHN B. FRETSON, M.D., OLDRICH RUBENCK, M.D.,
RALPH KELLY, B.A., HAROLD ROSE, Ph.D., JULIUS GORDON, Ph.D., LLOYD D. MACLEAN, M.D., FRCSC

TABLE 2. Morbidity and Mortality Based Upon Initial Skin Test

	Patients		Sepsis		Death	
	Num- ber	%	Num- ber	%	Num- ber	%
<i>Post-operative/post-trauma</i>						
Anergy	48	64	34	70.8	15	31.2
Rel. anergy	16	21.3	11	68.7	3	18.7
Normal	11	14.7	1	9.1	0	0
<i>Non-operative</i>						
Anergy	16	26.2	4	25	7	43.7
Rel. anergy	4	6.6	1	25	1	25
Normal	41	67.2	0	0	0	0
	61					

ANNALS
OF
SURGERY

Ann. Surg. • September 1977

1995

The Delayed Hypersensitivity Response and Host Resistance in Surgical Patients 20 Years Later

Nicolas V. Christou, M.D., Jonathan L. Meakins, M.D., Julius Gordon, Ph.D., John Yee, M.D.,
Mina Hassan-Zahrase, M.Sc., Carl W. Nave, M.D., Harry M. Shugart, M.D.,
and Lloyd D. MacLean, M.D.

ANNALS OF SURGERY
Vol. 222, No. 4, 534-548
© 1995 Lippincott-Raven Publishers

	Skin testing (within 24 h after admission)	Mortality	Nosocomial infection
n = 1211 surgical ICU patients	Positive 30 % (n = 369)	9 % (n = 31)	27 % (n = 99)
	+/- 23 % (n = 272)	25 % (n = 55)	33 % (n = 91)
	Negative 47 % (n = 570)	32 % (n = 184)	42 % (n = 237)

* p < 0.005

ANNALS
OF
SURGERY

Skin testing with 5 antigens (positive if ≥ 2 reacted, +/- if solely 1 reacted, negative if none reacted)

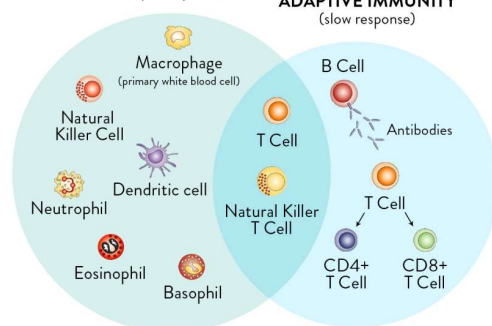
Main mechanisms sustaining immune dysfunctions in sepsis

Table 1

Sepsis-induced immune dysfunctions: pathophysiology at a glance

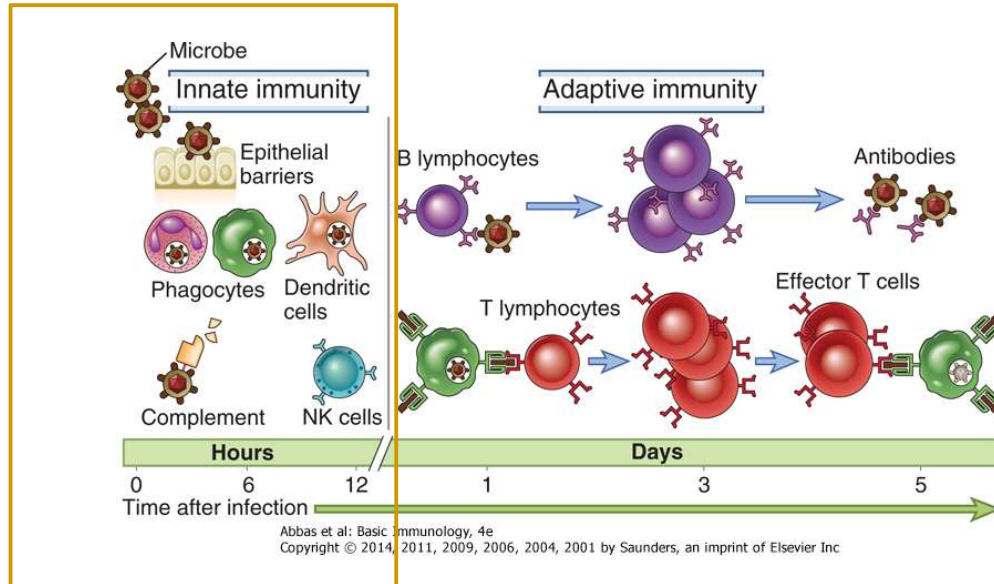
Mechanisms	Features of sepsis-induced immune alterations
Endotoxin tolerance	↓ pro-inflammatory ↑ anti-inflammatory cytokine production
Apoptosis	↓ Ag presentation capacity ↓ cell number
Energetic failure	Cell anergy Apoptosis Mitochondrial dysfunction
Anti-inflammatory mediators	↓ activating co-receptor 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

INNATE IMMUNITY (rapid response)

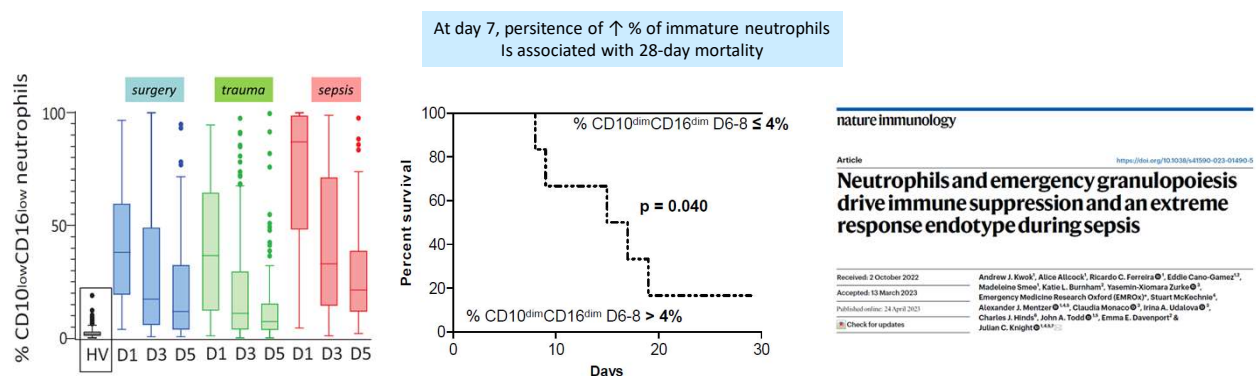


Are ICU injured patients really immunosuppressed ?

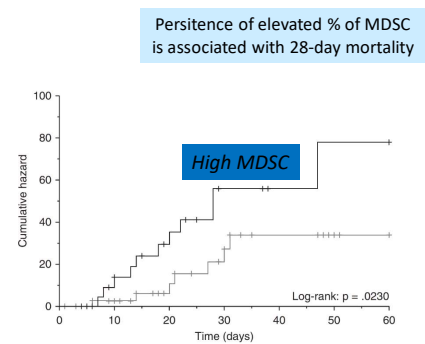
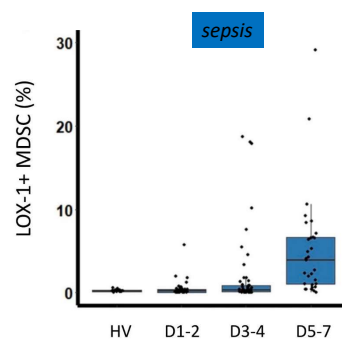
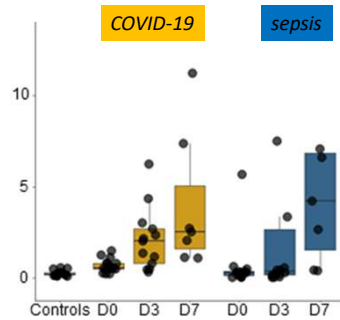
Impact on myeloid cells ?



Sharpe increase of immature immunosuppressive neutrophils



Delayed and progressive increase of MDSC LOX-1+



Couderau et al., 2024



Haem Rahimi et al., 2024

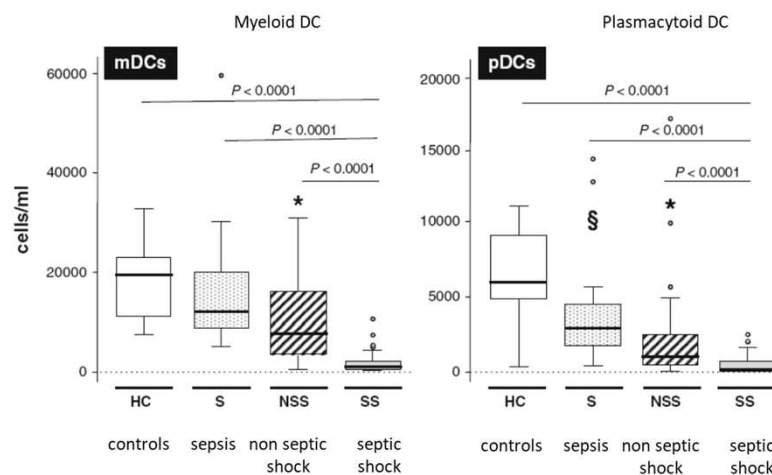
Uhel et al., 2017



Profound and persistent decrease of circulating dendritic cells is associated with ICU-acquired infection in patients with septic shock

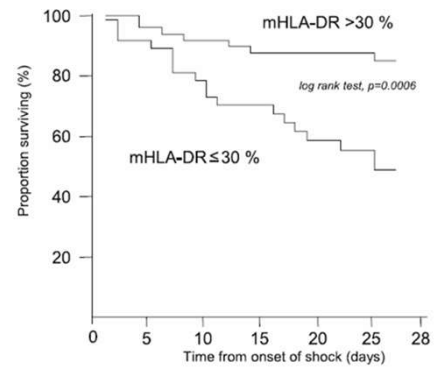
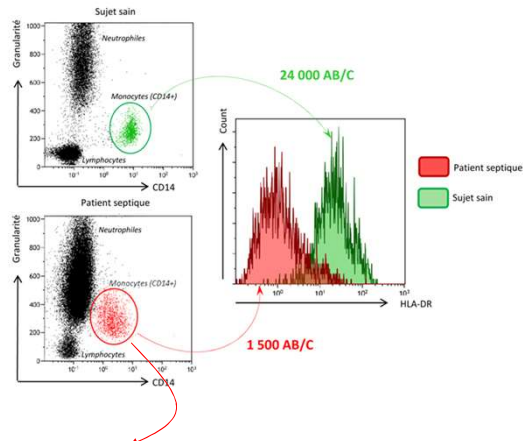


Grimaldi et al., 2009



Persisting low monocyte human leukocyte antigen-DR expression predicts mortality in septic shock

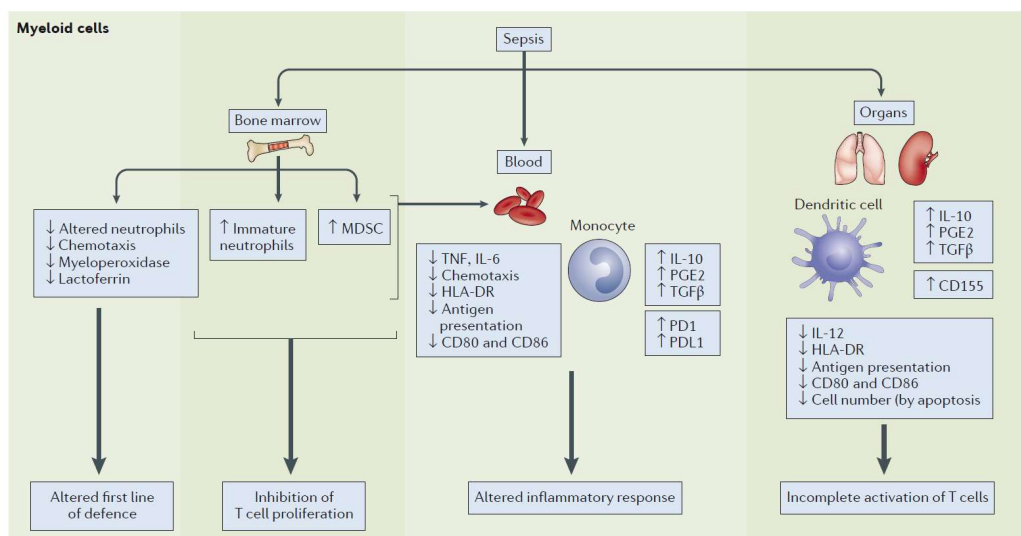
Monneret et al., 2006



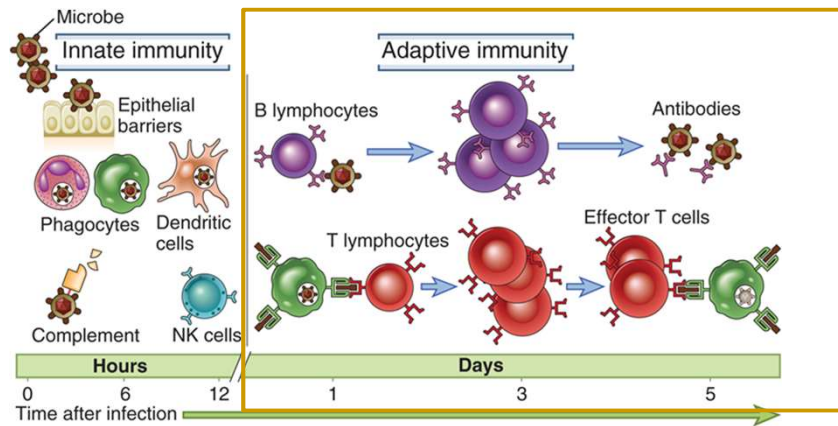
No Ag presentation
No inflammatory cytokine release

Multivariate analysis : mHLA-DR is an independent predictor of mortality (OR = 5) after adjustment for usual clinical confounders : SAPS II, SOFA, comorbidities

Myeloid cells (summary)



Impact on lymphocytes ?



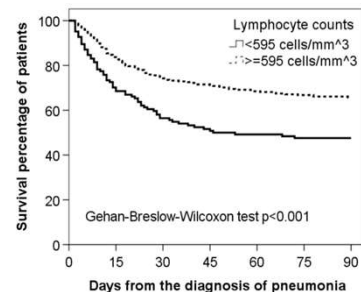
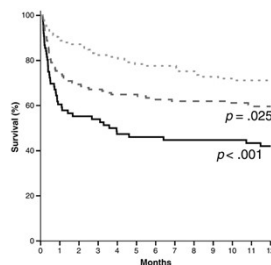
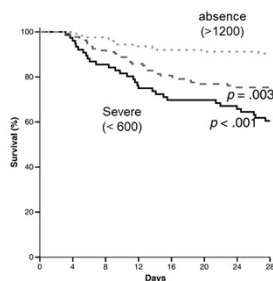
Abbas et al: Basic Immunology, 4e
Copyright © 2014, 2011, 2009, 2006, 2004, 2001 by Saunders, an imprint of Elsevier Inc

PERSISTENT LYMPHOPENIA AFTER DIAGNOSIS OF SEPSIS PREDICTS MORTALITY

Anne M. Drewry,* Navdeep Samra,[†] Lee P. Skrupky,[‡] Brian M. Fuller,^{*§}
Stephanie M. Compton,* and Richard S. Hotchkiss^{*†}

Lymphocytopenia as a Predictor of Mortality in Patients with ICU-Acquired Pneumonia

Lymphopenia < 600 cell / μ L is associated with mortality



SHOCK

SHOCK, Vol. 42, No. 5, pp. 383–391, 2014

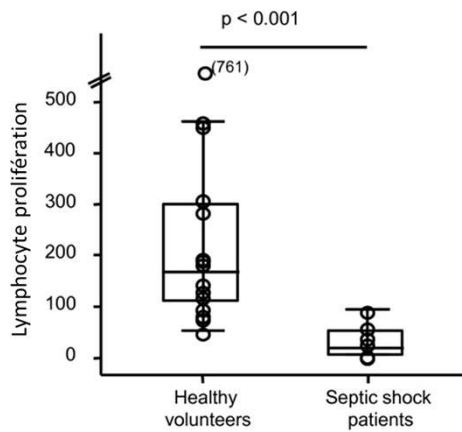
Ceccato A. et al., 2019



Journal of
Clinical Medicine

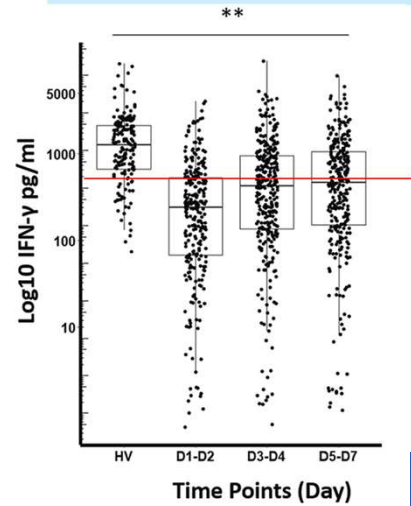
Loss of lymphocyte functions

Proliferation (sepsis)



Guignat et al. 2011

IFN- γ release (mixed ICU patients)



Haem Rahimi et al., 2024

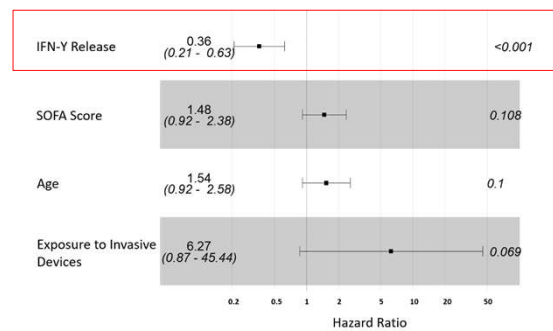
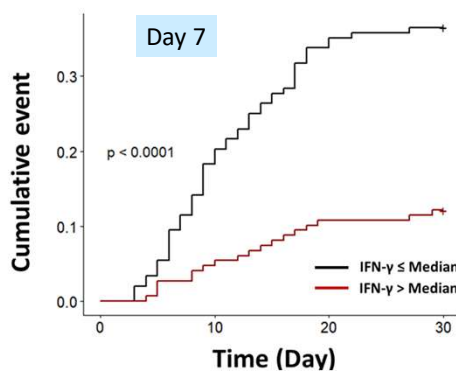


Interferon-Gamma-Release assay and absolute CD8 lymphocyte count for acquired immunosuppression monitoring in critically ill patients

Haem Rahimi et al., 2024



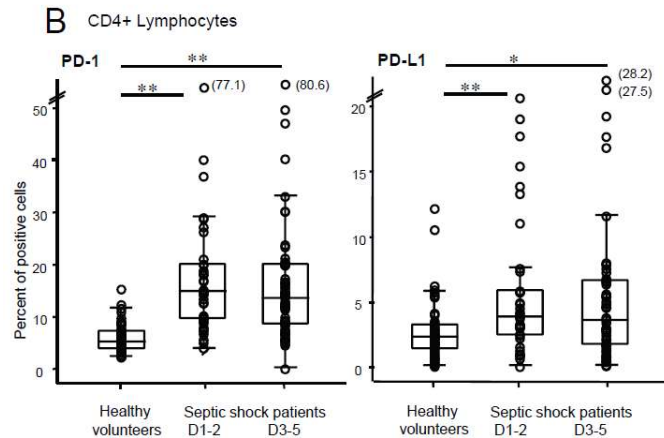
Functional testing (n = 350 ICU patients)
decreased ex vivo IFN- γ release is independently associated with worsening



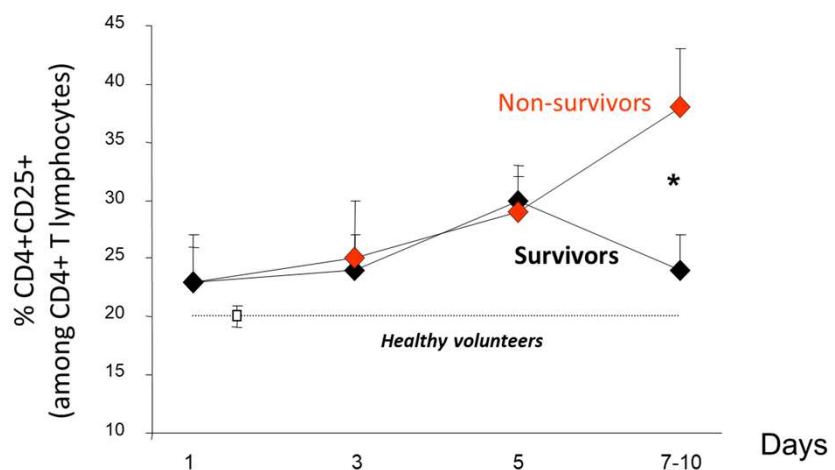
Haem Rahimi et al., 2024

Programmed death-1 levels correlate with increased mortality, nosocomial infection and immune dysfunctions in septic shock patients

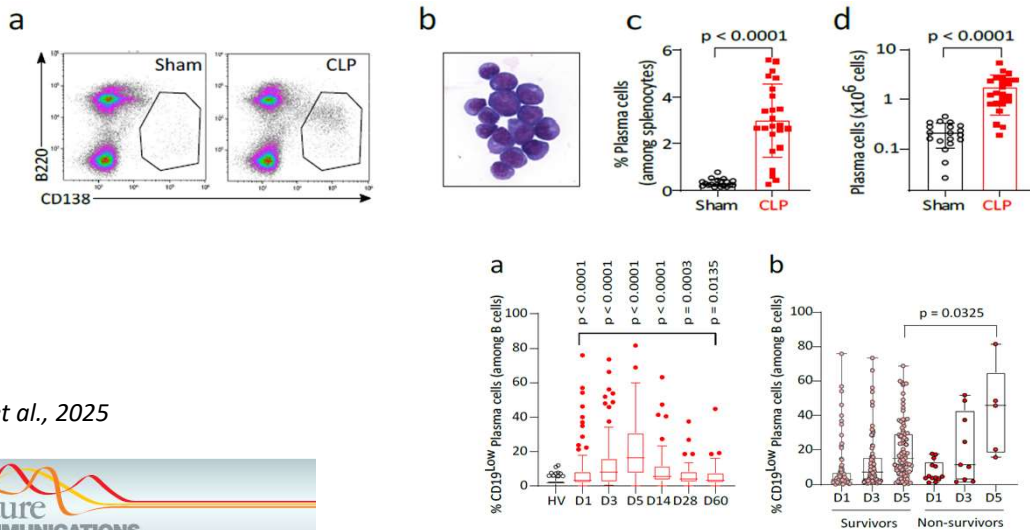
Caroline Guignant¹, Alain Lepape², Xin Huang³, Hakim Kherouf¹, Laure Denis¹, Françoise Poitevin¹, Christophe Malcus¹, Aurélie Chéron¹, Bernard Allaouchiche², François Gueyffier², Alfred Ayala³, Guillaume Monneret^{1,††} and Fabienne Venet^{1,†}



Marked elevation of human circulating CD4+CD25+ regulatory T cells in sepsis-induced immunoparalysis



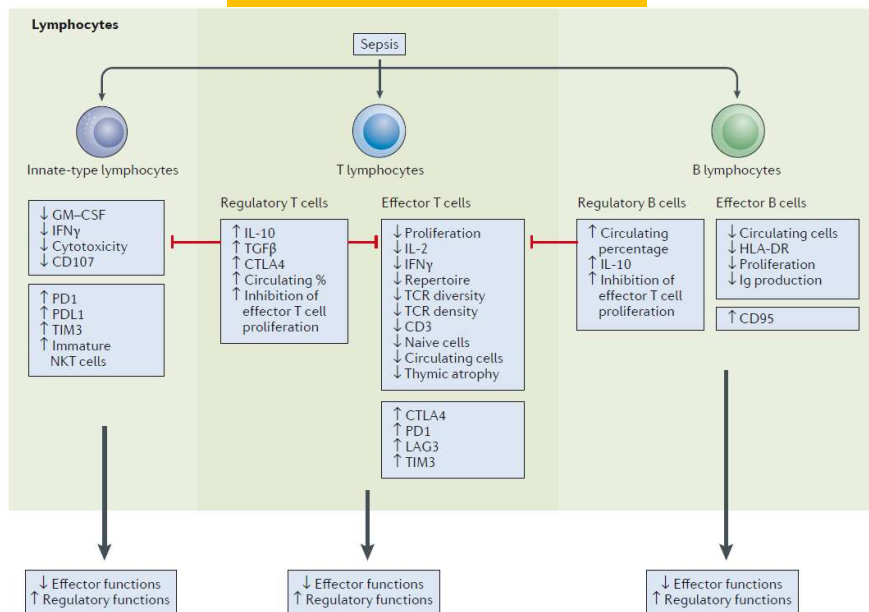
PD-L1 mediated T cell inhibition by regulatory plasma cells induced after sepsis



Gossez et al., 2025



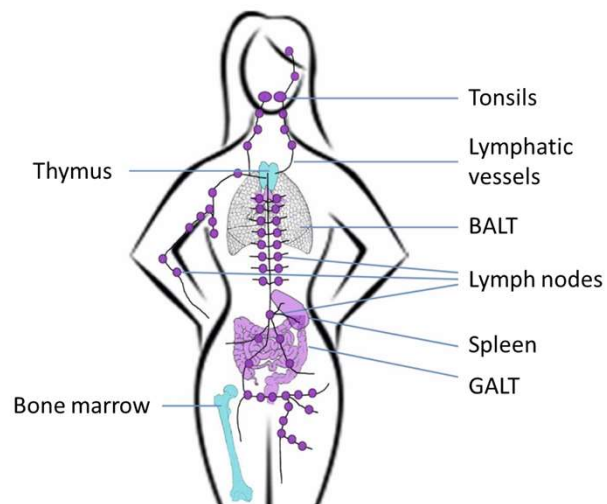
Lymphoid cells (summary)



nature
REVIEWS

Venet & Monneret, 2018

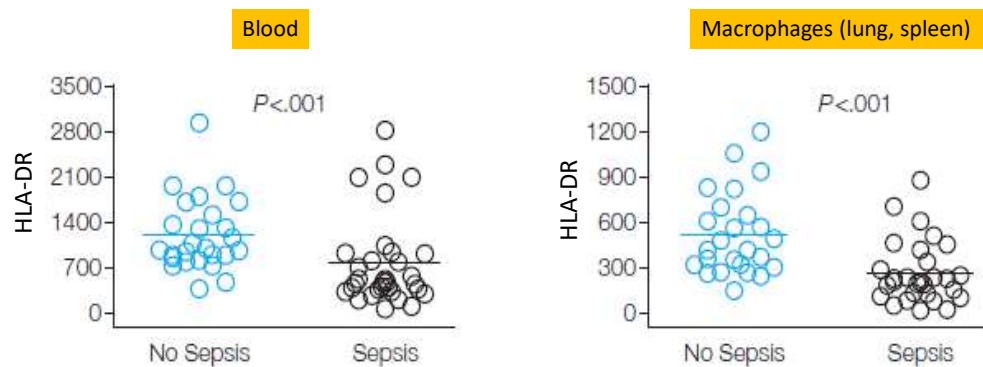
Impact on (lymphoid) organs ?



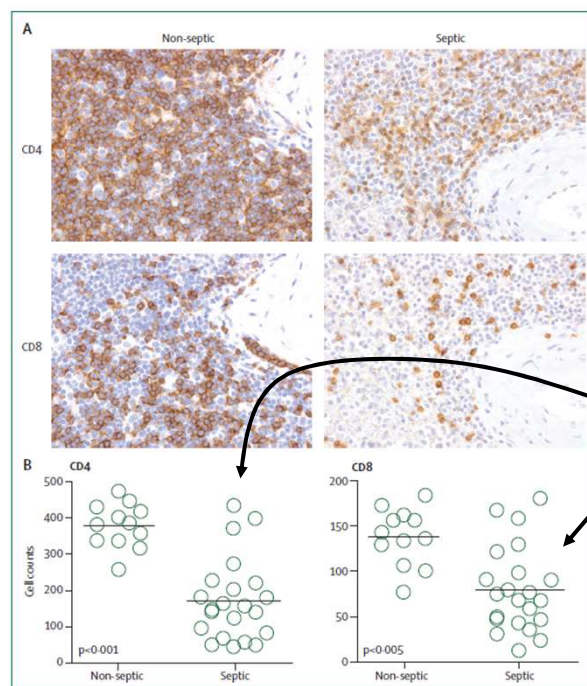
Immunosuppression in Patients Who Die of Sepsis and Multiple Organ Failure

CARING FOR THE
CRITICALLY ILL PATIENT

Boomer et al. JAMA, December 21, 2011—Vol 306, No. 23



=> Decreased mHLA-DR both in blood and lung / spleen

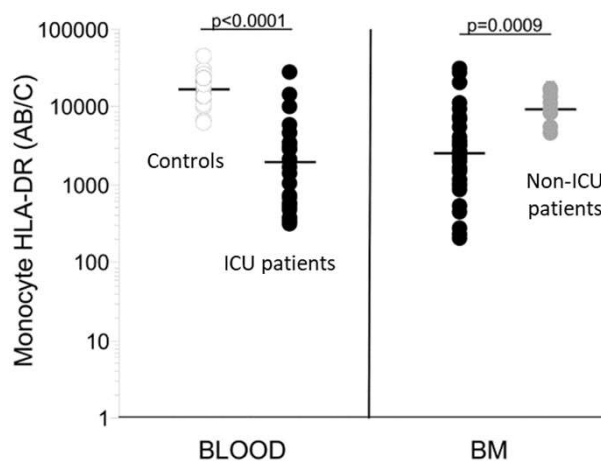


Loss of CD4 and CD8 Ly in spleen (post-mortem biopsies)

Figure 2: Depletion of splenic lymphocytes in septic patients

Hotchkiss et al., Lancet Infect Dis 2013

Downregulation of Blood Monocyte HLA-DR in ICU Patients Is Also Present in Bone Marrow Cells



=> Decreased mHLA-DR both in blood and bone marrow

PLOS ONE

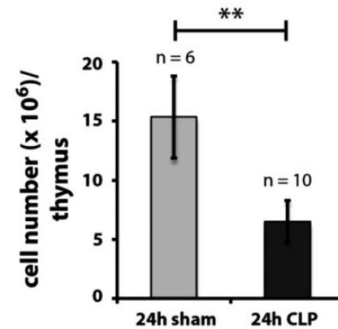
Faivre et al., 2016

Thymus

APOPTOTIC DIMINUTION OF IMMATURE SINGLE AND DOUBLE POSITIVE THYMOCYTE SUBPOPULATIONS CONTRIBUTES TO THYMUS INVOLUTION DURING MURINE POLYMICROBIAL SEPSIS

Christoph Netzer,^{*} Tilo Knappe,[†] Laura Kuchler,^{*} Andreas Weigert,^{*} Kai Zacharowski,[‡] Waltraud Pfeilschifter,[§] Gregory Sempowski,^{||} Michael J. Parnham,[†] Bernhard Brüne,^{*,†} and Andreas von Knethen^{*,†}

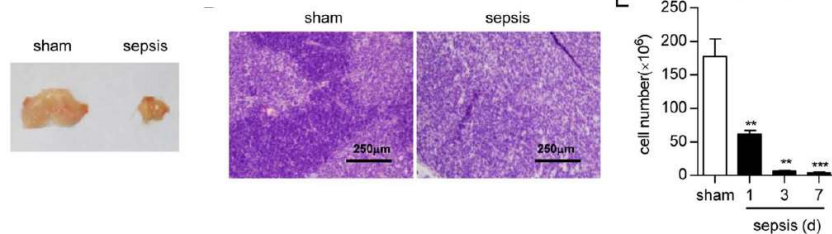
SHOCK, Vol. 48, No. 2, pp. 215–226, 2017



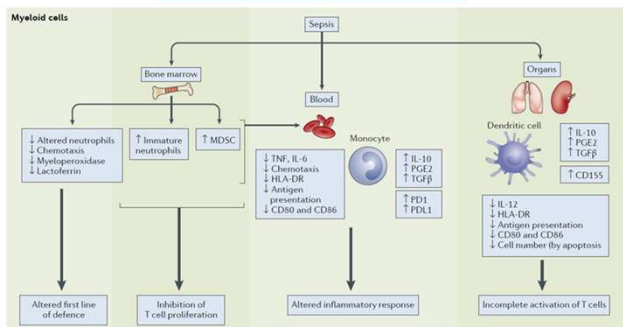
Sepsis-Induced Thymic Atrophy Is Associated with Defects in Early Lymphopoiesis

YAXIAN KONG,^{a,b} YAJIE LI,^{a,b} WEIMEI ZHANG,^{a,b} SHAOXIN YUAN,^{a,b} RENÉ WINKLER,^c ULRIKE KRÖHNERT,^c JUNYAN HAN,^{a,b} TAO LIN,^{a,b} YU ZHOU,^d PENG MIAO,^c BEIBEI WANG,^{a,b} JIANPING ZHANG,^{a,b} ZHENGYA YU,^e YU ZHANG,^d CHRISTIAN KOSAN,^c HUI ZENG^{a,b}

STEM CELLS 2016;34:2902–2915



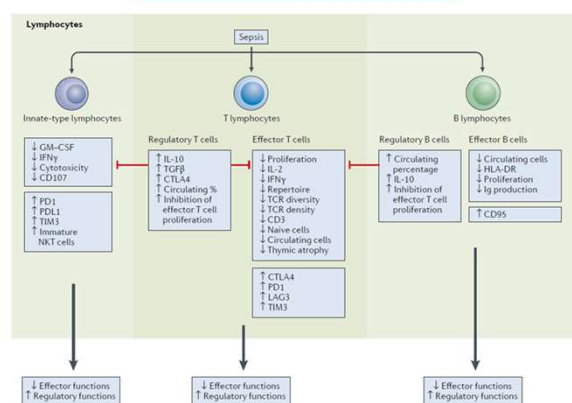
Myeloid cells (summary)



Organs

Thymic atrophy + ↓ Thymocytes + T diversity
Reprogramming in bone marrow : ↓ Ly + ↑ MDSC
Lymphopenia in Ly nodes

Lymphoid cells (summary)



Myeloid cells (summary)

Organs

- Thymic
- Reprogram
- Lymphopenia

nature REVIEWS

Cell count

- ↑ Immature neutrophils
- ↑ MDSC
- ↘ mHLA-DR
- ↘ Lymphopenia
- ↘ MAIT
- ↘ Effector T cells
- ↑ Treg
- ↑ Regulatory plasma cells

Functional testing

- ↘ Ag presentation
- ↘ Inflammatory cytokines
- ↘ T cytokines
- ↑ Suppressive cytokines
- ↘ Lymphocyte proliferation

Venet & Monneret, 2018

General definition of immunodepression

immune system's ability to fight infections (& cancer) is compromised or entirely absent

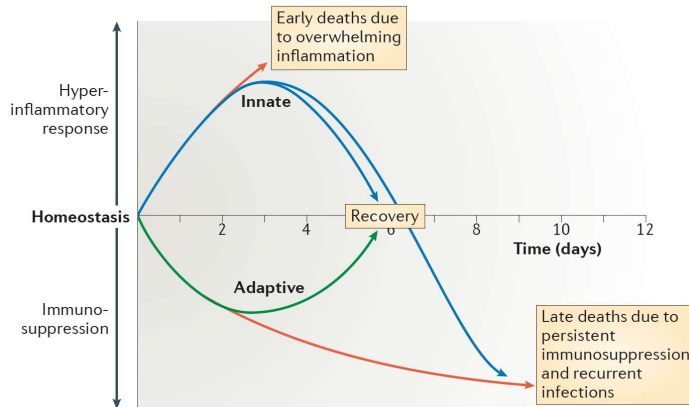
In the absence of clinical signs, immunosuppression is defined by the combination of:

A documented alteration in any aspect of immune function
(whether quantitative or qualitative, irrespective of the immune function affected or the underlying cause)
+
An increased occurrence of infections (according to international classification standards)
within a specific patient cohort.

This association must be independent of clinical confounders,
meaning it must persist in a multivariate analysis that accounts for potential confounding factors.

Adapted from Abbas AK et al. *Cellular and Molecular Immunology*. 7th edition, 2012
Chinen and Shearer, *J Allergy Clin Immunol* 2010
Monneret et al. *Cytometry A*, 2019 ; Venet et al. *NY Acad Sci* 2021

Increased secondary / nosocomial infections after sepsis



Decreased clearance of initial infection
(Torgersen 2009)

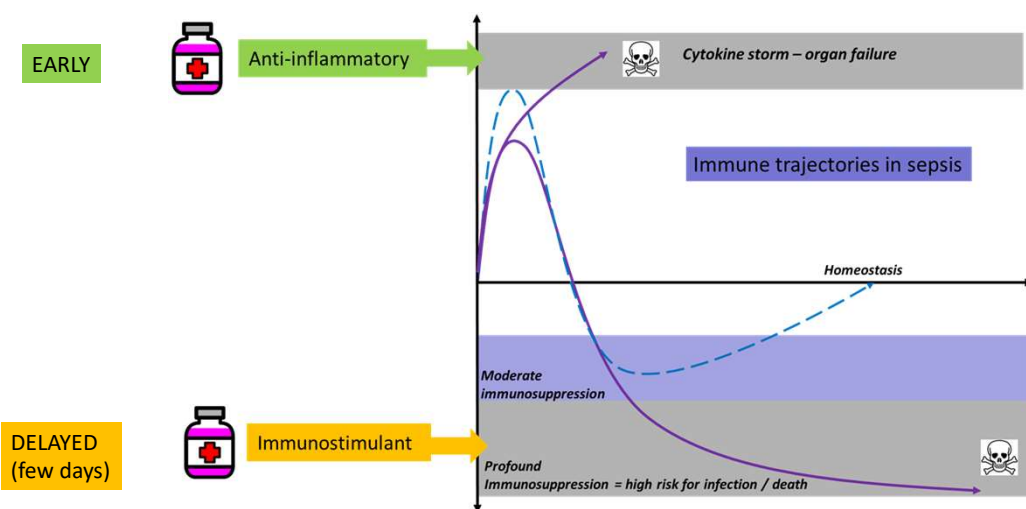
Severe fungal Infections
(Leroy, CCM 2009 ; Hatermink ICM 2003)

Viral reactivation : CMV, HSV
(Luyt, AJRCCM 2007 ; Limaye, JAMA 2008)

Increased nosocomial infections
(Landelle, ICM 2010, Grimaldi ICM 2011)

Aspergillosis ↑
Candida ↑
(severe COVID 19)

Rethinking immunotherapy in sepsis: a novel vision

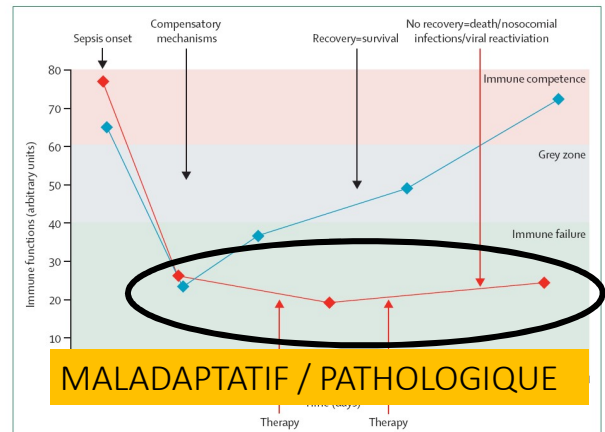
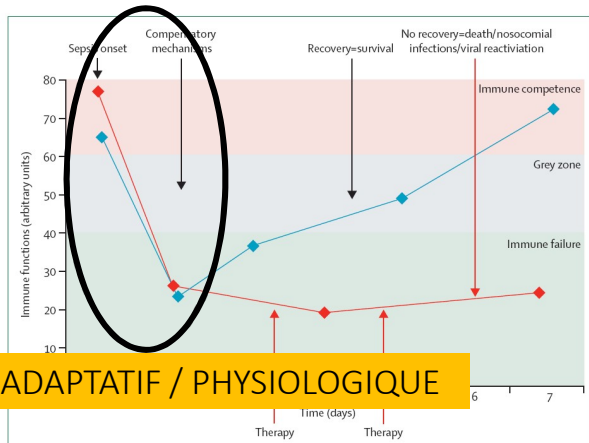


Monneret et al. Cyto A 2019

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

Richard S Hotchkiss, Guillaume Monneret, Didier Payen

THE LANCET
Infectious Diseases
2013



“one size fits all” does not work => Individualized medicine

Patients' heterogeneity



Infection

Exacerbated inflammation
Pathogens (PAMPs)
Injury (DAMPs)

Patients

Age
Comorbidities
CMV+ serology
Genetic
background
Microbiome

Central Regulation

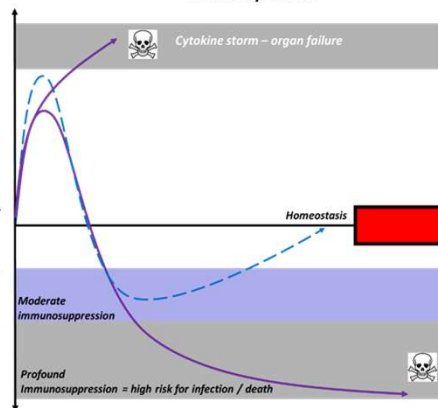
Sympathetic
Parasympathetic
HPA axis

Treatments

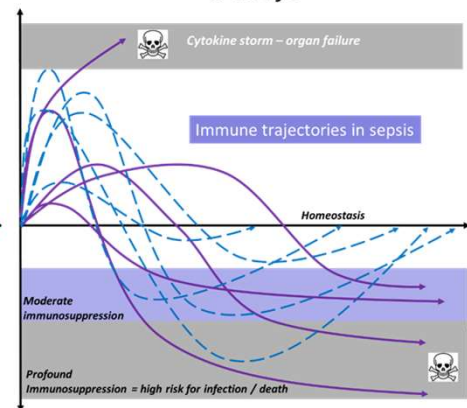
Antibiotics
Catecholamines
Blood transfusion
Steroids
Nutrition

Timing of
ICU admission

Conceptual

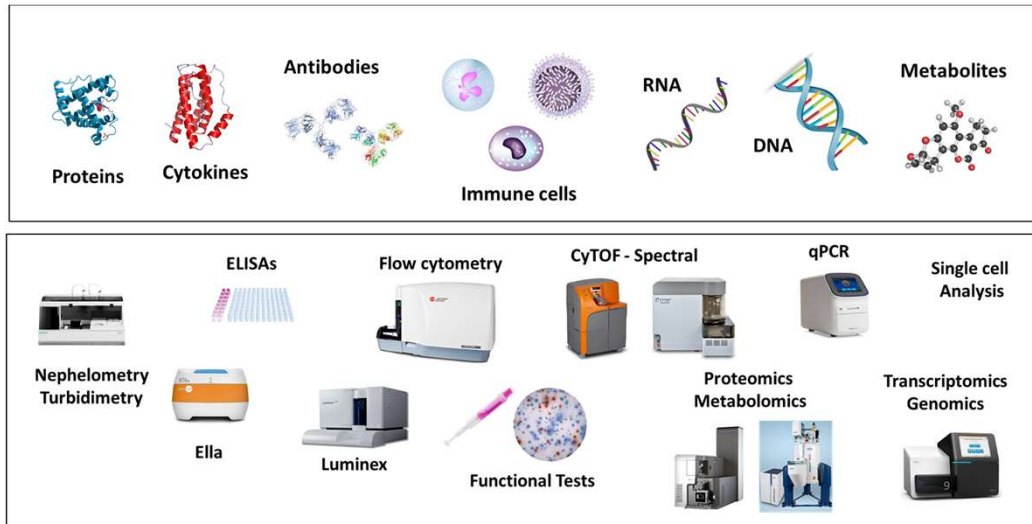


True life

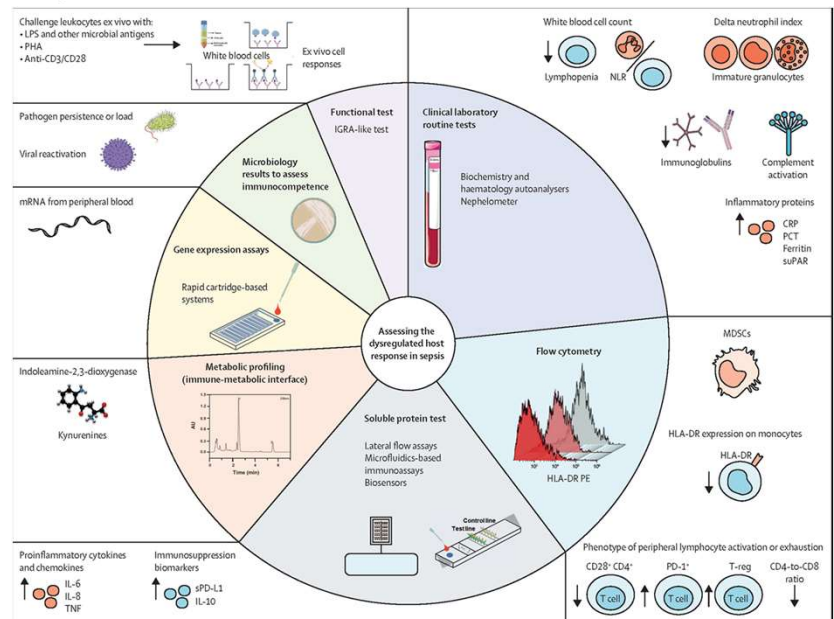


Monneret et al. Cyto A 2019

What parameters, what technologies: it is a bit of a mess (for intensivists)



Profiling the dysregulated immune response in sepsis: overcoming challenges to achieve the goal of precision medicine



Cajander et al. 2024
THE LANCET
Respiratory Medicine

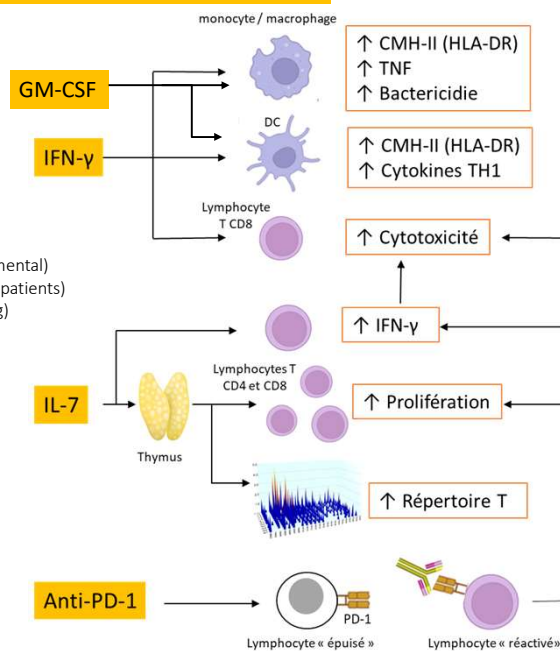


What parameters, what technologies ?
Let's simplify the stakes !

	automated ELISA / cell count	Flow cytometry	Functional tests	Transcriptomic signature	Single cell RNAseq
Availability	+++	++	++	+	-
Standardization	+++	++	+	+/-	-
Time-to-results	+++	++	+	+	-
Not expensive (< 10 €)	+++	++	++	++	-
Clinical Performances	+	+++	++	++ (to be confirmed)	(to be explored)
Publication potential	+	+	++	++	++++

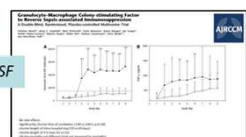
Immunotherapy in sepsis = current candidates

- + > 30 articles preclinical results (experimental)
- + > 20 articles preclinical results (ex vivo patients)
- + > 50 clinical cases or series (either drug)

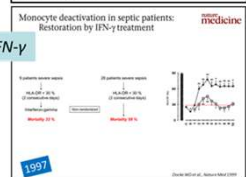


RCT

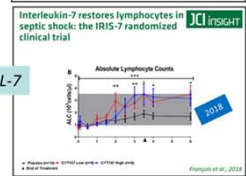
GM-CSF



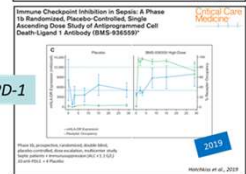
IFN-γ



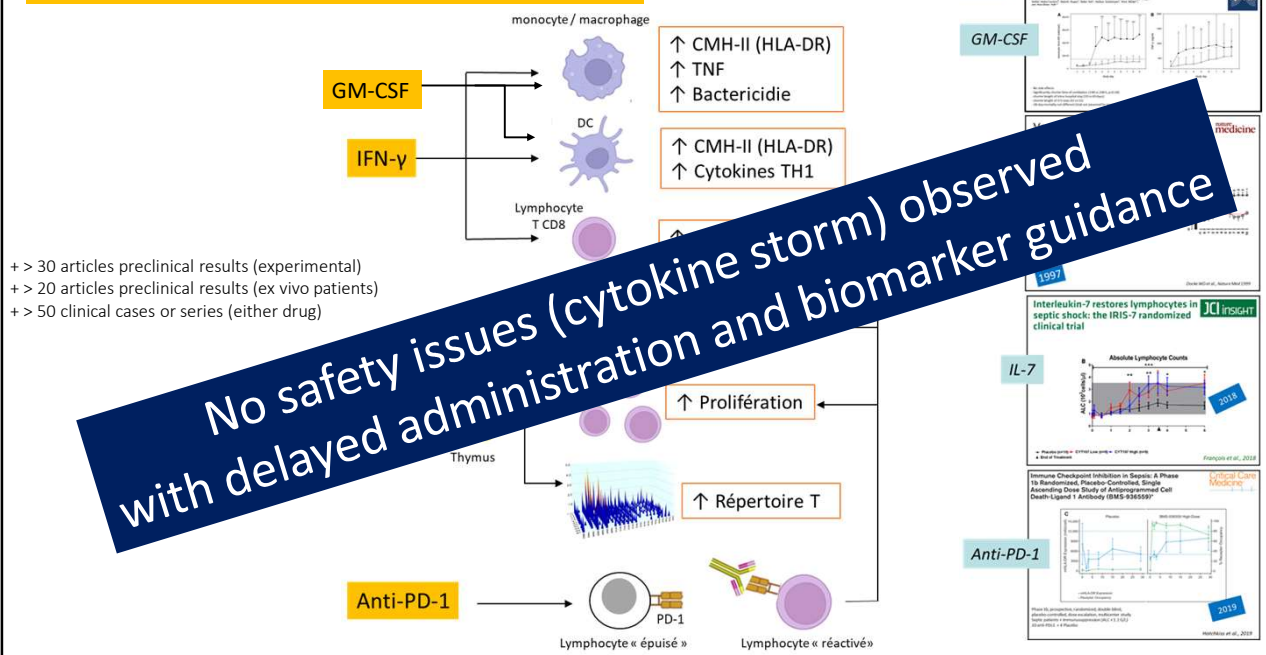
IL-7



Anti-PD-1



Immunotherapy in sepsis = current candidates



Immunostimulation in sepsis / ICU – multicentric RCT in progress

IFN-γ

IFN-γ : IMMUNOSEP (EU – M Netea & E Bourboulis) - EU
 IFN-γ : IGNORANT (F – AC Lukaszewicz) – HCL / BioMérieux
 IFN-γ : INFINITY (F – C De Roquetaillade & G Chousterman) PHRC-I
 IFN-γ : PLATINIUM (F – B. François) PHRC

mHLA-DR < 5 000 AB/C

mHLA-DR < 8 000 AB/C

GM-CSF

GM-CSF (pediatrics) : USA – M Hall (≈ 1000 patients)
 GM-CSF : SepTIC – UK – T Gordon (≈ 1300 patients)
 GM-CSF : sepsis (Partner therapeutics - US – Barda)

Ex vivo TNF release

Ly count < 1.1 G/L

mHLA-DR < 8 000 AB/C

IL-7

IL7 : AUS / NZ - S Pfinfer (≈ 1000 patients)

Ly count

Blood purification

Hemotune (CH)

mHLA-DR < 8 000 AB/C

CONCLUSION



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https://www.apmnews.com/story.php?objet=377374&idmail=.O.oQ4xQ035ib7LrDKvHBQowLnbigX4h1kTFHnkGuPYa-Z6uVyyDLdagl1o_vl8GK383TZateB46Y-ZyIRZFCcLL1EOyyf-L1nmUewe-Tb_jmQqI02RKRjY0yRZVRimiZ7zmseR2U-kt-ybdv5dM343YgBsGIF_QzLdFoTxjPu6DI0qHuof_G4RgMqRmgTihzqphIR0Q9XMsEzX_EqobJ6-P0hlokNQAQpCBRI18u0JJQM

DÉPÊCHE - Jeudi 06 janvier 2022 - 18:10

Un effort "majeur" reste à faire pour individualiser le traitement du Covid sévère

Le Pr Timsit a rappelé lors de son audition les différentes phases de la maladie: la partie virale initiale "pas très sévère", la partie immunologique qui a un effet délétère "considérable" sur l'organisme et, chez les patients les plus sévères, la phase "d'immuno-paralysie post-agressive" caractérisée par des surinfections et des complications infectieuses qui dégradent lourdement le pronostic des malades, en particulier les plus sévères.



Assemblée nationale, F, 6 janvier 2022

The right drug, at the right time in the right patient

Early step

CRP / PCT
IL-6
IL-18
Ferritin
suPAR
S100
Nucleosome
sTREM-1
....

Adult and pediatric ARDS:

Hypoinflammatory*
Hyperinflammatory*
(53–63)

Reactive and
uninflamed (63–64)

Adult sepsis:
Coagulation (dA, dB, dC, dD)* (43)

Proteins
Biomarkers
Proteomics



Under evaluation

RNA
Microarray
Bulk seq
Single cell seq

Adult sepsis:

SRS1 and SRS2*
Phenotypes (21–23)

Mars1—Mars4 (24)

Adult and pediatric sepsis:
Inflammopathic, Adaptive*,
and Coagulopathic (25–27)

mHLA-DR
CD4
MDSC
PD-1
Functional
testing

Adult sepsis flow cytometry:

Non-improvers,
decliners, improvers,
high expressors
(33–34)

Immunology
Immunophenotyping
Functional assay



Big data

PHENOTYPES

Patients' characteristics

Age, sex, comorbidities,
SAPS II, SOFA,
Type of germ, bacterial load,
organ, virulence factors...



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Delayed
immunosuppression

Thanks for your attention



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Immunology lab., Hôpital E. Herriot, Lyon, F
CIRI, Lyon, F

