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The Coagulopathy of Acute Sepsis

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Abstract

Purpose of Review—Sepsis, defined by the presence of infection and host inflammation, is a lethal clinical syndrome with an increasing mortality rate worldwide. In severe disease, the coagulation system becomes diffusely activated, with consumption of multiple clotting factors resulting in Disseminated Intravascular Coagulation (DIC). When present, DIC portends a higher mortality rate. Understanding the mechanisms that tie inflammation and diffuse thrombosis will allow therapeutic interventions to be developed. The Coagulopathy of Acute Sepsis is a dynamic process that is time and disease burden specific. Whole blood testing of coagulation may provide more clinically useful information than classical tests. Natural anticoagulants that regulate thrombosis are down regulated in sepsis. Patients may benefit from modulation of the coagulation system when systemic inflammation and hypercoagulopathy exist. Proper timing of anticoagulant therapy may ultimately lead to decreased incidence of multisystem organ dysfunction (MODS).

Recent Findings—The pathogenesis of coagulopathy in sepsis is driven by an up-regulation of procoagulant mechanisms and simultaneous down-regulation of natural anticoagulants. Inflammation caused by the invading organism is a natural host defense than cannot be eliminated during treatment. Successful strategies to prevent MODS center on stratifying patients at high risk for DIC and restoring the balance of inflammation and coagulation.

Summary—The prevention of DIC in septic patients is a key therapeutic target in preventing death from multisystem organ failure. Stratifying patients for therapy using thromboelastometry, specific markers for DIC, and composite scoring systems is an area of growing research.

Keywords

Sepsis; Coagulopathy Thrombosis; and Inflammation

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INTRODUCTION

Sepsis has been used to describe the dynamic and often life-threatening systemic host response to infection. For centuries, physicians have sought for clues to curb the burden of disease. In 1841, the Austrian physician Ignaz Semmelweiss observed, “The fingers and hands of students and doctors, soiled by recent dissections, carry those death-dealing cadaver’s poisons into the genital organs of women in childbirth.” From this astute observation, protocols for proper hand hygiene were developed in his local maternity ward and fetal deaths from sepsis dropped from 16 to 3%.[1]

Today, sepsis remains a leading cause of death worldwide and has an incidence between 75–300 per 100,000.[2, 3] In the United States, the economic burden of sepsis is astounding. Nearly $24 billion dollars are spent annually on septic patients with an increasing trend.[4] Sepsis alone carries a 25% mortality rate, but when combined with organ failure, this mortality rate doubles.[3]

Currently, much attention has been focused on the inflammatory host response in sepsis. Indeed, septic patients exhibit several biological markers for inflammation that often precede organ failure providing a causal relationship between the two.[5] The inflammatory response to infection may ultimately serve as a protective mechanism against microbial invasion, however when exaggerated due the severity of disease can ultimately lead to multisystem organ dysfunction (MODS). Inflammation and disturbances in coagulation are inseparably tied, with each acting as positive feedback for activation of the other.[6] Coagulation abnormalities are nearly universal in septic patients and likely play a key role in in MODS.[7] The Coagulopathy of Acute Sepsis (CAS) varies from overt thromboembolic disease to microvascular fibrin deposition. In severe cases, fulminant DIC presents with both thrombosis and diffuse hemorrhage.

CAS is likely driven by derangements of multiple pathways versus a single mediator which explains why many singe therapies have failed to improve outcomes.[4] This review will discuss the pathogenesis of coagulopathy in acute sepsis and how it relates to multisystem organ dysfunction. It will also focus on tools to measure coagulation status and possible therapeutic interventions.

MEASUREMENT OF COAGULATION IN SEPSIS

Measurement of the coagulation disturbances in acute sepsis is a complex and time sensitive endeavor that is best interpreted through serial measurements. Classical coagulation laboratory tests (CCT) such as prothrombin time, partial thromboplastin time, and fibrinogen have several limitations. First, plasma based testing of coagulation eliminates the platelet contribution to thrombosis. Platelets actively contribute to thrombosis by providing a surface for thrombin generation and recruiting clotting factors that propagate the coagulation system.[8] CCTs do not reflect in-vivo blood coagulation and do not provide qualitative or functional data. Alternatives to CCTs such as measurement of natural anticoagulants, markers of fibrinolytic activity, and molecular markers of DIC are not routinely available, are not validated to specific disease patterns, and may not be practical in the clinical setting.

Classical laboratory tests generally suffer from the same downfall: high sensitivity with low specificity. Table 1.

Whole Blood Viscoelastic Testing

Theoretically, viscoelastic measurements of whole blood should provide clinicians with insight into in-vivo coagulation. Used in a serial fashion, the evolution of coagulopathy in septic patients could be identified and used to guide therapy. Ideally, it could provide prognostic value for patients with sepsis that are at risk for developing MODS. Unfortunately, the quality of evidence supporting thromboelastometry (TEM) in routine sepsis monitoring is low to moderate.[9] In addition, studies using TEM in sepsis to determine proper therapy institution are lacking. Also, definitions for hyper- and hypocoagulation are not standardized and internal validity of their use in clinical trials is often a concern.[9] Concerning detection of coagulopathy in sepsis, a variety of studies showed heterogeneous results. Often when compared to CCTs and measured within the first 48 hours, TEM measurements were within normal ranges. Of note, patients that were deemed hypocoagulable (prolonged reaction time, reduced alpha angle, or deceased maximum amplitude) had increased mortality and were associated with DIC more often.[9] In a study of 30 patients with severe sepsis followed over 2 days, patients with higher Sequential Organ Failure Assessment (SOFA) and APACHE II scores had reduced maximum clot firmness and prolonged clot formation time.[10] Thromboelastometry may serve as a beneficial negative predictor for developing coagulopathy.

Concerning the prognostic value of thromboelastometry in determining mortality in acute sepsis, early hypocoagulability was an independent risk factor for 28-day mortality in a series of severely septic patients.[9, 11] Adamzik compared Simplified Acute Physiology Score II (SAPS II) and SOFA scores to ROTEM values and found good correlation between these systems. In fact, pathologically altered values in ROTEM correlated with 58.7% 30-day survival versus 85.7% when all values were normal. In this study of 98 patients, ROTEM predicted survival better than the SAPS II and SOFA.[12] Ostrowski used TEG to monitor severely ill patients upon admission to the ICU. Patients were found to be hypocoagulable 22%, normal 48%, and hypercoagulable 30%. Patients that were hypocoagulable more often progressed to MODS and death. Patients that were normal upon admission and developed hypocoagulation had an 80% mortality rate.[13] A key finding in most studies was that patients that were hypercoagulable or normal upon admission progressed to MODS and death less. This finding may allow for stratification of patients that are high risk of progressing to organ failure.

Platelet aggregometry offers another important viscoelastic measurement in sepsis. The test employs multiple platelet agonist and electrical impedance across coils to determine platelet function in sampled whole blood. Brenner performed multiplate testing in 90 patients, comparing 30 severely septic patients to 30 post-surgical, and 30 healthy patients. Septic patients displayed markedly reduced function to standard agonists compared to post-surgical and healthy volunteers.[14] The effects of thrombocytopenia and dysfunction have been clearly illustrated in the critically ill population, significantly increasing mortality when dysfunction is prolonged over an ICU stay.[15]

Composite Screening for Coagulopathy in Sepsis

Using combined data points to predict patients at risk for developing MODS from sepsis-induced coagulopathy is an area of interest in research. Diagnostic algorithms such as ISTH DIC score, SAPS II, SOFA, and APACHE II combined with classical and viscoelastic measurements may provide the most accurate prognostic values.[16] A 2005 study using composite scoring for coagulopathy revealed an evolution of coagulation disturbances that occurs in the first twenty-four hours of severe sepsis. Worsening coagulopathy in the first day was associated with greater 28-day mortality.[5] Koyama evaluated multiple plasma markers already evident in sepsis such as antithrombin-thrombin complex (TAT), Protein C (PC), and Plasminogen Activator Inhibitor-1 (PAI-1) to estimate mortality and the development of overt DIC. When these plasma markers were combined, the area under the curve in selecting patients that would develop overt DIC was 0.95.[17]

PATHOGENESIS OF THROMBUS FORMATION IN SEPSIS

Post-mortem autopsies of patients with severe sepsis routinely show diffuse bleeding with microvascular thrombus formation and end organ damage.[18] Animal studies utilizing endotoxemia have shown that it causes vascular fibrin deposition resulting in organ failure. Blocking or reversing the coagulopathy in these animals has been shown to reverse organ dysfunction.[19, 20] Finally, clinical outcome studies with patients diagnosed with DIC reveal increased mortality suggesting that prevention of DIC is a key therapeutic target.[21]

Procoagulant Up-Regulation

The host inflammatory response to an invading organism rapidly initiates a procoagulant state in the septic patient. Thrombin generation is detectable within a few hours in models where tumor necrosis factor and endotoxin were infused into human subjects.[22, 23] Additionally, endothelial injury that impairs key anticoagulant mechanisms is observed within 15 minutes of lipopolysaccharide infusion in rabbits.[24]

Key in the development of this procoagulant state is the interaction between tissue factor and inflammatory cytokine release. Tissue factor expression appears to be the initiating event in CAS. Tissue factor is responsible for binding and activating Factor VII on cell surfaces, thereby forming the enzyme-cofactor complex that results in amplified production of Factor Xa. Not only is tissue factor increased early in septic patients, but also impairment of the tissue factor pathway prevents coagulation abnormalities in animals.[25, 26] Debate over the primary source of tissue factor is ongoing as many cell types are capable of expressing tissue factor (TF). Endothelial cells and mononuclear phagocytes such as monocytes and macrophages can express TF, as can lung, kidney, and brain astrocytes.[27] Monocyte microparticles expressing TF in mice have also been shown to activate the coagulation system.[28] Proinflammatory cytokines such as TNF, IL-1, and IL-6 are up regulated after TF expression and play a major role in natural anticoagulant suppression and endothelial damage.[29]

Next, Platelet-Activating Factor (PAF) is directly released secondary to inflammation.[30] Platelet activation results in several accelerators of thrombosis. First, platelet p-selectin expression results in increased monocyte TF expression and platelet adhesion to leukocytes

and endothelium.[31, 32] Once adhered to leukocytes and endothelium, platelets serve as a surface for thrombin generation and cellular signaling of other coagulation factors.[8]

Anticoagulant Impairment

The impairment of three endogenous anticoagulants is evident in severe sepsis and contributes to hypercoagulopathy in the early inflammatory stage. Figure 1.

Tissue Factor Pathway Inhibitor (TFPI) is an early regulator of the coagulation pathway that is activated by tissue factor and FVIIa interaction. TFPI (previously known as Extrinsic Pathway Inhibitor) acts to prevent initial coagulation in two steps. First, TFPI binds to and inhibits FXa. Second, the TFPI-FXa complex binds to and inhibits TF-FVIIa thereby preventing early amplification of coagulation. TFPI is both consumed and degraded in sepsis leading to a procoagulant state.[33] TFPI is consumed quickly due to its relatively small concentration in plasma, approximately 1.0–2.5 nM.[34] Vascular endothelial cell expression of TFPI is also potentially degraded by plasmin, which is up regulated in early sepsis. This effect was demonstrated in baboons infused with E. Coli when TFPI activity was decreased coinciding with maximum TPA activity.[35]

Activated Protein C (APC) is a potent anticoagulant that also has profibrinolytic and antiinflammatory properties. Thus, APC derangement in sepsis significantly contributes to the early hypercoagulability. Protein C is activated by thrombin once bound to thrombomodulin. The Endothelial Protein C Receptor and Cofactor Protein S amplify its activation several fold.[36] Once activated, Protein C proteolytically cleaves Factor V and VII that are essential for the production of thrombin. Protein C synthesis is impaired while consumption and degradation by neutrophil elastase further diminishes its concentration in plasma.[29] Next, thrombomodulin expression is drastically reduced by inflammatory cytokines such as TNFα, IL-1, and IL-6.[37] Finally, EPCR is down regulated in severe sepsis thereby limiting activation of Protein C. Evidence also shows that due to endothelial damage, EPCR might be shed and not available for protein C augmentation. This effect occurs as early as day two in severe sepsis.[38]

The serine protease Antithrombin is a natural antagonist to thrombin that is activated several fold by circulating heparin-like substances. In severe sepsis, antithrombin synthesis is down regulated and consumption is markedly increased due to ongoing thrombin formation.[39] In addition, membrane bound heparin-like glycosaminoglycans on the endothelial surface are reduced by proinflammatory cytokines. This reduction further limits the bioactivity of antithrombin.[40]

Resistance To Fibrinolysis

In healthy human volunteers, the infusion of endotoxin produced a predictable and rapid change in the coagulation system. First, within 120 minutes inflammatory markers such as TNF and IL-6 rose with a concurrent rise in plasminogen activators indicating endothelial activation. Within 150 minutes, this was counteracted by an even greater and sustained rise in plasminogen activator inhibitor (PAI) thus supporting clot longevity.[23] It appears that both activated endothelial cells and platelets can express PAI.[41] Finally, the reduction in activated protein C (APC) due to reduced availability of thrombomodulin may also play a

role in decreased fibrinolysis. Less APC is available to inhibit PAI thus augmenting clot stability.[42]

Thrombin induces the formation of thrombin-activatable fibrinolysis inhibitor (TAFI), a protease enzyme that reduces clot permeability and increases clot firmness.[43] In sepsis, tissue factor mediated thrombin production and inflammation produces dense clots that are resistant to fibrinolysis. This is thought to be mediated by both TAFI and platelet polyphosphate secretion that makes TPA less effective.[44, 45] In addition, the secretion of neutrophil elastase degrades fibrinolytic proteases contributing to clot persistence. The production of such a tightly aggregated clot could be a mechanism of defense against bacterial secreted proteases that break down clot integrity and allow for dissemination.[46] In patients with meningococcal infections TAFI levels are markedly increased, correlate with disease severity, and is associated with higher mortality.[33]

Endothelial Damage

The vascular endothelium is an important regulator of hemostasis and a site of cellular interaction for immune cells. Endothelial cells (EC) mediate pro- and anti-inflammatory mechanisms, regulate fibrinolysis, regulate vasomotor tone, and have immune cell signaling capabilities.[47] Thus, the endothelium acts as an important barrier for host defense in bacterial invasion. The surface layer of endothelial cells is a negatively charged, micro-thin layer of glycosaminoglycans and glycoproteins called the glycocalyx. The intact glycocalyx repels circulating platelets and acts as an anticoagulant layer due to its rich supply of heparin sulfates.[47] Ideally, the endothelium can balance procoagulant and anticoagulant mechanisms after injury thereby opposing thrombin generation when vascular repair is complete. However, when local injury becomes systemic, as in sepsis, the balance shifts towards a procoagulant state.[48]

Increased vascular permeability secondary to inflammation is a hallmark of sepsis and contributes significantly to organ dysfunction and possibly coagulation disturbances. Because inflammation and coagulation are closely tied, therapies involved in endothelial protection may benefit coagulation abnormalities. Table 2 lists the multiple mechanisms that are implicated in endothelial damage leading to increased permeability.[48–52]

The early shift towards a procoagulant state in sepsis is mediated by proinflammatory markers that result in decreased expression of membrane bound proteins such as thrombomodulin.[53] Endothelial injury also causes shedding and decreased expression of EPCR.[38, 54] The down regulating effect of this on the Protein C pathway has been described earlier. Endothelial cellular apoptosis resulting from LPS or endotoxin causes intracellular histone release that exacerbates inflammation and induces thrombosis. Endothelial disruption in inflammatory syndromes such as sepsis results in rapid platelet adhesion that can lead to microvascular thrombosis.[50] Cumulatively, destruction of the endothelial cell layer importantly contributes to early coagulopathy in sepsis.

DISSEMINATED INTRAVASCULAR COAGULATION

Clinically, DIC is defined by simultaneous diffuse thrombosis and bleeding. Consumption of clotting factors due to ongoing thrombosis eventually leads to a hypocoagulable state. Relevant coagulation abnormalities are present in 50 to 70% of patients with severe infection, whereas about 35% of patients will actually meet the criteria for DIC.[55] The hallmark for treating DIC remains to eradicate the underlying cause of disease and support coagulation derangements as they occur. The manifestations of DIC though must still be addressed quickly as the mortality associated with this grave diagnosis is high. Diagnostic criteria for DIC have been developed that employ common lab and clinical criteria. The criteria can be used clinically to distinguish overt DIC with diffuse bleeding and non-overt DIC where anticoagulation therapy could be useful.[4]

PATHOGENESIS OF MULTISYSTEM ORGAN DYSFUNCTION

Severe sepsis associated organ dysfunction occurs due to multiple interactions between the proinflammatory state and hypercoagulation. The role of DIC as a causative factor in MODS is well supported. Alternatively, recent work has led to our understanding of other mediators of MODS, namely the effect of necrotic and apoptotic cellular release of intracellular proteins. High mobility group box 1 (HMGB-1) proteins originate from dying cells, are released into the host circulation causing systemic inflammation, and propagate thrombosis.[56] Macrophages, endothelial cells, and monocytes are all capable of releasing HMGB-1 proteins. These cytokine-activating proteins are persistently elevated in septic patients and are associated with lethality in mice models.[56] Other intracellular released proteins such as histones associated with neutrophil extracellular traps (NETS) are highly toxic to organs, induce inflammation, and promote thrombosis.[32, 57, 58] NETS are cast by inflammatory cytokines and platelet activation and are comprised of histone rich DNA fibers and antimicrobial proteins.[58] Histones (H3 and H4) induced thrombin generation by multiple mechanisms. First, extracellular histones dose dependently impair thrombomodulin activation of Protein C thereby reducing the natural anticoagulant APC and eliminating its anti-inflammatory properties.[57] Secondly, thrombin production was increased by histone mediated platelet activation and p-selectin expression. P-selectin expression increases platelet adhesion to endothelial cells and leukocytes.[32] Thus, HMGB-1 and histone release in to the circulation augment inflammation and thrombosis, promote cellular death, and potentiate multisystem organ dysfunction.[33]

THROMBOSIS AS A PROTECTIVE MECHANISM IN SEPSIS

Our understanding of thrombosis and inflammation in sepsis has evolved over decades of animal and human research. A key to understanding our early misconception of sepsis lies in how early animal studies were conducted. Commonly, models of mice employed intravenous administration of endotoxin or lipopolysaccharide (LPS) or even live bacteria such as *E. Coli*. Models of LPS and endotoxin infusion tended to uniformly overestimate the proinflammatory response in the host.[59, 60] Thus, early efforts targeted inflammation alone as a mediator of sepsis and were unsuccessful in the clinical setting. Likewise, universally inhibiting the coagulation system had deleterious effects as evidenced by the

higher mortality rate of patients that were hypocoagulable upon ICU admission and higher bleeding tendencies.[61] These strategies ignored the protective mechanism of compartmentalization. Compartmentalization involves the acute phase interaction of the proinflammatory response to elicit coagulation in attempt to sequester bacteria or invading organisms. Acute phase proteins such as fibrinogen and Factor V increase rapidly in acute sepsis augmenting the hypercoagulable response.[55, 62] Simultaneously, two powerful natural anticoagulants, Protein C and Antithrombin are down regulated. PC and AT could be viewed as negative acute phase proteins in this protective early mechanism.[63, 64] Today's model of sepsis is viewed as both proinflammatory and antiinflammatory or MARS (mixed antiinflammatory response syndrome).

THERAPIES DIRECTED TOWARDS MEDIATORS OF SEPSIS

Therapies directed toward the Coagulopathy of Acute Sepsis should ideally restore the balance of inflammation and coagulation without negatively influencing the host's response to infection. Several trials have failed to recognize inflammation as an important protective mechanism or used uniform therapy for patients in different stages of sepsis. Antibodies directed toward TNFα, IL-1 receptors, and endotoxin failed to demonstrate a reduction in mortality.[65–68] The failure of anticoagulant trials to show efficacy may be due to the inclusion of patients without DIC, uncertainty when to initiate treatment, and the tendency to underestimate the importance of bleeding.[69] This exemplifies the importance of developing specific diagnostic criteria for DIC that employs composite scoring systems, advanced markers for DIC, and thromboelastometry.

Tissue Factor Pathway Inhibitor

As described earlier, TFPI is rapidly consumed in sepsis. Earlier studies on the efficacy of TFPI replacement demonstrated that in patients with INR > 1.2, mortality was not changed and adverse bleeding events were increased.[70] However, subgroup analysis of this study did show that in patients with community acquired pneumonia (CAP) there was a trend toward survival. In 2011, Wunderink published results of a large placebo-controlled study in patients with CAP treated with recombinant TFPI and again found no survival benefit though biological activity in improving coagulation parameters was evident.[71]

Antithrombin

Antithrombin inhibits thrombin in a 1:1 manner and is maximally activated after interaction with receptors on the endothelial surface.[72] Antithrombin has antiinflammatory properties through its inhibition of thrombin-Factor X, a complex that stimulates IL-1 and IL-6. Recently, the Japanese Association of Acute Medicine DIC Committee evaluated antithrombin use in a prospective RCT. Patients with DIC treated with antithrombin over 3 days had faster recovery determined by DIC scores and did not have increased bleeding events.[73] In a nonrandomized larger study, Iba determined that in patients with low baseline antithrombin activity and sepsis, high dose antithrombin therapy 3000 IU/day (AT3000) was associated with improved survival (AT1500 65.2%, AT3000 74.7%).[74] Importantly, these studies used DIC scoring systems to determine overt DIC and proper timing of anticoagulation therapy.

Activated Protein C

It has been recognized for several years that a rapid decline in Protein C occurs in sepsis and that low levels of PC correlate with poor prognosis.[26] In 2001, the PROWESS study reported promising results of lower mortality with the use of recombinant APC (Xigris, Eli Lily).[75] However, it was later removed from the market when the PROWESS-SHOCK trial revealed no mortality benefit at 28 or 90 days.[61] Numerous clinical studies since then have looked at subsets of this population and determined that rAPC may have beneficial effects. Caserly evaluated 15022 patients registered with the Surviving Sepsis Campaign and found that groups treated with rAPC had reduced hospital mortality (OR 0.76, $p<0.001$). Also, hospital mortality was significantly reduced in patients that displayed multi-organ failure versus single organ failure (OR 0.82 versus 0.78).[76] A meta-analysis performed by Kalil in 2012 showed mortality benefit in patients with higher disease severity, but higher rates of adverse bleeding than were reported in the PROWESS trial. The results of this study indicated that rAPC could be beneficial in properly selected populations of septic patients.

Thrombomodulin

Thrombomodulin (CD141) is an endothelial transmembrane glycoprotein that has several regulatory functions in hemostasis. By binding thrombin, it prevents fibrinogen conversion to fibrin, and prevents thrombin from interacting with platelets. The thrombin-thrombomodulin complex activates Protein C resulting in a 100-fold increase in activity.[53] Recombinant thrombomodulin (rTM) has been studied in models of DIC and sepsis as well as clinical trials. Hoppensteadt's study of rTM in DIC revealed that markers of thrombin production such as thrombin-antithrombin complex (TAT) and prothrombin fragment (F1.2) are sequentially reduced with rTM treatment.[77] In a study of 234 patients comparing soluble thrombomodulin (ART-123) to heparin in the treatment of DIC caused by malignancy or infection, the rate of DIC resolution was 66.1% with ART-123 versus 49.9% with heparin.[78] In this study, a statistically significant lower rate of adverse bleeding events with ART-123 was noticed. In another study of 86 patients with sepsis induced DIC, mortality was lower and improved sequential SOFA scores were associated with infusion of rTM versus those not treated with rTM (37% vs. 58%, $p = 0.038$).[79] This was confirmed later in a study of 750 patients with sepsis and DIC where patients treated with ART-123 were associated with improved 28-day mortality.[80] Determining the optimal timing for treatment will be important for this promising DIC treatment.

Apoptosis

Model studies of septic mice treated with IL-7 have demonstrated benefit in reducing apoptosis of important CD4 and CD8 T-Cells and improved immune function. IL-7 appears to have anti-apoptotic functions essential to leukocyte survival.[81, 82] Targeting programmed cell death may have an important role in decreasing inflammatory histones and HMGB-1 that are released in to the systemic vasculature of septic patients.[83, 84] Immunomodulation studies such as this reinforce the intimate tie between coagulation and inflammation.

CONCLUSIONS

The host defense to infectious invasion is a highly regulated process involving inflammatory and antiinflammatory processes. In an attempt to compartmentalize invasion, the host creates hemostatic thrombin barriers and dense fibrin networks. Pathologically, these fibrin depositions can result in microvascular thrombus and result in end organ ischemia. Establishing an operational definition of sepsis and DIC that is heralded by biological markers is the first step in constructing new therapeutic trials. Finally, we must improve patient stratification and staging to determine optimal timing of interventions.[85]

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Key Points

- Inflammation and disturbances in coagulation are inseparably tied, with each acting as positive feedback for activation of the other.
- Coagulation abnormalities are nearly universal in septic patients and likely play a key role in multisystem organ dysfunction.
- Coagulopathy in sepsis is likely driven by derangements of multiple pathways versus a single mediator, which explains why many singe therapies have failed to improve outcomes.
- Therapies directed toward the Coagulopathy of Acute Sepsis should ideally restore the balance of inflammation and coagulation without negatively influencing the host's response to infection.
- Therapeutic strategies are time sensitive and should target patients at high risk for developing DIC.

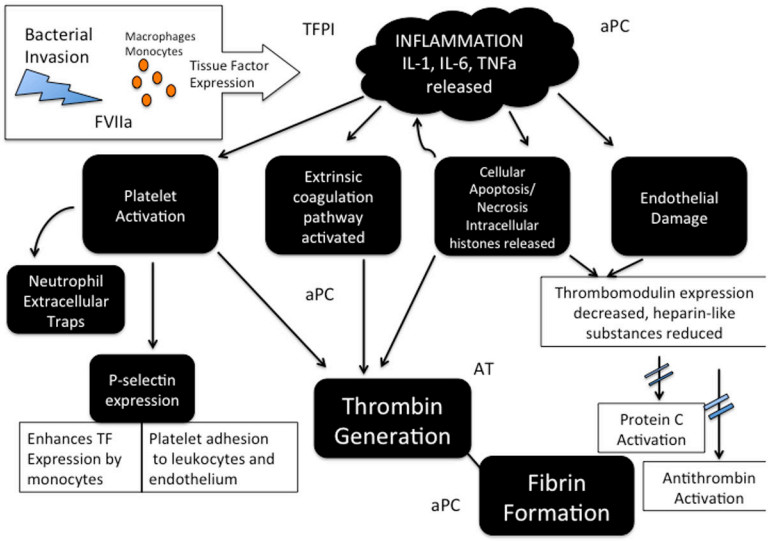

Figure 1.

Table 1

Classical Coagulation Testing in DIC

Platelet Count
PT/PTT/INR
Fibrinogen
Fibrinolysis Markers: D-dimer (Fibrin Degradation Products)
Anticoagulant Markers: Protein C, Antithrombin III
Fibrinolytic Activity: Plasminogen, alpha 2 antiplasmin
Antifibrinolytic Activity: Plasminogen Activator Inhibitor (PAI-1)
DIC Markers: Prothrombin Activation Fragment F1+2, FIX and FX activation peptides
Composite Scoring Systems

Table 2

Mechanisms of Vascular Damage in Sepsis

Pathway	Cause
Endothelial Denudation	LPS induces detachment of ECs from the basal membrane.
VE-cadherin Dislocation	Inflammation induces internalization of vascular joining proteins
Catecholamine induced damage	Elevated noradrenaline levels associated with glycocalyx disruption
Inflammatory cytokine suppression of EC anticoagulant receptors	EPCR and thrombomodulin are down regulated
NET induced EC death	NET associated histones and proteases are directly cytotoxic
Angiopoietin-Tie2	Angpt-2 sensitizes EC to inflammatory cytokines and promotes leakage
Endothelial apoptosis	LPS stimulates cell death