

# ATS Highlights 2023: Critical Care Assembly Early Career Professionals



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## ***Tell us about yourself.***

I am a Pulmonary and Critical Care physician-scientist dedicated to studying recovery from sepsis and critical illness. I completed Internal Medicine residency training at University Hospitals – Case Western Reserve and pulmonary/critical care fellowship at the University of Michigan, where I continue my clinical and research career.

## ***Tell us about your research.***

I am uniquely focused on understanding how dysregulated biology after sepsis contributes to poor long-term outcomes in sepsis survivors, such as new infections or respiratory failure. I study basic and translational mechanisms of dysregulated inflammation after sepsis with a particular interest in how long-term changes in monocytes and macrophage populations influence secondary responses in the lung. I am working to identify novel immune phenotypes which might act as biomarkers and/or causal mechanisms to help identify and treat patients at risk for poor outcomes after sepsis.

## ***Where do you see yourself in 5 years?***

Leading a translational research program utilizing sepsis survivor specimens and representative mouse models to identify and target novel immune phenotypes in sepsis survivors.

## ***How has the Critical Care Assembly contributed to your career?***

Through direct participation in the ATS international meeting and also the Early Career Professionals working group, I have found a network of peers, mentors, and collaborators which have been vital to the advancement of my career.



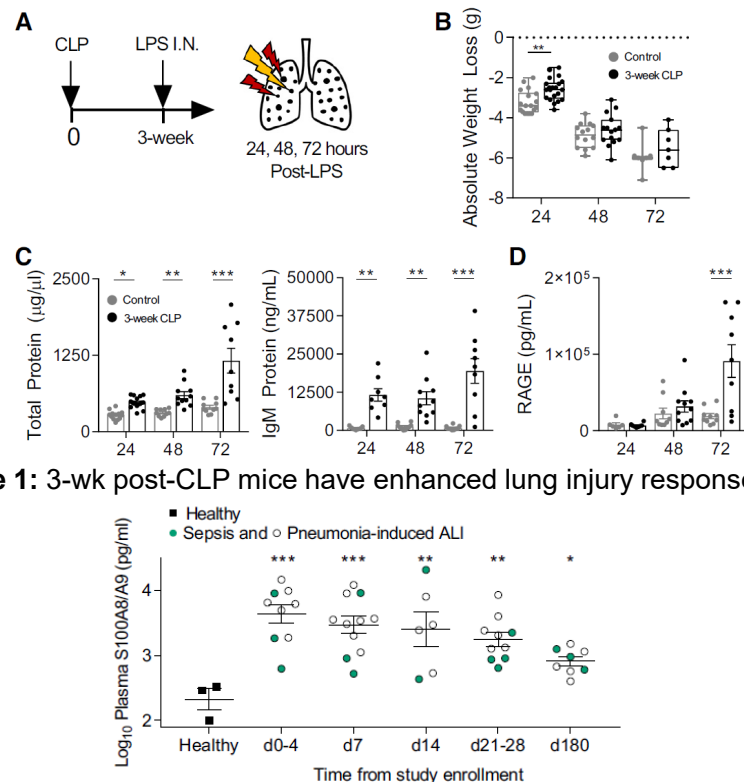
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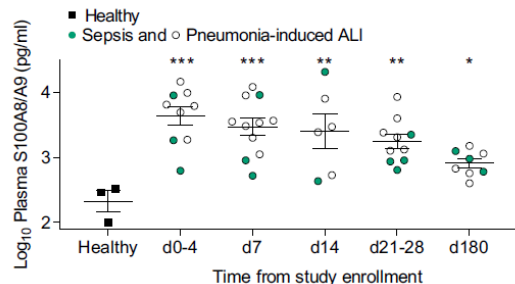
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**Figure 1:** 3-wk post-CLP mice have enhanced lung injury responses to LPS.



**Figure 2:** S100A8/A9 is persistently elevated in sepsis survivor mice (not shown) and humans.

**Long-term survivors of murine sepsis are predisposed to enhanced LPS-induced lung injury and proinflammatory immune reprogramming.**

**Denstaedt SJ**, Bustamante AC, Newstead MW, Moore BB, Standiford TJ, Zemans RL, Singer BH. (adapted from *Am J Physiol Lung Cell Mol Physiol*. 2021 Aug 1;321(2):L451-L465. doi: 10.1152/ajplung.00123.2021.)

**Rationale:** Millions of people who survive sepsis each year are rehospitalized and die due to late pulmonary complications. To prevent and treat these complications, biomarkers and molecular mediators must be identified. Persistent immune reprogramming in the form of immunoparalysis and impaired host defense is proposed to mediate late pulmonary complications after sepsis, particularly new pulmonary infections. However, immune reprogramming may also involve enhanced/primed responses to secondary stimuli, although their contribution to long-term sepsis complications remains understudied. We hypothesize that enhanced/primed immune responses in the lungs of sepsis survivors are associated with late pulmonary complications.

**Methods/Results:** To this end, we developed a murine sepsis model using cecal ligation and puncture (CLP) followed 3 wk later by administration of intranasal lipopolysaccharide to induce inflammatory lung injury. Mice surviving sepsis exhibit enhanced lung injury with increased alveolar permeability, neutrophil recruitment, and enhanced Ly6C<sup>hi</sup> monocyte *Tnf* expression. To determine the mediators of enhanced lung injury, we performed flow cytometry and RNA sequencing of lungs 3 wk after CLP, prior to lipopolysaccharide. Sepsis survivor mice showed expanded Ly6C<sup>hi</sup> monocytes populations and increased expression of many inflammatory genes. Of these, S100A8/A9 was also elevated in the circulation of human sepsis survivors for months after sepsis, validating our model and identifying S100A8/A9 as a potential biomarker and therapeutic target for long-term pulmonary complications after sepsis.

**Conclusions:** These data provide new insight into the importance of enhanced/primed immune responses in survivors of sepsis and establish a foundation for additional investigation into the mechanisms mediating this response.