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Embracing Physical and Neuropsychological Dysfunction in Acute Lung Injury Survivors: The Time Has Come

Over the last decade, ground-breaking advances have occurred in the management of acute lung injury (ALI), including low tidal volume ventilation and the implementation of a conservative fluid strategy (1, 2). As a result, more patients are surviving ALI. Based on an incidence of 190,000 cases per year and recent case fatality rates as low as 20%, there will be more than 150,000 new ALI survivors annually in the United States alone (3–5). The pulmonary and critical care community has started to focus on understanding and treating post-ICU-related nonpulmonary disorders that occur in the growing number of ALI survivors.

Much of the recent interest in post-ICU consequences has been concentrated on the neuromuscular dysfunction (6). Neuromuscular weakness is common in ALI survivors and unfortunately can persist for years after hospital discharge (7). After 5 years, the median distance walked in 6 minutes by ALI survivors was only 76% of the distance of an age-matched and sex-matched control population, consistent with a persistent reduction in exercise capacity (8). Psychological issues, including symptoms of depression, anxiety, and post-traumatic stress disorder, are also common in ALI survivors (9, 10). Initial studies reported that between 20 and 50% of ALI survivors had symptoms of depression after 1 year (11–13). Risk factors for post-ALI depressive symptoms include obesity, hypoglycemia, alcohol dependence, female sex, younger age, and cognitive dysfunction (14). Symptoms of moderate to severe depression also persist and remain in nearly 20% of ALI survivors after 5 years (15). These 5-year follow-up data suggest that the decrements in quality of life and exercise capacity may have resulted from persistent weakness, as well as a spectrum of neuropsychological impairments in ALI survivors.

In this issue of the *Journal*, Bienvenu and colleagues (pp. 517–524) prospectively followed 186 ALI survivors for 2 years (16). Patients were evaluated at 3, 6, 12, and 24 months after the onset of ALI. Depressive symptoms were assessed using the Hospital Anxiety and Depression Scale, and impaired physical function was defined by having at least two dependencies in instrumental activities of daily living in patients without baseline impairment. The point prevalence of depressive symptoms was 24% at 1 year and 32% at 2 years with an overall cumulative incidence of 40%. The 2-year cumulative incidence of impaired physical function was 66%. The presence of depressive

symptoms was independently associated with the development of impaired physical function.

This study provides another excellent picture of long-term outcomes in ALI survivors and adds significantly to our understanding of the complex interactions between physical and neuropsychological impairments. The outstanding follow-up rates and serial data collection reflect the extreme diligence of this research team and depict how post-ICU burden is sustained over time. Most importantly, this study confirms that depressive symptoms are common and persistent in ALI survivors. Healthcare providers who care for patients after ICU discharge should consider screening for symptoms of depression. The methodology of the present study also raises some concern about the interpretation of the results. The Hospital Anxiety and Depression Scale is a screening tool that has been validated to identify the presence of significant depressive symptoms or the risk of actual depression. The persistence of symptoms for more than 21 months suggests that some patients may have actual psychiatric diseases. Qualitative data from individual structured interviews would have been useful to distinguish true major depressive disorders from persistent depressive symptoms in ALI survivors and help understand who may benefit from therapeutic interventions. The investigators also did not collect information regarding the initiation of medical therapy or counseling for depressive symptoms in their cohort of ALI survivors. Some of the temporal variability and reported remissions in the incidence of depressive symptoms may have been related to the initiation of psychological therapies. Previous studies have suggested that decreased exercise capacity in ALI survivors has an impact on neuropsychological impairments (8). In the present study, objective measures of physical dysfunction such as a 6-minute walking test were not reported. It is reasonable to consider that having at least two dependencies in instrumental activities of daily living could result from primary pulmonary dysfunction as well as from other nonpulmonary impairments. These physical-psychological interactions have to be described in detail to design a multimodal intervention that may include both antidepressive therapies and pulmonary and physical rehabilitation. It is also possible that the multiple dependencies in instrumental activities may partially result from depression-related somatization in some ALI survivors.

This study also raises several fundamental questions that should generate future investigations concerning the care of ALI survivors. Some of the variability in the rates of neuromuscular dysfunction

and psychological symptoms may be related to the use of different diagnostic criteria across reported studies. Similar to the advantages obtained from developing the uniform American European Consensus Conference definition of ALI, a multidisciplinary group needs to standardize the diagnostic criteria for post-ICU neuromuscular, neurocognitive, and neuropsychological dysfunction. Are there modifiable ALI-specific factors that result in the increased prevalence of neuropsychological dysfunction, or are these symptoms of depression, anxiety, and post-traumatic stress disorder equally common in all survivors of critical illness? Future studies with properly identified control groups will be necessary to answer this question. How can subgroups of ALI survivors be identified that will benefit from potential targeted interventions to prevent and treat the development of psychological disorders? Patients at risk for post-ALI neurocognitive dysfunction can already be identified early in the course of their disease. Namely, better 1-year quality of life can be predicted by the absence of systemic corticosteroid treatment, the absence of illness acquired during the ICU stay, and rapid resolution of lung injury and multiorgan dysfunction (6). Research efforts that aim to risk stratify patients with ALI should be expanded. Finally, translational studies are necessary to identify the mechanisms that result in the development of neuropsychological symptoms to develop novel therapies for these patients.

Our present understanding of post-ALI dysfunction may be just the tip of the iceberg. This present study and the body of literature that served as its foundation have defined a new spectrum of neuromuscular and psychological issues that are becoming more evident because of the improvements in the acute care and outcome of patients with ALI. Additional clinically significant post-ALI disorders are likely to be identified with more comprehensive and longitudinal evaluations of these ALI survivors. As the delivery of critical care extends beyond the confines of the ICU and the hospital, multidisciplinary research efforts like that of Bienvenu and colleagues should ultimately result in dramatic improvements in the long-term outcome of these patients (16).

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Innate Immunity in Lung Fibrosis: A Therapeutic Role for Surfactant Protein D?

Idiopathic pulmonary fibrosis (IPF) is a progressive and ultimately fatal fibroproliferative disorder with a median survival of just 3 to 5 years following diagnosis (1), highlighting the need

for a clearer understanding of the pathobiology underlying the development of this devastating disease and alternative therapeutic approaches for its treatment.

In this issue of the *Journal*, Aono and coworkers (pp. 525–536) have addressed the potential of surfactant protein D (SP-D) in pre-clinical studies (2). Their aim was to elucidate the pathophysiological role of SP-D during lung inflammation and

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