

## Introduction

# Re-establishing organ function in severe sepsis: targeting the microcirculation

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Severe sepsis is defined as sepsis associated with acute organ dysfunction, and is a major cause of mortality in critical care patients. More than 750,000 cases of severe sepsis occur annually in the USA, and the syndrome causes 215,000 deaths in the USA every year [1]. Unfortunately, the incidence of severe sepsis is increasing faster than the mortality rate is decreasing, which suggests that current therapies are not effective enough. The key to increasing survival in severe sepsis patients is understanding more about the disease so that newer therapies can be better used, and more successful treatments can be developed.

Microcirculatory dysfunction has been identified as a key component in the pathophysiology of sepsis. If not corrected, microvascular dysfunction can progress to organ dysfunction and subsequent mortality. This suggests that targeting the microcirculation when treating sepsis might be an important step in increasing patient survival. However, in order to successfully restore microcirculatory dysfunction, it is necessary to understand how it occurs, how it contributes to organ dysfunction, and how various therapies act on the microvasculature.

This supplement begins with a series of three articles by Ellis and colleagues, Vincent and De Backer, and Ince that discuss the physiology of the microcirculation and how its monitoring system, which includes the endothelium and the erythrocytes, allows the regulation of oxygen delivery. In sepsis, this regulatory system fails, leading to tissue hypoxia despite adequate oxygen supply. Experimental and clinical data are available showing that reduced microcirculatory flow and increased heterogeneity of microvessel perfusion play an important part in organ dysfunction, and that the higher the degree of such disruption, the poorer the outcome. Indeed, it is possible that, even if systemic hemodynamic variables are corrected, microcirculatory distress can persist in a condition that has been termed microcirculatory and mitochondrial distress syndrome. This accentuates the need for techniques that are specifically designed to monitor microcirculatory

function, such as orthogonal polarized spectral imaging and sidestream dark-field imaging, in order to ensure that the correct therapeutic options are employed to help improve microvascular function.

Articles by Trzeciak and Rivers, and Bateman and Walley show that such experimental techniques are also extremely important in the study of the clinical manifestations of disordered microcirculatory perfusion in severe sepsis, and have allowed visualization of the microcirculatory response to therapeutic interventions at the bedside. This, in turn, has allowed the assessment of various treatment modalities, including vasodilators, in severe sepsis. The evidence suggests that early goal-directed therapy is effective, and it has also become clear that, clinically, resuscitation of mean arterial pressure and cardiac output alone is not enough to improve microvascular function, and that successful modulation of inflammation has a positive impact on endothelial function and the microcirculation. Thus, it follows that therapeutic agents with multiple mechanisms of action might be the best option for restoring microcirculatory function, thereby preventing organ dysfunction and death.

The final two articles from Hoffmann and colleagues and Macias and colleagues discuss the experimental and clinical evidence for the effectiveness of recombinant human activated protein C (drotrecogin alfa [activated]) in severe sepsis. Whilst its exact mechanism of action is not fully understood, it is believed that the anti-inflammatory and anticoagulatory properties of activated protein C are able to improve microvascular perfusion, and thus ameliorate organ function.

This supplement aims to provide the reader with a comprehensive overview of the role of the microcirculation in severe sepsis, how its dysfunction can, through various pathways, lead to organ failure and death, and how therapies with multiple mechanisms of action might be the best option for re-establishing organ function.

### **Competing interests**

J-FD is a consultant for Eli Lilly.

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### **Reference**

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