Role of Immune System against Sepsis

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Received: 15 June 2021		Accepted: 05 July 2021		Published: 02 September 2021

Abstract
Sepsis, which is a highly heterogeneous syndrome, can result in death as a consequence of a systemic inflammatory response syndrome. The activation and regulation of the immune system play a key role in the initiation, development and prognosis of sepsis.[1]

The roles of inflammation and coagulation in the pathophysiology of sepsis are described. Sepsis results when an infectious insult triggers a localized inflammatory reaction that then spills over to cause systemic symptoms of fever or hypothermia, tachycardia, tachypnea, and either leukocytosis or leukopenia. These clinical symptoms are called the systemic inflammatory response syndrome. Severe sepsis is defined by dysfunction of one of the major organ systems or unexplained metabolic acidosis. The inflammatory reaction is mediated by the release of cytokines, including tumor necrosis factor-alpha, interleukins, and prostaglandins, from neutrophils and macrophages. The cytokines activate the extrinsic coagulation cascade and inhibit fibrinolysis. Monocyte-macrophage cells and dendritic cells play a key role in the innate immune response. These cells have the ability to phagocytosis bacteria and interact with their products through an interaction with their pattern-recognition receptors.[13]

These overlapping processes result in microvascular thrombosis; thrombosis is one potential factor producing organ dysfunction. Activation of the coagulation system leads to consumption of endogenous anticoagulants (e.g., protein C and Anti- thrombin); this may be an important factor in the development of microvascular coagulation. Anti-inflammatory mediators as well as inflammatory mediators have a role in sepsis, and an excess of either can result in poor patient outcomes. Sepsis is a complex syndrome involving activation of a variety of systems.[2]

In this article, we try to further investigate
The role of the Human Immune System against various infections mostly Blood infection (Sepsis).

Keywords: Sepsis, Human Immune System, Blood infection, Immune response, Neutrophils, Macrophage

How to cite the article:
M. navaser, Noninvasive measurement of cerebral cortex hemoglobin oxygenation with Near-Infrared spectroscopy, Medbiotech J. 2021; 5(3): 13-20. https://doi.org/10.1001.1229025282021.05.03.3.1
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What is sepsis?
Sepsis is a common condition that is associated with unacceptably high mortality and, for many of those who survive, long-term morbidity. Increased awareness of the condition resulting from ongoing campaigns and the evidence arising from research in the past 10 years have increased understanding of this problem among clinicians and lay people, and have led to improved outcomes. The World Health Assembly and WHO made sepsis a global health priority in 2017 and have adopted a resolution to improve the prevention, diagnosis, and management of sepsis. In 2016, a new definition of sepsis (Sepsis-3) was developed. Sepsis is now defined as infection with organ dysfunction. This definition codifies organ dysfunction using the Sequential Organ Failure Assessment score. Ongoing research aims to improve definition of patient populations to allow for individualized management strategies matched to a patient’s molecular and biochemical profile. The search continues for improved diagnostic techniques that can facilitate this aim, and for a pharmacological agent that can improve outcomes by modifying the disease process.[8]
Sepsis remains a leading cause of death worldwide, despite advances in critical care, and understanding of the pathophysiology and treatment strategies. No specific therapy or drugs are available for sepsis. Neutrophils play a critical role in controlling infection under normal conditions, and it is suggested that their migration and antimicrobial activity are impaired during sepsis which contribute to the dysregulation of immune responses. Recent studies further demonstrated that interruption or reversal of the impaired migration and antimicrobial function of neutrophils improves the outcome of sepsis in animal models.[3].

Sepsis occurs when an infection exceeds local tissue containment and induces a series of deregulated physiologic responses that result in organ dysfunction. A subset of patients with sepsis progress to septic shock, defined by profound circulatory, cellular, and metabolic abnormalities, and associated with a greater mortality. Historically, sepsis-induced organ dysfunction and lethality were attributed to the complex interplay between the initial inflammatory and later anti-inflammatory responses. With advances in intensive care medicine and goal-directed interventions, early 30-day sepsis mortality has diminished, only to steadily escalate long after "recovery" from acute events. As so many sepsis survivors succumb later to persistent, recurrent, nosocomial, and secondary infections, many investigators have turned their attention to the long-term sepsis-induced alterations in cellular immune function. Sepsis clearly alters the innate and adaptive immune responses for sustained periods of time after clinical recovery, with immune suppression, chronic inflammation, and persistence of bacterial representing such alterations. Understanding that sepsis-associated immune cell defects correlate with long-term mortality, more investigations have centered on the potential for immune modulatory therapy to improve long-term patient outcomes. These efforts are focused on more clearly defining and effectively reversing the persistent immune cell dysfunction associated with long-term sepsis mortality.[4]

Sepsis is defined as a deregulated immune response to infection affecting millions of individuals per year and carries high morbidity and mortality rates even if appropriate care is provided. In the United States, sepsis is considered the most common cause of inpatient death, affecting 1.7 million adults per year and contributing to 270,000 deaths. Globally, there were an estimated 49 million cases of sepsis in 2017. Sepsis incidence and mortality rates varied significantly by region. Furthermore, sepsis can be difficult to accurately diagnose, is a diverse clinical syndrome, and there is no reference standard for diagnosis. Subjectivity in determining whether an infection is present and whether organ dysfunction is due to infection can be challenging.

![How to prevent sepsis](image-url)

*how to prevent sepsis
Published by WHO*
Neutrophils are a type of white blood cell that helps heal damaged tissues and resolve infections. Neutrophil blood levels increase naturally in response to infections, injuries, and other types of stress. They may decrease in response to severe or chronic infections, drug treatments, and genetic conditions. Neutrophils help prevent infections by blocking, disabling, digesting, or warding off invading particles and microorganisms. They also communicate with other cells to help them repair cells and mount a proper immune response. The body produces neutrophils in the bone marrow, and they account for 55–70 percent of all white blood cells in the bloodstream. A normal overall white blood cell level in the bloodstream for an adult is somewhere between 4,500 and 11,000 per millimeters cubed (mm$^3$).

When there is an infection or another source of inflammation in the body, special chemicals alert mature neutrophils, which then leave the bone marrow and travel through the bloodstream to the site in need.

Unlike some other cells or blood components, neutrophils can travel through junctions in the cells that line blood vessel walls and enter into tissues directly.[5]

Neutrophils play a critical role in the host defense against infection, and they are able to perform a variety of effector mechanisms for this purpose. However, there are also a number of pathological conditions, including autoimmunity and cancer, in which the activities of neutrophils can be harmful to the host. Thus the activities of neutrophils need to be tightly controlled. As in the case of other immune cells, many of the neutrophil effector functions are regulated by a series of immune receptors on the plasma membrane. Here, we review what is currently known about the functions of the various individual immune receptors and their signaling in neutrophils.[6]

While these immune receptors allow for the recognition of a diverse range of extracellular ligands, such as cell surface structures (like proteins, glycans, and lipids) and extracellular matrix components, they commonly signal via conserved ITAM or ITIM motifs and their associated downstream pathways that depend on the phosphorylation of tyrosine residues in proteins and/or inositol lipids. This allows for a balanced homeostatic regulation of neutrophil effector functions. Given the number of available immune receptors and their fundamental importance for neutrophil behavior, it is perhaps not surprising that pathogens have evolved means to evade immune responses through some of these pathways. Inversely, some of these receptors evolved to specifically recognize these pathogens. Finally, some interactions mediated by immune receptors in neutrophils have been identified as promising targets for therapeutic intervention.[6]

Neutrophils are the first line of defense in protecting the body from infection. Sepsis is defined as uncontrolled host responses induced by the microbial invasion and failure of neutrophils in the infection sites with deregulated immune responses to infection has been largely reported previously.[11, 14, 15, 16] Thus, re-evaluating of the pathophysiology of how sepsis influences the function and migration of neutrophils, as well as the signal pathways involved, may help to develop new and promising treatment strategies for sepsis. Moreover, based on the deregulated characteristics of neutrophils in sepsis, potential targets on neutrophils as diagnostic and/or prognostic biomarkers for sepsis are also discussed.[7]
Control of Infections by Neutrophils:
Neutrophils are leukocytes with multi-lobed nuclei that form in the bone marrow and are released in their mature form to the blood. Neutrophils have a short life span and do not show proliferative properties. Classically recognized as phagocytic cells, neutrophils are associated with the innate immune response. These cells are recruited to the site of the infection in response to chemotactic mediators, where they play antimicrobial roles.[9] The presence of neutrophils at the site of infection has been demonstrated to be essential for controlling the bacterial and fungal burden and avoiding the systemic spread of the infection. Indeed, depletion of neutrophils in mice infected with Staphylococcus aurous markedly reduced the clearance of the bacteria and also survival. Similarly, depletion of neutrophils in mice infected with Candida albicans induced dissemination of the fungus and led to a higher mortality rate. Likewise, neutropenia patients are more susceptible to bacterial and fungal infections. Neutrophils induce killing of pathogens via phagocytosis, degranulation, or even the release of intracellular components such as DNA, histones, and lytic proteins, which form neutrophil extracellular traps (NETs). Nitric oxide (NO), a mediator produced by the enzyme inducible nitric oxide synthase, is one crucial mediator of the microbicidal activity of neutrophils. Deletion of nitric oxide induces a high mortality rate due to impaired control of the infection, despite the presence of neutrophils in the locale of the infection.[10] Additionally, neutrophils are equipped with receptors that recognize pathogen-associated molecular patterns or damage-associated molecular patterns, initiating signaling cascades and leading to the production of inflammatory mediators to establish an appropriate response against the pathogen. This results in amplification of the inflammatory process, including emigration of the new waves of neutrophils to the site of infection.[10]

What are lymphocytes and what do they do?
Lymphocytes are cells that circulate in your blood that are part of the immune system. There are two main types lymphocytes: T cells and B cells. B cells produce antibody molecules that can latch on and destroy invading viruses or bacteria. T cells are direct fighters of foreign invaders and also produced cytokines, which are biological substances that help activate other parts of the immune system. One such part is called macrophages. These macrophages act to clean up the invaders and the dead tissue after an immune response.[11] There are two categories of lymphocytes known as B lymphocytes and T lymphocytes. These are commonly referred to as B cells and T cells.[12]
Both types originate from stem cells in the bone marrow. From there, some cells travel to the thymus, where they become T cells. Others remain in the bone marrow, where they become B cells. The job of B cells is to make antibodies, which are proteins produced by the immune system to fight foreign substances known as antigens. Each B cell is set to make one specific antibody. Each antibody matches an antigen in the same way that a key matches a lock, and when this happens, the antigen is marked for destruction.[12]

The job of T cells is to help the body kill cancer cells and control the immune response to foreign substances. They do this by destroying cells in the body that have been taken over by viruses or become cancerous. A third type of lymphocyte, known as a natural killer or NK cell, comes from the same place as B and T cells. NK cells respond quickly to several foreign substances and are specialized in killing cancer cells and virus-infected cells.[12]

Role of Circulating Lymphocytes in Patients with Sepsis:
The recent discovery of subsets of lymphocytes that are defined by their limited antigen receptor variability and are restricted to specific tissue may prove a link between immune activation and antibacterial defense during sepsis. “Innate lymphocytes” are defined by their limited antigen receptor variability, and, therefore, these T cells have a memory phenotype in the absence of deliberate immunization. The innate-like lymphocytes include natural killer T cells, gamma delta T cells, and mucosal-associated invariant T (MAIT) cells. MAIT cells are already primed to gastrointestinal flora and work in cooperation with the innate response to stave off infections. Furthermore, T lymphocytes play a critical role in the regulation of antimicrobial phagocytic and cytotoxic activity of the innate immune response cells. Interferon (IFN)-γ and granulocyte macrophage colony stimulating factor (GM-CSF), mainly produced by T lymphocytes, increase this defensive activity but other cytokines such as interleukin (IL)-10 have inhibitory effects. B lymphocyte response also plays an important role in the defensive host response. B cells produce cytokines, present antigens to T lymphocyte, and differentiate into antibody producing cells. Antibodies bound to bacteria may increase bacteria Opsonization and favor phagocytosis [13]. However, abnormal bacterial induced activation of T and B cells may be followed by inflammation and endothelial and tissue damage [13].

Blood lymphocyte dysfunction during sepsis has long been recognized with significant Lymphopenia and decreased lymphocyte T CD4+, CD8+, and natural killer (NK) cells. However, recently a renewed interest in lymphocyte dysfunction during sepsis emerged from studies demonstrating that immunosuppression was present not only in peripheral blood cells but also locally in organs in patients who died of sepsis [13].

B cells:
B cells are a very diverse immune cell population with varying functional and phenotypical attributes. Historically B cell function was understood to only encompass producing antibodies and plasma cells for long-term antibody responses. Conversely, a rapidly growing body of knowledge and collection of recent reports demonstrate that B cells play a much more pivotal role in sepsis immune biology than previously suspected. Clearly humans with septic shock have overall reductions in B cell numbers, however the most significant deficit in B cell number is in CD5+ B1a-type cells, which correlate and are predictive of survivors and non-survivors following episodes of sepsis. In mouse models of human sepsis, B cells are necessary to improve cytokine production, reduce bacterial load and improve survival through type I interferon signaling. A recent investigation identified an innate response activator (IRA) B cell population, which is phenotypically and functionally distinct from B1a cells and depends on PRRs, which produces granulocyte-macrophage-CSF (GM-CSF). Inhibition of IRA B cells impairs bacterial eradication, enhances a cytokine storm, and perpetuates the symptoms of septic shock. These recent clarifications position IRA B cells as immunological gatekeepers of bacterial infection elimination and simultaneously recognize IRA B cells as a new therapeutic target to improve survival in human sepsis.

Regulatory T cells:(T REG)
T REG are a master regulators of adaptive immunity that suppresses responses of other effector T cells subsets, helping to maintain self-tolerance and suppress autoimmune disease. In states of sepsis, critical illness and states of inflammation, TREGs potentiate deleterious Effector T cell (TEff) suppression that prolongs recovery and may dispose to increased complications. Increased T REG ratios are present early after episodes of sepsis and remain elevated in those patients who died from sepsis while hospitalized, placing a high level of attention on T REG function. Other reports relate that T REG number increases are due to effector TH cell loss.
from apoptosis rather than an absolute increase in T REG numbers. This observation suggests to many that T REGs are resistant to sepsis-induced apoptosis, thereby preventing the recovering immune system from mounting excessive autoimmune responses during the heightened initial inflammatory phase. Moreover, heat shock proteins and histones that induce mononuclear cell epigenetic changes also play a role as inducers of T REG in sepsis. Recent murine reports demonstrate that T REGs are detrimental to TEff proliferation and immune function.

Other members in immune system against sepsis:

*Monocytes and Macrophages

The impact of an episode of sepsis on human monocyte subpopulations has long been the subject of intense investigation over past half century. For decades it has been apparent that reduced mononuclear cell HLA-DR expression clearly correlates with human sepsis mortality. Moreover, the reduced capacity of blood monocytes from septic patients to release pro-inflammatory cytokines after endotoxin (LPS)
challenge has been described as “endotoxin tolerance”, which has been suggested to facilitate poor short and long-term sepsis outcomes. Although a sundry of complex mononuclear cell signaling pathways are altered and contribute to the establishment of endotoxin tolerance, the major implication on monocytes, and to a lesser extent macrophages, is reduced antigen presentation related to diminished HLA-DR cell surface expression. In addition to the clear and persistent reductions in HLA-DR cell surface expression, monocytes from septic patients also demonstrate a reduced ability to secrete the pro-inflammatory cytokines TNF, IL-1, IL-6, and IL-12 after LPS challenge. The reduced monocyte capacity to secrete pro-inflammatory cytokines suggest that intracellular signaling has shifted toward the production of anti-inflammatory mediators which are associated with hospital acquired, ongoing, and secondary infections which ultimately increase sepsis-associated mortality.

* Dendritic Cells (DCs)

DCs are traditionally characterized as either conventional DCs\(^1\) or plasmacytoid DCs\(^2\). CDCs are similar to monocytes and secrete IL-12, while pDCs, are similar to plasma cells and secrete large amounts of IFNα. cDCs and pDCs are of particular interest due to their enhanced apoptosis during sepsis and in patients who developed nosocomial infections. Although DCs have varying immune functions compared with monocytes, like monocytes, DCs also exhibit reduced HLA-DR expression and produce increased amounts of immune suppressive IL-10. Furthermore, coculture of DCs with T effectors induces T cell anergy and TREG proliferation, which both correlate with sepsis-induced immune dysfunction. A couple of recent investigations have demonstrated that prevention of sepsis-induced DC apoptosis or augmentation of DC function enhances sepsis long-term survival. Several reports demonstrate that immune suppression can be ameliorated by DC treatment with growth factor FMS-like tyrosine kinase 3 ligand (FLT3L).\(^{[14]}\)

**CONCLUSIONS**

Sepsis induces a multitude of defects in immunity that cause protracted inflammation, immune suppression, susceptibility to infections and insurmountable death. Although there are new cell-based methodologies available to identify patients with post-sepsis immune dysregulation, it is still unclear which interventions and at what time points targeting cell-specific deficits will be most beneficial for sepsis survival. Considering the overlapping, inter-related and interdigitating complexity of immune cell derangements, as well as the protracted and convoluted road to mortality, we believe that single-agent immune modulatory intervention as attempted in past sepsis trials will fail. Conversely, the notion of more thorough and rigorous patient stratification and selection, coupled with strategic and thoughtful long-term monitoring of immune function, combined with goal-directed immune modulatory therapy will, over time, provide optimal clinical benefit to those surviving initial sepsis.

**Reference**

“All have been confirmed in GOOGLE SCHOLAR”

- [11] National Human Genome Research Institute/Lawrence C. Brody, Ph.D.

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\(^1\) cDCs

\(^2\) pDCs