EDITORIAL

Evolution of neurocritical care

Peter LeRoux

Medicine always evolves. What we did or accepted as 'standard of care' 20 years ago or even five years ago is now very different in 2020. In particular, neocritical care that focuses on the care of critically ill patients with acute brain and nervous system disorders has grown significantly. In 2000, there were few if any dedicated neurocritical care units (NCCU). Today, data from PRINCE, a multicenter, international, point-prevalence, cross-sectional, prospective, observational, noninterventional study suggests that over two-thirds of patients with neurocritical disorders are managed in dedicated in NCCUs although there remains significant geographic variability [1]. This is important as accumulating data suggests outcomes are improved when appropriate patients are admitted to a dedicated NCCU [2].

The reasons for this association between improved outcome and NCCUs are uncertain but in part are likely associated with advances in technology, diagnostic tools, and care; better understanding of pathophysiology and organization of care. In this edition of *Current Opinion in Critical Care* (COCC), we have chosen to review ten topics that include prehospital care, diagnosis and monitoring, surgery, pharmacology, and ICU care that until recently were nonexistent, not – feasible or not well appreciated.

First, mobile stroke units (MSUs) are described. The MSU concept was first introduced in 2003 but it is only in recent years that MSUs have proliferated with a clear realization that 'time is brain,' and with advances in information technology and portable CT scanners. This concept is still evolving and rather than only help in stroke care may gradually morph into a neuro-ER or ICU that is taken to the patient for all types of acute brain injuries [3,4]. Second, in daily practice, the challenge for intensivists is to identify patients who are at risk for secondary injury, determine disease severity, and distinguish responders from nonresponders to therapy. Biomarkers can help answer these challenges, for example, troponin in cardiac disease. Although biomarkers have been used for many years in brain injury interest in their use has increased since the FDA-approved biomarkers (UCH-L1 and GFAP) in early 2018 to help evaluate mild traumatic brain injury (TBI). In addition, the recent advent of fourth-generation SiMoA technology has now made it possible to accurately quantify neurofilament light chain, a biomarker of axonal injury, in serum rather than in CSF [5,6]. The role of these molecular biomarkers, assays of biomarker panels and microRNAs, a novel class of molecules, in the ICU is discussed [7,8]. It is possible that at least some of these biomarkers will be part of routine NCCU practice in the near future.

Third, monitoring intracranial physiology and in particular multimodality monitoring (MMM) has become central to NCCU patient management and to individualized care [9]. Indeed, in a recent phase II randomized clinical trial (RCT), goal-directed therapy guided by brain oxygen, intracranial pressure (ICP), and cerebral perfusion pressure (CPP) monitoring appears to be superior to standard ICP and CPP guided therapy in severe TBI [10] and a phase III trial now is underway. However, most monitors of brain physiology are invasive. In recent years, technological advances have occurred in noninvasive neuromonitoring tools. In this edition of COCC, two such devices automated infrared pupillometry and optic nerve sheath diameter ultrasound are discussed. These tools now appear useful complements to MMM in neurocritical care, in particular in patients at risk for intracranial hypertension and for neuroprognostication after cardiac arrest [11].

Fourth ICP management is central to care of acute brain injury but questions have emerged about how best to assess and manage ICP [12]. Although metaanalysis of studies published since 2007 that include 25 229 patients shows improved survival in patients who receive an ICP monitor [13], it remains uncertain whether management of a single threshold makes an outcome difference. In addition, converging evidence from several different lines of research suggests that care based on only ICP and CPP thresholds may be an oversimplification of a complex problem [14–17]. Instead, additional measures of ICP, for example, ICP waveform analysis, RAP, pressure reactivity index (PRx), or

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CO_2 reactivity or use of other monitors, that is, MMM may be necessary to augment ICP care. Recent data processing advances and computerized bedside monitoring allow the interaction between ICP and mean arterial pressure or PRx to be continuously monitored. The concepts of optimal CPP (CPPopt) and arterial pressures (ABPopt) that uses PRx recently have been introduced into clinical practice. This allows patient specific thresholds to be targeted and can help decide whether to use ICP or CPP-based therapy [16,18,19]. In clinical studies, both CPPopt and ABPopt are associated with TBI outcome and fewer neurologic complications in cardiac surgery. This concept is discussed in a review on autoregulation-based therapy across a variety of neurologic disorders.

Fifth, two reviews address spontaneous intracerebral hemorrhage (ICH), the second most common subtype of stroke. Case fatality is high; approximately 60% at one year and only 20% of survivors are independent within six months. Intuitively surgery should help but RCTs using open surgical techniques have left a prevailing nihilism. However, surgical techniques have advanced and in particular minimally invasive techniques and those based on stereotaxic techniques have fostered a new optimism about ICH management and are discussed in a review on minimally invasive ICH surgery [20]. At the same time, as surgical techniques have advanced newer anticoagulation agents (direct oral anticoagulants) have proliferated [21] and these and vitamin K antagonists remain a common cause of ICH [22]. This has led to questions on how best to reverse these agents [23]. Specific reversal agents, for example, idarucizumab, andexanet alfa, and ciraparantag [24] now are available and are discussed in a review on anticoagulation reversal for ICH.

Sixth, the care of critically ill brain-injured patients is complex and requires a careful balance between cerebral and systemic treatment priorities. The evolution of neurocritical care has led to a realization that just treating the brain alone may not always suffice. Instead, a holistic targeted approach and management of extracranial issues are important [25,26]. This concept is discussed in a review on targeting the brain and the body in TBI. On the other hand, a simple concept, early mobilization has been demonstrated in general critical care to help improve short-term physical function, reduce ICU-acquired weakness and decrease the duration of mechanical ventilation or ICU stay [27]. Whether early mobilization improves long-term health-related quality of life (QOL) is still being elucidated and hence there remains a debate between ICU clinicians who advocate early mobilization based on current evidence and those who believe that early mobilization should be tested in clinical trials that examine long-term function and QOL. In addition, early mobilization traditionally has been avoided in neurocritical care for many diverse reasons. However, emerging evidence suggests that early mobilization is safe and feasible in many brain-injured patients including those with external ventricular drains [28,29]. There may also be benefit. For example, rest was regarded as the treatment for concussion. However, data from RCTs now show that subthreshold aerobic exercise may speed recovery and reduce the incidence of delayed recovery after concussion [30]. Caution is still required as this may be disease specific, for example, in acute ischemic stroke early mobilization may aggravate outcome [31]. It also remains unclear what is the character, dose, and optimal timing of early mobilization. These various concepts are discussed in a review on early mobility of neurocritical care patients.

In parallel with the many recent advances in neurocritical care, and better understanding of pathophysiology, neurocritical care has become better organized. In 2002, the Neurocritical Care Society (NCS), an international multidisciplinary organization that includes physicians, nurses, pharmacists, and advance practice providers was founded. Since then, it has grown immensely. In 2010 The Neurocritical Care Research Network was formed with the aim to promote investigator-initiated neurocritical care research and in 2012 the first NCS guidelines were published. This has culminated in the publication in 2018 of 'The Standards for Neurocritical Care Intensive Care Units' [32] and in 2019 of NCCU-specific 'Clinical Performance Measures' [33]. Quality improvement continues to mature in neurocritical care and is important because significant differences in structures and processes of care remain [34]. Furthermore, quality measures proposed for critical care in general may not always apply to neurocritical care [35]. In this COCC edition, recent contributions to quality improvement in neurocritical care and future directions, for example, disease-specific quality improvement measures are discussed [36].

The final topic addresses brain death and organ procurement. The demand for organs is increasing at a faster rate than that at which organs become available for transplantation. Creation of organ sharing networks has increased awareness and the likelihood of successful transplantation. However, neurointensivists play a critical role through the identification of potential donors and declaration of brain death. In addition, as discussed in this review, appropriate medical management and resuscitation of the potential donor after declaration of death by neurologic criteria can help improve graft survival. Recent clinical studies also have challenged traditional criteria for organ refusal and time to organ procurement [37–40]. This has led to new research and clinical trials in previously overlooked aspects of critical care which in turn may improve transplant numbers and recipient outcomes.

The advances described above have all been chronicled in many contributions to the scientific literature; the sheer volume of which makes it difficult for physicians to keep up to date. From this edition, we hope that the reader will gain a comprehensive understanding about recent advances in neurocritical care and an insight into ongoing controversies and potential future management. To do this, we have been fortunate to have reviews written by authors who are clinicians and researchers with extensive experience and expertise in the field. Each has provided an excellent and timely review.

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