Dexmedetomidine and Cognitive Dysfunction after Critical Illness

What Can (and Cannot) Be Extrapolated from Rodent Models

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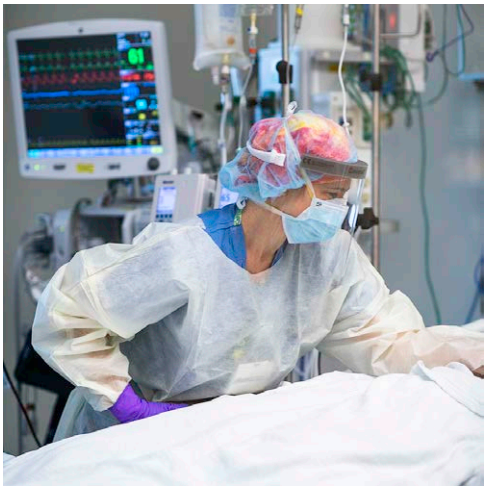
Historically, success in the intensive care unit (ICU) has been measured in easily quantifiable metrics such as mortality and length of stay. While these metrics have significant value, they do not take into account what a patient's life is like after ICU discharge. By understanding that success is not simply measured by leaving the ICU, the recent identification of post–intensive care syndrome has revolutionized the manner in which we think of successful outcomes after critical illness.[1] Unfortunately, a significant proportion of patients suffer from post–intensive care syndrome, in which they have long-term cognitive, physical, and emotional issues for extended periods of time—or permanently—after discharge from the ICU. Understanding how to prevent (or at least minimize) post–intensive care syndrome thus represents a new frontier in critical care.



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Neurocognitive dysfunction occurs in 70% of sepsis survivors with chronic critical illness.[2] A critical driver of sepsis-associated encephalopathy is uncontrolled neuroinflammation, which is precipitated by loss of blood–brain barrier function, as well as dysregulated peripheral-to-central signaling through vagal pathways.[3] Key cellular mediators of this neuroinflammation include monocytes, macrophages, and microglial cells, and their activation is associated with the development and persistence of inflammatory products in the central nervous system.

Cognition alterations often occur early in the course of an ICU stay necessitating pharmacologic sedation to either assure that a patient can synchronize with a ventilator or to prevent a patient from self-harm. Multiple different sedating agents are available targeting different neural pathways. One commonly used sedation agent is dexmedetomidine, an α2 agonist that also has activity for the imidazoline receptor, as well as the α1 receptor. Dexmedetomidine has numerous clinical benefits including a short half-life and minimal effects on respiratory drive, allowing patients to interact while on mechanical ventilation in a manner that is often not possible with other sedating agents. Preclinical work has demonstrated that dexmedetomidine decreases cognitive decline in mice in the postoperative setting *via* resolution of systemic and neuroinflammation. In a complementary set of studies presented in this issue of Anesthesiology, Li *et al.* sought to determine the impact of dexmedetomidine on cognitive decline in a rodent model, and more similar to medical than surgical illness.[4] The authors examined a variety of endpoints in young (12 week) mice subjected to a sterile inflammatory insult with lipopolysaccharide, a component of the cell wall in Gram-negative bacteria. Mice were then treated with dexmedetomidine in combination with blockers. At 3 days,

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the authors demonstrated that dexmedetomidine reversed cognitive dysfunction measured by decreased "freezing time" behavior. Mechanistically, this was mediated through α2 receptors as the reversal in cognitive decline was abrogated by α2 antagonists yohimbine and atipamezole, but was unaffected by the α1 antagonist prazosin. At 6 h, the authors also demonstrated that dexmedetomidine attenuated systemic and hippocampal release of macrophage-derived interleukin-1β through a α2-dependent mechanism. Similar findings were noted in the blood–brain barrier, where lipopolysaccharide-induced increased leakage was reversed by dexmedetomidine, a finding that was prevented by administering α2 inhibitors.

A common critique of preclinical studies of critical illness is that young mice are typically used despite the fact that the majority of patients in the ICU are aged. There are clear data that the host response changes significantly with age (so-called "inflam-aging"), which is a limitation in the utility of young mice to model older patients.[5] Cognizant of this disconnect, Li *et al.* took the unusual step of repeating many of their experiments in 12-month-old mice, which are middle aged based on murine life tables. Importantly, they found similar findings in freezing time and systemic and hippocampal inflammation in 12-month-old mice. This represents a notable (and unusual) experimental design that strengthens the data presented.

However, above and beyond the noble pursuit of mechanistic insights for the sake of scientific understanding alone, a key goal of translational research is that these insights ultimately play a role in improving human health. In this context, there are a few key experimental decisions that must be taken into account when determining the potential relevance of the study of Li *et al.* to the bedside of critically ill patients. First, while lipopolysaccharide is a model of a short-term proinflammatory state that rapidly returns to baseline (or results in a similarly rapid death in more severe models), it does not closely mimic any disease seen in the ICU. While historically lipopolysaccharide was used as a model of sepsis since it is an integral part of Gram-negative bacteria, there is expansive literature demonstrating the differences between lipopolysaccharide and more authentic models of sepsis,[6] which has resulted in international consensus guidelines explicitly recommending against using lipopolysaccharide to model sepsis.[7] Next, the cognitive issues seen with post–intensive care syndrome are long-term complications of critical illness. Short-term cognitive dysfunction in the ICU is often due to underlying metabolic issues. While this can be problematic in the acute setting, it is unclear whether reversal of murine cognitive dysfunction shortly after the onset of an inflammatory insult in mice bears any relation to the cognitive deficits patients have weeks or months after their ICU stay. It is also difficult to mechanistically understand how two doses of dexmedetomidine—a drug that is used as a continuous drip, often for days in critically ill patients—can lead to long-term changes in cognition, especially considering that the adrenergic nervous system is often altered and pharmacologically targeted in critical illness.

This begs the larger question, however, of how useful animal models of critical illness are. A long-standing debate regarding how well rodent models of critical illness mimic human illness has led to conflicting results even when analyzing the identical data set.[8,9] What is unfortunately unquestionable is that the overwhelming number of randomized controlled trials in the ICU fail to show benefit.[10] This lack of efficacy is especially glaring in sepsis, a disease responsible for nearly 20% of all deaths worldwide, which costs more than $60 billion annually in the United States alone.[11,12] Historically, much (if not most) sepsis research has utilized mouse models of sepsis. While this has resulted in a massive amount of mechanistic data, this approach has not yet been successfully translated into changes of treatment at the bedside, and multiple clinical trials based on successful therapies in mice have proven to be unsuccessful in the ICU. The causes of these failures are multiple. For instance, it is easy to see conceptually how translating findings in young, healthy, genetically homogenous mice to aged genetically diverse human patients with multiple comorbidities might be difficult.

Since sepsis impacts multiple organs, funding for research in this syndrome comes from multiple institutes at the National Institutes of Health (NIH). Of these, the National Institute of General Medical Sciences (NIGMS) provides the most funding for the field. Driven by a desire to translate discoveries to the bedside, NIGMS recently released "Priorities for Sepsis Research" for researchers submitting applications related to sepsis.[13] The purpose of the notice was to explicitly notify applicants of NIGMS's focus on areas that would "provide new knowledge of the mechanistic complexity of sepsis in humans and… [to] test strategies for translating this knowledge into improved diagnostics and therapies for sepsis patients." This official guidance lists 12 topics of interest to NIGMS that cover a remarkably wide range of potential research directions. In contrast, it only lists two areas of low priority: rodent models, "unless uniquely well justified in terms of potential for providing novel insights into human sepsis," and clinical trials. While the low priority of clinical trials is not a surprise given NIGMS's overall mission, the direction to de-emphasize rodent research represents a fundamental shift in NIGMS's approach toward sepsis. This approach also goes further than the advisory council to the NIGMS, which recommended broadly expanding approaches toward sepsis research (as in the final NIGMS priorities), but also recommended that NIGMS "support the standardization of animal models and the development of models that more closely mimic (1) non-immunological aspects of sepsis and (2) important co-morbidities in human sepsis" while additionally highlighting the strengths and weaknesses of existing rodent models.[14]

It is important to note that NIGMS priorities are unique to a specific NIH institute and are not common to the

other institutes with significant sepsis portfolios, such as the National Institute of Allergy and Infectious Disease and the National Heart, Lung, and Blood Institute. However, there are multiple sepsis projects that are not part of the missions of these other institutes and instead fit more naturally into the broader mission of NIGMS. We believe that in light of the inability to translate preclinical findings to the bedside to improve outcomes of septic patients, a rebalancing of priorities was a tremendous step forward that allows for a wider range of approaches to sepsis. At the same time, where this leaves excellent work like that of Li *et al.*—and multiple other investigators with sepsis-related questions that are best mechanistically approached *via* rodent studies—is unclear.

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Competing Interests

Dr. Coopersmith served on the National Advisory General Medical Sciences Council Working Group on Sepsis.

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