

Review Article

AN UPDATES ON THE SEPSIS CAUSING MULTIPLE ORGAN DYSFUNCTIONS

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ABSTRACT

Acquired immune deficiency syndrome, chronic obstructive pulmonary disease (COPD), cancer and immune suppressive agent initiate sepsis, following chronic situation change into septic shock. Sepsis is responsible for nearly 30% of the total neonatal deaths each year in developing countries. About 96% of infants had survived up to their first year of life, and 56% infant deaths took place within the first month after birth. Firstly, symptoms observed as abnormal body temperature, bradycardia, tachypnoea which needs common treatments for survival. Apoptosis, decreased anti-insulin hormone, abnormalities in coagulation, fibrinolysis, and immune suppressant are responsible for the generation of inflammation which induces sepsis and leads to dysfunction of vital organs such as; GIT, brain, kidney, liver, cardiac and other organs dysfunction. Treatment in sepsis includes antibiotics to suppress the infection, fluids and medicines through i. v. to maintain the blood pressure and stabilize blood circulation, while oxygen, plasma or blood products which correct any clotting problems. Fluid therapy in severe sepsis, corticosteroids, nutrition, vasopressors, inotropic therapy, selenium, bicarbonate therapy, deep vein thrombosis prophylaxis, stress ulcer prophylaxis, administration of immunoglobulins and renal replacement therapy are mandatory in chronic conditions.

Keywords: Sepsis, Inflammation, Septic shock, Apoptosis, Auto infectious disorder, Tachypnoea, Bradycardia, Organ dysfunctions

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INTRODUCTION

Septicemia has neither been an obligatory condition nor a helpful word for human being. The complication in the survival of patients due to acute organ dysfunction is termed as "severe sepsis" which describes the intensity of patient's condition. The strong prognostic value of hyperlactatemia and its association with other hemodynamic and perfusion abnormalities termed as "septic shock" [1]. Sepsis is an auto infectious disorder involving systemic inflammatory reactions to severe infection leading to deregulations in immunological function. It is a widespread infection along with a significant mortality rate and slight economic burden [2]. There are numerous unlike mechanisms contribute to promote sepsis in distinctive phases of systemic disease such as arthritis, peptic ulcers and appendicitis [3]. The biological mechanisms involve bacterially induced activation of cell-mediated immunity leading to cytokine production which ensuing synthesis and release of prostaglandins (PG), appears to trigger preterm labor [4]. Various infectious agents such as pathogens would lead to 'septicemia' generally cause acute organ dysfunction. Sepsis also activates the coagulation and fibrinolysis of endothelium cells to cause multiple organ dysfunctions along with concurrent downregulation of anticoagulants [5, 6].

The important function of endothelium is to down-regulating the anticoagulants TF pathway inhibitors, antithrombin, along with the protein C system and also inhibition relating fibrinolysis. Possible factors for septicemia are correlated to host's tendency for infection and increase the likelihood of multiple organ dysfunctions. There are many factors for infections that most frequently initiate the sepsis and septic shock, including chronic diseases (e. g., acquired immune deficiency syndrome, chronic obstructive pulmonary disease, cancer, etc.) and the use of immune suppressive agents [7].

Epidemiology

Mostly the infant mortality rate mutually caused by sepsis and is most likely responsible for 15-30% of the total neonatal deaths each year in developing countries. About 96% of infants had survived up to their first year of life, and 56% infant deaths occur in the first month after birth in which infants from teenage mothers had a higher risk of death. Maternal school attainment of secondary and above was associated with lower risk of infant death [8].

Global estimation of septic patients in the year 2013 showed about 30 million patients affected by sepsis, of which around 8 million patients die within 6 mo [9]. The diagnosed incident cases of sepsis will grow from 1,060,052 cases in 2013 to 1,129,816 cases in 2023, at an annual growth rate (AGR) of 0.66% over the forecast period. Throughout the forecast period, the US only goes to get the highest number of diagnosed incident cases of sepsis. The septic mortality cases will be increased from 439,015 cases in 2013 to 531,282 cases in 2023 at an AGR of 2.10%. Global data epidemiologists attribute the growth in the diagnosed incident cases of sepsis and its mortality cases in the 6 mo to changing population demographics in the respective markets [10]. The recently available data is shown that about 250,000 cases connected with gram-positive sepsis in each and every year as well as comparing around 150,000 cases connected with gram-negative sepsis [11]. The incidence connected with sepsis resulting more in infants is approximately 5.3/1000 patients <12 mo of age as well as 26.2/1000 patients older 65 y of age [12].

The majority of cases of sepsis are caused by bacterial and fungal infections, and very few are due to other infectious agents. It is generally begun infecting organ location wherever any device has been implanted i.e. skin, lung, GIT, surgical site, intravenous catheter, etc. The infecting agents or their toxins then spread directly or indirectly into the bloodstream. This enables them to spread to almost any other organ system.

The infection associated with sepsis includes:

- Lung infection (pneumonia)
- Appendicitis
- An infection of the thin layer of tissue that lines the inside of the abdomen (peritonitis)
- An infection of the bladder, urethra or kidneys (urinary tract infection)
- An infection of the gallbladder (cholecystitis) or bile ducts (cholangitis)
- Skin infections, such as cellulitis—this can be caused by an intravenous catheter that's been inserted through the skin to give fluids or medication

- Post-surgical infections
- Infections of the brain and nervous systems—such as meningitis or encephalitis
- Bone infection (osteomyelitis)
- Heart infection (endocarditis)

Common bacterial causes of sepsis are gram-negative bacilli (e. g. *E. coli*, *P. aeruginosa*, *E. corrodens*, and *H. influenza* in neonates). Other bacteria are also causing sepsis i.e. *S. aureus*, *Streptococcus* species, *Enterococcus* species and *Neisseria*; however, there are large numbers of bacterial genera that have been known to cause sepsis. *Candida* species are among the most frequent fungi that cause sepsis.

Symptoms

There are 3 categories of sepsis: Sepsis, severe sepsis, and septic shock. Sepsis can happen while patients are still in the hospital recovering from a procedure, but it is the extraordinary case [13]. It's important to seek immediate medical attention if patients have any of the below symptoms;

- Abnormal body temperature: Hypothermia < 96.8 °F (cold)
Hyperthermia > 100.4 °F (fever)
- Tachycardia (heart rate > 90 beats/min)
- Tachypnea (breathing rate > 20 breaths/min) or a rate sufficient to produce PaCO₂ < 32 mmHg
- Abnormal white blood cell count (> 12,000/mm³, < 4000/mm³, or > 10% immature forms)

The abnormal white blood cell count can be triggered by an infection, but it can also arise from noninfectious sources such as trauma, hemorrhage, burns, surgery, adrenal insufficiency, pulmonary embolism, ruptured an aortic aneurysm, myocardial infarction, occult hemorrhage, cardiac tamponade, post-cardiopulmonary bypass syndrome, autoimmune disorders, pancreatitis, vasculitis, anaphylaxis, drug overdoses. The earlier people seek treatment, the greater chances of survival [14].

Severe sepsis is sepsis plus one of the following clinical problems

- Cardiovascular system dysfunction
- Acute respiratory distress syndrome (ARDS)
- Dysfunction of more than two organs or systems [15]

Septic shock, in a patient with sepsis, is an acute circulatory failure with refractory hypotension that is unexplainable by other causes. The term "shock" describes a condition in which many tissues throughout the body become hypoxic due to poor perfusion. In shock, normal homeostatic mechanisms are either not functioning or not adequate to deliver enough oxygen to tissues. If it is not reversed, leads to organ failures and death [16].

Shock is categorized as follows

- *Hypovolemic*-The patient has suffered the massive loss of fluid (hemorrhage)
- *Cardiogenic*-The heart is unable to pump sufficient amount of blood (myocardial infarction)
- *Distributive*-Sufficient fluid cannot be kept inside the vasculature (anaphylaxis) [17, 18].

Pathophysiology

The indigenous immune system is comprised of cellular and humoral components. The humoral component includes interleukins and chemical mediators that are openly toxic toward the inside of a pathogen or that turn as a mediator for fresh cells. The cellular

component includes circulating monocytes, tissue macrophages, neutrophils and lymphocytes [19]. Prominently, innate immune system cells can fight attacking microbes directly without the participation of the adaptive immune system even though cellular interactions can be true of B and T lymphocytes which involve in three different types of dysfunction [20].

A. Cellular dysfunction

In sepsis, the cellular aspects are shown to be dysfunctional within the body owing to its excessive activation or depressed functions. It may be mediated through undesirable regulation of signaling pathways implicated in the reorganization of the pathogen and insensitive tissues, through direct suppression of the immune system or through the cell signaling action. While in the long term, through changes in the regulation of gene expression required for appropriate activation and effectors function of immune cells [21]. Cells respond to a very aggressive method because of undesirable activation, such as the excess release of neutrophils (unwanted toxins) that neighborhood damage cells or tissue [22]. The depressed function could be neutrophil inability to phagocytize and apparently targeting pathogens. Under normal conditions, bacteria enter into the body which causes activation of resident macrophages to remove out of the initial infection. Monocytes and macrophages tend to be critical cellular populations from the innate immune system [23] whose results are responsible for a multiple of functions include mediating inflammation, phagocytosis, repeated wound injury and remodeling (fig. 1).

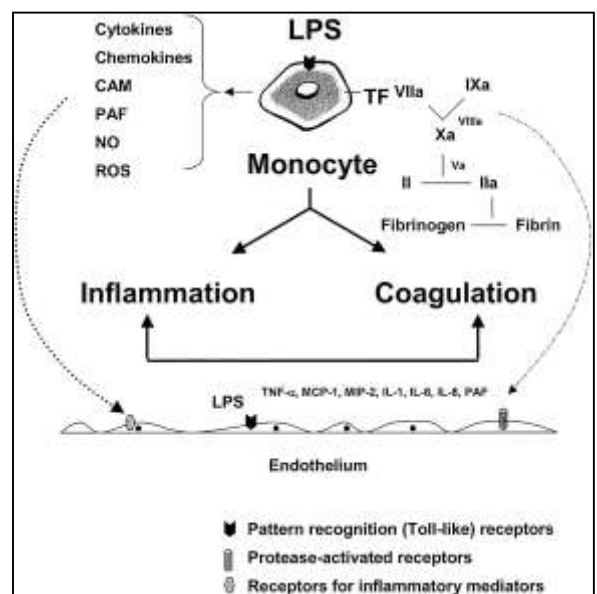


Fig. 1: The role of the monocyte and endothelium in mediating the host response to infection

Source-
<http://d3md5dngttnvbj.cloudfront.net/content/bloodjournal/101/10/3765/F1.large.jpg>

In many cases, the initial infectious offense is too perfect for occupant macrophages alone to eliminate out all the bacteria, while sometimes macrophage not able to remove out the pathogen or the causative agent. On the other hand, macrophages, in the M1 phenotype, start the immune system response by means of releasing inflammatory mediators including tissue necrosis factor (TNF), interleukin-1b (IL-1b), IL-6 and chemokine (C-X-C motif) ligand 8 protein (CXCL-8). The cell wall component of Gram-negative bacteria mainly Lipopolysaccharide (LPS), also encourages the release of associated bioactive mediators which include cytokines, prostaglandins, platelet activating element, O₂ free-radicals, and other mediators [24]. Among these kinds of mediators, cytokines as IL-1, IL-6, and TNF are now recognized as potent activators in the hypothalamus-pituitary-adrenal

(HPA) axis [25, 26]. This indicates endothelial cells to regulate the adhesion molecules up and activates the recruitment involving inflammatory cells to handle the infection. For example; M1 macrophage phenotype is stimulated by means of toll-like receptor (TLR) or Interferon-gamma (IFN-gamma) in signaling to produce pro-inflammatory cytokines and stimulate the killing of microbial pathogens and improving bactericidal activity. However, M2 phenotype is based inside the body and existence involving IL-4 and IL-13 inside placing parasitic infections and tissues upgrading [27].

B. Phagocytic cell dysfunction

Phagocytosis primarily involves recognition and engulfment of microorganism, resulting the causative pathogen to be killed by various mechanisms like the generation of reactive oxygen species (ROS), use of anti-bacterial proteases, peptides, and adjustments of pH. The way host individual responds to sepsis, mainly neutrophil recruitment, phagocytosis and pathogen killing ranges, specifically is invoked as a function of heterogeneity. However, neutrophils are very eminent for turmoil microbial bacterial infections; an elongated and vigorous reaction can be adverse towards individual causes to organ injury and leads to progress of organ failure. Macrophage inflammatory protein 2 (MIP-2), any CXC chemokine generated by macrophages throughout sepsis, binds towards chemokine receptor-1 and-2 (CXCR1 and CXCR2) on neutrophils [28,29]. Research demonstrates that deactivating the effect of associated CXCR₂ activation inside murine peritonitis resulted in a well attenuated neutrophil reaction with less organ damage as well as improved emergency in addition neutrophils have a task inside cell recruitment signaling [30]. The main focus of this review article is tantamount to observe that neutrophils recruited early to the site of a cutaneous in which *Staphylococcus aureus* infection is the predominant source of IL-1b, leading to amplification of the neutrophil response to abscess formation and bacterial clearance. These recruited inflammatory cells, containing the phagocytic cells (polymorph nuclear cells, monocytes, and macrophages) of the innate immune response and lymphocytes of the adaptive immune response to frequently become dysfunctional in sepsis [31].

C. Endothelial cell dysfunction

Endothelial cells are engaged as a critical barrier in between blood and tissue. In normal conditions, endothelial provides an surface to prevent the blood clotting through expressing thrombomodulin along with endothelial cell protein C receptor (EPCR), which support thrombin in generating activated protein C by tissue factor pathway inhibitor (TFPI) along with antithrombin attached to their exterior along with secreting tissue-type plasminogen activator, which promotes fibrinolysis [32]. The lipopolysaccharide of gram-negative bacilli makes up a cluster of differentiation 14 (CD14) which is lipopolysaccharide-binding protein complex. The peptidoglycan of gram-positive bacteria and the lipopolysaccharide of gram-negative bacteria to bind to TLR-2 and TLR-4, individually. The binding of TLR-2 and TLR-4 triggers intracellular signal-transduction pathways that lead to the stimulation of cytosolic, nuclear factor κ B (NF- κ B). Activated NF- κ B moves from the cytoplasm to the nucleus, binds to transcription initiation sites, and enhances the transcription of cytokines such as tumor necrosis factor α (TNF- α), interleukin-1 β , and IL-10. TNF- α and interleukin-1 β are proinflammatory cytokines that activate the adaptive immune response but also cause both direct and indirect host injury [33]. Cytokines activate endothelial cells by upregulating adhesion receptors and injured endothelial cells by inducing neutrophils, monocytes, macrophages, and platelets to bind with endothelial cells, leading to apoptosis, along with a loss in barrier functionality. The coagulation is triggered by activation of TNF on monocytes probably on endothelium and by the release every of von Willebr and factor (vWF), which enhances to platelet adhesion to the subendothelial surface and platelet aggregation [34].

Anticoagulant proteins in turn moderate cytokine-release tissue factor-factor VIIa (TF-FVIIa), FXa and thrombin, exert proinflammatory activity by cleaving mainly protease-activated receptors (PAR-1 and PAR-2). Activated protein C cleaves PAR-1 in an EPCR-dependent manner, and also modulates inflammation and apoptosis. This response is characterized by changes in smooth muscle cell changes resulting vasodilation as well as endothelial cell contraction, which allows for

leakage of proteins into the extravascular spaces and tissues. It also increases the expression of adhesion molecules such as selections that promote migration of leukocytes from the microcirculation into infected sites (fig. 2). This change in endothelial cell also results in endothelial-cell disruption, which disturbs their anticoagulant properties [35]. Endothelial interruption also occurs due to increased expression of adhesion molecules on the endothelial cells, helping connection regarding whitened blood cells [36].

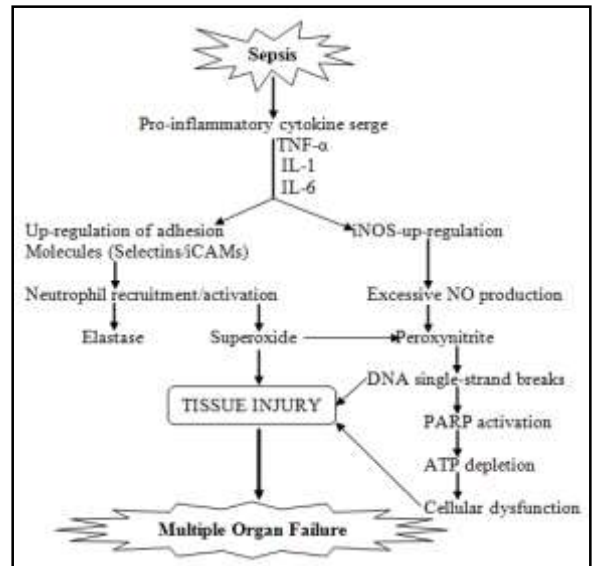


Fig. 2: Role of selectins and excessive nitric oxide in sepsis-related tissue injury

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<http://www.scielo.br/img/revistas/clin/v61n1/a12fig.01.gif>

Pathogenesis

The Lipopolysaccharide of gram-negative bacilli links to CD14 which is lipopolysaccharide-binding protein complex. The peptidoglycan of gram-positive bacteria and the Lipopolysaccharide of gram-negative bacteria to bind to TLR-2 and TLR-4, individually. Binding of TLR-2 and TLR-4 triggers intracellular signal-transduction pathways that lead to the stimulation of cytosolic NF- κ B. Activated NF- κ B moves from the cytoplasm to the nucleus, binds to transcription initiation sites (fig. 3), and enhances the transcription of cytokines such as TNF- α , interleukin-1 β and IL-10 [37,38]. TNF- α and interleukin-1 β are proinflammatory cytokines that activate the adaptive immune response but also cause both direct and indirect host injury which is described as following categories discussed below;

A. Apoptosis

Apoptosis play a major role in the pathogenesis of sepsis by delayed elimination of endothelial cells that should be removed i.e. neutrophils and prompt removal of those cells that should not be removed from i.e. lymphocytes [39]. In septic condition, apoptosis can be prompted by the absence of IL-2 or by the release of glucocorticoids, granzymes (death cytokines) and TNF. Apoptosis start through auto-activation of cytosolic and/or mitochondrial caspases, which can be influenced by the pro and anti-apoptotic members of the Bcl-2 family [40]. Endothelial cells will certainly undergo apoptosis through a bio-reaction to various mediators and few infectious agents. Nevertheless, endothelial cells usually resistant towards consequences regarding endotoxin, and some detectives include never show simpler proof endothelial cellular apoptosis in septic condition [41]. It can become powerfully assumed endothelial cells and usually dysfunctional throughout septic sufferers, within the system. Possession has been exhibited for increased apoptosis of dendritic cells. Macrophages, monocytes, and mucosal epithelial solar cells exist in septic sufferers [42].

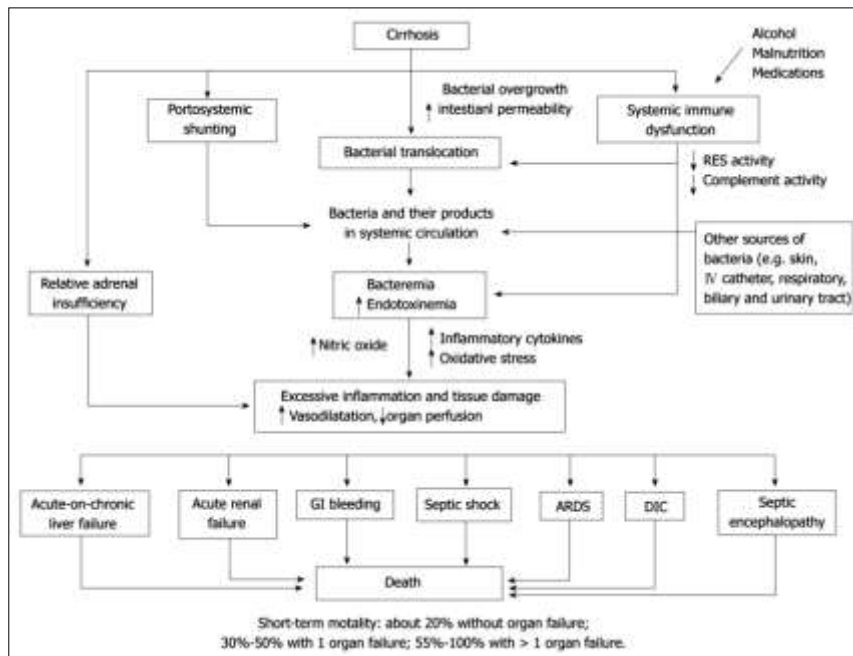


Fig. 3: Pathogenesis of sepsis caused by bacterial infection

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B. Coagulation abnormalities

The inflammatory state found in septic patients leads to numerous changes in the coagulation pathway, shifting the normal hemostatic balance toward a procoagulant state [43]. Severe sepsis is almost consistently related to altered coagulation, often resulting in disseminated intravascular coagulation [44]. The coagulation irregularity found in the patient sepsis range from to some extent prolonged bleeding times and mildly reduced platelet counts to fulminant disseminated intravascular coagulation (DIC) [45,46]. In general conditions anticoagulants (protein C and protein S), antithrombin III, and tissue factor–pathway inhibitor (TFPI) reduce coagulation, increase fibrinolysis, and eliminate microthrombin. Thrombin- α binds to thrombomodulin on endothelial cells, which intensely increase stimulation of protein C to form a complex with its cofactor protein S [47]. Activated protein C proteolytically deactivates factors Va and VIIIa and decreases the synthesis of plasminogen activator inhibitor 1 (PAI-1) (fig. 3). The relationship among inflammation and disordered coagulation occur by various interrelated mechanisms, mostly releases pro-inflammatory cytokines (IL-1, IL-6, IL-12 in addition to TNF- α) that induce expression of tissue component, reduced levels of antithrombin, inhibition in the normal anticoagulant proteins C system and disturbed fibrinolysis [48]. Unnecessary fibrin deposition is stimulated through coagulation with the movement of tissue component [49]. Microvascular thrombi intensify damage by the release of mediators and by microvascular obstruction, which causes distal ischemia and tissue hypoxia. Sepsis causes increases synthesis of PAI-1 and reduces the levels of protein C, protein S, antithrombin III, and TFPI. Lipopolysaccharide and tumor necrosis factor α (TNF- α) decrease the synthesis of thrombomodulin and endothelial protein C receptor (EPCR), thus decreasing the activation of protein C [50].

Lipopolysaccharide and TNF- α added to PAI-1 levels so that fibrinolysis is inhibited. Protease-activated receptors (PARs) generate the molecular link among coagulation in adding to inflammation [51]. PAR1 exerts cytoprotective consequences whenever triggered by means of activated proteins C or maybe low-dose thrombin even though experts disturbing effects on endothelial cell barrier function whenever stimulated by means of high-dose thrombin [52]. An exaggerated response, however, can lead to a situation in which coagulation itself contributes to disease in its most severe form causing microvascular thrombosis and organ

dysfunction, a syndrome known as disseminated intravascular coagulation (DIC) [53]. It is clearer that, components of the coagulation system are in a position to markedly modulate the inflammatory response [54].

C. Inhibition of fibrinolysis

In septic patients, the formation of fibrin triggers an early increase in the expression of plasminogen activators [55]. Although increased amounts of plasminogen activator antigen, fibrinolysis action is readily inhibited through both TNF- α and endotoxin-stimulated generation of the acute-phase protein i.e. PAI-1 [56]. In addition, thrombin-TM complex stimulates TAFI, which additionally inhibit fibrinolysis (fig. 4) [57]. The actual disordered coagulation, alterations in cellular and immune system regulations can lead to clinically observable derangements for which early goal-directed therapy, glycemic control and administration of steroids have been utilized for the treatment of the septic condition [58].

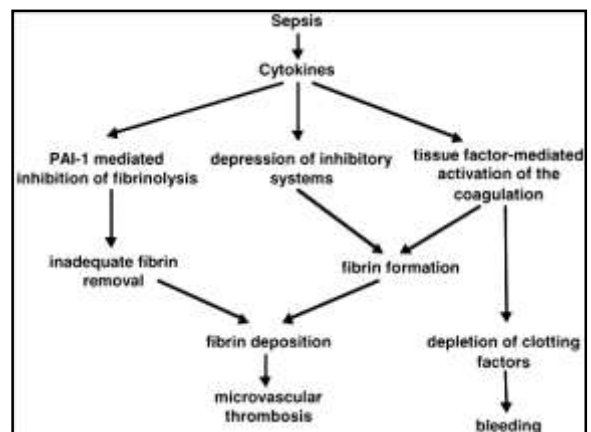


Fig. 4: The alteration of the coagulation pathway in severe septic condition

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D. Antithrombin

Antithrombin is the main inhibitor of both thrombin and factor Xa, which is significantly decreased in an inflammatory state such as sepsis. Numerous factors involve in decreasing the antithrombin like reduced hepatic synthesis of this negative acute phase protein responsible for the formation of thrombin-antithrombin complexes which results in consumption of antithrombin and degradation by elastase released from activated neutrophils [59, 60].

E. Anti-inflammatory and immunosuppressant

In the immune system harbors, humoral, cellular, and sensory mechanisms that reduce the particular potentially dangerous effects of the pro-inflammatory reaction [61]. Phagocytes can certainly transition to an anti-inflammatory phenotype, which promotes tissue repair, and regulatory T cells and myeloid-derived suppressor cells to reduce inflammation. Furthermore, the neuronal mechanism can certainly inhibit inflammation [62]. There is a subsequent norepinephrine discharge in the spleen and acetylcholine release by way of subset associated with CD₄ and T cells. The acetylcholine discharge targets on $\alpha 7$ cholinergic receptors on macrophages, decreasing the release of pro-inflammatory cytokines interruption of the neural-based system through vagotomy improves susceptibility to endotoxin shock, whilst stimulation from the efferent vagus neural or maybe $\alpha 7$ cholinergic receptors attenuates systemic swelling [63,64]. People who suffer initial sepsis yet remain influenced by widespread health care possess evidence of immunosuppression and partially mirrored through lowered phrase associated with human leukocyte antigen-antigen D-related (HLA-DR) in myeloid tissue [65]. Most of these patients frequently possess ongoing infectious *foci*, in spite of antimicrobial remedy, or probably reactivation connected with latent virus-like infection [66].

Multiple organ dysfunctions due to sepsis

Numerous mechanisms that trigger organ failure during sepsis are due to impaired tissue oxygenation. Several components including hypotension, diminished red cell deformability, along with microvascular thrombosis contribute to reduced oxygen delivery throughout septic shock [67]. Inflammation could potentially cause malfunction of the vascular endothelium, coupled with cell passing away along with a loss in barrier integrity, increase to subcutaneous edema along with body-cavity edema white mitochondrial impairment attributable to oxidative tension along with mechanisms affects the use of cellular oxygen use [68,69]. In addition, destruct mitochondrial release alarms into the extracellular natural environment, including mitochondrial DNA along with formyl peptides, which often can activate neutrophils along with additional

cell injury [70]. The following vital organs which become dysfunctional due to severe sepsis are discussed as follows;

(A) Brain dysfunction

Brain dysfunction is widespread in the septic patient but rarely noticed, despite its dramatic impact on consequence. The pathophysiology of sepsis complex, resulting from both inflammatory and non-inflammatory process that affects all type of brain cells. The brain response to systemic infection is physiologically triggered by an activation signal which is transmitted by three different pathways [71].

1. The neural pathway that desires to trigger of primary afferent nerves, such as the vagal or trigeminal nerves by connecting peripherally produced pathogen-associated molecular patterns (PAMPs) and cytokines.

2. The humoral pathway involves circulating cytokines. Cytokines reach in the brain at the level of the choroid plexus and the circumventricular organs that do not fall within the blood-brain-barrier (BBB).

3. The BBB alterations are prompted by the stimulation of cerebral endothelial cells marks the release of numerous mediators into the brain (fig. 5).

This stimulation is caused by the production of nitric oxide synthase-derived nitric oxide. All of these pathways trigger the stimulation of microglial cells, which are the resident immune cells of the brain. When microglial cells activated, may negatively affect the brain by the production of nitric oxide, cytokines, and ROS, which lead to cell death within vulnerable areas of the brain [72]. This production, itself responsible for an increase of the BBB alterations, thus causing a vicious circle of increasing brain dysfunction and injury. These mechanisms are compounded by widespread metabolic disturbances occur in septic patients, hemodynamic failure, use of medications, and iatrogenic and environmental factors. Septic-associated brain dysfunction may be associated with neurologic sequelae in survivors, including functional and cognitive decline, probably in neurodegenerative and/or ischemic mechanisms involve in moving of cytokines (fig. 5) [73]. This BBB disturbance elicited with the activation of cerebral endothelial cells results in the launch of numerous mediators into the brain. This kind of activation is a consequence of the mediator production in the beginning phase of sepsis, involving nitric oxide synthase-derived nitric oxide [74]. All of these pathways instigate the account activation involving microglial solar cells, which are the citizen immune solar cells of the brain. Any time initialized, microglial solar cells may be perhaps in a wrong way has an impact on serotonin levels with the production involving nitric oxide, cytokines, along with reactive oxygen will lead to mobile demise within vulnerable regions of serotonin levels [75].

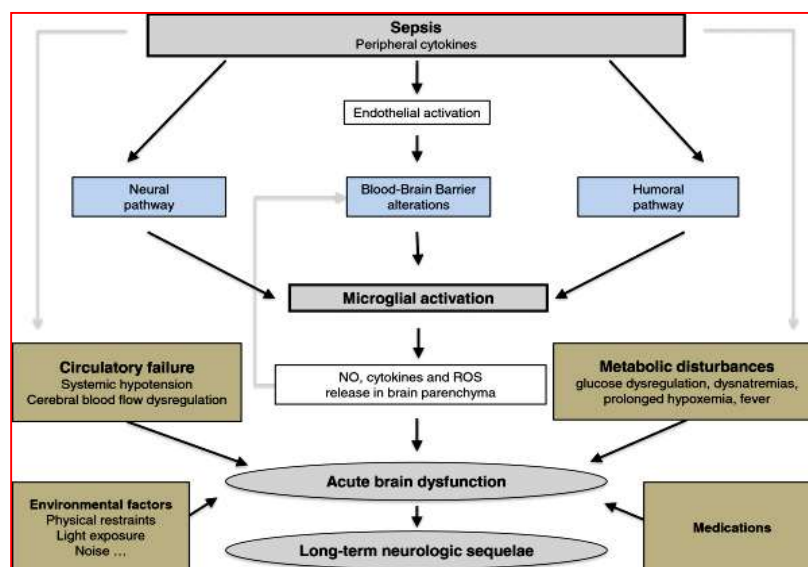


Fig. 5: The response of the brain to systemic infection is physiologically triggered by an activating signal that is mediated by three pathways

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This kind of production is generally, liable for a rise from the BBB modifications, thus causing a horrible circle involving raising brain malfunction along with harm. These things tend to be compounded by means of pervasive metabolic agitations that will arise in septic patients, hemodynamic disappointment, and use of medications, along with iatrogenic and environmentally friendly elements. Septic-associated brain malfunction could be associated with neurologic sequelae in survivors, which includes use and cognitive diminish, probably by means of neurodegenerative and/or ischemic mechanisms [76].

(B) Gastrointestinal dysfunction

The gastrointestinal tract may trigger damage due to sepsis. Overgrowth of the pathogen in the upper GI tract may be enunciated into the lungs, producing nosocomial or aspiration pneumonia [77]. The typical membrane function of the gut may be magnified, allowing translocation of bacteria, endotoxins, and usual digestive proteases into the systemic circulation and spreading the septic response. Septic shock may be a source of paralytic ileus that can lead to an interruption in the institution of enteral feeding. Access Nitric oxide production is defined as the causative agent of sepsis-induced ileus (fig. 6). The ideal level of nutritional consumption is carried forward within the aspect of high protein and calorie requirements. Narcotics and muscle relaxants can further worsen GI tract motility [78].

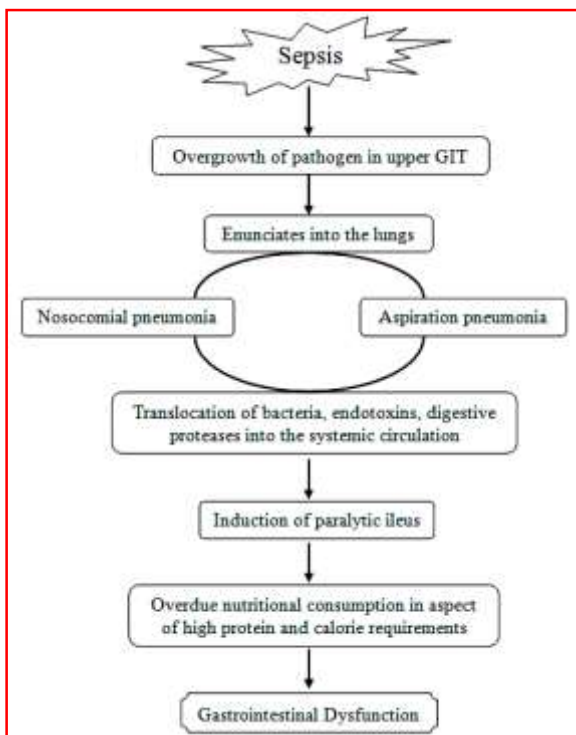


Fig. 6: Gastrointestinal dysfunction due to sepsis

Designed by Harikesh Maurya

(C) Kidney dysfunction

In severe sepsis, the overwhelming production of inflammatory humoral mediators and activation of the cellular system causes activation of sympathetic-adrenal axis with increased plasma levels of norepinephrine, renin-angiotensin-aldosterone system (RAAS) with elevated levels of angiotensin II and rise in vasopressin levels are often part of host response [79]. These mechanisms are largely responsible for the clinical manifestations of sepsis, including hemodynamic alterations that are characterized by vasodilation, a hyperdynamic circulation and microcirculatory changes contributing to inefficient oxygen extraction (fig. 7). The most significant alteration in glomerular function in sepsis decreases in glomerular filtration rate (GFR) [80].

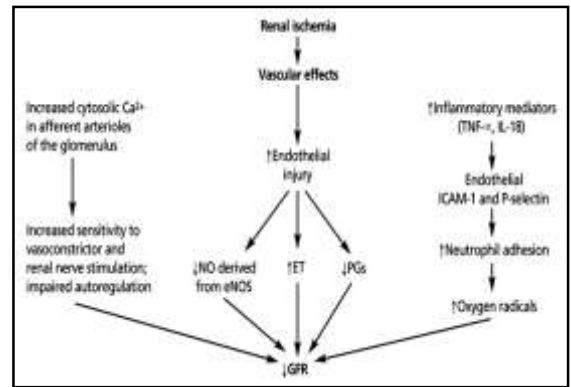


Fig. 7: Alteration of kidney function due to severe sepsis

Source-<http://jaoa.org/data/Journals/JAOA/932099/13fig.2.jpeg>

(D) Liver dysfunction

The most important role played by the liver is scavenging of bacteria, endotoxin, detoxification, and synthesizing proteins for metabolic, immune, and coagulation functions [81]. Numerous cells are involved in these processes i.e. hepatocytes (HCs), Kupffer cells (KCs), and sinusoidal endothelial cells (SECs) [82]. In septic shock, the liver contributes energetically to host defense and tissue repair through cross-link among hepatic cells and blood cells. Host cells will regulate their metabolic pathway to up-regulation of the inflammatory reaction, which is answerable for the rise in the production of acute-phase proteins mediated predominantly through IL-6 [83]. This shift indicates an increase in C-reactive protein (CRP), α-1-antitrypsin, fibrinogen, prothrombin, and haptoglobin levels, whereas the hepatic assembly of albumin, transferrin, and antithrombin is decreased. The liver releases an acute-phase protein designated as CRP after the beginning of infection or tissue damage. CRP is a scientific biomarker used to assess the presence of infection and sepsis [84]. Throughout sepsis, CRP has both proinflammatory and antiinflammatory effects. CRP may well recognize and adhere to bacteria and damaged cells to facilitate their removal through dealings with inflammatory cells and mediators. However, CRP also prevents the adhesion of neutrophils to endothelial cells, inhibits superoxide production, and increases IL-1 receptor antagonist (IL-1ra) production [85]. Despite the fact that IL-6 is the prototypical stimulus for the induction of CRP, other cytokines also play a role in its production [86]. Moreover, glucose metabolism is significantly altered because of an increase in glycogenolysis, gluconeogenesis and liver hypermetabolism, due to increased amino acid uptake (fig. 8) [87].

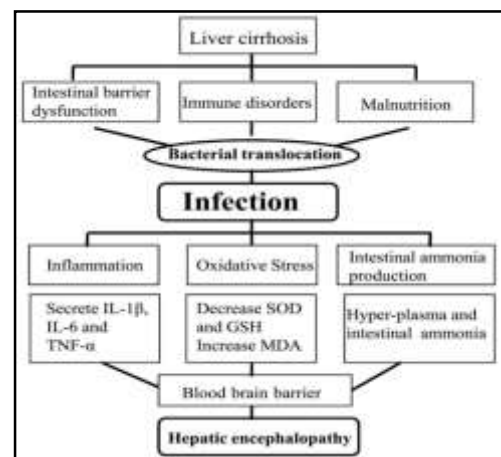


Fig. 8: Infection-induced hepatic encephalopathy in liver cirrhosis during severe sepsis

Source-https://www.spandidos-publications.com/article_images/etm/6/2/ETM-06-02-0584-g02.jpg

Bacterial toxin LPS can convince the production of a pro-IL-18 cytokine that has to be cleaved into a biologically active form by caspase-1-dependent processing. After maturation, IL-18 causes the secretion by hepatic lymphocytes of interferon-gamma (IFN- γ), which is itself responsible for blunt liver injury via apoptosis in human cancer cells, and the second elevation of TNF- α [88]. Interestingly, IFN- γ is also able to up-regulate the expression of the Toll-like receptor 4 [89], which participate in an inflammatory hyper-reactive response to LPS, leading to a potentially harmful, whole-body inflammation response. Like cytokines, reactive oxygen species are involved in the liver response to LPS [90].

The increased risk for sepsis may be assigned to bacteremia, particularly from intestinal bacterial translocation [91, 92]. Bacteremia increases the risk of spontaneous bacterial peritonitis which is noted in up to 15% of hospitalized cirrhotic patients and 3%-3.5% of asymptomatic outpatients with cirrhosis [93, 94], and it increases the risk of variceal hemorrhage. Bacterial translocation occurs in the setting of splanchnic vasodilation (which increases intestinal mucosal permeability) [95, 96], bacterial overgrowth secondary to delayed colonic transit time and structural damage of intestinal epithelial cells [97, 98].

(E) Cardiac dysfunction

Prolonged septic shock develops myocardial depression, due to a decreased ejection fraction. Sepsis-related changes in circulating volume and vessel tone certainly affect cardiac performance. Although the coronary circulation during sepsis is maintained or increased, while alterations in the microcirculation are to be expected ordinary. Mitochondrial dysfunction, another feature of sepsis-induced organ dysfunction, will also place the cardiomyocyte at risk of adenosine triphosphate depletion [99].

However, clinical studies have shown that myocardial cell death is rare and that cardiac function is fully reversible in survivors. Hence, functional rather than structural changes appear to be responsible for intrinsic myocardial depression during sepsis (fig. 9). The underlying mechanisms include down-regulation of β -adrenergic receptors, depressed post-receptor signaling pathways, impaired calcium liberation from the sarcoplasmic reticulum, and impaired electromechanical coupling at the myofibrillar level, and these changes are regulated by cytokines and nitric oxide [100].

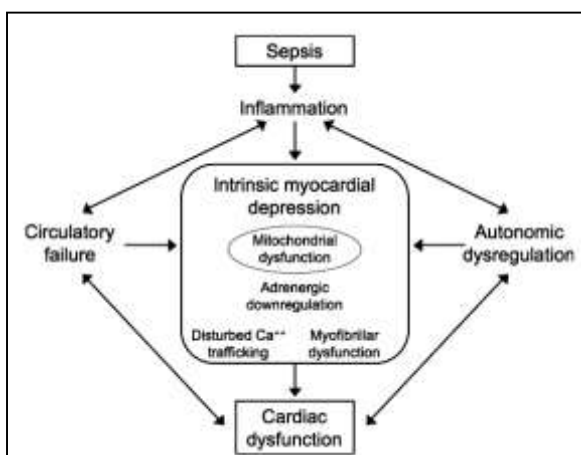


Fig. 9: Sepsis-induced cardiac dysfunction

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Treatment of sepsis

Treatment for sepsis varies, being dependent on the site and cause of the initial infection, the organs affected and the extent of any damage. Severe sepsis and septic shock are medical emergencies. Patients will be referred to hospital for diagnosis and treatment if

possible early signs of sepsis. Management of sepsis after admission to the hospital usually involves three treatments and three tests (called the "Sepsis six"). These should be initiated by the therapeutic team within an hour of diagnosis [101].

Tests will include:

- Taking blood cultures—to identify the type of bacteria causing sepsis
- Taking a blood sample—to assess the severity of sepsis
- Monitoring urine output—to assess severity and kidney function

Treatment involves:

- Giving antibiotics
- Giving fluids intravenously
- Giving oxygen

These treatments are described in more detail below

Emergency treatment

Patients will need emergency hospital treatment and may require admission to an intensive care unit (ICU) if the sepsis is severe or develop septic shock (blood pressure drops to a dangerously low level). Physicians are able to support any affected body functions, such as breathing or blood circulation, while the medical staff focuses on treating the infection [102]. Owing to problems with vital organs, people with severe sepsis are likely to be very ill and up to 4 in every 10 people with the condition will die. Septic shock is all the more serious, with an estimated 6 in every 10 cases proving fatal. However, if early identified and treated quickly, sepsis is treatable, and in most cases results in full recovery without lasting problems.

Antibiotics

The principal treatment for sepsis, severe sepsis or septic shock is antibiotics. In the case of severe sepsis and septic shock, antibiotics will be delivered by i. v. route and should start within an hour of diagnosis to reduce the risk of serious complications or death. It is generally replaced by tablets after 2 to 4 d.

(a) Types of antibiotics

Broad-spectrum antibiotics are given first because these are designed to work against a wide range of known infectious bacteria and usually cure most frequent infections. After confirmation of causative microorganism, the administration of specific antibiotics is mandatory.

(b) Viral infections

If the sepsis is caused by a virus, antibiotics won't work. Antibiotics are usually given anyway, because it would be too dangerous to delay treatment until tests confirm the exact cause. With a viral infection, patients will need to wait until the immune system starts to tackle the infection, although antiviral medication may be given in some cases.

Intravenous fluids

In severe sepsis or septic shock, body required increased amounts of fluid to prevent dehydration and kidney failure. Patients will usually be given fluids intravenously during the first 24-48 h after admission.

Oxygen

In severe sepsis or septic shock, body's oxygen demand will increase gradually. When the level of oxygen in the blood is depleted, patients will usually be given oxygen. This is either given through a mask or tubes in nostrils [103].

Treating the source of infection

If a source of the infection can identify, such as an abscess or infected wound, will also must to be treated initially. Example: Any pus may need to be drained away, and more serious cases, surgery may be needed to remove the infected tissue and repair any damage.

Maintaining blood pressure

Medications called vasopressors are used if patients have low blood pressure brought about sepsis. Vasopressors (dopamine and norepinephrine) are usually given intravenously while patients are in an ICU. Extra fluids may be provided intravenously to help increase blood pressure [104].

Other treatments

Patients may also require additional treatments such as:

- Corticosteroids or insulin medication
- A blood transfusion
- Mechanical ventilation
- Dialysis [105]

DISCUSSION

Sepsis is a life-threatening complication arising from an infection; it takes place when the body's response to the infection damages its own tissues and organs. In this article, we examined the pathophysiology of sepsis which involves causing multiple organ dysfunctions and also connections with function of endothelium and effect related to coagulation on inflammation in septic patients. It is seen that, the microorganism especially gram-positive bacteria are highly susceptible to host immune reactions causing infection, results in the release of cytokines and endothelial dysfunction of host tissue causing inflammation. There are numerous factors for infections that most frequently initiate the sepsis and septic shock, including chronic diseases (e. g., acquired immune deficiency syndrome, chronic obstructive pulmonary disease, and cancer) and the use of immune suppressive agents. However, early identified and treated quickly, sepsis is treatable, and in most cases results in full recovery without lasting problems.

Traditionally, pathophysiological approaches have been used for understanding of sepsis. In fact, the vast majority of basic studies in this field have focused on isolated and specific mechanisms of the host response. These data have led to linear models of pathophysiology for multiple organ dysfunctions due to sepsis, which in turn have guided the choice of therapeutic targets. The conception that the various components of the host response are aligned in series predicts that the attenuation of anyone component (TNF- α , PG, LPS) will abort the sepsis cascade. These models are giving way to a more realistic paradigm of nonlinear complexity, in which the various cell types, inflammatory mediators, coagulation factors, cell surface receptors, intracellular signaling pathways, transcription factors, and genes interact as part of spatially and temporally coupled networks. The nonlinear dynamics of the host response may provide an explanation, at least in part, the disappointing results of single-target therapy trials in severe sepsis.

One way to cope with the inherent complexity of the host response is to develop broad-base targeting schemes in which multiple components are attenuated at once, for example the inflammatory and coagulation cascades. It is perhaps by casting a wider "therapeutic net" that activated protein C succeeded, where so many other agents before it have failed.

An alternative approach is tantamount to target a non redundant component of the host response that is central to the initiation and perpetuation of the sepsis phenotype. Examples might include a single function of the endothelium (apoptosis), or a single transcription factor (TNF- α and interleukin-1 β). However, in designing such strategies, it is important that we acknowledge the unpredictable behavior of complex nonlinear systems and correct our expectations accordingly. An eminent scientific challenge for the 21st century is to learn how to leverage nonlinear interactions for mechanistic and therapeutic gain.

Myocardial depression is a well-recognized manifestation of organ dysfunction in sepsis. Echocardiographic studies suggest that 40% to 50% of patients with prolonged septic shock improve myocardial depression, as defined by a reduced ejection fraction. The degree of

myocardial structural derangement and functional impairment relates to the severity of illness. As sicker patients usually receive higher doses of vasoactive drugs, the physiologic cardiac response may be masked considerably. Various mechanisms can explain the development of septic myocardial depression, most of which are regulated by cytokines and NO.

Finally, it is worth considering that myocardial depression could protect the heart by reducing cellular energy expenditure in a situation when the energy generation is impaired due to mitochondrial dysfunction and microcirculatory abnormalities. Analogies can be important to consider ischemia-induced hibernation, a well recognized phenomenon in patients with ischemic heart disease, serving as a regulatory event that maintains myocardial integrity and viability. Parallel cellular changes to those seen during hibernation have been reported in septic animals in conjunction with diminished cardiac performance. This concept merits further investigation as it may carry major implications for patient management.

CONCLUSION

Despite further information about the pathophysiology and treatment of severe sepsis, this disorder continues to be associated with an unacceptably high mortality rate. Future breakthroughs will require a conceptual shift that emphasizes relationships between the numerous mediators and cells involved in host response. The endothelium is essential for initiating, perpetuating, and modulating the host response to infection.

Therapies targeting micro vascular dysfunction may have a significant impact on morbidity and mortality in sepsis. Based on the low ascorbate concentrations in septic patients, the improved micro vascular function and survival observed in septic animal models injected with vitamin C, the improved outcomes observed in critically ill patients administered i. v. vitamins C and E as adjuvant therapy, and the preservation of neutrophils' capacity to produce ROS during exposure to supra-physiological extracellular ascorbate levels, clinical trials of vitamin C injection as an adjunct therapy in sepsis should be undertaken.

A recent study demonstrated that activated protein C signals through PAR-1 in cultured endothelial cells, by an EPCR-dependent mechanism. Consistent with these results, both EPCR and PAR-1 were shown to be required for mediating the cytoprotective function of activated protein C in hypoxic cultured human brain endothelial cells and in a stroke model of mice. Collectively, these findings suggest that activated protein C signals through the PAR-1 receptor both *in vitro* and *in vivo*. Since PAR-1 is also a receptor for thrombin, these studies raise interesting questions as to how two distinct ligands, namely activated protein C and thrombin, mediate opposing PAR-1 responses (protective and pro-inflammatory responses, respectively).

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CONFLICT OF INTERESTS

The authors declared no conflict of interests with respect to the authorship and/or publication of this paper.

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