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Mechanisms of Organ Dysfunction in Sepsis

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INTRODUCTION

Development of organ dysfunction is the most important clinical event during sepsis, as it directly relates to mortality and morbidity. Although the new definition of sepsis captures this concept, centering the clinical essence of sepsis on the development of a ‘*life-threatening organ dysfunction caused by a dysregulated host response to infection*,’¹ our understanding of the mechanisms by which sepsis induces organ dysfunction remains incomplete. This knowledge gap is not trivial because mortality from sepsis continues to be very high,² therapeutic options are limited and nonspecific, and morbidity after sepsis remains a significant burden for patients after hospital discharge.³

In the past 15 years, several new concepts have shifted our understanding of what organ dysfunction means in the context of critical illness, and framed the study of possible mechanisms leading to organ dysfunction. Three of these disruptive ideas are of particular relevance here. The first is that organs can develop dysfunction during sepsis in the absence of decreased oxygen delivery,^{4,5} suggesting that tissue hypoxia may not be an isolated mechanism. This explains why perfusion-targeted therapeutic efforts may surmount only to partial or to no benefit.⁶ The second is that organ dysfunction can occur in the absence of significant cell death,^{7–9} suggesting the lack of function is not due to structural damage but, rather, to a shut-down of usual cellular activities. This has fueled speculation that early on, organ dysfunction may be an adaptive strategy to overwhelming inflammatory injury.¹⁰ Of course, should this process become sustained it will become maladaptive and carry the known association with poor prognosis. The third concept is the recognition that the action of the immune system against invading pathogens (also known as resistance capacity) is only part of the body’s defense mechanisms against infection. Only recently was the

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mechanism known as Tolerance in the fields of plant ecology and biology, and defined as the capacity of the host to limit cellular and tissue injury derived from immune or pathogen action, described in mammals.¹¹ Findings from experimental studies demonstrating that Tolerance mechanisms can confer organ protection and a survival advantage independent of the ability of the host to control the infection (ie, Resistance), provides a framework to investigate organ dysfunction and pathways leading to adaptation versus pathology.

Re-establishing tissue perfusion has been a cornerstone of early therapeutic rescue for patients with septic shock. Microvascular and endothelial dysfunction, autonomic failure, and characteristic bioenergetic and metabolic responses at the cellular level have been observed in multiple studies. Thus, many investigators propose targeting one or more of these mechanisms to reduce the development of sepsis-induced organ dysfunction. Interestingly, some investigators, citing the potential for adaptation (albeit resulting in transient loss of function), have speculated that some of these 'pathologic' alterations (eg, bioenergetic responses) may protect organs and tissues in the long run. Therefore, the aim of this review is to examine the current understanding of these various mechanisms in sepsis and their relation to organ dysfunction. Our goals will be to explore explanatory mechanisms as well as potential therapeutic targets.

MICROVASCULAR DYSFUNCTION

An early study by De Backer and colleagues¹² demonstrated that septic patients had altered microcirculatory flow by monitoring the sublingual microcirculation with a hand-held orthogonal polarization spectral imaging technique. The characteristic findings were a decrease in the proportion of perfused vessels, an increase in the proportion of vessels with poor flow (ie, intermittent or stopped flow), capillary drop-out (a decrease in total vessel density), and an increase in the heterogeneity of blood flow distribution.¹² These findings have now been reported by multiple independent studies, and have been demonstrated in the stomach, small intestine, colon, liver and kidney in animal models.¹³ Importantly, altered sublingual microcirculatory flow has been linked to organ failure and poor outcome in septic shock.¹⁴ What is less well understood is whether these alterations represent the cause or consequence of sepsis-associated organ failure.

Mechanisms of Microvascular Dysfunction: Endothelial Injury and Loss of Autoregulation

Although the mechanisms leading to microcirculatory dysfunction in sepsis are still incompletely understood, Fig. 1 summarizes the current conceptual framework. Such mechanisms revolve around the loss of autoregulation secondary to endothelial cell injury and altered retrograde endothelial cell-cell communication¹⁵; impaired red blood cell deformability¹⁶ and increased blood viscosity¹⁷; denudation of the glycocalyx (an organized layer of glycosaminoglycans that covers the luminal surface of the endothelium and has key biomechanical activities, including maintenance of blood flow and protection of the barrier function)¹⁸; platelet activation; leukocyte adhesion and rolling; and activation of the coagulation and complement systems.¹⁹ Nitric oxide (NO) may also contribute to microcirculatory dysfunction. Sepsis is characterized by a global increase in NO production; however, the expression of one of the key catalysts of NO production, inducible NO

synthase (iNOS), is heterogeneously distributed.²⁰ Such a distribution may parallel the heterogeneous flow patterns characteristic of septic microvascular dysfunction. Notably, selective inhibition of iNOS in sepsis has been associated with improvement in renal microcirculatory derangements and a decrease in functional renal impairment.²¹ In addition, endothelial NO synthase–derived NO, which is protective of the endothelium by inhibiting cell aggregation and promoting local vasodilatation, is decreased in sepsis, contributing to microcirculatory dysfunction.²²

Disrupted endothelial cell/glycocalyx lining results in interstitial edema, which is directly related to sepsis-induced organ failure.²³ The renal glomerular capillary endothelial cell glycocalyx seems to be particularly vulnerable to degradation in sepsis. In a cecal ligation and puncture (CLP) murine study, an increase in urinary albumin and ultrastructural changes of the glomerular filtration barrier were observed with decreased expression of syndecan-1, hyaluronic acid, and sialic acid, all significant glomerular glycocalyx components.²⁴ The cause of these barrier changes was linked to tumor necrosis factor (TNF)- α , as TNF administration to mice resulted in damage similar to lipopolysaccharide (LPS)-associated glomerular ultrastructural changes, whereas mice without TNF receptor-1 seemed resistant to LPS-induced changes in glomerular permeability.²⁵ A similar pathway of glycocalyx destruction has been observed in the lung, suggesting a common injury pathway.²⁶ In the lung, destruction of the alveolar endothelial glycocalyx stimulates increased endothelial cell fluid conductivity and results in pulmonary edema and sepsis-induced lung injury.²⁷ In the liver, sinusoidal endothelial architecture alterations have been linked to sepsis-induced hepatocellular injury and liver dysfunction. In a mouse LPS model, LPS injection resulted in loss of sieve-plate architecture of the hepatic sinusoidal endothelium, with resulting decrease in flow velocities, increase in leukocyte adhesion and sequestration, and increase in flow heterogeneity with supply/demand mismatch.²⁸

Consequences of Altered Microvascular Flow

Altered microvascular flow potentially compromises tissue perfusion. Tissue perfusion depends on 2 essential characteristics: diffusion and convection. Diffusion is contingent on vessel density; as vessel density increases, the distance oxygen will need to diffuse to reach target cells decreases and vice versa. Convection depends on red blood cell velocity and hemoglobin saturation.²⁹ Thus, a decrease in capillary density (ie, capillary dropout) will induce tissue hypoxia by a diffusion-related mechanism, whereas a decline in the proportion of vessels with adequate flow (ie, increase in proportion of vessels with intermittent and stop flow) will induce tissue hypoxia by a convection-related mechanism. Functional capillary density (FCD), estimated as the perfused vessel density (PVD), reflects the number of small vessels (less than 20 μm) that are perfused continuously in a given area.³⁰ It provides a collective estimate of the derangements due to both diffusion (capillary density) and convection (capillary flow). Physiologically, a reduction in FCD/PVD reduces the surface area for capillary exchange, decreases the available oxygen for diffusion, and increases oxygen and nutrient diffusion distance.

An additional characteristic of the altered microcirculation in sepsis is the increased heterogeneity of blood flow distribution. Although heterogeneity is expected to occur in

healthy individuals due to blood flow–metabolic demand coupling, sepsis induces a significant increase in the heterogeneity of flow, presumably uncoupling oxygen delivery from demand and, thus, making oxygen and nutrient delivery less efficient.³¹ Fig. 2 describes the decreased efficiency of increased heterogeneous flow relative to normal or homogeneously decreased flow conditions, specifically, the impact of cells with capillary flow in excess of demand (luxury flow) relative to cells with capillary flow too distant from perfused vessels (ie, hypoxic). The capillary oxygen saturation of perfused vessels that match metabolic demand is low in sepsis, suggesting sustained tissue uptake of delivered oxygen.³² Because extraction is determined by metabolic demand, capillaries providing luxury flow will contribute to increased venous oxygen saturation (SvO₂). The decrease in capillary oxygen tension with an observed preservation or elevation in SvO₂ is termed the oxygen partial pressure gap; this indicates both a regional deficiency in oxygen supply and the presence of functional shunting.³³ Insufficient blood flow to match the local tissue metabolic demands is also characterized by a decrease in carbon dioxide (CO₂) washout with an increase in venous CO₂ content and partial pressure (PCO₂), resulting in an increase in the venoarterial difference of PCO₂ (PCO₂ gap). During sepsis, high PCO₂ gaps have been documented and an inverse relationship between PCO₂ gap and microcirculatory flow has been observed,³⁴ suggesting the presence of areas of stagnant flow with lack of removal of CO₂ or, alternatively, at risk of tissue hypoxia. Additionally, capillary leak in sepsis secondary to endothelial and glycocalyx damage limits the potential of crystalloid and colloid administration to reestablish intravascular volume and promotes interstitial edema. Furthermore, interstitial edema may impair blood flow by increasing venous pressure, resulting in areas of microvascular stasis and decreased PVD.³⁵

In addition to the risk of hypoxia, decreased local blood flow velocity may be associated with an amplification of the inflammation signal. In a porcine model of endotoxemia, decreased leukocyte velocity and increased leukocyte transit time were observed in areas of sluggish flow in myocardial capillaries.³⁶ As a prolonged transit is inherently accompanied by an increased time of exposure to cytokine-secreting leukocytes and the associated pathogen- and damage-associated molecular patterns, areas of sluggish flow show increased signs of focal oxidative stress and cellular injury. In a murine CLP model, an increase in reactive oxygen (ROS) and reactive nitrogen species (RNS) was observed within 4 hours of pathogen exposure and predominantly localized to areas of decreased or no blood flow.³⁷

METABOLIC REPROGRAMING

Resistance and Tolerance

The host response against infection has been traditionally attributed to the capacity of the host's immune system to recognize, target, and eliminate foreign microbial agents with the aim to control pathogen load, a process known as resistance.³⁸ However, an alternative approach to pathogen defense, first described in plants but later described in mammals, is the capacity of the host to limit injury derived either from the infectious agent or from its own immune response. This process is known as tolerance and is characteristically independent of resistance.³⁸ For example, heme oxygenase-1 (HO-1) expression in the setting of malaria infection protects against cell-free hemoglobin-induced organ dysfunction and has been

shown to improve survival independent of a persistent parasite burden.³⁹ Expression of HO-1 during sepsis has a similar effect, decreasing sepsis-induced acute kidney injury (AKI) and improving survival, independent of the capacity of the host to control the bacterial burden.⁴⁰ Although little is known about the specific tolerance pathways triggered to protect a host in response to different threats, this concept lends a framework to understand the potential effect of metabolic adaptations on cell and organ protection and portrays the trade-off in terms of organ dysfunction.⁴¹

Metabolic Reprogramming as a Cell Survival Strategy

The cellular metabolic downregulation observed in early sepsis is proposed to be adaptive with the aim to reprioritize energy consumption to limit additional injury, maintain energy balance, prevent DNA damage, and preserve cellular composition.^{10,42} Hochachka and Guppy⁴³ proposed that cells exposed to persistent hypoxic conditions responded by decreasing O₂ demand, a mechanism called oxygen conformance. Buck and Hochachka⁴⁴ confirmed this by demonstrating that sea turtle hepatocytes downregulated energy consumption up to 10-fold in response to hypoxia, by following a hierarchical shutdown of high-energy consumptive processes, including protein synthesis, while maintaining life-sustaining processes, such as preservation of membrane potentials. Schumacker and colleagues⁴⁵ demonstrated a similar mechanism in rodent hepatocytes that, in response to chronic (but not acute) hypoxia, suppressed their respiratory rate up to 40% to 60%, demonstrating this is a conserved mechanism across species.

Therefore, transient loss of function seems to be a conserved cellular adaptive mechanism that may explain early organ dysfunction in response to sepsis. In the heart, sepsis induces a loss of contractility without cardiomyocyte death. This loss has been associated with protein downregulation and decreased activity of mitochondrial cytochrome c oxidase.^{46,47} Improvement of cytochrome c oxidase activity by exogenous cytochrome c restored cardiac contractility,⁴⁷ suggesting a direct relationship between mitochondrial alterations and loss of organ function. In the lung, energy sinks, such as the sodium and chloride transporters and ATPase-linked transmembrane pumps, are inactivated and internalized during sepsis, avoiding the overtaxing use of energy, while hindering the ability of the alveolar epithelium to clear fluid from the alveolar space and resulting in pulmonary edema (Fig. 3).⁴⁸ In the kidney, inflammation induced by LPS or proinflammatory cytokines results in downregulation of chloride and sodium channels, the most relevant energy sinks in the tubular epithelial cell (see Fig. 3).⁴⁹ This mechanism has been suggested to link tubular injury and glomerular filtration in ischemia reperfusion,⁵⁰ as an increase in tubular chloride concentration (not reabsorbed because of downregulation of channels) beyond the proximal tubule activates tubuloglomerular feedback at the level of the macula densa,⁵¹ resulting in reduced glomerular filtration rate by constriction of the afferent arteriole. However, this mechanism has yet to be demonstrated in the context of sepsis.⁵² In the liver, decreased synthesis of excreted proteins and impaired transformation of exogenous and endogenous toxins is observed in sepsis.⁵³ Hotchkiss and colleagues⁷ have shown that human sepsis is characterized by a paucity of cell death in several organs, with the exception of the gut, the immune system, and the spleen, where more apoptosis was found to occur relative to other organs. During sepsis, the barrier function of the gut epithelia is altered because of increased

epithelial apoptosis⁵⁴ and decreased crypt proliferation,⁵⁵ which results in an increase in mucosal permeability and bacterial translocation (see Fig. 3).⁵⁶ Although the role of energy regulation in the induction of intestinal epithelial apoptosis is unclear, there is evidence to suggest that T CD4⁺ lymphocytes confer protection from apoptosis⁵⁷; thus, T CD4⁺ apoptosis during sepsis may contribute to intestinal epithelial apoptosis. Finally, cellular metabolic reprogramming in response to sepsis may be orchestrated by several coordinated programs, including shifts in metabolic ATP generation (between oxidative phosphorylation [OXPHOS] and glycolysis), inhibition of mitochondrial respiration, activation of quality-control mitochondrial processes, and induction of cell cycle arrest.

Metabolic Reprogramming: From Oxidative Phosphorylation to Aerobic Glycolysis

The preferential oxidation of glucose through glycolysis despite the availability of oxygen (ie, aerobic glycolysis), a phenomenon known as the Warburg effect, is of particular interest. Although largely observed in cancer cells, immune cells also use this mechanism in response to inflammatory stimulation.⁵⁸ Using this mechanism, immune cells reprogram the pathways of energy generation such that housekeeping functions are sustained through OXPHOS, whereas the energy required for activation is derived from aerobic glycolysis. Furthermore, experimental models of sepsis have shown an early response characterized by a metabolic shift toward aerobic glycolysis in renal tissue of rodents exposed to CLP.⁵⁹ Despite being less energetically efficient than OXPHOS, there are at least 2 advantages of using glycolysis for activation roles. First, it allows for the production of essential structural components, such as fatty acids, amino acids, and nucleotides, while producing sufficient energy for cell survival.⁶⁰ Second, because of shunting of glycolytic intermediaries through the pentose phosphate pathway, increased glycolysis results in an increase in nicotinamide adenine dinucleotide phosphate (NADPH),⁶¹ which is key to reducing oxidative damage from the production of mitochondrial ROS. On the other hand, failure to restore OXPHOS at later stages of experimental sepsis has been shown to perpetuate a proinflammatory state that limits organ function and survival.⁶² Accordingly, multiple studies have shown that the stimulation of OXPHOS promoters in experimental sepsis was protective against organ damage and improved survival.^{62–64} The shifts in cellular metabolism in inflammatory cells have been shown to be secondary to the complex interaction of important cellular regulation nodes that include the Akt/mammalian target of rapamycin complex 1 (mTORC1)/hypoxia inducible factor 1 alpha (HIF-1 α) pathway driving the initial shift toward glycolysis,⁶⁵ and sirtuins (particularly Sirt1 and 6) driving the switch back to OXPHOS at a later stage (Fig. 4).⁶⁶

Respiratory Electron Transport Chain Inhibition

The effect of sepsis on mitochondrial respiration and on specific electron transport chain complexes has been documented in both animal models⁴² and human sepsis.⁶⁷ Complex I and IV activity of the mitochondrial electron transport chain was significantly reduced in skeletal muscle biopsies of critically ill patients, with nonsurvivors demonstrating a more profound reduction in activity and a concomitantly greater reduction in tissue ATP.^{67,68} These events have also been documented in the liver in rodent models of sepsis,⁴² suggesting this is not specific to skeletal muscle but rather a potentially universal mechanism. Mitochondrial complexes I and IV are susceptible to persistent inhibition by

nitrosylation, a reaction facilitated by RNS, that is elevated in the setting of sepsis,^{69,70} limits cell death, and, importantly, is reversible to reestablish normal organ function.

Cellular Regulation of Mitochondria: Mitophagy and Biogenesis

Increased autophagy, the cellular digestion of unnecessary or dysfunctional components, has been observed in multiple organs during the early stages of experimental sepsis^{71–73} and has been documented in human sepsis.⁷¹ Autophagy occurs during sepsis in response to Toll-like receptor 4 (TLR-4)-mediated inflammation,⁷⁴ oxidative stress,⁷⁵ and mitochondrial membrane depolarization due to uncoupled respiration from ATP production in the electron transport chain.⁷⁶ In this context, sepsis-induced inhibition of electron transport chain complexes may serve as a signaling mechanism to activate autophagy. Activation of autophagy is clinically relevant because lack of initiation of the autophagic response is associated with prolonged critical illness and lack of recovery from organ dysfunction.⁷⁷ Furthermore, pharmacologic enhancement of autophagy by inhibiting mTOR with temsirolimus or epirubicin results in protection from AKI⁷⁸ and in improved survival,⁷⁹ respectively, in murine models of LPS-induced sepsis. By contrast, inhibition of autophagy by blocking vacuolar sorting protein 34 (VPS34), a central protein in promoting autophagic signaling, resulted in increased liver dysfunction.⁷² The autophagic response has also been suggested to be an integral mechanism of metabolic reprogramming in response to inflammation because removing dysfunctional mitochondria and decreasing mitochondrial mass can decrease ROS-induced injury and OXPHOS, particularly in the acute shift toward aerobic glycolysis.⁴¹

Mitophagy is coupled to mitochondrial biogenesis by redox pathways and TLR-9–dependent mechanisms.⁸⁰ Replenishment of the mitochondrial pool may be integral in recovery from sepsis. Accordingly, Peroxisome proliferator-activated receptor gamma coactivator 1- α (PGC-1 α), a transcriptional coactivator of mitochondrial biogenesis, was shown to be increased in muscle biopsies of sepsis survivors as compared with nosurvivors.⁶⁸ Furthermore, exogenous activation of mitochondrial biogenesis with inhaled carbon monoxide during experimental sepsis was protective from hepatic injury.^{81,82}

Regulation of the Cell Cycle

Mitochondria are also involved in regulation of the cell cycle⁷⁶ and may induce cell cycle arrest as a protective mechanism. In its simplest terms, the cell cycle is the progression of the cell through specific phases in preparation for cell division (including G0, G1, S, G2, and M for mitosis). During this progression, the cell seems to use specific checkpoints to verify it is ready to advance to the next stage. The G1-S checkpoint seems to be important from an energy standpoint because it is at this stage that mitochondria coalesce into a giant mesh,⁸³ presumably to increase energy availability for replication of DNA during G2. During these checkpoints, the cell seems to verify if it is ready to advance to the next stage. If not ready, cell cycle arrest can prevent the energetic cost of replication but can also prevent cell death in the setting of cell injury (Fig. 5). This prevention is supported by the findings of Yang and colleagues⁸⁴ who demonstrated that G1-S cell cycle arrest was associated with AKI after CLP-induced sepsis, and recovery, with progression to G2. Interestingly, the recently approved AKI biomarkers, tissue inhibitor of metalloproteinases-2 and insulinlike growth

factor-binding protein 7, are known to induce G1 cell cycle arrest. These biomarkers were superior to other markers for identifying the risk of AKI during critical illness, including sepsis.⁸⁵

ORGAN CROSSTALK

Dysfunctional organs may impact other remote organs through complex, and incompletely understood, biological communication processes known as organ crosstalk. Kidney-brain crosstalk was observed in animal models of AKI in which local renal inflammation secondary to TNF α administration was associated with a disrupted, more permeable blood-brain barrier and activation of brain astrocytes.⁸⁶ Glial fibrillary acidic protein, a cellular marker of brain inflammation, was elevated in animal models of AKI but was not elevated in animal models of liver injury, suggesting specificity for AKI.⁸⁶ In other animal models, AKI has been associated with alterations in cerebral neurotransmitter concentrations and depletion of brain catecholamine concentrations.^{87,88} Lung-brain crosstalk occurs in patients following lung injury with subsequent development of brain damage despite otherwise normal prior neurologic function.⁸⁹ This neuropathology was shown to be independent of hypoxia in a porcine model of acute lung injury in which similar levels of hypoxemia were achieved by pulmonary lavage and decreased fraction inspired oxygen, with lavage animals ultimately showing greater brain damage.⁹⁰

Differentiating crosstalk from other inflammatory syndromes is difficult. For example, LPS-challenged rats subjected to moderate positive end expiratory pressure (7 cm H₂O) and low tidal volume ventilation showed decreased lung injury and systemic inflammation compared with rats ventilated with high tidal volumes; yet, expression of c-Fos, an early marker of neuronal activation in the brain, was similarly elevated in the same regions of the brain in both LPS and high tidal volume groups.^{91,92} Inflammatory crosstalk via systemic cytokines between the kidney and lungs has been observed in preclinical and clinical studies with ventilator-induced lung injury (VILI) associated with high tidal volume mechanical ventilation contributing to the development of AKI.⁹³ There seems to be a unique pattern of renal inflammation in kidney-lung crosstalk. A mouse model of AKI with subgroups exposed to CLP, VILI, and sham demonstrated an elevation in vascular endothelial growth factor, an angiogenic and endothelium activating protein, and vascular cell adhesion protein 1, a leukocyte adhesion molecule, in only those animals within the VILI subgroup.⁹⁴ In a murine model of AKI and bacterial pneumonia, AKI alone did not cause clinically significant acute lung injury; however, in the setting of bacterial pneumonia, AKI did attenuate pulmonary neutrophil recruitment and increase bacterial load with resulting compromised oxygenation.⁹⁵

Although not solid organs, the coagulation and complement systems influence each other through interrelated pathways in the setting of sepsis. This relationship is observed in early sepsis with coinciding robust complement activation and the potential for disseminated intravascular coagulation. Complement end products increase thrombogenicity of the blood, induce procoagulant and antifibrinolytic proteins, and inhibit anticoagulant pathways.^{96,97} C3 convertase inhibition in bacteria-induced sepsis in baboons prevented sepsis-induced complement activation, decreased thrombocytopenia and coagulopathy, and preserved

endothelial anticoagulant properties.⁹⁸ Coagulation factors also impact complement activation. Thrombin and coagulation factor Xa directly activate components of the complement cascade⁹⁹; protein C inhibits complement activation,¹⁰⁰ and coagulation factor XIIa directly activates the classic complement pathway.¹⁰¹

Autonomic Nervous System

A conceptual extension of this crosstalk involves communication between the autonomic nervous system and immune system in the setting of inflammation. Increased circulating catecholamines in early sepsis enhances the initial inflammatory response. In addition to autonomic neurons, leukocytes can synthesize catecholamines¹⁰² and express adrenergic receptors, demonstrating neurotransmitter-influenced lymphocytic trafficking, vascular perfusion, and immune cellular proliferation and apoptosis.¹⁰³ Furthermore, portal venous drainage of gut-derived catecholamines can alter the functional state of the liver Kupffer cells and hepatocytes through α_2 -adrenergic receptor signaling.^{104,105}

Vagus afferents stimulated by cytokines and inflammatory molecules promote vagal nerve efferent cholinergic signaling, inhibiting the excessive release of TNF and other proinflammatory cytokines.¹⁰⁶ This cholinergic signaling is communicated via α -7 nicotinic acetylcholine receptors found on macrophages and other immune cells.¹⁰⁷ This inflammatory reflex for excessive proinflammatory signaling also extends to efferent vagal communication with the splenic nerve.¹⁰⁸ Vagal nerve stimulation 24 hours after CLP-induced sepsis in a murine model improved survival.¹⁰⁹ On the other hand, vagotomy was associated with increased proinflammatory cytokine levels in endotoxemic animals.¹⁰⁶

SUMMARY

Sepsis is a complex syndrome characterized by significant clinical heterogeneity, in which morbidity and mortality are driven by organ dysfunction. Importantly, organ dysfunction in sepsis is now recognized to be more than just the consequence of decreased tissue oxygen delivery and instead involves multiple responses to inflammation, including endothelial and microvascular dysfunction, immune and autonomic dysregulation, and cellular metabolic reprogramming. Experimental data suggest that targeting these mechanisms may result in organ protection and offer survival advantage. However, it also underscores that the effect of targeting these mechanistic pathways on short- and long-term outcomes depends highly on the timing of therapeutic intervention. In moving forward, efforts to understand the adaptive or maladaptive character of these mechanisms, to discover phase-specific biomarkers to guide therapy and to conceptualize these mechanisms in terms of resistance and tolerance will provide a structured research platform, a translational gateway, and an opportunity to improve patient outcomes.

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KEY POINTS

- Organ dysfunction in sepsis involves multiple mechanisms, including endothelial and microvascular dysfunction, immune and autonomic dysregulation, and cellular metabolic reprogramming.
- Both adaptive and pathogenic responses result in decreased organ function; the clinical phenotype involves a mixture of these responses in a complex, time-dependent way.
- The concept of resistance is well engrained in medicine; but tolerance is less well understood and potentially as important, especially for the critically ill and injured.
- Multiple forms of organ crosstalk have been identified, helping to explain the multiple organ dysfunction that is characteristic of sepsis.

Fig. 1.

Mechanisms leading to microcirculatory dysfunction: damage- and pathogen-associated molecular patterns (DAMPs and PAMPs), oxidative stress, and altered nitric oxide production contribute to endothelial dysfunction. As a result, glycocalyx denudation alters the colloid osmotic gradient between the capillary lumen and protein-rich area protected by the glycocalyx layer, leading to increased capillary leak and to increased adhesion of platelets and neutrophils. An inducible nitric oxide synthase (iNOS)-dependent decrease in endothelial nitric oxide synthase (eNOS)-derived nitric oxide production results in loss of endothelial protection via loss of direct vasodilation and loss of platelet aggregation and leukocyte activation inhibition and platelet adhesion and coagulation cascade activation in the setting of endothelial dysfunction. VCAM-1, vascular cell adhesion protein 1. (*Adapted from Gómez H, Kellum JA. Sepsis-induced acute kidney injury. Curr Opin Crit Care 2016;22(6):546–53.*)

Fig. 2.

Decreased efficiency of oxygen delivery with heterogeneous flow. In normal microcirculatory flow, cells extract oxygen to meet oxygen consumption (VO_2) requirements. Homogeneously decreased flow results in decreased oxygen delivery (DO_2) but preserved extraction and VO_2 , with a resulting decrease in venous oxygen saturation (SvO_2). In the presence of heterogeneous flow, despite preservation of total oxygen delivery, only a portion of capillaries is perfused. Cells too distant from perfused vessels do not receive enough oxygen to meet metabolic requirements and become hypoxic. Therefore, provided no changes in VO_2 , hypoxic regions could be found in the presence of an elevated SvO_2 . (Modified from De Backer D, Ospina-Tascon G, Salgado D, et al. Monitoring the microcirculation in the critically ill patient: current methods and future approaches. *Intensive Care Med* 2010;36:1813–25; with permission.)

Fig. 3.

Common epithelial functions in health and in sepsis. Vectorial transport in the lung becomes altered in sepsis causing loss of polarity and barrier function (A); epithelial barrier function in the intestine becomes impaired in sepsis causing increased permeability and bacterial translocation (B); and communication and signaling in the kidney becomes associated with cell-cell, paracrine, and endocrine communication in sepsis (C). Cl, chloride; H₂O, water; I-FABP, intestinal-fatty acid binding protein; IGFBP-7, insulinlike growth factor binding protein-7; IL-18, interleukin-18; K, potassium; KIM-1, kidney injury molecule-1; KL-6, Krebs Von den Lungen-6; Na, sodium; NGAL, neutrophil gelatinase-associated lipocalin; PAMPs, pathogen-associated molecular patterns; sRAGE, soluble receptor of advanced glycation end products; TGF, transforming growth factor; TIMP-2, tissue inhibitor of metalloproteinases-2; ZO, zonula occludens. (From Acute dialysis quality initiative 14. Available at: www.adqi.org. Accessed June 7, 2017; with permission.)

Fig. 4.

Inflammation-induced metabolic shift from OXPHOS to aerobic glycolysis. In monocytes, the shift toward aerobic glycolysis has been attributed to the activation of HIF-1 α . This shift results in increased expression of cytoplasm glucose transporters, enhanced activity of glycolytic enzymes, expression of pyruvate kinase isoform M2 (PKM2, slows conversion of phosphoenolpyruvate to pyruvate), and expression of pyruvate dehydrogenase kinase (PDHK, limits pyruvate entrance into Krebs cycle). A shift back to OXPHOS has been attributed to the nicotinamide adenine dinucleotide (NAD)-dependent deacetylases (sirtuins) SirT1 and SirT6, which blocks the HIF-1 α axis. ACC, acetyl CoA carboxylase; Akt, serine/threonine-specific protein kinase; AMP, adenosine monophosphate; ATP, adenosine triphosphate; cpt1, carnitine palmitoyl transferase; HIF-1 α , hypoxia inducible factor-1 alpha; IL, interleukin; IL-1, IL-4, IL-6, and IL-10, interleukin 1, 4, 6 and 10, respectively; LDH, lactate dehydrogenase; M1, macrophage activation phenotype with inflammatory functions; M2, macrophage activation phenotype with anti-inflammatory functions; MCP-1, monocyte chemoattractant protein-1; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex; NAD⁺/NADH, oxidized/reduced nicotinamide adenine dinucleotide; PDH, pyruvate dehydrogenase; PGC-1 α , Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; Sirt1,6, sirtuin 1 and 6; T-CD4⁺, T lymphocyte-cluster of differentiation 4; Th17, T helper 17 cell; TNF, tumor necrosis factor; Treg, regulatory T cell. (Adapted from Gómez H, Kellum JA, Ronco C, et al. Metabolic reprogramming and tolerance during sepsis-induced AKI. *Nat Rev Nephrol* 2017;13(3):143–51.)

Fig. 5.

Inflammation-induced metabolic reprogramming. Exposure of tubular epithelial cells to damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) leads to changes in metabolic regulation within the cell that can impact cell survival, organ function and, possibly, repair events after injury subsides. The image shows 3 possible domains of acute-phase metabolic regulation, including triggering of mitochondrial quality control processes including mitophagy and biogenesis, shifting metabolism from OXPHOS toward glycolysis, and inducing cell cycle arrest. FAO, fatty acid oxidation; IGFBP7, insulinlike growth factor-binding protein 7; OXPHOS, oxidative phosphorylation; TIMP-2, tissue inhibitor of metalloproteinases-2; TLR-4, toll-like receptor-4. (*Adapted from* Gómez H, Kellum JA. Sepsis-induced acute kidney injury. *Curr Opin Crit Care* 2016;22(6): 546–53.)