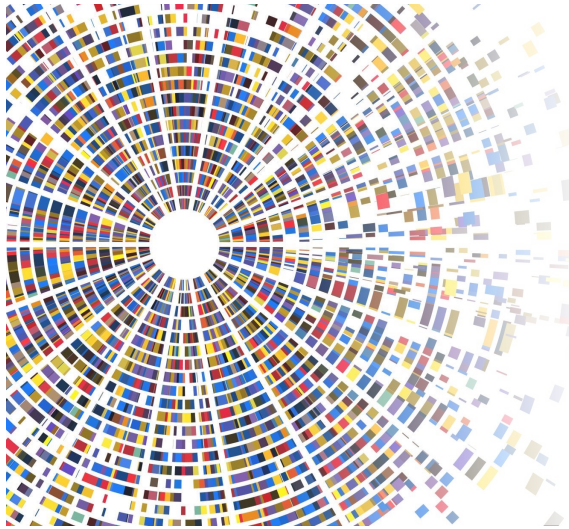


GLI STATI IPER INFIAMMATORI.

LA NUOVA FRONTIERA DELLA TERAPIA INTENSIVA.

SEPSIS Global Impact

Prevalence in ICU:

- **ICU Patients:** Sepsis affects approximately 1 in 5 ICU patients.
- **Mortality Rate:** The 90-day mortality rate fin ICUs is about **30-40%.**
- **Septic Shock: 30% to 50%** depending on healthcare settings.

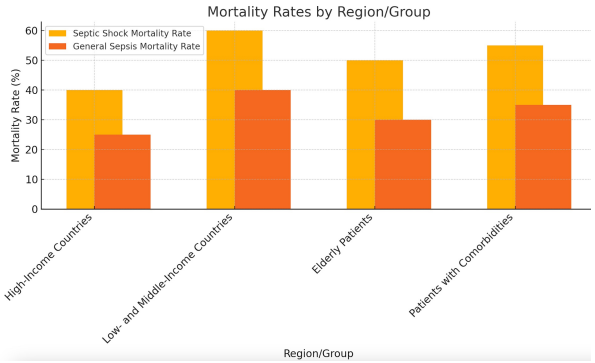
Regional Differences:

- **High-Income vs. Low-Income Countries**
- **Resource Availability**

Risk Factors:

- **Age and Comorbidities:** (e.g., diabetes, cardiovascular diseases).
- **Infections Leading to Sepsis**

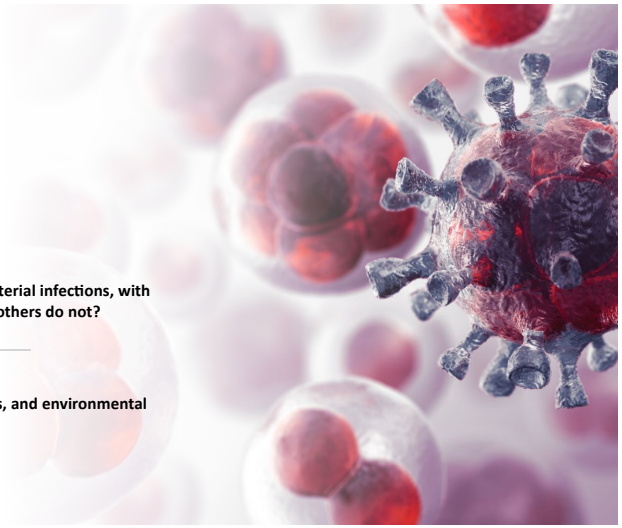
SEPSIS



septic shock vs. controlled infection

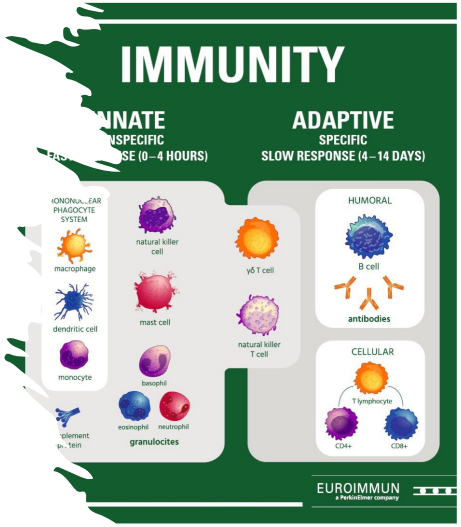
Why patients react differently to bacterial infections, with some developing septic shock while others do not?

host factors, pathogen characteristics, and environmental influences



Host Immune Response Differences

- **Genetic Variability**: Certain genetic polymorphisms affect immune function, including variations in **TLR (Toll-like receptor)** signaling, cytokine production (e.g., IL-1, TNF-α, IL-6), and complement system activation.
- **HLA (Human Leukocyte Antigen) Type**: Different HLA haplotypes influence how the immune system recognizes and responds to bacterial antigens.
- **Innate Immune Variability**: Some individuals have an exaggerated immune response (cytokine storm), while others have a more controlled inflammatory reaction.

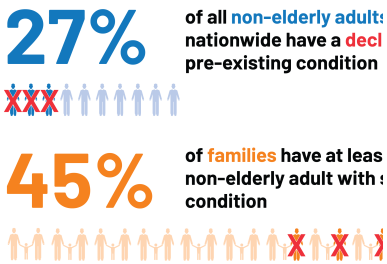


Pathogen Factors

- **Virulence Factors**: Some bacteria produce **superantigens (e.g., Staphylococcus aureus, Streptococcus pyogenes)** that cause massive cytokine release, leading to toxic shock and sepsis.
- **LPS (Lipopolysaccharide) Load**: Gram-negative bacteria (e.g., *E. coli, Klebsiella pneumoniae*) release LPS, which triggers a strong inflammatory response via TLR4 activation.
- **Bacterial Load**: Higher bacterial counts can overwhelm the immune system, leading to uncontrolled systemic infection.

Preexisting Conditions

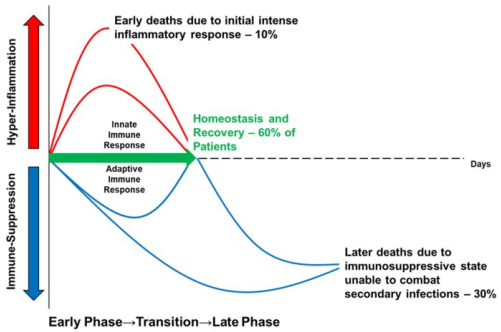
- **Comorbidities**: Diabetes, chronic kidney disease, heart failure, and liver disease impair immune responses, increasing susceptibility to sepsis.
- **Immunosuppression**: Cancer, HIV/AIDS, or immunosuppressive therapy (e.g., steroids, chemotherapy) reduce the ability to mount an effective immune response.
- **Malnutrition**: Deficiencies in essential nutrients (e.g., zinc, vitamin D) can weaken immune function.



PRE-EXISTING CONDITION	COVERAGE
• Hearing/Vision Impairement	**YES**, if stable for more than a year
• Physical Disability	**YES**, if stable for more than a year
• Hypertension	**YES**, if stable for a specific time period
• Asthma	**YES**, if stable for a specific time period
• Diabetes	**YES**, if stable for a specific time period
• Epilepsy	**YES**, if stable for a specific time period
• Mental Illness	**YES**, if stable for more than a year
• Terminal Illnesses *(Cancer)*	**NO**, not Covered

Note : *Always check the policy document carefully before purchasing travel insurance*

Onshore Kare



Immune Dysregulation: Hyperinflammatory vs. Immunoparalysis

- Some individuals exhibit **excessive cytokine release (hyperinflammation)** leading to septic shock, multiple organ dysfunction syndrome (MODS), and death.
- Others develop **immune exhaustion (immunoparalysis)** with reduced monocyte function and T-cell anergy, making them susceptible to secondary infections.

SEPSIS

Hyperinflammatory Phase:
- Uncontrollable surge of inflammatory cytokines.
- Leads to hyperinflammatory response (tissue damage).

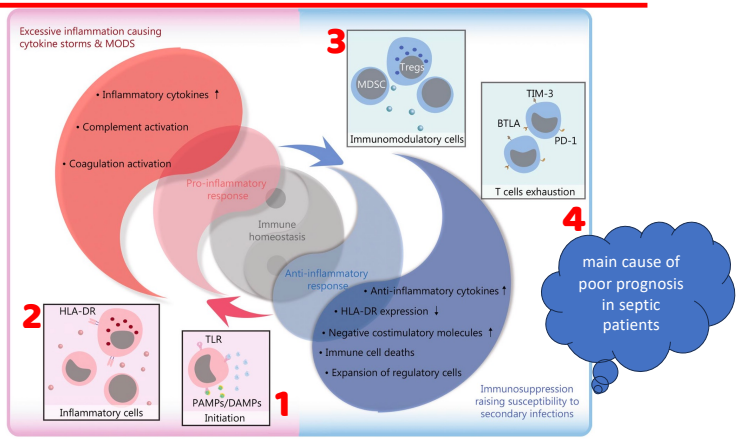
balancing

Immunosuppressive Response:
- host's immune system →immunosuppression.

Pathophysiological Impact:
- hyperinflammation/immunosuppression complicates management of sepsis

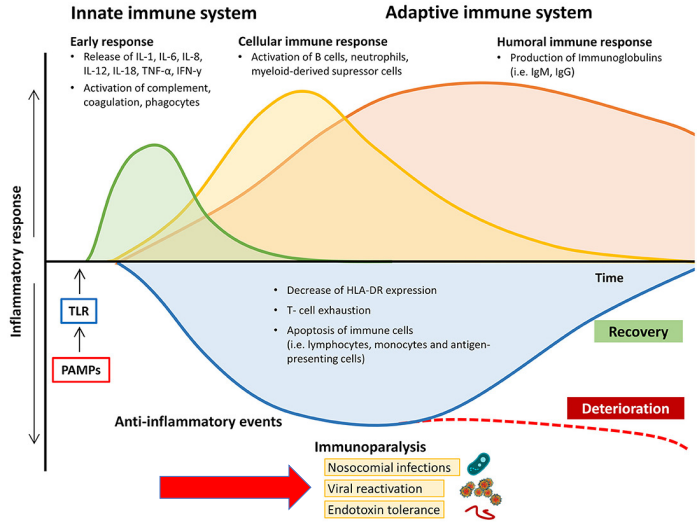
- **Characteristics of Immunosuppression:**
  - **Accumulation of Anti-inflammatory Cytokines:** Elevated levels of cytokines like IL-10.
  - **Impaired Immune Cell Function:** Reduced activity of immune cells, leading to compromised defense mechanisms.
  - **Over-proliferation of Suppressor Cells:** Increased numbers of myeloid-derived suppressor cells and regulatory T cells, which further dampen the immune response.
  - **Depletion of Immune Effector Cells:** Loss of key immune cells through various forms of cell death, weakening the body's ability to fight infections.

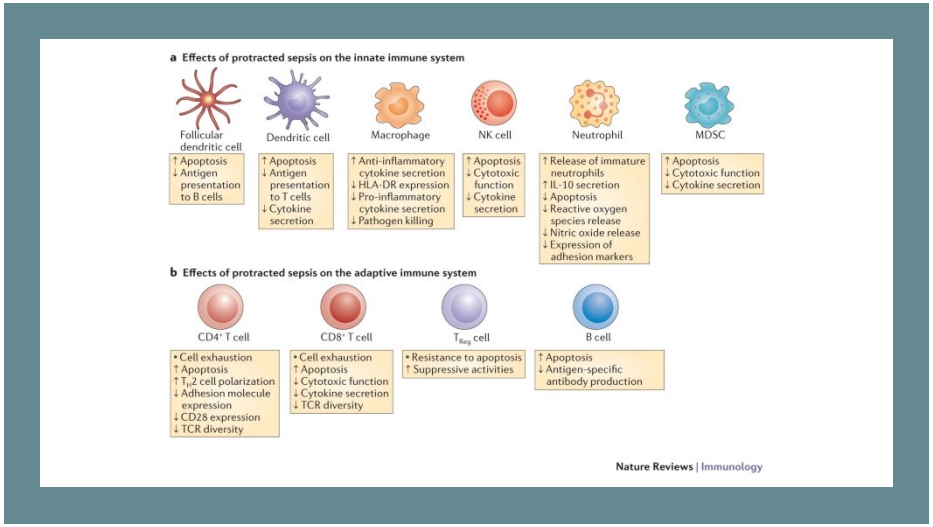
Immune homeostasis



Liu *et al. Military Medical Research (2022)*

Immune homeostasis



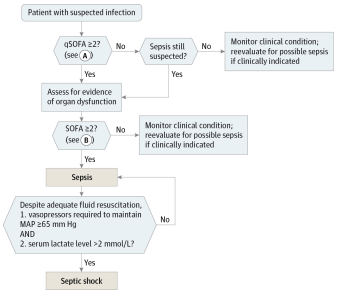


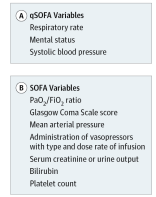
JAMA Network

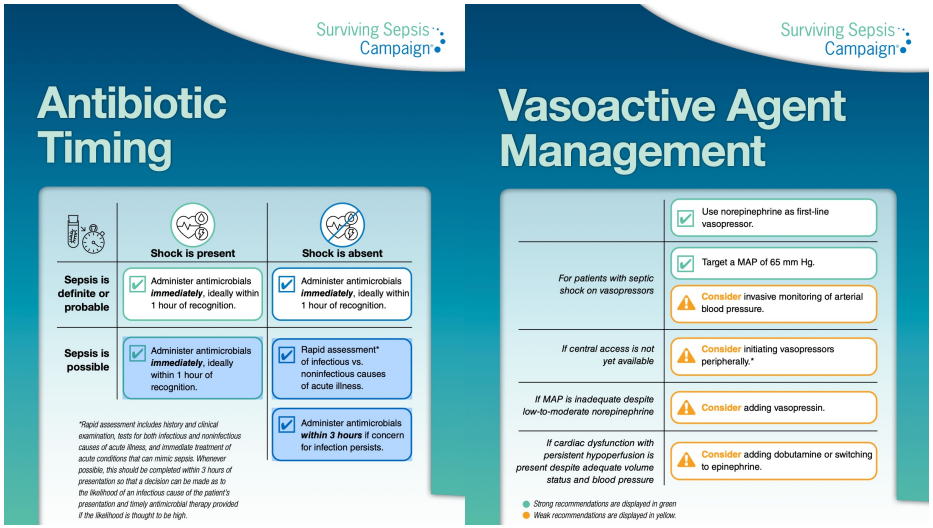
From: **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)**

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

What are we doing on these patients?







SPECIAL ARTICLE

Executive Summary: Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock 2021

lar instability of sepsis. In the Rivers' Early Goal Directed Therapy (EGDT) study, 4.9 L of crystalloid was given in the first 6 h and 13.4 L in the first 72 h [1]. The Surviving Sepsis Campaign recommends "aggressive fluid resuscitation during the first 24 h" of management [2]. These guidelines require patients with hypotension or a lactate concentration >4 mmol/L, to receive a 30 m crystalloid within 3 h of triage, with repeate achieve a central venous pressure of 8–15 Consequently, large volumes of fluid are adr septic patients during the first day of ICU ad

Let's do some maths

- **70 kg x 30 ml = 2100 ml in the first 3 h (plus boluses)**

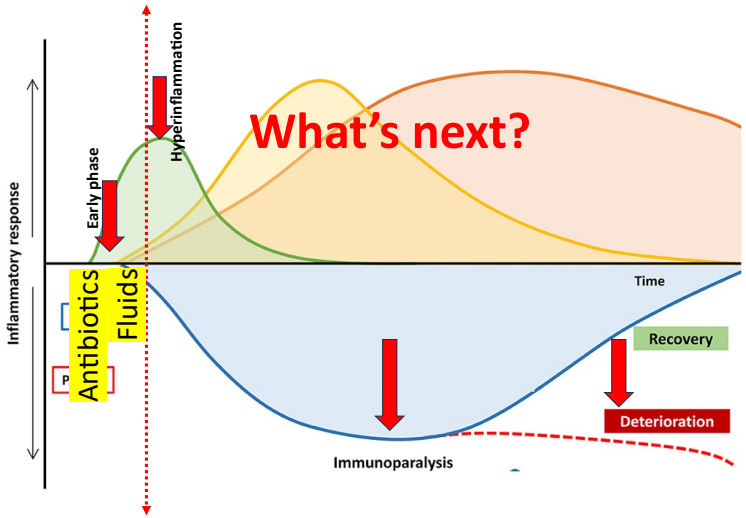
Marik *et al. Annals of Intensive Care* 2011, **1**:1
http://www.annalsofintensivecare.com/content/1/1/1

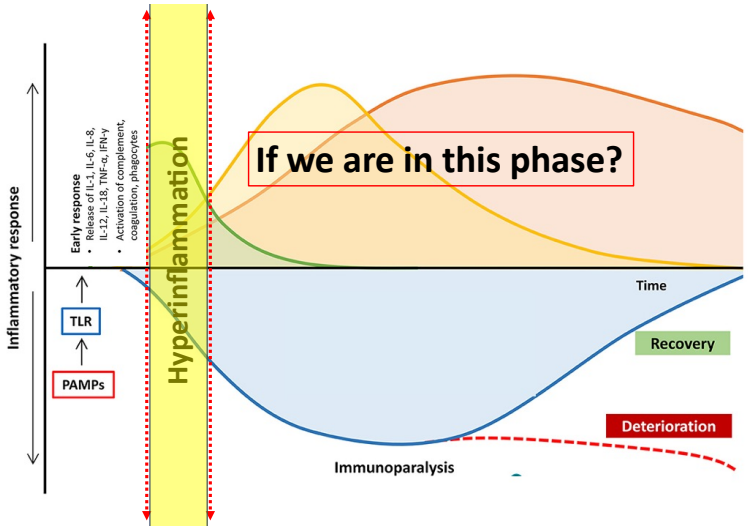
Annals of Intensive Care
a SpringerOpen Journal

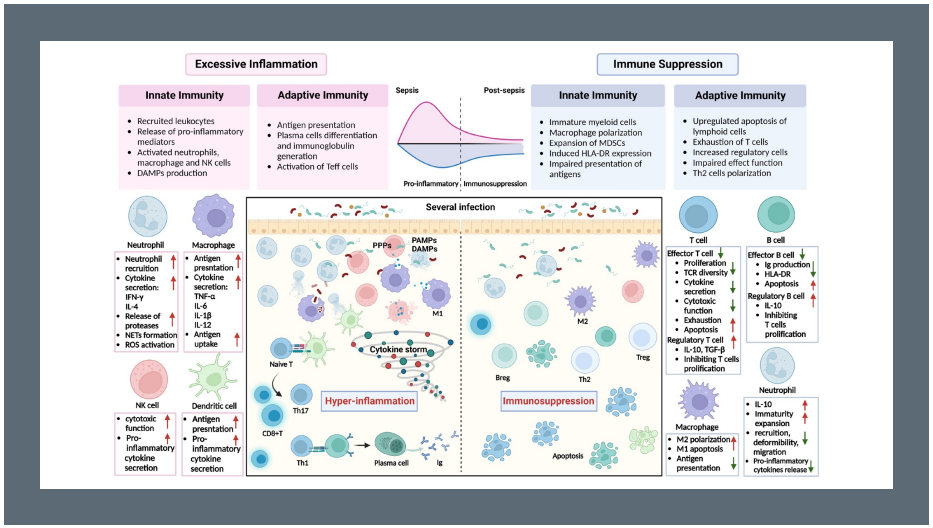
REVIEW Open Access

Hemodynamic parameters to guide fluid therapy

Paul E Marik[1*], Xavier Monnet[2], Jean-Louis Teboul[2]







Hyper Inflammatory Syndromes (HIS)

- Excessive and dysregulated immune response leading to widespread inflammation and potential organ dysfunction.
- **Key Features:**
- **Overproduction of pro-inflammatory cytokines (cytokine storm).**
- **Involvement of multiple organ systems.**
- **Can be triggered by infections, autoimmune diseases, and therapies.**

Heterogeneous cohort of patients with sepsis

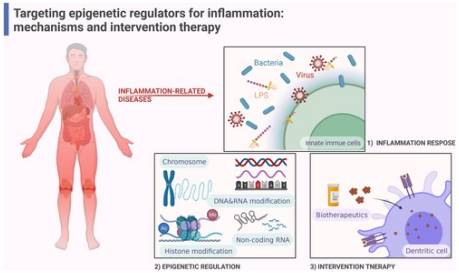
Epigenetic Regulation in Sepsis

What is Epigenetic Regulation?

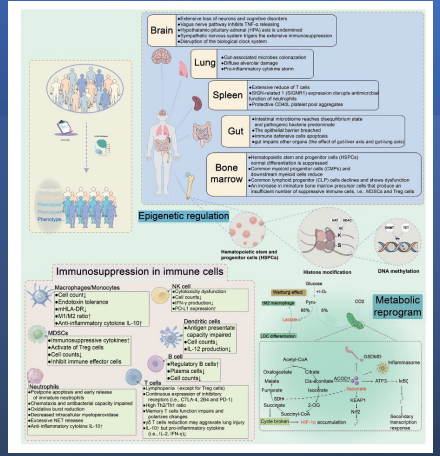
🔹 **Changes in gene expression** without altering the DNA sequence.
🔹 Acts like "tags" on DNA to turn genes **on** or **off**.
🔹 Affects how immune cells respond to infection and inflammation.

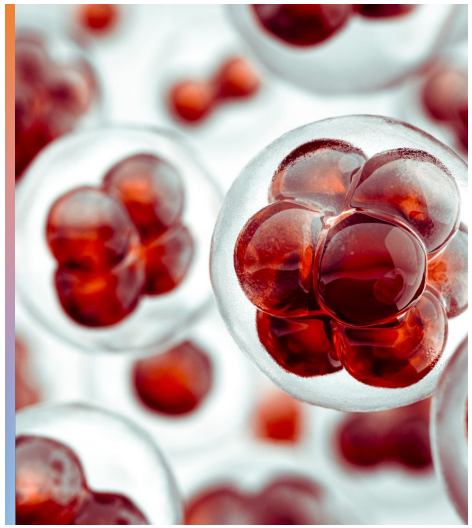
Key Epigenetic Mechanisms

📌 **Histone modifications** (HAT & HDAC): Control DNA accessibility.
📌 **DNA methylation**: Silences or activates immune response genes.
📌 **Non-coding RNAs**: Regulate inflammation and immune function.



Impact on Sepsis
✅ Can **enhance or suppress** immune response.
❌ Dysregulation leads to **immune paralysis** or **hyperinflammation**.
💡 **Therapeutic Target**: Modifying epigenetic pathways may restore immune balance.





Metabolic Reprogramming in Sepsis

What is Metabolic Reprogramming?

🔹 Cells switch their **fuel source** to adapt to stress or infection.
🔹 Alters energy production to support immune activation.

Key Changes in Sepsis

📌 **Glycolysis Activation**: Increases ATP for rapid immune response.
📌 **Mitochondrial Dysfunction**: Leads to energy crisis and organ failure.
📌 **Altered Lipid Metabolism**: Affects inflammatory signaling.

Impact on Sepsis
✅ Helps immune cells respond efficiently.
❌ If dysregulated, it can **worsen inflammation or cause organ damage**.
💡 **Therapeutic Target**: Drugs modifying metabolism (e.g., Nrf2 activators) may improve outcomes.

Key Characteristics of Hyper Inflammatory Syndromes

Immune Dysregulation:

Uncontrolled immune activation leading to systemic inflammation.

Cytokine Storm:

Excessive release of cytokines like IL-6, TNF-α, and IL-1β.

Organ Dysfunction:

Affects lungs, heart, kidneys, and liver.

Examples include ARDS, cardiac failure, and renal impairment.

Common Syndromes:

Sepsis, Cytokine Release Syndrome (CRS), Hemophagocytic Lymphohistiocytosis (HLH), Macrophage Activation Syndrome (MAS).

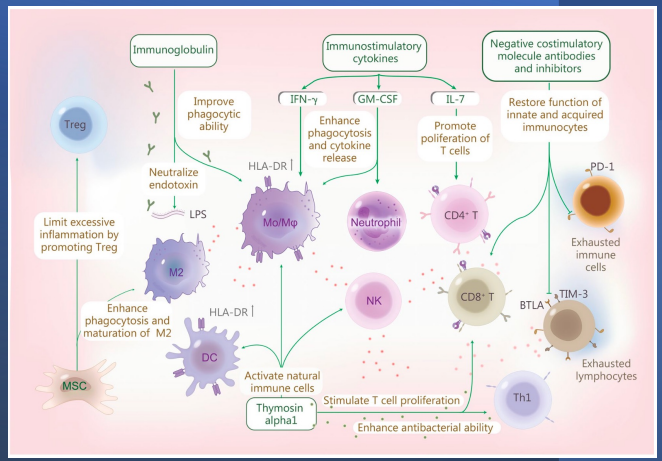
Diagnosis and Treatment Strategies

Diagnosis:

- **Laboratory Tests:** Elevated CRP, ferritin, and cytokine levels.
- **Imaging:** Assess organ involvement using CT, MRI, or ultrasound.
- **Clinical Assessment:** Identify symptoms and potential triggers.

Treatment Approaches:

- **Anti-inflammatory Therapies:** Corticosteroids, NSAIDs, cytokine inhibitors (e.g., tocilizumab).
- **Immunosuppressive Agents:** Anakinra, cyclosporine.
- **Supportive Care:** Respiratory support, fluid management.
- **Targeting Underlying Causes:** Antimicrobial therapy, addressing autoimmune triggers.



Anakinra – IL-1 Receptor Antagonist

What is Anakinra?

- A **recombinant IL-1 receptor antagonist (IL-1Ra)**.
- Blocks **IL-1α and IL-1β**, reducing inflammation.

Mechanism of Action

- **Prevents IL-1 from binding** to its receptor.
- Reduces the production of **pro-inflammatory cytokines**.
- Helps **modulate excessive immune activation** in sepsis.

Uses in Medicine

- ✅ **Sepsis & Septic Shock**: Reduces cytokine storm and inflammation.
- ✅ **Rheumatoid Arthritis**: Controls chronic inflammation.
- ✅ **Still's Disease & MAS (Macrophage Activation Syndrome)**: Regulates immune overactivation.

Potential Benefits in Sepsis

- ✓ Reduces **hyperinflammation** and **organ damage**.
- ✓ **Improves survival** in select septic patients with high IL-1 levels.
- ✓ May help prevent **immune dysfunction** in later sepsis stages.

Tocilizumab – IL-6 Receptor Inhibitor

What is Tocilizumab?
🔷 A **monoclonal antibody** targeting the **IL-6 receptor**.
🔷 Blocks IL-6 signaling, reducing inflammation and cytokine-driven damage.
Mechanism of Action
📌 Binds to **IL-6 receptor (IL-6R)**, preventing IL-6 from exerting pro-inflammatory effects.
📌 **Lowers CRP levels**, reducing systemic inflammation.
📌 Helps mitigate **cytokine storm** in hyperinflammatory states.

Uses in Medicine
✅ **Cytokine Release Syndrome (CRS)**: Used in **COVID-19** and CAR-T therapy-induced hyperinflammation.
✅ **Sepsis & Septic Shock**: Investigated for its role in modulating inflammation.
✅ **Rheumatoid Arthritis & Giant Cell Arteritis**: Controls IL-6–mediated inflammation.
Potential Benefits in Sepsis
✓ **Reduces IL-6–driven cytokine storm**.
✓ May **improve hemodynamics** and prevent organ failure.
✓ Helps **balance immune response** without excessive suppression.