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Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care

A statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine

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The Neurocritical Care Society affirms the value of this consensus statement as an educational tool for clinicians.

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This article is being simultaneously published in *Neurocritical Care* and *Intensive Care Medicine*.This article is endorsed by the Neurocritical Care Society (NCS), the European Society of Intensive Care Medicine (ESICM), the Society for Critical Care Medicine (SCCM) and the Latin America Brain Injury Consortium and is being simultaneously published in Neurocritical Care and Intensive Care Medicine. It will be published in Intensive Care Medicine in an abridged version.

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Abstract Neurocritical care depends, in part, on careful patient monitoring but as yet there are little

data on what processes are the most important to monitor, how these should be monitored, and whether monitoring these processes is cost-effective and impacts outcome. At the same time, bioinformatics is a rapidly emerging field in critical care but as yet there is little agreement or standardization on what information is important and how it should be displayed and analyzed. The Neurocritical Care Society in collaboration with the European Society of Intensive Care Medicine, the Society for Critical Care Medicine, and the Latin America Brain Injury Consortium organized an international, multidisciplinary consensus conference to begin to address these needs. International experts from neurosurgery, neurocritical care, neurology, critical care, neuroanesthesiology, nursing, pharmacy, and informatics were recruited on the basis of their research, publication record, and expertise. They undertook a systematic literature review to develop recommendations about specific topics on physiologic processes important to the care of patients with disorders that require neurocritical care. This review does not make recommendations about treatment, imaging, and intraoperative monitoring. A multidisciplinary jury, selected for their expertise in clinical investigation and development of practice guidelines, guided this process. The GRADE system was used to develop recommendations based on literature review, discussion, integrating the literature with the participants' collective experience, and critical review by an impartial jury. Emphasis was placed on the principle that recommendations should be based on both data quality and on trade-offs and translation into clinical practice. Strong consideration was given to providing pragmatic guidance and recommendations for bedside neuromonitoring, even in the absence of high quality data.

Keywords
Consensus development conference · Grading of Recommendations Assessment Development and Evaluation (GRADE) · Brain metabolism · Brain oxygen · Clinical trials · Intracranial pressure · Microdialysis · Multimodal monitoring · Neuromonitoring · Traumatic brain injury · Brain physiology · Bioinformatics · Biomarkers · Neurocritical care · Clinical guidelines

Introduction

The Neurocritical Care Society (NCS) in collaboration with the European Society of Intensive Care Medicine (ESICM), the Society for Critical Care Medicine (SCCM), and the Latin America Brain Injury Consortium (LABIC) commissioned a consensus conference on monitoring patients with acute neurological disorders that require intensive care management.

Patient monitoring using some, many, or all of the techniques outlined in this consensus document is routinely performed in most neurocritical care units (NCCU) on patients with acute neurological disorders who require critical care. In many institutions the combined use of multiple monitors is common, a platform often termed "multimodality monitoring" (MMM). The use of such tools to supplement the clinical examination is predicated by the insensitivity of the neurologic examination to monitor for disease progression in patients in whom the clinical features of disease are confounded by the effects of sedation, analgesia, and neuromuscular blockade, or in deeply comatose patients (e.g., malignant brain edema, seizures, and brain ischemia) where neurological responses approach a minimum and become insensitive to clinical deterioration. Several considerations frame our subsequent discussion:

1. As with general intensive care, basic monitoring such as electrocardiography, pulse oximetry, and blood pressure supports the management of critically ill neurological patients. The use of these monitoring modalities has become routine despite limited level I evidence to support their use. It is not our intention to make recommendations for such monitoring, except where such recommendations are directly relevant to clinical care of the injured or diseased nervous system.
2. We accept that imaging is indispensable in the diagnosis and management of the critically ill patient with neurological disease, perhaps more so than any other area of intensive care medicine. However, with a few exceptions we have elected not to focus on imaging but rather will concentrate on bedside tools that can be used in the intensive care unit (ICU).
3. It is not our intent to discuss or recommend therapy in any of the settings we address. This may seem to be a somewhat arbitrary distinction, but the distinction allows us to focus our questions on the act of monitoring rather than the act of treatment. It must be recognized that no monitor in the end will change outcome. Instead it is how that information is interpreted and integrated into clinical decision-making and then how the patient is treated that will influence outcome. For many of the processes monitored, effective treatments have still to be fully elucidated or remain empiric rather than mechanistic. In this context, monitoring can be valuable in learning about pathophysiology after acute brain injury (ABI) and potentially help identify new therapies.

4. The purpose of this consensus document is to provide evidence-based recommendations about monitoring in neurocritical care patients, and to base these recommendations on rigorously evaluated evidence from the literature. However, we also recognize that, in many cases, the available evidence is limited for several reasons:
   (a) Some monitors have strong anecdotal evidence of providing benefit, and formal randomized evaluation is limited by real or perceived ethical concerns about withholding potentially life-saving monitors with an outstanding safety record.
   (b) Important physiological information obtained from several monitors may translate into outcome differences in select patients, but this benefit is not universal and is diluted by the patients in whom such effects are not seen. However, we still do not have a clear basis for identifying the cohorts in whom such benefit should be assessed.
   (c) The process by which we identify treatment thresholds based on monitoring and the process to integrate multiple monitors are still being elucidated.
5. The monitoring tools we discuss fall into several categories, and their nature and application predicate how discussion of their utility is framed. Some of these tools [e.g., intracranial pressure (ICP), brain oximetry, and microdialysis] meet the definition of bedside monitors, and are assessed in terms of their accuracy, safety, indications, and impact on prognostication, management, and outcome. However, other tools (e.g., biomarkers and tests of hemostasis) are used intermittently, and are best dealt with in a different framework. Our choice of review questions addresses this difference.
6. In addition to the discussion of individual monitors we also include some correlative essays on the use of monitoring in emerging economies, where we attempt to identify how our recommendations might be applied under conditions where there are limited resources. This discussion also provides a useful framework for minimum standards of monitoring and assessment of the effects in a wider conversation.
7. This issue also includes two other correlative essays. One focuses on metrics for processes and quality of care in neurocritical care that provides an organizational context for the recommendations that we make. Finally, we provide a separate discussion on the integration of MMM, which draws on the rapid advances in bioinformatics and data processing currently available. In each of these cases we recognize that the field is currently in a state of flux, but have elected to provide some recommendations in line with the data currently available.
8. The intent of this consensus statement is to assist clinicians in decision-making. However, we recognize that this information must be targeted to the specific clinical situation in individual patients on the basis of clinical judgment and resource availability. We therefore recognize that, while our recommendations provide useful guidance, they cannot be seen as mandatory for all individual clinician–patient interactions.

Given this background, and recognizing the clinical equipoise for most of the brain monitors that will be discussed, we assess basic questions about monitoring patients with acute brain disorders who require critical care. Our recommendations for monitoring are based on a systematic literature review, a robust discussion during the consensus conference about the interpretation of the literature, the collective experience of the members of the group, and review by an impartial, international jury.

Process

A fundamental goal in the critical care management of patients with neurological disorders is identification, prevention, and treatment of secondary cerebral insults that are known to exacerbate outcome. This strategy is based on a variety of monitoring techniques that includes the neurological examination, imaging, laboratory analysis, and physiological monitoring of the brain and other organ systems used to guide therapeutic interventions. The reasons why we monitor patients with neurological disorders are listed in Table 1. In addition rather than focus on individual devices we chose to review physiological processes that are important to neurocritical care clinicians (Table 2). Each of these topics is further reviewed in individual sections contained in the electronic supplementary information (ESM) and in a supplement to Neurocritical Care. The reader is referred to these sections for further details about the review process, evidence to support the recommendations in this summary document, and additional citations for each topic.

Representatives of the NCS and ESICM respectively chaired the review and recommendation process. Experts from around the world in the fields of neurosurgery,

Table 1 Reasons why we monitor patients with neurologic disorders who require critical care

Detect early neurological worsening before irreversible brain damage occurs
Individualize patient care decisions
Guide patient management
Monitor the physiologic response to treatment and to avoid any adverse effects
Allow clinicians to better understand the pathophysiology of complex disorders
Design and implement management protocols
Improve neurological outcome and quality of life in survivors of severe brain injuries
Through understanding disease pathophysiology begin to develop new mechanistically oriented therapies where treatments currently are lacking or are empiric in nature

Table 2 Physiological processes that are important to neurocritical care clinicians that were selected for review in the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care

Topic section
Clinical evaluation
Systemic hemodynamics
Intracranial pressure and cerebral perfusion pressure
Cerebrovascular autoregulation
Systemic and brain oxygenation
Cerebral blood flow and ischemia
Electrophysiology
Cerebral metabolism
Glucose and nutrition
Hemostasis and hemoglobin
Temperature and inflammation
Biomarkers of cellular damage and degeneration
ICU processes of care
Multimodality monitoring informatics integration, display and analysis
Monitoring in emerging economies
Future directions and emerging technologies

neurocritical care, neurology, critical care, neuroanesthesiology, nursing, pharmacy, and informatics were recruited on the basis of their expertise and publication record related to each topic. Two authors were assigned to each topic and efforts were made to ensure representation from different societies, countries, and disciplines (Appendix 1 ESM). The review and recommendation process, writing group, and topics were reviewed and approved by the NCS and ESICM. A jury of experienced neurocritical care clinicians (physicians, a nurse, and a pharmacist) was selected for their expertise in clinical investigation and development of practice guidelines.

The authors assigned to each topic performed a critical literature review with the help of a medical librarian according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [1]. The review period included January 1980–September 2013 and was limited to clinical articles that included more than five subjects and were published in English. The focus was on adult patients and brain disorders. The literature findings were summarized in tables and an initial summary that included specific recommendations was prepared. The chairs, co-chairs, and jury members, each assigned to specific topics as a primary or secondary reviewer, reviewed these drafts. The quality of the data was assessed and recommendations developed using the GRADE system [2–10]. The quality of the evidence was graded as:

- *High* Further research is very unlikely to change our confidence in the estimate of effect.
- *Moderate* Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- *Low* Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- *Very low* Any estimate of effect is very uncertain.

The GRADE system classifies recommendations as strong or weak, according to the balance among benefits, risks, burden, and cost, and according to the quality of evidence. Keeping those components separate constitutes a crucial and defining feature of this grading system. An advantage of the GRADE system is that it allows for strong recommendations in the setting of lower quality evidence and therefore is well suited to the intended monitoring questions. Recommendations are stated as either strong ("we recommend") or weak ("we suggest") and based on the following:

- The trade-offs, taking into account the estimated size of the effect for the main outcomes, the confidence limits around those estimates, and the relative value placed on each outcome
- Quality of the evidence
- Translation of the evidence into practice in a specific setting, taking into consideration important factors that could be expected to modify the size of the expected effects.

Each topic was then presented and discussed at a 2-day conference in Philadelphia held on September 29 and 30, 2013. The chairs, co-chairs, jury, and each author attended the meeting. In addition representatives from each of the endorsing organizations were invited and 50 additional attendees with expertise in neurocritical care were allowed to register as observers. Industry representatives were not allowed to participate. Each author presented a summary of the data and recommendations to the jury and other participants. Presentations were followed by discussion focused on refining the proposed recommendations for each topic. Approximately one-third of the conference time was used for discussion. The jury subsequently held several conference calls, and then met again at a subsequent 2-day meeting to review and abstract all manuscripts and finalize the summary consensus statement presented here. They reviewed selected key studies, the recommendations made by the primary reviewers, and the discussion that took place at the conference. Strong consideration was given to providing guidance and recommendations for bedside neuromonitoring, even in the absence of high quality data.

Caveats and limitations to the process

The setting of these recommendations, monitoring, makes it difficult to use all of the normal considerations used to make decisions about the strength of recommendations, typically of a treatment [4], which include the balance between desirable and undesirable effects, estimates of effect based on direct evidence, and resource use since monitoring has no proximate effects on outcome. Instead it typically modifies treatment and can only influence

outcome through such modulation. Our confidence in the estimate of effects in most analyses was not derived from methodologically rigorous studies, because few such studies exist, but often driven by epidemiological studies and investigations of clinical physiology, which usually provided indirect evidence, with several potential confounders.

Given these limitations, decisions on recommendations are driven by an expectation of values and preferences. Given the limited outcome data of both benefit and harm associated with neuromonitoring, we relied on inferences from observational studies and extrapolation from pathophysiology to estimate the effect and effect size of potential benefit and harm. We concluded that the avoidance of permanent neurological deficit would be the dominant driver of patient choice. Given that the diseases and disease mechanisms we monitor are known to be damaging, and given that the time available for intervention is limited, we made these extrapolations unless there was real concern about benefit or evidence of harm. This approach to deciding on recommendations was universally adopted by all members of the multispecialty, multidisciplinary, multinational panel. Though there was some variation in initial opinions, careful consideration of the available evidence and options resulted in relatively tightly agreed consensus on recommendations.

Summary of recommendations from the individual consensus conference topics

Clinical evaluation

Questions addressed

1. Should assessments with clinical coma scales be routinely performed in comatose adult patients with ABI?
2. For adult comatose patient with ABI, is the Glasgow Coma Scale (GCS) or the Full Outline of Unresponsiveness (FOUR) score more reliable in the clinical assessment of coma?
3. Which pain scales have been validated and shown to be reliable among patients with brain injuries who require neurocritical care?
4. Which pain scales have been validated and shown to be reliable among patients with severe disorders of consciousness [minimally conscious state (MCS) and unresponsive wakefulness syndrome (UWS)]?
5. Which "sedation" scales are valid and reliable in brain-injured patients who require neurocritical care?
6. What other sedation strategies may lead to improved outcomes for brain-injured patients?
7. Which delirium scales are valid and reliable in brain-injured patients who require neurocritical care?

Summary

All clinical scales of consciousness should account for the effects of sedation and neuromuscular blockade. Inter-rater reliability assessments of the GCS report a range of kappa scores, but the GCS is a strong prognostic marker and indicator of need for surgery in traumatic brain injury (TBI) [11], of clinical outcome in posterior circulation stroke [12], and following cardiac arrest [13]. In isolation, the GCS is disadvantaged by the confounders produced by endotracheal intubation, and by the lack of measurement of pupillary responses (which are strong predictors of outcome). However, the prognostic information provided by pupillary responses can be integrated with the GCS to provide greater specificity of outcome prediction [14]. Newer devices provide objective measurement of pupillary diameter, and the amount and speed of pupillary response, but additional research is necessary to confirm the role of these devices in caring for brain-injured patients.

Sedation, potent analgesics (e.g., opioids), and neuromuscular blockade remain a problem for any clinical scale of consciousness. However, in the non-sedated (or lightly sedated but responsive) patient, the recently devised FOUR score, which measures ocular (as well as limb) responses to command and pain, along with pupillary responses and respiratory pattern [15], may provide a more complete assessment of brainstem function. Volume assist ventilator modes may confound differentiation between the two lowest scores of the respiratory component of the FOUR score. The FOUR score has been shown to have good inter-rater reliability [16] and prognostic content in a range of neurological conditions, and may show particularly good discrimination in the most unresponsive patients. However, experience with this instrument is still limited when compared to the GCS. Current evidence suggests that both the GCS and FOUR score provide useful and reproducible measures of neurological state, and can be routinely used to chart trends in clinical progress.

Brain-injured patients in NCCU are known to experience more significant pain than initially presumed [17]. While any level of neurological deficit can confound assessment of pain and agitation, perhaps a greater barrier arises from perceptions of clinicians who feel that such assessments are simply not possible in such patient populations. In actual fact, up to 70 % of neurocritical care patients can assess their own pain using a self-reporting tool such as the Numeric Rating Scale (NRS), while clinician rated pain using the Behavioral Pain Scale (BPS) is assessable in the remainder. Assessing pain in patients with severe disorders of consciousness such as vegetative state (VS) and minimally conscious state (MCS) is a greater challenge, but is possible with Nociception Coma Scale-revised (NCS-R) [18].

The assessment of sedation in the context of brain injury is challenging, since both agitation and apparent sedation may be the consequence of the underlying neurological state, rather than simply a marker of suboptimal sedation. However, both the Richmond Agitation Sedation Scale (RASS) and the Sedation-Agitation Scale (SAS) [19] provide workable solutions in some patients.

"Wake-up tests" in patients with unstable intracranial hypertension pose significant risks and often may lead to physiological decompensation [20], and show no proven benefits in terms of in duration of mechanical ventilation, length of ICU and hospital stay, or mortality. However we recognize that in some patients (e.g., those with aneurysmal subarachnoid hemorrhage (SAH) requiring neurological assessment) a balance will need to be struck between the information gained from clinical evaluation and risk of physiological decompensation with a wake-up test. In such circumstances, the benefit of a full neurological assessment may be worth a short period of modest ICP elevation. The Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC) was strongly recommended for delirium assessment by the 2013 PAD Guidelines [19]. While delirium assessment has been reported in stroke [21], generalizability of this data is limited, and even within this study, as the majority of patients were unassessable. The ICDSC may be preferred since it does not score changes in wakefulness and attention directly attributable to recent sedative medication as positive ICDSC points. It is important to emphasize that a diagnosis of delirium in a neurocritical care patient may represent evidence of progress of the underlying disease, and must prompt an evaluation for a new neurologic deficit or specific neurologic process.

Recommendations

1. We recommend that assessments with either the GCS (combined with assessment of pupils) or the FOUR score be routinely performed in comatose adult patients with ABI. (Strong recommendation, low quality of evidence.)
2. We recommend using the NRS 0–10 to elicit patient's self-report of pain in all neurocritical care patients wakeful enough to attempt this. (Strong recommendation, low quality of evidence.)
3. We recommend in the absence of a reliable NRS patient self-report, clinicians use a behavior-based scale to estimate patient pain such as the BPS or CCPOT. (Strong recommendation, low quality of evidence.)
4. We recommend use of the revised NCS-R to estimate pain for patients with severely impaired consciousness such as VS or MCS, using a threshold score of 4. (Strong recommendation, low quality of evidence.)
5. We recommend monitoring sedation with a validated and reliable scale such as the SAS or RASS. (Strong recommendation, low quality of evidence.)
6. We recommend against performing sedation interruption or wake-up tests among brain-injured patients with intracranial hypertension, unless benefit outweighs the risk. (Strong recommendation, low quality of evidence.)
7. We suggest assessment of delirium among neurocritical care patients include a search for new neurologic insults as well as using standard delirium assessment tools. (Weak recommendation, low quality of evidence.)
8. We recommend attention to level of wakefulness, as used in the ICDSC, during delirium screening to avoid confounding due to residual sedative effect. (Strong recommendation, low quality of evidence.)

Systemic hemodynamics

Questions addressed

1. What hemodynamic monitoring is indicated in patients with ABI?
2. What hemodynamic monitoring is indicated to diagnose and support the management of unstable or at-risk patients?

Summary

Cardiopulmonary complications are common after ABI, and have a significant impact on clinical care and patient outcome [22–26]. Among several hypotheses, the main mechanism of cardiac injury following ABI (e.g., SAH) is related to sympathetic stimulation and catecholamine release [27–29]. All patients with ABI admitted to the ICU require basic hemodynamic monitoring of blood pressure, heart rate, and pulse oximetry. Some stable patients will require nothing more than this, but many will need more invasive and/or sophisticated hemodynamic monitoring. Monitoring of systemic hemodynamics contributes to understanding the mechanisms of circulatory failure, and detecting or quantifying inadequate perfusion or organ dysfunction. Although there is limited evidence, cardiac output should be monitored (invasively or non-invasively) in those patients with myocardial dysfunction or hemodynamic instability [30]. Whether this also applies to patients on vasopressors to augment cerebral perfusion pressure (CPP) rather than for hemodynamic instability should be decided on a case-by-case basis. The various hemodynamic devices available have differing technical reliability, clinical utility, and caveats, but limited studies are available in acute brain-injured patients. Baseline assessment of cardiac function with echocardiography may be a useful approach when there

are signs of cardiac dysfunction. Methods for evaluation of fluid responsiveness are similar to the ones used in the general ICU population.

Recommendations

1. We recommend the use of electrocardiography and invasive monitoring of arterial blood pressure in all unstable or at-risk patients in the ICU. (Strong Recommendation, moderate quality of evidence.)
2. We recommend that hemodynamic monitoring be used to establish goals that take into account cerebral blood flow (CBF) and oxygenation. These goals vary depending on diagnosis and disease stage. (Strong recommendation, moderate quality of evidence.)
3. We recommend the use of additional hemodynamic monitoring (e.g., intravascular volume assessment, echocardiography, cardiac output monitors) in selected patients with hemodynamic instability. (Strong recommendation, moderate quality of evidence.)
4. We suggest that the choice of technique for assessing pre-load, after-load, cardiac output, and global systemic perfusion should be guided by specific evidence and local expertise. (Weak recommendation, moderate quality of evidence.)

Intracranial pressure and cerebral perfusion pressure

Questions addressed

1. What are the indications for monitoring ICP and CPP?
2. What are the principal methods of reliable, safe, and accurate ICP and CPP monitoring?
3. What is the utility of ICP and CPP monitoring for prognosis in the comatose TBI patient?

Summary

Monitoring of ICP and CPP is considered to be fundamental to the care of patients with ABI, particularly those in coma, and is routinely used to direct medical and surgical therapy [31]. ICP and CPP monitoring are most frequently studied in TBI, but can play a similar role in conditions such as SAH and ICH among other disorders. Increased ICP, and particularly that refractory to treatment, is a well-described negative prognostic factor, specifically for mortality [32–34]. There are well-established indications and procedural methods for ICP monitoring, and its safety profile is excellent [35]. The threshold that defines intracranial hypertension is uncertain but generally is considered to be greater than 20–25 mmHg, although both lower and higher thresholds are described [36]. The recommendations for an optimal CPP have changed over time and may in part be associated with the variability in how mean arterial pressure (MAP) is measured to determine CPP [37] and depend on disease state. In addition, management strategies based on population targets for CPP rather than ICP have not enhanced outcome [38], and rather than a single threshold optimal CPP, values may need to be identified for each individual [39]. There are several devices available to measure ICP; intraparenchymal monitors or ventricular catheters are the most reliable and accurate, but for patients with hydrocephalus a ventricular catheter is preferred. The duration of ICP monitoring varies according to the clinical context.

Recently, our core beliefs in ICP have been challenged by the BEST-TRIP trial [40]. While this study has high internal validity, it lacks external validity and so the results cannot be generalized. Furthermore, the trial evaluated two treatment strategies for severe TBI, one triggered by an ICP monitor and the other by the clinical examination and imaging rather than the treatment of intracranial hypertension. In this context it must be emphasized that clinical evaluation and diagnosis of elevated ICP was fundamental to all patients in BEST-TRIP, and hence the study reinforces that evaluation and monitoring, either by a specific monitor or by an amalgamation of clinical and imaging signs, is standard of care.

ICP treatment is important and is best guided by ICP monitoring, clinical imaging, and clinical evaluation used in combination and in the context of a structured protocol [41–43]. We recognize that this may vary across different diagnoses and different countries. Today, a variety of other intracranial monitoring devices are available, and ICP monitoring is a mandatory prerequisite when other intracranial monitors are used, to provide a framework for optimal interpretation.

Recommendations

1. ICP and CPP monitoring are recommended as a part of protocol-driven care in patients who are at risk of elevated intracranial pressure based on clinical and/or imaging features. (Strong recommendation, moderate quality of evidence.)
2. We recommend that ICP and CPP monitoring be used to guide medical and surgical interventions and to detect life-threatening imminent herniation; however, the threshold value of ICP is uncertain on the basis of the literature. (Strong recommendation, high quality of evidence.)
3. We recommend that the indications and method for ICP monitoring should be tailored to the specific diagnosis (e.g., SAH, TBI, encephalitis). (Strong recommendation, low quality of evidence.)
4. While other intracranial monitors can provide useful information, we recommend that ICP monitoring be

used as a prerequisite to allow interpretation of data provided by these other devices. (Strong recommendation, moderate quality of evidence.)
5. We recommend the use of standard insertion and maintenance protocols to ensure safety and reliability of the ICP monitoring procedure. (Strong recommendation, high quality of evidence.)
6. Both parenchymal ICP monitors and external ventricular catheters (EVD) provide reliable and accurate data and are the recommended devices to measure ICP. In the presence of hydrocephalus, use of an EVD when safe and practical is preferred to parenchymal monitoring. (Strong recommendation, high quality of evidence.)
7. We recommend the continuous assessment and monitoring of ICP and CPP including waveform quality using a structured protocol to ensure accuracy and reliability. Instantaneous ICP values should be interpreted in the context of monitoring trends, CPP, and clinical evaluation. (Strong recommendation, high quality of evidence.)
8. While refractory ICP elevation is a strong predictor of mortality, ICP per se does not provide a useful prognostic marker of functional outcome; therefore, we recommend that ICP not be used in isolation as a prognostic marker. (Strong recommendation, high quality of evidence.)

Cerebral autoregulation

Questions addressed

1. Does monitoring of cerebral autoregulation help guide management and contribute to prognostication?
2. Which technique and methodology most reliably evaluates the state of autoregulation in ABI?

Summary

Pressure autoregulation is an important hemodynamic mechanism that protects the brain against inappropriate fluctuations in CBF in the face of changing CPP. Both static and dynamic autoregulation have been monitored in neurocritical care to aid prognostication and contribute to individualizing optimal CPP targets in patients [44]. Failure of autoregulation is associated with a worse outcome in various acute neurological diseases [45]. For monitoring, several studies have used ICP (as a surrogate of vascular caliber and reactivity), transcranial Doppler ultrasound, and near-infrared spectroscopy (NIRS) to continuously monitor the impact of spontaneous fluctuations in CPP on cerebrovascular physiology, and calculated derived variables of autoregulatory efficiency. However, the inconsistent approaches to using such devices to monitor autoregulation make comparison difficult, and there are no good comparative studies that permit us to conclusively recommend one approach in preference to another.

In broad terms, the preservation or absence of pressure autoregulation can influence blood pressure management following brain injury. Patients who show preserved autoregulation may benefit from higher mean arterial and CPP as part of an integrated management scheme for ICP control, while those who show pressure passive responses may be better served by judicious blood pressure control. Critical autoregulatory thresholds for survival and favorable neurological outcome may be different, and may vary with age and sex. The brain may be particularly vulnerable to autoregulatory dysfunction during rewarming after hypothermia and within the first days following injury [46].

More refined monitoring of autoregulatory efficiency is now possible through online calculation of derived indices such as the pressure reactivity index (PRx) [45]. About two-thirds of TBI patients have an optimum CPP range (CPPopt) where their autoregulatory efficiency is maximized, and that management at or close to CPPopt is associated with better outcomes [47]. The safety of titrating therapy to target CPPopt requires further study, and validation in a formal clinical trial before it can be recommended.

Recommendations

1. We suggest that monitoring and assessment of autoregulation may be useful in broad targeting of cerebral perfusion management goals and prognostication in ABI. (Weak recommendation, moderate quality of evidence.)
2. Continuous bedside monitoring of autoregulation is now feasible, and we suggest that should be considered as a part of MMM. Measurement of pressure reactivity has been commonly used for this purpose, but many different approaches may be equally valid. (Weak recommendation, moderate quality of evidence.)

Systemic and brain oxygenation

Questions addressed

1. What are the indications for brain and systemic oxygenation in neurocritical care patients?
2. What are the principal methods of reliable and accurate brain oxygen monitoring?
3. What is the safety profile of brain oxygen monitoring?
4. What is the utility of brain oxygen monitoring to determine prognosis in the comatose patient?
5. What is the utility of brain oxygen monitoring to direct medical and surgical therapy?
6. What is the utility of brain oxygen monitoring to improve neurological outcome?

Summary

Maintenance of adequate oxygenation is a critical objective of managing critically ill patients with neurological disorders. Assessing tissue oxygenation provides vital information about oxygen supply and consumption in tissue beds. Inadequate systemic and brain oxygen aggravates secondary brain injury. Multimodality brain monitoring includes measuring oxygenation systemically and locally in the brain. Systemic oxygenation and carbon dioxide (CO_2) can be measured invasively with blood gas sampling and non-invasively with pulse oximetry and end-tidal CO_2 devices. There is extensive research in the general critical care population on safety and applicability of systemic oxygen and carbon dioxide monitoring. PaO_2, SaO_2, and SpO_2 are indicators of systemic oxygenation and useful to detect oxygenation decreases. Periodic measurements of PaO_2 and SaO_2 and continuous SpO_2 measurements should be used to guide airway and ventilator management in patients who require neurocritical care [48, 49]. $PaCO_2$ is a reliable measurement of hyper- or hypocapnia and is superior to $ETCO_2$ monitoring. The continuous monitoring of $ETCO_2$ and periodic monitoring of $PaCO_2$ assists in ventilator management [50]. The optimal target values for PaO_2, SaO_2, and SpO_2 specific to the NCCU patient population are still being elucidated. Normoxemia and avoidance of hypoxemia and hyperoxemia should be targeted.

Brain oxygen measurements include two invasive bedside techniques, brain parenchymal oxygen tension ($PbtO_2$) and jugular bulb oxygen saturation ($SjvO_2$), or a non-invasive bedside method, NIRS. Normal $PbtO_2$ is 23–35 mmHg [51]. A $PbtO_2$ threshold of less than 20 mmHg represents compromised brain oxygen and is a threshold at which to consider intervention. Decreases below this are associated with other markers of cerebral ischemia or cellular dysfunction although exact values vary slightly with the type of parenchymal monitor used and should be interpreted on the basis of probe location identified on a post-insertion CT [52, 53]. However, $PbtO_2$ is not simply a marker of ischemia or CBF. $PbtO_2$ monitoring is safe and provides accurate data for up to 10 days with measured responses to interventions (e.g., changes in CPP, ventilator targets, pharmacologic sedation, and transfusion) and can be used to guide therapy [54]. Observational studies suggest a potential benefit when $PbtO_2$-guided therapy is added to a severe TBI management protocol, but there remains clinical equipoise.

$SjvO_2$ values differ from $PbtO_2$ in what is measured and can be used to detect both ischemia and hyperemia. Positioning, clot formation on the catheter, and poor sampling technique can influence $SjvO_2$ accuracy and errors are common so making $SjvO_2$ monitoring more difficult to use and less reliable than $PbtO_2$ monitoring [55]. Normal $SjvO_2$ is between 55 and 75 %. Cerebral ischemia is present when $SjvO_2$ is less than 55 % [56], but cannot reliably be assumed to be absent at higher values since regional abnormalities may not be detected [57]. The majority of $SjvO_2$ studies are in severe TBI patients with limited studies in SAH, ICH, or ischemic stroke patients. $SjvO_2$ values can guide therapy [58] but have not been shown to improve outcomes. NIRS has several limitations in adult use [59]. There are limited small observational studies with conflicting results about desaturations related to cerebral perfusion, vasospasm, head positioning during impending herniation, pharmacologic interventions, and changes in MAP/CPP. There are no studies that demonstrate that data from NIRS use alone can influence outcomes in adult neurocritical care.

Recommendations

1. We recommend systemic pulse oximetry in all patients and end-tidal capnography in mechanically ventilated patients, supported by arterial blood gases measurement. (Strong recommendation, high quality of evidence.)
2. We recommend monitoring brain oxygen in patients with or at risk of cerebral ischemia and/or hypoxia, using brain tissue ($PbtO_2$) or/and jugular venous bulb oximetry ($SjvO_2$)—the choice of which depends on patient pathology. (Strong recommendation, low quality of evidence.)
3. We recommend that the location of the $PbtO_2$ probe and side of jugular venous oximetry depend on the diagnosis, the type and location of brain lesions, and technical feasibility. (Strong recommendation, low quality of evidence.)
4. While persistently low $PbtO_2$ and/or repeated episodes of jugular venous desaturation are strong predictors of mortality and unfavorable outcome, we recommend that brain oxygen monitors be used with clinical indicators and other monitoring modalities for accurate prognostication. (Strong recommendation, low quality of evidence.)
5. We suggest the use of brain oxygen monitoring to assist titration of medical and surgical therapies to guide ICP/CPP therapy, identify refractory intracranial hypertension and treatment thresholds, help manage delayed cerebral ischemia, and select patients for second-tier therapy. (Weak recommendation, low quality of evidence.)

Cerebral blood flow

Questions addressed

1. What are the indications for CBF monitoring?
2. Do the various CBF monitors reliably identify those patients at risk for secondary ischemic injury?

3. What CBF neuromonitoring thresholds best identify risk for ischemic injury?
4. Does use of CBF neuromonitoring improve outcomes for those patients at risk for ischemic injury?

Summary

Measurement of CBF has long been used in experimental models to define thresholds for ischemia leading to interest in monitoring CBF in patients, in large part because ischemia can underlie secondary cerebral injury. In addition to radiographic methods (not covered here) several devices can be used at the patient's bedside to monitor for CBF changes. These radiographic studies, particularly PET, have demonstrated that cellular injury often can occur in the absence of ischemia [60, 61]. Advances in our understanding of the pathophysiology of TBI and ICH suggest, however, that traditional ischemic thresholds may not always apply and CBF data should be coupled with measurements of metabolic demand.

Flow can be continually monitored in a single small region of brain using invasive thermal diffusion flowmetry (TDF) or, less commonly, laser Doppler flowmetry (LDF) [62, 63]. The utility of these probes is limited by their invasive nature, small field of view, and uncertainly as to where they should be placed. TDF use is limited by reduced reliability in patients with elevated systemic temperatures. There are few data regarding ischemic thresholds for these devices.

Blood flow in larger regions of brain can be estimated by transcranial Doppler ultrasonography (TCD), although accuracy may be limited by operator variability. TCD is primarily used to monitor for vasospasm following aneurysmal SAH. TCD also can be used to identify TBI patients with hypoperfusion or hyperperfusion and so guide their care. However there is a far greater body of literature describing TCD use in SAH. TCD can predict angiographic vasospasm with good sensitivity and specificity [64, 65] but is less accurate in predicting delayed ischemic neurological deficits [66]. Predictive power is improved with the use of transcranial color-coded duplex sonography (TCCS) [67]. Inclusion of the Lindegaard ratio [68] and the rate of the increase in velocities [69] in interpreting the data improves performance. There are no published studies that demonstrate enhanced outcomes that result from implementation of a treatment strategy directed only by neuromonitoring devices that assess CBF or ischemic risks.

Recommendations

1. We recommend TCD or TCCS monitoring to predict angiographic vasospasm after aneurysmal SAH. (Strong recommendation, high quality of evidence.)
2. We suggest that trends of TCD or TCCS can help predict delayed ischemic neurological deficits due to vasospasm after aneurysmal SAH. (Weak recommendation, moderate quality of evidence.)
3. We suggest that TCCS is superior to TCD in the detection of angiographically proven vasospasm after aneurysmal SAH. (Weak recommendation, low quality of evidence.)
4. We suggest that TCD or TCCS monitoring can help predict vasospasm after traumatic SAH. (Weak recommendation, very low quality of evidence.)
5. We suggest that a TDF probe may be used to identify patients with focal ischemic risk within the vascular territory of the probe. (Weak recommendation, very low quality of evidence.)
6. We suggest use of a TCD screening paradigm using Lindegaard ratios or comparisons of bi-hemispheric middle cerebral artery mean velocities to improve sensitivity for identification of vasospasm-associated ischemic damage. (Weak recommendation, low quality of evidence.)
7. We suggest that TDF probes used to assess ischemic risk after aneurysmal SAH should be placed in the vascular territory of the ruptured aneurysm. (Weak recommendation, very low quality of evidence.)

Electrophysiology

Questions addressed

1. What are the indications for electroencephalography (EEG)?
2. What is the utility of EEG following convulsive status epilepticus (cSE) and refractory status epilepticus?
3. What is the utility of EEG or evoked potentials (EPs) in patients with and without ABI, including cardiac arrest, and unexplained alteration of consciousness?
4. What is the utility of EEG to detect ischemia in patients with SAH or acute ischemic stroke (AIS)?
5. Should scalp and/or intracranial EEG be added to patients undergoing invasive brain monitoring?

Summary

Electroencephalography and EPs are the most frequently used electrophysiological techniques used in the ICU [70]. EEG provides information about brain electrical activity and it is essential to detect seizures, including duration and response to therapy and can help outcome prediction after coma [71–74]. Seizures are frequent with and without ABI in the ICU, and are mostly nonconvulsive. Further, some patients will have cyclic seizure patterns, which will only be detectable by continuously (cEEG) recorded data [75]. However, data to support the benefit of continuous over routine EEG recordings, typically no longer than 30-min duration (sometimes called spot EEG), to detect seizures is very limited. Routine

EEG will miss nonconvulsive seizures (NCSz) in approximately half of those with seizures when compared to prolonged monitoring [76]. Advances in neuroimaging have limited the application of EPs in many ICUs, but in select patients EPs can help in outcome prediction.

The optimal montage and number of electrodes to record EEG in the ICU is uncertain and the practicality of placing many electrodes in an electrophysiologically unfriendly environment needs to be considered. Quantitative EEG algorithms have been developed to support the time-consuming expert review of cEEG recordings in the ICU setting. Several studies have highlighted concern regarding the use of bispectral index score (BIS) measurements as an EEG quantification tool, stressing large intra- and inter-individual variability, as well as interferences. Data do not support the use of BIS for brain-injured patients in the ICU.

Recommendations

1. We recommend EEG in all patients with ABI and unexplained and persistent altered consciousness. (Strong recommendation, low quality of evidence.)
2. We recommend urgent EEG in patients with cSE that do not return to functional baseline within 60 min after seizure medication and we recommend urgent (within 60 min) EEG in patients with refractory SE. (Strong recommendation, low quality of evidence.)
3. We recommend EEG during therapeutic hypothermia and within 24 h of rewarming to exclude NCSz in all comatose patients after cardiac arrest (CA). (Strong recommendation, low quality of evidence.)
4. We suggest EEG in comatose ICU patients without an acute primary brain condition and with unexplained impairment of mental status or unexplained neurological deficits to exclude NCSz, particularly in those with severe sepsis or renal/hepatic failure. (Weak recommendation, low quality of evidence.)
5. We suggest EEG to detect delayed cerebral ischemia (DCI) in comatose SAH patients, in whom neurological examination is unreliable. (Weak recommendation, low quality of evidence.)
6. We suggest continuous EEG monitoring as the preferred method over routine EEG monitoring whenever feasible in comatose ICU patients without an acute primary brain condition and with unexplained impairment of mental status or unexplained neurological deficits to exclude NCSz. (Weak recommendation, low quality of evidence.)

Cerebral metabolism

Questions addressed

1. What are the indications for cerebral microdialysis monitoring?
2. What is the preferred location for a microdialysis probe?
3. What is the utility of cerebral microdialysis in determining patient prognosis?
4. What is the utility of cerebral microdialysis in guiding medical and surgical therapy?

Summary

Brain metabolism in humans can be monitored at bedside using cerebral microdialysis. Brain extracellular concentrations of energy metabolism markers, including lactate, pyruvate, and glucose, are accurately measured by microdialysis. Their variations over time, and in response to therapy, can help clinical management [77, 78] and are not markers of ischemia alone but also reflect energy metabolism in the brain [79, 80]. In TBI, cerebral microdialysis may contribute to prognostication and abnormalities appear to be associated with long-term tissue damage [81, 82]. In SAH microdialysis may provide insight into inadequate energy substrate delivery [83] and on markers of delayed cerebral ischemia [84].

Cerebral microdialysis has an excellent safety record. However, there are limitations in that it is a focal measurement, disclosing different metabolite concentrations when inserted in pathological or preserved brain areas and so microdialysis should be interpreted on the basis of location defined by post-insertion CT [85]. The technique can be labor intensive for bedside point of care monitoring and interpretation. Metabolite collection also occurs over time (e.g., 60 min) and so data is delayed rather than real-time. Microdialysis when used with other monitors can enhance understanding of brain physiology and also when used for research may provide novel insights into pathophysiological mechanisms and on various treatment modalities that directly affect brain metabolism and function.

Recommendations

1. We recommend monitoring cerebral microdialysis in patients with or at risk of cerebral ischemia, hypoxia, energy failure, and glucose deprivation. (Strong recommendation, low quality of evidence.)
2. We recommend that the location of the microdialysis probe depend on the diagnosis, the type and location of brain lesions, and technical feasibility. (Strong recommendation, low quality of evidence.)
3. While persistently low brain glucose and/or an elevated lactate/pyruvate ratio is a strong predictor of mortality and unfavorable outcome, we recommend that cerebral microdialysis only be used in combination with clinical indicators and other monitoring

modalities for prognostication. (Strong recommendation, low quality of evidence.)
4. We suggest the use of cerebral microdialysis to assist titration of medical therapies such as systemic glucose control and the treatment of delayed cerebral ischemia. (Weak recommendation, moderate quality of evidence.)
5. We suggest the use of cerebral microdialysis monitoring to assist titration of medical therapies such as transfusion, therapeutic hypothermia, hypocapnia, and hyperoxia. (Weak recommendation, low quality of evidence.)

Please consult the relevant ESM for the following topics: Glucose and nutrition (ESM 2), hemostasis and hemoglobin (ESM 3), temperature and inflammation (ESM 4), cellular damage and degeneration (ESM 5), and ICU processes of care and quality assurance (ESM 6).

Multimodality monitoring: informatics, data integration, display, and analysis

Questions addressed

1. Should ergonomic data displays be adopted to reduce clinician cognitive burden?
2. Should clinical decision support tools be adopted to improve clinical decision-making?
3. Should high-resolution physiologic data be integrated with lower resolution data?
4. Should human-centered design principles and methods be used to develop technology interventions for the ICU?
5. Should devices use data communication standards to improve data connectivity?
6. Should multiparameter alarms and other methods of 'smart' alarms be adopted to comply with the Joint Commission mandate requiring hospitals to address alarm fatigue?

Summary

Multimodal monitoring generates an enormous amount of data, including written, ordinal, continuous, and imaging data, in the typical patient with a neurologic disorder in the ICU. The frequency and resolution at which physiological data are acquired and displayed may vary depending on the signal, technology, and purposes [137, 138]. Clinicians may be confronted with more than 200 variables when evaluating a patient [139], with the risk of "information overload" that can lead to preventable medical errors [140]. In addition, data are essentially meaningless unless annotated so that providers can search for "epochs of interest", effects of therapies, or identify potential artifacts.

All relevant patient data, acquired at various resolution rates, have to be integrated, since dynamic systems are based on relationships that can only be understood by data integration. However, there are several obstacles to this, such as proprietary drivers from commercial vendors and time-synchronization among others. Hence, standardization of an informatics infrastructure including data collection, data visualization, data analysis, and decision support is essential [141]. The goal of data visualization and a clinical informatics program is to provide clinical decision support that enhances clinician situational awareness about the patient state. Ergonomic data displays that present results from analyses with clinical information in a sensible uncomplicated manner improves clinical decision-making [142]. This field of bioinformatics is rapidly evolving and dynamic and so its role in critical care is still to be fully elucidated.

Recommendations

1. We recommend utilizing ergonomic data displays that present clinical information in a sensible uncomplicated manner to reduce cognitive load and improve judgments of clinicians. (Strong recommendation, moderate quality of evidence.)
2. We suggest using clinical decision support tools such as algorithms that automatically process multiple data streams with the results presented on a simple, uncomplicated display. (Weak recommendation, moderate quality of evidence.)
3. We recommend adopting a database infrastructure that enables the integration of high-resolution physiologic data (including EEG recordings) with lower resolution data from laboratory and electronic health care systems. (Strong recommendation, low quality of evidence.)
4. We recommend following an iterative, human-centered design methodology for complex visualization displays to avoid adversely affecting clinical decision-making. (Strong recommendation, moderate quality of evidence.)
5. We recommend that device manufacturers utilize data communication standards including time synchronization on all devices to improve usability of its data. (Strong recommendation, low quality of evidence.)
6. We recommend adopting "smart" alarms in the ICU to help address alarm fatigue. (Strong recommendation, low quality of evidence.)

Please consult ESM 7 for the discussion on monitoring in emerging economies.

Future directions and emerging technologies

Multimodality monitoring including clinical and laboratory evaluation, imaging, and continuous physiologic data

is an important feature of neurocritical care. The future appears bright and likely will be driven by studies that address the principal limitations to our knowledge, documented in this consensus, and by the desire to develop more specific and less invasive brain monitors. It is difficult to demonstrate that any single monitor or combination of monitors has a positive effect on outcome, since outcome is influenced by the therapeutic plan driven by monitoring, not by monitoring itself. Furthermore, information derived from monitors of when and how to treat or how to integrate information from various monitors is still being elucidated. Hence, we need to develop more evidence on how various monitors used in neurocritical care can influence care and outcome. To that end, small, randomized studies that focus on intermediate outcomes or biomarker outcomes seem to be a reasonable approach [149] although careful observational studies can also help advance understanding of physiology.

Important enhancements in data display, integration, and analysis will be forthcoming as the field of bioinformatics continues to evolve. However, this will depend on close collaboration between industry, engineers, clinicians, and regulatory bodies to ensure standardization of device, data element terminology, and technologies. During the next 5 years, we likely will see the development and implementation of several visualization and presentation interfaces that will serve to integrate the data into a time-aligned stream of information. Advanced data visualization and interpretation systems, which include algorithms to detect (1) trends in physiological changes [150]; (2) autoregulation [45]; (3) optimum CPP [151]; (4) patient-specific rather than population-specific thresholds [137]; (5) reasons for physiologic alterations [152] and other predictive methods [153, 154] to find the ideal physiological state for each individual throughout their clinical course, will become commonplace. There will be development and validation of several monitors that are currently just being introduced at the bedside or are planned, such as next generation NIRS-DCS [155], optic nerve sheath ultrasound [156], pupillometry [157], direct current EEG for cortical spreading depolarization (CSD) [158], and TCD-based non-invasive measures of ICP [159].

Devices used to monitor patients with neurologic disorders are experiencing technological advancements leading to high functionality, non-invasive devices, ease of operation, and miniaturization. These technologies and others likely will become increasingly used to better monitor patients who are at risk of neurological deterioration. The challenge will be to integrate some or all of the multimodality monitors in an organized way to enhance patient care, and to avoid data misinterpretation [160, 161]. This challenge will likely be met through rigorous training of clinicians with expertise in neurocritical care rather than by one or more definitive studies. However multicenter collaborative research through careful observation will help understand how care based on monitoring impacts outcome including long-term outcome and quality of life after ICU care. In the end, MMM is an extension of the clinical exam and cognitive skill set of the clinician, and is only as good or as useful as the clinical team who is using the monitor and available therapeutic options.

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