Recommendations for the use of multimodal monitoring in the neurointensive care unit

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Purpose of review
Multimodal monitoring (MMM) is routinely applied in neurointensive care. Unfortunately, there is no robust evidence on which MMM-derived physiologic variables are the most clinically relevant, how and when they should be monitored, and whether MMM impacts outcome. The complexity is even higher because once the data are continuously collected, interpretation and integration of these complex physiologic events into targeted individualized care is still embryonic.

Recent findings
Recent clinical investigation mainly focused on intracranial pressure, perfusion of the brain, and oxygen availability along with electrophysiology. Moreover, a series of articles reviewing the available evidence on all the MMM tools, giving practical recommendations for bedside MMM, has been published, along with other consensus documents on the role of neuromonitoring and electroencephalography in this setting.

Summary
MMM allows comprehensive exploration of the complex pathophysiology of acute brain damage and, depending on the different configuration of the pathological condition we are treating, the application of targeted individualized care. Unfortunately, we still lack robust evidence on how to better integrate MMM-derived information at the bedside to improve patient management. Advanced informatics is promising and may provide us a supportive tool to interpret physiologic events and guide pathophysiological-based therapeutic decisions.

Keywords
brain tissue oxygen, cerebral perfusion pressure, intracranial pressure, multimodality monitoring, neurophysiological monitoring

INTRODUCTION

Management of patients with acute brain injury (ABI) requires rapid and accurate diagnosis of pathologic intracranial events and brain function monitoring, especially based on brain-derived physiologic information. Even if no single monitor will improve outcome *per se*, if the findings obtained from such devices are not associated with effective therapeutic interventions, a monitoring-based approach could still be essential to overall improve neurological outcome and quality of life in survivors of severe brain damage [1]. It should primarily guide clinicians to understand ABI mechanisms, eventually clinical deterioration, and tailor therapy to the individual patient [2▪▪]. Considering the wide number of clinical and physiological variables that can be collected after ABI, multimodal monitoring (MMM), which is defined as the simultaneous evaluation of cerebral function from multiple modalities in a single patient associated with an integrated interpretation, has been proposed (Fig. 1). Unfortunately, there is no strong evidence on which processes are the most important to monitor, how and when these should be monitored, and whether monitoring these processes is cost-effective and impacts outcome in this patient population. Ideally, MMM should be a continuous, comprehensive monitoring setting, that would not miss clinically significant events [2▪▪,3]. Moreover, all the data should be collected simultaneously, time synchronized, and displayed in an

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KEY POINTS

- Given the complexity of ABI pathophysiology, a single monitoring system appears insufficient to adequately explore brain physiology and guide critical care.
- MMM allows exploration of the complex pathophysiology of acute brain damage and the application of targeted individualized care.
- MMM is routinely used in neurocritical care even if uncertainty remains on the most clinically relevant physiologic variables, how and when they should be monitored, and whether MMM impacts outcome.

integrated fashion, using a simple, interactive interface that allows the plotting of integrated waveforms, images, and trends.

Recently, the Neurocritical Care Society and the European Society of Intensive Care Medicine promoted a multidisciplinary, multinational panel aimed to evaluate the available evidence and give practical recommendations for bedside MMM. Despite limited high-quality data, a systematic review of the existing literature until 2013 was successfully performed. Along with a summary document [2▪▪], a number of satellite documents have recently been published in a supplement to *Neurocritical Care* [4–19]. Here, we aimed to summarize the most recent studies that examined the potential utility of different MMM techniques currently used in critically ill patients with ABI. For the sake of space, we will review only clinical, intracranial pressure (ICP) and cerebral perfusion pressure (CPP), brain tissue oxygen ($PbtO_2$), and electrophysiological monitoring.

CLINICAL MONITORING

Neurological examination remains the cornerstone for the assessment of patients with ABI or

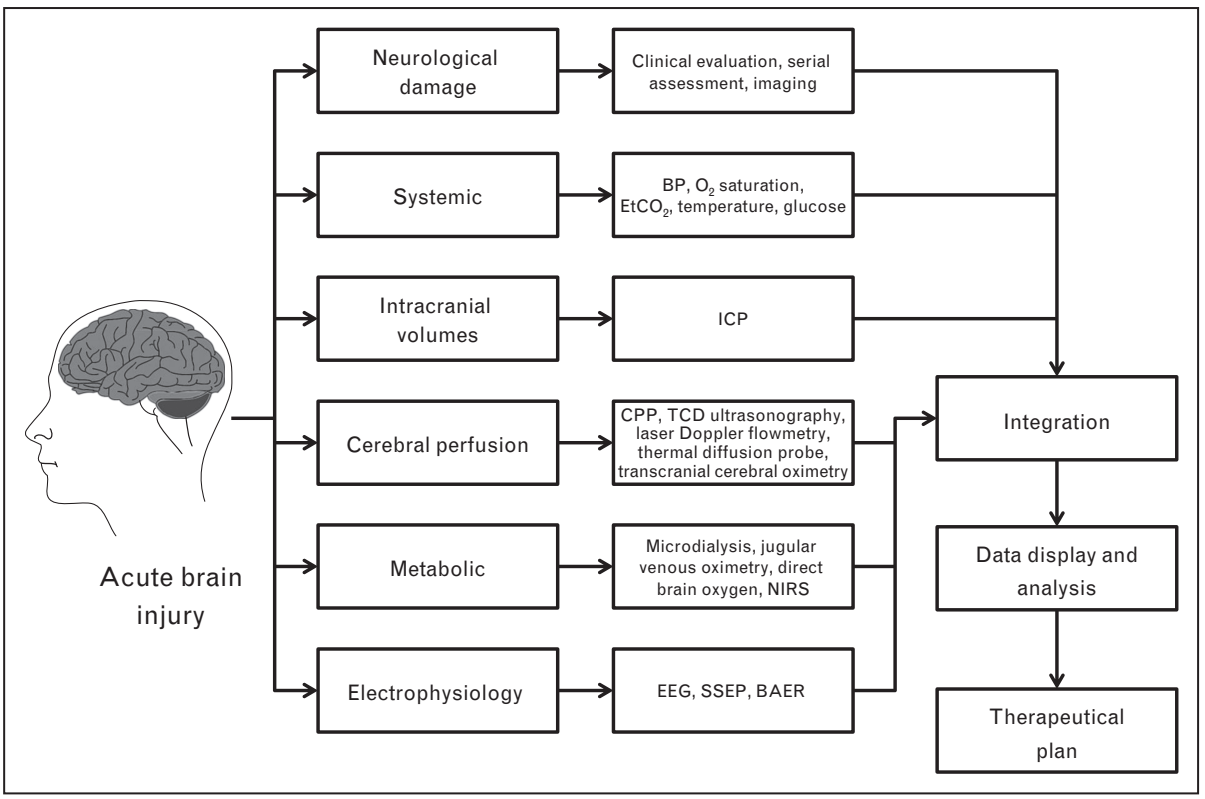

FIGURE 1. Schematic overview of multimodality monitoring (MMM). The complexity of acute brain damage could be explored with MMM, that is, the simultaneous evaluation of cerebral function from multiple modalities in a single patient, applying different configurations depending on different exploratory targets. All the information collected needs to be integrated and the relationship between variables needs to be evaluated. Integration helps clinicians to understand ABI mechanisms and tailor therapy to the individual patient. Advanced informatics is required for interpreting physiologic events and for a pathophysiological-based decision support tool. ABI, acute brain injury; BAER, brainstem auditory-evoked response; BP, blood pressure; CPP, cerebral perfusion pressure; EEG, electroencephalography; $EtCO_2$, end-tidal CO_2 concentration; ICP, intracranial pressure; NIRS, near-infrared spectroscopy; SSEPs, somatosensory-evoked potentials; TCD, transcranial Doppler.

developing a secondary cerebral complication during their critical illness [20▪]. The role of clinical assessment is to grade the severity of cerebral damage, detect the occurrence of further neurological deterioration, and quantify the effects of therapy in patients with ABI [16]. The importance to assess cognition and brainstem function together with the common evaluation of consciousness and motor response have been stressed [20▪,21]. Whenever possible, sedation should be minimized, to allow repeated neurological examination. In a recent study in patients with ABI, despite sedation, interruption was associated with an increase in ICP and CPP, and it did not translate into a relevant alteration of cerebral metabolism and oxygenation [22▪▪]. There are various numerical clinical scales that quantify the degree of brain injury. The Glasgow Coma Scale (GCS), defined more than 40 years ago, remains the most widely used [23]. The early combination of GCS and pupillary reactivity was confirmed as highly predictive of patient outcome at 6 months in a cohort of 445 patients with traumatic brain injury (TBI) [24]. However, an initial mild GCS score does not preclude lesion progression and the need for a neurosurgical intervention in patients with an intracranial injury [25▪]. Also, age affects the relationship between GCS and anatomic TBI severity, with elderly patients having better GCS scores than younger despite similar brain damage [26]. As GCS does not directly evaluate brainstem function, the full outline of unresponsiveness score, which also includes brainstem reflexes, has been validated, although its superiority to predict patient outcome when compared with GCS remains controversial [27,28]. Finally, pupillary reflex assessment could be misleading in the clinical practice; as such, pupillary reactivity tested with an infrared pupillometer was more accurate than clinical pupillary evaluation in identifying postanoxic comatose patients with poor outcome and had comparable prognostic accuracy for outcome prediction than electroencephalography (EEG) and somatosensory-evoked potential [29▪].

INTRACRANIAL AND CEREBRAL PERFUSION PRESSURE MONITORING

ICP monitoring has been widely used for the management of ABI over the last decades [30,31▪]. Recently, the effectiveness of ICP monitoring in patients with TBI has been challenged by the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST-TRIP) trial [32], leading some clinicians to question the value of ICP measurement in TBI. At this stage, to carefully analyze and adequately interpret this important study is of utmost importance [33–36]. The BEST-TRIP trial compared two management protocols, one ICP based and the other driven by computed tomography scan and neurologic examination. This trial did not question the value of ICP monitoring *per se*, but rather evaluated two different methods for severe TBI management. ICP monitoring did not alter patient prognosis; however, it was indeed effective to guide ICP management, because it was associated with a more judicious use of treatments to control ICP, such as osmotherapy. Therefore, the BEST-TRIP trial reinforces the concept that continuous evaluation and monitoring of elevated ICP together with clinical and imaging signs of swelling should still be considered as the standard of care for the management of TBI.

Several questions still remain unanswered and the future challenges are to better identify those patients requiring ICP monitoring and better evaluate ICP thresholds that should trigger specific therapies [37,38]. Increased ICP, and particularly when refractory to treatment, is a well described negative prognostic factor, especially for mortality [39]. Although we still define intracranial hypertension as an ICP above 20 mmHg, both lower and higher ICP thresholds have been reported to be associated with poor outcome [40]. The adjusted odds ratio of mortality comparing 10-mmHg increases in mean ICP was 3.12 and higher average ICP was associated with long-term diminished functional status and neuropsychological functioning. Also the recommendations for an optimal CPP have changed over time and depend on disease state [31▪]. Management strategies based on optimizing and increasing CPP (i.e., with fluids and/or vasopressors) rather than decreasing ICP have not improved outcome [41]; also, CPP values should be adjusted for each individual rather than use a single threshold [31▪]. Indeed, monitoring cerebral autoregulation may be useful in identifying the optimal CPP targets in TBI [42] and patients with subarachnoid hemorrhage (SAH) [43,44]; continuous bedside assessment of autoregulation is now feasible and should be considered as an important part of MMM [7].

In conclusion, monitoring of ICP and CPP should be incorporated in the management and therapy of patients with ABI [3], particularly those in coma after TBI [5], although it may also be considered in other conditions, such as SAH [45] and intracranial hemorrhage [6]. Intraparenchymal ICP monitors and external ventricular drains are equally reliable in providing a measure of ICP with the understanding that device location relative to a lesion is a major determinant of ICP. Nevertheless, the use of an external ventricular drain is the preferred method to monitor ICP, particularly in the

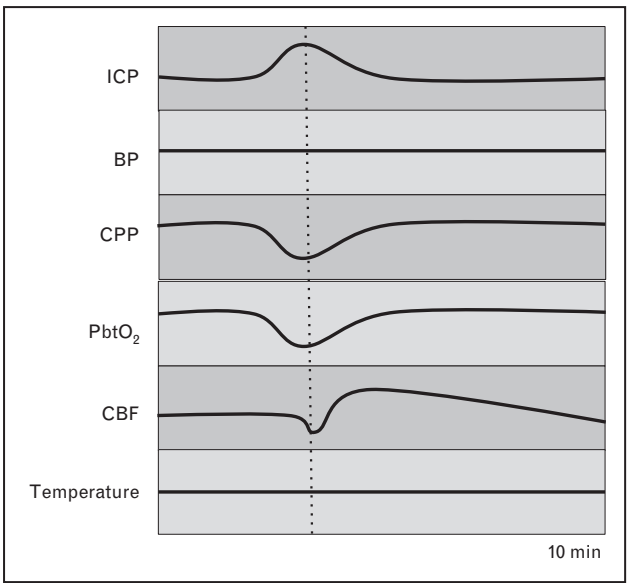

FIGURE 2. Schematic draft of multimodal brain monitoring recording during an ICP rise. Rise in ICP courses with relatively stable systemic variables such as blood pressure (BP) but is accompanied by an important decrease in CPP, CBF, and $PbtO_2$. A mannitol bolus has been infused (dotted line). Relationship between the phenomena and the response to the therapy could be appreciated only with a MMM approach. CBF, cerebral blood flow; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MMM, multimodal monitoring; $PbtO_2$, brain tissue oxygen.

setting of hydrocephalus [6]. Noninvasive devices do not reliably quantify ICP [46]. However, they may be used to estimate ICP when invasive monitoring is not feasible, along with information from imaging [47–49]. It remains a mandatory prerequisite, exploring the volume relationship inside the skull, when other intracranial monitors, exploring other domains, are used to provide a framework for optimal interpretation (Fig. 2).

BRAIN TISSUE OXYGEN MONITORING

$PbtO_2$ sensors monitor the balance between oxygen delivery and consumption. Catheters are generally placed adjacent to an ICP catheter and allow continuous measure of $PbtO_2$ locally, in an area of about 15–20 mm^2 around the probe [50]. Devices for $PbtO_2$ monitoring provide safe and accurate monitoring for up to 7–10 days [8]. Normal $PbtO_2$ averages 35–50 mmHg, with lower values observed after ABI. Values below 20 mmHg are considered abnormal, that is, 'brain hypoxia'. Although the critical threshold to drive therapy may vary between 15 and 20 mmHg, $PbtO_2$ monitoring might help with the management of brain-injured patients. However, given the different physiologic determinants of $PbtO_2$ [51], the reasons for low $PbtO_2$ values may be multifactorial and several interventions have then the potential to effectively treat brain hypoxia [52]. Modeling clinical data [53] could help clarifying this complexity. Survivors clustered at $PbtO_2$ around 25 mmHg and nonsurvivors around 18 mm Hg, with two clusters: high ICP/low $PbtO_2$ and low ICP/low $PbtO_2$. Moreover, incremental supranormal FiO_2 levels are not the solution because they are associated with increased cerebral excitotoxicity documented by microdialysis, independent from $PbtO_2$ and other important cerebral and systemic determinants [54], potentially aggravating secondary brain damage after severe TBI.

$PbtO_2$ monitoring helps to identify individual 'optimal' CPP, that is, a CPP level to prevent/treat brain hypoxia and monitor the effect of hemodynamic interventions [55,56]. Assessment of cerebrovascular reactivity can be the first step in approaching the relations among cerebral blood flow, oxygen delivery and demand, and cellular metabolism. In a recent review [57], 32 observational studies and two randomized controlled trials were screened with a total of 1161 patient observations. Although overall quality of evidence was moderate and several methodological biases were found in these studies, knowledge of the status is not only essential for CPP optimization but should also provide information to guide the interpretation and interventions targeted to $PbtO_2$ and lactate/pyruvate ratio. It could be the first step in approaching the relations among cerebral blood flow, oxygen delivery and demand, and cellular metabolism.

Reduced $PbtO_2$ was associated with worse outcome after TBI and, to a lesser extent, SAH although the relationship between $PbtO_2$-directed therapy and long-term outcome remains controversial [58]. In a recent study on 64 patients with SAH [59], 530 episodes of brain hypoxia were recorded and treated with 1052 different interventions. In multivariate regression analysis, only young age and response to $PbtO_2$-directed intervention significantly correlated with good outcome. Particularly, patients with favorable outcomes had a mean response rate to $PbtO_2$-directed interventions of 70 vs. 45% only in patients with poor outcomes. $PbtO_2$ can also help in understanding the effects of other therapies on cerebral oxygenation and, thus, in limiting their potential side-effects. In a small study, parenteral diclofenac infusion to control fever was studied in 21 patients with SAH [60]. A rapid drug infusion produced a decrease in mean arterial pressure and CPP necessitating therapeutic interventions. Although cerebral metabolism showed no significant changes after diclofenac

infusion, $PbtO_2$ decreased by 13%, resulting in brain hypoxia in 38% of patients.

ELECTROPHYSIOLOGY

The role of electrophysiological tests, especially EEG, has rapidly expanded in the context of monitoring, early diagnosis, and prognostication among critically ill patients with impaired consciousness. In a recent systematic review, EEG was recommended for the monitoring of generalized convulsive status epilepticus and to rule out nonconvulsive seizures (NCSz) in brain-injured and comatose critically ill patients without primary brain injury who do not show any clear signs of cerebral damage [61▪▪]. During cooling after cardiac arrest, seizures occurred in 5/33 patients whereas 11/33 patients had seizures at some time during hospitalization; nine of them died during hospitalization compared with 11/22 patients without seizures [62]. In acute neurological diseases (n = 170 patients), NCSz were detected in 21% of patients. Clinical seizures preceded EEG diagnosis only in 25% of cases whereas subtle clinical findings, such as oral or ocular muscular movements and/or gaze deviation, were found in 50% of these patients [63▪]. Thus, most of the NCSz would go unrecognized in comatose ICU patients in the absence of EEG monitoring.

EEG improves the accuracy of coma prognostication after cardiac arrest and critical illness [64▪▪]. In a study including 62 patients with postcardiac arrest coma, all patients with absent background reactivity on the EEG (58%) at normothermia eventually died. On the contrary, initial background reactivity was present in 26 patients and 16/26 of them eventually survived. The presence of generalized periodic epileptiform discharges was found in five patients and only one survived [65]. In another cardiac arrest cohort, the combination of clinical examination, EEG reactivity, and neuron-specific enolase levels had the highest predictive performance (area under the curve: 0.89 for mortality and 0.88 for poor outcome) for prognostication [64▪▪]. An important limitation of this approach is that the visual analysis of EEG background and reactivity is not standardized and may not always be consistent between EEG examiners. Using an automated EEG analysis, using burst–suppression ratio and approximate entropy, would be optimal in this setting and indeed it was shown to be accurate to quantify brain damage in 46 cardiac arrest survivors, showing a very good agreement with a visual score from a certified neurologist [66]. Other automatic approaches using EEG-based evaluation of auditory functions, the so-called mismatch negativity – an automatic frontocentral EEG component occurring at 100–150 ms after the onset of a sound deviation – have been tested: one study showed that an intact auditory processing was present even in comatose patients with extended brain damage after cardiac arrest, whereas a deterioration of auditory discrimination over time was highly predictive of poor outcome [67].

Although continuous EEG (cEEG) is recommended over intermittent EEG to monitor comatose patients with status epilepticus or with persistent impaired consciousness [61▪▪], there are still uncertainties about the superiority of cEEG over an intermittent approach in this setting, and about some important technical aspects, such as the optimal EEG duration and montage required [9]. Indeed, cEEG and intermittent EEG showed a very high agreement to evaluate background discontinuity, EEG reactivity, and epileptiform activity, both during hypothermia and at normothermia in comatose cardiac arrest patients [9,68▪]. However, these results were valid only if intermittent EEG was repeated several times during the first 48 h after ICU admission in these patients. Indeed, when compared with a single standard EEG, cEEG improved seizure detection but at higher costs [69]. Finally, early use of EEG may impact the clinical management of critically ill patients with altered mental status; in one study, Zehtabchi *et al.* [70] showed that in comparison with no monitoring, the use of EEG was associated with a change in diagnostic work-up in 49% of patients and of the therapeutic plan in 42% of cases. These changes took place immediately after the EEG results, supporting the concept that EEG may be relevant in the evaluation of such patients.

A few studies have shown that evoked potentials may be useful to evaluate the degree of consciousness impairment and the extent of brain damage in critically ill patients and provide some information on prognosis. As such, middle latency auditory-evoked potentials were able to effectively quantify the degree of consciousness in comatose patients admitted to the emergency department [71]. Also, the brainstem auditory-evoked response, which is sensitive to pontomesencephalic integrity, showed early significant changes in V waves and V latency in case of transtentorial brain herniation and/or increased ICP [72]. Thus, this methodology could be used as an interesting alternative to monitor brainstem compression in comatose patients with an acute brain damage at risk for intracranial hypertension. Finally, middle latency-evoked potentials (i.e., N60) were better predictors for favorable outcome in 112 patients with severe ischemic brain injuries, that is, stroke and postanoxic injury, than cortical N20 potentials [73].

CONCLUSION

Given the complexity of ABI pathophysiology, a single monitoring system appears insufficient to adequately explore brain physiology and guide critical care. In this setting, MMM seems preferable and may be recommended for the management of patients with ABI. The different monitoring modalities and configuration are highly linked with the pathological condition we are treating. At the edge of the spectrum, MMM should integrate neurophysiological information with neuroimaging and different continuous physiologic data – such as ICP, CPP, and $PbtO_2$ – with EEG-derived parameters. Despite major technological advances over the past decades in the ability to monitor the injured brain, further study is needed to examine whether the integration of all this information and the implementation of MMM will translate into improved patient management and outcome. The cost-effectiveness of such approach should also be demonstrated. At this stage, there is also the need for the development of next-generation informatics tools to correctly interpret complex physiologic events and derive more precise therapeutic algorithms based on sound pathophysiological background that would allow clinicians to optimize targeted individualized care at the bedside.

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Conflicts of interest

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