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Title: Angiopoietins: Possible biomarkers in severe pneumonia?

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Body: In severe pneumonia, endothelial permeability may develop due to an inadequate host-pathogen interaction and might lead to acute lung injury (ALI). The angiopoietins Ang-1 and Ang-2 are centrally involved in inflammation and permeability. Ang-1 reduces endothelial inflammation whereas Ang-2 enhances the impact of inflammatory stimuli on the endothelium. In murine pneumococcal pneumonia, we previously observed that therapeutic application of Ang-1 attenuated lung injury in severe pneumonia, and pretreatment with specific siRNA against Ang-2 reduced pneumolysin (PLY) induced permeability in isolated perfused mouse lungs (ERS2011). In this study, Ang-1 and Ang-2 were quantified in serum of patients with lethal (n=58) and non-lethal (n=42) pneumonia (CRB65 0-3;CAPNETZ) as well as patients with pneumonia-induced ALI (VALIDstudy, n=44). Stimulating human umbilical vein endothelial cells (HUVEC) with PLY, we measured Ang-2 levels after 3 hours and investigated the impact of Ang-2 on endothelial barrier function in vitro. At the time of pneumonia diagnosis, patients with subsequently lethal pneumonia had higher Ang-2 serum levels than patients with non-lethal pneumonia. Ang-2 levels correlated with procalcitonin concentrations. In pneumonia-induced ALI reduced serum Ang-1 and increased serum Ang-2 converged to normal amounts within 7 days. PLY stimulation increased Ang-2 release from HUVEC, and Ang-2 caused a rapid permeability increase in HUVEC monolayers. Our combined results suggest that angiopoietins may play an important role in the development of lung failure in pneumonia. Current further investigations in larger patient cohorts may validate Ang-2 as biomarker for improved risk stratification in pneumonia.