Scientific Research Publishing

Open Journal of Emergency Medicine, 2023, 11, 126-154
https://www.scirp.org/journal/ojem
ISSN Online: 2332-1814
ISSN Print: 2332-1806

The Slippery Slope of Sepsis

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How to cite this paper: Gernon, L.W. (2023) The Slippery Slope of Sepsis. *Open Journal of Emergency Medicine*, **11**, 126-154.
https://doi.org/10.4236/ojem.2023.113014

Received: July 20, 2023
Accepted: September 24, 2023
Published: September 27, 2023

Abstract

Mortality, morbidity, early recognition, and treatment of sepsis remain a diagnostic dilemma for clinicians, in addition, the timely diagnosis of sepsis represents an ongoing clinical challenge. This review looks at the challenges of early recognition, the scope of the problem, the immunologic basis of the sepsis cascade, new frontiers related to interventions, and the role of antibiotics in an era of antimicrobial resistance. In **Figure 1**, once a patient is on the slippery slope of sepsis, the ability to reverse the momentum is challenging; hoping antibiotics, fluid resuscitation, vasopressors may buy time for the immunologic cascade to equilibrate to its homeostatic balance. While the development of septic shock is much more complex than pathogen proliferation, our understanding of the pathogenesis and ability to therapeutically intervene is in its infancy. Patients with sepsis frequently present for urgent medical care with undifferentiated infection and nonspecific symptoms. As 80% of patients with sepsis are initially treated in an Emergency Department, the burden of early recognition and intervention falls squarely on the shoulders of Emergency Department Clinicians. [1] This is an entity that occurs in all age groups, without regard to race, geography, or health status. Survival and mortality related to this clinical entity are poorly understood. Our understanding of sepsis needs to expand beyond the downstream effects and collateral damage of multiorgan dysfunction and failure. Immunologically, the antigenic triggers, be it invasive infection, severe injury, and systemic inflammation without concomitant infection, elicit similar pattern recognition receptors and innate host responses. If you are lucky enough to have survived an acute episode of sepsis, patients with sepsis often develop new adverse sequelae after treatment, a concept called persistent critical illness or post sepsis syndrome, characterized by long-term disability, and worsening chronic health conditions requiring re-hospitalization. [2]

Keywords

Sepsis, Antibiotics, Antimicrobial Resistance, Immunology, Blood Cultures,

PCR Diagnostics, Septic Shock, Antimicrobial Stewardship, Blood Stream Infections, Persistent Critical Illness, Post Sepsis Syndrome, SIRS, Blood Stream Infections, Sepsis Biomarkers, Endothelial Dysfunction, Persistent Critical Illness

1. Overview

The worldwide increase in the incidence of sepsis/septic shock emerges as one of the leading causes of death, especially in critically ill patients. The clinical challenge is the early diagnosis of sepsis, reliable laboratory markers, interventions, and treatments for upstream factors rather than the hope and pray remedy of supportive care while the immune system cycles between a hyperinflammatory and immune paralysis response. Forty percent of septic patients are culture negative [3], which implies we need to do a better job in being able to isolate pathogens, as broad-spectrum antibiotics continue to be a front-line intervention, or that sepsis is more than pathogen proliferation and a hyperinflammatory response.

In the United States, 9% of hospitalized patients are admitted with sepsis, a trend that has been increasing annually. [4] Although the mortality of sepsis has decreased in recent years, it is the main cause of mortality worldwide. [5] In the USA, sepsis is the most common cause of hospital deaths and costs more than US $24 billion annually. [6] [7] The annual burden of sepsis is now estimated to be 48.9 million sepsis cases with 11 million deaths worldwide, representing 19.7% of all global deaths. [8] A true global incidence of sepsis is difficult to appreciate and is under reported, relying on hospital databases from middle and high-income countries. In developing countries, many patients who die of sepsis do not have access to hospitals and end up dying at home.

Sepsis-induced "immunosuppression" or "immunoparalysis" is now thought to be one of the main drivers of mortality and morbidity in patients, which has led to the interest in immunostimulatory compounds as a potential new therapy.

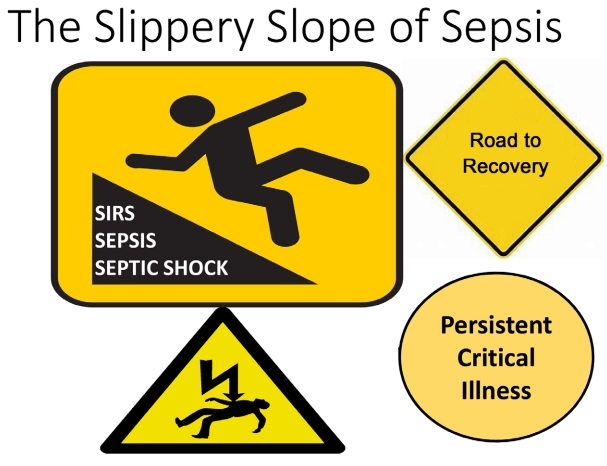

Figure 1. The slippery slope of sepsis.

Despite over 100 therapeutic clinical trials in sepsis, no FDA-approved treatment options currently exist that improve sepsis survival. [9]

The rapid emergence of resistant bacteria is occurring worldwide, endangering the efficacy of antibiotics, which have transformed medicine and saved millions of lives. Many decades after the first patients were treated with antibiotics, bacterial infections have again become a threat. The antibiotic resistance crisis is attributed to the overuse and misuse of these medications, as well as a lack of new drug development by the pharmaceutical industry due to reduced economic incentives and challenging regulatory requirements. [10]

2. What Is Sepsis and Septic Shock?

A recent definition of sepsis indicates a life-threatening organ dysfunction condition caused by a dysregulated host response to infection and injury, [11] limiting the capacity to restore homeostasis [12] and resulting in a stage of immune dysfunction or anergy. [13] [14] Sepsis incidence peaks in early childhood, due to the immaturity of the immune system, with a second peak in incidence among older adults, the phenomena of immunosenescence combined with co-morbidities of diabetes, renal disease, cirrhosis, heart disease, cancer, and the use of immunosuppressive medications as noted in **Figure 2**. There is no typical patient with sepsis, as there are no approved drugs that specifically target sepsis. Sepsis is very much like heart failure and is due to multifactorial causes which are poorly understood but do relate to immune over reaction and dysfunction. Sepsis is a systemic condition that affects all organs and tissues, with the endothelium being one of the first cell types to encounter and respond to the insult. The pathophysiology of sepsis can be described as a pro- and anti-inflammatory disequilibrium syndrome.

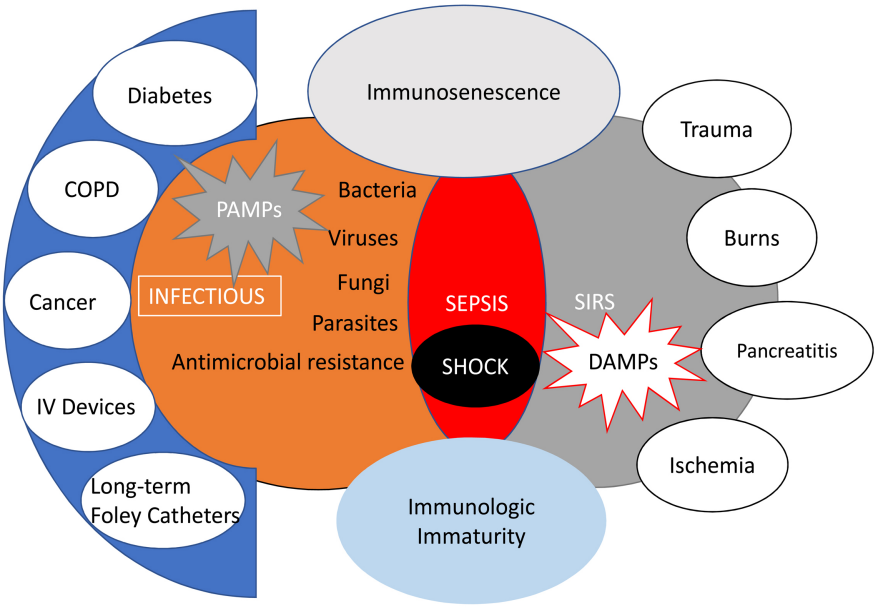

Figure 2. Multifactorial paradigm contributing to sepsis and septic shock.

Multiple definitions for septic shock are currently in use, however, patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%. [15]

Globally, among all age groups, the most common underlying cause of sepsis is diarrheal disease with road traffic injuries in a close second place. Recent global data on sepsis mortality shows lower respiratory infections as the most common precipitating factor, yet 47% of global deaths due to sepsis were from non-infectious causes. [8] Sepsis accounts for 19.4 and 31.5 million episodes annually, worldwide, with 5.3 million deaths. [16] Despite a 20% decrease in the incidence since 1990, the medical cost for treatment and support of these patients has skyrocketed. [17] The global incidence of sepsis is underestimated as prior reviews have mined data from death certificates which are notoriously flawed when it comes to cause of death, or data obtained from electronic health records from higher-income countries using ICD codes related to hospitalized patients.

3. Early Detection

Early diagnosis of sepsis is challenging because of the nonspecific signs and symptoms. There is an unmet need for diagnostic tools differentiating between bacterial and non-bacterial causes of sepsis. Prediction tools and risk stratification algorithms play a vital role in the evaluation and management of acutely ill and injured patients, however, any tool without a clinician maintaining a high index suspicion and constant re-evaluation of a patient is bound to fail.

4. Clinical Screening Paradigms for Detection of Early Sepsis/Shock

Predicting the outcomes of patients with infection continues to be a topic of interest. To date, there is no single biomarker or "sepsis algorithm" that can be used to predict sepsis satisfactorily. Efforts to combine predictors, such as the quick sequential organ failure assessment (qSOFA) score and the chills, hypothermia, anemia, red cell distribution width and malignancy (CHARM) score, systemic inflammatory response (SIRS) score, national early warning (NEWS) score, national institute for health and care excellence (NICE) sepsis guidelines, rapid emergency triage and treatment system (RETTS) are evidence that researchers hope to develop a feasible and accurate prediction model for clinical utility.

In a meta-analysis comparing the prognostic accuracy of qSOFA, SIRS, and NEWS to predict mortality in patients with suspected sepsis, qSOFA could identify more patients with a higher risk of death but has a low sensitivity. [18] In one large study, the sensitivity of positive qSOFA was 63% with a positive predictive value of 17% meaning 83% of patients would get unnecessary antibiotics.

[19] Many Clinicians may argue that any scoring system needs to have a higher sensitivity rather than specificity because the cost of delaying or missing treatment (increased lethality) caused by false negatives is greater than the exposure and cost of unnecessary antibiotics from false positives. SIRS criteria on the other hand are overly sensitive, with low specificity leading to unnecessary testing and antibiotic exposure. [20] Unfortunately, the accuracy of clinically implemented diagnostic criteria including qSOFA, SIRS, and Logistic Organ Dysfunction Score, is ambiguous. [21]

Sepsis is not a disease, but a clinical condition characterized by several confounding clinical and laboratory parameters. As clinicians, we lack an adequate screening test with high enough sensitivity to ensure rapid identification and intervention as we do for acute coronary syndrome and acute stroke. Many times, early recognition is left to the gestalt, gut feeling of the treating clinician.

5. Vital Signs

Heart Rate (HR) and Systolic Blood Pressure (SBP), among other vital signs, have been used to assess the hemodynamic status on arrival at the Emergency Department (ED). However, these parameters can be normal, even in critically ill patients. The Modified Shock Index (MSI) which is HR/Mean Arterial Pressure (MAP) may be useful to determine the clinical severity of illness. Several large retrospective studies have shown that any shock index (SI) calculation (MSI, age SI, Pediatric adjusted Shock Index) is superior to the SBP in identifying critically ill patients. [22] Trending SI over time may identify patients at risk of septic shock and can predict vasopressor use or mortality. [23] In the pediatric population, the Pediatric adjusted shock index (SIPA) has also been used as a noninvasive marker of mortality risk in pediatric sepsis. [24]

6. Clinical Gestalt

Clinical gestalt is the theory that healthcare practitioners actively organize clinical perceptions into coherent construct wholes. It is more than a "gut feeling". This is pattern recognition and is characterized as a heuristic approach to decision-making. At present, the literature suggests that experience does positively influence decision-making accuracy as experienced clinicians have better pattern recognition skills. [25] Gestalt and tools for decision-making have marginal utility and can be prone to error. Up to 35% of these errors caused by overconfidence can cause harm to patients. [26]

In a Pediatric study of community-acquired pneumonia, Clinicians did not perform well at predicting outcomes in those with low-moderate predicted risk of sepsis. [24] Generally, Clinicians tend to underestimate the severity of disease. [27] [28] There is thus, a need to develop evidence-based clinical decision rules to supplement clinical judgment, particularly for cases in which risk may be unclear or as newer clinicians are developing their clinical acumen.

7. Laboratory (Biomarkers)

Are there reliable biomarkers for screening patients at high risk for sepsis?

7.1. Complete Blood Count

The complete blood count (CBC) is an easy test to perform, cost-effective and can be performed expeditiously. The parameters of this test can provide a crude analysis of the innate immune system. It comprises the total white cell count (WBC) and a differential of several types of white cells (Neutrophils, Basophils, Eosinophils and Lymphocytes) indicating the medullary response to the antigenic stimuli from inflammation or infection. It has poor specificity as alterations are seen in non-infectious disorders such as connective tissue diseases and malignancies. [29] The total value of the WBC is a poorly performing diagnostic test of infection.

Lymphocytes are a key component of the adaptive immune system. In septic patients, there is an early depletion of lymphocytes due to apoptosis (premature natural cell death), which leads to lymphopenia. Several studies have suggested that persistent lymphopenia in the early phase of sepsis is associated with poor outcomes and an increased risk of 28-day mortality. [30]

Neutrophils are the first sentinel responders in the nonspecific immune response to an antigen and execute microbial killing by phagocytosis and oxidative bursts. Severe bacterial infections induce the release of both mature and immature forms of neutrophils from the bone marrow through emergency granulocyte maturation. During sepsis, these cells undergo reduced migration, altered antimicrobial activity and delayed apoptosis leading to the worsening of sepsis by immune dysfunction and persistent inflammation. With ongoing infection and clinical deterioration, the release of these immature neutrophils forms neutrophil extracellular traps (NETs) that are triggered by cytokines, chemokines, platelet agonists and antibodies. [31] The overproduction and decreased degradation of NETs are associated with hypercoagulation and endothelial damage. [32] As a diagnostic and prognostic indicator for sepsis, neutrophilia may be seen in response to stress, smoking, inflammatory bowel disorders, hepatitis, Down syndrome, Obesity and Pregnancy. [33]

Eosinophils have been recognized in modulating local and systemic immune and inflammatory responses, particularly those involving helminth infections, allergic conditions, and systemic immune and inflammatory responses such as sepsis. The reduction in eosinophils (eosinopenia) during sepsis is a well-described phenomenon. [34] Conventional sepsis biomarkers such as C reactive protein (CRP) and procalcitonin (PCT) remain superior to eosinopenia. [35]

Platelets are well known for their function to orchestrate an intravascular immune defense response helping to sequester pathogens by releasing, microbiocidal molecules and chemokines, signal immune cells, and promoting neutrophils and monocytes to differentiate into Macrophage antigen-presenting cells. Persistent sepsis associated with severe thrombocytopenia is a harbinger associated

with increased mortality. [36]

7.2. Procalcitonin (PCT)

The diagnostic use of procalcitonin for bacterial infections remains a matter of debate. PCT is a chemokine for blood monocytes. Low PCT levels can be used to rule out the presence of bacteremia, which may be useful in determining the need for antibiotics [37], akin to a negative D-dimer in conjunction with a low Wells score, excluding an acute proximal deep venous thrombosis. [38]

A recent study of septic patients suggests a procalcitonin level cut-off value of 10.3 ng/ml could identify infection caused by gram-negative bacteria v. gram-positive bacteria with a specificity of 80.2% and may help with appropriate antimicrobial therapy when blood culture results are not available, unequivocal, or the infection site is unclear. [39] Procalcitonin is most useful for antibiotic de-escalation and not for the diagnosis of sepsis. [40]

7.3. Lactate

Serum lactate has evolved into a marker of illness severity and prognosis in patients with sepsis, yet there is a discordance of critically ill patients with sepsis with normal lactate levels. [41] Due to its availability and strong association with disease severity and patient outcome, lactate has an outstanding role as a diagnostic marker and as a marker of disease progression. The following conditions and scenarios can increase serum lactate levels; strenuous physical activity, tissue hypoxia, cellular stress, infection, critical illnesses, physiologic conditions causing increased glycolysis, increased production, decreased clearance, and medications (ß2-adrenergic agonists such as albuterol or epinephrine) through induction of glycolysis or inhibition of lactate metabolism (metformin). [42] Hyperlactatemia is conventionally equated with "hypoperfusion" in many clinical settings, a potentially harmful oversimplification. [43] The mechanism of hyperlactemia in sepsis is multifactorial and due to factors beyond hypoxic tissue injury alone. In all forms of acute circulatory failure, a decrease in lactate levels is associated with a more favorable outcome. From this we can form our first conclusion: If lactate levels DO NOT decrease following the initiation of treatment, something is wrong. [44] The initial treatment of hyperlactatemia in patients with sepsis should be directed at improving tissue oxygen delivery. This is most effectively accomplished by improving global blood flow, which aims to improve microcirculatory perfusion. When started immediately it will improve survival by 20%. [45] The goal of resuscitation is to restore microcirculatory perfusion, not macro hemodynamics. A lactate level greater than 18 mg per dL (2 mmol per L) is a diagnostic criterion for septic shock in Sepsis-3. [46] Elevated lactate levels should not be dismissed in a patient with sepsis, even with normal blood pressure. Lactate measurements should be obtained every four to six hours until levels have normalized. Lactate-guided fluid resuscitation reduces overall mortality compared with no lactate monitoring. [47]

7.4. Blood Cultures

Blood stream infections (BSI) and sepsis are mistakenly confused and interchangeably used. BSI is a component of sepsis. Major bloodstream isolates include S. aureus, *E. coli*, Klebsiella spp., *Pseudomonas aeruginosa*, Enterococci, Streptococci, and coagulase-negative staphylococci. [48] Only 30% of patients who meet the sepsis criteria have positive blood cultures. [49] The presence of bacteremia or fungaemia may be separated into a continuous or intermittent form, with the intermittent form being more prevalent. Bacteremia can be classified in addition to infections that originate within the vascular system (*i.e.*, endovascular grafts, endocarditis, intravascular devices) or infections that access the blood stream through the lymphatics (*i.e.*, pneumonia, soft tissue abscesses). Blood and other body fluid cultures remain the gold standard for confirming bacterial and mycotic infections. The dilemma of blood cultures is ensuring proper sterile technique to minimize contamination, adequate volume is sampled, a minimum of two sets, and length of time for growth to be noted (two to five days). When standards are not adhered to, patients are subject to further testing, prolonged hospitalization exposure to unnecessary antibiotics leading to antimicrobial resistance and further delays in adequate treatment for septic patients. A recent review of blood culture utility of patients seen in the Emergency Department suggests that blood cultures are not recommended for patients with cellulitis, simple pyelonephritis, and community-acquired pneumonia, because the chance of a false-positive culture is greater than the prevalence of true-positive cultures. Blood cultures are recommended for patients with sepsis, meningitis, complicated pyelonephritis, endocarditis, and health care-associated pneumonia. [50] Because sepsis is clinically difficult to diagnosis, we rely on scored clinical parameters paradigms for early recognition. Unfortunately, all these parameters have low sensitivity. Many times, blood cultures are not drawn or inappropriately drawn. The yield of positive blood cultures based on an immune naive or immature population (pediatrics) with fever is only 3.4%, with a known source such as pneumonia at 3.6%, and urinary tract infections at 10%. [51] In the Prehospital Antibiotics Against Sepsis trial (PHANTASi) routine blood cultures in pneumonia had low yield and utility irrespective of severity and risk, over 56% of those patients who met clinical sepsis criteria had culture-negative sepsis [52], which begs the question of whom and when should blood cultures be drawn?

To help address this concern a rule created by Shapiro *et al.* with a high sensitivity of 97% for detecting true bacteremia has been utilized, **Figure 3**. [53] No clinical criteria are infallible, clinical judgment, a high index of suspicion in conjunction with a scoring system can be helpful in early diagnosis and management of a difficult to recognize clinical entity.

7.5. Polymerase Chain Reaction (PCR) Technologies for Rapid Blood Culture Identification (BCID)

Although real-time quantitative (qPCR), microarray technology, nanoparticle-based

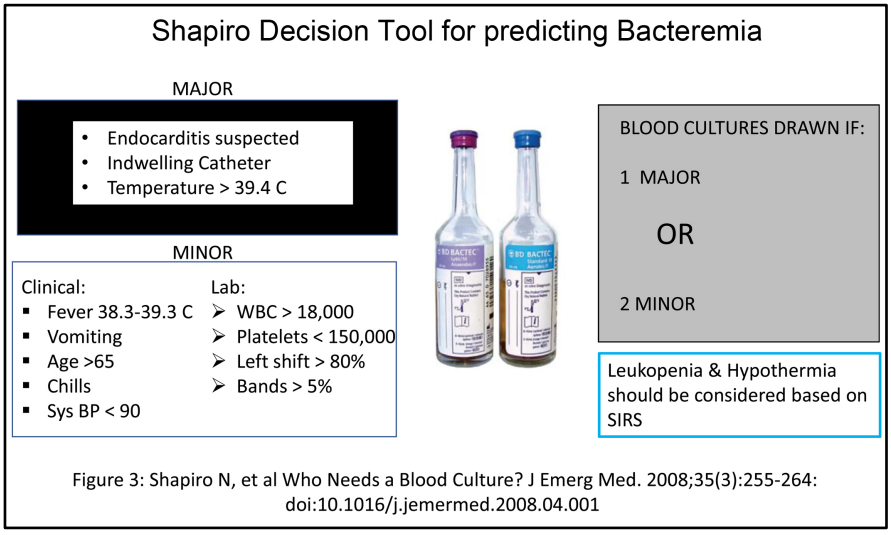

Figure 3. Shapiro decision tool for predicting bacteremia. Source: Shapiro N, *et al.* (2008) Who Needs a Blood Culture? J Emerg Med, 35(3): 255-264. https://doi.org/10.1016/j.jemermed.2008.04.001

assays, and sequencing can shorten the turnaround time to hours, they are often not sensitive enough to detect bacteria at low concentrations. Recently, metagenomic next-generation sequencing (mNGS) and droplet digital PCR (ddPCR) has shown exciting potential in pathogen detection for patients with suspected BSIs.

7.6. Combined Biomarkers (Procalcitonin, C Reactive Protein, Neutrophil and Lymphcyte Count, Lactate)

Over 180 biomarkers have been unsuccessfully evaluated for use in sepsis over the past 5 decades. In the past, procalciton in and C-reactive protein have been most widely used but are limited in their ability to distinguish sepsis from other inflammatory conditions or to predict the outcome. [54]

Based on a recent Swedish study, combinations of biomarkers appear to be a useful approach to improve the diagnostic accuracy for bacterial sepsis, with the caveat that, not having a common standard indicating a high probability of sepsis with several measurements of multibiomakers into one variable for clinical use and the issue of availability and expense in resource-limited areas. [55]

Given the complexity of sepsis, the search for the "holy grail" biomarker(s) for detection of early sepsis continues to elude us. The best panel of biomarkers for the diagnosis of sepsis, or for estimation of the risk of developing severe sepsis, will include both pro-inflammatory and anti-inflammatory markers. Given the heterogeneity and complexity of sepsis, no biomarker has sufficient accuracy to differentiate sepsis from other non-infectious causes of systemic inflammation, and biomarkers can only be used as adjuncts to clinical judgment, in defining when to start antibiotics. The light piercing through the canvas of sepsis for early diagnosis may rest with rapid, affordable mRNA PCR technology.

8. Immunology

William Osler observed, "The ill patient appears to die from the body's response to an infection rather than from the infection itself". [56] An astute observation, though unbeknownst, was describing the immune response. Historically the observation and understanding of sepsis in initial stages being difficult to recognize when most amenable to treatment and later with more obvious signs becomes more difficult to treat is a similar dilemma faced by the modern-day clinician. Despite the advances in medicine and years of research, the intricate molecular and cellular mechanisms involved in the response to sepsis remain poorly understood. [57]

The guardians of our defense system consist of the innate and adaptive immune responses to any perceived antigen (bacterial. fungal, parasitic, viral, toxin). The innate system is rapidly activated with white cell components, antigen-presenting cells/dendritic cells (macrophages), complement and coagulation pathways to destroy and restrict a local infection from progressing into a systemic infection. The two cells traversing both the innate and adaptive immune system are natural killer (NK) and T helper cells. NK cells have cytotoxic effects and secrete proinflammatory cytokines which enhance the pro-inflammatory and anti-microbial functions of other white cell lines as depicted in **Figure 4**. [58] NK cells are speculated to be the promoter of systemic infection. Therefore, the adverse effects of NK cells are mediated by their ability to amplify the proinflammatory response or directly cause organ injury by cytotoxicity, suggesting

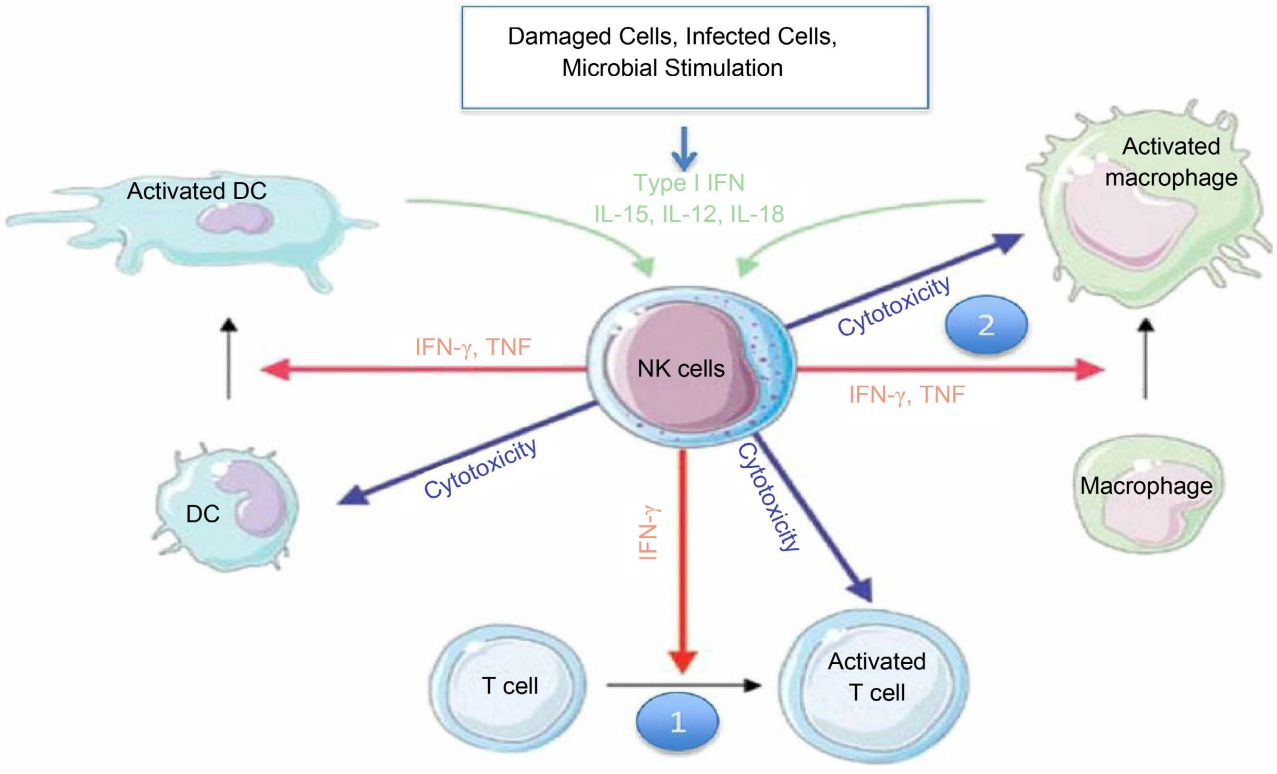

Figure 4. Immune response to Infection/Inflammation.

excessive activation of these cells results in a poor prognosis for a septic patient. [59]

Chase, Christopher & Thakur, Neelu & Darweesh, Mahmoud & Morarie-Kane, Susan & Rajput, Mrigendra. (2015). Immune response to bovine viral diarrhea virus—Looking at newly defined targets. Animal health research reviews/Conference of Research Workers in Animal Diseases. 16. 4-14. 10.1017/S1466252315000110.

8.1. The Complement System in Sepsis

C3a, C4a, and C5a are elevated in the initial stages of sepsis. C5a by binding to the C5a receptor activates neutrophils to migrate into inflamed tissue and remove pathogens and debris. [60] Excessive activation of C5a in sepsis causes aggravation of systemic inflammation, progressive apoptosis of lymphocytes, and even dysfunction of neutrophils. [61] One of the upstream interventions currently in clinical trials (sepsis and Covid), is the use of monoclonal antibodies that target C5a and the C5a receptor site. [62]

8.2. Role of Cytokines

Cytokines are the extensive communication network directing and signaling cells into a proinflammatory or anti-inflammatory state as seen in **Figure 5**. In time the balance of these cytokines maintains the normal homestatic state. The inability to turn on or turn off the signaling to the infectious/inflammatory process results in profound immunosuppression or a persistent inflammatory response.

The cytokine cascade is an enduring inflammatory state driven by dysfunctional innate and suppressed adaptative immunity that culminates in persistent injury and death. [63]

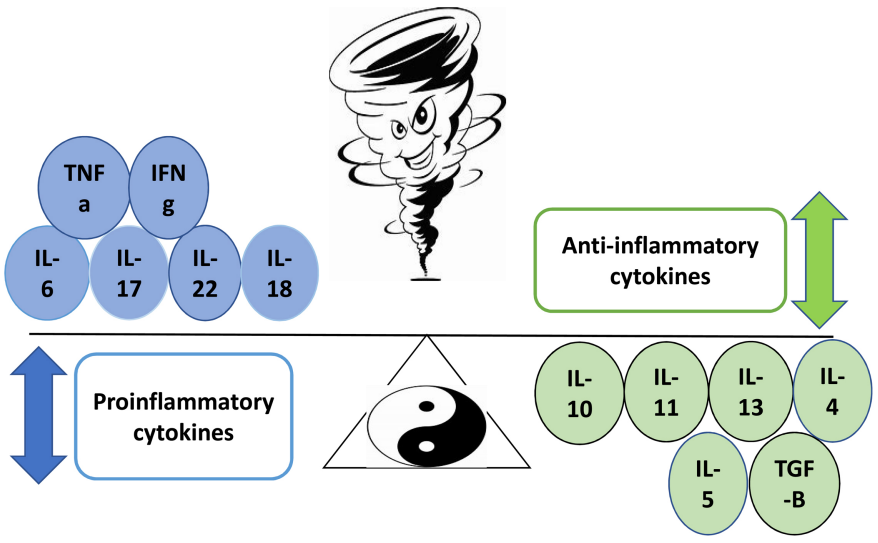

Figure 5. Homeostatic balance between proinflammatory and Anti-inflammatory cytokines.

Pro-inflammatory cytokines contribute to the procoagulant state, and increased production of free oxygen radicals (ROS) and nitric oxide (NO). Excessive production of NO is one of the causes of vasodilation and impaired response to vasoconstrictive factors (vascular hypo-reactivity), a component of the pathophysiology of septic shock. [64] The procoagulant state leads to thrombosis in the microcirculation, which in turn can cause organ hypoxia (thus the utility of serial lactate measurements in sepsis), disruption and function of the endothelium glycocalyx lining causing fluid shifts from the intravascular to extravascular space and the release of endothelium adhesion molecules attracting neutrophils which lead to tissue damage. [65]

As sepsis progresses as seen in **Figure 6**, the inflammatory reaction gradually changes from overactivation to immunosuppression, the activation of anti-inflammatory mediators (IL-4, IL-10, IL-13) to restore regulated immune homeostasis, with the main manifestations being decreased immune cell counts, immune paralysis and the dysregulation of the orderly spontaneous death of cells after stimulation otherwise known as autophagy, which is a process that recycles damaged proteins or organelles. The occurrence and development of abnormal autophagy, being overwhelmed or the release of danger-associated molecule patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) in response to perturbed homeostasis induce the assembly of inflammasomes, leading to multi-organ dysfunction syndrome (MODS) in sepsis patients. [66] [67] One strategy of trying to filter out cytokines from the blood stream may be promising, but difficult to randomize and the few studies published have a small population set making it difficult to recommend as a current modality for sepsis treatment. [68] [69]

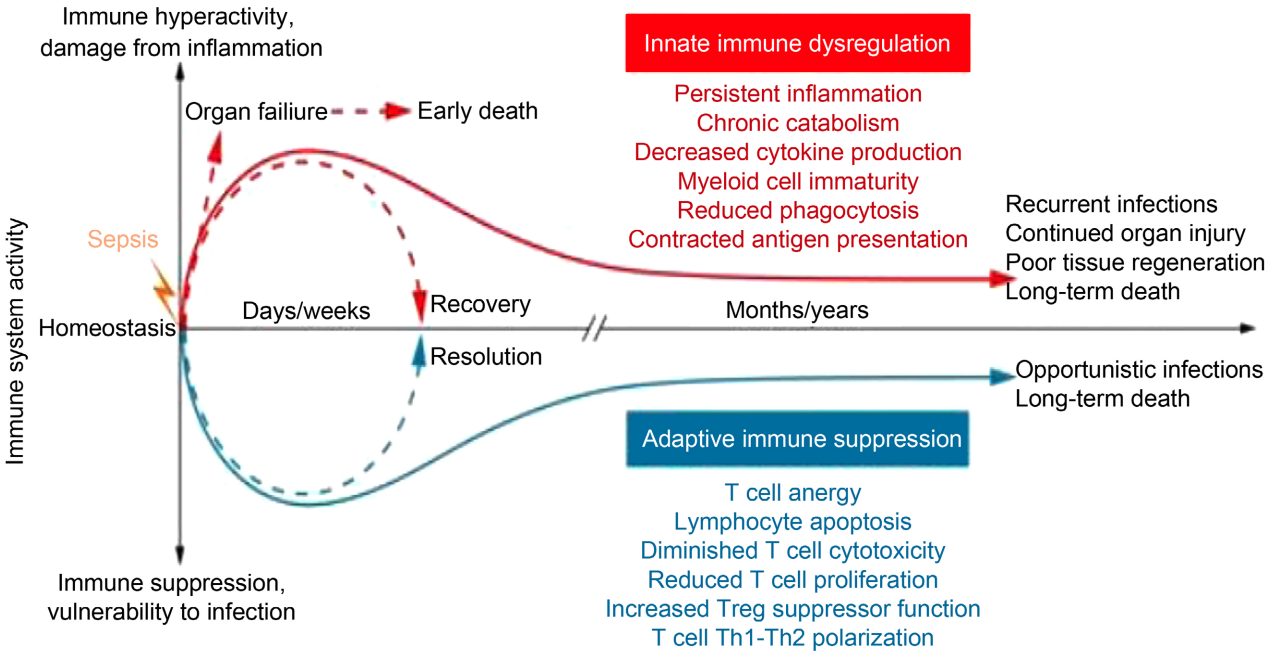

Figure 6. Immune dysregulation in sepsis J Clin Invest. 2016; 126(1): 23-31. https://doi.org/10.1172/JCI82224.

8.3. What Is the Immunologic Role of the Endothelium in Sepsis and Inflammatory States?

The key to understanding the immunology of sepsis may be the "bridge" between local and systemic immune processes, the endothelium. The endothelial response to any systemic acute or chronic inflammatory response, as seen in sepsis, chronic kidney disease, coronary artery disease and thrombotic stroke can be summarized as a change from an anticoagulant mode to procoagulant state, a loss of the protective glycocalyx barrier, and increased vascular permeability. These are active contributors to sepsis and as such represent a major target for therapy. [70] Vascular endothelial cells are among the first cells in the body to encounter circulating bacterial molecules. Endothelial cells possess mechanisms that recognize structural patterns of bacterial pathogens and subsequently initiate the expression of inflammatory mediators. [71] Vascular endothelial cells are lined by a protective glycocalyx barrier inhibiting coagulation and leukocyte adhesion. Shedding and disruption of the glycocalyx can be triggered by the release of TNF-alpha. The shedding of this protective barrier leads to vascular permeability augmenting inflammation and activating the clotting cascade. [72] While it is accepted that disruption of the glycocalyx adds to the organism-wide insult in sepsis, it remains unclear if maintaining or restoring the glycocalyx by itself would have a mortality benefit. [73]

Endothelial dysfunction as seen in sepsis is associated with impairment of the three main anticoagulation mechanisms, antithrombin, the protein C system and tissue factor-mediated thrombin generation.

During sepsis, endothelial cells amplify the immune response and activate the coagulation system. In response to cytokines produced by immune cells, the endothelium expresses adhesion molecules and produces vasoactive compounds, inflammatory cytokines, and chemo-attractants, thus switching from an anticoagulant to a procoagulant state. These responses contribute to local control of infection, but systemic activation can lead to microvascular thrombosis, capillary permeability, hypotension, tissue hypoxia, and tissue damage. [74]

In abdominal trauma, the direct mechanism of traumatic injury, increased intra-abdominal pressure and compartment syndrome alter organ perfusion leading to organ failure. [75] The disruption of the endothelial layer in the gastrointestinal tract (GIT) resulting in an alteration of the immunologic homeostasis and the migration of microorganisms from the GIT to other systems is believed to be the underlying pathophysiology for the sepsis syndrome. [76] This endothelial intestinal barrier function in trauma might result in the translocation of gut bacteria and endotoxins to the systemic circulation, initiating the aggravated inflammatory response. [77]

8.4. Lymphatic System

The role of lymph nodes as antigen processing centers is well known. For many years we have assumed the lymphatic system is a passive drainage system, with-

out a clear understanding of its role in the immunology of sepsis. Lymphatic vessels are tubular structures composed of a single layer of oak-leaf-shaped lymphatic endothelial cells. The afferent lymphatic vessels absorb interstitial fluid from the blood to be processed and filtered at a lymph node before being transported by the efferent lymphatics into the blood circulation. [78] Endothelial cells within this system regulate specific biological processes, such as tumors and inflammation. The fundamental cause of sepsis is the inability to resolve inflammation which is closely related to the function of the lymphatic system. [79] Could the inflammatory storm during sepsis be caused by disorders in lymphatic flow? The role of lymphatic vessels in the onset of sepsis remains unclear, but could they be a conduit for multiorgan dysfunction syndrome? It is known that the most severely damaged organs in sepsis patients are usually the lungs, kidneys, and the heart. [80]

8.5. Cerebral Dysfunction

Sepsis can cause acute cerebral dysfunction, characterized by delirium, coma, and cognitive dysfunction, known as septic encephalopathy. Septic encephalopathy develops in 53% of patients with sepsis. [81] In addition, septic encephalopathy is associated with increased mortality and a 2.22-fold increased risk of developing dementia in the long term. [82] The underlying mechanisms of cerebral dysfunction in sepsis, suggest that endothelial cell degeneration, enhanced blood-brain barrier (BBB) permeability, and tight junction protein loss, promote and trigger the influx of inflammatory mediators, such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, into the brain. [83] [84] Systemic inflammation, such as sepsis, produces nitric oxide (NO), which plays a key role in endotoxin-induced vasodilation and myocardial dysfunction. Endothelial injury results in microvascular thrombosis, vasodilation, and hypotension, which leads to tissue hypoxia and multi-organ dysfunction. [85] Similar processes may occur in the brain, and if left untreated for an extended period, can lead to neuronal cell death and brain atrophy. [86] Sepsis-associated brain injury may lead to amyloid β (Aβ), and tau protein deposition as seen in patients with Alzheimer's disease. [87] As a result of the immunologic response to sepsis, patients may experience acute and long-term cognitive impairments.

8.6. How Does the Hypothalamic-Pituitary-Adrenal (HPA) Axis Moderate and Help Restore Immune Homeostasis?

Activation of the hypothalamic-pituitary-adrenal (HPA) axis by immune cell-derived cytokines is an important regulatory process to support homeostasis and survive the life-threatening impact of excessive inflammation on the host. The coordination of inflammation and its impact on the host cannot be fully understood as an isolated function of bone marrow-derived cells as it is the combined effect of the nervous and immune systems that maintain homeostasis. It is the feedback between these two systems that orchestrates a balanced immune

response leading to the restoration of hemostasis during inflammation. The regulatory feedback loops coordinating between immune, neuroendocrine, and nervous systems comprise an afferent (sensory) and an efferent (regulatory) component. PAMPs activate the immune system and afferent system (through the vagus nerve), activating inflammatory cytokines and neurotoxic mediators. The HPA axis afferent signals trigger the efferent response of the central nervous system and activate the sympathetic nervous systems and parasympathetic nervous systems as illustrated in Figure 7.

Impaired homeostasis due to sepsis is not exclusively in the prevue of the immunologic system but also involves the critical regulatory feedback loop that links the immune neuroendocrine and nervous systems. In sepsis, the release of proinflammatory cytokines (e.g., TNF alpha) induces dysfunction of endothelial cells causing blood-brain barrier (BBB) leakage, ischemia, microhemorrhage and hypoperfusion, leading to changes in the cerebral white matter, acutely presenting as altered mental status and long-term cognitive impairment. [88] The pro-inflammatory increase in cytokine concentrations, e.g., IL-1, in the periphery increases the turnover of noradrenaline (NE) in the hypothalamus and increases peripheral plasma and brain noradrenaline metabolism and extracellular levels. [89] [90] Similarly, intracerebroventricular and peripheral injection of interferon (IFN)-α or IL-1β produces a sustained increase in the sympathetic activity of the splenic nerve and increases the turnover of NE in the spleen. The dictum of the fight or flight reaction with HPA activation has been, that acute elevations in cortisol levels are beneficial to promoting survival of the fittest, however, chronic exposure to stress results in the reversal of the beneficial effects, with long-term cortisol exposure becoming maladaptive, which can lead to a broad

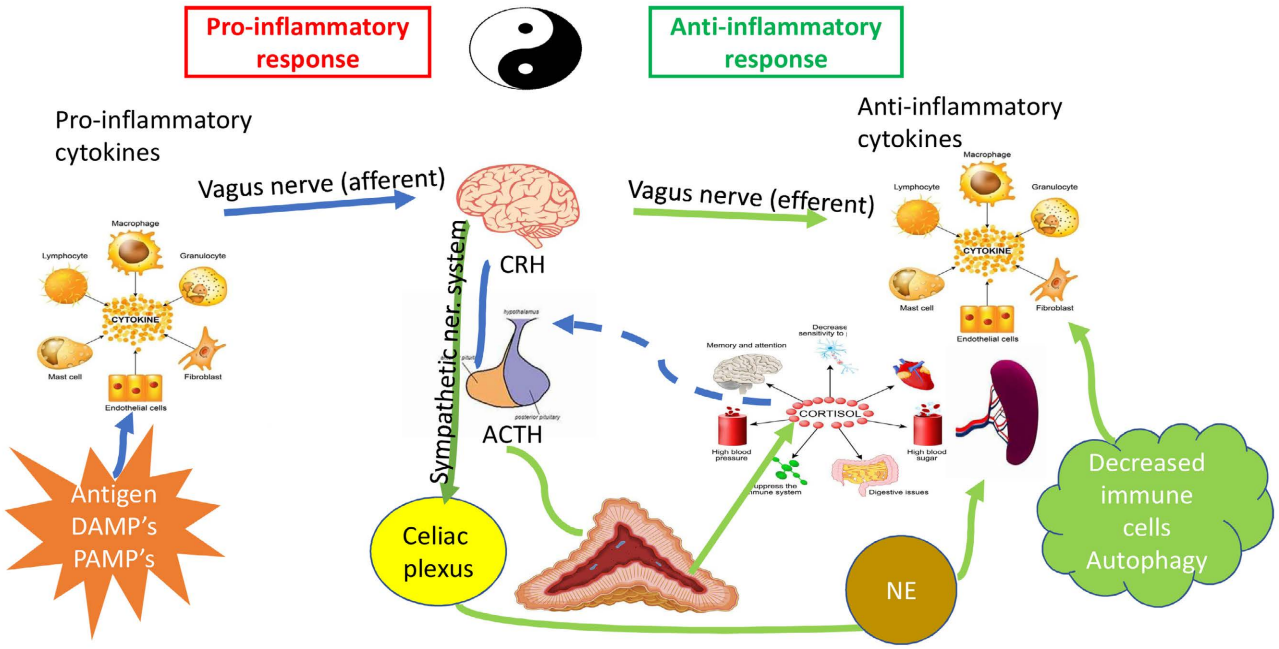

Figure 7. Pro and anti-inflammatory response of the HPA Axis.

range of problems including metabolic syndrome, obesity, cancer, mental health disorders, cardiovascular disease and increased susceptibility to infections. [91]

The prominent role of proinflammatory molecules and pathways suggests a possible therapeutic role for corticosteroid therapy in the management of severe sepsis and septic shock. [92] Despite decades of experimental animal and human trials, the role of corticosteroid therapy, and the role of the hypothalamic-pituitary-adrenal (HPA) axis in sepsis, remains uncertain and controversial. [93] There may be a role for low-dose corticosteroids in fluid-resuscitated vasopressor-dependent patients only with septic shock. [94] Glucocorticoid resistance (GCR) is a well-known manifestation of sepsis and may contribute to the failure of corticosteroids to improve sepsis patients. One of the most promising candidates to revert GCR is the antioxidant vitamin C. Preclinical studies demonstrated the synergistic effect of adding vitamin C to corticosteroid therapy on endothelial barrier function and intestinal mucosa injuries in sepsis models [95] [96] In summary, corticosteroids may have beneficial effects on the pathophysiology of septic shock. It seems only to protect the sickest subgroup of septic shock patients when treated early after shock onset. [97]

Recently, two retrospective studies evaluated the efficacy of combining corticosteroid therapy with vitamin C and thiamin (HAT therapy), revealing reduced hospital mortality from 40.4% in the control group to 8.5% in the sepsis patients receiving the combination therapy, with no increase in adverse effects [98].

8.7. The Long-Term Consequences of Sepsis, Persistent critiCal Illness (PCI)/Chronic Critical Illness (CCI)

PCI or CCI is a subset of elderly adults having chronic underlying medical conditions, requiring longer-term acute care and mechanical ventilation resulting in persistent multiorgan failure with high mortality at 6 months and severe cognitive impairment post the initial injury/infection as shown in **Figure 8**. [99] Despite a small proportion of critical care patients fitting this category, the group requiring mechanical ventilation beyond 4 days ranks third in total Medicare charges. [100] The one-year mortality rates for chronic critical illness/persistent critical illness patients are high, from 37% - 72%. [101] [102] Many patients with CCI do not appear to recover homeostatic balance within the Hypothalamic Pituitary Axis and this ongoing imbalance contributes to prolonged deterioration. [103] Despite the advances in critical care management the number of patients with long-term functional disabilities resulting from CCI/PCI continues to increase.

8.8. What Is the State of Immunotherapy for Sepsis and How Can We Restore Immune Homeostasis?

Understanding the hyperinflammatory response and immunoparalysis seen in sepsis is key to the development of upstream interventions. Most clinical trials of

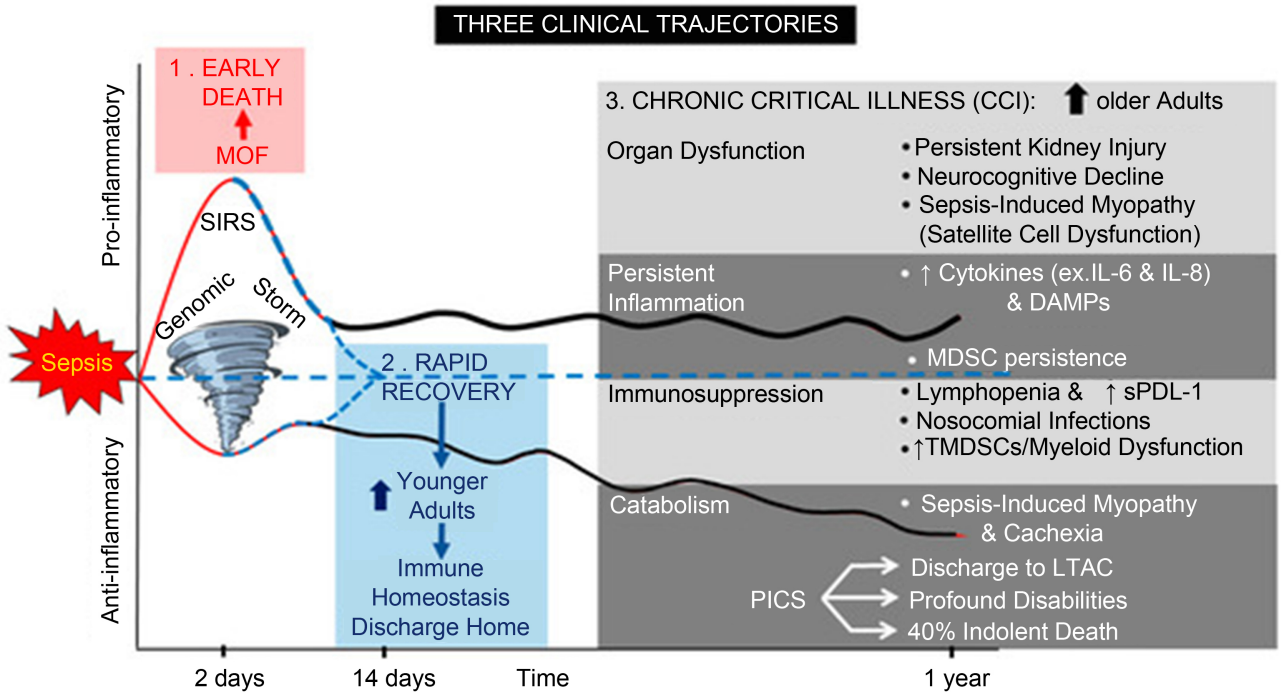

Figure 8. Proposed hypothesis for Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS) in sepsis survivors. Abbreviations: MDSC—myeloid-derived suppressor cell; DAMP—damage-associated molecular protein; LTAC—long-term acute care facility. Darden DB, Kelly LS, Fenner BP, Moldawer LL, Mohr AM, Efron PA. Dysregulated Immunity and Immunotherapy after Sepsis. Journal of Clinical Medicine. 2021; 10(8): 1742. https://doi.org/10.3390/jcm10081742.

novel sepsis therapies have focused on broad samples of patients with different pre-septic immune statuses and infection-specific pathophysiology. Over 100 clinical trials attempting to modulate the immune response to sepsis have failed. [104] This failure is, due to the heterogeneity of the sepsis syndrome. [105] Patients vary by pathogen, site of infection, comorbidity, host response, and duration of infection prior to receiving care. A recent study of 266 patients presenting to the Emergency Departments, using gene expression profiling to examine the underlying molecular responses in infection and sepsis, sorted patients into 5 endotypes: Neutrophilic-Suppressive (NPS), associated with neutrophil activation and immune suppression; Inflammatory (INF), associated with an increased pro-inflammatory response, e.g., increased NF-κB expression; Innate Host Defense (IHD), associated with interleukin signaling; Interferon (IFN), associated with increased IFN-α, β, γ; and Adaptive (ADA), associated with a variety of pathways including increased adaptive immunity. Each endotype was characterized by a signature of approximately 200 genes and was validated in a subset of the Emergency Department (ED) cohort. The NPS and INF endotypes identified those with more severe sepsis. In particular, the NPS endotype exhibited the longest hospital stays, the highest sequential organ failure assessment (SOFA) scores, and had worst overall survival. Conversely, the ADA pathway was associated with a more benign course. [106] To the average practicing Clinician, this sounds impractical, expensive, esoteric, and not widely available. If we were able

to extend these analyses to identify severity markers and/or endotype status within the first hours of ED admission, this would enable more timely, aggressive and/or immunomodulatory interventions to prevent the further progression to severe sepsis, while sparing broad-spectrum antibiotics when not needed. Tailoring chemotherapy to individual needs, genetic markers and response to treatment are where our Oncology colleagues have advanced. The dawning for sepsis treatment is around the corner and requires innovation, risk stratification along early identification.

8.9. Appropriate Antibiotic Usage in an Era of Antimicrobial Stewardship

The difficulty in distinguishing between bacterial and non-bacterial etiologies is also a major cause of the misuse of antibiotics. Inappropriate or prolonged use of antibiotics may lead to the emergence of antibiotic-resistant bacteria and various adverse events, whereas antibiotic underuse due to delayed or missed diagnosis may result in worsened conditions and medical complications. Sepsis occurs often in patients with infection, but 40% - 50% of the cases occur from noninfectious sources. Of the infectious etiologies, the most common source of sepsis in hospitalized patients is infections of the lower respiratory tract, followed by intra-abdominal, bloodstream, intravascular line infections, and urinary tract infections. [107]

MRSA nasal screen has a high negative predictive value (NPV) for ruling out MRSA in pneumonia and other sites. [108] [109] Evidence indicates that negative MRSA nasal screens may be used to de-escalate or withhold anti-MRSA antibiotics in pulmonary infections and intra-abdominal infections. [110] [111] Currently, nasal MRSA swabs are used for determining isolation precautions. This method also had utility in helping clinicians to better predict a patient's probability of MRSA infection and in guiding antimicrobial decisions. [112] The use of a MRSA nasal screen may potentially spare and prolong the effectiveness of Vancomycin for serious MRSA infections without creating vancomycin resistance.

Recently, a large clinical study confirmed that the early identification and treatment of sepsis, including the use of antibiotics within the first 3 h of admission, improved outcomes. [113] While it is recognized that failure to administer effective anti-microbial therapy will at some point be detrimental to patient outcomes, the exact period when this shift begins to occur remains unknown. The metrics to measure quality of care in severe sepsis and septic shock, with the administration of antibiotics within three hours of ED triage or within one hour of recognition of severe sepsis/septic shock did not confer mortality benefit. [114] The use of inappropriate antibiotics is associated with up to a 34% increase in mortality. [115] [116] In addition to reducing pathogen load, some antibiotics have immunomodulatory properties that might be useful in treating the excessive inflammation found in septic patients. Preclinical work identified macrolide

and tetracycline antibiotics as promising immunomodulators. [117] Antibiotic therapy should be narrowed or redirected once culture results are available, and the causative organism identified. This approach reduces the risk of antimicrobial resistance, drug toxicity, and overall treatment cost as depicted in **Figure 9**. However, concerns have also been raised regarding the prolonged use of antibiotics as well as their administration when it is not necessarily due to the increasing incidence of antibiotic-resistant pathogens. [118] [119] Differentiating infectious etiologies from noninfectious causes of sepsis in a timely manner is key to the initiation of broad-spectrum antibiotic and antifungal agents and balancing antimicrobial stewardship. On the horizon are gene-expression assays using reverse transcriptase PCR technology to discriminate sepsis from non-infectious systemic inflammation. This gene technology is being extended to bacterial vs. viral vs. invasive fungal infections. Rapid and affordable genomic technology is part of the early sepsis recognition that may dramatically reduce the global morbidity and mortality associated with this clinical paradigm.

Antibiotics are different from all other drugs; they not only affect the individual to whom they are given but also the entire community, through selection for resistance. They have been a pillar of medicine and are being used worldwide on an enormous scale, from counterfeiting to human, veterinary, and agricultural use. In many countries, antibiotic use exceeds one course per capita per year. In 2010, the top seven antibiotic classes were consumed in an estimated 70 billion individual doses, which equates to about 10 pills, capsules, or teaspoons for every man, woman, and child on earth an annual rate that is rising. [120] This magnitude of use is based at least in part on the perception, among both health professionals and the public, that antibiotics are completely safe.

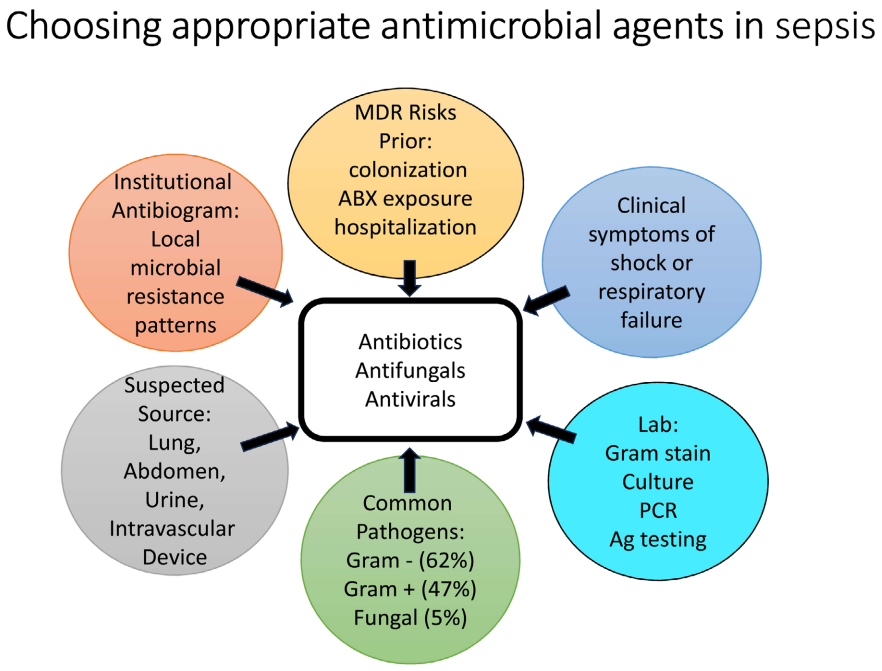

Figure 9. Antimicrobial Stewardship and target multidrug resistance (MDR).

9. Conclusions

The development of septic shock is more complex than the proliferation of pathogens and a derailed immune system. The immune response is influenced by factors such as age, comorbidity, environmental factors and the microbiome. There is no molecular signature able to diagnose sepsis. Pathogenesis is complex, with many immune and non-immune mediators. Recent studies have identified sepsis endotypes with different clinical and molecular profiles. The host-response to sepsis therefore differs per patient, implying the need for different treatment strategies. Timely administration of antibiotics improved outcomes in patients with septic shock; however, the association between early antibiotic administration and outcome was not as clear in those with sepsis without shock. [121] The diastolic arterial pressure (DAP) as a marker of vascular tone, helps identify patients unresponsive to 1 - 2 liters of crystalloid fluid resuscitation needing norepinephrine urgently. [122] The complexity of sepsis is responsible for the failure of therapies that specifically target a given mediator. Given the complexity of events during sepsis, it seems unlikely that a single therapeutic agent may overcome all known complications. There is no "magic bullet" or "one size fits all" approach to sepsis. Most strategies are targeted to points downstream of the initial complex network of events leading to sepsis. It remains highly desirable to identify and therapeutically target the crucial upstream triggers based on sepsis endotypes. The clinical paradigm will be identifying those patients with sepsis who most likely benefit from either immunostimulatory or immunosuppressive therapy, and accurate monitoring of both the immune and treatment response. This will be the new frontier in sepsis/septic shock treatment.

Competing Interests

None declared.

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