Sepsis and Cytokines: Science, Reality and Legends

Didier Payen, MD, PhD
Emeritus Professor at Paris 7 University, Sorbonne, cité
UMR INSERM 1160
dpayen1234@orange.fr
SEPSIS: MORE COMPLEX THAN WE PRACTICE!

• What is pivotal for the clinicians? The selection of patients on the basis of biomarkers and/or functional defects ➔ specific insights into the expression or activity of the therapeutic target

• Sepsis can be seen as an unbalance between the host response and host tolerance of it
  • Role of virulence
  • Role of genetic susceptibility
  • Role of pre-sepsis conditions
  • Role of intensity of host response for a given individual capability
  • Role of the delay during sepsis for starting treatment
Rationale

- **Sepsis**: not simply increased inflammation and/or immune suppression, but also a **fundamental reorganization of immune and metabolic cell processes**.

- Measures of inflammation and suppression **reflect this acute cellular reprogramming**.

- It remains **difficult to compose an overarching framework** of the key mechanisms that drive sepsis-associated pathology.
Rationale

• **In sepsis**, the *immune system* has departed *from* homeostasis in two opposite directions: *excessive inflammation* and *immune suppression*

• In studies investigating immune response ➔ *the first measurements at admission to ICU ➔* no insights into the *direction and time course* of the host response *before* the clinical recognition
First, Know...
Second, Understand...
Third, acting...
1994 Matzinger: Stranger/Danger model

**Pathogen-Associated Molecular patterns**
- Bacteria $\rightarrow$ PAMPs
- Fixed at cell receptors
- TLRs, NODs, etc...
- Induce DNA transcription $\Rightarrow$ *mediators synthesis*

**Damaged-Associated Molecular patterns**
- Necrotic cells $\rightarrow$ DAMPs
- **Criteria for DAMPs**
  - *Alone* should induce *biological response* without contamination (PAMPs = 0)
  - Being efficient at physiol [ ]
  - Their blockade $\Rightarrow$ inhibits their action
    *mediators synthesis*
After processing pathogens components (PAMPs), they are presented as a complex antigenic peptides - MHC class II molecule on the surface of APC to be recognized by T cell receptors (TCR)
The Immune « Synapse »

Activating
Inhibiting
Left: conventional antigen and right superantigen presentation (adapted from Lancet Resp Dis 2002).

Release of cytokines after SAgS is 1000 times higher than with conventional Ags

- streptococcal SAgS
- staphylococcal enterotoxin (SE)-B
Mechanisms for inducing sterile inflammation (adapted from Nat R Immunol 2016).
“Dendritic cells and other innate determinants of T helper cell polarisation” (Walsh and Mills 2013)
Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

Richard S. Hotchkiss¹, Guillaume Monneret² and Didier Payen³

Impact of sepsis on innate and adaptive immune cells

- Effects of protracted sepsis on the innate immune system

- Follicular dendritic cell
  - ↑ Apoptosis
  - ↓ Antigen presentation to B cells

- Dendritic cell
  - ↑ Apoptosis
  - ↓ Antigen presentation to T cells
  - ↓ Cytokine secretion

- Macrophage
  - ↑ Anti-inflammatory cytokine secretion
  - ↓ HLA-DR expression
  - ↓ Pro-inflammatory cytokine secretion
  - ↓ Pathogen killing

- NK cell
  - ↑ Apoptosis
  - ↓ Cytotoxic function
  - ↓ Cytokine secretion

- Neutrophil
  - ↑ Release of immature neutrophils
  - ↑ IL-10 secretion
  - ↓ Apoptosis
  - ↓ Reactive oxygen species release
  - ↓ Nitric oxide release
  - ↓ Expression of adhesion markers

- MDSC
Sepsis-induced immunosuppression: from cellular dysfunctions to immunotherapy

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

Richard S. Hatchkiss¹, Guillaume Monneret² and Didier Payen³

**Phase 1**

Early deaths due to overwhelming inflammation

= 50% of 28 days mortality

**Phase 2**

Post-Agressive Immuno-Depression (PAID) Synd

**Phase 3**

Late deaths due to persistent immunosuppression and recurrent infections

The time phases
Conversion ➔ Median fluorescence intensity (MFI) ➔ number of PE molecule per cell ➔ number of antibody bound per cell (AB/C) ➔ allow to compare different cytometers and set up.
Automated bedside flow cytometer for mHLA-DR expression measurement: a comparison study with reference protocol

Mehdi Zouiouich\textsuperscript{1,2}, Morgane Gossez\textsuperscript{1,2}, Fabienne Venet\textsuperscript{1,2}, Thomas Rimmelé\textsuperscript{2,3} and Guillaume Monneret\textsuperscript{1,2,4}

Conclusions: This fully automated table top cytometer appears to be a suitable tool for ICU patient monitoring and on-going clinical trials as there is no sample preparation and no need for specific skills in flow cytometry. Upon validation in
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
Cytokine storm and sepsis disease pathogenesis

Benjamin G. Chousterman¹² · Filip K. Swirski³ · Georg F. Weber⁴

« Cytokines » The angular stone of the conceptual changes in pathophysiology of infection

- Broad category of small proteins (< 40kDa) ➔ cell signaling

**COMMUNICATION ROUTES FOR CELL-TO-CELL EXCHANGE:**

- Autocrine, para, endocrine ➔ immunomodulator(s)

- Impressive list (> 100 genes encoding for) of proteins classified on:
  - Interleukins
  - Chemokines
  - Interferons
  - TNF
  - Growth factors
INTERLEUKINES the most important Gp

- **Secreted by** Leukocytes & Ecells
- **Cell signaling & promotes** activation, proliferation, death, motility of IMMUNE CELLS
- **Artificially divided in Pro- and Anti**
- **Pro-inflammatory** THE «LEADERS»
  - IL-1β, IL-6, IL-12, and IL-17 crucial importance.
  - Activates via receptors the amplification cascade and synthesis for IL-6, IL-8, MCP-1, COX-2, IκBα, IL-1α, IL-1β, and MKP-1.
  - IL-6 (INFβ) pleitropic; role is complex and controversial; family of molecules; works via receptors; main source MΦ, associated with mortality in sepsis; contribution: not yet clarified; activity modulated by soluble receptor
INTERLEUKINES the most important Gp

• *IL-12*
  - induces the *differentiation of naïve T cells* into type 1 helper T cells (TH1) and *activates NK cells*;
  - *These cells produce large amount of INFγ ➔ activation, proliferation, death, motility* of IMMUNE CELLS

• *Interferons:*
  - 3 types
  - Produced *mainly by CD4, CD8, and NKCells*
  - Used to *define TH1-type cells*
  - Promotes inflammation in sepsis
CHEMOKINES (8-12 kDa)

• Soluble, not specialized
• Needs specific receptors coupled to G Proteins
• 4 types according to AA sequence and spacing between Cyst residues
• Cell specific for Mono, neutro, T Lympho
• In sepsis:
  • Major role in orchestration of host response to infection
    • Leuco recruitment
    • Release immune cells from BM
• Lack of CKs: immuno-suppression and risk of infection
Knowing this, How to establish a therapeutic strategy?

We can debate...

- arthritis
- activated cells
- bilirubin
- hyperlipidemia
- endotoxin
- Cytokines
Early Use of HF in severe sepsis

- Higher rate of AKI/ARF; p < 0.05
- Higher frequency of RRT use; p < 0.05
  19/37 in HF group
  8/39 in Conventional group

Early use of CHF in severe sepsis cannot be recommended to
Reduce OF or to improve mortality
Conclusions: In the IVOIRE trial, there was no evidence that HVHF (at 70 mL/kg/h) compared with SVHF (at 35 mL/kg/h) reduces 28-day mortality or contributes to early improvements in haemodynamic or organ function. HVHF, as applied in this trial, cannot be recommended for treatment of septic shock complicated by AKI.
PMX trial: impact on outcome

- **ABDOMIX-trial** 2015 *Intensive Care Med*(abdominal SShock);
  - 232 Pts, 18 Centers, PMX (2 sessions) started with 12hrs after surgery;
    - Shocked patients; adequacy of surgical procedure assessment
  - **1ary end-point**: mortality day 28
  - **2ary end-point**: mortality day 90 & SOFA

- **Results:**
  - Mortality day 28: 27.7 PMX vs 19.5% NS
  - Mortality day 90: NS (33.6% vs 24%); SOFA evol° day 0 to day 7: NS
  - Same results in patients completing the 2 sessions
PMX trial: impact on cytokines

• **ABDOMIX-trial** 2017 *Shock (abdominal SShock)*;
  - 232 Pts, 18 Centers, PMX (2 sessions) started with 12hrs after surgery;
    - Shocked patients; adequacy of surgical procedure assessment
  - **Aim**: influence on plasma cytokines (10 pro- & anti-); no difference at baseline for the 2 groups.
  - **Results**:
    - Plasma TNFα, IL-1β, IL-10, IL-6, IL-1RA decreased significantly over time in both groups.
    - After 2nd PMX session or at corresponding time in controls: plasma levels of cytokines did not differ between the two groups.
    - **IL-17** (cytokine from Ly TH17 having protective role in host defense against pathogens) decreased only in PMX gp (p <0.045)
  - **Comment**: PMX does not influence plasma cytokines levels
EUPHRATES trial: impact on outcome

- **EUPHRATES-trial** 2010 to 2016... *(Trials 2014; JAMA 2018)*
  - 450 **SShock** Pts + **indirect high LPS level** (EAA), 50 Centers, **PMX (2 sessions)** started with 24hrs of enrollment;
  - **1ary end-point:** mortality day 28
  - **2ary end-point:** mortality day 90, 6 & 12 months
  - **Results:**
    - No significant difference in mortality at day 28 (37.7 PMX vs 34.5%)
    - Even on more severe patients (SOFA > 9)

**CONCLUSIONS AND RELEVANCE** Among patients with **septic shock** and **high endotoxin activity**, **polymyxin B hemoperfusion** treatment plus conventional medical therapy compared with sham treatment plus conventional medical therapy **did not reduce mortality at 28 days**.