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Building consensus on ICU-acquired weakness

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ICU-acquired weakness may begin within hours of mechanical ventilation [1], may affect patient management and outcome during the ICU stay [2, 3] and may contribute to functional disability for years after hospital discharge [4, 5]. In many ways, it has been one of the most profound and relatively invisible legacies of critical illness until fairly recently. At present, there are a number of barriers that thwart our attempt to study this clinical entity. There is no consensus on risk factors or modifiers, how and when it should be diagnosed, how to name and categorize these nerve and muscle lesions according to the severity or heterogeneity and limited data on very long-term outcome. In light of these limitations, it is unclear how to risk stratify for this dysfunction and this impairs our ability to tailor specific interventions with appropriate timing and intensity during the recovery continuum.

In this issue of Intensive Care Medicine, Hough et al. contribute important new observations to the burgeoning literature on ICU-acquired weakness [2]. Their findings

support prior observations that neuromuscular dysfunction after ICU is common and provoke further debate about the precise role of corticosteroids in the development and/or exacerbation of this condition. In their secondary analysis of the dataset from the ARDS Network randomized controlled trial of methylprednisolone versus placebo, they reported evidence of neuromyopathy in 34% of patients and this was associated with prolonged need for mechanical ventilatory support, return to mechanical ventilation, and delayed return to home after critical illness. These authors were unable to establish a significant association between treatment with methylprednisolone and increased risk of neuromyopathy [2]. It was a very smart and economical strategy to use this pre-existing dataset to gain more insights into some fundamental questions about incidence, and the relationship between corticosteroid administration and weakness in survivors of ARDS. The authors enhanced the rigor of their study by investigating a more specific definition of neuromyopathy (early neuromyopathy), in an attempt to establish a more compelling temporal relationship between steroid use and the development of clinically apparent weakness. As well, they attempted to minimize the impact of nonrandom misclassification of sick patients with unrecognized neuromuscular disease as non-cases by restricting their eligibility to those who were alive to 60 days or hospital discharge. The one major limitation of this study, however, was the inherent difficulty in case ascertainment from chart review and the attendant challenges with bias introduced as part of differential surveillance, diagnosis and nomenclature used to capture the spectrum of clinically apparent weakness.

The incidence of neuromyopathy in this study, although significant, is almost half of that reported previously in another population of ARDS patients and is clearly variable across populations of ICU patients [3, 6–8]. This heterogeneity in incidence rates serves to emphasize the multiplicity of factors that may influence the development,

exacerbation, regression and ascertainment of these lesions, and thus the reported incidence across studies. Differences in incidence may, in fact, be a true reflection of differences in severity of illness or individual vulnerability across patient populations, or of concurrent established risk factors for neuromuscular dysfunction, such as severe sepsis with multiple organ dysfunction or hyperglycemia [9]. However, process or practice pattern variability may also potentially alter reported weakness. For example, an ICU culture that promotes early mobility may alter the natural history of weakness in their population and lower reported incidence. In addition, the differential application of cointerventions that influence its development or regression may also bias these estimates. The ascertainment of new cases of weakness, as mentioned previously, may be influenced by many factors including severity of illness as discussed by Hough et al. the presence or absence of systematic daily screening and surveillance for weakness [6], an ICU culture of wakefulness versus coma [10], and access to neurological expertise and technology to assist with diagnosis (EMG/NCS) [3].

Challenges with ascertainment of weakness are compounded by the lack of uniformity of diagnostic criteria, nomenclature and taxonomy. At present, several different terms for clinically apparent weakness exist in the literature and include critical illness polyneuropathy (CIPN), critical illness polyneuropathy and myopathy (CIPNM), ICU-acquired paresis (ICUAP), critical illness myopathy and or neuropathy (CRIMYNE), and critical illness neuromuscular abnormalities (CINMA). There is no consensus on nomenclature and no consensus on diagnostic criteria for each and this represents a significant limitation in our ability to develop a unified research agenda for this condition. Another layer of complexity is that muscle and nerve pathology often co-exist in the same patient and it may be very difficult, if not impossible, to differentiate these two lesions, understand discrete risk factors and outcomes for each [9].

Hough et al. failed to identify a statistically significant relationship between proximate steroid administration and their 28-day outcome but this was in the context of a study design with limitations related to ascertainment bias and potential contributions from unmeasured or unknown confounders. This relationship continues to remain somewhat uncertain but it is difficult to discount all concern about the contribution of exogenous systemic corticosteroids to ICU-acquired weakness in light of the compelling animal data that support this relationship [11]. As well, there are data to suggest that endogenous hypercortisolemia in association with trauma or severe critical illness may also be deleterious, and in combination with bedrest, may significantly contribute to loss of lean muscle mass and death [12]. There is considerable controversy in the literature at present about the appropriate indications for corticosteroid treatment in critically

ill patients and the specific approach to corticosteroid insufficiency. Current recommendations support only prescription of corticosteroids for vasopressor-dependent shock and early severe ARDS, and in light of the potential for causing or exacerbating weakness, it seems reasonable to adopt a more conservative approach to prescription of steroids at present. [13].

The paucity of data on the natural history of ICU-acquired weakness and uncertainty about appropriate outcome measures is also problematic. There is no agreement on which outcome measures should be collected to capture clinically important weakness and over what time period. These data are essential to facilitate risk stratification and understanding of optimal timelines to implement potential rehabilitation programs. Given the association between ICU-acquired weakness, and both ICU-based and longer-term outcomes, we may need to compartmentalize outcome measures and their interventions within discrete time frames: within ICU, in hospital, and short- and longer-term post-hospitalization periods so that we can design therapies for these specific times but also determine whether short-term benefits from an upstream intervention persist or decay over the longer term. For example, it would be important to evaluate whether early ICU-based physiotherapy not only alters short-term strength measures and ICU-based outcomes but also alters the natural history of functional, exercise and quality of life outcomes over years after ICU discharge.

The American Thoracic Society published guidelines on outcomes research in Critical Care in 1999 and this was at a time when many of the more detailed functional and neuropsychological outcomes data had not yet been published [14]. It may be timely to revisit this document and incorporate some of these measures into a new, revised minimal dataset as was discussed in this document for ARDS. It may be important to give consideration to inclusion of patient-centered measures to capture functional and neuropsychological disability and to structure their collection within a care continuum so that specific needs can be addressed and optimized within specific time frames.

As a start, we may wish to consider the following: (1) incorporating a systematic and daily surveillance for weakness into our routine medical assessment [6]; (2) prioritize an awake, communicative and mobile culture in our intensive care units to improve case ascertainment [10, 15]; (3) reach consensus on working diagnostic criteria, nomenclature and taxonomy for ICU-acquired weakness to facilitate future research work; (4) prioritize longer-term natural history studies to facilitate risk stratification, and determination of what is reversible and amenable to rehabilitative intervention, and ascertainment of optimal timing and intensity of treatment [16]; and (5) promotion of study of the biology and basic science of muscle and nerve injury associated with critical illness.

In summary, Hough et al. have demonstrated that ICU-acquired weakness is common and consequential and yet, we still know very little about its risk factors, pathophysiology, natural history and potential treatment. It would appear that the very first step is to acknowledge that we have not been looking hard enough for this and

are currently engaged in clinical practices that obscure our ability to diagnose this problem. As well, we do not have a unified language to talk with each other about this clinical syndrome and this will only delay important future research efforts in this area.

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