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ICU-Acquired Weakness, Chronic Critical Illness, and the Persistent Inflammation-Immunosuppression and Catabolism Syndrome

Tyler J. Loftus, MD, **Frederick A. Moore, MD, FACS, MCCM**, and **Lyle L. Moldawer, PhD**

University of Florida Department of Surgery and Sepsis and Critical Illness Research Center in Gainesville, Florida

Keywords

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We congratulate Dr. Witteveen and the members of the MARS consortium for their prospective investigation of systemic inflammatory marker patterns among patients with intensive care unit (ICU)-acquired weakness (AW) (1). This well-designed observational study provides a detailed description of a morbid condition that is becoming more and more common. Almost 50% of critically ill patients with at least 48 hours of mechanical ventilation demonstrated evidence of ICU-AW.

Although the enrollment strategy successfully identified a relatively heterogeneous population of critically ill patients, there was a common theme that was unrelated to inclusion criteria: 79% of the total study population and 88% of all patients with ICU-AW had sepsis, defined as presence of SIRS plus antibiotic administration. Patients with ICU-AW also had a median ICU length of stay of 16 days, versus only seven days among patients without ICU-AW, and had higher sequential organ failure assessment (SOFA) scores. These findings suggest that the ICU-AW cohort was composed of patients who would have succumbed to multiple organ failure in previous eras; in modern ICUs, these patients survive, and develop chronic critical illness (CCI) (2) and the persistent inflammation-immunosuppression and catabolism syndrome (PICS) (3). ICU-AW may be a manifestation of these conditions.

Although the study by Witteveen et al. was not designed to assess whether the subjects had persistent inflammation juxtaposed with simultaneous suppression of adaptive immunity, or whether patients with ICU-AW were also experiencing protein catabolism, these scenarios seem likely based on previous findings (3). Although plasma elevations in IL-6, IL-8, IL-10, and fractalkine generally occurred prior to measurement of muscle strength testing in both groups, elevated concentration of these cytokines may be best understood as representative

Please address correspondence to: Lyle L. Moldawer, PhD, Robert H. and Kathleen M. Axline Basic Science Professor of Surgery, Director, Sepsis and Critical Illness Research Center, University of Florida College of Medicine, PO Box 100108, 1600 SW Archer Road, Gainesville, FL 32610-0019, Phone: 352-265-0494, Fax: 352-265-0676, moldawer@surgery.ufl.edu.

of persistent inflammation rather than its cause. To understand what drives persistent inflammation and elevation of inflammatory cytokines on a mechanistic level, we must also consider non-infectious conditions like extended ventilator support, immobility, exposure of extracellular matrix by injured tissues, and chronic low grade organ injury (SOFA) driving the release of endogenous danger signals (4).

Persistent inflammation in critically ill patients is generally associated with protein wasting, abnormal hematopoiesis, and immune suppression, often leading to secondary infections and/or viral reactivation. Although not reported here, one could reasonably expect that patients with extended ICU stays and prolonged mechanical ventilation would likely have increased frequency of secondary infections (5). These infectious events would only serve to exacerbate inflammation, immune suppression, and protein wasting.

Witteveen et al. are to be congratulated for making this important contribution to our understanding of ICU-AW. Importantly, ICU-AW needs to be considered in the context of a holistic approach to an understanding of CCI. PICS was originally proposed as a hypothesis that could be experimentally tested in preclinical and clinical settings (3). As evidence accumulates for the existence of a common underlying pathophysiology for many of the conditions that adversely affect critically ill patients, we hope that the scientific community will continue to work together in elucidating this pathway, and to promote the development of novel management strategies and therapies targeting this pathway.

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