Immunological Aspect of Septic Shock

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ABSTRACT

Septic shock is clinically characterized by hypotension necessitating vasoactive support that fails to react to fluid resuscitation in patients with suspected or microbiologically confirmed infections leading to severe organ failure without an identified etiology. Predisposing factors for septic shock arises when the body's reaction to an infection impairs tissue perfusion and oxygen utilization, resulting in end-organ malfunction and heightened mortality risk. The etiologies of septic shock differ between adults and children. The mechanisms contributing to the predisposition for severe sepsis are numerous: diminished complement levels, children's exposure to outdoor environments or crowded settings, reduced protein levels, accelerated metabolic rates, heightened incidence of heart failure, prior antidotal or clinical exposure, and fluctuating rates of infections caused by pathogenic organisms. Endothelial dysfunction, a primary cause of septic shock, impairs microvascular perfusion and tissue oxygenation in sepsis. Septic shock is commonly linked to coagulation disorders and a heightened prevalence of venous thromboembolism. The principal phases of biomarkers in septic pathobiology encompass a pro-inflammatory and anti-inflammatory phase, along with cellular dysfunction. In summary, the cytokines and chemokines IL-1β, IL-6, IL-8, IL-18, and CCL2 possess considerable predictive significance for septic shock. The new personalized medicine that considers significant immunological indicators may result in more focused therapies in the future. The primary message of this immunological approach is that inflammation, which significantly contributes to the progression of septic shock, is an early occurrence in its pathogenesis.

Keywords: Septic shock, immunology, innate immunity, adaptive immunity, Immunological Biomarkers

INTRODUCTION TO SEPTIC SHOCK

Sepsis is a major cause of morbidity and mortality worldwide due to an exaggerated systemic inflammatory response to severe infections that have remained poorly understood, even if many studies have investigated their underlying mechanisms (1, 2). Septic shock can be fatal; the models' clinical utility in human septic shock, is particularly related to the immunological "phenomenon" observed in this human condition. Septic shock is characterized by a dysregulated host response to infections that leads to life-threatening organ dysfunctions, that annual worldwide fatalities could exceed 11 million by 2020, resulting in more than 350,000 deaths daily. Although its global prevalence is unknown, nevertheless, rates are increasing. Early treatment for severe sepsis and septic shock is crucial, given the high risk of death (3, 4, 5). The Third International Consensus definitions defined septic shock as "life-threatening organ dysfunction caused by a

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dysregulated host response to infection."(6, 7), this definition was updated in 2016, revising "severe sepsis" to "sepsis with organ dysfunction" and "septic shock" to "sepsis with refractory hypotension." It is considered a time-sensitive disease, and for this reason, should be recognized promptly with efficient pre-hospital systems and in-hospital services reducing the delay between diagnosis and management. (8, 9, 10)

Clinical Definition

Septic shock is clinically defined as the occurrence of hypotension requiring vasoactive support that does not respond to fluid resuscitation in patients with suspected or microbiologically proven infection responsible for acute organ dysfunction not explained by an identifiable cause. Organ dysfunction is defined according to several scores including the Sequential Organ Failure Assessment (SOFA) score, the Acute Physiological Assessment (APA) and Chronic Health Evaluation (CHE), and the Quick (SOFA), SOFA score. In these scores, altered consciousness, systolic blood pressure ≤ 100 mm Hg, and widely distributed mottled skin are used as surrogate indicators for possible altered perfusion and tissue hypoxia (3, 6).

Predisposing Factors: Septic shock occurs when the body's response to an infection compromises tissue perfusion and oxygen utilization, leading to end-organ dysfunction and an increased risk of mortality. Although all patients with severe infections are at risk of decompensating into septic shock, certain predisposing factors increase the risk of suffering this acute complication. (11). Such predisposing factors can be stratified as either host or environmental factors, and a complete understanding of these factors can help modify management, assess risk, and prevent its occurrence. Co-infection, HIV, or CD4 count less than 200 cells/mm3, and immunosuppression are notable factors. Host factors represent the patient-specific characteristics that may lead to an increased risk of developing septic shock. (12)(13) This commonly involves medical comorbidities such as diabetes, chronic kidney disease, congestive heart failure, advanced age, cirrhosis with portal hypertension, or cachexia secondary to chronic illness, and these patients are therefore at an inherent risk of developing septic shock. A proportion of these comorbidities reduce the likelihood that a patient with an infection will present with fever. This occurs because of impairments in the immune system that delay normal body temperature regulation. (14).

Environmental factors are those that increase the risk of the majority of the patient population suffering from septic shock and are therefore at an inherent risk of developing septic shock if infected. The following is a list of the most commonly cited environmental factors leading to septic shock. The cloud model should consider setting as a risk factor for the nursing home. In specific patients, the cloud model may also consider the following environmental emergency room or hospital setting as high risk for septic shock. This is when a provider feels the risk of serious infection is increased due to performing invasive procedures and antibiotics received in the hospital setting within 90 days of their current presentation. (15) . Of those risk factors that are known, the environment of a facility can play a significant role in the transmission of microorganisms that cause septic shock. As facilities contribute to an increased likelihood of exposure to pathogens that can infect, predisposing the patients inside to have higher risk profiles for septic shock, these two factors are highly connected. Specific settings with an increased prevalence of such infections include hospitals as well as other healthcare environments. There are several reasons that patients in such facilities are more prone to acquiring infections, making them more likely to develop septic shock. (16)(17)

The invasiveness of many common procedures and interventions available in a healthcare facility can facilitate the introduction of some types of microorganisms into sterile body cavities. This is particularly problematic when considering the need to utilize many invasive procedures to pursue the diagnostic isolation of a microorganism, which may be challenging otherwise. The use of a central venous catheter increases the odds of infection by the microorganism introduced through the catheter's insertion site. While preventive measures can reduce these risks, infections may still periodically occur due to the entry of surrounding skin flora. The widespread use of antibiotics in numerous healthcare settings impacts the microorganism population. Across the sectors of healthcare, microorganisms have developed resistance to these widely available drugs and now require stronger or harsher treatment courses. A host with a weakened immune response is not able to surmount infections precipitated by such resistant microorganisms. A patient

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contracting one of these highly resistant microbes in a hospital is at an increased risk of septic shock. Some regulatory practices are in place to prevent hospital-acquired infections, along the lines of strict infection control protocols.

Host Factors Septic shock occurs when the body's response to an infection compromises tissue perfusion and oxygen utilization, leading to end-organ dysfunction and an increased risk of mortality. Although all patients with severe infections are at risk of decompensating into septic shock, certain predisposing factors increase the risk of suffering this acute complication. (18). Such predisposing factors can be stratified as either host or environmental factors, and a complete understanding of these factors can help tailor management, assess risk, and prevent its occurrence. Co-infection, HIV, or CD4 count less than 200 cells/mm3, Native American or rural descent, Southwestern states, and immunosuppression are notable factors. Host factors represent the patient-specific characteristics that may lead to an increased risk of developing septic shock. (19)(20)(21),these commonly involves medical comorbidities such as diabetes, chronic kidney disease, congestive heart failure, advanced age, cirrhosis with portal hypertension, or cachexia secondary to chronic illness, and these patients are therefore at an inherent risk of developing septic shock. A proportion of these comorbidities reduce the likelihood that a patient with an infection will present with fever. This occurs because of impairments in the immune system that delay normal body temperature regulation.

Septic shock is the final common pathway for many different infectious processes. Due to this, almost anyone can develop a severe infection through a break in the skin, an injury, or a medical procedure. However, some intrinsic host factors place one at increased risk of developing septic shock from an infectious process. In addition to a significant risk for infection, multiple chronic medical conditions are also associated with impaired immune function, an important factor for the development of septic shock. (22)(23)

The presence of more than one of these factors (particularly age and chronic comorbid conditions) increases the risk of developing severe sepsis and septic shock more than any single one on its own. Patients who have undergone chemotherapy and have an absolute neutrophil count of less than 500 are at increased risk for bacterial and fungal infections because these cells are necessary for fighting infections. Children have less of the immunoglobulin M needed to fight encapsulated organisms. (24)(25

The reasons for developing septic shock are different in adults than in children. The mechanisms of predisposition to developing severe sepsis are many: lower complement levels, children spending time outside the home or in crowds, lower levels of proteins, faster rates of metabolism, increased prevalence of heart failure, previous antidotal or clinical exposure, and varying incidence of causative organism infections. (26)(27)(28)(29)

Immunocompromised states such as neutropenia or the presence of indwelling venous catheters increase the risk of developing severe sepsis. About 20% of established immunosuppressed cancer patients who develop severe sepsis from an acute modulating illness die. (30)(31)

PATHOPHYSIOLOGY OF SEPTIC SHOCK

Sepsis is a complex syndrome that arises in the body as a result of infection, leading to a dysregulated immune response. The precise mechanism by which infection gives rise to this pathological condition has been characterized. Infection leads to the production of pathogen-associated molecular patterns and danger-associated molecular patterns. (32)

These patterns are the result of microbial metabolism and are classic telltale indicators of infection. The other patterns arise from tissue damage. These patterns trigger the production of pro-inflammatory cytokines that recruit various cells of the immune system to the site of infection. The recruited cells of the immune system have the ability to secrete additional pro-inflammatory cytokines, further expanding the influence of

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inflammation beyond its originating tissue. Under normal circumstances, this immune response would subside after infection is cleared. However, in cases of septic shock, the inflammatory response becomes uncontrolled. (33)(34)

This uncontrolled inflammatory response invariably leads to a state known as endothelial dysfunction. Endothelial tissue is a critical component of the circulatory system, consisting of a lining of specialized cells known as endothelial cells. Modulating these cells is a fundamental mechanism by which the body regulates vascular smooth muscle. These cells can sense the presence of vasodilation and vasoconstriction at the capillary bed and take in glucose and other critical substances from the blood for delivery to other parts of the body. When these cells cease to function properly, the result is widespread vasodilation, hypotension, and loss of blood pressure. Inflammatory cytokines also directly influence vascular permeability; therefore, this lowering of blood pressure can be exacerbated by increased vascular leakage. In addition to vasodilation and increased permeability, metabolic functions of these cells are also disrupted. This leads to reduced oxygen consumption, which could exacerbate organ dysfunction in a state already characterized by reduced standard flow and delivery of oxygen to organs meant by the circulatory system. The result is not only hypotension but a further reduction in tissue perfusion at the level of capillaries. (35)((36)(37)(38)

Pathophysiology of Infection and Immune Response

The infection, or presence of a replicating pathogen in the host, represents the initial trigger of septic shock. Although initial insults to the host that can lead to sepsis and multiple organ dysfunction (such as trauma, burns, ischemia) do not represent classical infection processes, they similarly lead to activation of the immune response resulting in local and systemic inflammation. Depending on the microconidia concentration and the host's immune status, the host can quickly eliminate these opportunistic spores or develop a systemic infection. Finally, although a wide array of pathogens can cause systemic infections and septic shock, this text will mainly focus on worm infections because of their major impact on resource-poor areas of the world. For many infections, the overwhelming innate and adaptive immune response also plays a large role in the pathogenesis of disease and the associated systemic inflammation, since the balance between protective vs. pathological immunity represents a common denominator in many insults.

During the initial stages of infection, host sentinels recognize conserved patterns on the surface of pathogens or released by stressed or dying cells via a set of "pattern recognition receptors" which include selected Toll-like receptors. This ultimately leads to engagement of the p- and i-PRR signaling pathways and activation of transcription factors that translocate into the nucleus and initiate the transcription of pro-inflammatory mediators' genes and activation of the adaptive immune response that ultimately will generate a large pool of long-lived effector and memory anti-parasite responses. These steps lead to the rapid release of pro-inflammatory markers with high inflammatory potential but also of anti-inflammatory and pro-resolution compounds. As a result, more tissue damage occurs, increasing inflammation and further drawing more immune cells to the site. Tissue damage can also be caused by the release of toxins from certain types of bacteria.

Endothelial Dysfunction

Endothelial Dysfunction Endothelial dysfunction, a central mechanism of septic shock, compromises microvascular perfusion and tissue oxygenation in sepsis. The inflammatory response to an infectious challenge leads to an increased production of endothelial nitric oxide synthase (eNOS)-derived nitric oxide, probably activated by the Toll-like receptor 4 (TLR4)-dependent signaling cascades (39, 40 ,41)

The induced excessive NO production suppresses reactive oxygen species (ROS) production and nerve-evoked vasoconstriction, predisposing to reversible distributive shock. Besides the excessive vasodilatation, endothelial dysfunction increases the capillary endothelium glycocalyx alterations and hence results in an increased vascular permeability, predominantly around the postcapillary venules and precapillary arterioles (42, 43, 44).

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The leakage of endothelial integrity and storage capacity appears to be one of the leading pathophysiological mechanisms of the damage of the activation and the consequent vasoplegia. Conceptually, the disturbed microcirculation leads to profound loss of fluid volume from the intravascular compartment, which physiologically results in reduced cardiac preload when systemic vascular resistance is steadily decreased. When the left ventricular (LV) end-diastolic pressure is declining, cardiac output (CO) and global tissue perfusion are deeply affected, both caused by obstruction of tissue oxygen thermo-environment. In the early phase of septic shock, the reduction in CO is compensated by increasing heart rate and sympathetic activity due to the peripheral increased production of endogenous substances. In fact, vasoplegia creates a mismatch between the increased myocardial oxygen demand and the reduced myocardial oxygen consumption, due to impaired myocardial beta-adrenergic functioning (45, 46,47).

The impaired myocardial beta-receptor transduction is caused by the increased expression and plasma levels of G protein-coupled receptor kinase leading to a dramatic decrement in the beta-adrenergic signaling. The heart rate eventually declines due to worsening clinical state and progress towards hypodynamic septic shock. Besides the widely investigated and assumed role for vasoplegia in septic shock, inflammation increases the expression of adhesion molecules on the vascular endothelium to mediate the tunneled procession of the 'rolling' and 'adherent' leukocytes to the infectious site, which is a physiologically intended phenomenon of the immune response to infection and is a prerequisite for subsequent opsonization and phagocytosis of microbial contaminants. The adhesion of the leukocytes to the endothelium further contributes to the inflammatory damage to the endothelium, i.e., circulating leukocytes can abolish via mechanisms of destructive metabolism and contribute to insulin resistance of the endothelium, further contributing to the intricate pathophysiological mechanism of the vicious circle proposed. The aforementioned changes are central to the pathogenesis of septic shock since they outline the initial injury of the vital organ and constitute its progression to multiple organ failure. Restoring an appropriate function of the endothelium could contribute to the successful treatment of patients with septic shock. (48, 49)

Coagulation Abnormalities

Septic shock is typically associated with coagulation abnormalities and an increased incidence of venous thromboembolism. In the initial phase of sepsis, the inflammatory response often results in a state of hypercoagulability characterized by elevated endogenous thrombin and platelet activation, in addition to disseminated intravascular coagulation. During this time, the levels of anticoagulant protease, such as protein S, tissue factor pathway inhibitor, and antithrombin, decrease, which are probably caused by liver failure, a compensatory response to the anticoagulant consumption, or an increased consumption due to their high activation of inflammation. At the cellular level, microcirculatory coagulation and thrombus formation in the capillaries and venules of several organs, however, occur in a relatively late phase or do not happen at all. ((50)

However, disseminated intravascular coagulation is a strong predictor of organ dysfunction and mortality, especially when microangiopathic coagulopathies develop as a result of both hypoperfusion and endothelial dysfunction/inflammation. By the time a diagnosis of septic shock is made, many septic patients have entered the phase of impaired anticoagulation and fibrinolysis with depletion of coagulation factors. During septic shock, the coagulation system seems to play a contradictory, apparently protective role, and a prothrombotic role leading to immunothrombosis. Although the abnormalities of coagulation seen at the bench and bedside are typically classified with a seminologic approach, clinicians seem to understand their dynamic changes and bridge to the bedside. The concept of the three phases of hemostatic response to injury might explain at least partially these observations and simplify the approach to the bedside with a therapeutic purpose. Predisposing factors and pathophysiology of septic shock management and outcome of septic patients thus depend on the fine balance between hemostasis stimulation to avoid bleeding and thrombosis inhibition to avoid organ dysfunction. (51)(52)(53)

The interaction of the pathogen with the host defense system leads to immune activation and an uncontrolled and inadequately regulated systemic inflammatory response. Although the clinical signs occur system-wide,

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the basic biochemical dysfunctions of septic shock are primarily localized in the microcirculation and are accompanied by changes in systemic metabolic functions (3, 7,). The most important mechanisms to explain hemodynamic and systemic metabolic dysfunction in septic shock include endothelial dysfunction, coagulopathy and inflammation, microcirculation disorder, and apoptosis of different cells. These pathophysiological changes are initiated simultaneously by a complex interplay between the invasions of pathogens, their defense directed primarily against hyperinflammatory status, and regulation of the host defense system's immune capacity. The hyperactivated immune system accumulates various immune processes resulting in a systemic inflammatory response directed against pathogen-associated molecular patterns (54,55,56).

IMMUNE RESPONSE IN SEPTIC SHOCK

Septic shock is defined as the complex pathological processes triggered by infection. Hyperactivated immune response is the key pathogenic aspect of septic shock. Innate and adaptive immune systems actively participate in this deleterious response. During the initial phase of infection, in order to protect from immediate peril, an individual's body sets off innate immune defenses. This acute response, characterized by activation of phagocytic cells and release of pro-inflammatory chemokines and cytokines, leads to the elimination of pathogens, removal of damaged tissues, and repair of affected systems. Innate immune response is activated within minutes to hours after inoculation and disappears rapidly after the threat is either eliminated or passed (57,58). Continued or repeated execution of innate immune response in severe infection may occur due to: continuous presence of pathogens; entry of pathogens into sterile body compartments; release of Damage-associated molecular pattern molecules (DAMPs) by stressed neutrophils, macrophages, and endothelial cells; or epithelial barrier coding due to introduction of mechanical ventilator or medical device resulting in sustained release of DAMPs (59,60).

Innate Immune Response

The innate immune response works as the frontline host defense against infection, including septic shock. As an immediate response to pathogens invading the host, it requires no prior exposure to pathogens or their products. Its cellular components include neutrophils as the first leukocytes recruited to an inflammatory site, monocytes, basophils, eosinophils, and NK cells. Macrophages and dendritic cells also participate in a phagocytosis event and can directly be activated by using various TLR ligands and through autocrine secretion of IL-1. In contrast, endothelial cells, fibroblasts, epithelial cells, and adipocytes can sense PAMPs via TLRs, RIG-I, or NOD, and produce pro-inflammatory cytokines (8, 61). Exaggerated innate immune responses result in severe immune-inflammatory tissue damage and multi-organ injury, early and adequate innate host responses may prevent infections from developing into septic shock. Sequestering uncontrolled host responses may fail to clear pathogens in the host, finally causing progressive infections to deteriorate into septic shock (62,63).

Adaptive Immune Response

The adaptive immune response (also called acquired immunity) is specific, has immunological memory, and provides long-term protection against pathogens. Similar to Pattern recognition receptors (PRRs), the adaptive immune system can recognize a vast variety of antigens; cells that finalize this task are B and T lymphocytes. T lymphocytes (T-cells) are responsible for additional stimulation of macrophages and neutrophils and are classified into killer T lymphocytes, helper T lymphocytes, and suppressor T lymphocytes. CTLs destroy virus-infected cells and tumor cells. In response to activation by APCs through the intermediate of MHC-II and TCR, Th cells differentiate into different T-helper cell subsets that have specific functions. Several T-helper cell subsets have been classified, such as Th1, Th2, Th17, TFH, and TFH2 cells. The acquired immune system can also generate memory cells. This means an enhanced immune response can occur if the individual encounters an identical antigen again. B lymphocytes (B-cells) are categorized depending on their origin and location, i.e., where they matured and where they develop their effector function (64,65).

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IMMUNOLOGICAL BIOMARKERS IN SEPTIC SHOCK

Immunological biomarkers are key components for the early assessment of the immune response in septic shock. Thus, this review focuses on analyzing health indicators from the basic and advanced immunological findings, with a focus on molecular biomarkers. The systemic human inflammatory response is the result of a combined interaction between several signaling molecules, like cytokines. Cytokines play a central role in the pathogenesis of sepsis and septic shock, playing a dual role in promoting and repressing inflammation, and in the adaptive immune response. The major endothelial and inflammatory cells of the blood compartment are an important source of these immune mediators. Among the cytokines, the pro-inflammatory and the immune modulatory chemokines are particularly interesting, as they guide the white cells to the site of bacterial infection and the immune cellular crosstalk. Indeed, both chemokines and cytokines have prognostic value because they are used to define a set of plasma from the affected patients (7, 66,

Another important biomarker of septic shock is macrophage migration inhibitory factor, which acts like a pro-inflammatory cytokine, and its receptor CD74 plays an important role in disease severity. Four major stages of biomarkers of septic pathobiology reflect a pro- and anti-inflammatory phase and cellular dysfunction. In conclusion, among the cytokines and chemokines, IL-1β, IL-6, IL-8, IL-18, and CCL2 have significant prognostic value for septic shock; however, the existing data are insufficient to justify a routine application of measurement in the clinical arena. Additionally, novel biomarkers, such as extracellular histone and free DNA, thiols with redox potential, and apoptosis-related fecal markers, are intensively studied as biological markers of septic shock. Also, several immune cell monoclonal antibodies on very early presentation of immune cellular dynamics are described, such as CD11b, CD64, human leukocyte antigen – DR isotype HLA-DR, or co-stimulatory molecules CD40, CD80, and CD86. All could have early diagnostic and prognostic value. Determination of biomarkers could be useful to differentiate between septic arthritis and pseudo-septic arthritis. Immunological biomarkers' response to treatment is still sporadically assessed, but personalized treatment tailored to the immune markers can be developed with high potential to increase patient survival. In addition, the type of the causing pathogen of microbic invasion can modify and reduce systemic inflammation, including predominantly bacterial or viral agents, which could also be important in diagnostic approaches (67, 68, 69).

Cytokines and Chemokines

Cytokines and chemokines are key mediators of the pathological immunological processes involved in septic shock. Pro-inflammatory cytokines such as interleukin (IL)-1, IL-1β, tumor necrosis factor (TNF)-α, IL-6, and chemokines induce the inflammatory process. Several other cytokines such as IL-10 are anti-inflammatory. IL-1 is responsible for initiating fever and chemotaxis. TNF-α is released earlier than IL-1, and it increases vascular permeability. IL-6 has a fatigue goodness factor and stimulates the synthesis of acute-phase proteins in the liver. Chemokines are involved in a wide range of physiological and pathological processes. For example, monocyte chemoattractant protein-1 (MCP-1) plays a role in the inflammatory response in infections, and MCP-1 gene-unrelated polymorphism can make the gene promoter more susceptible to septic shock. IL-10 has a direct suppressive effect on cell-driven immunity, especially on mononuclear cells. Systemic longitudinal changes of these mediators are very informative as biomarkers for patient outcomes. Systemic longitudinal elevations of IL-1β, soluble IL-2 receptor (sIL-2r), and IL-6 are associated in a stepwise manner with the progression from compensatory anti-inflammatory response syndrome (CARS) to mixed antagonist response syndrome (MARS), and finally to septic shock associated with high mortality (70). Elevation of IL-10 has a protective effect at all stages (CARS, MARS, and septic shock) by indicating the direction of the patient’s overall immune response. In puerperae with severe sepsis, IL-8 elevation has a protective effect. IL-10 elevation is associated with protection, although acute-phase related cytokines predict the clinical outcome of sepsis. Moderate IL-10 decreases pro-inflammatory cytokine interferon (IFN)-γ and increases anti-inflammatory cytokine IL-4 rather than immediately reducing pro-inflammatory mediators (71). This is called 'cytokine rebalancing' in the treatment of sepsis. Some

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cytokines were found to elevate, while cytokines such as monocyte chemoattractant protein (MCP-1) in some patients failed to increase, indicating two possible immunological situations. In conclusion, cytokine response alone can give immunological or immunopathogenic information complementing classical methods in the diagnosis of sepsis and septic shock (72).

Cell Surface Markers

Several surface molecules could provide the landscape of the immunological discussion associated with septic shock in various parts of the human organism. CD277 or butyrophilins are known immunological checkpoint inhibitors. Surprisingly, for the first time, it has been reported that the CD277 antibody levels are altered in septic shock conditions (73,74)

Utilizing another panel of thirteen B cell-associated cell surface markers resulted in the profiling of over-activated, exhausted, and dysfunctional immune statuses. This three B cell profile dating enabled distinctive overall patient prognosis to be undertaken. Including the major prognostic link between plasma cells and post-septic illness survival is possible with these analyses (75,76).

Toll-Like Receptors (TLRs)

The innate immunity response to septic shock is initiated by pathogen-sensing receptors, also called pattern recognition receptors (PRRs). Among PRRs, toll-like receptors (TLRs) appear to have a central position. TLRs are type 1 transmembrane proteins and are divided into multiple domains: (1) a large extracellular domain that is essential for pathogen-associated molecular pattern recognition; (2) a short transmembrane domain of approximately 25 amino acids; and (3) a conserved cytoplasmic tail termed the toll/interleukin-1 receptor domain, which is involved in intracellular signaling (77,78). TLR family members sense both bacterial and viral-derived antigenic compounds and are involved in the indoctrination of the immune system. One of their key roles is to orchestrate the initiation of an immune response during infection, and they potentiate the immune response to infection by triggering the release of pro-inflammatory mediators such as nitric oxide and pro-inflammatory cytokines (79,80,81).

In response to bacterial or viral infections, members of the TLR family initiate intracellular signaling pathways that lead to the expression of genes involved in early host defense. Dysregulation of TLR signaling has been postulated as being an important factor in the pathogenesis of sepsis, with hyper-responsiveness likely to worsen outcomes. TLRs have unique and non-redundant functions, with different members recognizing distinct ligands. These ligands include a variety of structurally diverse and unrelated molecules expressed by different classes of pathogens or different evolutionary stages of a pathogen. This ligand diversity reflects the fundamental nature of the co-evolution arms race between host and pathogen, where the immune system evolves to recognize molecules that are common to pathogens but not mammalian cells (72,73,66).

IMMUNOMODULATORY THERAPIES IN SEPTIC SHOCK

The use of non-selective inhibitors of the immune response has not proved to be effective, as septic shock is almost never about immune suppression, novel therapeutic strategies have been tested with the aim of restoring immune homeostasis. The therapies that are currently being considered are corticosteroids and intravenous immunoglobulins. Corticosteroids can shorten the time to hemodynamic stabilization and to vasopressor independence in refractory septic shock, and can improve the outcome in adrenal insufficiency (75). They act by reducing the inflammatory response through the modulation of cytokine production and of genes that trigger inflammation, and may also improve the vascular signal component and immune cell functions. The effect of intravenous immunoglobulins is to support the immune response. In patients with septic shock and documented hypogammaglobulinemia, they shorten the time to bacterial clearance and can lower mortality when administered in monotherapy. Other immunomodulatory approaches are under

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development. Similarly to corticosteroids, the potential benefits of intravenous immunoglobulins could depend on the characteristics of the patients and of the infectious agents (68).

Corticosteroids

Corticosteroids have always been of great interest to many doctors involved in the treatment of septic shock and organ failure. Corticosteroids can influence and dampen the inflammatory and immune response, which is unleashed and can become harmful in septic shock. Numerous clinical trials have been conducted to assess the effectiveness of corticosteroids in septic patients, in which, unfortunately, it was not possible to establish their true value (41). To date, although their anti-inflammatory, immune-modulating, and vasoactive properties are very well known, not all their mechanisms of action at fine levels are fully understood. From an immunological point of view, these hormones may have multiple effects: regulation of the production of pro-inflammatory and chemotactic mediators at the level of monocytes/macrophages, inhibition of T-cell activation, influence on the release of cytokines by T helper lymphocytes, and the ability to block the first steps of migration of various categories of inflammatory cells(42,43)

Intravenous Immunoglobulins

Intravenous immunoglobulins (IVIGs) are being discussed as a promising therapeutic option in patients with septic shock. The effect of intravenous immunoglobulins in sepsis and septic shock is diverse: the immunological effects of IVIGs are due to an increase in opsonization, a decrease of toxins and other inflammatory mediators, as well as an alteration of the inflammatory responses (by reducing activation and adhesion of certain cell types). Different analyses have shown a decrease in infection rates and a possible reduction of mortality in clinical patients. However, this advantage did not work in other investigations. (77,37)

EMERGING RESEARCH AND FUTURE DIRECTIONS

Over the past few years, a randomized double-blind controlled trial showed the first promising findings on inhibiting TNF with a monoclonal anti-TNF antibody. Another approach focuses on personalized treatment; not all patients benefit from anti-inflammatory strategies, making a precision microbiome profile and therapeutic concept useful only if used individually. From several ongoing or recently published studies, it is clear that only some patients with septic shock develop immune suppression and only some of them have a worse outcome (78). In the context of precision medicine, this implies the need to characterize the presence of infectious, inflammatory, and septic immune resistance and immune paralysis in individual patients. Future investigations on septic shock or sepsis should focus only on immunosuppressed patients, as immunomodulatory and immunostimulatory agents should only target patients with immune suppression (79).

By 2030, we can look forward to the release of health care professionals from the burden of the constant identification of the latest Systemic inflammatory response syndrome (SIRS) consensus to improve diagnosis, to the agreement of a task force skillfully set up to guide us towards the selection of the antibiological anti-Drosophila immune deficiency (anti-IMD) therapy (80). Our final goal would be to set up two research projects based on the state of the art published documents: start creating a database with microbiomic changes over time in parallel with the IMD status of the patients in the shock section only, which would give us new key factors; in the immune suppression and refractory immuno paralysis later on, interfering with the microbiome (49).

CONCLUSION AND CLINICAL IMPLICATIONS

The key message of this immunological approach is that the inflammation that plays a major role in the evolution of septic shock is an early event in its pathophysiology. The crucial role played by inflammation in the risk of the subsequent occurrence of septic shock means that the development of new powerful

immunosuppressive agents opens up potential new clinical treatment strategies. The personalized medicine that is emerging and taking into account important immune markers could lead to more targeted treatments in the future. Knowing the imminent integration of these experimental approaches into the practice of care, it appeared essential not only to take stock of the current knowledge, but to define an ambitious roadmap resulting from a consensus between health professionals and methodological experts on research aspects, to reply to still unresolved issues that need to be addressed. To do this, an ad hoc transversal working group has enabled the effective collaboration of many professionals from various specialties that intervene in the care of an anaphylactic emergency. These include allergists, anesthesiologists, pediatricians, those in the emergency room, ITU, medicines, hospitalized medicine, and intensive medicine or emergency medicine. Close collaboration between paramedics and nurses has also been initiated (81).

The current lack of health appropriate human and financial resources seems to prevent the organization of these protocols in all health structures. The need to train medical and paramedical professionals in the prevention, diagnosis, and management of anaphylactic shock is therefore essential if these protocols are to be put in place. In the future as well as the involvement of patient associations and health professionals, as well as an inclusive communication on the regional territory seem to be essential to raise public awareness of the symptoms of the disease, its seriousness and the urgency to act and consult (82). All these requirements were presented by the regional prefectural team unanimously in the thematic committee. They pointed out the lack of a circular of guidelines for the organization of care.

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