Zagreb Spring Symposium of Applied CVascular Physiology & Treatment

Is sepsis an immunological disease? Then…

Didier Payen, MD,PhD

Emeritus Professor
University Paris 7 Denis Diderot

Thank You Ina, so « amazing » energy to achieve it…

Nice, Octobre 2022

Immunité-inflammation: nouveaux concepts

Didier Payen, MD,PhD

Professor Emérite
Université Paris 7, Denis Diderot

Le Sepsis: est une maladie immunologique? Si oui, y a-t-il des conséquences thérapeutiques?

Didier Payen, MD,PhD

Professeur Emérite
Université Paris 7 Denis Diderot

What is factually observed?

Quels sont aspects factuels?

The Facts

- Only **30% of patients** suffering from **severe sepsis** have **positive blood culture ➔ 70 % do not!**
- **Inflammation can persist despite adequate treatment** against pathogens
- **Endocarditis** patients **rarely (2%) experienced septic shock**, despite frequent **positive BC**
- **Severe infections can be controlled only by immunomodulation** without traitement against pathogen. Ex: **COVID-19**
- **Secondary infections** rate is **relatively incompressible** (20 to 30%) and can be controlled by **immuno-stimulation**

During 20 yrs, what happened?

- Sepsis **definition** more or less **stable till the Sepsis 3, more concerned by OF**
- **Epidemiology** ➔ ↗**incidence, age, comorbidities**
- **Better education**, **faster diagnosis**, **reasonable recommendations (SSC x 3)**
- **Huge technological progresses**: **genotyping**; **transcriptomic**; **proteomic**; **metabolomic**…
- More clear picture of **immuno-inflammatory processes**
- **Reasonable supportive therapy**: **Fluid amount**; **pressors**; **ventilation**; **RRT**; **ECorp Circ…**

In sepsis, what is killing patients?

- **Infection itself? Probaly not initially**
- **Shock and Hypoperfusion: do the patient died because of shock or with shock?**
- **Systemic inflammation? ➔ modulation might be a major advance**
- **Energetic failure? Protection or recovery from cell energetic failure might be successful…**
- **High susceptibility… genetic factors; epigenetic …**

THE PRINCIPLES AND PRACTICE OF MEDICINE

DESIGNED FOR THE USE OF PRACTITIONERS AND STUDENTS OF MEDICINE

BY

THE LATE SIR WILLIAM OSLER, BT., M.D., F.R.S.

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**.

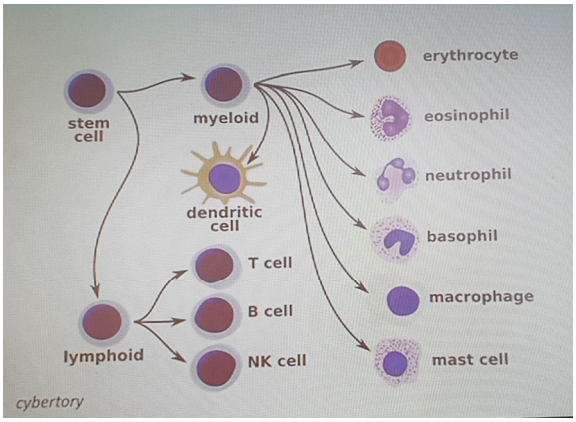
- **Some families seem more susceptible than others**;
- The **blood-serum of persons suffering from advanced chronic disease** was found to **be less destructive to the *staphylococci aureus* than normal human serum**

Let's refresh your knowledge

Quelques rappels…

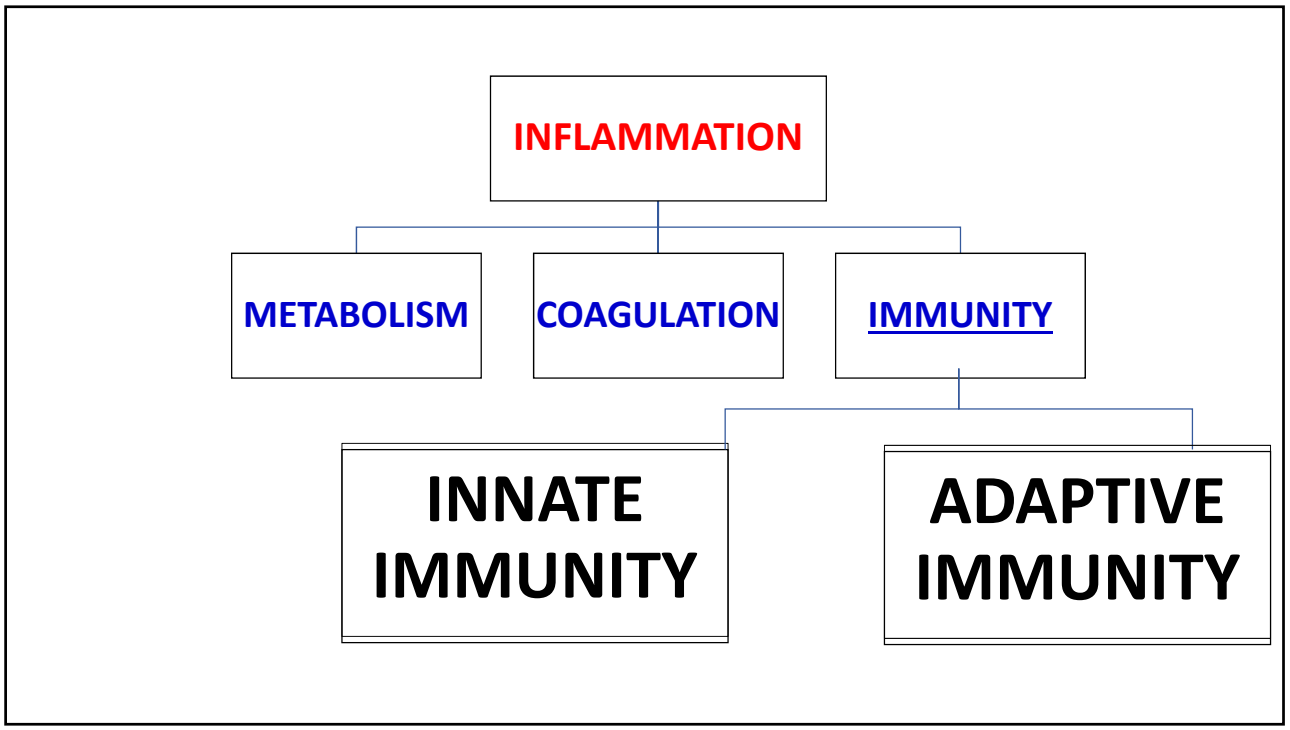
The key cells of immune system

- **Resident cells in tissues**
  - Ex: *macrophages; dendritic cells; mast cells*
- **Circulatory cells**
  - Ex: *neutrophils; monocytes; eosinophils; lymphocytes*
- **Tissue cells**
  - Ex: *epithelial cells (structural)*



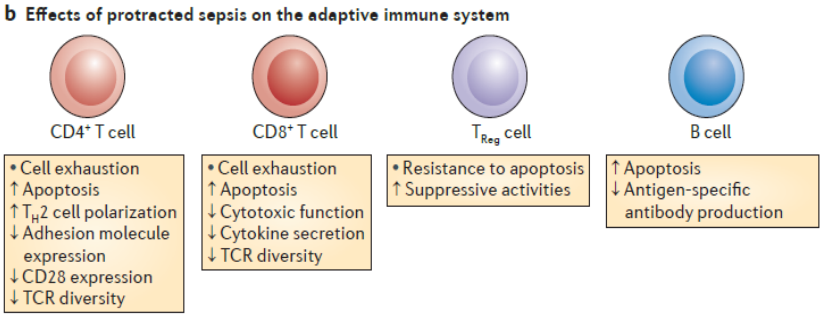
The actors of the immune response

- **Innate response**: **monocytes macrophages dendritic cells**
  - ***Cellular plasticity***: **dendritic cells ↔ monocytes ↔ macrophage**
  - ***Immune memory* : epigenetic** = **"Trained Immunity" +++ for BCG**
  - ***APCells to* Lymphocytes (HLA class I; II)**
- **Adaptive response**: "naïve" 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***



Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

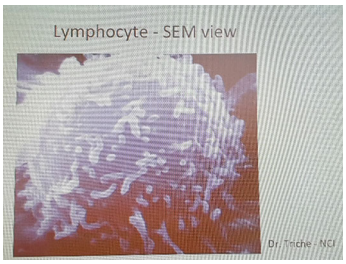
Richard S. Hotchkiss[1], Guillaume Monneret[2] and Didier Payen[3]



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

Chronology of the immune response against 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**

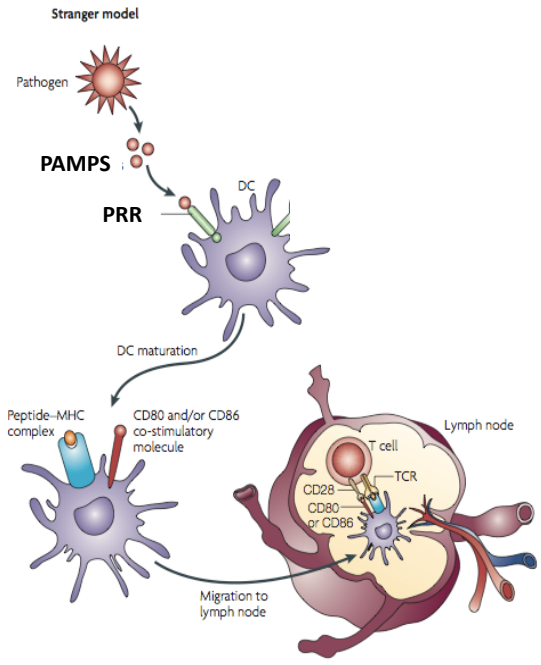


Sepsis: we better understand and conceptualize …

From the last 20 years, concept moved a lot… especially

- **from infection itself to immuno-inflammatory response leading to Organ Failure,**
- **with a kinetic of rapid changes in patterns.**

Le concept… le modèle « étranger » et le modèle « danger »

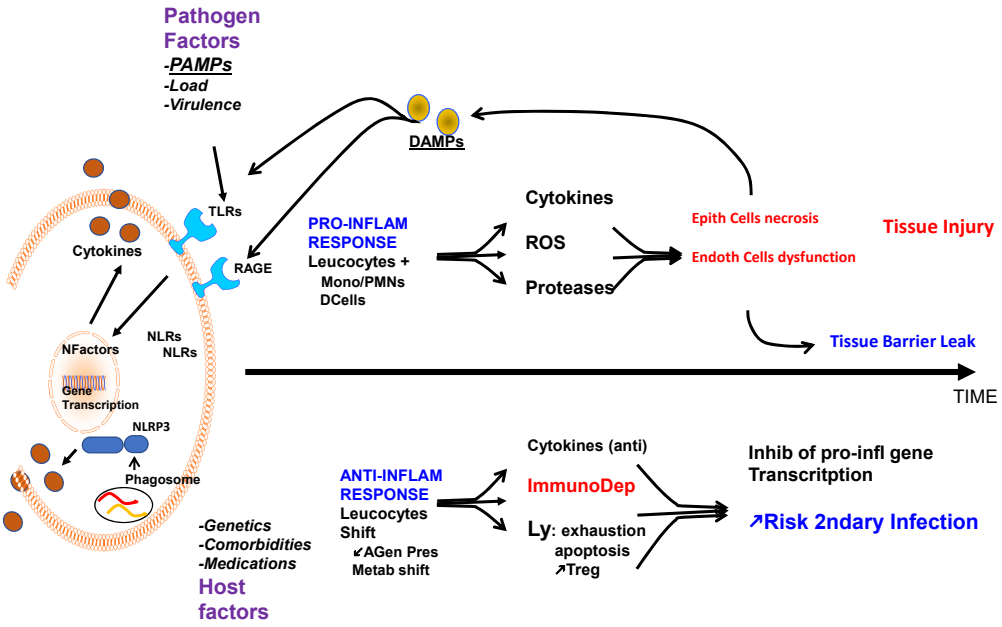


1994 Matzinger:

Stranger/Danger model

Pathogen-Associated Molecular patterns

- Bacteria → **PAMPs**
- **Fixed at cell receptors**
- **TLRs, NODs, etc…**
- **Induce DNA transcription** → ***mediators synthesis***



La chronologie est cruciale…

Immunity

Human Monocytes Undergo Functional Re-programming during Sepsis Mediated by Hypoxia-Inducible Factor-1α

Irina N. Shalova,[1] Jyue Yuan Lim,[1] Manesh Chittezhath,[1] Annelies S. Zinkernagel,[2,6] Federico Beasley,[2] Enrique Hernández-Jiménez,[3] Victor Toledano,[3] Carolina Cubillos-Zapata,[3] Annamaria Rapisarda,[4] Jinmiao Chen,[1] Kaibo Duan,[1] Henry Yang,[1] Michael Poidinger,[1] Giovanni Melillo,[5] Victor Nizet,[2] Francisco Amalich,[3] Eduardo López-Collazo,[3] and Subhra K. Biswas[1,*]

Immunity *42*, 484–498, March 17, 2015

The dynamic nature of sepsis ➔ at least 2 phases have been recognized:

- an ***early inflammatory*** **phase and**
- a ***late immunosuppressive phase***

Early phase: ➔ ***leukocyte activation, cytokine storm,*** *and a* ***systemic inflammatory response***

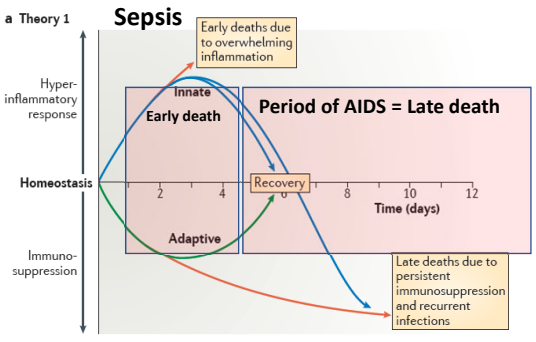
Later phase: ➔ ***immunosuppression, leukocyte deactivation, increased risks of secondary infection, and higher mortality***

more complicated because the *overlapping between* inflammatory and immunosuppressive processes

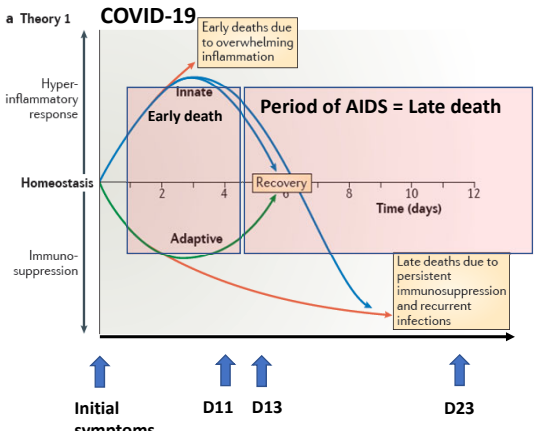
➔ May explain the FAILURE of numerous RCTs
➔ to REDUCE MORTALITY

Chronology in Sepsis & COVID-19 clinic, biology, inflammation ➔ longitudinal studies

AIDS: Acute Immuno-Depressed Syndrome



Hotchkiss, R, Monneret G, Payen, D
Nature Review Immunol 2013



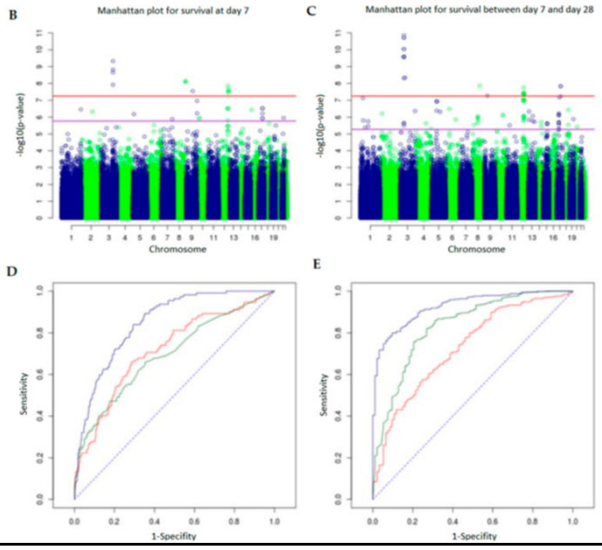
Payen, D, Cravat M, et al
Frontiers Immunol 2020

Genetic Predisposition to the Mortality in Septic Shock Patients: From GWAS to the Identification of a Regulatory Variant Modulating the Activity of a CISH Enhancer

Int. J. Mol. Sci. **2021**, 22, 5852.

International Journal of Molecular Sciences

*Florian Hosteit, Audrey Brisebarre, Claire Dupuis, Sabrina Baaklini, Denis Puthier , Christine Brun, Lydie C. Pradel, Pascal Rihet, and Didier Payen 4,**



832 Multicentic septic shock patients
(PROWESS data base)

Association of **139 SNPs with death**. The **most significant SNPs** were within the **CISH gene involved in cytokine regulation**

Manhattan plots show the association of **SNPs** with
(B) Early mortality: the GWAS **identified 12 SNPs**
(C) Late mortality: the GWAS **identified 16 SNPs ≠ than early**

ROC curves for **the prediction of early (D)** and **late (E) mortality** with **SAPS II**(red), **SNPs** (green), and **both** (blue).

Phase 1

Acute phase

Despite progresses in supportive therapies (adequate fluid management; limitation on iatrogenic complications, …)

still 50% of the patients who die, are dying during the 1st post-admission 4 days

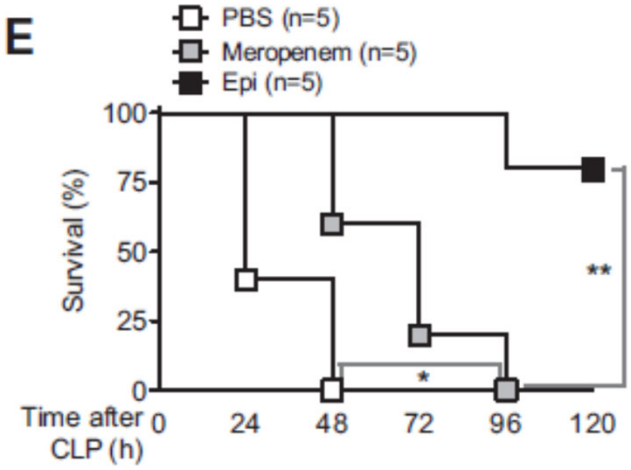
Is is time for another approach?

Anthracyclines Induce DNA Damage Response-Mediated Protection against Severe Sepsis

Immunity Article

Immunity 39, 874–884, 2013

Nuno Figueiredo, … and Luis F. Moita



- **epirubicin** i.p. **at the time of CLP** and **again 24 hr later increased the survival (p < 0.001)**
- **Independently from mouse strain**
- " " " " of **sepsis origins** (pneumonia or peritoneal sepsis
- **epirubicin-treated + CLP** has **similar bacterial load in blood and organs** 24 hr post-CLP ➔ **inflammation kills, not infection!**
- a **substantial reduction in the levels of inflammatory mediators** (TNF, IL-1β, IL-6, and HMGB1)

Is it relevant for the clinician?

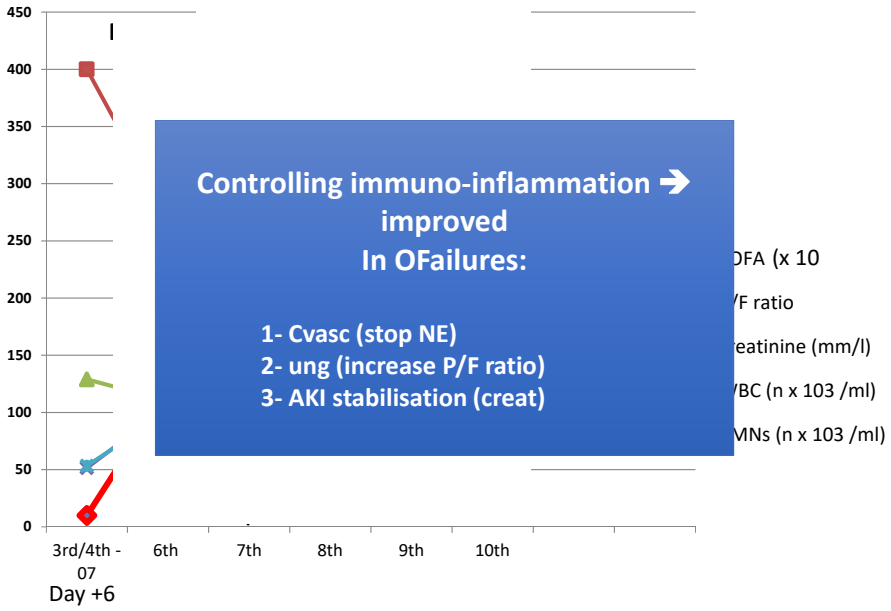
D0: Oesophagectomy

D1 Early post-operative period
-***Hypoxemia*** with pleural effusion ➔ **chest drainage**
-***CCVasc collaps*** responding to **fluid challenge**
-***Acute Kidney Injury*** AKIN3

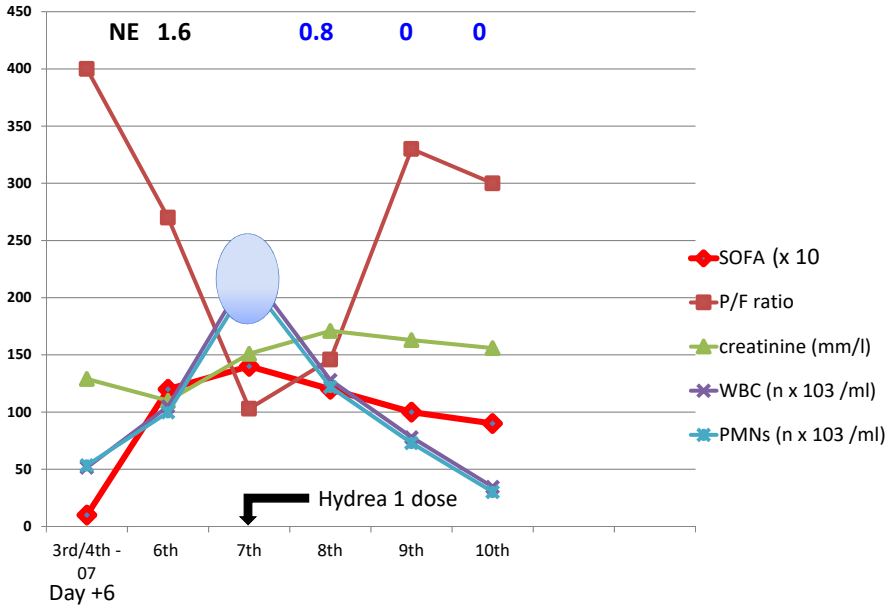
D8: severe SIRS
WC↗ from 6 400 to 64 600
BAL: 10^2 Citrobacter, ECBU (-), HC (-), HC sur PAC (-), Plèvres (-)
OGDF: No fistulae
TDM IV opacifié: ***NO leak, NO mediastinitis***

D11: M O S F
GB: **223 000 98% PMNs (Chronic ttmt fro ITP with GFactor)**
BC+ : multiple bateria Serratia et Citrobacter, **Tracheal asp** ***>10 ^{7} Citrobacter***,
OGDF & **TDM** no fistulae
AB: 3 molecules (Cefotax; linezolid; Imipenem)

Let's see the results of immune monitoring….



Let's see the results of immune monitoring….



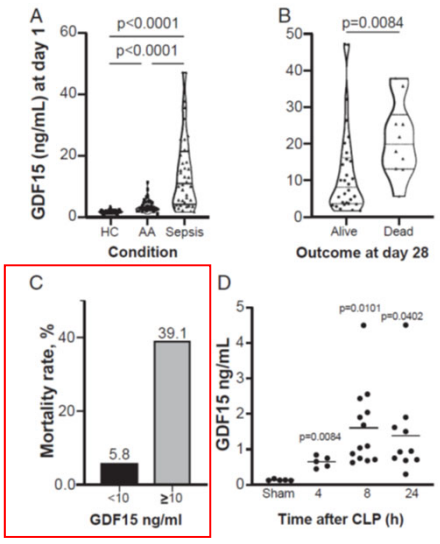
CXCL5-mediated recruitment of neutrophils into the peritoneal cavity of *Gdf15*-deficient mice protects against abdominal sepsis

Isa Santos[a,b,1], Henrique G. Colaço[a,1], Ana Neves-Costa[a,1], Elsa Seixas[a], Tiago R. Velho[a], Dora Pedroso[a], André Barros[a], Rui Martins[a], Nuno Carvalho[c,d], Didier Payen[e], Sebastian Weis[f,g,h], Hyon-Seung Yi[i], Minho Shong[j], and Luís F. Moita[a,1,2]

PNAS USA. 2020 Jun 2; 117(22): 12281–12287.

Significance

Sepsis remains a leading cause of death. New insights into its pathophysiology are likely to be key to the development of effective therapeutic strategies against sepsis. Given the role of GDF15 in metabolism regulation and in cachexia during late stages of cancer, features that also occur in sepsis, elucidation of the possible mechanistic role of GDF15 in sepsis is of great importance. We find that septic patients have very high levels of GDF15 in the peripheral blood, which correlate with clinical outcomes. Using *Gdf15*-deficient mice, we show that GDF15 plays a causal role in sepsis by delaying the local control of infection. These findings suggest GDF15 as a potential therapeutic target in sepsis secondary to a bacterial infection.



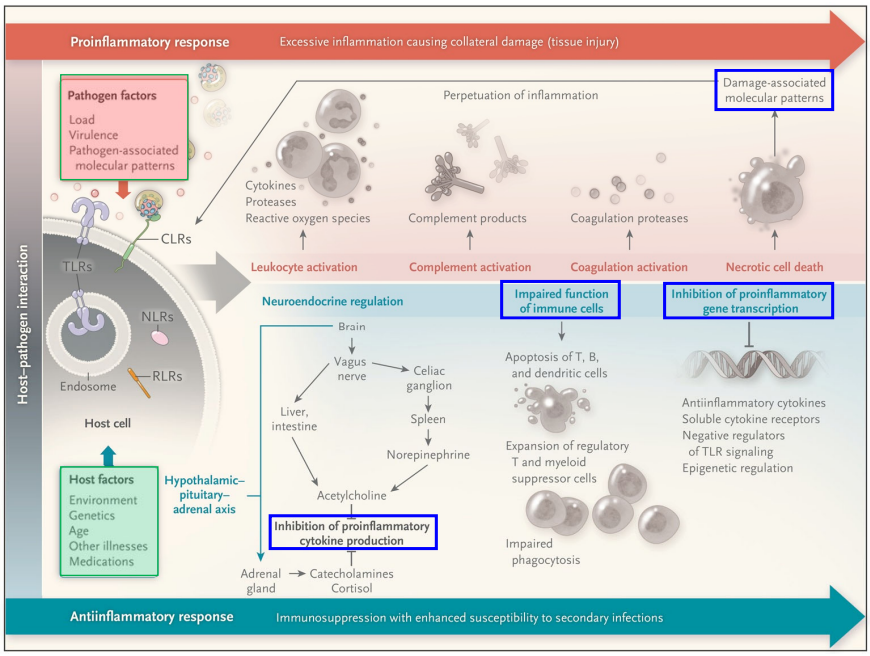
GDF15 (induced by infection)

(A) Serum levels in the **AA** and **SS** compared with the HC group.
(B) Serum levels of GDF15 in **septic patients D1 of ICU admission & outcome at D28 post admission**.

Phase 2

Starts early and lasts more than 5 days

It is the Host Response to Sepsis that kills more than the infection?



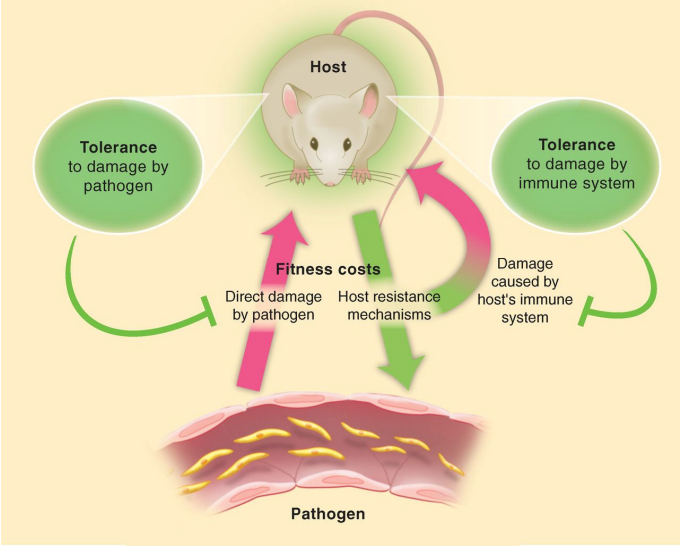
NEJM 2013; 369: 840

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

Disease Tolerance as a Defense Strategy

Ruslan Medzhitov,[1*] David S. Schneider,[2*] Miguel P. Soares[3*]

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

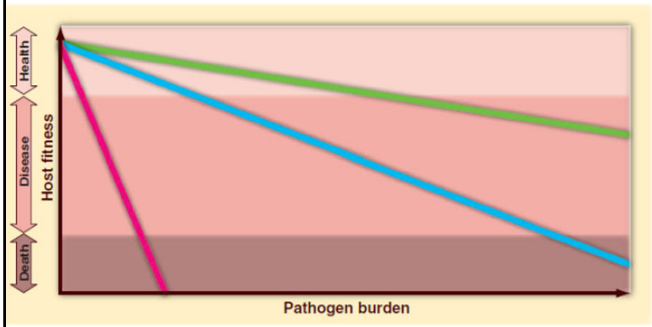


Medzhitov et al. Science 2012; 355:936-41

Disease Tolerance as a Defense Strategy

Ruslan Medzhitov,[1]* David S. Schneider,[2]* Miguel P. Soares[3]*

Tissue tolerance to damage may largely differ



g. 2. Different tissues and physiological processes vary in tolerance capacity. Tissues depicted in red ve the lowest tolerance to damage, the blue has an intermediate tolerance, and the green has the ghest tolerance capacity.

Science AAAS

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

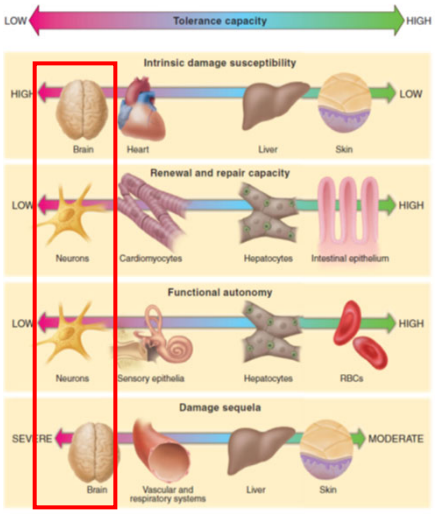


Fig. 3. Tolerance capacity is a function of intrinsic damage susceptibility, repair capacity, functional autonomy, and damage sequelae of different tissues and organs. Although tissues generally tend to fall at the same ends of the four spectra, the four characteristics do not necessarily correlate with each other.

Un des meilleurs marqueurs pour évlauer l'état immunitaire en pratique clinique…

Expression à la surface monocytaire sanguine de l'HLA-DR

(marqueur de l'expression du MHC class II)

Synapse immunitaire entre immunité innée et adaptative

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

Crit Care Med 2009 Vol. 37, No. 10

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

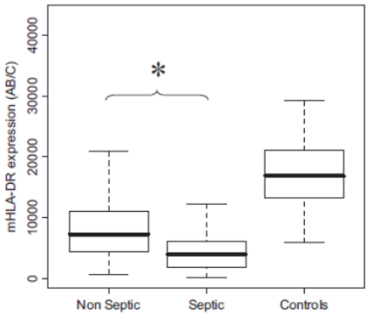


Table 2. Severity scores, early mHLA-DR within the first 3 days after admission and 28-day mortality in different patient categories

Categories	Sepsis (n = 90)	Neurologic (n = 85)	Hemorrhagic (n = 29)	Trauma (n = 20)	Postop (n = 16)	Miscellaneous (n = 43)
SAPS II	46 (33–59)	37 (30–49)	32 (24–50)	32 (22–38)	26 (24–34)	43 (32–55)
SOFA day 0	5 (2–10)	4 (3–7)	6 (4–8)	3 (2–5)	3 (1–6)	3 (2–6)
Early mHLA0DR	2843 (1329–5829)	7174 (4708–10345)	7219 (3556–11046)	5164 (2552–12581)	8303 (3850–10210)	4847 (2235–11337)
28-day mortality, n; (%)	12 (13.3)	15 (17.6)	6 (20.7)	1 (5.0)	1 (6.2)	3 (7.0)

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

Annals of Intensive Care (2022) 12:39
https://doi.org/10.1186/s13613-022-01010-y

C. de Roquetaillade[1,7*†], C. Dupuis[2], V. Faivre[3], A. C. Lukaszewicz[4], C. Brumpt[5] and D. Payen[6†]

1053 Pts; 592 pts: 2 HLA-DR Mes

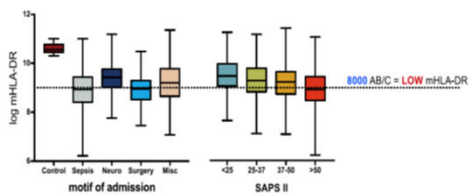


Fig. 1 Initial mHLA-DR measurement according to the motif of admission and initial severity, comparison with controls. Low mHLA-DR expression is defined by a level < 8000AB/C

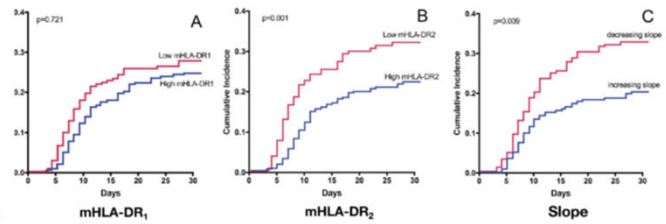
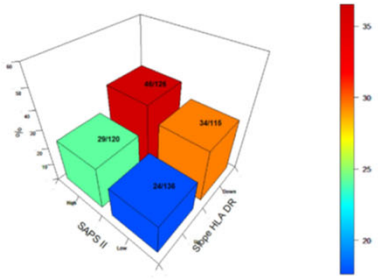


Fig. 2 Cumulative incidence of the occurrence of nosocomial infection depending on different levels of early mHLA-DR expression (**A**), second mHLA-DR expression (**B**), and depending on the trend of mHLA-DR (**C**) in patients with two measurements ($n = 592$). Low mHLA-DR expression is defined by a level < 8000. *p*-value estimated by a multivariate subdistribution survival model



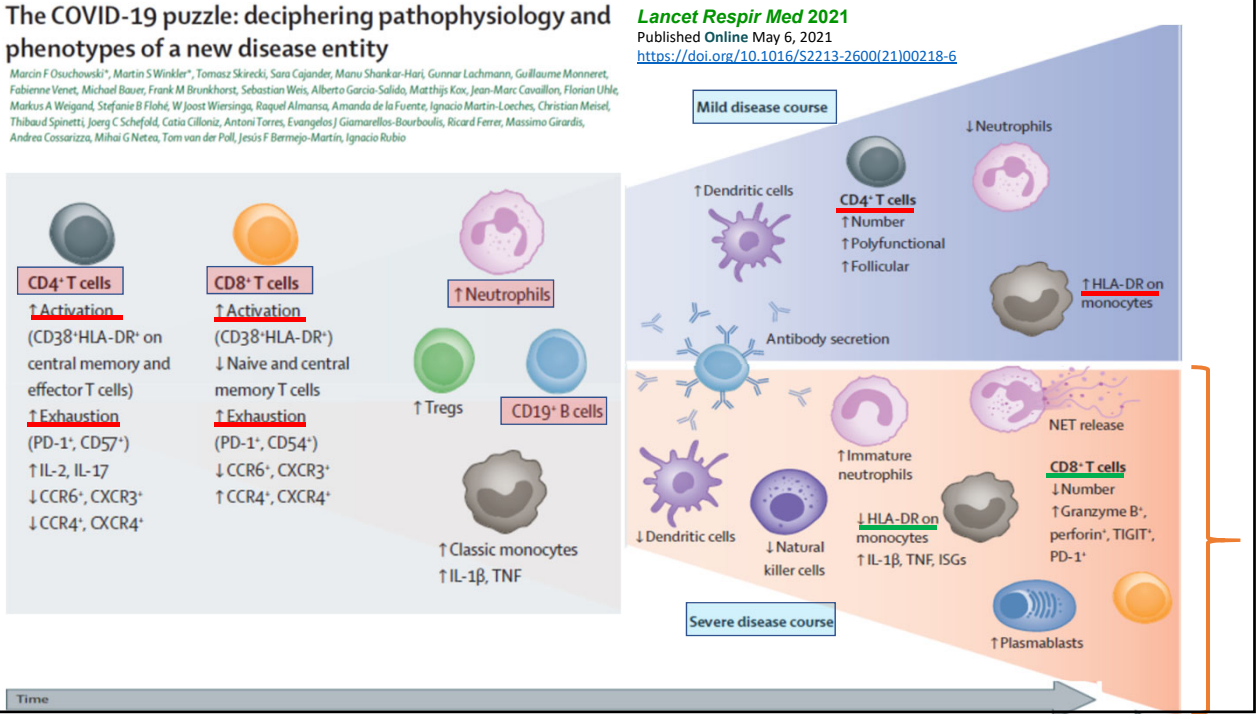
Relation between SAPS II—the slope of mHLA-DR and the occurrence of secondary infection at day 28.

The COVID-19 clinical phenotypes

The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity

Marcin F Osuchowski*, Martin S Winkler*, Tomasz Skirecki, Sara Cajander, Manu Shankar-Hari, Gunnar Lachmann, Guillaume Monneret, Fabienne Venet, Michael Bauer, Frank M Brunkhorst, Sebastian Weis, Alberto Garcia-Salido, Matthijs Kox, Jean-Marc Cavaillon, Florian Uhle, Markus A Weigand, Stefanie B Flohé, W Joost Wiersinga, Raquel Almansa, Amanda de la Fuente, Ignacio Martin-Loeches, Christian Meisel, Thibaud Spinetti, Joerg C Schefold, Catia Cilloniz, Antoni Torres, Evangelos J Giamarellos-Bourboulis, Ricard Ferrer, Massimo Girardis, Andrea Cossarizza, Mihai G Netea, Tom van der Poll, Jesús F Bermejo-Martín, Ignacio Rubio

Lancet Respir Med 2021
Published **Online** May 6, 2021
https://doi.org/10.1016/S2213-2600(21)00218-6



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*†]

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

Patients' characteristics	
Age (y.o.)	66 [60; 72]/(54|75)
Gender (male)	12 (80)
BMI (kg/m²)	29 [24.5; 32]/(22|43)
Outcomes	
VAP	4 (26.7)
Delay before VAP (miss=11)	13.5 [7; 15.5]/(1|17)
ICU LOS	12 [10; 23]/(5|30)
Death	3 (20)
On admission	
Delay 1st Symptoms	9 [7; 14]/(1|18)
SAPS2	49 [42; 65]/(22|80)
SOFA	7 [4; 8]/(4|12)
SOFA resp	3 [3; 4]/(0|4)

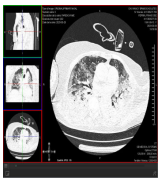
Metabolic parameters		
Albuminemia (miss=1) (g/l)	25.5 [23.1; 27.4]/(18.2|31.5)	35–52
Cholesterol (miss=8) (g/l)	3.2 [2.5; 4]/(1.8|4)	< 2
TG (miss=4) (g/l)	2.1 [1.3; 2.4]/(1.1|2.8)	<1.5
Glycemia (g/l)	1.5 [1.2; 1.8]/(0.9|3.3)	<1.2
Lactate (mM/l)	1.3 [1; 1.5]/(0.8|1.6)	<2
Nonspecific markers of inflammation		
PCT (miss=2)	0.9 [0.5; 3.1]/(0.1|37)	
CRP (miss=1) mg/ml	174.4 [134; 284]/(85|389.2)	0;0–10.0
LDH	439.5 [397; 525]/(388|885)	120–246
Ferritin (miss=3) (µg/l)	888.5 [451; 2385]/(348|7200)	22–322
Ddimers (miss=1) (µg/l)	1742 [1599; 3220]/(804|10000)	45–500
Fibrinogen (miss=2) (g/l)	7.8 [6.5; 8.2]/(4.3|9.9)	1.7–4
C3 (miss=7) (g/l)	1.6 [1.4; 1.8]/(1.2|2.4)	0.9–1.7
C4 (miss=7) (g/l)	0.4 [0.3; 0.4]/(0.3|0.5)	0.12–0.36

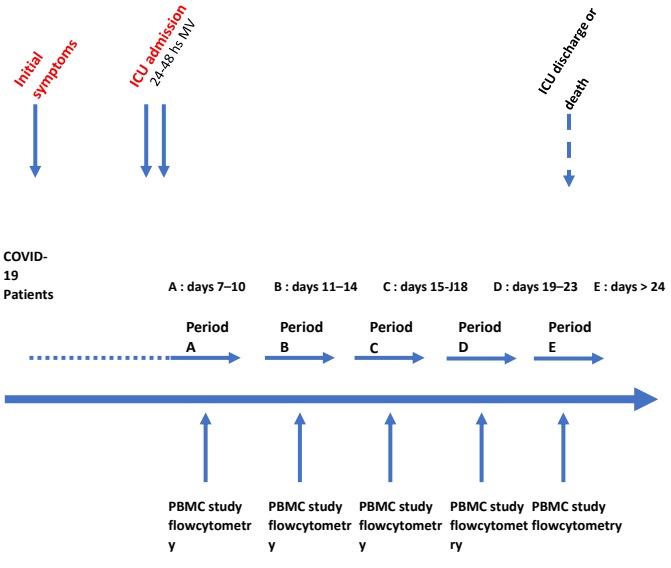
frontiers in Immunology

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

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

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*†]





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

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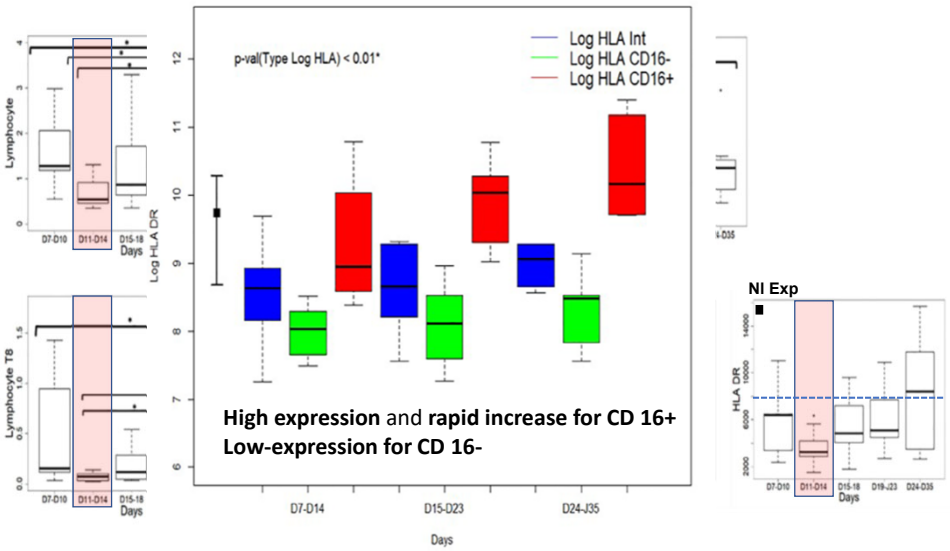
Time evolution of sub-pop of immune cells and HLA-DR exp referring to initial symptoms



High expression and **rapid increase for CD 16+**
Low-expression for CD 16-

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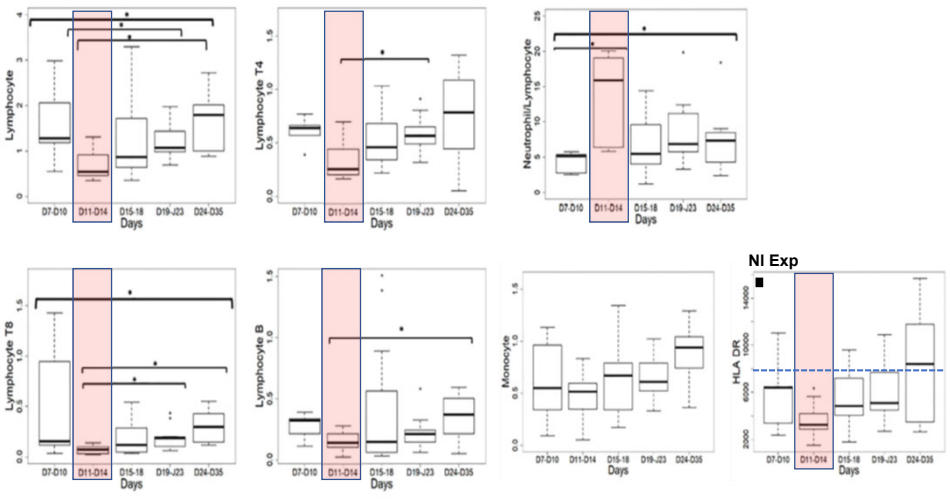


To conclude

- Yes, Sepsis is an inflammatory disease with fast track phases
- As a consequence, therapeutic strategies have to integrate the kinetic of the process
- Nothing is good or bad, it has to be adapted to the patient's tolerability
- What could be initially efficient might be dangerous later on: ex GCst in COVID-19…
- Immunoscope is then required, cheap, easy to get, repeatable, and quantifiable…

The Immunoscope…

Inflammation monitoring is crucial

to know at which immune phase the patient is.

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

Monitoring innate immune alterations in sepsis and related therapies

at least 1500 patients

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

Cohort of 13 post sepsis or septic shock patients

criteria to decide IFNγ:

(1) **an ICU stay over 7 days**;

(2) a **repeatedly diagnosed secondary infections /colonization** or an **uncontrolled initial infection *despite adequate antimicrobial therapy and/or interventional procedure***;

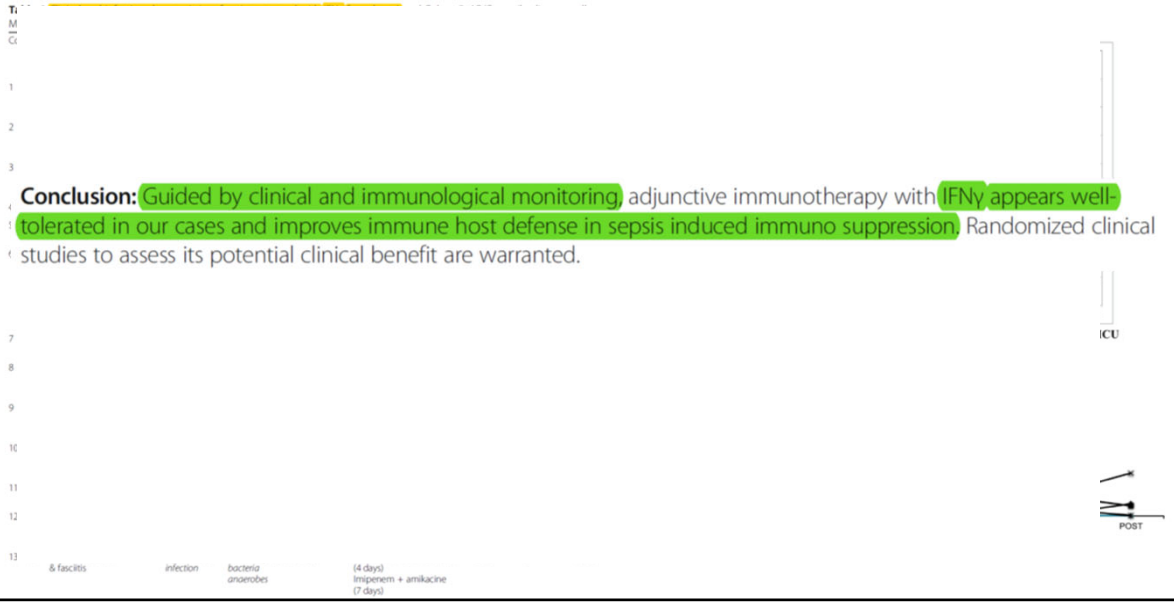
(3) a **stable (at least 2 measurements) low level of mHLA-DR expression** (<8,000 antibody bound/cell (AB/C in our laboratory).

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†]

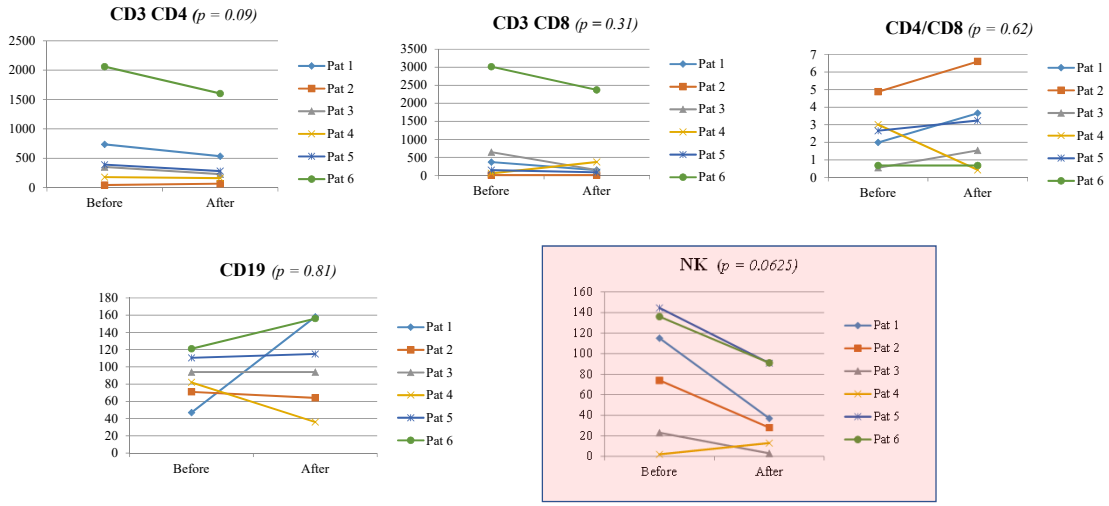
Payen *et al. BMC Infectious Diseases* (2019) 19:931
https://doi.org/10.1186/s12879-019-4526-x

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

Conclusion: Guided by clinical and immunological monitoring, adjunctive immunotherapy with IFNγ appears well-tolerated in our cases and improves immune host defense in sepsis induced immuno suppression. Randomized clinical studies to assess its potential clinical benefit are warranted.



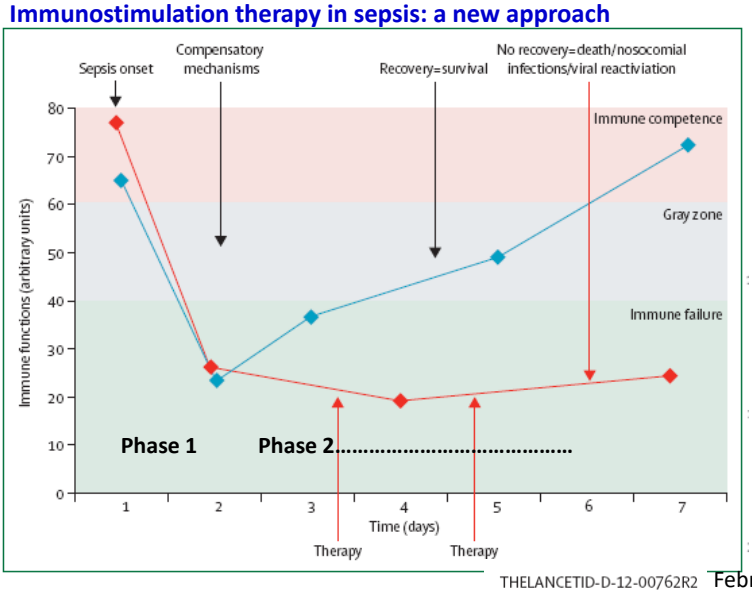
Immuno-phenotyping of white cells (flowcytometry)



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



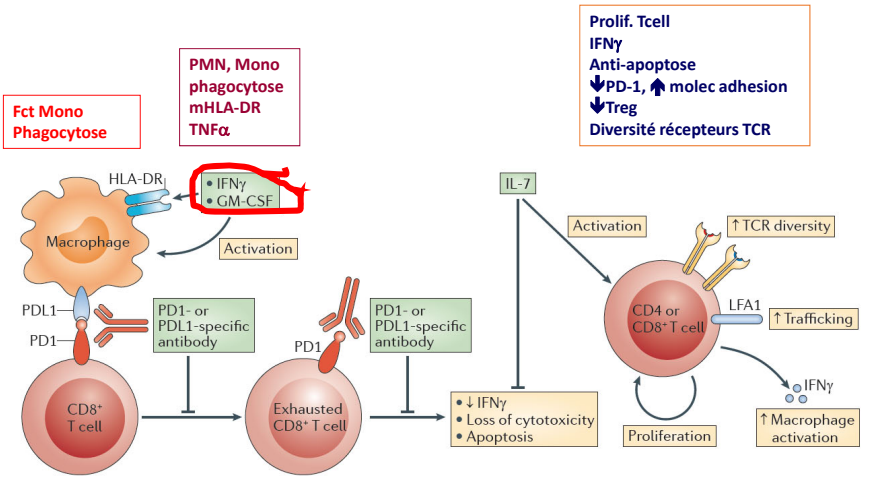
THELANCETID-D-12-00762R2 February 2013

Quelles consequences thérapeutiques ?

L'immunosuppression?

Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

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



IFNγ: signalling, epigenetics and roles in immunity, metabolism, disease and cancer immunotherapy

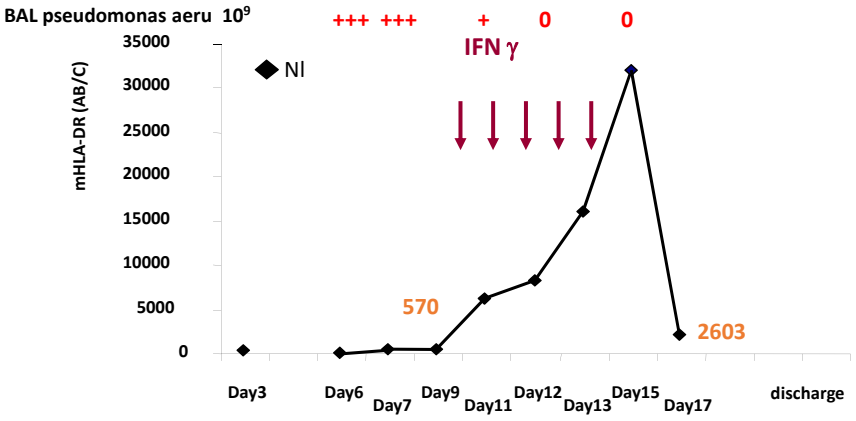
NATURE REVIEWS | IMMUNOLOGY © 2018

What is interferon γ?

- produced by **innate-like lymphocytes** and by **adaptive lymphocytes:**
  - ***T helper 1 (TH1) cells*** and ***cytotoxic T lymphocytes*** (CTLs), in response to ***cytokine*** and ***antigen stimulation***.
- acts on **its receptor** ➔ **rapid and transient activation of nuclear factors** *(Janus kinase (JAK)–signal transducer)* and **activator of transcription** (STAT) **signaling** and **interferon-stimulated gene** (ISG) *induction*.
- Over time, **the cellular IFNγ response evolves +++**
  - **impacting** the **expression** and **function** of various **enzymes** and **regulators** of **metabolism**, **chromatin** and **transcription** ➔ **reprogrammed cellular state**

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

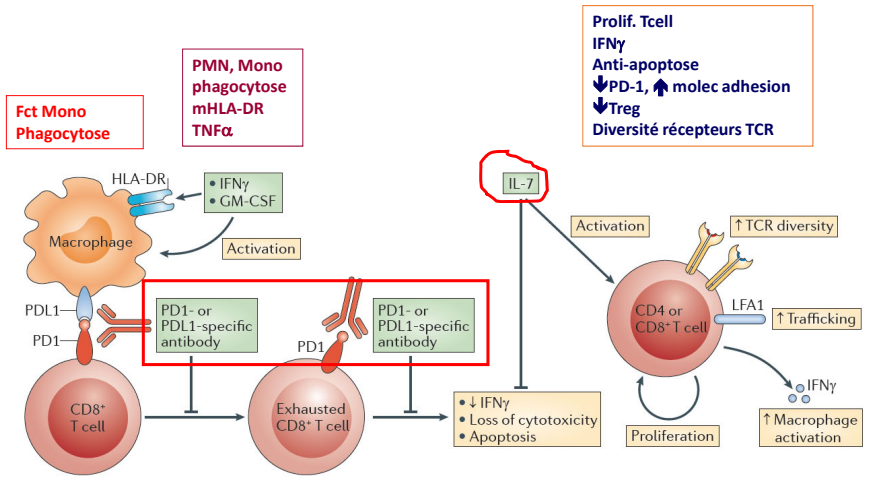
Anne-Claire Lukaszewicz, MD; Marion Grienay, MD; Matthieu Resche-Rigon, MD, PhD; Romain Pirracchio, MD; Valérie Faivre, PhD; Bernadette Boval, MD; Didier Payen, MD, PhD



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

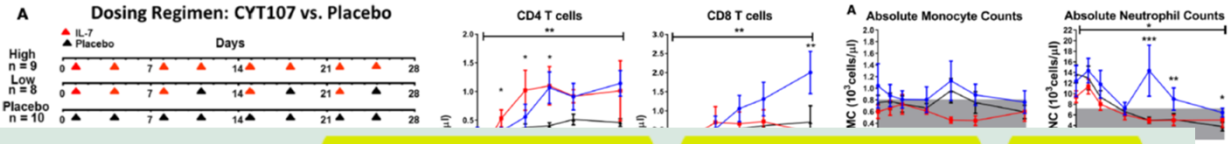
Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

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

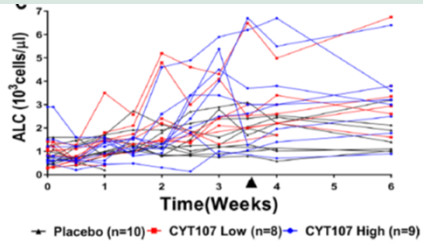


Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial

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.



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

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

ORIGINAL RESEARCH
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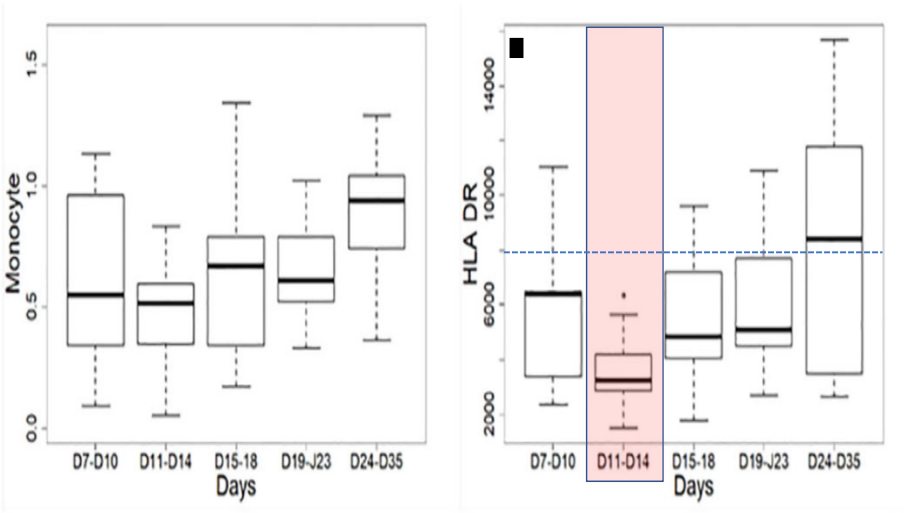
Time evolution of sub-pop of immune cells and HLA-DR exp referring to initial symptoms

NI Exp



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CASE REPORT
published: 07 April 2021
doi: 10.3389/fimmu.2021.645124

S Dickel[1]*, C Grimm[1], K Amschler[2], S Schnitzler [1], J Schanz[3], O Moerer[1], D Payen[4], B Tampe[5] M Winkler[1]

Case Report: Interferon-γ Restores Monocytic Human Leukocyte Antigen Receptor (mHLA-DR) in Severe COVID-19 With Acquired Immunosuppression Syndrome

Methods: We report a case of one-time INFy injection (100 mcg s.c.) in a superinfected 61-year-old man with COVID-19–associated acute respiratory distress syndrome (ARDS), with monitoring of mHLA-DR expression and clinical tolerance.

Observations: Low mHLA-DR pretreatment expression (26.7%) was observed. IFNy therapy leading to a rapid increase in mHLA-DR expression (83.1%).

Conclusions: Severe ARDS in a COVID-19 patient has a deep reduction in mHLA-DR expression concomitantly with secondary infections. The unique IFNy injection was safe and led to a sharp increase in the expression of mHLA-DR. Based on immune and

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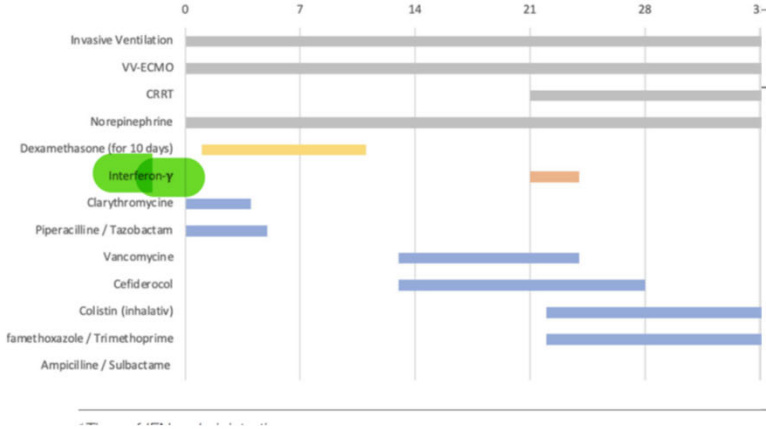
CASE REPORT
published: 01 November 2021
doi: 10.3389/fimmu.2021.753849

Case Report: Interferon- γ Rescues Monocytic Human Leukocyte Antigen Receptor (mHLA-DR) Function in a COVID-19 Patient With ARDS and Superinfection With Multiple MDR 4MRGN Bacterial Strains

Clemens Grimm[1], Steffen Dickel[1], Julian Grundmann[1], Didier Payen[2], Julie Schanz[3], Andreas Erich Zautner[4], Björn Tampe[5], Onnen Moerer[1] and Martin Sebastian Winkler[1]*

Timeline ICU Course



	5	6	7	8
	28-35	35-42	42-49	49-56
	36.0	41.1	49.5	43.1
	96.5	84.3	96.9	82.5
	13.6	18.3	23.1	10.6
	267.0			
	3.1	56.0	5.3	0.8
	12	11	10	10
	0.15	0.15	0.12	0.48
	110	330	330	330

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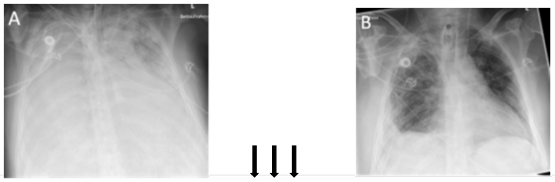
CASE REPORT
published: 01 November 2021
doi: 10.3389/fimmu.2021.753849

Clemens Grimm[1], Steffen Dickel[1], Julian Grundmann[1], Didier Payen[2], Julie Schanz[3], Andreas Erich Zautner[4], Björn Tampe[5], Onnen Moerer[1] and Martin Sebastian Winkler[1]*

Case Report: Interferon- γ Rescues mHLA-DR Function in a **COVID-19 Patient With ARDS** and **Superinfection** with Multiple MDR 4MRGN Bacterial Strains



Week		1	2	3	4*	5	6	7	8	9
Days		0-7	7-14	14-21	21-28	28-35	35-42	42-49	49-56	56-63
Laboratory findings										
HLA (CD3+)	%				22.8	36.0	41.1	49.5	43.1	
M-HLA (CD14+)	%				33.7	96.5	84.3	96.9	82.5	
Monocytes	%									
Leukocytes	10^3/µl	18.9	19.2	11.5	11.9	13.6	18.3	23.1	10.6	19.7
CRP	mg/L	3.0	44.6	296.4		267.0				63.4
PCT	µg/L	0.2	0.1	0.5	7.3	3.1	56.0	5.3	0.8	0.2
Clinical findings										
SOFA		5	7	7	11	12	11	10	10	6
Norepinephrine	µg/kg/min	0.11		0.12	0.67	0.15	0.15	0.12	0.48	

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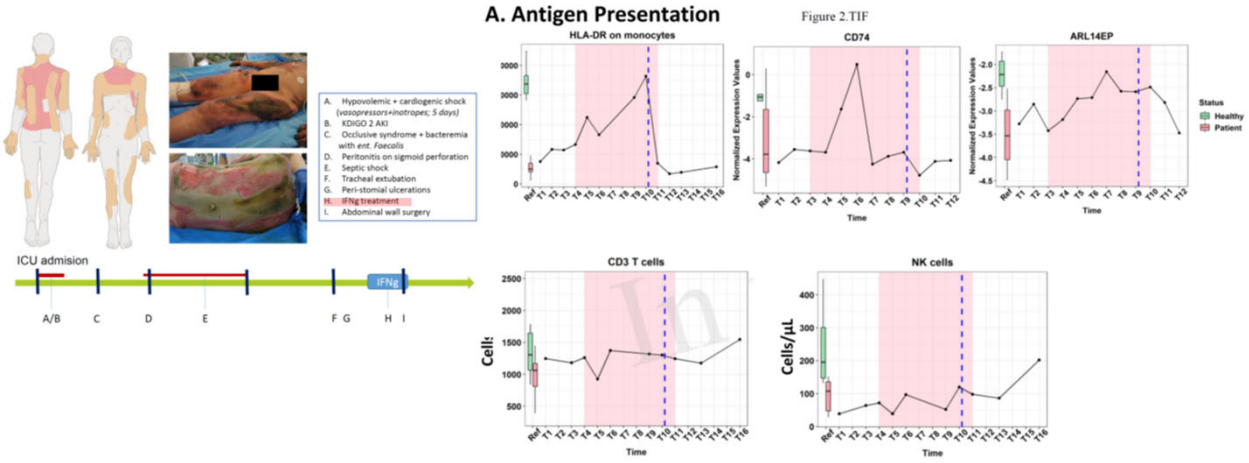
Interferon gamma as an immune modulating adjunct therapy for invasive mucormycosis after severe burn -a case report

Dina M. Tawfik[1], Caroline Dereux[2], Jan-Alexis Tremblay[3], Andre Boibieux[2], Fabienne Braye[2], Jean- Baptiste Cazauran[2], Meja Rabodonirina[2], Elisabeth Cerrato[1], Audrey Guichard[1], Fabienne Venet[4], Guillaume Monneret[1, 4], Didier Payen[5], Anne-Claire Lukaszewicz[2], Julien Textoris[6, 1*]



To conclude

- **PAIDs** is a **synd** that concerns **all acute situations**, particularly **severe sepsis; it is always present 1 or 2 days after injury**
- **IMMUNOSCOPE IS ESSENTIAL**
  - **Blood measurements: WBC (fractions), NCLRatio; semi-quantitative cytokine level**
  - **Flowcytometry: HLA-DR; Ly sub-populations**
- **HLA-DR is a good candidate** and is **cheap** and **fast** to be measured, in association with **semi-quantitative IL-6, IL-10 levels**.
- **Immuno-stimulation by IFNγ seems to be well tolerated; can be given repeatedly, can be used in pediatric pts, even under anti-rejection treatment for transplant.**

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

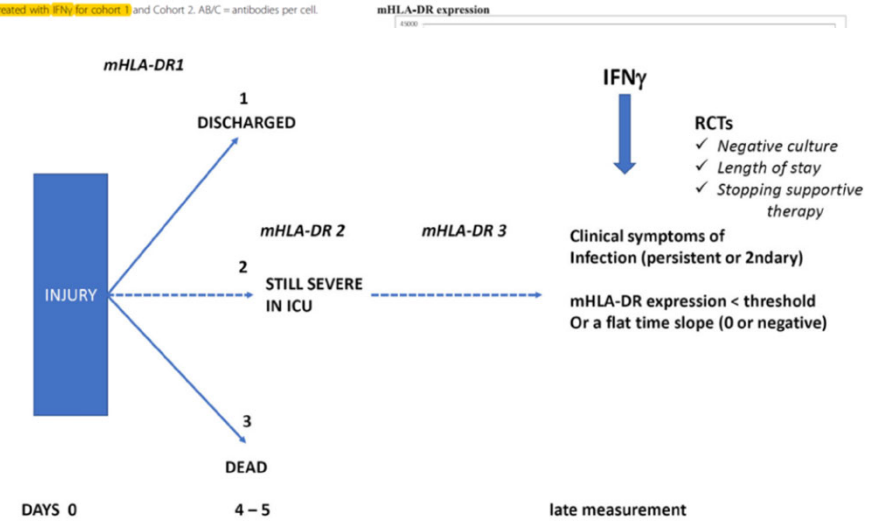
Multicentric experience with interferon gamma therapy in sepsis induced immunosuppression. A case series

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 at admission
1	30	Cardiac arr
2	83	Postop cardiogenic shock
3	73	Cardiogenic 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-acidos
13	82	Rectal Fistu & fasciitis

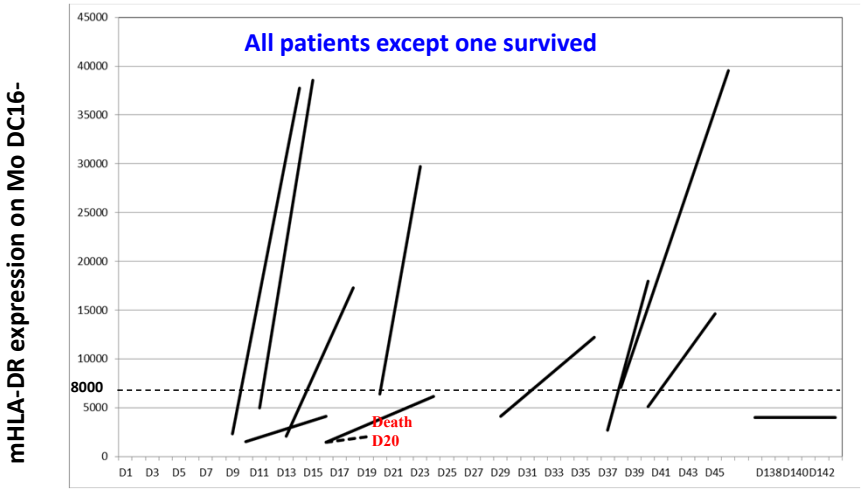
(7 days)



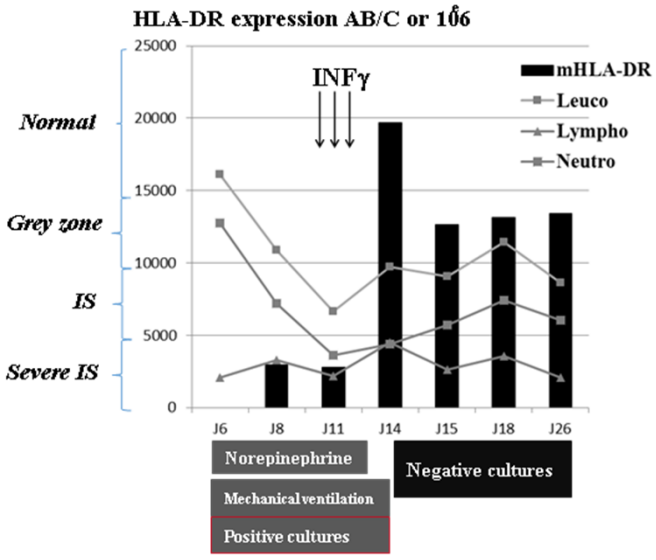
Cohort of 13 post sepsis or septic shock patients

100 mcg subcut (Imukin®, Boehringer, Ingelheim, Germany) as previously reported, during **at least 3 days with a maximum duration of 8 days**

Delay from admission: 18.6 Days



Days in ICU



All immunosupppressive treatment to prevent rejection was maintained

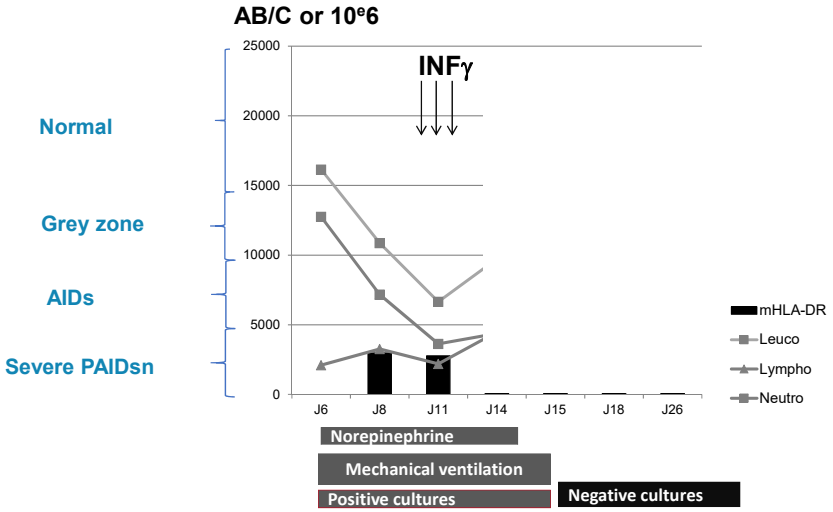
22 months old boy OLT (biliary atresia), was admitted for **cholangitis** with **emergence of MAXI-resistant *Pseudomonas aeruginosa*** and **catheter-related ESBL-producing *Klebsiella pneumonia* infection**.

The **persistent severity (+ acquired colistin resistance) motivated the decision to treat the child by IFNγ (repetitive low mHLA-DR expression (= 2773 AB/C) ➔ IFNγ 20mcg x 3 days**

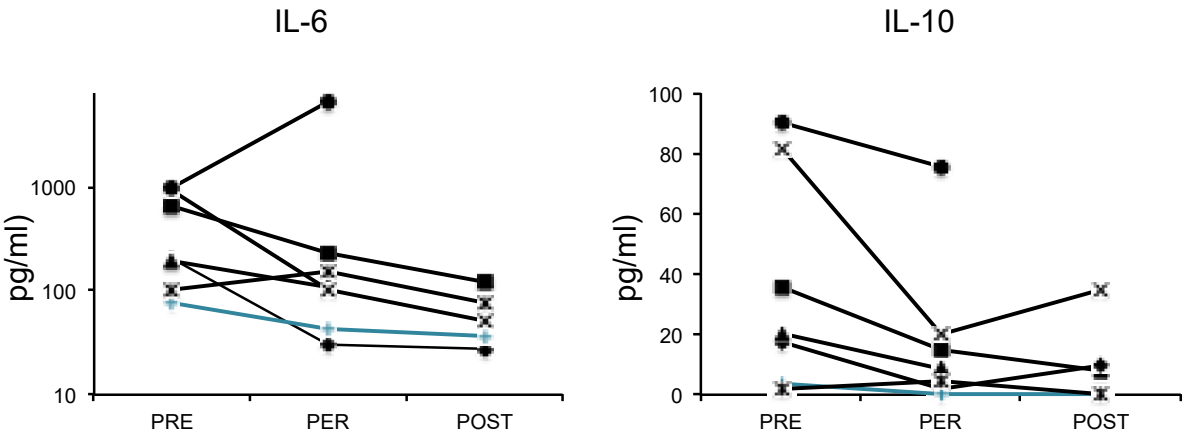
day 1 IFNγ, the **HD and patient status improved spectacularly ➔ child extubated (day 2)**.

mHLA-DR expression increase was rapid and sustained

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



Evolution on IL-6 and IL-10 plasma levels

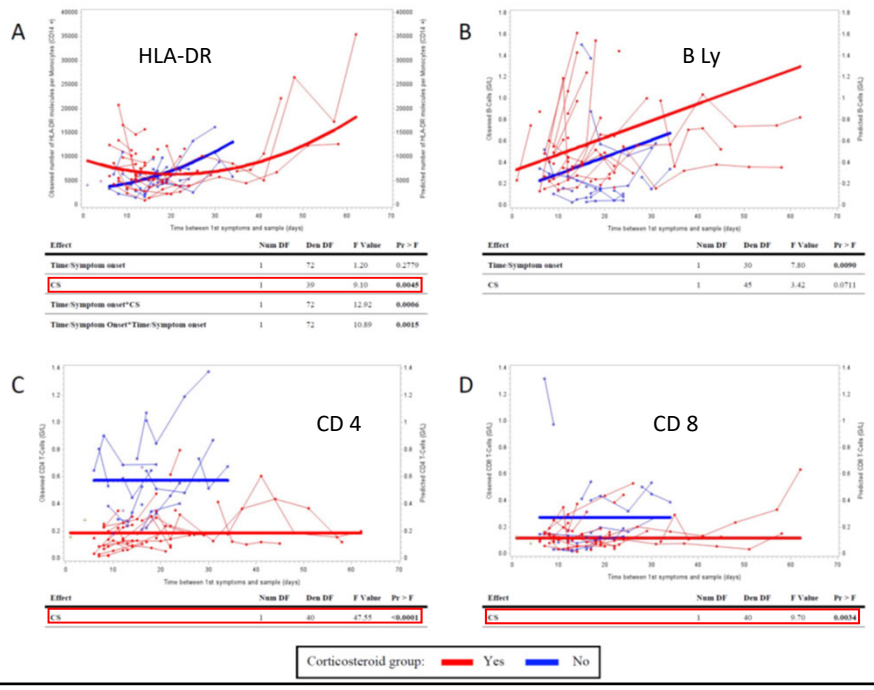


Effect of glucocorticoids on human inflammation in severe ICU COVID-19: our results…

Variable	A: < D15	B: D15-D23	C: after D 23	Normal Range	p-A*	p-B*	p-C*
Non specific markers of inflammation							
Fibrinogen (g/L)				1.7 - 4.0	**0.011**	0.259	0.537
No CS	8 85 (6.4-11.0)	7.90 (5.75-9.30)	7.40 (5.50-8.90)				
CS	7.00 (4.7-10.1)	6.95 (3.90-8.90)	6.92 (6.15-8.65)				
D-Dimer (µg/L)				<500	**0.021**	0.551	0.723
No CS	2454 (1868-4462)	1439 (1051-2225)	1583 (960-2436)				
CS	1228 (534-10000)	1022 (442-7396)	2322 (1277-2781)				

Variable	A: < D15	B: D15-D23	C: after D 23	Normal Range	p-A*	p-B*	p-C*
Innate immunity							
HLA-DR (AB/C)				16884 (5842–29175)	**0.038**	0.978	0.658
No CS	3330 (2305-6349)	5760 (4710-7541)	6629 (4929-12079)				
CS	7102 (4815-10174)	5291 (3820-9748)	7026 (5749-8548)				
HLA-DR CD16- (AB/C)					**0.014**	0.934	0.790
No CS	2540 (1696-4570)	4744 (3064-6179)	4858 (2977-8072)				
CS	5740 (3616-9793)	4404 (2978-6863)	5210 (4233-5520)				
HLA-DR interm (AB/C)					**0.072**	0.642	0.537
No CS	4697 (2993-8982)	10623 (6088-15069)	9916 (5633-25529)				
CS	8990 (4975-16340)	7882 (6092-19432)	13825 (9499-16293)				
HLA-DR CD16+ (AB/C)					0.471	0.891	0.262
No CS	19714 (8101-34843)	28671 (18550-38491)	17337 (17262-61055)				
CS	25495 (13425-43846)	31547 (17576-42681)	38877 (12865-55668)				

Adaptative Immunity							
Lymphocyte (10^9/L)				1.8 (1.0–2.8)	0.741	0.805	0.790
No CS	0.78 (0.52-1.38)	1.09 (0.73-1.71)	1.49 (1.18-2.01)				
CS	0.89 (0.63-1.41)	1.17 (0.64-1.35)	1.45 (1.14-1.79)				
B-Cells (10^9/L)				0.2 (0.1–0.5)	**0.021**	**0.015**	0.084
No CS	0.19 (0.13-0.28)	0.15 (0.07-0.37)	0.19 (0.12-0.50)				
CS	0.41 (0.24-0.62)	0.44 (0.29-0.61)	0.71 (0.36-0.87)				
B-Cells (%)					**0.001**	**0.002**	**0.045**
No CS	20.6 (17.8-25.8)	13.6 (9.7-21.0)	12.9 (10.8-19.0)				
CS	46.0 (37.1-51.5)	44.1 (36.5-51.4)	41.0 (30.6-46.9)				
T-Cells (10^9/L)				1.2 (0.7-2.1)	0.568	0.934	0.929
No CS	0.50 (0.30-0.91)	0.78 (0.53-1.13)	1.03 (0.86-1.43)				
CS	0.63 (0.41-1.05)	0.80 (0.45-0.97)	10.07 (0.59-1.34)				
CS	46.0 (37.1-51.5)	44.1 (36.5-51.4)	41.0 (30.6-46.9)				
T-Cells (10^9/L)				1.2 (0.7-2.1)	0.568	0.934	0.929
No CS	0.50 (0.30-0.91)	0.78 (0.53-1.13)	1.03 (0.86-1.43)				
CS	0.63 (0.41-1.05)	0.80 (0.45-0.97)	10.07 (0.59-1.34)				
CD8+ Cells (10^9/L)				0.4 (0.2–0.9)	0.420	0.186	0.340
No CS	0.09 (0.03-0.15)	0.13 (0.11-0.40)	0.32 (0.22-0.48)				
CS	0.10 (0.08-0.17)	0.09 (0.06-0.15)	0.17 (0.10-0.27)				
NK-Cells (10^9/L)				0.3 (0.09–0.6)	0.095	0.187	**0.024**
No CS	0.12 (0.04-0.17)	0.14 (0.07-0.18)	0.15 (0.10-0.20)				
CS	0.18 (0.10-0.27)	0.24 (0.10-0.35)	0.43 (0.23-0.41)				

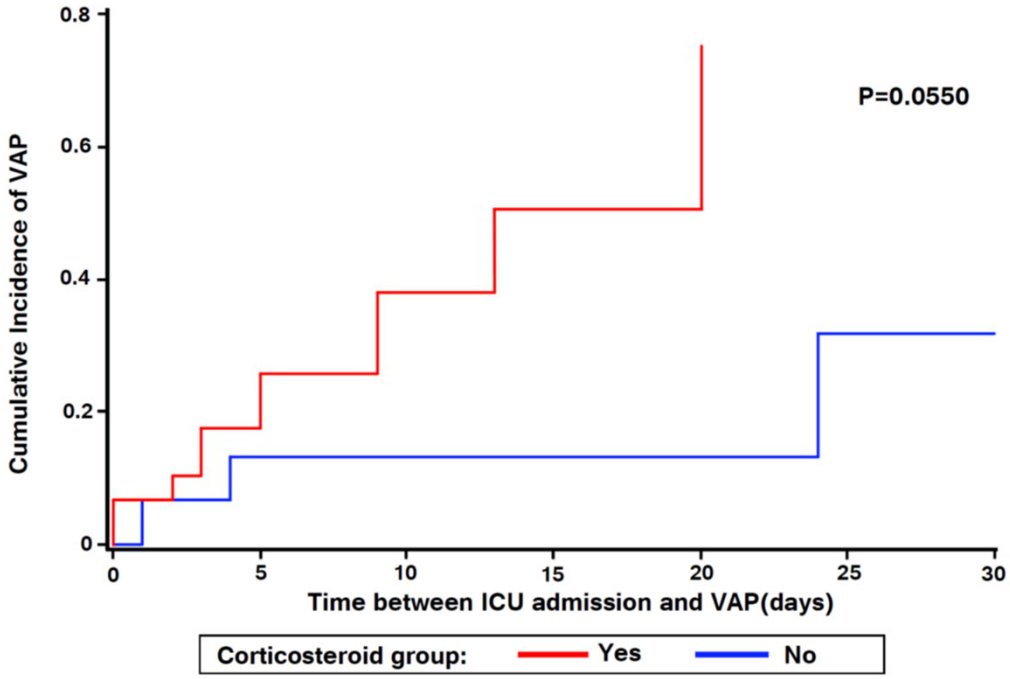


Effect	Num DF	Den DF	F Value	Pr > F
Time/Symptom onset	1	72	1.20	0.2779
CS	1	39	9.10	**0.0045**
Time/Symptom onset*CS	1	72	12.92	**0.0006**
Time/Symptom Onset*Time/Symptom onset	1	72	10.89	**0.0015**

Effect	Num DF	Den DF	F Value	Pr > F
Time/Symptom onset	1	30	7.80	**0.0090**
CS	1	45	3.42	0.0711

Effect	Num DF	Den DF	F Value	Pr > F
CS	1	40	47.55	**<0.0001**

Effect	Num DF	Den DF	F Value	Pr > F
CS	1	40	9.70	**0.0034**



To conclude

- **IMMUNOSCOPE IS ESSENTIAL**
  - Blood measurements: WBC (fractions), NCLRatio; semi-quantitative cytokine level
  - Flowcytometry: HLA-DR; Ly sub-populations
- **Initial phase with excessive inflammation might be modulated by different drugs to limit the tissue damage induced by inflammation.**
  - Anti-tumoral drug?
  - GCs for COVID-19
- **Late phase with immunodepression: Immuno-stimulation by IFNγ seems to be well tolerated; can be given repeatedly, can be used in pediatric pts, even under anti-rejection treatment for transplant**
- **HLA-DR is a good candidate to characterize the inflammatory status:** cheap and fast to be measured, in association with semi-quantitative IL-6, IL-10 levels.

Immune regulation by glucocorticoids

Derek W. Cain and John A. Cidlowski

NATURE REVIEWS | IMMUNOLOGY

2017

Perspectives

Clinical efficacy in COVID-19 patients requiring O2 is clear:

- The **molecular** and **cellular mechanisms** that underlie **immunoregulatory** effects of GCs **are still being to be elucidated**.
- **Substantial gaps in our knowledge** of GCs mediated regulation of immunity, especially **regarding cell-lineage –specific functions**.
- **Adverse effects of excess GCs** are wide-ranging. **A deeper understanding is necessary to achieve a safe GCs therapy.**

If MHC class II expression is depressed, could stimulation help to severe cases?

In summary …

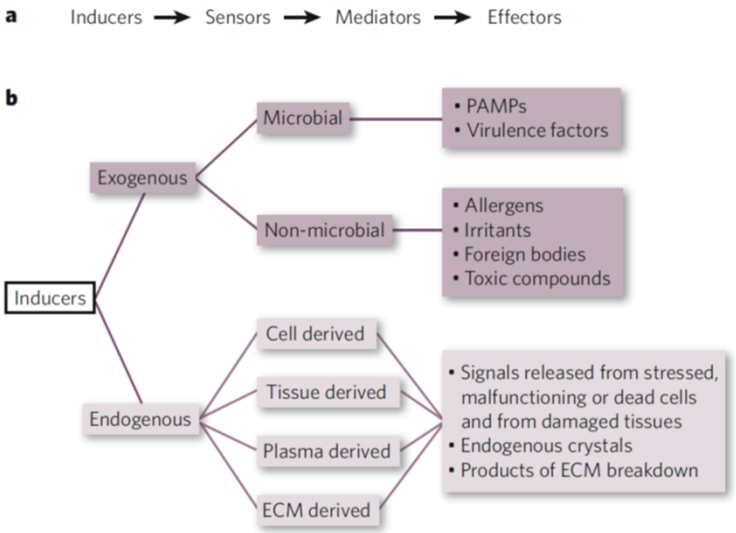
- **Over simplistic view** leads to **mistakes**: ➔ **RCTs always failed** despite solid basic science background
- **Infection does not kill by itself but mainly the host response**
  - **Concept of septic phases**
  - **Inflammation Bmarkers; organ damage BMarkers, etc…**
- **Time for infection treatment is crucial (SSC x 3)**
  - **Golden hours; AB administration; fluid is necessary but not too much! Pressors YES but for what BP level?**
- **Elderly patients SHOULD be treated.**
- **Exp models** are **not easily transposable to human beings**

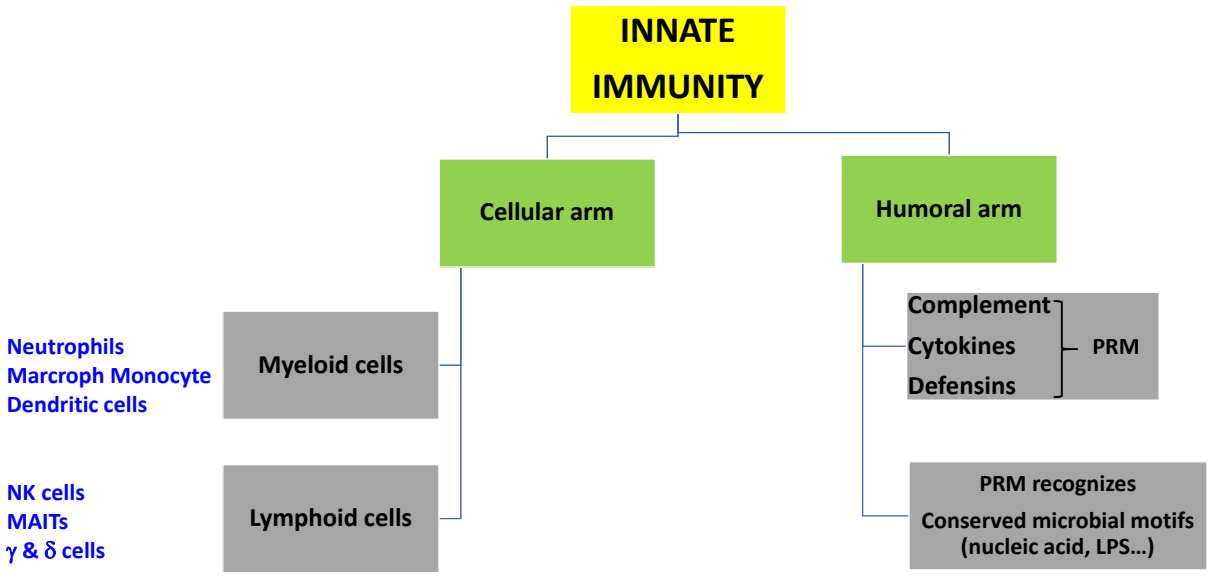
Origin and physiological roles of inflammation

NATURE|Vol 454|24 July 2008|doi:10.1038/nature07201

Ruslan Medzhitov[1]

The inflammatory pathway.





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

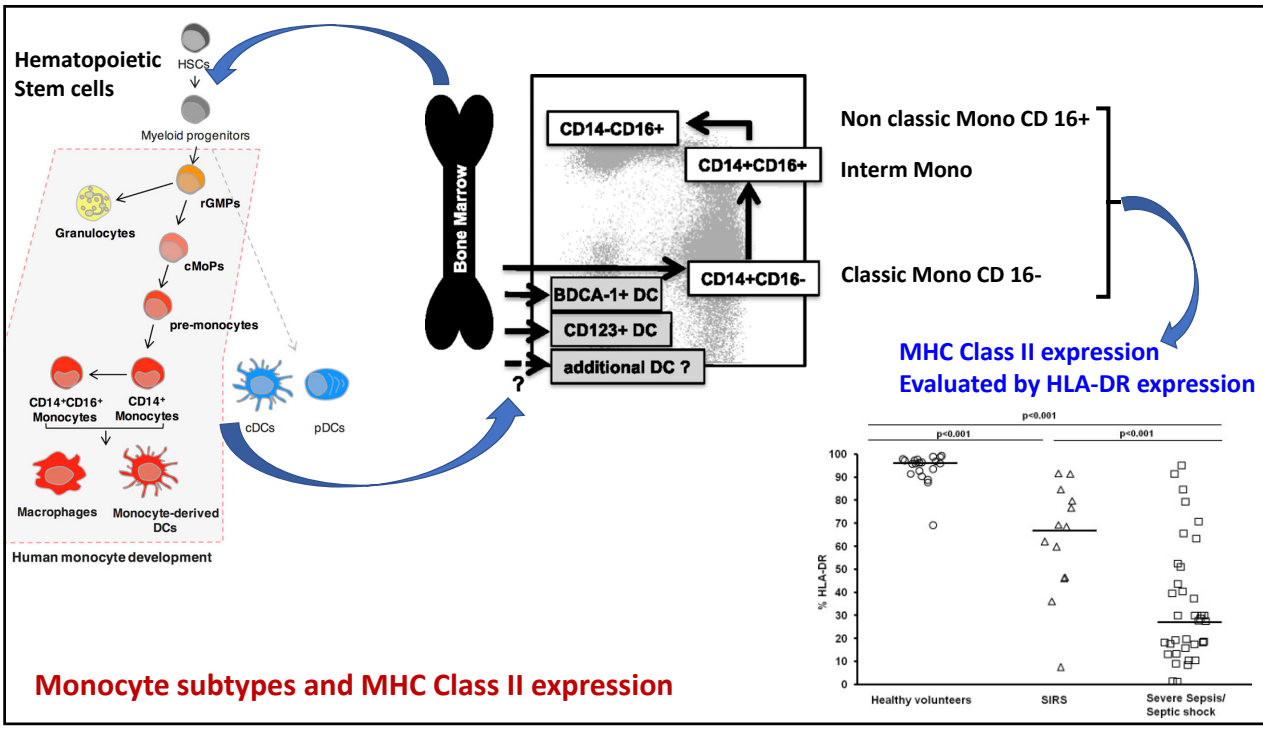
Refreshing knowledge

Immune system: ***AP Response; innate immunity; adaptive immunity with cellular and humoral components…***

Infection phases: **early *vs* late**

AIDsyndrome: Acquired Immuno Depressed Syndrome

HLA-DR and MHC Class II and CIITA: (MHC class II transactivator) ➔ antiviral activity by activation of invariant chain CD 74 ➔ block SARS-Cov-2 entry *(Science 2020)*



Monocyte subtypes and MHC Class II expression

How dying cells alert the immune system to danger

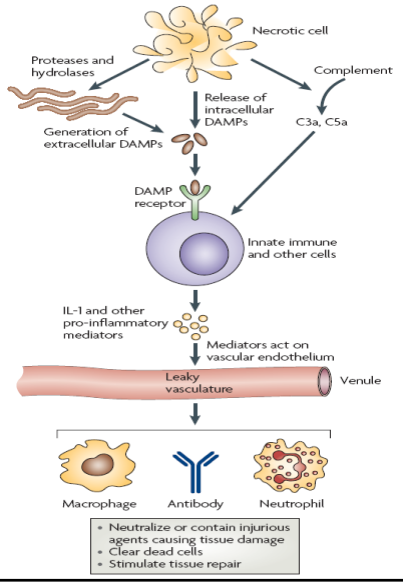
Hajime Kono and Kenneth L. Rock

NATURE REVIEWS | IMMUNOLOGY VOLUME 8 | APRIL 2008 | 279

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

Cell death and inflammation.

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



Is it relevant for the clinician?

D0: Oesophagectomy

D1 Early post-operative period

-***Hypoxemia*** with pleural effusion ➔ **chest drainage**
-***CCVasc collaps*** responding to **fluid challenge**
-***Acute Kidney Injury*** AKIN3

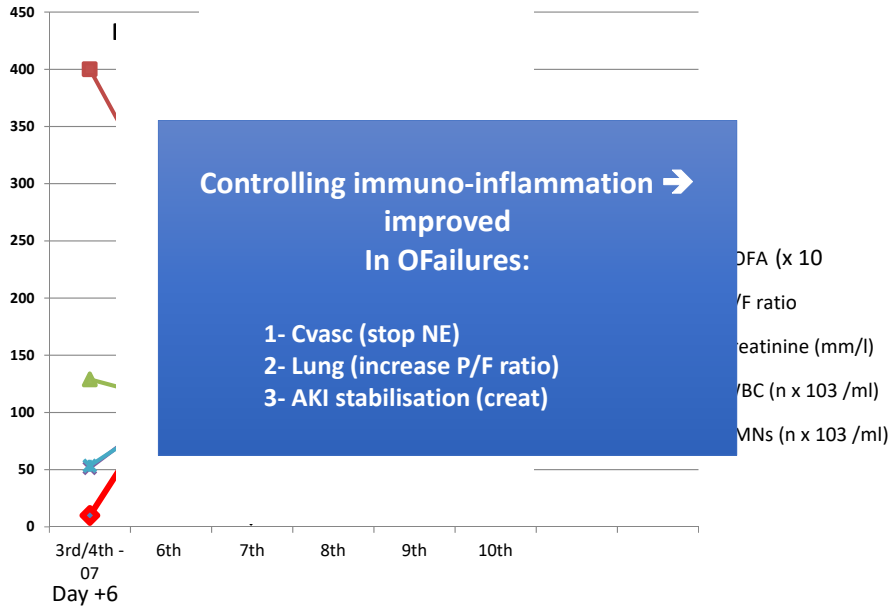
D8: severe SIRS

WC↗ from 6 400 to 64 600
BAL: 10^2 Citrobacter, ECBU (-), HC (-), HC sur PAC (-), Plèvres (-)
OGDF: No fistulae
TDM IV opacifié: ***NO leak, NO mediastinitis***

D11: M O S F

GB: **223 000 98% PMNs (Chronic ttmt fro ITP with GFactor)**
BC+ : multiple bateria Serratia et Citrobacter, **Tracheal asp** ***>10 ^{7} Citrobacter***,
OGDF & **TDM** no fistulae
AB: 3 molecules (Cefotax; linezolid; Imipenem)

Let's see the results of immune monitoring….



Immunity

Human Monocytes Undergo Functional Re-programming during Sepsis Mediated by Hypoxia-Inducible Factor-1α

Irina N. Shalova,[1] Jyue Yuan Lim,[1] Manesh Chittezhath,[1] Annelies S. Zinkernagel,[2,6] Federico Beasley,[2] Enrique Hernández-Jiménez,[3] Victor Toledano,[3] Carolina Cubillos-Zapata,[3] Annamaria Rapisarda,[4] Jinmiao Chen,[1] Kaibo Duan,[1] Henry Yang,[1] Michael Poidinger,[1] Giovanni Melillo,[4] Victor Nizet,[2] Francisco Arnalich,[5] Eduardo López-Collazo,[3] and Subhra K. Biswas[1,*]

Immunity 42, 484–498, March 17, 2015

In line with the **dynamic nature of sepsis**, **2 phases have been recognized** in this disease: an **early inflammatory phase and a late immunosuppressive phase**

Early phase: *characterized by* ***leukocyte activation, cytokine storm****, and a* ***systemic inflammatory response***

Later phase: *characterized by* ***immunosuppression, leukocyte deactivation, increased risks of secondary infection, and high mortality***

more complicated with the *overlapping co-existence* of inflammatory and immunosuppressive processes

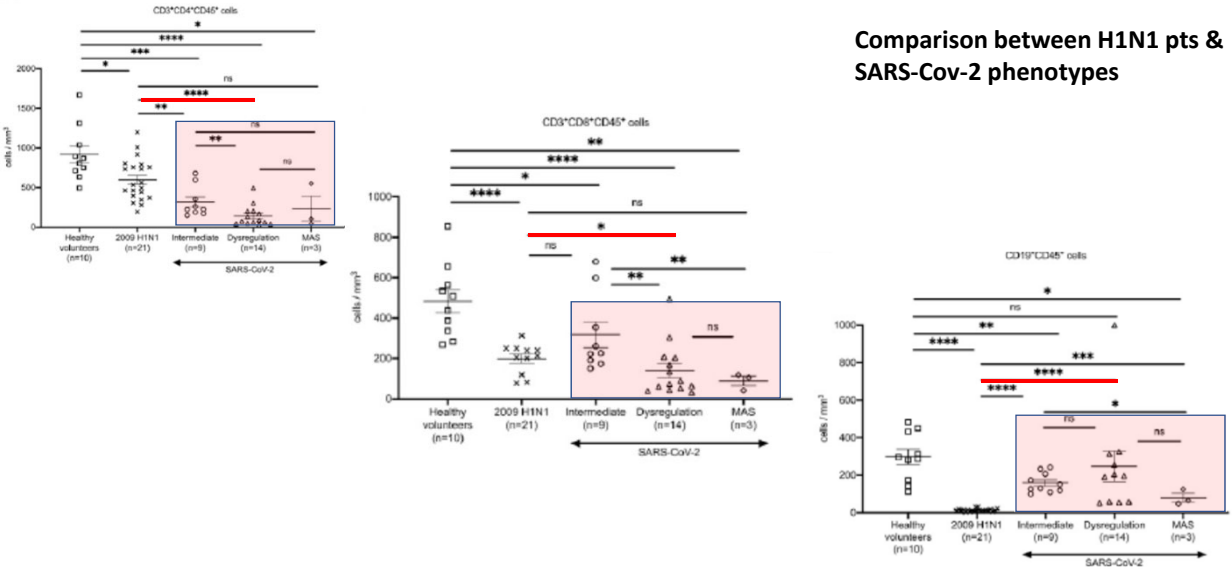
➔ **The FAILURE of numerous RCTs to REDUCE MORTALITY**

Cell Host & Microbe

Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure

Evangelos J. Giamarellos-Bourboulis, Mihai G. Netea, Nikoletta Rovina, ..., Nikolaos Koulouris, Charalambos Gogos, Antonia Koutsoukou

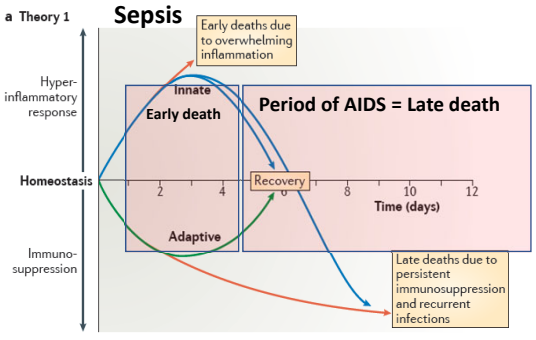
Giamarellos-Bourboulis et al., 2020, Cell Host & Microbe 27, 1–9
June 10, 2020 © 2020 Elsevier Inc.
https://doi.org/10.1016/j.chom.2020.04.009



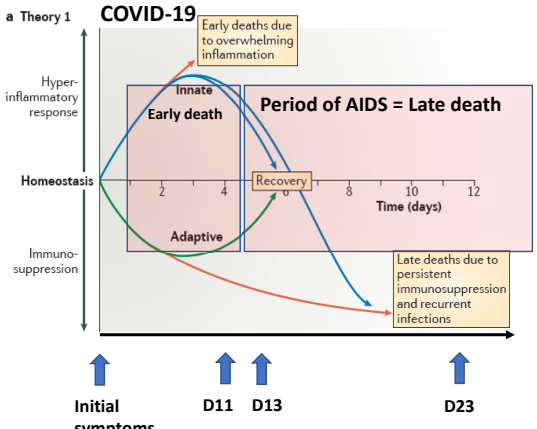
Comparison between H1N1 pts & SARS-Cov-2 phenotypes

Sepsis & COVID-19 clinic, biology, inflammation evolve overtime ➔ longitudinal studies

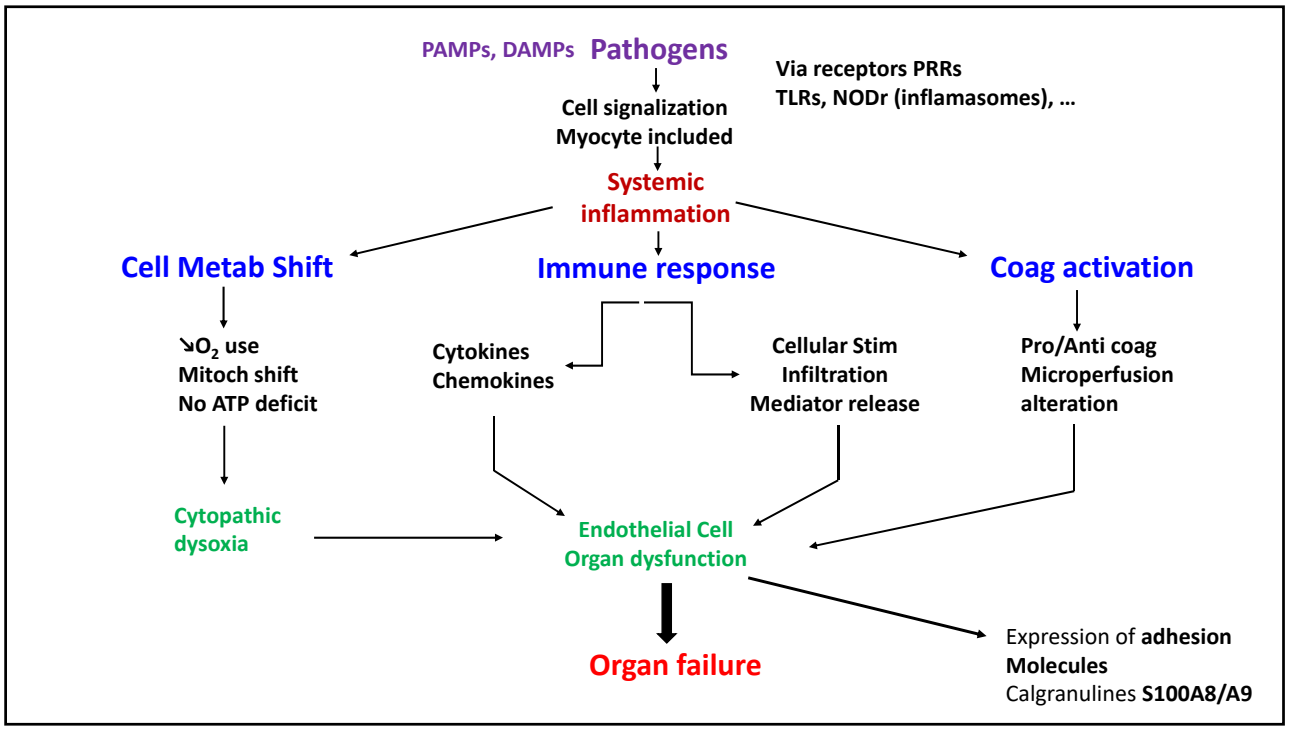
AIDS: Acute Immuno-Depressed Syndrome



Hotchkiss, R, Monneret G, Payen, D
Nature Review Immunol 2013



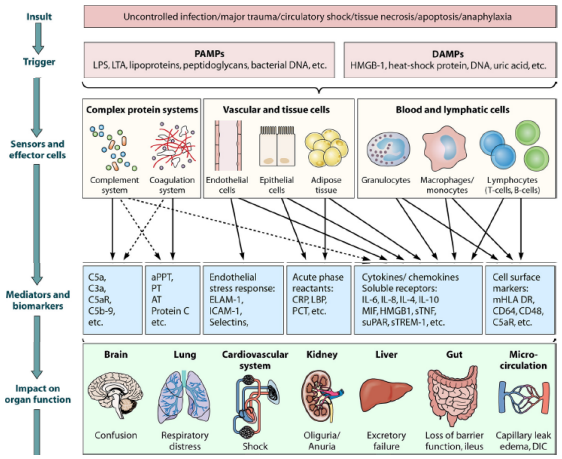
Payen, D, Cravat M, et al
Frontiers Immunol 2020



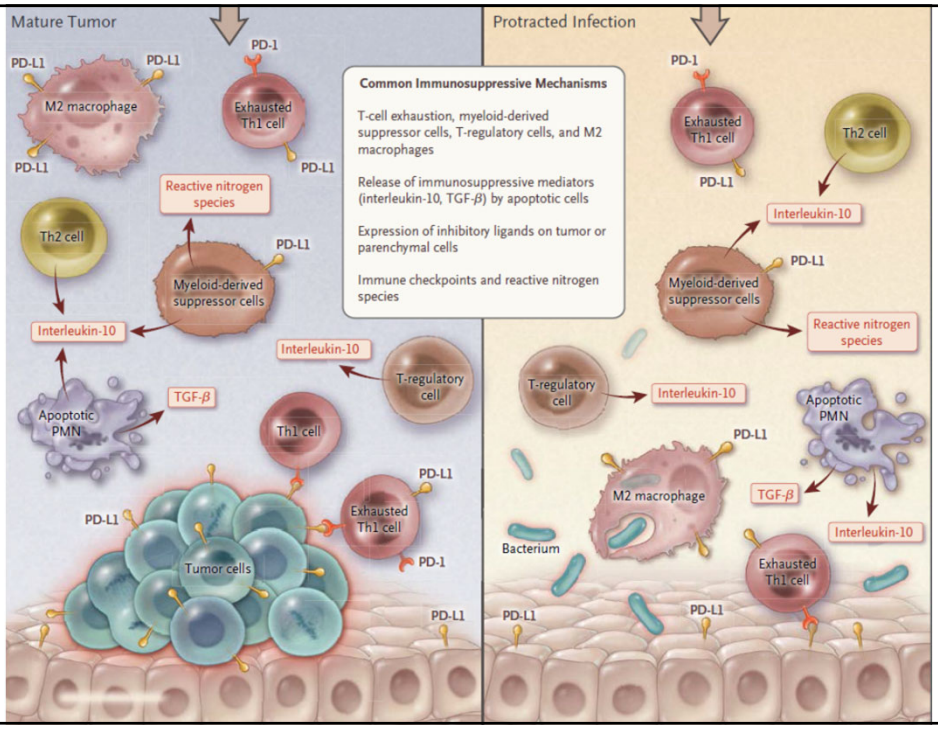
New Approaches to Sepsis: Molecular Diagnostics and Biomarkers

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

Clinical Microbiology Reviews October 2012 Volume 25



Globally, similar mechanisms for all tissues ➔ dysfunction


Mature Tumor
Protracted Infection
Common Immunosuppressive Mechanisms
T-cell exhaustion, myeloid-derived suppressor cells, T-regulatory cells, and M2 macrophages
Release of immunosuppressive mediators (interleukin-10, TGF-β) by apoptotic cells
Expression of inhibitory ligands on tumor or parenchymal cells
Immune checkpoints and reactive nitrogen species
PD-1
PD-L1
M2 macrophage
Exhausted Th1 cell
Th2 cell
Reactive nitrogen species
Myeloid-derived suppressor cells
Interleukin-10
Apoptotic PMN
TGF-β
T-regulatory cell
Th1 cell
Tumor cells
Bacterium