Angiopoetin-1, Angiopoietin-2 and VEGF in Sepsis.

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**Background:** Sepsis is a systemic inflammatory response to a microbial pathogen that often results in increased hemodynamic shock, end-organ damage, and death. Advances have been made in the use of antibiotics, source control, and supportive care yet severe sepsis remains a highly lethal disease and biologically significant diagnostic tools and markers of prognosis remain poorly defined. Recent findings suggest that growth factors may play a role in the host response in sepsis. Endothelial growth factors including Vascular Endothelial Growth Factor (VEGF), Angiopoietin-1 (Ang-1) and Angiopoietin-2 (Ang-2) are known to play essential roles in angiogenesis and vascular remodeling. The Angiopoietins are a family of vascular growth factors that act predominantly on the endothelium via the Tie-2 receptor. Although their relationship is complex Ang-1 and Ang-2 appear, in part, to have opposing functions in their contributions to vascular development. Ang-1 stabilizes endothelial cell resulting in decreased vascular permeability while Ang-2 destabilizes blood vessels in the absence of VEGF. Ang-2 is already known to be increased in severe sepsis and septic shock and is associated with disease severity and appears to be associated with mortality.

**Specific Aim:** To examine Ang-2, Ang-1, and VEGF levels in human subjects admitted to the ICU with sepsis and to determine the relationship of these markers to severity of illness and mortality.

**Hypothesis:** Ang-2 levels in the first 24 hours of admission to the ICU will be elevated in patients with presumed sepsis and higher Ang-2 levels will correlate with a higher severity of illness. Higher levels of Ang-1 relative to Ang-1 will be associated with higher severity of illness and mortality. Lower levels of VEGF in association with elevated Ang-2 will be associated with higher severity of illness and increased mortality.

**Methods:** Subjects were identified for enrollment by reviewing admissions to the Yale MICU service (Yale Human Investigation Committee Protocol #26460). Standard consensus definitions of sepsis were used to determine clinical categorization. Consent for participation in the study was obtained and plasma and serum samples were collected within the first 24 hours of admission to the MICU. Samples were processed and stored in a -90 degree Celsius freezer for future analysis. Levels of the circulating mediators Ang-2, Ang-1 and VEGF were determined by ELISA. Patient charts were reviewed for clinical data including information to determine admitting diagnosis, severity of illness score, and mortality. Association between mediators and severity of illness and mortality was evaluated using non-parametric methods (Spearman and Mann Whitney U).

**Results:** Ang-2, Ang-1, and VEGF were readily detected in all specimens. Ang-2 is strongly associated with severity of illness whereas Ang-1 and VEGF are not. Mortality appears to be increased in those with high levels of Ang-2 relative to Ang-1 and low in those with high levels of VEGF compared to Ang-2.