Brain Disorders in Critical Illness

Mechanisms, Diagnosis, and Treatment

Edited by

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Foreword

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As patients emerge from the terror and abyss of early life-threatening illness, many critical care physicians have learned the wisdom of asking them – or their loved ones when the patient cannot interact and communicate – a simple but probing question: “What do you hope will be achieved by our treatments here in the intensive care unit?” Unfortunately the question is more often asked in those circumstances that lead care providers to predict that the chances for survival and recovery are becoming remote. I believe that if we asked this more routinely, of those dramatically improving and hence lifting our pride in the power of our healing, as well as those dying and bringing us to acknowledge the limitations of our interventions and engaging our commitment to provide comfort to all, the answer would be fairly straightforward and akin to: “To return to my life as I knew it” or “To be myself again.”

In my experience our patients and their families show extraordinary realism and resilience. What they mean by those simple statements are not first and foremost that their hearts, and lungs, and kidneys, and limbs all return to their level of function before devastating illness or injury, although this is of course a deep wish. Yes, we discuss whether the dialysis machine or mechanical ventilator will be temporary and if it is to be eventually withdrawn what the path to liberation will entail. But their most fervent wish is to have their loved one return home. And in addition to their return to home and community and job, that they would be the same person, with the personal history, memories, ability to interact, personality and personhood that they recently left behind. In the hierarchy of all of the organs that we discuss on rounds each day when we use our organ- and problem-based approach to organize our findings and plans, they wish most to have their brains back.

Paradoxically, this pre-eminent priority embedded in their simple answers to our question is often precisely what we are least able to address, because we lack insight into what has happened to their brain in the course of critical illness, and what the arc of recovery might be. There are reasons the field of critical care medicine has found itself lacking in response to this patient-oriented outcome and priority. We are a young field of medicine, which arose in response to technology expansion and its geographic concentration in hospital units. Early means were developed and refined by pioneers of the field to halt lethal organ failure, to provide an opportunity to diagnose and treat underlying diseases and return patients to an increasingly stable state. We learned that the interplay of these disease processes and our life-support systems was complex and we wisely chose to define critical illness syndromes characterizing the state of our patients, such as the Systemic Inflammatory Response Syndrome. Careful exploration of organ function under our watch taught us that even when the patient became ill from a seemingly localized problem, such as an inflamed pancreas, coagulation, liver, renal, lung, and brain dysfunctions were more often than not present. We assumed, perhaps overly optimistically, that these organ dysfunctions seemingly acquired during critical illness would be shed if the fundamental problem was properly identified and treated, at least if our patient did not march inexorably into a dreaded state of refractory multi-system organ failure.

Because our healthcare systems lack ideal longitudinal care and follow-up – in fact far from ideal for either patients or care providers – our early hopeful supposition that conditions such as ICU delirium would be temporary and shed as the patient improved was not much tested before our own eyes. However, our increasing success in treating life-threatening illness generated large populations of survivors of critical illness, and this reality coupled with the dedication and insight of early investigators describing long-term outcomes from critical illness have challenged our early halcyon projections of recovery from presumed temporary brain dysfunction. Seminal studies of patients recovering from the acute respiratory distress syndrome (ARDS), understandably focusing upon serial lung function improvement over time, described
major neurocognitive and neuropsychiatric problems persisting for years after the lung injury that so captured our attention, even when a clear and defined structural brain injury appeared absent. It was most often these deficits of the brain and psyche that precluded patients from returning to the full aspects of their premorbid lives, and which dominated their assessment of the quality of their lives.

Somewhat late to the table for the reasons stated above, a large multi-disciplinary group of investigators has arisen across the world, bringing the perspectives and tools of critical care medicine, neurology, psychology, psychiatry, pharmacology, neuroimaging, and rehabilitation medicine to this clinical problem. A handful of descriptive studies has now exploded in only a few years to become literally hundreds of publications defining, describing, and exploring the mechanisms of brain dysfunction acquired during and persisting after diverse critical illnesses. Accordingly, it is timely for the creation of a textbook to summarize where we are in this nascent field, and what the best paths to further study and treatment of our patients might be. Brain Disorders in Critical Illness, created by senior editors Robert Stevens, Tarek Sharshar, and Wes Ely, is a tour de force in the pursuit of this mission.

The assembled authors are leaders from the fields of inquiry needed to address the central questions that have arisen about brain dysfunction in critical illness. The reader will be presented with an organization of material that is logical and thorough. It begins with a section on the epidemiology and outcomes that have been increasingly described in the literature based upon longitudinal study of critically ill patients. It then moves to a series of chapters describing behavioral neurology in the ICU, a necessary preamble to then describe biological mechanisms for dysfunction of the central nervous system with emphasis on those mechanisms most plausibly operative during the diverse insults that produce critical illness. A series of chapters then address the dilemma of diagnosis. We are still at a point of determining if there are truly unique types of injury occurring during typical treatments in the ICU, or whether we are witnessing injuries akin to those previously described during other processes (e.g., cardiopulmonary bypass, hypoxia, anesthesia), and how we may assemble tools and then definitions to identify at-risk patients during their ICU stay for special attention downstream. While we certainly are early in the course of even understanding this problem (or how many different problems the general observations will yield), the next section addresses some early studies of promising means of preventing and even treating brain dysfunction in the critically ill. Finally, the last section describes those relatively specific encephalopathies (e.g., hepatic encephalopathy, sepsis) that have been the subjects of study in their own right in the past.

Emerging fields benefit enormously from thoughtful pauses that inventory existing information, organize findings into comprehensible frameworks, offer new paradigms for understanding what has been described, and at least name the demon when there are large gaps challenging our understanding. This textbook provides those valuable contributions to the field of critical care medicine, and the authors are to be commended for their accomplishments. It is my hope the book will stimulate as much new thought and discovery as it reviews, and if so it will be poised for an even more exciting second edition in the near future.
Introduction

Tarek Sharshar, E. Wesley Ely, and Robert D. Stevens

In recent years there has been widespread acknowledgment that critical illness has a fundamental neurological dimension. A broad body of work has demonstrated that severe illnesses, possibly in conjunction with practices and interventions in the ICU, are responsible for neurological complications which have a major impact on short- and long-term outcome. This neurological burden is almost certainly an indirect product of intensive care itself, with increasing numbers of patients surviving to the recovery phase of critical illness. Scientific exploration of the relevance and impact of ICU-acquired neurological disorders has been led by an initially small, but rapidly expanding, group of dedicated researchers.

An illustration of this process is the work on delirium which started with observational studies and now includes large, multicenter randomized trials. Delirium is a complex and fascinating syndrome as its pathophysiology, expression, and severity is heavily dependent on the underlying disorder (e.g., sepsis, hepatic failure), while understanding of its biological mechanisms draws on concepts from neurology, neuropharmacology, neuroimmunology, and the cognitive neurosciences. The association between delirium and age- or disease-associated cognitive impairment is clearly reciprocal, possibly implicating subtle shifts between chronic and acute neuroinflammatory states.

Another illustration is anoxic-ischemic encephalopathy resulting from cardiac arrest, which has been the object of a major research effort mobilizing intensivists, neurologists, neurophysiologists, and neuroradiologists in order to develop prognostic models and to assess therapeutic strategies. Anoxic-ischemic encephalopathy is also a clinical paradigm for understanding the biology of consciousness and consciousness disorders.

Critical illnesses are life-threatening disturbances of homeostasis. The central nervous system is a major regulator of homeostasis, responding to physiological challenges via behavioral, neuroendocrine, autonomic, and neuroinflammatory responses. A major task for research in critical illness is to understand the fundamental differences between adaptive and maladaptive homeostatic responses, a task which will require rigorous scientific evaluation of interactions between immunological, endocrine, and autonomic systems. Knowledge of these interactions is likely to yield breakthroughs in the treatment of life-threatening diseases such as sepsis, ARDS, and their associated neurological sequelae.

Collectively, constructs elaborated in this book underscore the central relevance of neuroscience in the realm of critical care medicine, not only for clinicians in the ICU who are routinely facing acute neurological syndromes, but also for clinical and translational researchers who are evaluating novel therapeutic interventions and innovative methods to map brain perturbations via advances in neuroimaging and electrophysiology.

This book provides an overview of brain disorders in critical illness, of which delirium and anoxic-ischemic encephalopathy are emblematic. But the overarching goal is to construct a biological framework for understanding these disorders. It is our conviction that insights and methods developed in neuroscience will be the main driver of scientific progress in the neurology of critical illness. We would like to extend our deepest appreciation to each author for having enthusiastically accepted to contribute to this book. As editors of this “first-ever textbook” synthesizing Brain Disorders in Critical Illness we look forward to advances in care that will bring more complete healing to our patients globally as they emerge from ICUs and put the pieces of their lives back together.