

# New Strategies for Treatment of Humans With Acute Lung Injury/Acute Respiratory Distress Syndrome

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Acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) in humans, whether associated with infectious (viral, bacterial) or chemical agents or due to unknown causes, represent conditions that can lead to acute respiratory failure due to inadequate gas exchange in lungs. Some cases of ALI and ARDS resolve in a matter of days; others are associated with disabling interstitial pulmonary fibrosis that may be lethal or cause long-term disability [1]. The causes of these complications are poorly understood. To date, there are no Food and Drug Administration–approved drugs for treatment of either ALI or ARDS.

The study by Sun et al in this issue of *Clinical Infectious Diseases* used the H7N9 virus, which was responsible for the epidemic of severe viral pneumonia and multiorgan failure in 2013 in China and was associated with high mortality. African green monkeys were used in the current study and rapidly (within 2–3 days) developed respiratory failure and systemic inflammation. Evidence for complement activation has been described in

viral and bacterial pneumonia in animals as well as humans, although the role of complement in the progression and ultimate clinical outcomes are poorly understood. Sun et al provide evidence for complement activation within 2–3 days after infection of monkeys with the H7N9 virus, based on the presence of complement activation products in lung and in plasma. As would be expected, serum also contained proinflammatory cytokines and chemokines.

One of the surprises in the H7N9 model of respiratory dysfunction is the extensive amount of inflammation and buildup of inflammatory cells, along with evidence of tissue injury involving the trachea, the bronchial system, and the alveolar compartment, and evidence of what appears to be vasculitis. The most important and novel aspect of this report is the protective effects of a neutralizing monoclonal antibody (mAb) to C5a. This mAb did not react with C5, leaving the distal complement pathway intact. Evidence of the protective effects of the mAb (IFX-1) is shown by reduced viral titers, reduced buildup of both polymorphonuclear leukocytes (PMNs) and macrophages in lungs, and reduced levels of proinflammatory cytokines and chemokines in serum. Treatment with the mAb also appeared to be heart-protective based on gross and microscopic pathological changes. Similar outcomes were found in lungs

from H7N9-infected monkeys treated with IFX-1 antibody.

It is intriguing that treatment of infected monkeys with the mAb also reduced the viral titer in lung, suggesting that inflammation and lung injury caused by the H7N9 virus, together with the generation of C5a, all conspired to accentuate and accelerate viral replication together with the adverse responses in the lungs and heart. These studies suggest the possibility that, in the early stages of viral (and perhaps bacterial) pneumonia, interception and neutralization of C5a may hold promise for therapeutic advantage in humans. In the setting of sepsis both in humans and in rodents (with polymicrobial sepsis), there is compelling evidence for complement activation and generation of C5a, which interacts with its receptors (C5aR1, C5aR2), resulting in a cytokine “storm,” loss of innate immunity, immunosuppression, and multiorgan failure [2]. In vivo neutralization of C5a or absence of either C5a receptor was protective [3]. Most recently, experimental ALI induced in mice with recombinant C5a or with lipopolysaccharide caused intense lung inflammatory injury associated with complement activation. Engagement of C5a with its receptors led to the appearance of extracellular histones in bronchoalveolar lavage fluid (BALF). Airway instillation of histones resulted in intense lung injury and inflammation, together with fibrin clots in pulmonary veins [4].

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Accordingly, interception of the early phases of these events, using targeted in vivo neutralization of C5a, may represent a novel approach in suppressing the early events in ALI or ARDS.

In the setting of ALI both in humans and in mice, histone presence has been found in BALF, and a linkage with engagement of the NLRP3 inflammasome has been recently demonstrated [5]. Others have shown that when PMNs are incubated in vitro or in vivo with C5a, neutrophil extracellular traps (NETs) develop. NETs contain strands of DNA that are associated with various granule products from PMNs (myeloperoxidase, elastase, matrix metalloproteinases) as well as the presence of extracellular histones [6]. NETs were not found when mouse peritoneal macrophages were exposed to C5a,

and PMN depletion resulted in a dramatic reduction in BALF levels of histones, associated with improved functional parameters in lungs. It seems reasonable to conclude that much is being learned about ALI/ARDS as well as pathophysiological events in sepsis. Hopefully, this information may lead to new strategies for more effective treatment of humans with sepsis and with ALI/ARDS.

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