Crit Care Med. Author manuscript; available in PMC 2012 March 01.

Published in final edited form as:
Crit Care Med. 2011 September ; 39(9): 2203–2204. doi:10.1097/CCM.0b013e31821f02bf.

Angiopoietins as prognostic biomarkers and effector molecules in severe sepsis

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Keywords

angiopoietins; sepsis; outcome

Editor

I read with interest the article by Ricciuto et al. and the accompanying editorial (1) . I was disappointed to read in the editorial, that "the study by Ricciuto " was the first to depict Ang-1 as an independent factor related to an unfavourable outcome", when we had published a study in *Critical Care* last year in which we reported that low Angiopoietin-1(Ang-1) levels were independently associated with mortality (2). We examined the relationship between mortality from severe bacterial infection and Ang-1, Ang-2 and the growth factors vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). We found that lower plasma VEGF, PDGF, FGF and Ang-1 and higher Ang-2 concentrations were associated with an unfavourable outcome (2).

To our knowledge, our study is the largest published study on Ang-1 and Ang-2 in patients with severe bacterial infection. The paper by Ricciuto et al. (1) reports data on 70 patients, whereas our study reported 293 children, thus our study was well powered to detect differences in Ang-1 levels between survivors and non-survivors. The mortality in our cohort was 22% compared to the mortality of 44% in the study by Ricciuto et al.. We used samples analysed from ethylenediaminetetraacetic acid (EDTA) plasma, and produced the same findings as Ricciuto et al. , so we do not believe that this explains the discrepancy found between the study by Ricciuto and previous studies. Another strength of our study is that we had a group of healthy non-septic children as controls, allowing us to detect spurious differences that might have been due to sample handling, and also allowing us to assess the possible effects of other asymptomatic co-infections.

Our paper reported significant negative correlations between plasma Ang-1 and plasma interleukin-1 Ra (IL-1Ra) and plasma interleukin-6 (IL-6), and significant positive

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correlations between Ang-2 and plasma IL-1Ra, plasma IL-6, plasma interleukin-8 (IL-8) and plasma interleukin-10 (IL-10). We also showed that the ratio of Ang-2 to Ang-1 was higher on non-survivors compared to survivors, p=0.03 (2). We demonstrated significant correlations between Ang-2 and Blantyre Coma Score (a measure of disease severity) and admission lactate (r=−0.43 and r=0.33, p<0.0005 respectively).

In conclusion, we support the findings of Ricciuto et al. that angiopoietins are clinically informative biomarkers of disease severity and outcome in severe sepsis. Our data also strongly support the concept that the angiopoietins are biomarkers as well as effector molecules in sepsis. We believe that the investigation of host mediators that directly influence endothelial function might be a valuable approach to improve our understanding of the pathophysiology of sepsis.

Acknowledgments

Dr. Carrol received funding from the Wellcome Trust.

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