

Review Article



Biomarkers and Associated Immune Mechanisms for Early Detection and Therapeutic Management of Sepsis

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Conflict of Interest

The authors declare no potential conflicts of
interest.

Abbreviations

BBB, blood brain barrier; CCR2, C-C
chemokine receptor type 2; CLP, cecal
ligation and puncture; CNS, central nervous
system; CRP, C-reactive protein; DAMP,
damage-associated molecular pattern; MAC,
membrane attack complex; MMP, matrix
metalloproteinase; MPO, myeloperoxidase;

ABSTRACT

Sepsis is conceptually defined as life-threatening organ dysfunction that is caused by a dysregulated host response to infection. Although there has been significant advancement in recent decades in defining and understanding sepsis pathology, clinical management of sepsis is challenging due to difficulties in diagnosis, a lack of reliable prognostic biomarkers, and treatment options that are largely limited to antibiotic therapy and fundamental supportive measures. The lack of reliable diagnostic and prognostic tests makes it difficult to triage patients who are in need of more urgent care. Furthermore, while the acute inpatient treatment of sepsis warrants ongoing attention and investigation, efforts must also be directed toward longer term survival and outcomes. Sepsis survivors experience incomplete recovery, with long-term health impairments that may require both cognitive and physical treatment and rehabilitation. This review summarizes recent advances in sepsis prognosis research and discusses progress made in elucidating the underlying causes of prolonged health deficits experienced by patients surviving the early phases of sepsis.

Keywords: Sepsis; Inflammation; Innate immunity

INTRODUCTION

Sepsis is a life-threatening condition that is triggered by microbial infection and characterized by an uncontrolled and detrimental host inflammatory immune response. Over 1.7 million people develop sepsis in the U.S. each year, which accounts for 25%–30% of hospital deaths and over 270,000 deaths annually (1). Worldwide, there are nearly 50 million cases of sepsis per year and sepsis accounts for nearly 20% of all deaths (2). In recent years it appears the incidence and mortality of sepsis remain unchanged, with approximately 20% of patients dying in the hospital or being discharged to hospice care (1). Further improvement in clinical outcomes will likely require improvements in diagnostic methods that allow rapid recognition and the discovery of novel treatments that influence clinically relevant aspects of sepsis pathology. The former will likely require new diagnostic biomarkers and the latter will require discovery of novel prognostic biomarkers that may define the most clinically important pathophysiological pathways to target for therapeutic manipulation.

NLR, Nod-like receptor; PAMP, pathogen-associated molecular pattern; PCT, procalcitonin; PICS, post-intensive care syndrome; PRR, pattern recognition receptor; SOFA, sequential sepsis-related organ failure assessment; TF, transcription factor; VLA-3, very late antigen-3; WBC, white blood cell

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DEFINITION

For nearly 25 years, sepsis has been defined as systemic inflammatory response syndrome caused by infection (3). This concept was revised in 2016 and the current definition of sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection (4). However, defining the presence, source, and specific microbiological pathogen of infection is often challenging in the clinical environment. Bacteria are responsible for most cases of sepsis, but viral, fungal, or parasitic infections can also trigger the syndrome. A large national cohort study indicates the most common sites of infection were the lungs, genitourinary tract, abdomen, and direct intravascular devices (5). However, in many cases an infectious source cannot be defined, especially early in the course of illness. It is often even more challenging to identify the pathogenic organism causing the infection. Blood cultures are only positive in 30%–40% of all septic patients (1), and the likelihood of positive cultures varies depending on the source of infection. Culturing techniques often take days to turn positive, thus levels of uncertainty are high early in the course of illness when prompt intervention is important, especially in the presence of hypotension. In recent years, a number of technologies have emerged in an effort to reliably and rapidly diagnose sepsis, but none have yet to be widely incorporated into clinical practice (6,7). Due to frequent diagnostic uncertainty (8), it is not particularly surprising that available time-sensitive sepsis treatments are often delayed (9). In an effort to achieve more rapid management, state and federal governments have instituted mandated reporting of sepsis care “bundles” (10), which focus on the first 6 h of management and consist of basic diagnostic tests, supportive measures, and prompt antibiotic therapy (11). While early evidence suggests bundle management may be effective, it could be advantageous to incorporate complementary strategies focusing on manipulation of downstream pathophysiological events that occur once sepsis diagnosis is confirmed and the clinical trajectory is defined (12).

Sepsis mortality occurs due to vital organ dysfunction, driven in part by microvascular dysfunction characterized by impaired vascular barrier function, infiltration of hyperinflammatory immune cells, excessive coagulation, impaired vasoregulation, and ischemia, ultimately resulting in multiorgan failure and death (4). Although treatment often involves broad-spectrum antibiotics and fluid resuscitation, these basic efforts may be insufficient for recovery. Despite elimination of the microbial source of sepsis, the maladaptive immune response can persist, leading to ongoing multi-organ injury. The challenge ahead is to define elements of this complex, uncontrolled immune response that are amenable to therapeutic intervention.

CLINICAL DIAGNOSIS AND MANAGEMENT

The diagnosis of unstable patients with sepsis cannot wait the hours or days often required to confirm infection. Therefore, clinical criteria are utilized for identification of patients with probable sepsis. The onset of sepsis is characterized by various clinical surveillance definitions. Clinical scores classically include measurements of body temperature, blood pressure, white blood cell (WBC) counts, respiratory function, and cognitive ability. The criteria are WBC counts of $>12,000/\text{mm}^3$ or $<4,000/\text{mm}^3$, hyperthermia ($>38^\circ\text{C}$) or hypothermia ($<36^\circ\text{C}$), a heart rate of >90 beats/min, and respiratory rates of >20 breaths/min (3). The presence of 2 or more of these criteria and a suspected or confirmed source of infection have defined sepsis syndrome for over 2 decades. More recently, new classification

criteria have been proposed that define sepsis as suspected or confirmed infection associated with new or worsening vital organ dysfunction, defined by a change in the sequential sepsis-related organ failure assessment (SOFA) score of ≥ 2 (4).

The standard early treatment of critically ill septic patients includes intravenous fluid resuscitation and broad-spectrum antibiotics (11). Importantly, early administration of antibiotic treatment may be one of the most powerful ways to decrease mortality (9,13,14). Therefore, early detection and immediate treatment are imperative to save patients, as the risk of mortality can increase by 10% with every hour of delayed intervention (14).

Outcome prediction for sepsis patients is imperative for treatment decisions and resource allocation and is the driving influence behind the new sepsis 3 definitions. Studies of outcome prediction using clinical parameters have been conducted using large datasets that may include thousands of patients (15). While these studies are useful for clinical identification of subjects at risk of experiencing poorer outcome, they do not shed light on to pathophysiological pathways that could generate new treatment targets. Therefore, they do not provide insights that allow clinicians to tailor treatment according to the patient's biological response to infection, and this type of personalized medicine approach is probably necessary for substantive progress in reducing sepsis morbidity and mortality (12).

Biomarkers

There is ongoing intense interest in identifying biomarkers both for the diagnosis and prognostication in sepsis patients. Identifying new prognostic markers could be an important step in developing novel treatment strategies. Conventional sepsis biomarkers include circulating factors released from specific organ systems, surface molecules expressed on overactivated cells, or metabolites secreted from damaged tissues (16).

C-reactive protein (CRP) and procalcitonin (PCT) are 2 of the most widely studied biomarkers in the diagnosis of severe sepsis (17). CRP is synthesized in the liver during very acute phases of systemic inflammation, and it plays a role in complement activation, typically through the signaling of classical cascade initiator molecules. CRP concentrations in serum can be measured very quickly, and levels can fluctuate in very short periods of time, contributing to its sensitivity and usefulness as a biomarker (18,19). However, CRP levels vary highly among septic individuals, and for accurate and predictive measurements, CRP must be compared to the individual's own baseline. Often, this is difficult or even impossible, as patients may be infected and septic long before ICU admission. PCT may be even less useful, as its levels do not correlate well with SOFA scores, lengths of stay in the hospital, or even patient mortality (20). PCT may still be useful in combination with other tools and sepsis scoring methods, but as a single factor for diagnosis or prognosis, it falls short. CRP and PCT have been held as gold standards for predicting sepsis outcomes, but the requirements for sepsis diagnosis must already be in place (21).

In comparison to circulating factors as biomarkers, other methods use the detection of upregulated proteins on the surfaces of activated immune cells. Chemokine receptors, including C-C chemokine receptor type 2 (CCR2) and CX3CR1, are useful biomarkers that are expressed on monocytes during sepsis (22). CCR2 is highly upregulated on "inflammatory monocytes" and coincides with the rapid release of these cells from sites of maturation, including the bone marrow and spleen. CX3CR1 is more likely to be found on "patrolling monocytes", which are a less hyperinflammatory version of the same cell type. Both

molecules serve specialized functions that are crucial in the context of sepsis and are thus considered useful biomarkers of persistent inflammation (23-25).

In addition to chemokines and their receptors, integrins are a family of molecules expressed on the surfaces of circulating immune cells that facilitate their binding and extravasation into inflamed tissues. Recently, it has been shown that integrin $\alpha_3\beta_1$ or very late antigen-3 (VLA-3) is highly expressed on a subset of neutrophils, causing them to exhibit hyperinflammatory behaviors that include excessive extravasation into tissues (26). Other important molecules present on cells during the immune response to infection include Fc receptors. These specialized molecules exist in many subclasses and bind to the constant portions of antibodies, which may be bound to foreign antigens such as bacteria to mark them for clearance. One such molecule is Fc-gamma (γ)-receptor-1 (CD64), which binds to monomeric IgG antibodies with very high affinity (27,28). Neutrophil CD64 expression is an excellent biomarker that indicates active infection, as its expression is only increased during sepsis and is negligible on resting neutrophils (29). Combining clinical variables with immune cell activation markers such as VLA-3 and CD64 expression to create a sepsis risk prediction score is may provide greater diagnostic and prognostic accuracy than any of these parameters alone (Table 1).

Table 1. Sepsis biomarkers

Marker	Function	Clinical relevance	Ref.
Soluble			
Lactate	Byproduct of glucose metabolism, produced from pyruvate during anaerobic metabolism	<ul style="list-style-type: none"> Hyperlactatemia indicative of cell hypoxia states when aerobic is converted to anaerobic metabolism Also elevated with reduced lactate clearance from sepsis-induced liver dysfunction Also elevated with excess glycolysis, thiamine deficiency, and other conditions, therefore non-specific 	(30,31)
Blood pH	Indicative of metabolic acidosis, a result of increased anion production	<ul style="list-style-type: none"> Acidified blood correlates with a decrease in tissue perfusion and contributes to reduced cardiac contractility, ATP generation, and negatively impacts the immune response Can be a result of other disease states, and not specific to sepsis 	(32,33)
CRP	Binds to pathogens and dying cells to facilitate enhanced phagocytosis and clearance	<ul style="list-style-type: none"> Produced by the liver at early phases of sepsis in response to bacterial infection, but also as a response to many other inflammatory stimuli 	(34-36)
PCT	Prohormone of calcitonin secreted in response to bacterial stimulation	<ul style="list-style-type: none"> PCT concentrations above 0.1 ng/mL indicative of bacterial infection Half-life is relatively short, and concentrations can normalize quickly 	(36,37)
HMGB-1	HMGB-1 protein binds to DNA and creates a scaffold for chromatin formation	<ul style="list-style-type: none"> Alarmin released from cells under stress During sepsis, can bind inflammatory mediators such as RAGE and TLRs Higher levels in the blood indicative of inflammation, however not specific to sepsis 	(38,39)
Cell surface			
CD64	High affinity Fc-g-receptor, highly expressed on macrophages and eosinophils, binds to immunoglobulins and mediates clearance of antibody coated cells	<ul style="list-style-type: none"> Expressed on neutrophils only during sepsis, specifically during bacterial infections 	(36,40)
VLA-3 ($\alpha_3\beta_1$)	Member of the integrin family, mediates adhesion of immune cells to fibronectin and collagen in extracellular matrices during cell migration	<ul style="list-style-type: none"> Upregulated on hyperinflammatory neutrophils exclusively during sepsis, distinguishing from sterile inflammation or SIRS 	(26,41,42)
CCR2	Chemokine receptor 2, expressed on monocytes and some macrophages to facilitate chemotaxis and regulation of tissue specific immune cell homing	<ul style="list-style-type: none"> Higher expression levels during sepsis indicative of pro-inflammatory monocyte egress from bone marrow and subsequent infiltration into inflamed tissues 	(23,43-45)
CX3CR1	Fractalkine receptor, highly expressed on tissue-resident macrophages, facilitates leukocyte adhesion and migration during steady state	<ul style="list-style-type: none"> Expressed on monocytes during immunosuppressive phases of sepsis 	(22,25,46-48)

SIRS, systemic inflammatory response syndrome; HMGB-1, high mobility group protein B1; RAGE, receptor for advanced glycation end products.

INFLAMMATORY MEDIATORS OF SEPSIS

Even when sepsis is promptly diagnosed at the time of hospital admission, the diagnosis is changed about a third of the time when additional clinical information becomes available later during the hospital stay. Inaccuracies in diagnosis and prognosis stem from the marked heterogeneity of patients with severe sepsis. This heterogeneity originates largely from variation in the immune responses of patients with regard to the phase of the sepsis inflammatory cascade. Following sections will describe the diversity and heterogeneity of the sepsis-associated inflammatory pathways.

Recognition of molecular patterns

The host response to pathogen invasion is initiated by the pattern recognition receptors (PRRs) of the innate immune system, which recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). PAMPs are unique motifs found on microbes that are recognized by PRRs and allow the innate immune system to distinguish self from non-self, while DAMPs are a sign that there is damage to the host. Both PAMPs and DAMPs function as “molecular warnings” that activate circulating and tissue-resident immune cells. The broad nature of the innate immune system's response to infection and damage is largely facilitated by well-conserved subclasses of PRRs (49). PRRs are made up of several distinct subfamilies of receptors, including TLRs, Nod-like receptors (NLRs), RIG-I-like receptors, AIM2-like receptors, and C-type lectin receptors (50).

During sepsis, PRRs play a critical role in initiating the response to infection. Perhaps the most well studied PRRs are TLRs and NLRs, which bind a multitude of both PAMPs and DAMPs that are displayed during sepsis. TLRs exist in both the cell membrane and endosomal compartments and distinguish extracellular and intracellular pathogens, respectively. Transmembrane TLRs mainly recognize microbial membrane components such as LPS by TLR4, lipoproteins, peptidoglycans, lipoteichoic acids, zymosan, and mannan by TLRs 1, 2, and 6, and flagellin by TLR5. Intracellular TLRs detect nucleic acids from both bacterial and viral sources that include dsDNA (TLR3), ssRNA (TLR7), and CpG-DNA motifs (TLR9), in addition to profilin, a component of the parasite *Toxoplasma gondii* (TLR11) (51,52). TLRs also respond to host products such as heme or high mobility group protein B1 through TLRs 4 and 2, respectively (53).

NLRs recognize various ligands from microbial pathogens and host cells. NLRs sense viral ssRNA (NOD2), bacterial flagellin (NLRB), and cytosolic products of host stress, such as ATP. Activation of NLRs leads to distinct functional mechanisms, including the formation of the inflammasome, transcriptional activation of proinflammatory cytokines, and autophagy (54).

Other PRRs include P2X and P2Y receptors, which respond to host nucleotide products such as ATP, ADP, UTP, and UDP (55). Heat shock proteins and uric acid are other examples of host products that innate immune cells can sense as a sign of cellular damage (56). All PRRs exert a multitude of functions that ultimately lead to cell secretion of antimicrobial products or signals to other cells.

During sepsis, sustained immune activation is achieved by initial infection and recognition of foreign material through PAMPs, followed by the release of host components during tissue damage (DAMPs or alarmins), leading to a vicious cycle of amplified inflammation. The innate immune system response is absolutely necessary as the first line of defense towards

pathogen invasion, yet the pathophysiology of sepsis occurs when these same immune cells become overactivated and dysregulated. In this regard, PRRs have been established as therapeutic targets during sepsis. This field of research is very dynamic and numerous clinical trials are in place that test the efficacy of various TLR antagonists, with the majority of studies centered around TLR4. Many small molecule drugs are in the earlier stages of clinical trials but appear to be well tolerated by healthy subjects (57-59). Unfortunately, at present, treatments targeting specific elements of the dysregulated immune response of sepsis remain elusive.

Proinflammatory cytokine responses

Many signal transduction pathways stemming from activation of PRRs culminate in the activation of transcription factors (TFs), including interferon-regulatory factors and the master regulator NF- κ B (60). These TFs result in the expression and secretion of proinflammatory cytokines such as IL-6 and IL-12 and IFNs, which are required for host defense against pathogens and long-term adaptive immunity (61). Another well-characterized example of PRR downstream signaling is inflammasome-mediated induction of caspase-1, an enzyme that cleaves the pro-forms of IL-1 β and IL-18 to mediate their release (62). The -proinflammatory cytokines IL-1 β , IL-18, IL-6, or TNF- α may be double-edged swords, as these cytokines have essential functions in signaling to other immune cells but ultimately exacerbate inflammation and contribute to many harmful symptoms of sepsis. IL-6 activates prostaglandin E2 in thermoregulatory neurons within the hypothalamus, where downstream signaling results in hyperthermia or fever (63). TNF- α is an especially important multifunctional molecule that is produced during sepsis. Among other effects, it causes a hypercoagulable state promoting intravascular clotting and disrupting microvascular blood flow, a hallmark of sepsis pathology (64).

Targeting TNF- α and IL-1 β is a novel pharmacological modulation strategy for treating sepsis. Although blocking these proinflammatory cytokines proved efficacious in mouse models of disease (65), clinical trials in humans were unsuccessful (66). Antagonists of IFN- γ similarly did not improve mortality rates when given intravenously to severely septic patients (67). The bulk of these randomized trials occurred decades ago. To date, there are still no cytokine modulators on the market for sepsis treatment. However, other soluble factors are therapeutic targets, and some play even more extensive roles during severe sepsis and the outcome. One such example is the activation of humoral immune components known as complement.

Complement

Complement activation occurs via 3 different routes: classical, alternative, and mannose binding lectin pathways (68). All 3 have multiple unique factors, but all converge on the C3 component and culminate in the formation of the membrane attack complex (MAC) (69). The MAC creates a transmembrane pore in a target cell, facilitating lysis and death. Targets include bacteria or infected host cells, making regulating of the complement pathway essential during sepsis. The antimicrobial properties of complement include direct lysis of microorganisms, opsonization of cells as markers for phagocytosis, and signaling molecules that coordinate further responses to infection (70). Complement release and activation occurs rapidly after pathogen invasion, and each pathway's components are tightly regulated by a systematic cascade of events when the system is functioning normally. Complement components are made primarily by endothelial cells in the liver, but during inflammation, they can also be synthesized and released by immune cells.

The production and circulation of complement factors are highly upregulated during sepsis. While the protective functions of complement are an essential facet of innate immunity, complement factor concentrations are strongly and positively associated with disease prognosis (70). Complement is comprised of multiple fluid-phase and membrane-associated proteins, which must be tightly regulated to distinguish self from non-self (71). Multiple factors exist to control the activation and assembly of the complement cascade, including endogenous inhibitors that sequester complement components in the absence of infection. Sepsis is frequently marked by a loss of complement regulation, which can include both overactivation and deficiency. Exploitation of the complement cascade has been a focus of research for the past 20 years. A therapeutic strategy targeting complement has been tested in autoimmune diseases, transplant-related complications, and neurodegeneration (72).

Coagulation factors

During acute inflammation, the coagulation system is diffusively and systemically activated, resulting in disseminated intravascular coagulation (73). Different degrees of hemostatic dysregulation occur at different timepoints throughout sepsis, resulting in both bleeding abnormalities and tissue ischemia. This makes therapeutic manipulation of the coagulation cascade extremely challenging. Furthermore, clot formation and disruption both have noncanonical roles outside of hemodynamic processes. These include host defense against pathogens and clearance of infection. This interconnection between coagulation and immune pathways is called immunothrombosis (74). Small amounts of controlled clot formation can trap circulating pathogens and impede dissemination of these pathogens through circulation and into tissues (75). Despite this, the majority of therapeutic treatments targeting the coagulation cascade are inhibitory. The administration of DNase was designed to directly prevent the nets that are formed during immunothrombotic bacterial sequestration (76). The majority of anticoagulation therapies are targeted towards deactivating specific components of the coagulation cascade. For example, several antithrombin therapies have been tested in multiple clinical trials worldwide, with mixed results (77). Some antithrombin-based anticoagulant therapies have resulted in a modest change in septic outcomes, decreasing 28-day mortality by up to 9% (77). The benefits and risks of antithrombin treatment are still under active investigation, as antithrombin therapy increases the likelihood of bleeding events in up to 7% of severely septic patients without a significant reduction in the 28-day all-cause mortality (78,79).

Leukocyte recruitment

The most essential mediators of sepsis pathology are the cells of the innate immune system. Neutrophils and monocytes are the 2 cell types that are primarily responsible for preventing the progression of microbial infection. In the context of sepsis, however, abundance and widespread activation of these cell types facilitates much of the damage seen during the acute phases of the disease.

Neutrophils

Neutrophils display various cell surface molecules that recruit them from their site of maturation in the bone marrow into circulation and peripheral tissues. Once exited from the bone marrow, neutrophils follow endogenous chemokine gradients that localize them to sites of infection, where they are subsequently recruited by bacterial products and complement factors (80). Under infection and host stress conditions, neutrophils release their granules, which exist in primary, secondary, and tertiary forms. Some of the main antimicrobial components secreted by neutrophils include myeloperoxidase (MPO), ROS,

azurocidin (primary), cathelicidin (secondary), peptidoglycan recognition proteins (tertiary), and their own DNA and histones via the generation of neutrophil extracellular traps (81). The antimicrobial properties of neutrophils are critical for the disruption of bacterial cell membranes, resulting in pathogen clearance (81).

Granules released from neutrophils also mediate their extravasation from circulation into tissues. Matrix metalloproteases (MMPs), in particular MMP9, are found in the brain following acute ischemic injury (82). MMP9 was first described in neutrophils and is released from primary granules following neutrophil activation. Release of MMP9 facilitates the breakdown of tight junction proteins, including claudin-5, occludin, and zonula occludens-1, which are all found between endothelial cells, including those of the blood brain barrier (BBB) (82,83). Therefore, hyperinflammatory neutrophils releasing MMP9 are capable of breaching the endothelial layer that separated circulating leukocytes from tissues, including the brain, thus allowing more immune cells to infiltrate organs and promote damage.

Although neutrophils become hyperactivated and induce much of the tissue damage observed during sepsis, they are also essential for the clearance of pathogens. Therefore, extensive research has been devoted to further understanding and exploiting the mechanisms behind neutrophil dysfunction during inflammation. Exploration of neutrophil heterogeneity within different diseases has uncovered the potential for perturbing the distribution of neutrophil subpopulations. During tumorigenesis, neutrophils have been reported to exist in a state between a pro- and anti-inflammatory phenotype (84), similar to what has been described in M1 vs M2 macrophages (85). Here, N1 vs N2 neutrophils may have similar traits to their macrophage counterparts, and in the context of sepsis, controlling the infiltration of one type over the other may prove advantageous from a therapeutic standpoint. As previously stated, integrin VLA-3 is upregulated on a subpopulation of hyperinflammatory neutrophils during sepsis (26). VLA-3^{high} neutrophils exhibit elevated MPO and proinflammatory cytokine production, lending to their antimicrobial properties but also to their infliction of tissue damage (26). How to best control the neutrophil response is still under active investigation.

Monocytes

Monocytes are another crucial cell that migrates to inflamed tissue sites during the first few hours of infection. During infection, monocytes further differentiate into macrophages. Monocytes and macrophages specialize in phagocytosis and the removal of pathogens, antigen presentation, and the production of cytokines and chemokines to facilitate communication with the adaptive immune system (86). Like neutrophils, monocyte recruitment and migration depend on chemotactic cues and adhesion to the vascular endothelium. Additionally, there are numerous subpopulations of monocytes that are broadly categorized as “classical” and “nonclassical” subtypes. The chemokine and fractalkine receptors CCR2 and CX3CR1, respectively, are commonly used to identify “inflammatory” (classical) vs “patrolling” (nonclassical) populations. Inflammatory monocytes are typically CCR2^{high} Ly6C⁺ CX3CR1^{low} and are rapidly recruited to damaged and inflamed tissues, whereas patrolling monocytes are CCR2^{low} Ly6C⁺ CX3CR1^{high}, allowing these cells to circulate and clear damaged cells to facilitate repair (87). During sepsis, CCR2^{high} monocytes extravasate into tissues, where they secrete proinflammatory cytokines and growth factors and transport antigens to draining lymph nodes to activate the adaptive immune response (88). During infection, CX3CR1⁺ monocytes are found in circulation and localized to the marginal zone of the spleen, where their purpose is to phagocytose bacteria and recruit additional inflammatory monocytes (89).

To identify the function of monocytic chemokine receptors during sepsis, several studies have used cecal ligation and puncture (CLP) to investigate the role of monocyte trafficking. Andonegui et al. (44) revealed that targeting CCR2+ inflammatory monocytes during septic peritonitis led to significantly fewer infiltrating cells in the central nervous system (CNS) by 24 h post-infection. This finding was critical, as decreased monocyte recruitment to the brain correlated with fewer behavioral abnormalities in these animals at 9 weeks after infection (44). Furthermore, in the absence of nonclassical CX3CR1+ monocytes during CLP, mortality rates increased from 33% in wild-type to 75% in CX3CR1 knockout mice within 7 days of polymicrobial peritonitis when these patrolling monocytes were not present to clear bacteria (90). Thus, both classical and nonclassical monocyte recruitment is important for bacterial clearance and sepsis recovery. Furthermore, chemokine receptors such as CCR2 and CX3CR1 are only partially responsible for the process that facilitates migration into inflamed tissues.

Tissue-resident macrophages

An indispensable role of monocyte trafficking during sepsis is to deliver tissue-resident macrophages, which exist in a temporary or permanent state after differentiation. Macrophages received their name over 100 years ago, when Élie Metchnikoff coined the term “phagocytosis” (91). It is often thought that the main purpose of macrophages is to clear debris and dying cells from tissues, both during homeostasis and disease. Tissue-resident macrophages are critical innate immune sentinels that recognize pathogens via PRRs and signal to other cells. As a first line of defense, resident macrophages are considered “gatekeepers” of the tissues, where they rapidly respond to infection and initiate recruitment of circulating/inflammatory innate cells. Our knowledge of their diverse functions has since expanded, including their ability to crosstalk with other cells, secrete both pro- and anti-inflammatory cytokines, and even present antigens during pathogen invasion (92). During acute inflammation, macrophages serve as acute sensors of their environment, which is critical during the initiation of sepsis.

More recently, research devoted to exploring the ontogeny of tissue-resident macrophages has accelerated our understanding of their regulation and roles in peripheral tissues. Resident macrophages make up a diverse population with unique developmental origins. The majority of tissue-resident macrophages are derived from embryonic precursors and can be self-maintained throughout the lifetime of the host (93). The homeostatic support provided by these cells is achieved through tissue repair and crosstalk with other cells. Although tissue-resident macrophages are typically seeded in early development during embryogenesis, they may be replenished by bone marrow-derived monocytes during infection and inflammation (94). The contribution of adult myeloid progenitors to tissue-resident macrophages is context- and organ-dependent. In many different diseases, such as cancer, colitis, and sepsis, tissue-resident macrophages and their replenishment are required for host immunity (95-98). During disease progression, tissue-resident macrophages exhibit increased plasticity and adapt rapidly to changing microenvironments. Tissue specification determines macrophage function, highlighting the need for a focus on individual organ systems. Every organ contains its own form of sentinel macrophage, with considerable research concentrating on microglia in the brain, Kupffer cells in the liver, and macrophages in the peritoneal cavity.

Kupffer cells are the largest population of tissue-resident macrophages in the body, perhaps explaining the extensive research surrounding their homeostatic functions during inflammation (99). Kupffer cell activity changes based on the disease scenario, promoting tissue repair during drug-induced injury (100) but also contributing to chronic damage in

the context of fatty-liver diseases (101). As is the case with most immune sentinels, Kupffer cells have both beneficial and harmful effects during sepsis. Some research shows deleterious consequences of Kupffer cells on the liver sinusoidal endothelial vasculature (102), while other studies show that these cells protect the endothelium (103). As is frequently the case during sepsis-related organ dysfunction, damage versus protection appears to be a fine balance that depends on timing and location.

Microglia are tissue-resident macrophages in the CNS and have a unique morphology and purpose throughout the lifetime of the host. Their role during brain development includes phagocytosing dead cells and debris while also promoting synapse formation and reorganization (104-106). While the brain is historically considered an immune-privileged area, microglia also serve as the interface between the nervous and peripheral immune systems. During sepsis, the BBB breaks down, and immune privilege is lost. At this time, microglia continue to provide support and feedback to local neurons but also become activated in the context of massive systemic inflammation. Overactivation of microglia exerts detrimental effects on neuronal structure, but much of this damage may be the direct result of peripheral immune cell infiltration. Microglial function during sepsis is a surprisingly understudied field, but new advances in understanding the robust response to infection in the brain are quickly growing (45,107).

SEPSIS RESOLUTION AND TISSUE REPAIR

Patient survival is highly dependent on the ability to overcome the dampened immune response and regain control and balance of both hyper- and anti-inflammatory modulation. The onset of tissue repair must start with the resolution of infection and clearance of microbial products (108). The resolution of inflammation is very complicated and involves more than just the termination of proinflammatory responses. Although pathogen invasion may be under control, the body must also limit the release of DAMPs from damaged cells (109). There are several complex subcellular processes that eliminate damage signals and promote wound healing and regeneration.

Clearance of molecular patterns that can further activate cells is essential in promoting inflammatory resolution. Eradication of PAMPs and DAMPs is facilitated by autophagy. Autophagy is an elegant and precise way for the cell to recycle and dispose of its own damaged organelles, residual pathogenic material, and cellular proteins (108,110). By decreasing the likelihood of further immune cell stimulation, autophagy is used globally throughout the body and relies heavily on subcellular checkpoints that decide whether a cell lives or dies. Recently, there has been evidence to support a link between autophagy and apoptosis. During sepsis, rapid influx and turnover of effector cells in tissues require both self-consumption and cell death. While the turnover and destruction of organelles within cells and cells within organisms are functionally distinct mechanisms (111), the theory that autophagy and apoptosis pathways share molecular signals is becoming widely accepted (112).

Apoptosis is a programmed cell death process that is executed in both endogenous and paracrine manners. During sepsis, effector cells are constantly turning over and require continuous clearance and repopulation in infected tissues. Apoptosis precedes many downstream effector functions, including direct signaling to phagocytes to commence efferocytosis. Efferocytosis is defined as phagocytosis of dying cells and is crucial during

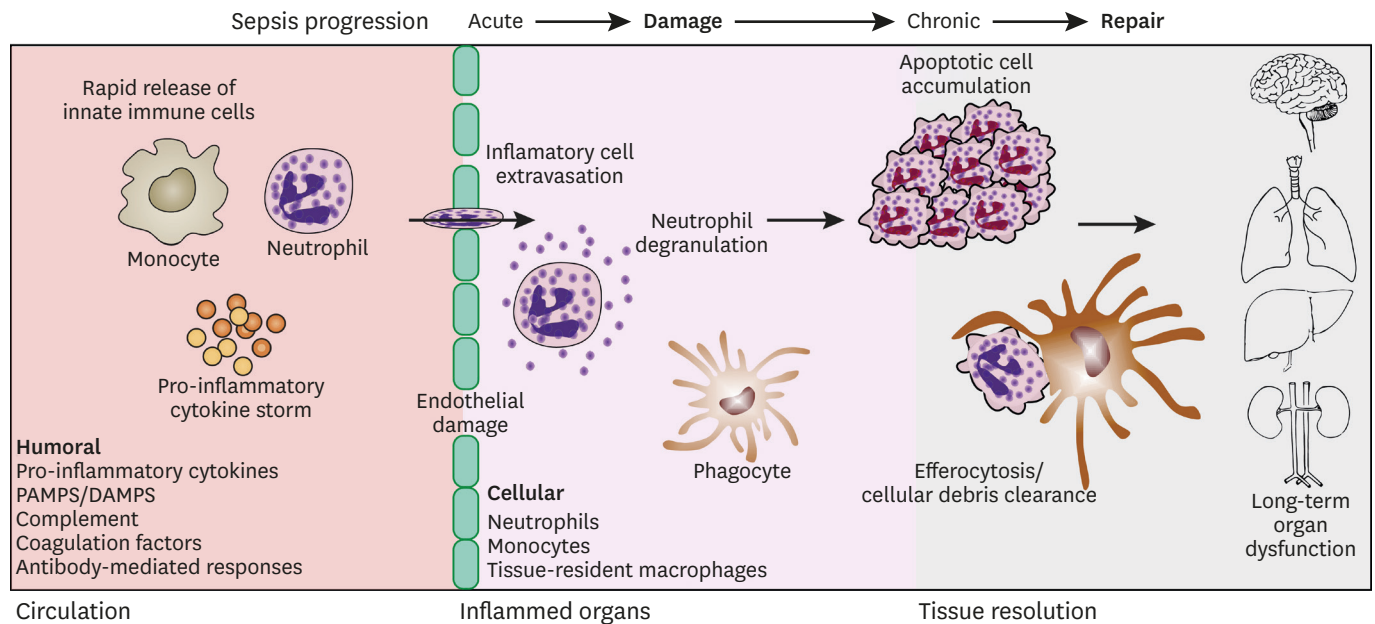


Figure 1. Cartoon of working model of host immune responses from early sepsis progression to the chronic phase after resolution of inflammation.

inflammatory resolution. The ability of phagocytic cells to engulf billions of cellular corpses during and after systemic inflammation is one of the hallmark features of successful recovery (**Fig. 1**) (113). Macrophages that engulf apoptotic cells contain metabolite-sensing equipment in the form of nuclear receptors that are directly involved in the regulation of inflammation (114). Several reports have demonstrated the anti-inflammatory properties of efferocytosis, including its most obvious role in sequestering and limiting the spread of DAMPs by dying cells, which would perpetuate inflammation (114). Furthermore, efferocytosis induces the production of anti-inflammatory cytokines such as IL-10 and TGF- β , which act on local microenvironments or within the phagocyte itself (115). The unique ability of efferocytosis to promote a resolution phenotype makes it one of the most crucial features of sepsis recovery.

CHALLENGES IN RECOVERY

Although acute management of sepsis accounts for a significant clinical and financial burden to society, recovery after sepsis is delayed and often incomplete (**Fig. 1**). These patients often experience post-intensive care syndrome (PICS), defined as “new or worsening problems in physical, cognitive, or mental health status arising after a critical illness and persisting beyond acute care hospitalization” (116). An increasing number of clinics have been established to evaluate and treat these patients (117). A number of landmark epidemiologic studies have clearly documented deficits in physical, mental, and cognitive health in survivors of critically ill patients with sepsis (118-120), but the underlying pathophysiology of PICS is not well understood.

Prolonged organ dysfunction

Long-term organ dysfunction after sepsis is poorly understood, but the acute inflammatory process likely plays a role. The potential link between acute illness/inflammation and the

occurrence of persistent vital organ dysfunction is exemplified by the cognitive deficits of PICS. During acute illness, 3 quarters of critically ill patients experience sepsis-associated delirium, a symptom that develops during systemic inflammation and ranges from confusion to coma (120). In turn, the duration of delirium during acute illness is correlated with the severity of persistent cognitive dysfunction as measured a full year after hospital discharge (120). In a large cohort investigation performed within the Health and Retirement Study, functional disability and cognitive impairment were examined in patients before and after a sepsis hospitalization. This study was able to compare patients to their own baselines before sepsis and indicated marked cognitive decline that remained even 3 years after recovery from acute illness (119). The study found that many survivors had difficulties in everyday tasks such as grocery shopping, managing money, or using the telephone.

Although there is extensive research devoted to understanding the mechanisms and prevention of brain injury during sepsis, very little is currently known. One theory involves brain microglial cells. Microglia are immune sentinels that are unique in their ability to self-renew and/or survive throughout the lifetime of the host. With sepsis leading to permanent defects in multiple organ systems such as the brain, a role for long-lived tissue-resident macrophages in prolonged immunity and inflammation is a hypothesized target in research on long-term cognitive impairment. To date, multiple theories regarding the role of microglia during sepsis-induced neuroinflammation have been identified. Infiltration of peripheral immune cells undoubtedly influences brain-resident macrophages, both through direct and indirect contacts (45,121,122). Current research exploring the relationships between infiltrating and sentinel immune cells during inflammation is rapidly growing.

Tolerized immunity

Sepsis survivors have an increased incidence of rehospitalization after discharge, and these readmissions are frequently infection-related (123-125). The concept of cellular reprogramming is new in the immunology field but is quickly being accepted as an important component of immune system rechallenge. Patients who are discharged from hospitals after sepsis often experience persistent low-grade inflammation and increased immunosuppression, in part due to elevated levels of the anti-inflammatory cytokines IL-10, PD-L1, and IL-7, which are found up to one year after recovery (126). Evidence of protracted immune disorders begs the question of the possibility of tolerized immunity.

Several reports have examined the potential for innate immune cells to retain memory (127-129). While it is a widely accepted aspect of the adaptive immune system, memory in the innate immune system is more controversial. Understanding cellular reprogramming has opened up the field considerably, with current literature highlighting the remodeling of epigenetic landscapes as a way for cells to incur permanent genetic changes (130). A popular example of this phenomenon arises in endotoxin tolerance, which can be achieved by TLR-induced chromatin modification (131). LPS-induced tolerance has also been observed in microglia, where primary exposure to TLR4 stimulation directly influences future responses to endotoxin (132). Enhancement of microglial proinflammatory reactions to secondary exposure has also been linked to numerous neurodegenerative diseases, including Alzheimer's disease, stroke, and Parkinson's disease (132). The concept of innate immune cell memory could have significant impact on our ability to treat sepsis, particularly its longer-term adverse health consequences.

DISCUSSION

There have been large investments devoted to clinical investigations manipulating both the hyperinflammatory and immunosuppressive states of sepsis. Unfortunately, most therapeutic treatments have failed in clinical trials, a harsh reality reflected in the number of sepsis-related deaths each year. Sepsis remains one of the most fatal diseases worldwide.

The ever-expanding networks and connections between both proinflammatory and anti-inflammatory mediators in sepsis provide an unparalleled level of complexity. The interplay between the innate immune system, tissue-resident macrophages, adaptive immunosuppression, and abundant circulating humoral factors leave myriad possibilities for investigation. The acute phase of sepsis requires further understanding to effectively dampen early and excessive host responses. However, the later stages of sepsis deserve special focus, as cellular and metabolic reprogramming probably exert important roles in the longer survival and health of acute sepsis survivors. The search for new and effective therapeutic innovation is complex and successes will require coordinated multidisciplinary efforts by a diverse array of biomedical researchers. We are hopeful that collaborative research and technological advances will aid in defining new diagnostic and prognostic biomarkers and yield effective therapeutic advances.

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