The pathophysiology of sepsis—2021 update: Part 1, immunology and coagulopathy leading to endothelial injury

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Abstract

Purpose. To provide an overview of current literature on the pathophysiology of sepsis, with a focus on mediators of endothelial injury and organ dysfunction.

Summary. Sepsis is a dysregulated response to infection that triggers cascades of interconnected systems. Sepsis has been a significant cause of mortality worldwide, and the recent viral pandemic that may produce severe sepsis and septic shock has been a major contributor to sepsis-related mortality. Understanding of the pathophysiology of sepsis has changed dramatically over the last several decades. Significant insight into the components of the inflammatory response that contribute to endothelial injury and trigger coagulation pathways has been achieved. Similarly, characterization of anti-inflammatory pathways that may lead to secondary infections and poor outcome has illustrated opportunities for improved therapies. Description of an increasing number of important mediators and pathways has occurred and may point the way to novel therapies to address immune dysregulation. Pharmacists will need a fundamental understanding of the overlapping pathways of the immune response to fully prepare for use of novel treatment options. While pharmacists typically understand coagulation cascade how to utilize anticoagulants, the issues in sepsis related coagulopathy and role of mediators such as cytokines and complement and role of activated platelets and neutrophils require a different perspective.

Conclusion. Pharmacists can benefit from understanding both the cellular and organ system issues in sepsis to facilitate assessment of potential therapies for risk and benefit.

Keywords: coagulopathy, cytokines, endothelial injury, immune response, inflammation, sepsis

Our understanding of the pathophysiology of sepsis-induced organ dysfunction has accelerated in recent years with improved appreciation of the importance of the immune system response and its interaction with the vascular endothelium, which can produce microvascular injury. This overview of important concepts will focus on describing cellular mechanisms of injury in part 1 and organ system dysfunction in part 2. While some aspects of monitoring and therapeutic interventions will be discussed, the reader is referred to other sources for more comprehensive information and guidance.[1-3] Similarly, while some aspects of viral sepsis, as noted in patients with the coronavirus disease 2019 (COVID-19) will be discussed, it should be viewed as preliminary information based on an evolving understanding.[4]

Epidemiology

Sepsis is a significant contributor to mortality. Prior to the onset of the COVID-19 pandemic in 2020, the Centers for Disease Control and Prevention (CDC) estimated that 1.7 million adults in America develop sepsis annually and that nearly 270,000 die of the sepsis.[5] The majority have sepsis onset outside the hospital but commonly have at least 1 comorbidity and exposure to the healthcare system prior to hospitalization for sepsis.[6] Further, CDC estimates that one-third of patients who die in a hospital have sepsis and that 90-day mortality in adult patients with sepsis is 32%, although the majority die within 5 days of diagnosis.[5,6] Factors associated with higher mortality include immunosuppression, cirrhosis, vascular disease, and failure to have received influenza or pneumococcal vaccination. Worldwide, the best estimate of sepsis incidence is 48.9 million cases per year (in 2017), with 11 million deaths; almost half of those deaths were in children.[7] While the tally is not yet complete, the worldwide pandemic caused by severe acute respiratory

syndrome coronavirus type 2 (SARS-CoV-2) has contributed to over 194 million sepsis cases and over 4.1 million deaths as of July 2021.

Brief history

While infection-related deaths have been recognized since the beginning of recorded medical history, the modern definition of sepsis has been fine-tuned over the last 3 or 4 decades with increasing awareness of molecular and clinical factors, immunology, and vascular responses. The first formal definition was published in 1992 and categorized patients on a continuum including systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis (evidence of infection with organ dysfunction), septic shock, and multiple organ dysfunction syndrome (MODS).[8] However, the definition has evolved through the efforts of the international Surviving Sepsis Campaign (SSC) and a series of guideline statements that are updated every 4 or 5 years.

The most recent SSC guidelines were published in 2017 and were supported by publication of implementation advice and care bundles to optimize procedures and processes.[1,9] This version of the SSC guidelines utilized the Sepsis-3 definition, which describes sepsis as a dysregulated host response to infection and septic shock as a subset with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality.[1,9] However, much of these guidelines is based on data from older sepsis definitions and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology along with meta-analysis and input from multiprofessional international experts. These guidelines direct therapeutic interventions that will not be discussed in here but include early empiric antimicrobial therapy, fluid resuscitation with dynamic assessment of hemodynamic endpoints, source control, and optimized supportive

care measures. Guidelines for the management of patients with severe COVID-19 and sepsis are also available. These are similar to the prior sepsis guidelines, with discussion of specific therapies for viral sepsis.[10]

Definition of sepsis/shock vs other shock states

Shock may develop because of cardiogenic, hypovolemic, obstructive, or distributive/vasodilatory etiologies. Septic shock is the most common form of distributive/vasodilatory shock related to release of vasoactive mediators such as prostacyclin and nitric oxide (NO). These mediators suppress autoregulation of blood flow and perfusion in central, regional, and microcirculatory beds and produce vasodilation and eventually hypotension. The hypotension is exacerbated by inflammatory injury to the vascular endothelium leading to loss of integrity and increased permeability with leakage of fluid and protein into the perivascular tissues and lymphatics (historically known as third-spacing). Thus, septic shock has elements of hypovolemic shock. Septic shock may also have features of cardiogenic shock because of myocardial depressant effects of a variety of circulating mediators.

Identification of patients with possible sepsis has been facilitated with electronic early warning systems that look for a pattern in signs and symptoms of monitored patients.[11] A systematic review indicated that early warning via digital alerts of possible sepsis and a rapid clinical response is associated with reduced hospital and intensive care unit length of stay. However, since sepsis is a syndrome, clinical assessment is needed to confirm a diagnosis and exclude other causes of abnormal vital signs. Digital sepsis markers may include at least 2 positive SIRS criteria and a suspected or present source of infection; abnormal temperature (>38°C or <36°C), elevated respiratory rate (>20 breaths per minute),

elevated heart rate (>90 beats per minute), abnormal white blood cell count (<4,000/mm^3 or >12,0000/mm^3). The presence of hypotension (systolic blood pressure of <90 mm Hg) or an elevated lactate level are considered severe sepsis (per the older definition), and septic shock is defined as persistent sepsis despite fluid resuscitation. Clinical signs such as fatigue, weakness, sweating or clammy skin, blotchy or discolored skin, and nausea, vomiting, or diarrhea help to establish a presumptive sepsis diagnosis. Laboratory values can also help reinforce the diagnosis of sepsis and identify the cause of the infection. Sampling blood, urine, and sputum for culture or infection detection through use of biomarker panels and drawing blood for laboratory assessment of chemistry, hematology, and coagulation values are routine and will be discussed in greater detail. Appropriate imaging should be done to further define a potential site of infection, such as the lungs (pneumonia), when indicated by the clinical examination.

Clinical manifestations of sepsis

Infection triggers a complex set of pathways that are intended to recognize the infection, control spread of the pathogen, and initiate repair mechanisms. Most episodes resolve with some localized inflammation (warmth, redness, and swelling), but a more severe or generalized infection or one caused by a virulent pathogen can trigger a systemic response (eg, fever, tachycardia, tachypnea) and progress to involve tissues at other sites, organ dysfunction, and ultimately shock. The most common sites of infection are pulmonary, abdominal, or in the urinary tract, and these should be examined as possible sources. Initially, compensatory sympathetic mechanisms reduce the ability to detect a progressive illness, until they are exhausted and a sepsis symptoms become profoundly

apparent. Clinicians should be cognizant of the subtle initial findings and have a high index of suspicion for sepsis when these are present.

Immune response to infection

The immune response to infection includes a complex array of cellular and chemical mediators that flow in cascades leading to activation or inhibition of other components, depending on the microenvironment and probably the timing of the process (Figure 1).[12] When balance of these counterregulatory processes is maintained, homeostasis will be readily restored after infection or injury. When the process is significantly dysregulated, the consequences may be severe, leading to progressive inflammation and MODS. As will be discussed below, there is substantial cross talk and interaction between the immune response, coagulation system, tissue injury processes, and inflammatory vs anti-inflammatory effects. Therapies that target a single component have largely failed due to unintended effects on interacting processes or perhaps from improper timing of initiation, reflecting our nascent understanding of those processes. The recent pandemic of SARS-CoV-2 infection has accelerated the understanding of viral inflammatory pathways while further illustrating our knowledge deficiencies.

Chemical and immune mediators

When a pathogen breaches the physical barriers of the skin or the gastrointestinal, respiratory, or genitourinary tracts, it triggers an immune response. The specific responses are related to the inciting pathogen, load, and virulence. Most rapid is an innate response of fluid-phase and cellular defense mechanisms mounted within minutes to hours based on recognition of molecular patterns of a previously encountered pathogen. The innate

response includes a highly interactive response that includes white blood cells (neutrophils, monocytes, and macrophages), dendritic cells, innate lymphoid cells, and the complement system.[13] Neutrophils represent 50% to 70% of circulating leukocytes and are effector cells of the innate immune system. The activated neutrophil goes through stages that include chemotaxis to trigger migration to the site of injury, rolling along the vascular endothelium, adhesion, and penetration through the vascular wall. Chemotaxis is impaired during conditions that are associated with increased susceptibility to infection, such as diabetes mellitus, viral infections, and tropical diseases, as well as persistent sepsis. Once the neutrophil has found and recognized a pathogen, phagocytosis, or ingestion, leads to superoxide anion production of reactive oxygen species (ROS) in a controlled fashion within the phagolysosome. In sepsis, ROS production may be uncontrolled and cause local release of these toxic substances, leading to more widespread inflammation and increased microvascular permeability (Figure 2).[14] Neutrophils also use nonoxidative mechanisms to kill pathogens by fusing granules containing digestive protease enzymes with the phagolysosome. Excessive inflammation may lead to widespread degranulation and release of proteases, leading to more systemic and local endothelial damage. The third important mechanism for pathogen elimination is formation of neutrophil extracellular traps (NETs) through release of DNA, chromatin, and granule proteins for extracellular killing. The neutrophil may die during this process, referred to as NETosis, which is discussed later in this article. Immature neutrophils, or bands, are identified via a complete blood count and are a marker of progressive infection indicating early release of neutrophils from the marrow.

As mentioned, the innate response occurs when a pathogen is recognized from prior exposure. It is an interaction between pathogen-associated molecular patterns (PAMPS) and

pattern recognition receptors (PRRs) that activate and amplify the immune response leading to the clinical and cellular manifestations of sepsis (Figure 3).[15,16] Common PRRs include toll-like receptors (TLRs), retinoic acid inducible gene 1 (RIG-1)–like helicases, and nucleotide oligomerization domain (NOD) leucine-rich proteins; these are collectively known as inflammasomes. The various TLRs are specific to the pathogen (bacterial, viral, or fungal, etc.). The inflammasomes trigger other pathways such as complement (C), phagocyte, and natural killer (NK) cell pathways.[17] Specifically, TLRs trigger a cascade leading to activation of cytosolic nuclear factor kappa B (NF-κB) that induces genes to produce proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), chemokines such as intracellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1), and NO and other ROS. Tissue injury triggers a similar cascade when damage-associated molecular patterns (DAMPS) such as the high mobility group protein B1, heat shock proteins, S100 proteins, mitochondrial DNA, and other metabolic molecules cause similar pathological or clinical processes.[16,18] The innate immune response is designed to eradicate the DAMPs and PAMPs but has the potential to become excessively activated in sepsis and lead to overwhelming inflammation.

An additional pathway for pathogen clearance is the C system. It is a cascade of proteins that are part of the innate immune defense but also impact tissue regeneration and renovation, embryogenesis, and neuronal junction regulation.[17] The many soluble and surface-bound proteins in the C system interact through 3 main pathways leading to activation of C3 and C5. These anaphylatoxins (C3a and C5a) form a complex to lyse bacteria, stimulate phagocytosis, trigger an oxidative burst, and amplify inflammation. Excessive amounts of C5a lead to neutrophil dysfunction and reduced bacterial killing, indicating that a deficiency or excess are both problematic. Complement activity is regulated

by soluble and cell membrane–bound inhibitors. Some PAMPs such as endotoxin can upregulate the number of C3a receptors on neutrophils and enhance the immune response, triggering NET formation. Complement release may also injure endothelial barriers and contribute to endothelial and organ dysfunction.[19]

The upregulation of inflammatory gene transcription and activated neutrophils contribute to the second phase of immunity known as the adaptive response in the days post infection (Figure 1).[12] Lymphocytes are released from hematopoietic stem cells in the marrow. In circulation, B lymphocytes mature into plasma cells that produce organism-specific antibodies. Antibodies attach to antigens and mark the invader for destruction by other immune cells, including macrophages that engulf and clear cellular debris and microbes through phagocytosis.

Another group of lymphocytes migrate to the thymus gland for activation and mature into distinct subtypes known as helper, killer, or regulatory T cells that produce cytokines. A surface glycoprotein, cluster of differentiation (CD) determines the role. The type 1 helper T cell (Th-1) secretes proinflammatory cytokines (TNF-α, IL-1β, IL-2, and interferon-ɣ), and type 2 (Th-2) secretes anti-inflammatory cytokines (IL-4, IL-10, and IL-13). Both have CD4+ surface markers. Killer T cells exhibit CD8+ surface markers. Dendritic cells are accessory cells for communication between the innate and adaptive systems and are in tissues that serve as a barrier with the external environment, such as skin and the lining of the nose, lungs, or gastrointestinal tract; and within most lymphoid tissue. Dendritic cells process antigen material from pathogens and present it to the T cells, leading to additional recruitment and inflammation through cytokines and chemokines. They also help B cells maintain their immune memory. Another member of the cell line, hemophagocytic

macrophages, may be activated and contribute to the anemia, lymphopenia, and thrombocytopenia seen in severe infections by destroying healthy tissue and cells.

An important location for immune cells is the gastrointestinal-associated lymphoid tissue (GALT), where there is a well-regulated interplay between antigen-presenting dendritic cells, intestinal macrophages, and adaptive immune cells.[20] This local immune response neutralizes luminal PAMPs and bacteria and can secrete cytokines in response to an invader; this is an important part of the innate immune response. With hypoperfusion, the gut barrier may be disrupted, allowing translocation of bacteria and PAMPs and triggering an inflammatory response in the portal and lymphatic circulation that can worsen shock. These mediators flow to the liver, causing hepatic inflammation and amplification of the response leading to systemic injury. The complex of changes in the intestinal microbiome that occur with a reduction in protective anaerobes has been termed a *pathobiome* and can further contribute to local inflammatory dysregulation. Antibiotics, proton pump inhibitors, opioids, vasopressors, and parenteral instead of enteral feeding can alter the microbiome.[21] Thus, a multitude of immune cells and mediators contribute to and fuel the inflammatory response in sepsis.

Excessive release of inflammatory mediators has been termed *cytokine storm* although the intensity and specific pattern of mediators depends on the timing of measurement and nature of the pathogen and there is no universal definition.[22] Despite various potential triggers, clinical features are similar, with fever, fatigue, anorexia, headache, rash, diarrhea, arthralgia, myalgia, and neuropsychiatric findings. While organ dysfunction may follow these episodes, it is unclear whether it is a directly cytokine-induced injury or the combined impact of inflammation, coagulation, and direct tissue injury. Specific markers of inflammation have been measured, including elevations in nonspecific C-reactive

protein (CRP), D-dimer, and ferritin as well as hypertriglyceridemia, leukocytosis or leukopenia, anemia, and thrombocytopenia. Cytokines including INF- ɣ, IL-6, IL-10, and soluble IL-2 receptor α (IL-2ra, a marker of T cell activation) may be measured and are variably elevated in sepsis, but cytokine levels are typically not emergently available to guide treatment decisions. Cytokine storm is a potential concern in patients with COVID-19, but the cytokine and inflammatory marker values reported so far in these patients were not higher than those observed in other sepsis syndromes, acute respiratory distress syndrome (ARDS), or hemophagocytic lymphohistiocytosis (HLH) or following treatment with chimeric antigen receptor (CAR) T-cell therapy.[23] In any of these conditions, a failure of negative feedback mechanisms likely contributes to unregulated inflammation, although application of anti-inflammatory therapies has not been demonstrated to have a consistent outcome benefit; discussion of these therapies is beyond the scope of this article but has been reviewed in detail.[22] Dexamethasone therapy for up to 10 days was shown to be an effective anti-inflammatory therapy for patients with COVID-19 requiring oxygen, and anti-interleukin agents may be added for selected patients with rapid respiratory deterioration.[24]

While inflammation was historically thought to be the biggest problem in sepsis, it is now hypothesized that an anti-inflammatory response can lead to a longer-term critically ill state and greater susceptibility to secondary infections. This has been termed *persistent inflammation-immunosuppression and catabolism syndrome* (PICS) and is characterized by prolonged critical illness, organ dysfunction, protein catabolism, and poor nutrition. Patients may exhibit weakness, cachexia, and poor wound healing leading to poor functional outcomes, the need for discharge to a facility for ongoing care, and ultimately low survival.[25] It is proposed that in some patients with acute sepsis, the bone marrow is repopulated with hematopoietic stem cells and immature myeloid cells. The normal maturation of immature

myeloid cells may be blocked and the cells instead may become myeloid-derived suppressor cells (MDSCs), resulting in the expansion of a heterogeneous population of these cells with immunosuppressive and inflammatory properties.[26] Data establishing an association between these cellular changes and PICs are limited, and research is ongoing, and a broad array of therapeutic interventions will likely be needed to impact outcomes. Another contributor to PICs may occur after macrophages clear dead cells through phagocytosis and their processes shift toward a more anti-inflammatory profile. Regardless of the specific mechanism, it is apparent that the immune system may become downregulated and dysfunctional, rendering the host more susceptible to infection or unable to clear existing infection.

Coagulopathy

The immune response to infection does not occur without complex interaction with other systems, including the coagulation system. Sepsis is characterized by a shift in balance toward procoagulant factors and a decrease in natural anticoagulants. Cytokines promote the expression of tissue factor from a variety of cells, including monocytes, stimulating the extrinsic coagulation system and factor VII and thrombin activation along with the intrinsic system, causing further amplification. The complex interplay of pro- and anticoagulation forces in healthy and dysregulated states is illustrated in Figure 2.

Platelets

Platelets are an important component of coagulation, providing a rapid response following vascular injury. Activated platelets recruit neutrophils to the site of inflammation, secrete adenosine diphosphate (ADP), von Willebrand factor (vWF), thromboxane A2,

growth factors, serotonin, and coagulation factors. The integrins are a group of receptors on the platelet that are known best for their use in glycoprotein IIb/IIIa inhibitor therapies, but there are several others that contribute to aggregation. The P-selectin receptors mediate thrombogenic and inflammatory responses by interacting with neutrophils, monocytes, and T-lymphocytes. However, platelets also trigger endothelial cell release of unusually large vWF multimers that anchor to the endothelial cells in long strips and further recruit activated platelets, further contributing to microthrombi (Figure 2).[14] The combination of inflammation and microthrombi leads to endothelial cell damage and macrothrombosis with alterations of critical tissue perfusion. Consumption of activated platelets leads to thrombocytopenia, a common finding in sepsis. Thrombocytopenia is an important risk marker of prognosis, like other biomarkers, though persistently low values or a downward tangent may be more important than the absolute value measured.[27]

The role of therapeutic anticoagulation remains poorly defined for most patients with sepsis. The challenges of coagulopathy are magnified in COVID-19, with widespread reports of micro- and macrovascular thrombosis despite prophylactic anticoagulation.[28] A leading hypothesis is related to viral entry into endothelial cells and endotheliitis, hyperinflammation, with platelet and NET interactions (NETosis); see Figure 2.[14] Tissue NETs have a beneficial effect by trapping circulating bacteria, viruses, and other pathogens, but also cause platelet activation, aggregation, and further promote thrombosis by triggering factor V activation and thrombin generation.[29,30]

In a normal state, the endothelium maintains a balance between endogenous coagulation and anticoagulation. Sepsis may reduce production of natural anticoagulants such as antithrombin III (ATIII), activated protein C (aPC), protein S, thrombomodulin (TM), and tissue factor pathway inhibitor (TFPI) by the vascular endothelium, leading to a

procoagulant state with excessive thrombin and fibrin production.[31] Attempts to replace individual forms of these anticoagulants have not been consistently helpful in improving patient outcomes.[32]

Thrombosis and fibrin clot formation is balanced by a fibrinolytic mechanism. Plasmin is the only activator of fibrinolysis, and the balance between tissue-derived plasminogen activator (PA) and PA inhibitor 1 (PAI-1) in turn regulates plasmin activity. Sepsis is complicated by a failure of endogenous fibrinolytic pathways due to elevated PAI-1 and thrombin-activated fibrinolysis inhibitor, contributing to persistence of thrombosis.[33] Hypercoagulation may lead to consumption of coagulation factors and in its extreme can lead to disseminated intravascular coagulation (DIC) and a vicious cycle of thrombosis and bleeding. In sepsis, the D-dimer level is a biomarker of the degree of thrombosis and thrombolysis but may be elevated in a variety of other conditions, including venous thromboembolism, DIC, malignancy, and trauma. Significant D-dimer elevation in sepsis is generally associated with poor prognosis, although it may not occur in sepsis when the fibrinolytic pathway is highly suppressed. D-dimer elevations are reported in the most critical COVID-19 cases, and the response to therapeutic anticoagulation may be an important outcome predictor. Failure to lower D-dimer or a trend of higher levels after anticoagulation has been associated with higher mortality in patients with COVID-19, especially those with 3- to 4-fold D-dimer increases.[34,35] Individual D-dimer assays report specific ranges, and clinicians need to note the format of units (µg/mL vs µg/L).

Many septic patients present with elevated neutrophils, facilitating the diagnosis of infection. However, neutropenia (defined as an absolute neutrophil count of <1,500/µL) may also occur in overwhelming sepsis due to consumption and/or marrow suppression and is a poor prognostic sign. Neutrophil turnover is usually precisely controlled by a variety of

mechanisms. As mentioned, NETosis leads to rapid neutrophil consumption, lysis, and release of alarmins, proteolytic enzymes, and radical oxygen species. It is a type of programmed cell death, or apoptosis.[14,36] Another form of cell death is autophagy, defined as degradation of cell components in a lysosome. Autophagy is an important component of the inflammatory system, helping the host to activate immune responses and limiting the degree of uncontrolled inflammation by removing inflammatory cells and unneeded proteins that would otherwise lead to chronic inflammation.

As discussed, injury to the vascular endothelium from inflammation/thrombosis leads to increased permeability—which is a benefit in that it allows neutrophils to penetrate to a site of injury/infection but also a detriment when triggered in other vascular beds, leading to leakage of proteins and fluid into the extravascular tissues. An important component of the vascular endothelium is the glycocalyx (Figure 2).[14] This is a gel-like layer covering the luminal surface of the vascular endothelium.[37] It was once thought to be a passive physical barrier but is now known to be an active biochemical regulator of permeability, thrombosis, cytokine signaling, and other processes. This layer is damaged during inflammation after activation of metalloprotease, heparinase, and hyaluronidase enzymes by cytokines and ROS. Further, sepsis therapy with overaggressive fluid resuscitation leading to vascular overdistention also contributes to glycocalyx degradation due to physical shear forces, and atrial natriuretic peptide released from atrial stretching is also a trigger for injury.[38,39] Susceptibility to injury varies in different organ systems, in part due to the glycocalyx's thickness and the amount of negatively charged proteins within the gel. Sepsis contributes to decreased thickness that can be measured by orthogonal phase spectrometry in the sublingual microvasculature and by several other methods, primarily for research purposes.[40] Albumin is a positively charged molecule that interacts with the

glycocalyx components and acts to regulate the gradient across the vascular endothelium, and while it may be protective, it has not been shown to impact patient outcomes.[41] Thus, the volume and type of fluid used in resuscitation is important. With injury, measurable components of the glycocalyx such as syndecan-1, heparan sulfate, and hyaluronan are released into circulation and may become useful clinical biomarkers for prognostication.[37,39] It appears that avoidance of over-resuscitation and volume overload are important factors in sepsis outcome and that attention to the microcirculation is as important as attention to the macrocirculation. Pharmacists can play an important role in optimizing fluid resuscitation.[42]

Conclusion

An understanding of the pathophysiology of sepsis at the cellular level is important to appreciate the complex nature of intersecting pathways in sepsis and factors contributing to organ dysfunction. The clinical manifestations of sepsis and organ dysfunction are obviously important to a clinician and will be discussed in part 2 of this series.

Disclosures

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Figure 1. Illustration of the many potential pathways and responses in sepsis.[12] In sepsis, host response is characterized by 2 mechanisms: a physiologic defensive mechanism

mounted through immune system and a pathologic destructive mechanism mounted through the endothelial system. The physiologic response and pathologic clinical syndromes are notated in this figure. It is now known that the complement system, while protecting the host through activation of its innate immune system, could trigger harmful endothelial pathogenesis. This dual role of the complement system can be viewed as similar to normal hemostasis, which protects humans in the event of external bodily injury but also may cause harm in the form of intravascular injury through thrombogenesis. APC indicates antigen presenting cell; DIC, disseminated intravascular coagulation; DIT, disseminated intravascular microthrombosis; EA-VMTD, endotheliopathy-associated vascular microthrombotic disease; MAHA, microangiopathic hemolytic anemia; MODS, multiorgan dysfunction syndrome; MOF, multiorgan failure; NO, nitric oxide; IF, interferon; IL, interleukin; LPS, lipopolysaccharide; SIRS, systemic inflammatory response syndrome; TNF, tumor necrosis factor; TTP, thrombotic thrombocytopenic purpura.

Figure 2. Sepsis-induced dysregulation leads to activation of coagulation, with inflammatory changes in the glycocalyx leading to microvascular coagulation and thrombus formation.[14] Both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) can stimulate monocytes through specific pattern-recognizing receptors expressed on the cell surface. Activated monocytes release cytokines and chemokines that activate platelets, neutrophils, and endothelial cells. Monocytes and other cells release extracellular vesicles (EVs) that express procoagulant tissue factor (TF) and phosphatidylserine (PS) on their surfaces. Healthy endothelial cells maintain their

antithrombogenicity by producing nitric oxide (NO) and prostacyclin (PGI2) and expressing glycocalyx and its binding protein antithrombin (AT). Damaged endothelial cells change their properties to procoagulant after disruption of the glycocalyx, with expression of ultralarge von Willebrand factor (VWF). Neutrophils play pivotal roles in the activation of coagulation by expressing tissue factor and releasing granule proteins and chemical mediators. Neutrophils also activate coagulation by expelling neutrophil extracellular traps (NETs) through NETosis. NETs are composed of procoagulant DNA, histones, and other DAMPs. cf-DNA indicates cell-free deoxyribonucleic acid; HMGB1, high-mobility group box; RBC, red blood cell (erythrocyte); PAI-1, plasminogen activator inhibitor 1. Reproduced, with permission, from reference 14.

Figure 3. The acute inflammatory response mediated by the release of pro-inflammatory cytokines. Mediators of inflammation and the systemic response may be triggered by pathogens or by cellular injury.[16] Following pathogen-associated molecular pattern (PAMP) or damage-associated molecular pattern (DAMP) recognition, pattern recognition receptors (PRRs) trigger proinflammatory and antimicrobial responses by inducing the release of a broad range of cytokines. The archetypical pro-inflammatory cytokines tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), and interleukin-6 (IL-6) are rapidly released upon PRR activation, and they all act as endogenous pyrogens by increasing the hypothalamic thermoregulatory set-point. In addition, TNF-α and IL-1β orchestrate the release of chemokines and expression of leukocyte adhesion molecules on vascular endothelium, promoting the rapid and efficient recruitment of leukocytes towards inflammatory foci. TNF-α is also responsible for multiple hallmark signs of inflammation by inducing local vasodilation (rubor and calor) and vascular leakage (causing swelling).

Furthermore, IL-1β evokes inflammatory hyperalgesia and is well known for its induction of IL-6. IL-6, in turn, is a major inducer of acute-phase protein production by hepatocytes. Reproduced from reference 16, an open access article distributed under the terms of the Creative Commons Attribution License.

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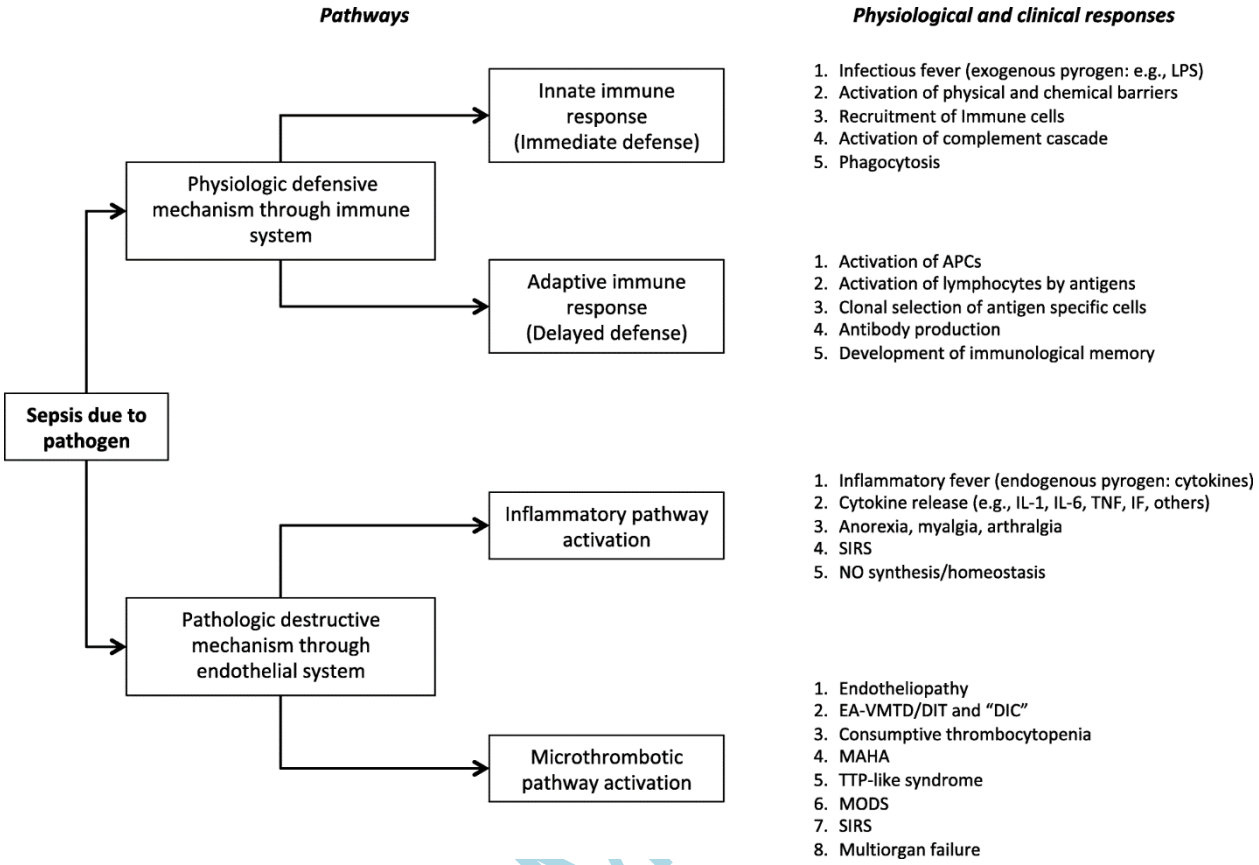
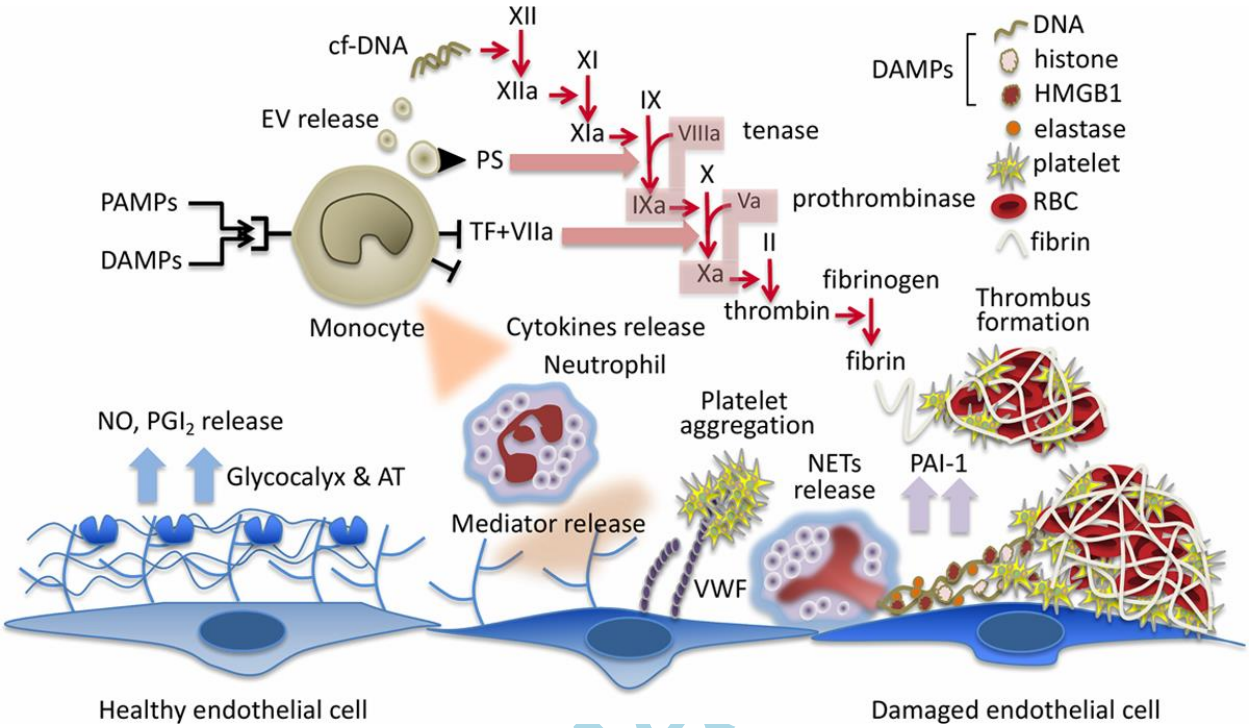
Key Points

- Pharmacists should understand key inflammatory pathways involved in sepsis syndrome as a prelude to application of novel anti-inflammatory therapies.
- Coagulopathy and thrombosis are important pathways in sepsis that can lead to endothelial injury and organ dysfunction.
- Dysregulation of chemical and molecular mediators of the immune response contribute to poor outcomes in septic shock.

[fig 1]



[fig 2]



[fig 3]