Biomarkers Angipoietin-1,-2 and Endocan biomarkers for sepsis

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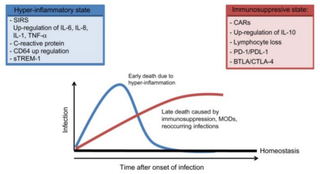
Abstract

According to the CDC, sepsis when an infection spreads throughout the body leading to extreme conditions: increased heart rate, confusion, shortness of breath, and organ failure (1). Current biomarkers such as lactate and procalcitonin are often not accurate nor precise. An ideal biomarker for sepsis should confirm or predict that a patient has sepsis and what their risk factor for more complications. Sepsis risk factors are associated with vascular endothelial dysfunction, therefore biomarkers indicating the condition of the vascular endothelium are appropriate. The markers Angiopoietin-1, -2 and Endocan are biomarkers can provide more accurate and precise prognostic and diagnosis value in sepsis identification and treatment than current biomarkers.

Introduction

According to the CDC, sepsis is the 11th leading cause of death with 1.7 million patients developing sepsis and 270,000 dying (2). The general consensus is that the development of sepsis occurred in two stages: a cytokine storm, a proinflammatory reaction, and compensatory anti-inflammatory response system (CARS). Theses immune responses sepsis may evolve may not follow from a one-two step, but may occur due to the interactions of the various immunodeficiencies and cellular processes . Death often caused by sepsis, as seen in Fig 1, are often caused because of these two stages (1).

Fig 1 Death due to sepsis is often cause either due to the hyper-inflammatory stage or in the CARS stage (1).



Infections that can result in Sepsis occur in the lungs, skin, tissue but can affect circulatory vessels, lymphatic vessels, and organs. As a result sepsis can cause death due to organ failure. To decrease mortality associated with sepsis, competent biomarkers are needed to help with diagnosis and treatment.

Biomarkers found in the body need to reliably analyze the disease condition and provide some prognostic value to aid treatment. In cases such as sepsis, the ideal biomarker should allow medical profession to identify patients who have various levels of sepsis, help identify patients who could develop sepsis, or aid in the treatment in patient with sepsis. The ideal end goal of a biomarker needs to be to help lower the overall mortality rate of sepsis.

Sepsis often involves the vascular endothelium. Therefore, biomarkers involved with either stabilizing or de-stabilizing the condition and function of vascular endothelium should be used.

Method Selection

This project is a literature review discussion of how the biomarkers Endocan and Angiopoitein-1,2 can improve the diagnostic and prognostic indication of sepsis better than current biomarkers used, such as procalcitonin or lactate. Material used in this review included the following topics: Sepsis, Endocan, and Ang-1,2.

Endocan

Endothelial reaction to inflammation can be caused by sepsis, Spontaneous bacterial peritonitis, and acute respiratory distress syndrome (ARDS) ARDS. Pro-inflammatory cytokines such as TNF-α and IL-1 β increase release of endocan from endothelial cells (4). This increased release of endocan in response to various interactions may correlate to the degree of sepsis. Higher endocan levels have a positive correlation to increased degrees of sepsis in diseases such as (ARDS) and spontaneous bacterial peritonitis (SBP).

The risk factor of SBP developing in cirrhosis patients was determined using such indicator as cytokines and endocan. An increase in cytokines may result in an increase in endocan. Patients with cirrhosis had higher levels of endocan than the normal population (Fig 2). Patients who died of sepsis had elevated endocan levels compared to patients with sepsis who survived (4).

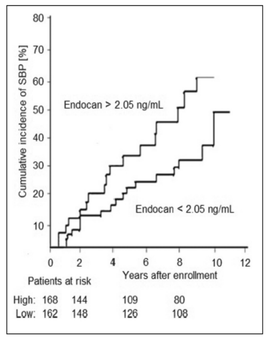


Fig 2. Cirrhosis patient population that had Endocan levels higher than 2.05 ng/mL had higher rates of SBP as compared to patient population that had lower levels of Endocan < 2.05 ng/mL (4).

For example, patients with sepsis that developed into acute respiratory distress syndrome (ARDS) had higher endocan levels (Fig. 3) (5).

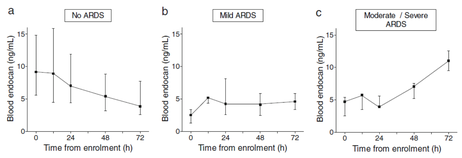


Fig 3. Relationship of degree of sepsis to the development of ARDS in mice models (5).

Angiopoietin-1, -2

Along with endocan, angiopoietins have a correlation with inflammation and sepsis. A biomarker that seems to be a good indicator for sepsis is Angiopoietin-1 (Ang-1) and Angiopoietin-2 (Ang-2). In relation to tyrosine kinase receptor Tie2, Ang-1 is released from the endothelium as an anti-inflammatory and Ang-2 as a pro-inflammatory. Ang-1 connects to Tie-2 actions via enzyme action to stabilize Tie-2 and Ang-2 connects to Tie-2 to de-stabilize Tie-2actions (6).

Ang-1, produced by pericytes, smooth muscle cells and fibroblast, is found on the extracellular matrix. Ang-1/Tie2 binding is thought to promote vessel stabilization, anti-inflammatory, pro-survival and anti-permeability signaling through phosphorylation of Tie2. In contrast, in an autocrine response, activated ECs rapidly release stored-preformed Ang-2. Ang-2/Tie2 binding is believed to produce vessel destabilization, pulmonary leakage and inflammation (6).

High Ang-2 levels are associated with sepsis severity and multiple organ dysfunction in sepsis in vitro and in vivo (7) High levels of Ang-2 is found in the blood of trauma patient and is associated with endothelial dysfunction poor outcomes. Ang-2 levels correlate with disease severity. In patients with suspected infection within the first hour of hospitalization had higher Ang-2 levels (3). Strong association with DAN and coagulopathy in trauma patients (5). In mice models, after a hemorrhage occurred in the lungs, Ang-2 levels increased directly after the event, decreased and steadily increased as compared to the normal 'Naïve' control as seen in Fig 4.

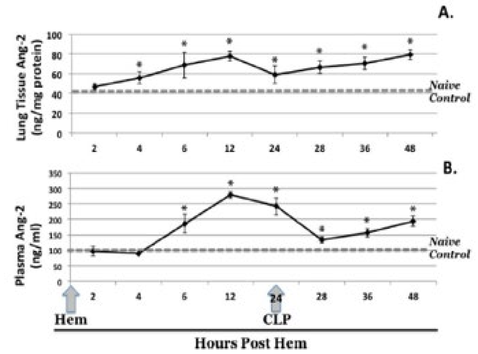


Fig. 4. After hemorrhage in the lungs, Ang-1 and Ang-2 levels increase as compared to the native control. Two periods of Ang-1, Ang-2 release. First shortly after the initial hemorrhage and second CLP (5).

Treatment target Ang-2, especially the use of monoclonal antibody target against Ang-2, have been show to reduce damage done to the endothelium cells (3). In Ang-2 KO mice, mice with sepsis exhibit greater survival and less vascular inflammation (3)

Conclusion

Angiopoietin-1, -2 levels change in response to sepsis and other stresses. Because of Ang-1 action of promoting vascular stability and Ang-2 action of de-stabilizing the vascular endothelium, their levels can help identify the general state of the vascular. Treatments involving blocking Ang-2 have been show to improve mice models and may be useful treatment in patients. Elevated endocan levels are strong indicators of sepsis and may be useful as predictors of patient conditions. Due to the small sample cohorts for all the studies, much research needs to be done to confirm all of these results.

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