# Acute Respiratory Distress Syndrome

## Biomarkers, Mechanisms, and Water Channels

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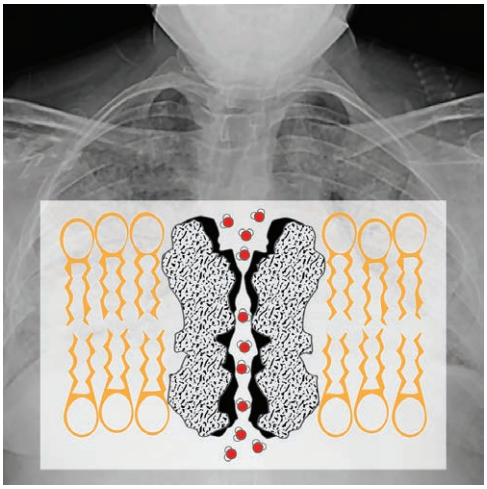
Despite five decades of research since its description in 1967, the acute respiratory distress syndrome (ARDS) remains a frequent killer among critically ill patients. Insight into the detrimental effects of mechanical ventilation has improved supportive therapy (*e.g.*, low tidal volume ventilation and prone positioning), yet all pharmacologic or cell therapy–based interventions have so far failed, and mortality remains unabatedly high at up to 40%. One important confounder that may have precluded the development of effective pharmacotherapies so far is the fact that ARDS is a syndrome rather than a disease. In other words, ARDS reflects the result of a diverse range of direct pulmonary or indirect extrapulmonary triggers or diseases. These include bacterial and viral pneumonia, aspiration of gastric contents, lung contusion, or inhalation injury—all causes of "direct" lung injury, as well as multiple causes of "indirect" lung injury such as sepsis, severe trauma, transfusions, pancreatitis, or drug reactions. Although these different etiologies share common pathologic features in terms of an excessive inflammatory response, alveolo–capillary barrier failure, and formation of a proteinaceous lung edema, and they are identified by a few generalized clinical features (bilateral opacities on chest imaging, respiratory failure not fully explained by cardiac failure, and impaired oxygenation: the 2012 Berlin definition of ARDS), this does not mean that they share similar disease pathways. Patient factors—both genetic and acquired—will likely impact not only on individual susceptibility, but also on the course of the disease and the effectiveness of specific treatments. Although a single therapeutic "magic bullet" may work in a highly standardized preclinical model with syngenic, same-sex animals without comorbidities, it will fail in a real-world scenario of ARDS. This is not a shortcoming of the animal model—the same limitations apply for cell or organoid systems, isolated human lungs, or even healthy volunteers—but it is inevitable if we insist on a simplistic "one size fits all" solution that may not be achievable.



**"Genetic studies…have revealed associations between genotype and outcome in patients with ARDS."**

The realization that not all ARDS patients are the same coincides with the recent surge for "precision medicine," and together these have sparked the interest in meaningful patient stratification.[1] In the current issue of Anesthesiology, Rahmel *et al.*[2] now report an association between the −1364A/C promoter single nucleotide polymorphism in the gene *AQP5* encoding for the water channel aquaporin 5 and outcome in ARDS. In 136 patients with ARDS associated with bacterial pneumonia, the authors detected a higher survival rate (86%) for carriers of the C-allele *versus* 62% in patients with an AA genotype.

This finding complements a series of genetic studies that have revealed associations between genotype and outcome in patients with ARDS. For example, specific variant alleles of the platelet activating factor acetylhydrolase (inactivates platelet activating factor, an important mediator of ARDS) are associated with both reduced platelet activating factor acetylhydrolase activity in plasma and survival.[3] More recently, genome-wide association studies identified the association of a variant within the *FER* gene (it encodes a nonreceptor protein tyrosine kinase involved in growth factor signaling) with survival in ARDS.[4] Exome-wide genotyping discovered a single-nucleotide polymorphism within the *LRRC16A* gene, encoding an F-actin capping protein that is associated with the development of ARDS in an at-risk

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population.[5] These and similar studies demonstrating association of ARDS risk or outcome with genetic polymorphisms in genes encoding for vascular endothelial growth factor, angiotensin-converting enzyme, tumor necrosis factor, interleukin 8, hypoxia-inducible factor 1α, adiponectin, prolyl-hydroxylase 2, or plasminogen activator 1 have led to the idea that early detection of specific genetic polymorphisms might ultimately guide individualized therapy in ARDS.

The findings by Rahmel *et al.*[2] not only add another important piece to the puzzle when considering screening for genetic polymorphisms as a biomarker in clinical ARDS, but also add a novel potential pathophysiologic role for aquaporins in acute lung injury. Soon after the discovery of the first aquaporin by Peter Agre, M.D. (Johns Hopkins University, Baltimore, Maryland) in 1993, the identification of an abundant expression of AQP5 in the apical membrane of alveolar type-1 cells sparked interest into the role of this water channel in the formation (and resolution) of lung edema. Yet, although AQP5 deletion reduced osmotic water permeability between capillaries and distal airspaces by about 10-fold, AQP5-deficiency showed hardly any effect on hydrostatic edema formation and no impairment of active edema resolution in mice.[6] Nonetheless, AQP5 in the lung is downregulated by classic stimuli of acute lung injury such as lipopolysaccharide or ischemia-reperfusion (although not by overventilation), and *Aqp5*-deficient mice develop aggravated lung injury after infection with *Pseudomonas aeruginosa*.[7] Together these findings suggest a potential role of functional AQP5 for the integrity of the alveolo–capillary barrier. However, *Aqp5*-deficiency confers a survival benefit in mice after intraperitoneal endotoxin.[8] In their current article, the authors elegantly bring together these seemingly discrepant findings by hypothesizing that AQP5 may facilitate immune cell migration and thus promote elimination of bacterial infection, while at the same time aggravating host tissue damage during sterile infection (*e.g.*, triggered by endotoxin). As the C-allele of the *AQP5* −1364A7C promoter is associated with lower AQP5 expression compared with normal (*i.e.*, the AA genotype), the latter may have originally conferred evolutionary benefit yet proves detrimental in the age of antibiotics and mechanical ventilation.

In parallel with genetic traits, stratification of ARDS has focused on etiology, usually direct *versus* indirect lung injury. Indeed, direct ARDS may have a higher mortality than indirect ARDS and is associated with a different profile of plasma biomarkers (surfactant protein D—direct; angiopoietin-2—indirect).[9] Also, these phenotypes seem to differ in their response to positive end-expiratory pressure and prone positioning. So far, no coherent effort has been made to synthesize stratification of patients based on etiology with patient genotype as both a prognostic tool and a guide for therapy. In fact, perhaps the most successful recent approach used an entirely different strategy: in their 2014 hallmark paper, Calfee *et al.*[10] used latent class analysis of 31 clinical, biochemical, and physiologic parameters to differentiate between a "hyper-inflammatory" phenotype and one characterized by less severe inflammation and shock. These two phenotypes differed markedly in their response to high positive end-expiratory pressure and to pharmacotherapy with simvastatin.[10,11] It seems fair to speculate that these phenotypes, which reflect acquired traits on the background of individual genotypes, add a third dimension to patient stratification. Combined consideration of disease triggers and etiology, patient genotype, and acquired traits may provide for a more comprehensive stratification. This may at first be laborious and would require sizeable patient cohorts, yet could be aided by state-of-the-art intelligent analytical tools. In the end, just as for ARDS therapy, there is presumably no single "magic bullet" for ARDS biomarkers and patient stratification.

## Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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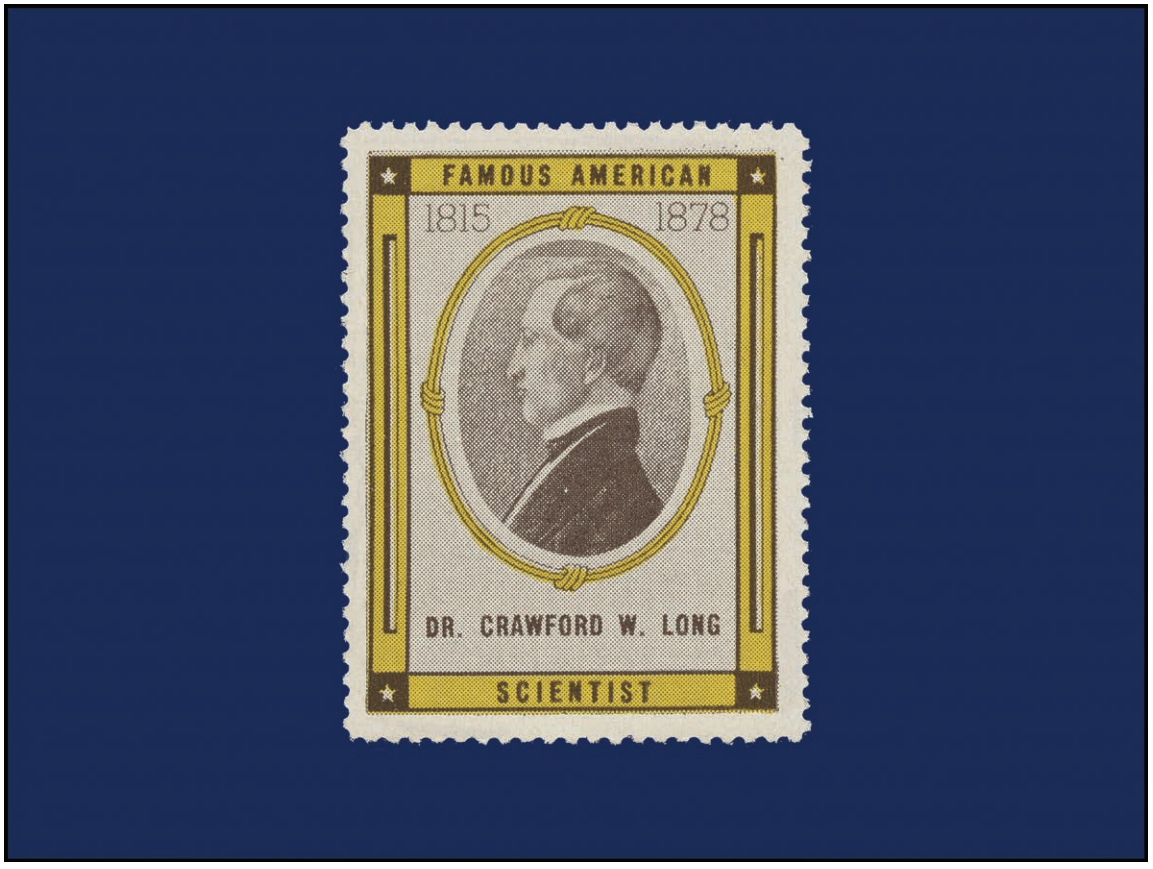
# Etherist Crawford Long on a Cinderella Stamp




By founding the Cinderella Stamp Club (1959), editing their journal *The Cinderella Philatelist*, and authoring their classic 152-page book *Cinderella Stamps* (1970), British brothers Leon and Maurice Williams popularized the collecting of stamp-like but nonpostal "emissions." Philatelist James Mackay defined Cinderellas as "virtually anything resembling a postage stamp, but not issued for postal purposes by a government postal administration." For anesthesiologists, one of the more interesting Cinderella stamps is this one (*above*) depicting the left profile of pioneering etherist Crawford W. Long, M.D. (1815 to 1878) of Jefferson, Georgia. This yellow-and-gray Cinderella was likely issued around 1940, the year that the U.S. Postal Service released its red-colored 2-cent postage stamp honoring Dr. Long. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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