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Can We DAMPen the Cross-Talk between the Lung and Kidney in the ICU?

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Recommended Reading from University of California, San Diego Division of Pulmonary and Critical Care Medicine Fellows; Atul Malhotra, M.D., ■■■

Chawla L, *et al.* Impact of Acute Kidney Injury in Patients Hospitalized with Pneumonia. *Crit Care Med* (1)

Reviewed by Mark L. Hepokoski

Preclinical and clinical studies have demonstrated multiple relevant lung–kidney interactions (2, 3). For example, chronic obstructive pulmonary disease (COPD) and ventilator-induced lung injury promote endothelial inflammation in the lung and kidney (2, 4). Furthermore, the development of renal injury in patients with pulmonary disease is important clinically, as acute kidney injury (AKI) is associated with increased mortality and poor long-term functional outcomes (5). In this study, Chawla and colleagues hypothesized that patients with combined AKI and pneumonia would have a higher incidence of mortality and permanent renal dysfunction after hospitalization than patients with AKI or pneumonia alone (1).

This was a retrospective analysis from a Veterans Affairs database that included 54,894 hospitalized patients. The authors compared three groups on the basis of International Classification of Diseases, Ninth Revision codes, including those with AKI (8,437, 15.4%), pneumonia (33,067, 60.2%), and AKI with pneumonia (13,390, 24.4%). The primary endpoint was a composite of major adverse kidney events after discharge, defined as a permanent 25% decrease in estimated glomerular filtration rate from baseline, need for chronic dialysis, and death. They observed that the patients with pneumonia with AKI had the highest mortality (3,168 [37.6%] vs. 14,114 [42.7%] vs. 6,867 [51.3%]; all $P < 0.0001$) and major adverse kidney events after discharge (AKI, 4,434 [52.6%] vs. pneumonia, 15,825 [47.9%] vs. AKI with pneumonia, 8,262 [61.7%]; all $P < 0.0001$).

The excess mortality as a function of number of organ failures is not surprising. However, what brings novelty to this study was the observation that postdischarge outcomes are worse when AKI accompanies pneumonia than AKI or pneumonia alone. These findings are particularly critical with increasing emphasis on AKI recovery and post-ICU syndromes (6). The mechanisms of pneumonia-induced kidney failure are unclear but point to the need for further research into lung–kidney cross-talk. For example, future studies could focus on remote organ complications of pneumonia as a means to improve outcomes.

The results presented may have been overestimated, as the authors were unable to identify severity of illness on the basis of the provided International Classification of Diseases, Ninth Revision codes. However, these data clearly advance the field of lung–kidney interactions, and we are excited by the progress being made. Novel strategies aimed at mitigating detrimental cross-talk between the lung and kidney have great potential to improve short- and long-term outcomes in critically ill patients. Only by further investigation into mechanisms of organ cross-talk are new therapeutic approaches likely to emerge. ■

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Krychtiuk KA, *et al.* Mitochondrial DNA and Toll-Like Receptor-9 Are Associated with Mortality in Critically Ill Patients. *Crit Care Med* (7)

Reviewed by Amy L. Bellinghausen

Mitochondria, whose origins are as unicellular organisms, are known to release molecules that activate the innate immune system during cellular injury (8). These molecules are detected by toll-like receptors, similar to the process of detecting bacterial antigens. For example, extracellular mitochondrial DNA (mtDNA) fragments have been shown to potentiate systemic inflammation via toll-like receptor 9 (TLR9), and circulating mtDNA levels correlate with lung and kidney injury and ICU mortality (9, 10). Krychtiuk and colleagues sought to investigate further the causative role of mtDNA in organ failures by investigating if plasma mtDNA is more predictive of mortality when associated with increased TLR9 expression (7).

In this single-center, prospective observational study, blood was sampled from 228 consecutive patients within the first 24 hours of admission to an academic ICU in Austria. Samples were analyzed for total copy number of mtDNA using quantitative real-time polymerase chain reaction targeting mtDNA-specific primers as well as TLR9 expression in circulating monocytes using flow cytometry (mean fluorescence intensity). Blood from 20 healthy control subjects was also collected. Investigators used multivariate analyses to assess the impact of mtDNA and TLR9 expression on 30-day mortality. As anticipated, levels of plasma mtDNA were significantly higher in ICU patients than in healthy control subjects (24.1 ng/ml; interquartile range [IQR], 10.7–42.6 ng/ml; vs. 13.8 ng/ml; IQR, 6.5–28.5 ng/ml; $P < 0.05$). Furthermore, mtDNA level had predictive value beyond Acute Physiology and Chronic Health Evaluation II, as demonstrated by an elevated C-statistic, suggesting that mtDNA may be an independent prognostic indicator. Also noted were higher levels of mtDNA in nonsurvivors (26.9 ng/ml; IQR, 11.2–60.6 ng/ml; vs. 19.7 ng/ml; IQR, 9.5–34.8 ng/ml; $P < 0.05$), an effect that appears to be mediated by TLR9 (only patients with elevated levels of TLR9 expression showed a correlation between elevated mtDNA and mortality). These findings point to a potential role of TLR9-associated inflammation in mediating death in patients with elevated circulating mtDNA levels.

A potential limitation to generalizability is that the most common diagnosis in the ICU population studied was cardiopulmonary resuscitation, followed by heart failure and cardiac surgery, representing a group that may differ from that of many medical ICUs. However, other studies have demonstrated similar findings of elevated mtDNA in a variety of critically ill populations (11). Although unable to establish a causal link, this study suggests that mitochondrial injury and release of mtDNA into the circulation may be a key part of the final common pathway for inflammation and mortality in multiple organ failure syndromes. ■

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Simmons JD, *et al.* Mitochondrial DNA Damage Associated Molecular Patterns in Ventilator-associated Pneumonia: Prevention and Reversal by Intratracheal DNase I. *J Trauma Acute Care Surg* (12)

Reviewed by Christine M. Bojanowski

Ventilator-associated pneumonia (VAP) remains a common diagnostic and treatment challenge. Recent studies have shown that extracellular mtDNA released from injured cells during oxidant stress or bacterial infection may represent a novel mechanism of injury yielding a potential therapeutic target (13). In the lung, mtDNA are known to function as damage-associated molecular patterns (DAMPs) that cause endothelial barrier injury and pulmonary edema (14, 15). In this translational study, Simmons and colleagues (12) aimed to assess the use of intratracheal DNase in the prevention and treatment of VAP, with the hypothesis being that the administration of intratracheal DNase would enhance the clearance of mtDNA. Importantly, DNase is already U.S. Food and Drug Administration approved as a mucolytic in cystic fibrosis and thus may be readily implemented in the ICU.

Accordingly, the investigators used a ventilated rat model to determine if the use of DNase prevented or reversed DAMP-induced lung injury. Intratracheal *Pseudomonas aeruginosa* (PA 103) significantly increased both the amount of perfusate mtDNA DAMPs (ng/ml) and degree of lung injury as suggested by vascular filtration coefficient (Kf, expressed as ml/min/cm H_2O/100 g.). Intratracheal DNase administration was effective in both prevention and reversal experiments on the basis of the significant reduction of mtDNA DAMPs (18.9 ± 2.6 vs. 3.0 ± 0.2 and 39.9 ± 6.3 vs.11.5 ± 3.8; $P < 0.05$) and Kf (0.73 ± 0.2 vs.0.20 ± 0.01 and 1.29 ± 0.05 vs. 0.18 ± 0.003; $P < 0.05$).

The investigators then prospectively enrolled consecutive patients ($n = 31$) admitted to the ICU who were suspected to have VAP. DAMPs were measured from BAL fluid and serum at the time of suspected diagnosis, with serum levels measured again at 24 to 48 hours. Patients with culture-positive VAP had significantly higher mtDNA DAMPs in both the BAL fluid and the serum at 24 hours than those without VAP (248.70 ± 109.7 vs. 43.91 ± 16.61, $P < 0.05$; and 159.60 ± 77.37 vs. 10.43 ± 4.36, $P < 0.05$; respectively).

This intriguing study reveals the association between bacterial pneumonia and the accumulation of mtDNA DAMPs in both the lung and serum in humans. In their preclinical model, this study also suggests the potential role of DNase in the prevention and treatment of VAP. We would speculate that a decrease in the total concentration of circulating mtDNA may also occur after DNase therapy and could

theoretically influence the risk of remote organ failures, such as AKI, in patients with VAP. We support further basic and clinical research regarding the role of mtDNA DAMPs in the ICU. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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AUTHOR QUERIES

1 AU: Please provide position title for Dr. Malhotra with respect to the fellowship program (e.g., Program Director or Faculty Advisor).

2 AU: Per journal style, author disclosures of potential conflicts of interest (or lack thereof) should appear online, as indicated by the sentence at the end of the text. Therefore, the sentence beginning "As an Officer of the American Thoracic Society" has been deleted here; please confirm that this appears in the appropriate disclosures form. However, acknowledgments of financial support should appear in a first-page footnote. Please correct if necessary.