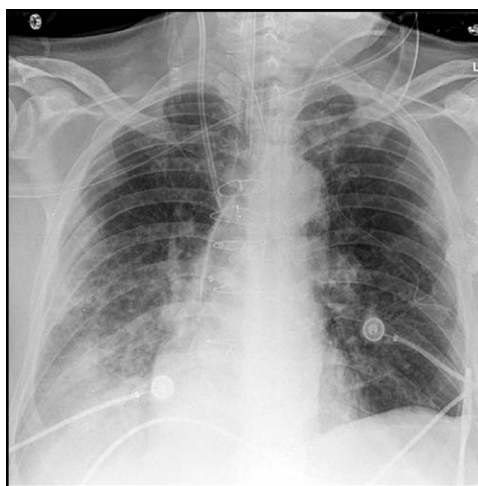# Transforming High Risk to High Yield

Karsten Bartels, M.D., Almut Grenz, M.D., Ph.D., Holger K. Eltzschig, M.D., Ph.D.

ACUTE respiratory distress syndrome (ARDS) remains a major contributor toward perioperative morbidity and mortality. Although the crude mortality rates in earlier clinical trials from the ARDS Clinical Trials Network were comparatively higher than that reported in more recent studies of this group (35 and 26%, respectively),[1] others have found that there has been little if any success in improving survival from ARDS over time.[2] Hence, the lack of effective approaches for prevention and therapy of ARDS has driven multiple efforts with the goals to better understand the molecular processes in the development and endogenous recovery of lung injury,[3,4] to design novel therapeutic approaches targeting these processes,[5,6] and to conduct clinical trials to evaluate meaningful outcomes after interventions.[7] A major challenge for the practicing clinician is to determine which patient



*"[T]he work by Kor et al. can eventually help bridge a critical gap between innovative therapies developed from mechanistic experimental models and the design of clinical studies."*

would be most likely to benefit from such novel but potentially expensive and side effect–laden therapy. The clinical scientist is confronted with a similar predicament: to demonstrate effectiveness of any preventative intervention, studying it in a high-risk population is desirable. This permits limiting sample size and thus makes a trial more feasible. In this issue of Anesthesiology, Dr. Daryl J. Kor from the Department of Anesthesiology at the Mayo Clinic in Rochester, Minnesota, and his colleagues from the U.S. Critical Illness and Injury Trials Group provide us with important new insight on the prediction of postoperative lung injury.[8] Using primary data from the previously conducted prospective multicenter Lung Injury Prevention Study,[9] Kor *et al.* studied the performance of their formerly developed surgical lung injury prediction (SLIP) model[10] in a large multicenter-derived data set of diverse high-risk surgical patients. Although the original SLIP score did not perform well in identifying patients, who progressed to ARDS, the authors derived a modified scoring system (SLIP-2) that did.

The anesthesiologist Dr. Bjørn Ibsen at the Hospital for Communicable Diseases in Copenhagen (Professor of Anaesthesiology, University of Copenhagen, Copenhagen, Denmark) (1915–2007) revolutionized the management of acute respiratory failure during the 1952 polio outbreak in Denmark.[11] The innovative concept of using cuffed endotracheal tubes and manual artificial ventilation outside of the operating room marks a founding innovation in the field of critical care medicine. In the ensuing years, artificial ventilation for acute respiratory failure became a prevalent characteristic of many patients admitted to an intensive care unit. Lung injury leading to ARDS can occur not only as a consequence from direct tissue injury but also can be triggered through indirect insults stemming from systemic illness such as sepsis and shock. The realization that mechanical ventilation itself can be not only therapeutic but in fact the culprit and perpetrator for the development and progression of ARDS has led to the concept of ventilator-induced lung injury. Hence, most approaches for therapy of ARDS revolve around strategies aimed at limiting further injury. Current concepts include low tidal volume ventilation with appropriate positive end-expiratory pressure and inspired oxygen concentration, restrictive fluid management, consideration of early pharmacologic paralysis, and prone positioning. Multiple promising interventions, such as administration of antioxidant nutritional supplements, steroids, and high-frequency oscillatory ventilation, have failed to provide tangible benefits in most randomized clinical trials. Some examples of innovative pharmacologic and nonpharmacologic treatment strategies currently under investigation include usage of bone marrow–derived multipotent mesenchymal stem cells,[5] activation of regulatory T-cells,[3] stabilization of hypoxia-inducible factor 1A,[4] modulation of adenosine metabolism,[6] as well as usage of extracorporeal membrane oxygenation.[12]

Reflecting the multifactorial etiology of ARDS and consistent with previous findings, Kor *et al.* identified the

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following variables to be associated with a high risk for the development of ARDS and thus essential components of their SLIP-2 scoring algorithm: sepsis, high-risk cardiac and aortic surgery, emergency surgery, cirrhosis, admission other than from home, respiratory rate, arterial oxygen saturation, and oxygen requirement. The original SLIP score was derived from secondary analysis of a prospective cohort investigation of 4,366 surgical patients at the Mayo Clinic. Of the patients included in the original SLIP study, 2.6% developed early postoperative acute lung injury/ARDS[10]; whereas, 7.5% of the 1,562 patients in their current study carried this diagnosis.[8] Clearly, the two populations studied were quite heterogeneous and the newly derived SLIP-2 algorithm is likely to perform better in more acutely ill patients. The poor performance of the previously reported SLIP algorithm in the dataset used for their current study emphasizes the need for accurate, validated prediction models. Here, the work by Kor *et al.* can eventually help bridge a critical gap between innovative therapies developed from mechanistic experimental models and the design of clinical studies. Given that the SLIP-2 score was derived from a high-risk patient cohort from multiple centers, it would be a valuable tool for designing clinical trials testing novel approaches in similar populations (fig. 1).

Although the application of an algorithm that has not been validated in an independent cohort will preclude widespread adoption at this time, three key conclusions should be highlighted. First, the proposed SLIP-2 scoring system would likely facilitate studying preventative strategies for ARDS in high-risk surgical patients. The ability to limit sample sizes without compromising statistical power would increase feasibility and possibility for success of future clinical trials. Second, the prospect of enabling clinicians to predict the likelihood of a surgical patient to develop postoperative ARDS could permit deployment of perioperative interventions that are more likely to impact meaningful clinical outcomes. Third, the current study serves as yet another example of the fruitful collaboration amongst the U.S. Critical Illness and Injury Trials Group. In conclusion, the authors should be congratulated on their work and we are hopeful that their efforts will continue to sustainably advance the field of critical care medicine.
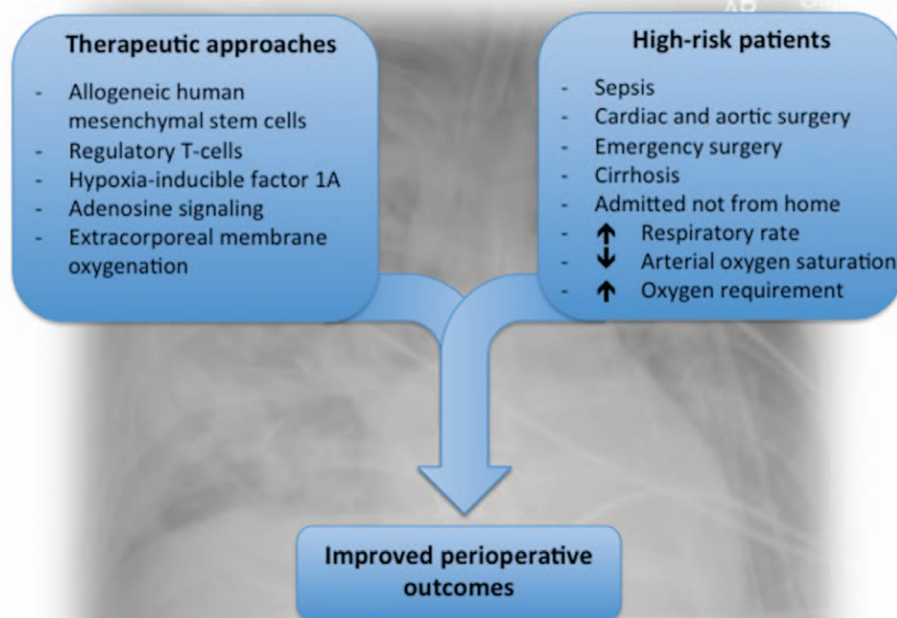


**Fig. 1.** Accurate predicative algorithms to identify surgical populations at high risk for acute respiratory distress syndrome can inform the design of high-yield clinical trials. Examples of promising therapeutic approaches that are currently under investigation include use of allogeneic human mesenchymal stem cells,[5] activation of regulatory T-cells,[3] pharmacologic stabilization of hypoxia-inducible factor 1A,[4] modulation of adenosine metabolism,[6] and deployment of extracorporeal membrane oxygenation.[12] The surgical lung injury prediction model-2 score was derived from a high-risk patient population from multiple centers and is associated with the development of postoperative acute respiratory distress syndrome.[8] Knowledge of acute respiratory distress syndrome risk factors permits design of efficient clinical trials to test novel therapies and hopefully improve patient outcomes.

## Competing Interests

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