**Factors Affecting the Pathophysiology of Sepsis, an Inflammatory Disorder: Key Roles of Oxidative and Nitrosative Stress**

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**Abstract:**

Sepsis, one of the primary causes of mortality in the intensive care units of hospitals, occurs due to the host’s dysregulated immune responses to an infection. As a consequence, persistent systemic inflammation along with suppressed adaptive immunity ensues, resulting in deranged metabolism, recurrent infections, tissue damage and multiple-organ failure. The uncontrolled oxidative stress mediated by the imbalance between the generation of reactive oxygen species and their neutralization by the host’s antioxidant system is involved in inflammation induced damage. The profound deleterious effects in the host range from mitochondrial dysfunction and endothelial damage to reduced cardiac output. Therefore, antioxidant therapy was actively considered to have therapeutic benefits in sepsis patients. Although successful in animal models, antioxidant therapy did not show efficacy in clinical trials with sepsis patients. Another key molecule that may dictate the outcome and prognosis during sepsis is Nitric Oxide (NO). This pleiotropic molecule plays a central role in inflammation and is critical for leukocyte recruitment at the site of inflammation. NO is synthesized by three different isoforms of Nitric Oxide Synthases (NOS) and significantly high and sustained levels of NOS2 have been reported in sepsis. Abundant literature supports the protective roles of NO during sepsis; however, there is ambiguity in various reports. The administration of NO donors in clinical trials for sepsis treatment has encountered limited success. NO, during sepsis, acts like a double-edged sword: Increased NO levels can result into hypotension whereas reduced levels contribute to poor organ perfusion and an elevated susceptibility to infection. Therefore, several parameters need to be evaluated while considering the potential of NO based therapy during sepsis.

**Keywords**: Sepsis, Reactive Oxygen Species, Reactive Nitrogen Species, Nitric Oxide Synthase