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REVIEW ARTICLE

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

Peter Le Roux · David K. Menon · Giuseppe Citerio · Paul Vespa · Mary Kay Bader · Gretchen M. Brophy · Michael N. Diringer · Nino Stocchetti · Walter Videtta · Rocco Armonda · Neeraj Badjatia · Julian Böesel · Randall Chesnut · Sherry Chou · Jan Claassen · Marek Czosnyka · Michael De Georgia · Anthony Figaji · Jennifer Fugate · Raimund Helbok · David Horowitz · Peter Hutchinson · Monisha Kumar · Molly McNett · Chad Miller · Andrew Naidech · Mauro Oddo · DaiWai Olson · Kristine O'Phelan · J. Javier Provencio · Corinna Puppo · Richard Riker · Claudia Robertson · Michael Schmidt · Fabio Taccone

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

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

P. Le Roux (✉)
Brain and Spine Center, Suite 370, Medical Science Building, Lankenau Medical Center, 100 East Lancaster Avenue, Wynnewood, PA 19096, USA
e-mail: lerouxp@mlhs.org

D. K. Menon
Neurosciences Critical Care Unit, Division of Anaesthesia, University of Cambridge Consultant, Addenbrooke's Hospital, Box 93, Cambridge CB2 2QQ, UK
e-mail: dkm13@wbic.cam.ac.uk

G. Citerio
NeuroIntensive Care Unit, Department of Anesthesia and Critical Care, Ospedale San Gerardo, Via Pergolesi 33, 20900 Monza, Italy
e-mail: g.citerio@hsgerardo.org

P. Vespa
David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA
e-mail: PVespa@mednet.ucla.edu

M. K. Bader
Neuro/Critical Care CNS, Mission Hospital, Mission Viejo, CA 92691, USA
e-mail: Marykay.Bader@stjoe.org

G. M. Brophy
Virginia Commonwealth University, Medical College of Virginia Campus, 410N. 12th Street, Richmond, VA 23298-0533, USA
e-mail: gbrophy@vcu.edu

M. N. Diringer
Neurocritical Care Section, Department of Neurology, Washington University, Campus Box 8111, 660 S Euclid Ave, St Louis, MO 63110, USA
e-mail: diringerm@neuro.wustl.edu

N. Stocchetti
Department of Physiopathology and Transplant, Milan University, Neuro ICU, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Via F Sforza, 35, 20122 Milan, Italy
e-mail: stocchet@policlinico.mi.it

W. Videtta
ICU Neurocritical Care, Hospital Nacional 'Prof. a. Posadas', El Palomar, Pcia de Buenos Aires, Argentina

R. Armonda
Department of Neurosurgery, MedStar Georgetown University Hospital, Medstar Health, 3800 Reservoir Road NW, Washington, DC 20007, USA

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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.

N. Badjatia
Department of Neurology, University of Maryland Medical Center, 22 S Greene St, Baltimore, MD 21201, USA

J. Böesel
Department of Neurology, Ruprecht-Karls University, Hospital Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany

R. Chesnut
Harborview Medical Center, University of Washington, Mailstop 359766, 325 Ninth Ave, Seattle, WA 98104-2499, USA

S. Chou
Department of Neurology, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA

J. Claassen
Neurological Intensive Care Unit, Columbia University College of Physicians and Surgeons, 177 Fort Washington Avenue, Milstein 8 Center room 300, New York, NY 10032, USA

M. Czosnyka
Department of Neurosurgery, University of Cambridge, Addenbrooke's Hospital, Box 167, Cambridge CB2 0QQ, UK

M. De Georgia
Neurocritical Care Center, Cerebrovascular Center, University Hospital Case Medical Center, Case Western Reserve University School of Medicine, 11100 Euclid Avenue, Cleveland, OH 44106, USA

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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

A. Figaji
University of Cape Town, 617 Institute for Child Health, Red Cross Children's Hospital, Rondebosch, Cape Town 7700, South Africa

J. Fugate
Mayo Clinic, Rochester, MN 55905, USA

R. Helbok
Neurocritical Care Unit, Department of Neurology, Innsbruck Medical University, Anichstr.35, 6020 Innsbruck, Austria

D. Horowitz
University of Pennsylvania Health System, 3701 Market Street, Philadelphia, PA 19104, USA

P. Hutchinson
Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Box 167, Cambridge CB2 2QQ, UK

M. Kumar
Department of Neurology, Perelman School of Medicine, University of Pennsylvania, 3 West Gates, 3400 Spruce Street, Philadelphia, PA 19104, USA

M. McNett
Nursing Research, The MetroHealth System, 2500 MetroHealth Drive, Cleveland, OH 44109, USA

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

C. Miller
Division of Cerebrovascular Diseases and Neurocritical Care, The Ohio State University, 395W. 12th Ave, 7th Floor, Columbus, OH 43210, USA

A. Naidech
Department of Neurology, Northwestern University Feinberg, SOM 710, N Lake Shore Drive, 11th floor, Chicago, IL 60611, USA

M. Oddo
Department of Intensive Care Medicine, Faculty of Biology and Medicine University of Lausanne, CHUV University Hospital, BH 08-623, 1011 Lausanne, Switzerland

D. Olson
Neurology, Neurotherapeutics and Neurosurgery, University of Texas Southwestern, 5323 Harry Hines Blvd, Dallas, TX 75390-8897, USA

K. O'Phelan
Department of Neurology, University of Miami, Miller School of Medicine, JMH, 1611 NW 12th Ave, Suite 405, Miami, FL 33136, USA

J. J. Provencio
Cerebrovascular Center and Neuroinflammation Research Center, Lerner College of Medicine, Cleveland Clinic, 9500 Euclid Ave, NC30, Cleveland, OH 44195, USA

C. Puppo
Intensive Care Unit, Hospital de Clinicas, Universidad de la República, Montevideo, Uruguay

R. Riker
Critical Care Medicine, Maine Medical Center, 22 Bramhall Street, Portland, Maine 04102-3175, USA

C. Robertson
Department of Neurosurgery, Center for Neurosurgical Intensive Care, Ben Taub Hospital, Baylor College of Medicine, 1504 Taub Loop, Houston, TX 77030, USA

M. Schmidt
Columbia University College of Physicians and Surgeons, Milstein Hospital 8 Garden South, Suite 331, 177 Fort Washington Avenue, New York, NY 10032, USA

F. Taccone
Laboratoire de Recherche Experimentale, Department of Intensive Care, Erasme Hospital, Route de Lennik, 808, 1070 Brussels, Belgium

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 below sections and in a supplement to Neurocritical Care. The reader is referred to the supplement 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, 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). 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.

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

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 the 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 Pain, Agitation, and Delirium (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 pressure 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. Clinical series suggest 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 it 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. Partial arterial oxygen pressure (PaO_2), arterial oxygen saturation (SaO_2), and pulse oximetry (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.)

Glucose and Nutrition

Questions Addressed

1. Can measuring energy expenditure with indirect calorimetry be used to monitor the nutritional requirements in patients who require neurocritical care?
2. What methods are useful when monitoring the response to nutritional interventions?
3. Is there utility in monitoring gastric residuals in patients receiving enteral nutrition?
4. How should glucose monitoring be performed in the acute critical care period after brain injury?
5. Should monitoring of serial blood glucose values be performed routinely during the critical care after acute brain injury?

Summary

The monitoring of glycemic control and nutritional status are important features of intensive care [86], and interface with multimodality monitoring in important ways. Early profound hyperglycemia is independently associated with poor prognosis after TBI, stroke, and SAH. Several lines of evidence support a need to avoid hypoglycemia, low brain glucose, and extreme hyperglycemia during intensive care and reinforce the need for accurate, reliable, and frequent glucose measurements [87]. Use of acute point-of-care testing of arterial or venous blood, and the use laboratory-quality measures of glucose are critical [88, 89]. Understanding glycemic control is central to determining the status of energy substrate delivery to the brain and assists in understanding the findings observed using cerebral microdialysis [90, 91]. At the same time, the assessment of nutritional status and protein balance is important, albeit more challenging, to reliably and repeatedly perform in the ICU. Several tenets of clinical care have recently been questioned, including the use of indirect calorimetry, energy estimation formulas [92], and the monitoring of gastric residuals [93]. Many studies support the concept that acute brain injury induces a hypercatabolic state, and hence caloric and protein supplementation are needed. However, changing strategies of sedation and therapeutic normothermia may affect the metabolic state, and hence justify a need to establish measures of nutritional balance. The influence of inadequate protein balance may influence glycemic control and hence brain metabolism, but this linkage remains poorly studied at this time.

Recommendations

1. We suggest against the routine monitoring of nutritional requirements with measurement of energy expenditure by indirect calorimetry or the use of estimating equations for assessing nutritional requirements (Weak recommendation, Low quality of evidence).
2. We recognize that accurately measuring nitrogen balance is difficult, but where this is possible we suggest that this may be used to help assess the adequacy of nutritional support (Weak recommendation, Very low quality of evidence).
3. We suggest against the use of anthropometric measurements or serum biomarkers as a method by which to monitor the overall responsiveness of nutritional support. (Weak recommendation, Very low quality of evidence).
4. We recommend against routine monitoring of gastric residuals in mechanically ventilated patients (Strong recommendation, High quality of evidence).
5. We recommend that arterial or venous blood glucose be measured by a laboratory-quality glucose measurement immediately upon admission, to confirm hypoglycemia, and during low perfusion states for patients with acute brain injury (Strong recommendation, High quality of evidence).
6. We recommend serial blood glucose measurements using point-of-care testing should be performed routinely during critical care after acute brain injury. (Strong recommendation, High quality of evidence).

Hemostasis and Hemoglobin

Questions Addressed

1. What are the indications for monitoring hemoglobin?
2. How should hemoglobin monitoring be performed in acute brain injury?
3. When and how frequently should hemoglobin be measured?
4. What hemostatic monitoring parameters should be performed in acute brain injury and in the perioperative setting?

Summary

Anemia and bleeding are frequent in patients who suffer severe neurologic insults and are associated with worse outcomes [94]. Serial measurements of hemoglobin (Hgb) concentration are necessary to assess and monitor for the development of anemia. Non-invasive monitoring of Hgb limits blood loss, but has suboptimal accuracy and precision compared to standard laboratory testing. Efforts to minimize volume of blood sampled for laboratory assessment are effective in ameliorating anemia [95]. No data establish benefit of a particular frequency of Hgb monitoring. Transfusion has been linked to worse outcomes [96], although the interaction with anemia makes separating their effects difficult. The transfusion threshold used in general critical care may not apply to all patients with acute neurological disorders and may vary with pathology, the patient, and their cerebrovascular reserve.

Point-of-care-testing (POCT) detects the effect of non-steroidal anti-inflammatory drugs on platelet activity [97] and can be used to monitor normalization of platelet function after drug withdrawal [98] and platelet transfusion [99], but data are limited. In patients taking novel oral anticoagulants, information regarding time of last dose ingestion, renal function, and age may help determine plasma concentrations [100]. Thrombin time, PT, and aPTT can be used to help monitor these agents and may suggest anticoagulant effect, but may not be accurate at low concentrations. The direct thrombin inhibitor (DTI) assay determines both the anticoagulant activity and plasma concentration of dabigatran [101], whereas specific factor Xa assays can detect the presence of rivaroxaban, apixiban, or edoxaban. These assays are beginning to become more widely available in the clinical environment.

Pre-operative screening for neurosurgical procedures routinely includes a bleeding history [102] and measurement of the PT and aPTT [103]. Yet, whether minimal elevations of the PT or INR correlate with increased bleeding risk is uncertain and may depend in part on the procedure [104]. An INR <1.6 and a platelet count $>100{,}000$ are reasonable goals but depend on patient disease. ICP monitor placement in patients with liver failure often leads to hemorrhage [105] and accurate assessment of hemostasis is of paramount importance. The INR is traditionally used to guide treatment; however, it is widely acknowledged to be inaccurate in this population [106].

Recommendations

1. We recommend that monitoring Hgb should be done in all patients (Strong recommendation, Moderate quality of evidence).
2. We recommend that central laboratory methods be used for the accurate and reliable monitoring of hemoglobin and hemostatic values (Strong recommendation, Moderate quality of evidence).
3. POCT may help identify coagulopathy or antiplatelet agent use in patients with TBI, SAH, and ICH where there is a concern for platelet dysfunction (Strong recommendation, Moderate quality of evidence).
4. POCT may be used to monitor the response to interventions intended to improve platelet function. (Weak recommendation, Very low quality of evidence).
5. In patients who require neurosurgical intervention, a detailed family history and structured screening about bleeding disorders and bleeding after traumatic events, should be elicited. (Strong recommendation, Moderate quality of evidence).
6. Determination of time of last ingested dose, renal function, age, and other medications ingested is recommended to assist in determination of plasma concentration of the new anticoagulants. (Strong recommendation, High quality of evidence).
7. We suggest that, if available, new specific assays for the new oral anticoagulants be used to assess coagulation status in neurologic emergencies. (Weak recommendation, Low quality of evidence).
8. In patients with liver failure, routine tests of coagulation may not accurately reflect hemostatic balance. Advanced tests of coagulation, point-of-care devices, and consultation with a hematologist are suggested. (Weak recommendation, Low quality of evidence).

Temperature and Inflammation

Questions Addressed

1. Does continuous monitoring of temperature improve our discrimination of bad outcomes more than episodic monitoring?

2. Does monitoring of temperature improve our ability to discriminate infection versus brain-derived fever?
3. Is brain temperature or core body temperature optimal to determine temperature in critically ill neurologic patients?
4. How should shivering be monitored in patients receiving therapeutic temperature modulation?
5. What inflammatory cells predict outcome in acute brain disease?
6. Is there utility in monitoring inflammatory mediators?

Summary

In patients with acute brain injury, the incidence of fever is greater than in general ICU patients and is a marker for poor outcome. Patients who have active treatment of fever have less evidence of metabolic crisis diagnosed by cerebral microdialysis [107] and induced normothermia can help control intracranial pressure [108]. The temperature cut off for fever is unclear, but the common definition of fever is a systemic temperature elevation greater than 38.2 or 38.5 °C There is little evidence that temperature monitoring can discriminate between central fever and other causes although some studies suggest that the area under the curve of a fever curve is higher in patients with a presumed central fever [109, 110].

Temperature can be monitored from a number of different sites. Rectal and bladder temperatures are more closely associated with pulmonary artery catheter temperatures, whereas oral temperatures are superior to axillary and tympanic measurements [111, 112]. In brain-injured patients central and brain temperature show good correlation and so core temperature is a reasonable surrogate for brain temperature. Knowledge about temperature (brain or core) can be important in assessing accuracy of other monitors including from some types of brain oxygen and CBF devices. Shivering results in increases in resting energy expenditure and in the systemic rate of oxygen consumption (VO_2) [113] and can adversely affect brain metabolism [114]. Hourly measurements using the Bedside Shivering Assessment Scale (BSAS) are a reliable method by which to adjust anti-shivering therapy [115].

In SAH, comparison of neutrophil percentage in ventricular fluid in the first three days to other predictive scales suggests that it has good negative predictive value for patients who may develop delayed deterioration [116]. There is no evidence to support the use of WBC counts or indices of WBC to discriminate between infection and inflammatory changes in patients with EVDs. There are a variety of inflammatory markers that can be monitored: CRP and Pro-calcitonin are most frequently measured. While CRP may provide indirect confirmation of an infection or response to therapy, it does not reliably discriminate between bacterial meningitis from other forms of inflammation and has poor predictive value in SAH, ICH, or stroke. Pro-calcitonin does not appear to be a useful monitoring technique to investigate infections in brain-injured patients [117].

Recommendations

1. In patients with acute neurological injury, we recommend continuous monitoring of temperature when feasible and, at least hourly if not feasible (Strong recommendation, Low quality of evidence).
2. We recommend that temperature monitoring alone cannot be used as a tool to discriminate infectious fever from central or neurogenic fever (Strong recommendation, Low quality of evidence).
3. We recommend monitoring core body temperature as a surrogate of brain temperature unless brain temperature is available from devices placed for other reasons (Strong recommendation, Low quality of evidence).
4. We recommend hourly monitoring for shivering with the BSAS during therapeutic temperature modulation. (Strong recommendation, Moderate quality of evidence).
5. We suggest daily measurement of blood leukocyte counts in patients with SAH who are at risk for delayed deterioration. (Weak recommendation, Low quality of evidence).
6. We suggest against monitoring routine ventricular fluid WBC counts to discriminate whether patients with EVDs have infection. (Weak recommendation, Low quality of evidence).
7. We suggest against monitoring inflammatory mediators routinely. (Weak recommendation, Low quality of evidence).
8. We suggest monitoring brain temperature when such a device is placed for other reasons. (Weak recommendation, Low quality of evidence).

Cellular Damage and Degeneration

Questions Addressed

1. Are there cellular/molecular biomarkers that help predict long-term neurological prognosis in comatose cardiac arrest patients, either treated or not treated with therapeutic hypothermia (TH)?
2. Are there cellular/molecular biomarkers that help predict (a) long-term outcome and (b) development of vasospasm and/or DCI after SAH?

3. Are there cellular/molecular biomarkers that help predict (a) long-term outcome and (b) incidence of malignant cerebral ischemia or hemorrhagic transformation following AIS?
4. Are there cellular/molecular biomarkers that help predict (a) long-term outcome and (b) hematoma expansion and cerebral edema following intracerebral hemorrhage (ICH)?
5. Are there cellular/molecular biomarkers that help predict (a) long-term outcome and (b) cerebral edema and ICP elevation after TBI?

Summary

Numerous candidate molecular biomarkers have been identified and are potentially associated with outcome and disease-specific secondary complications of acute brain injury. Most biomarkers have real-world challenges related to lack of availability, lack of agreement about sample collection and processing protocols, wide ranges of threshold values, poor definition of biomarker time course, and biological, treatment, and laboratory standardization.

Neuron specific enolase (NSE) is probably the most widely studied currently available biomarker in the context of cardiac arrest. Early studies suggested that an elevated NSE at 24–72 h post-cardiac arrest had 100 % specificity for poor outcomes in patients not treated with TH [73]. This finding has been broadly confirmed in other reports, although the cutoff values vary between studies. However, this relationship no longer holds in patients who are treated with TH, and elevated NSE at 24–48 h post-cardiac arrest can be seen in these patients who survive with good outcome [74]. While S100B and combinations of biomarkers have also been evaluated in cardiac arrest treated with TH, and sometimes found to perform better than NSE, none of the data provide robust enough outcome prediction to justify routine clinical use in this setting [118].

No biomarkers have been validated in large cohort studies in acute ischemic stroke, SAH, or ICH. While individual small studies have explored several biomarkers, none has provided data of adequate quality to allow clinical prognostication and decision support. Several biomarkers have been studied in larger cohorts of patients with TBI, but sample sizes are still relatively small in the context of this highly heterogeneous disease [119, 120]. Although one meta-analysis supports the use of S100B as a biomarker of severity and outcome in TBI [121], clinical implementation of this monitoring strategy is limited, in part because S100B is not brain specific.

A number of experimental biomarkers (e.g., glial fibrillary acid protein [GFAP], matrix metalloprotease-9 [MMP-9], ubiquitin c-terminal hydrolase L1 [UCH-L1], and alpha-II spectrin breakdown products [SBDP]) have been suggested to hold promise in acute neurological disease, but have not undergone substantive evaluation and are not in routine clinical use [119, 122, 123]. Although some data suggest that the combination of multiple biomarkers or biomarkers and other monitoring modalities can improve precision [118–120, 124, 125], large prospective studies are necessary to determine which of these biomarkers can be used clinically, to help direct therapy and predict outcome.

Recommendations

1. In comatose post-cardiac hypoxic-ischemic encephalopathy (HIE) patients not treated with TH, we suggest the use of serum NSE in conjunction with clinical data for neurologic prognostication (Weak recommendation, Moderate quality of evidence).
2. We recommend against the use of serum NSE for prognostication in HIE treated with TH (Strong Recommendation, Moderate quality of evidence).
3. We recommend against the routine use of molecular biomarkers for outcome prognostication in AIS, SAH, ICH, or TBI (Strong Recommendation, Low quality of evidence).

ICU Processes of Care and Quality Assurance

Questions

1. In critically ill patients with acute brain injury, how does care by a dedicated neurointensive care unit/team impact outcomes?
2. In the neurocritical care population, how does use of evidence-based protocols impact patient outcomes?
3. What are key quality indicators for ICU processes of care and are these applicable to the neurocritical care population?

Summary

Patients with neurological conditions account for 10–15 % of all intensive care unit (ICU) admissions. In patients with critical neurologic illness patient care in specialized neurocritical care units or by physicians and nursing staff with expertise in neurocritical care within a general critical care unit appear to have a positive impact on mortality, length of stay, and in some cases, functional outcome [126–131]. By contrast delays in care may adversely affect outcome [132, 133]. The results, however, are heterogeneous and whether the relationship is

causal is still being elucidated. In these studies, various practice modifications, such as implementation of disease or treatment specific protocols or bundles of care, staffing requirements, and clustering of neurocritical care patients within a multidisciplinary unit, are also temporally associated with outcome improvements.

Implementation of and adherence to evidence-based protocol-directed care in the neurocritical care population has also been shown to be important [134]. Significant evidence exists supporting quality indicators that include measures of process (appropriate delivery of health care), outcome (measured endpoints of care), and structure (adequate resources to provide health care), for the general ICU population [135], but there is limited research about their specific use in neurocritical care. Although quality indices for neurocritical care have been proposed, additional research is needed to further validate these measures, since there appear to be differences between neurocritical care and general critical care patients in large acuity-adjusted benchmark studies [136].

Recommendations

1. We recommend that critically ill patients with acute brain injury be managed either in a dedicated neurocritical care unit or by clinical teams with expertise in neurocritical care (Strong recommendation, Moderate quality of evidence).
2. We recommend implementation of and monitoring adherence to evidence-based protocols, in the neurocritical care population (Strong recommendation; Moderate quality of evidence).
3. We recommend that the incidence of ventriculostomy-related infections may be a useful indicator of quality of care (Strong recommendation, Moderate quality of evidence).
4. We recommend that use of protocols for moderate glycemic control is a useful indicator of quality of care in neurocritical care patient populations (Strong recommendation; Moderate quality of evidence).
5. We suggest that other known ICU processes of care including pressure ulcers, central line-associated blood stream infections, and catheter-associated-urinary tract infections may be useful as indicators of general intensive care, but none are specific indicators of quality in the neurocritical care population (Weak recommendation, Low quality of evidence).
6. We suggest that ventilator-associated pneumonia should not be regarded as a quality indicator in the neurocritical care population (Weak recommendation, Low quality of evidence).

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.)

Monitoring in Emerging Economies

Questions Addressed

1. Are there differences between high-income countries (HICs) and low- and middle-income countries (LAMICs) in baseline characteristics for neurocritical care patients or selection of patients for study?
2. What is the availability/penetration of various monitoring technologies/ neurocritical care in emerging economies?
3. Does MMM benefit patients in LAMICs and is it cost effective?
4. What are the challenges to instituting MMM in resource-constrained environments?

Summary

The burden of disease and so the need for care often is greater at hospitals in emerging economies. For example, 90 % of trauma-related deaths are estimated to occur in the developing world [143]. Emerging economies represent a heterogeneous group of countries. Furthermore, there may be differences in economic scale and available resources in HICs even within cities and health care systems. The selection criteria for ICU admission are not clearly defined in most studies and ICU bed availability is an important factor in resource-limited settings, whereas decisions about futility become important in HICs. Even in middle-income environments, some severe TBI patients are ventilated in general wards influenced by bed availability and the expected outcome [144]. In addition, in large studies, the demographics of the studied population in LAMICs often differ from that in HICs [145].

Advanced monitoring in neurocritical care is uncommon in emerging economies. Some exceptions do occur and monitoring ICP, brain oxygen, CBF, continuous EEG, jugular venous saturation, and microdialysis, often in combination, have all been described at centers based in emerging economies; but are concentrated where there is an interest in neurocritical care and in particular from Latin America, Malaysia, South Africa, and China (e.g. [146, 147]). ICP monitoring often is considered a fundamental tool in neuromonitoring, but in emerging economies is not commonly employed outside of specialist centers. However, there also is great variability in use of these devices even within HICs [43]. In LAMICs ventricular, subdural or subarachnoid catheters often are used instead of the more expensive parenchymal devices; this can affect interpretation of comparative studies. A recent randomized, controlled trial (RCT) conducted in general ICUs in Bolivia and Ecuador, introduced ICP to an environment where they had not been used previously to evaluate two management protocols in severe TBI [40]. Outcome was similar in the two treatment groups and has raised questions about the value of advanced monitoring in this environment. However, the use of ICP monitors was associated with more efficient care, which may prove to be important in cost-effective care in a resource-limited environment. Furthermore, ICP monitoring may help reduce the frequency of potentially inappropriate ICP-lowering therapies. There is indirect evidence to support aggressive management for severe TBI in LAMICs, including the use of advanced monitoring. Decision analysis suggests that this can be associated with cost-effective outcome enhancement [148]. There is no evidence that patients in LAMICs should be treated differently than patients in HICs.

It should be recognized there is a wide range in expertise and resources not only within the LAMICs but also within individual HICs. Several challenges to develop advanced neurocritical care exist in LAMICs. These are difficult to quantify, given the spectrum across LAMICs, and are best described in a qualitative manner. We encourage the use of the highest possible tier of monitoring when applicable to optimize the potential benefit from the monitoring.

However, we recognize that particular institutional and economic circumstances may influence priorities of care, and there is a need for flexibility to meet the clinical demands under variable constrictions. There should be a balance between desire to establish essential monitoring with the notion that there is a valid need for advanced and expert systems given the differing sophistication of the various centers, regions, and nations.

Recommendations

1. We recommend that collaborative multi-center studies are needed to address the differences in patients baseline characteristics (Strong recommendation, Moderate quality of evidence).
2. We recommend that comparative studies must control for differences in patient baseline characteristics and comparison between HICs and LAMICs should be made only where there is sufficient data about classification, case selection, and clinical outcome assessment. (Strong recommendation, Low quality evidence).
3. We recommend that guidelines for monitoring neurocritical care patients for emerging economies should consider regional variations and recommendations for monitoring where these do not currently exist must be carefully considered (Strong recommendation, Moderate quality evidence).
4. We recommend that ICP monitoring should be used preferably where there is neurocritical care clinical expertise and in an appropriate intensive care setting. (Strong recommendation, Moderate quality evidence).
5. We recommend that the role and cost/benefit ratio of MMM in individual LAMICs, and also HICs, must be weighed against the overall priorities for delivering basic health care at individual centers (Strong recommendation, Low quality evidence).

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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Appendix

Consensus Statement Chairmen	Peter Le Roux, David Menon, Giuseppe Citerio, Paul Vespa
Jury	Mary Kay Bader, Gretchen M. Brophy, Michael N. Diringer, Nino Stocchetti, Walter Videtta
Topic	**Authors**
Clinical Evaluation	Richard Riker, Jen Fugate
Systemic Hemodynamics	Fabio Taccone, Giuseppe Citerio
Intracranial Pressure and Cerebral Perfusion Pressure	
- Traumatic brain injury:	Randal Chesnut, Walter Videtta, Paul Vespa, Peter Le Roux
- Conditions other than TBI:	Raimund Helbok, DaiWai Olson, Paul Vespa, Peter Le Roux
Cerebrovascular Autoregulation	Marek Czosnyka, Chad Miller
Systemic and Brain Oxygen	Mauro Oddo, Julian Boesel
Cerebral Blood Flow	Chad Miller, Rocco Armonda
Electrophysiology	Jan Claassen, Paul Vespa
Cerebral Metabolism	Peter Hutchinson, Kristine Oã Phelan
Nutrition and Glucose	Neeraj Badjatia, Paul Vespa
Hemostasis and Hemoglobin	Andrew Naidech, Monisha Kumar
Temperature and Inflammation	Javier Provencio, Neeraj Badjatia
Biomarkers of Cellular Damage and Degeneration	Sherry Chou, Claudia Robertson
ICU Processes of care and Quality assurance	Molly McNett, David Horowitz
Multimodality Monitoring Informatics, Integration and Display, Analysis	Michael Schmidt, Michael DeGeorgia
Monitoring in Emerging Economies	Anthony Figaji, Corina Puppo
Future Directions and Emerging Technologies	Peter Le Roux, Paul Vespa and David Menon

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