PHYSIOPATHOLOGY OF SHOCK

- Definitions
- Types of Shock
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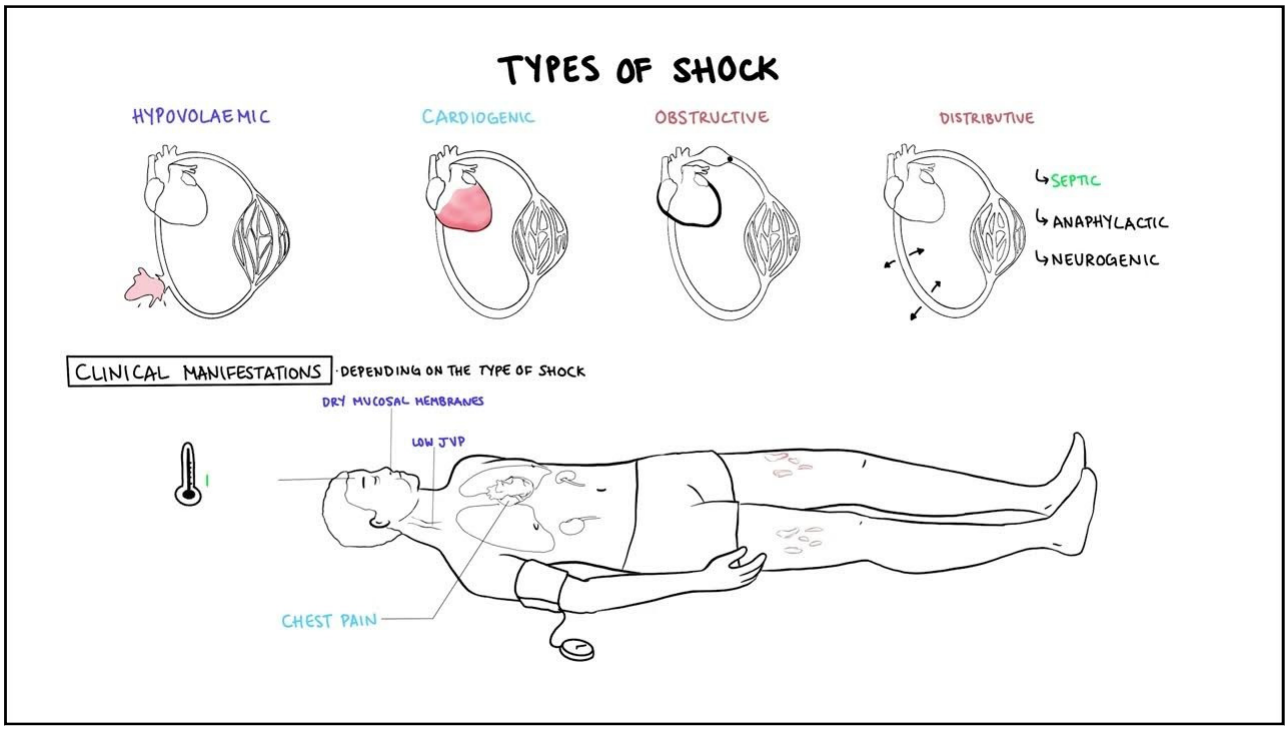
Luís Carlos de Souza Ferreira
Laboratory for Vaccine Development
Microbiology Department
lcsf@us´p.br

Shock – definitions and types

- Shock is a life-threatening manifestation of circulatory failure. Circulatory shock leads to cellular and tissue hypoxia resulting in cellular death and dysfunction of vital organs. Effects of shock are reversible in the early stages, and a delay in diagnosis and/or timely initiation of treatment can lead to irreversible changes, including multiorgan failure (MOF) and death.
- Four broad categories of shock: hypovolemic, cardiogenic, obstructive and distributive.



Hypovolemic Shock

- **Hypovolemic shock is characterized by decreased intravascular volume and increased systemic venous assistance (compensatory the mechanism to maintain perfusion in the early stages of shock). In the later stages of shock due to progressive volume depletion, cardiac output also decreases and manifest as hypotension.**
- **hemorrhagic hypovolemic shock**
- Gastrointestinal bleed (both upper and lower gastrointestinal bleed (e.g., variceal bleed, portal hypertensive gastropathy bleed, peptic ulcer, diverticulosis) trauma
- Vascular etiologies (e.g., aortoenteric fistula, ruptured abdominal aortic aneurysm, tumor eroding into a major blood vessel)
- Spontaneous bleeding in the setting of anticoagulant use.
- **non-hemorrhagic hypovolemic shock :**
- GI losses - the setting of vomiting, diarrhea, nasogastric suction, or drains.
- Renal losses - medication-induced diuresis, endocrine disorders such as hypoaldosteronism.
- Skin losses/insensible losses - burns, Stevens-Johnson syndrome, Toxic epidermal necrolysis, heatstroke, pyrexia.
- Third-space loss - in the setting of pancreatitis, cirrhosis, intestinal obstruction, trauma.

Cardiogenic Shock

- **Due to intracardiac causes leading to decreased cardiac output and systemic hypoperfusion**.
- Cardiomyopathies - include acute myocardial infarction affecting more than 40% of the left ventricle, acute myocardial infarction in the setting of multi-vessel coronary artery disease, right ventricular myocardial infarction, fulminant dilated cardiomyopathy, cardiac arrest (due to myocardial stunning), myocarditis.
- Arrhythmias - both tachy- and bradyarrhythmias
- Mechanical - severe aortic insufficiency, severe mitral insufficiency, rupture of papillary muscles, or chordae tendinae trauma rupture of ventricular free wall aneurysm.

Obstructive Shock

- **Mostly due to extracardiac causes leading to a decrease in the left ventricular cardiac output**
- Pulmonary vascular - due to impaired blood flow from the right heart to the left heart. Examples include hemodynamically significant pulmonary embolism, severe pulmonary hypertension.
- Mechanical - impaired filling of right heart or due to decreased venous return to the right heart due to extrinsic compression. Examples include tension pneumothorax, pericardial tamponade, restrictive cardiomyopathy, constrictive pericarditis.

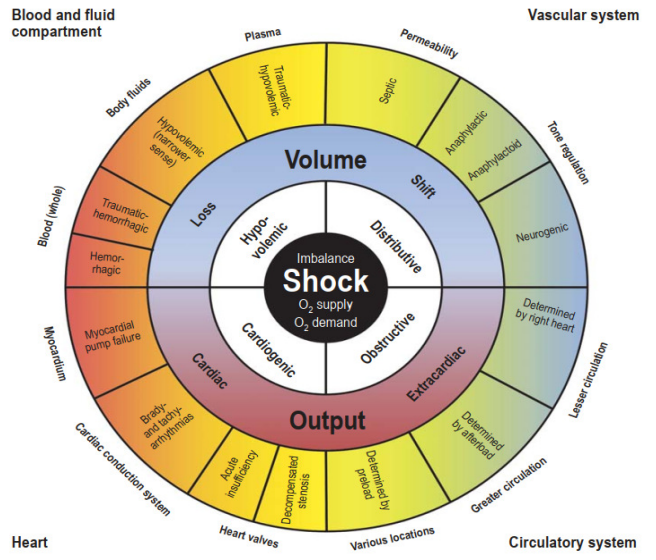
Distributive Shock

- Caused by peripheral vasodilatation.
- **Systemic Inflammatory Response Syndrome -** Systemic inflammatory response syndrome (SIRS) is a clinical syndrome of the vigorous inflammatory response caused by either infectious or noninfectious causes. Infectious causes include pathogens such as gram-positive (most common) and gram-negative bacteria, fungi, viral infections (e.g., respiratory viruses), parasitic (e.g., malaria), rickettsial infections. Noninfectious causes of SIRS include, but are not limited to, pancreatitis, burns, fat embolism, air embolism, and amniotic fluid embolism.
- **Anaphylactic Shock -** Anaphylactic shock is a clinical syndrome of severe hypersensitivity reaction mediated by immunoglobulin E (Ig-E), resulting in cardiovascular collapse and respiratory distress due to bronchospasm.
- **Neurogenic Shock -** Neurogenic shock can occur in the setting of trauma to the spinal cord or the brain. The underlying mechanism is the disruption of the autonomic pathway resulting in decreased vascular resistance and changes in vagal tone.
- **Endocrine Shock -** Due to underlying endocrine etiologies such as adrenal failure (Addisonian crisis) and myxedema.
- **Septic Shock -** Sepsis is defined as life-threatening organ dysfunction resulting from dysregulated host response to infection. Septic shock is a subset of sepsis with severe circulatory, cellular, and metabolic abnormalities resulting in tissue hypoperfusion manifested as hypotension.

Sepsis and Septic Shock

- Sepsis is defined as life-threatening organ dysfunction resulting from dysregulated host response to infection. Septic shock is a subset of sepsis with severe circulatory, cellular, and metabolic abnormalities resulting in tissue hypoperfusion manifested as hypotension leading to disseminated intravascular coagulation (DIC), multiple organ dysfunction symdrome (MODS).

Four types of SHOCK



ynoptic view of the four types of shock (inner, white field) with the organ systems primarily associated with them (outer corners), sites

Standl et al. Dtsch Arztebl.,2018

BACTEREMIA X SEPTICEMIA X SEPSIS X SEPTIC SHOCK

SIRS - Sepsis – Severe Sepsis – Septic shock

World Health Organization

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WHO calls for global action on sepsis - cause of 1 in 5 deaths worldwide

8 September 2020 | News release | Geneva | Reading time: 2 min (631 words)

The World Health Organization's first global report on sepsis finds that the effort to tackle millions of deaths and disabilities due to sepsis is hampered by serious gaps in knowledge, particularly in low- and middle-income countries. According to recent studies, sepsis kills 11 million people each year, many of them children. It disables millions more.

But there's an urgent need for better data. Most published studies on sepsis have been conducted in hospitals and intensive care units in high-income countries, providing little evidence from the rest of the world. Furthermore, the use of different definitions of sepsis, diagnostic criteria and hospital discharge coding makes it difficult to develop a clear understanding of the true global burden of sepsis.

"The world must urgently step up efforts to improve data about sepsis so all countries can detect and treat this terrible condition in time," says Dr Tedros Adhanom Ghebreyesus, WHO Director-General. "This means strengthening health information systems and ensuring access torapid diagnostic tools, and quality care including safe and affordable medicines and vaccines."

Sepsis occurs in response to an infection. When sepsis is not recognized early and managed promptly, it can lead to septic shock, multiple organ failure and death. Patients who are critically ill with severe COVID-19 and other infectious diseases are at higher risk of developing and dying from sepsis.

Even sepsis survivors are not out of danger: only half will completely recover, the rest will either die within 1 year or be burdened by long-term disabilities.

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Sepsis

19 July 2023

Key facts

- **A recent scientific publication estimated that in 2017 there were 48.9 million cases and 11 million sepsis-related deaths worldwide, which accounted for almost 20% of all global deaths (1).**
- **In 2017, almost half of all global sepsis cases occurred among children, with an estimated 20 million cases and 2.9 million global deaths in children under 5 years of age (1).**
- **Regional disparities in sepsis incidence and mortality exist; approximately 85% of sepsis cases and sepsis-related deaths worldwide occurred in low- and middle-income countries (1).**
- **Health care-associated infections are one of the most frequent types of adverse event to occur during care delivery and affect hundreds of millions of patients worldwide every year.**

Overview

Sepsis is a serious condition that happens when the body's immune system has an extreme response to an infection. The body's reaction causes damage to its own tissues and organs.

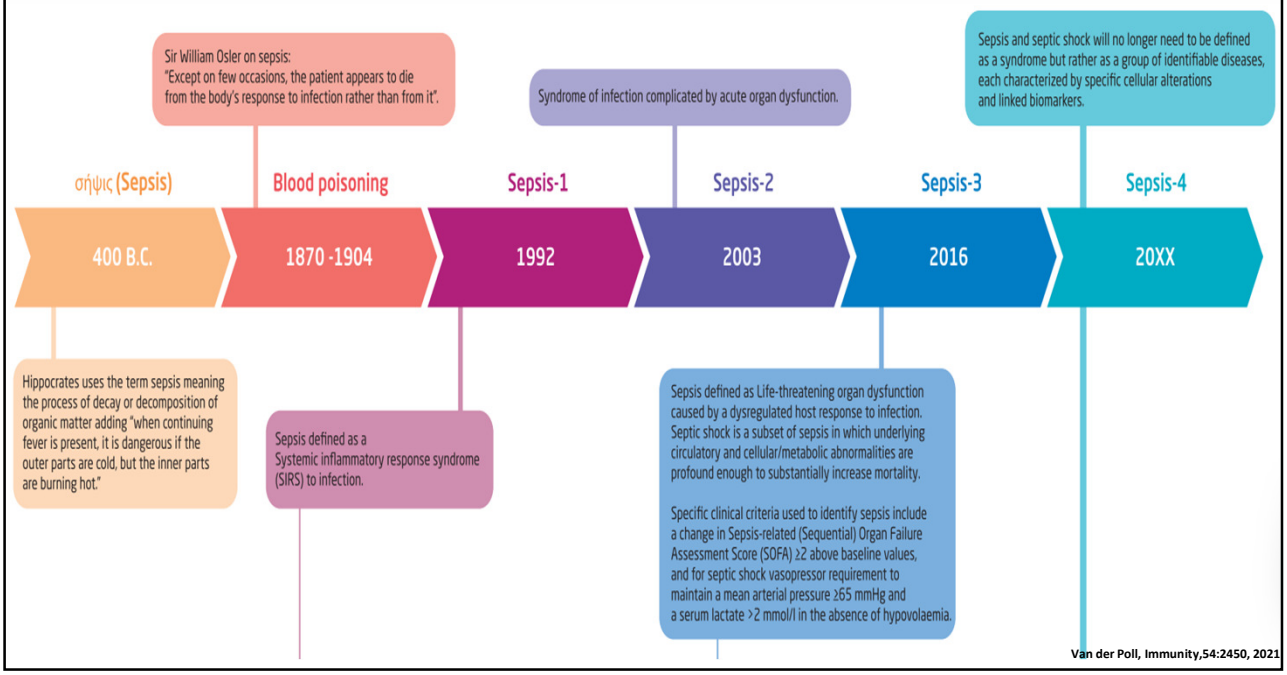
Sepsis can affect anyone, but people who are older, very young, pregnant or have other health problems are at higher risk.

Common signs of sepsis include fever, fast heart rate, rapid breathing, confusion and body pain. It can lead to septic shock, multiple organ failure and death.

Sepsis is usually caused by bacterial infections but may be the result of other infections such as viruses, parasites or fungi.

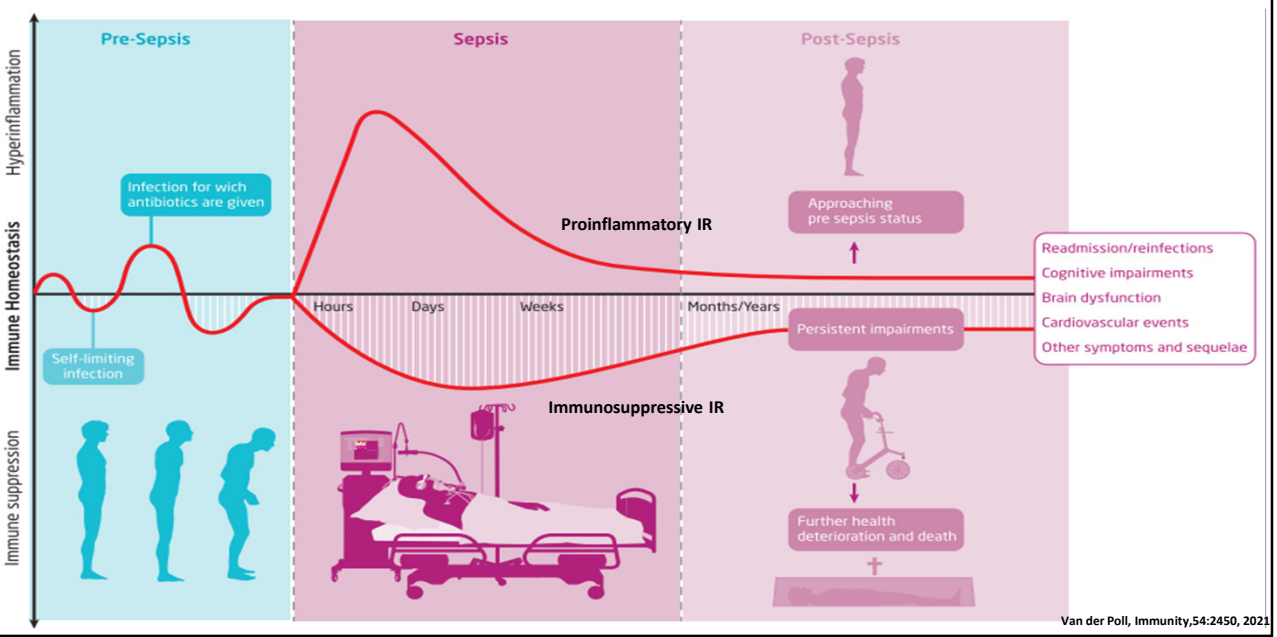
Each year, sepsis is responsible for at least 11 million deaths worldwide. In Brazil, approximately 400,000 cases of sepsis are recorded in adult patients each year. Of these, 240,000 die, a rate of 60%. Among children, the annual number of cases is 42,000, of which 8,000 do not survive, representing a rate of 19%. The current situation shows that Brazil has a much higher mortality rate due to sepsis than developing countries, indicating that there is a need for greater attention to the problem and faster diagnosis. To raise awareness of the disease and to reinforce to health professionals the importance of acting quickly in these cases, September 13 was established as World Sepsis Day.

The evolving meaning of Sepsis



Van der Poll, Immunity,54:2450, 2021

Immune trajectories and outcome pre-, during and post sepsis



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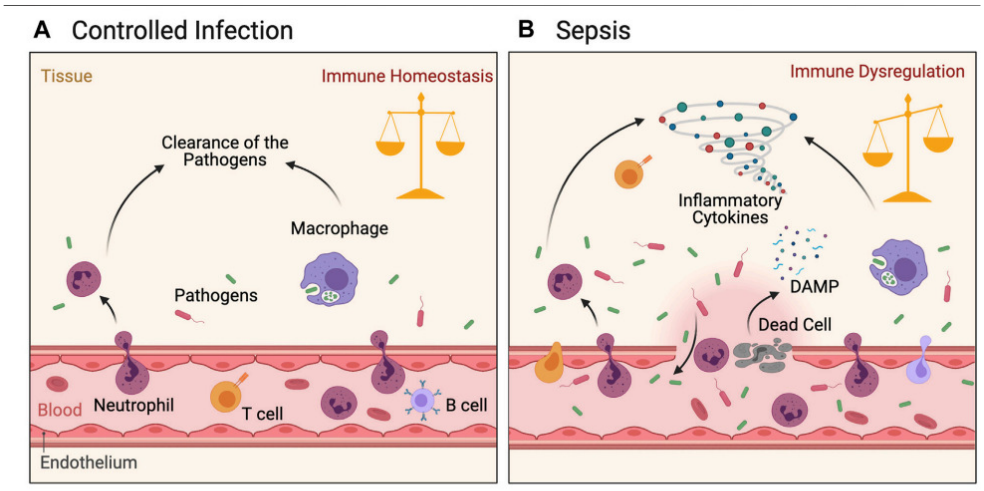


FIGURE 1 | Immune response following pathogen infection. Figure **(A)**: Pathogen invasion induces local inflammatory response in tissues. The activated innate immune and adaptive immune cells migrate locally to tissues, inhibit microbe duplication and systematic dissemination, and finally clear the pathogen. Inflammation is controlled and immune balance of the body is achieved. **(B)**: Heavy load infection accompanied by local damage activated innate and adaptive immune cells are in a hyperinflammatory state under the dual effects of pathogens and DAMPs. The cytokine storm generated by these cells inhibits the pathogens to a certain extent, but also leads to further tissue damage. Microbes migrate to the whole body through damaged blood vessels, causing a strong inflammatory response and thus leading to systemic immune dysregulation and injury.

Chen and Wei , 2021

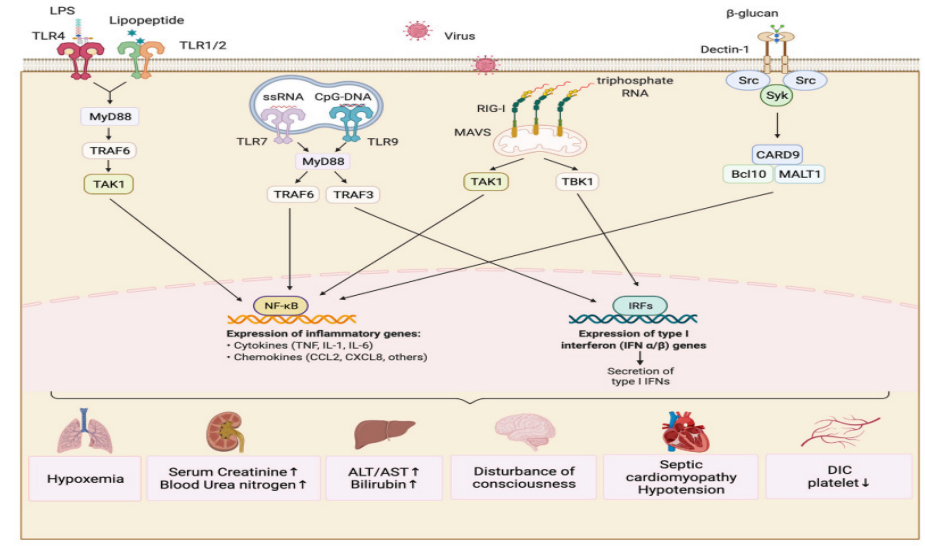
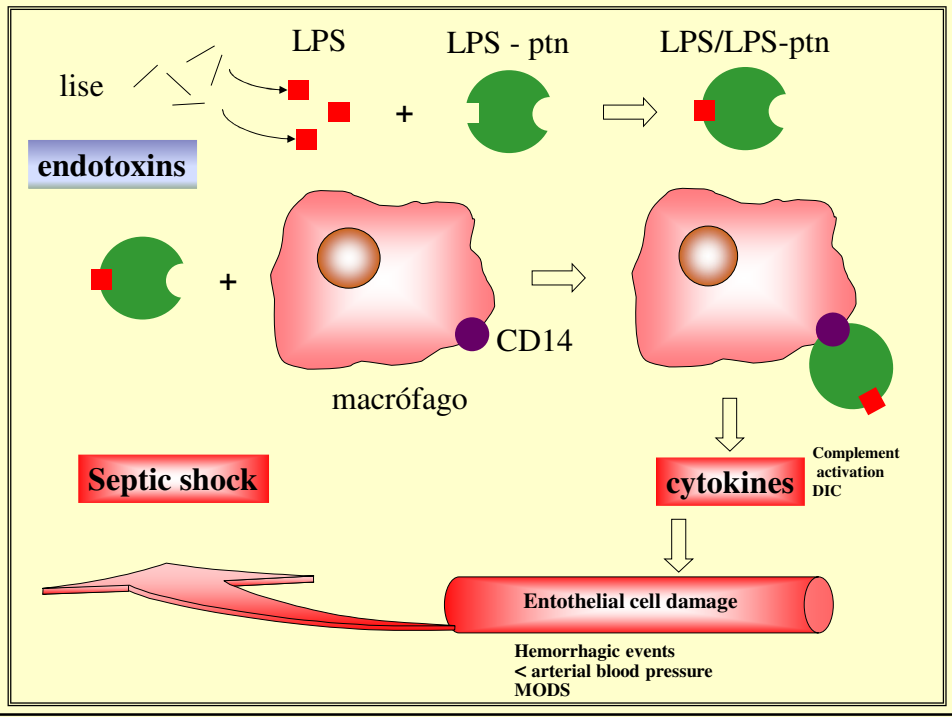
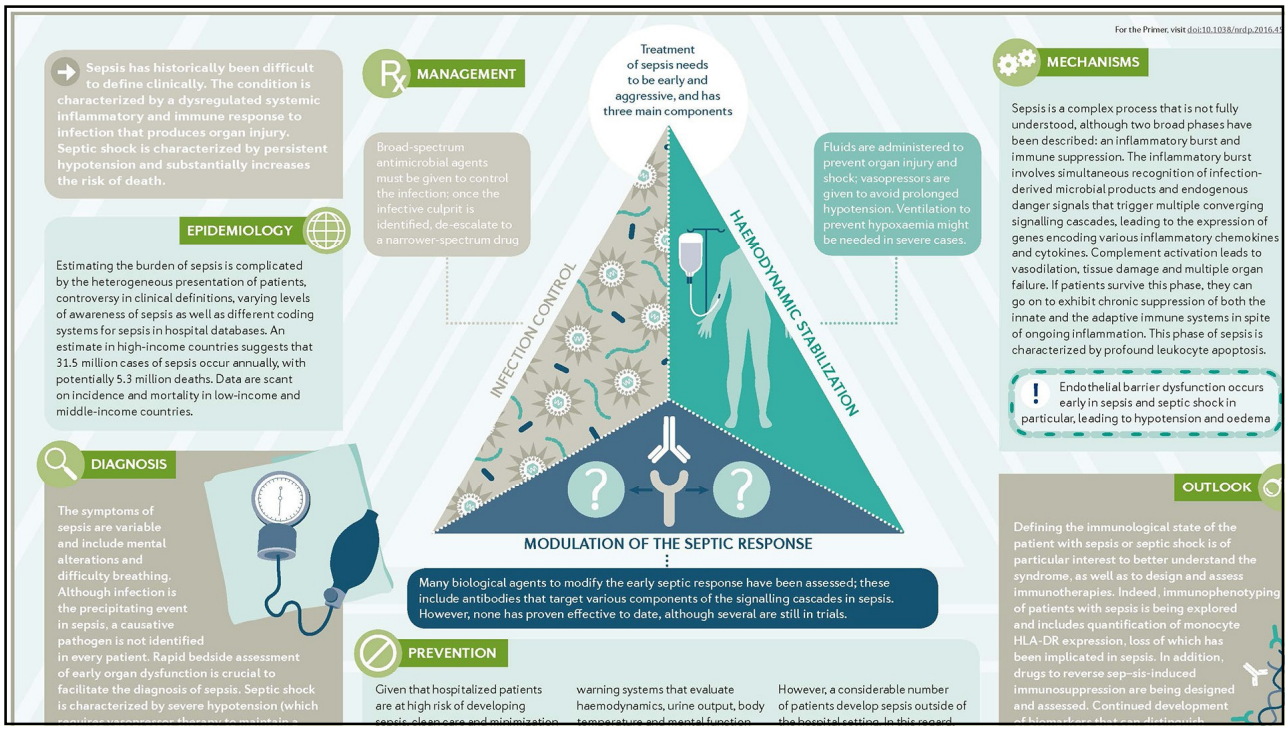


FIGURE 2 | Immunity mechanism of sepsis induced by different pathogens. The predominant pathogens that cause sepsis are bacteria, fungi and viruses. The lipopolysaccharide (LPS) in the outer membrane of Gram-negative bacteria can be recognized by TLR4, while the lipoprotein in the cell wall of Gram-positive bacteria can be bound to TLR2/TLR1. They activate the downstream signaling molecule of MyD88 and ubiquitinate TRAF6. Ubiquitinized TRAF6K recruits the TAK1-TAB1/2 protein complex, while TAK1 kinase activates the transcription factor NF-kB and facilitates the production of key pro-inflammatory cytokines such as IL-1, IL-6, and TNF. Fungus β-glucan and mannose are commonly recognized by CLRs which mobilizes Syk protein kinases to coordinate the innate immune response, and eventually activate NFkB to produce pro-inflammatory factors through the CARD9/BCL10/MALT1 complex. ilfluenza viruse causing common viral infection in sepsis can be recognized by RIG-I in the cytoplasm and signal to TAK1 and TBK1 through oligomerization of MAVs molecules on mitochondria, which ultimately activates NF-kB and IRF family transcription factors and promotes the production of inflammatory factors and type 1 interferon. These changes cause damage to important viscera of





Nosocomial infections - NI

Any infection acquired after the patient's hospitalization (minimum of 72 hours), which manifests itself during the patient's stay in the hospital, or after discharge, and which may be related to the hospitalization, is a hospital infection (nosocomial). Although they can be controlled, they are not eradicable.

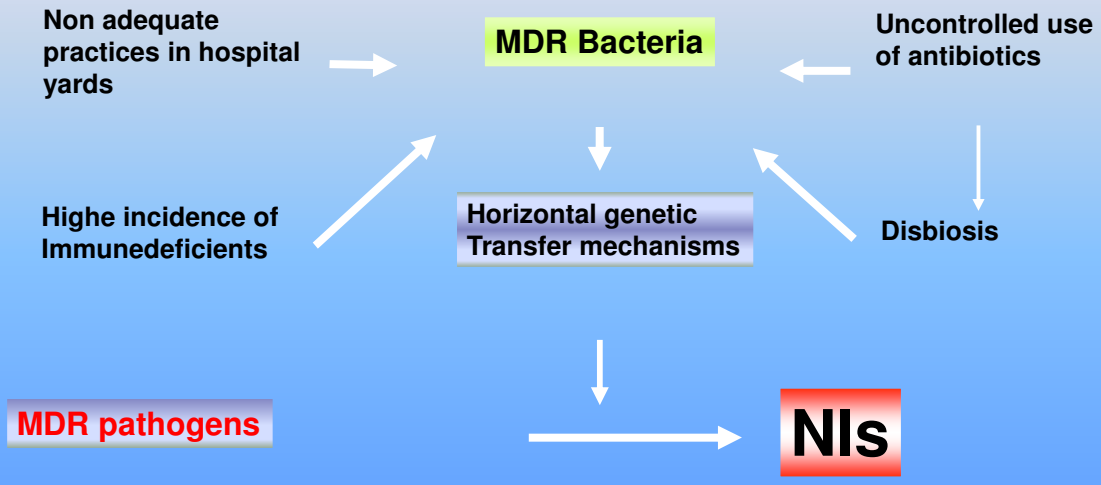
INCIDENCE OF NI

It varies depending on the country, geographic region, hospital, treatment unit and population served. In developed countries it ranges from 5 to 20% of hospitalized patients. In developing or underdeveloped countries it can reach 30% to 50% of hospitalized patients.
Brazil - >45.000 deaths/year
World – 8/1,000 death rate – 7 millions deaths/year

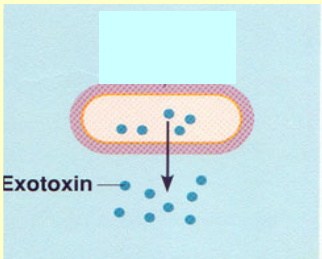
Major causative agents of sepsis in NI

Pseudomonas sp	20%
Klebsiella sp	20%
Staphylococcus aureus	20%
E. coli e outras entéricas	15%

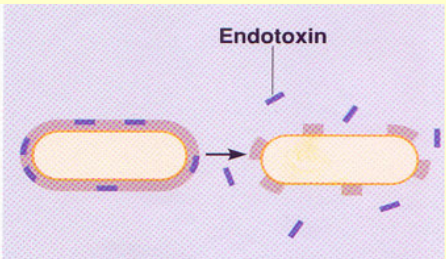
Factors associated with NIs



Bacterial Toxins



Protein toxins produced internally and released into the external environment. They are not part of the cellular structure.



Non-protein toxins released after cell death and lysis. They represent structural components of the bacterial cell envelope

Toxic Shock syndrome (Superantigens)

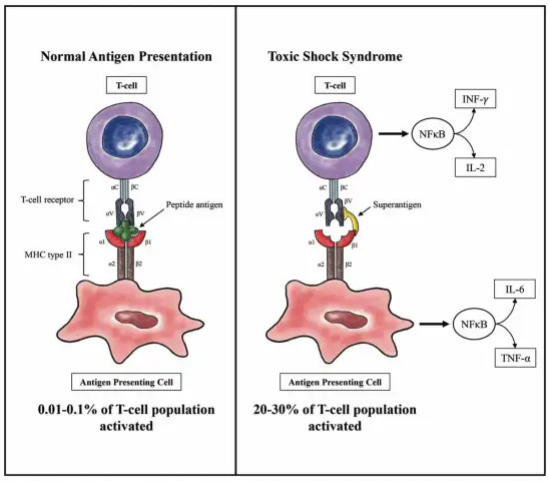
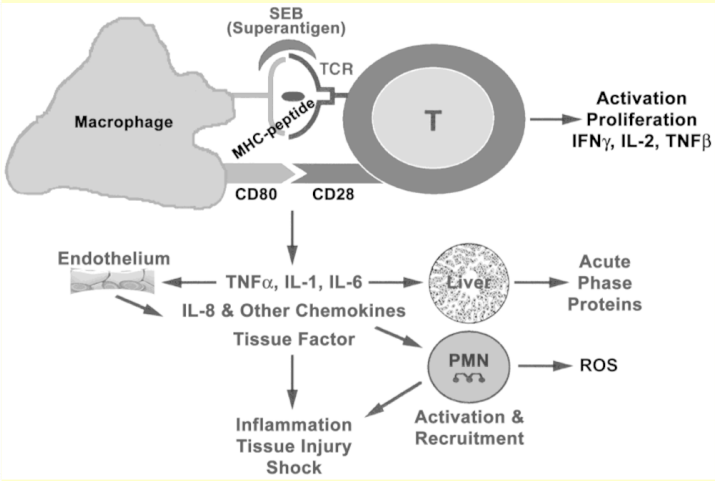


Fig. 4. Schematic of normal T-cell activation and abnormal T-cell activation induced by superantigen. Note that more inflammatory markers are secreted downstream than are shown in the figure.
Celie KB et al. PMID 33133879



Ethiological agents

- *S. aureus*
- *Streptococcus pyogenes* - Toxic Shock Syndrome

Videos

- https://www.youtube.com/watch?v=emOgJCoUy6Q – septic shock
- https://youtu.be/-bt-H5VQl5E - septic shock
- https://www.youtube.com/watch?v=qSams9-onRs - superantigens animation
- https://www.youtube.com/watch?v=AOLzM_pDbas&t=3s – toxic shock

References

- **doi:10.1038/nrdp.2016.45 - Sepsis and septic Shock**
- **doi: 10.1016/j.immu.2021.1010.012 – The immunology of septic shock**
- **doi:10.339/toxins2082177 Staphylococcal and Streptococcal superantigen Exotoxins**

Question for the class

- What is the impact of Septic shock on deaths caused by COVID-19?