Mechanisms of Organ Dysfunction in Sepsis

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KEYWORDS

• Sepsis • Organ dysfunction • Microcirculation • Mitochondria • Metabolism • Inflammation

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.

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]

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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 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 colleagues[12] demonstrated that septic patients had altered microcirculatory flow by monitoring the sublingual microcirculation with a handheld 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.