Critical illness creates new neurocognitive and functional disabilities and further compromises preexisting organ dysfunction. These are truths borne out in multiple international studies. Recovery from severe illness is complex and relies on a fragile interdependence of adequate premorbid organ reserve, attentive care in the intensive care unit (ICU), timely and individualized rehabilitation, ongoing access to responsive health care professionals, and extensive personal and family resources. In short, getting better is difficult.

In their seminal work from 1999, Hopkins and colleagues established that survivors of the acute respiratory distress syndrome (ARDS) had important decrements in multiple cognitive domains, and these investigators highlighted hypoxemia during the ICU stay as a key contributor to dysfunction. These observations have been confirmed, but they have been largely confined to discrete patient groupings, such as patients with sepsis or ARDS or the elderly and challenged by incomplete follow-up and poorly characterized ICU-based risk factors or other risk modifiers.

In this issue of the *Journal,* Pandharipande and colleagues report the results of a large, multicenter, prospective cohort study to evaluate cognitive outcomes in a mixed medical–surgical population. This article unequivocally establishes that critical illness promotes the development of new and clinically important cognitive impairment, regardless of age, burden of coexisting conditions, or diagnosis at hospital admission. The investigators set a new standard for longitudinal cognitive-outcome studies by means of the following: systematic evaluation of cognitive impairment at baseline; detailed assessment of potential confounders, including cerebrovascular risk, delirium, and frailty; comprehensive cataloguing of drug exposure in the ICU; evaluation of genetic predisposition to cognitive dysfunction with the use of apolipoprotein E; and the Herculean efforts expended to track patients and conduct blinded cognitive assessments by professional psychologists in a diverse patient sample across multiple centers. The public health effect of neurocognitive morbidity after critical illness is undeniable.

In this generalizable study sample, a longer duration of delirium was strongly associated with worse global cognitive impairment and executive dysfunction that mirrored the disability observed in patients with moderate traumatic brain injury and mild Alzheimer’s disease. But not all patients had delirium, and some of the patients with cognitive dysfunction at 3 months showed improvement by 12 months. Furthermore, prior observations suggesting that drug exposures in the ICU are clear risk factors for long-term brain dysfunction were not supported by the current study.

Acquired or exacerbated brain injury is complex and multifactorial, as highlighted by these important data. Delirium is a pivotal risk factor for brain dysfunction, but its specific contribution remains elusive. Individual vulnerability and brain reserve intersect with a host of insults and risk modifiers that occur before, during, and after the injury of critical illness. The evaluation of apolipoprotein E in the current study is a clear signal that markers of genetic susceptibility belong in future outcome studies of critical illness. Building risk models with genetic markers that further inform robust molecular mechanisms of differential brain injury and repair are the beginning. We also need to understand the diverse neuroanatomical correlates for this dysfunction to determine whether discrete changes in neuroimaging findings correspond to prognosis or rehabilitative potential.

Loss to follow-up, study withdrawal, and death may each threaten internal validity in cohort studies, and the current work is no exception. Despite laudable follow-up efforts, there were important differences between the patients who completed neurocognitive testing and those who did not in terms of level of education, sex, frailty, and level of activity, and hence there is the possibility that patients who were sicker and more vulnerable were underrepresented. Going forward, it is crucial to understand the reasons for loss to follow-up and study withdrawal so that we can capture the full spectrum of disability. Insights from qualitative interviews may be helpful, and offsite or home visits may need to become standard practice for future follow-up work.

Physical activity may be an important risk

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**Disability after Critical Illness**

Margaret Herridge, M.D., M.P.H., and Jill I. Cameron, Ph.D.
modifier of neurocognitive outcome, and understanding the role of exercise during and after critical illness is essential. However, addressing ICU-acquired weakness in isolation is not sufficient, because the return to functional independence is complex and multidimensional. It would be important to gain an appreciation of how the brain–activity interface affects functional independence, quality of life, and patient-centered outcomes. In addition, more information is needed about the effect of cognitive dysfunction on job loss, health care utilization, and family caregivers.

The family caregiver for the critically ill patient undergoes unremitting stress in the face of the uncertain outcome for their loved one. This life experience is transformative. Family caregivers of persons who have had a sudden-onset illness, such as critical illness, stroke, or traumatic brain injury, may have new and often devastating mood disorders, including major depressive episodes and post-traumatic stress disorder.

This experience is uniquely stressful for this caregiver group because the onset of illness is abrupt and there is little time to assimilate their family member's new neurocognitive or physical disabilities, to comprehend that these may persist, or to prepare for the demands as a caregiver. Unfortunately, when family caregivers suffer from emotional distress, this may compromise the care provided to the family member, including the patient’s rehabilitation, and the sustainability of providing care in the home. Therefore, it is crucial for future research and intervention programs after critical illness to consider its effect on the patient and the family.

In summary, the findings of Pandharipande and colleagues unequivocally show that neurocognitive dysfunction is an important and prevalent public health concern after critical illness. These data underscore that surveillance and intervention for delirium remain crucial to best ICU practice, as does an ICU culture of wakefulness and mobility. Clinical-risk groupings and risk modifiers need to be further delineated by means of genetic and basic science work in large and diverse patient samples and mapped to neuroanatomical structure and function and relevant long-term patient-centered and family-centered outcomes. This will complete the vision of a longitudinal approach to critical illness. Basic research and translational collaborations need to be prioritized and are the crucial next steps. Without this detailed knowledge, we are merely guessing about how to proceed. Risk stratification will help distinguish between patients who can regain functional independence and those who have exhausted their organ reserve and rehabilitative potential and who live in the purgatory of chronic critical illness only to have unacceptably poor outcomes.

While we wait to accrue more mechanistic basic data and consider their implications for treatment and rehabilitation, we continue to accumulate a catalogue of neurocognitive and functional morbidity. This new knowledge provides detailed education for patients, families, ICU stakeholders, primary care physicians, and health policy makers and should fuel an informed discussion about what it means for our patients to survive an episode of critical illness, how it changes families forever, and when the degree of suffering and futility becomes unacceptable from a patient-centered and societal standpoint.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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