Published in final edited form as:

Neurocrit Care. 2014 December; 21(Suppl 2): S282–S296. doi:10.1007/s12028-014-0077-6.

The International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: A List of Recommendations and Additional Conclusions:

A Statement for Healthcare Professionals From the Neurocritical Care Society and the European Society of Intensive Care Medicine

Peter Le Roux,

Brain and Spine Center, Lankenau Medical Center, Suite 370, Medical Science Building, 100 East Lancaster Avenue, Wynnewood, PA 19096, USA

David K. Menon,

Division of Anaesthesia, Neurosciences Critical Care Unit, Addenbrooke's Hospital, University of Cambridge, Box 93, Cambridge CB2 2QQ, UK

Giuseppe Citerio,

Department of Anesthesia and Critical Care, Ospedale San Gerardo, Via Pergolesi 33, 20900 Monza, Italy

Paul Vespa.

David Geffen School of Medicine at UCLA, Los Angeles, CA 90095, USA

Mary Kay Bader,

Neuro/Critical Care CNS Mission Hospital, Mission Viejo, CA 92691, USA

Gretchen Brophy,

Departments of Pharmacotherapy & Outcomes Science and Neurosurgery, Virginia Commonwealth University, Medical College of Virginia Campus 410 N. 12th Street, Richmond, VA 23298-0533, USA

Michael N. Diringer,

Department of Neurology, Neurocritical Care Section, Washington University, Campus Box 8111 660 S Euclid Ave, St Louis, MO 63110, USA

Nino Stocchetti,

Department of Physiopathology and Transplant, Milan University, Fondazione IRCCS Cà Granda Ospedale, Maggiore Policlinico, Via F Sforza 35, 20122 Milan, Italy

Walter Videtta,

ICU Neurocritical Care, Hospital Nacional 'Prof. a. Posadas', El Palomar - Pcia, De Buenos Aires, Argentina

Rocco Armonda,

P. Le Roux, lerouxp@mlhs.org.

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

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

Neeraj Badjatia,

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

Julian Bösel,

Department of Neurology Ruprect-Karls, University Hospital Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany

Randall Chesnut,

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

Sherry Chou,

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

Jan Claassen,

Department of Neurology and Neurosurgery, Columbia University College of Physicians & Surgeons, 177 Fort Washington Avenue, Milstein 8 Center Room 300, New York, NY 10032, USA

Marek Czosnyka,

Department of Neurosurgery, Addenbrooke's Hospital, University of Cambridge, Box 167, Cambridge CB20QQ, UK

Michael De Georgia,

Department of Neurology, University Hospital Case Medical Center, Case Western Reserve University School of Medicine, 11100 Euclid Avenue, Cleveland, OH 44106, USA

Anthony Figaji,

Department of Pediatric Neurosurgery, 617 Institute for Child Health Red Cross Children's Hospital Rondebosch, University of Cape Town, Cape Town 7700, South Africa

Jennifer Fugate,

Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Raimund Helbok,

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

David Horowitz,

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

Peter Hutchinson,

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

Monisha Kumar,

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

Molly McNett,

The MetroHealth System, 2500 MetroHealth Drive, Cleveland, OH 44109, USA

Chad Miller,

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

Andrew Naidech,

Department of Neurology Northwestern, University Feinberg SOM, 710 N Lake Shore Drive, 11th Floor, Chicago, IL 60611, USA

Mauro Oddo,

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

DaiWai Olson,

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

Kristine O'Phelan,

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

J. Javier Provencio,

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

Corinna Puppo,

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

Richard Riker,

Critical Care Medicine Maine Medical Center, 22 Bramhall Street, Portland, ME 04102-3175, USA

Claudia Roberson,

Department of Neurosurgery, Ben Taub Hospital, Baylor College of Medicine, 1504 Taub Loop, Houston, TX 77030, USA

Michael Schmidt,

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

Fabio Taccone

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

Abstract

Careful patient monitoring using a variety of techniques including clinical and laboratory evaluation, bedside physiological monitoring with continuous or non-continuous techniques and imaging is fundamental to the care of patients who require neurocritical care. How best to perform and use bedside monitoring is still being elucidated. To create a basic platform for care and a foundation for further research 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 develop recommendations about physiologic bedside monitoring. This supplement contains a Consensus Summary Statement with recommendations and individual topic reviews as a background to the recommendations. In this article, we highlight the recommendations and provide additional conclusions as an aid to the reader and to facilitate bedside care.

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; Bio-informatics; Biomarkers; Neurocritical care; Clinical guidelines

Introduction

The word "monitor" is derived from the Latin "monere" (to warn). Careful patient monitoring is central to the care of patients who require neurocritical care, in large part to detect evolving secondary brain insults while they are still reversible. In addition, monitoring can help better understand what is happening in an individual patient and so develop personalized targeted care. This becomes important because of the failure of many trials in neuroprotection.

There are many techniques available with which a patient can be monitored, and the vast majority of patients admitted to neurocritical care units are monitored with a combination of tools including clinical and laboratory evaluation, imaging, and bedside physiologic devices. However, what processes to monitor, how best to monitor, and whether information derived from a monitor or combination of monitors, influences outcome are still subject to debate and discussion. Therefore, 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 to summarize current literature on bedside monitoring in neurocritical care in an evidence-based format to provide a foundation for care and future research. While imaging is indispensable, we chose to limit the review to physiological processes that are important to the care of patients with acute brain injury and that can be monitored at bedside.

Process

The process used to develop these recommendations is described in detail in the "Consensus Summary Statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care" at the beginning of this supplement [1]. Briefly, representatives of the NCS and ESICM chaired the consensus process. Experts from around the world in the fields of neurosurgery, neurocritical care, neurology, critical care, neuroanesthesiology, nursing, pharmacy, and informatics were recruited based on their

expertise and publication record. Seventeen individual topics were chosen for review and two authors assigned to each topic. In addition, a jury of experienced neurocritical care clinicians was selected for their expertise in clinical investigation and development of practice guidelines. The authors assigned to each topic performed a critical literature review according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [2] with the help of a medical librarian. Evidentiary tables were prepared and preliminary recommendations and conclusions developed and reviewed by the chairs, authors, and jury. The quality of the data was assessed and recommendations developed using the GRADE system [3–5].

Each topic was then presented and discussed at a 2-day conference in Philadelphia held on September 29 and 30, 2013. The jury subsequently held several conference calls, and then met again at a subsequent 2-day meeting to finalize the summary consensus statement published in this supplement. In this article, we list the recommendations, adjudicated upon by the jury and additional conclusions provided by the authors and discussed by members of the consensus conference but not voted upon.

Recommendations and Conclusions

The reader is referred to the Summary Statement and the individual topic reviews for abbreviations and literature discussion supporting the recommendations and conclusions.

Clinical Evaluation

- We recommend that assessments with either the Glasgow Coma Scale (GCS)
 (combined with assessment of pupils) or the full outline of unresponsiveness
 (FOUR) score be routinely performed in comatose adult patients with acute brain injury (strong recommendation, low quality of evidence).
- 2. We recommend using the Numeric Rating Scale (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 Behavioral Pain Scale (BPS) or CCPOT (strong recommendation, low quality of evidence).
- **4.** We recommend use of the revised Nociceptive Coma Scale (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 Sedation-Agitation Scale (SAS) or Richmond Agitation Sedation Scale (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, e.g., the confusion assessment method for the ICU (CAM-ICU) or intensive care delirium screening checklist (ICDSC) (weak recommendation, low quality of evidence).

8. We recommend attention to level of wakefulness, as used in the ISDSC, during delirium screening to avoid confounding due to residual sedative effect (strong recommendation, low quality of evidence).

Additional Conclusions

 Processed EEG monitoring to guide sedation titration may reduce drug doses and hasten wake-up time in select patients (low quality of evidence).

Systemic Hemodynamics

Recommendations (and See Summary Statement)

- 1. We recommend the use of electrocardiography and invasive monitoring of arterial blood pressure in all unstable or at-risk patients in the intensive care unit (strong recommendation, moderate quality of evidence).
- 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).

Additional Conclusions

Can monitoring of Systemic Hemodynamics Help Understand the Mechanisms of Circulatory Failure, Inadequate Perfusion, or Organ Dysfunction?

- Use of echocardiography can be used to detect LV dysfunction in the early phase after subarachnoid hemorrhage (SAH) (low quality of evidence).
- Evaluation of systolic and diastolic dysfunctions in SAH patients can be an important marker of cardiac but not pulmonary injury (very low quality of evidence).
- Monitoring preload can help understand the mechanisms of pulmonary edema (PE) after SAH (very low quality of evidence).

 Measuring lactate levels on admission and during the first 48 h after cardiac arrest (CA) can help assess global perfusion and the severity of post-resuscitation shock (very low quality of evidence).

Does Hemodynamic Monitoring Have a Specific Role in Optimizing Brain Perfusion and Oxygenation or Brain-Specific Therapy?

 Early optimization of cardiac index (CI) and preload during SAH-induced vasospasm can help improve regional cerebral oxygenation and CBF (very low quality of evidence).

What is the Impact of Systemic Hemodynamic Monitoring and Related Therapies on Morbidity, Mortality, and Neurological Outcome?

- Use of systolic and diastolic dysfunctions to predict poor outcome after SAH is not always reliable (low quality of evidence).
- Hemodynamic monitoring-guided therapy can help reduce complications and improve outcome in SAH patients at risk for delayed cerebral ischemia (DCI) (moderate quality of evidence).
- Lactate levels on admission and lactate clearance may be used to evaluate prognosis of patients after CA (very low quality of evidence).
- ScvO₂-guided therapy may help improve hemodynamic stability and reduce mortality in patients after CA (low quality of evidence).

How can Fluid Responsiveness be Assessed in Acute Brain Injury (ABI) Patients?

• Use of SVV or dICV monitoring can help predict fluid responsiveness in patients with acute brain injury (moderate quality of evidence).

What Hemodynamic Monitoring is Indicated in ABI Patients, in Particular to Diagnose and Support the Management of Unstable or At-Risk Patients?

- Trans-pulmonary thermodilution (TT) but not echocardiography can be regarded as an equivalent to PAC to measure CO (moderate quality of evidence).
- Pulse contour wave analysis (PCWA) devices may underestimate CO in cases of altered vascular resistances or concomitant use of mechanical ventilation (moderate quality of evidence).
- TT but not PCWA should be used to measure CO during therapeutic hypothermia in survivors from CA (low quality of evidence).

Intracranial Pressure and Cerebral Perfusion Pressure: Fundamental Considerations and Rationale for Monitoring

Recommendations (and See Summary Statement)

- 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).

Additional Conclusions

Does ICP Monitoring Provide Useful Information on Injury Severity/ Prognosis?

 ICP monitoring is a valuable indicator of severe traumatic brain injury (sTBI) severity, and can predict mortality, particularly when the elevation pattern and refractoriness to treatment are included (moderate quality of evidence).

• ICP monitoring is a valuable indicator of sTBI severity, but is a marginally useful tool in predicting morbidity among survivors the value of which is enhanced when the pattern of elevation and refractoriness to treatment are included (moderate quality of evidence).

The ICP course should not be used independently for prognosis estimation (moderate quality of evidence)

Is ICP Monitoring a Necessary Component of Systems of sTBI Management that Reliably Produce Superior Outcomes?

- ICP monitoring should be considered a useful adjunct to aggressive treatment approaches to sTBI associated with improved recovery (moderate quality of evidence).
- Protocolized treatment of sTBI, including management of intracranial hypertension, is recommended to improve treatment efficiency (high quality of evidence).
- Protocolized treatment of sTBI, including management of intracranial hypertension, is recommended to increase the likelihood of consistently achieving better recovery (moderate quality of evidence).
- ICP monitoring should not be used as an independent indicator of quality of care (moderate quality of evidence).

Does Successfully Managing Intracranial Pressure Improve Outcome?

- Aggressive, attentive care is recommended to manage ICP in sTBI because successful control of intracranial hypertension is associated with improved outcome (moderate quality of evidence).
- Intracranial pressure monitoring is recommended as an adjunct to aggressive, attentive care in sTBI because it facilitates effective and efficient treatment of intracranial hypertension (moderate quality of evidence).

Is There an Optimal ICP Treatment Threshold the Maintenance of which is Critical to Optimize Recovery?

- Although there are no rigorously determined ICP threshold values for all sTBI patients or individual subgroups, it is reasonable to set the treatment threshold at 20–25 mm Hg at the onset of management (moderate quality of evidence).
- Because ICP values above 20–25 mm Hg may be well tolerated, it is reasonable to consider raising the treatment threshold when clinical evidence supports such a decision and it is favorable to the overall management of the patient although methods to guide such a decision are currently under-developed (low quality of evidence).
- Since ICP refractory to management efforts to maintain it below 20–25 mm Hg is not uniformly associated with unfavorable outcome, decisions on limiting care

- must include other outcome predictors in addition to the ICP course (low quality of evidence).
- Further research into the relationship between ICP and outcome will benefit from automated, high-resolution monitoring and alternate forms of analysis (e.g., AUC, trending, etc.) (low quality of evidence).

Are There Clinical or CT Findings that Predict the Development of Intracranial Hypertension and So Can Guide Decision Making About ICP Monitor Placement?

- sTBI patients with an abnormal admission CT should be considered at high risk (incidence >50 %) of intracranial hypertension unless the CT finding is that of uncomplicated diffuse axonal injury (low quality of evidence).
- sTBI patients with a normal admission CT but any combination of admission hypotension, age >40 years, and severe neurological status (GCS motor <3 or pupillary abnormalities), or a lengthy inability to follow the patient's exam, should be considered at high risk (incidence >50 %) of intracranial hypertension (low quality of evidence).
- sTBI patients with a normal admission CT who do not meet the above criteria
 may be considered at low likelihood of developing intracranial hypertension (low
 quality of evidence).
- sTBI patients with uncomplicated diffuse axonal injury on admission CT may be considered at low likelihood of developing intracranial hypertension (low quality of evidence).
- Patients initially managed without monitoring whose exam does not improve should undergo repeat CT imaging (low quality of evidence).

Intracranial Pressure and Cerebral Perfusion Pressure Monitoring in Non-TBI patients: Special Considerations

Additional Conclusions

- ICP and CPP monitoring should be used in SAH, ICH, and other non-TBI
 conditions in patients who are at risk of elevated ICP based on clinical and/or
 imaging features (low quality of evidence).
- ICP monitoring should be considered for patients at high risk for developing hydrocephalus, or those with clinical or radiographic evidence of hydrocephalus (moderate quality of evidence).
- All poor grade SAH patients should be monitored and be considered for multimodality monitoring (low quality of evidence).
- The use of an external ventricular drain (EVD) is the preferred method to monitor ICP in the setting of hydrocephalus in ICH or SAH patients (low quality of evidence).

Intraparenchymal ICP monitors and EVDs are equally reliable in providing a
measure of ICP with the understanding that device location relative to a lesion is
a major determinant of ICP (moderate quality of evidence).

- Non-TBI patients who require monitoring should receive an invasive device (either intraparenchymal or intraventricular) rather than a non-invasive device (low quality of evidence).
- Non-invasive devices do not serve as reliable ICP monitors, however, they may
 be used to estimate ICP when invasive ICP monitoring is not feasible (low
 quality of evidence).
- Ipsilateral monitoring is preferred when the goal is to reduce ICP in the lesioned hemisphere (moderate quality of evidence).
- Persistent or refractory intracranial hypertension may be useful as a prognostic marker in non-TBI patients (low quality of evidence).
- Use of EVD clamping trials can be used to define the group of patients who require a permanent VP shunt (moderate quality of evidence).
- ICP monitoring should be initiated or maintained for patients who undergo hemicraniectomy in the setting of cerebral edema (low quality of evidence).
- A combination of ICP and CPP monitoring along with waveform analysis, ICP variability and the integration of other physiologic data may help improve outcomes (weak quality of evidence).
- For patients at risk for elevated ICP use of continuous ICP monitoring to alert clinicians is preferred over intermittent assessment (moderate quality of evidence).

Cerebral Autoregulation

Recommendations (and See Summary Statement)

- 1. We suggest that monitoring and assessment of autoregulation may be useful in broad targeting of cerebral perfusion management goals and prognostication in acute brain injury (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 multimodality monitoring. 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).

Additional Conclusions

Given the absence of a proven method to target CPP in individual patients,
 CPPopt (the CPP level or range at which PRx is minimal) may help in individualizing CPP therapy (low quality of evidence).

Systemic and Brain Oxygenation

Recommendations (and See Summary Statement)

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 (PbtO₂) or/and jugular venous bulb oximetry (SjvO₂); the choice of which depends on patient pathology (strong recommendation, low quality of evidence).
- 3. We recommend that the location of the PbtO₂ 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 PbtO₂ 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).

Additional Conclusions

Brain Oxygen

- PbtO₂ monitoring is safe and it can provide accurate data for up to 7–10 days (low quality of evidence).
- Probe location influences PbtO₂ data and so all information should be interpreted according to a post-insertion CT scan (low quality of evidence).
- PbtO₂ monitoring should be part of a multimodal monitoring approach and used at least in combination with ICP monitoring (low quality of evidence).
- PbtO₂ is a complex variable that is sensitive to CBF, including CPP and MAP;
 PaCO₂, PaO₂, and FiO₂, temperature and oxygen consumption/delivery and so should be interpreted in the context of other clinical and physiologic factors (low quality of evidence).
- In severe TBI, reduced PbtO₂ is a useful outcome marker (increased mortality, lower GOS score) when integrated with other clinical and imaging information (low quality of evidence).
- Several interventions (e.g., alteration in CPP, sedation, FiO₂ or PEEP and RBC transfusion) can improve PbtO₂; the optimal PbtO₂ therapeutic algorithm is still

- being elucidated and hence therapy should be provided in a patient and pathology-specific manner (low quality of evidence).
- A $PbtO_2$ <20 mmHg be considered a threshold at which to initiate therapy (low quality of evidence).
- PbtO₂-guided therapy combined with ICP/CPP therapy is associated with improved outcome after severe TBI in some but not all studies and should be used in select patients with severe TBI (low quality of evidence).
- PbtO₂ data can be used to titrate individual CPP/MAP targets and red blood cell
 transfusion targets, ventilator targets (PaCO₂, PaO₂, FiO₂, PEEP), and, with ICP
 monitoring, interventions (e.g., moderate hyperventilation, osmotherapy,
 ventriculostomy, therapeutic hypothermia, or decompressive craniectomy) to
 manage intracranial hypertension (moderate quality of evidence).
- PbtO₂ monitoring can help guide management of comatose patients (GCS < 9) after TBI and SAH; the role in other conditions e.g., ICH and AIS is still to be elucidated (low quality of evidence).
- PbtO₂ (and the online correlation between PbtO₂ and CPP, also called the
 oxygen pressure reactivity index, ORx) can help detect delayed cerebral ischemia
 after SAH in patients with MCA and ICA aneurysms, but is less reliable in
 patients with VBA or ACA aneurysms (very low quality of evidence).

SjvO₂ Monitoring

- SjvO₂ monitoring should be part of a multimodal monitoring approach and used at least in combination with ICP monitoring (low quality of evidence).
- Where there is a choice PbtO₂ monitoring maybe preferred before SjvO₂
 monitoring because SjvO₂ monitors generally require frequent recalibration, are
 associated with several complications (e.g., catheter misplacement, colonization/
 infection) and are less accurate than PbtO₂ monitors (low quality of evidence).
- SjvO₂ has low accuracy to detect regional ischemia and so its use is best considered in select TBI patients with global abnormalities (low quality of evidence).
- An SjvO $_2$ <55 % can be considered as the threshold for abnormality and to start intervention (low quality of evidence).
- In patients with severe TBI, abnormal SjvO₂ and AVDO₂ are useful
 physiological markers associated with poor prognosis (increased mortality, lower
 GOS score) when used with other clinical and physiologic data (low quality of
 evidence).
- SjvO₂ data can help guide management of select TBI patients in coma (GCS < 9) (low quality of evidence).

 SjvO₂ therapy (using higher MAP/CPP and optimized volume management to augment CBF) does not improve outcome of severe TBI patients and so SjvO₂based therapy alone should not be used after TBI (high quality of evidence).

 There are too few data on how SjvO₂ monitoring may help manage secondary brain damage in patients with coma (GCS < 9) after SAH, ICH, and large ischemic stroke (very low quality of evidence).

Near Infrared Spectroscopy (NIRS)

- NIRS monitoring in the ICU is safe but despite some interesting research
 approaches, there is currently insufficient and controversial data as to how NIRS
 can be used to guide management and so NIRS, alone, should not be used for
 routine clinical monitoring of ABI patients (low quality of evidence).
- The NIRS signal is considerably affected by patient conditions and the
 correlation with other oxygenation or perfusion monitors is not consistent in
 several studies and so when used, NIRS should be used to answer research
 questions but not to guide routine management of ABI patients (low quality of
 evidence).
- When used, NIRS should be integrated into a multimodal monitoring concept (low quality of evidence).

Systemic Oxygen Monitoring

- Systemic oxygen monitoring is indicated to detect disturbances in oxygenation
 and guide ventilation management in neurocritical care and in particular in the
 patient that is ventilated, has signs of respiratory compromise, is sedated, or has a
 decline in level of consciousness (low quality of evidence).
- PaO₂ and SaO₂ should be measured regularly by ABG and SpO₂ continuously
 by pulse oximetry as part of multimodality concept in every neurocritical patient
 that is ventilated, sedated, has a decline in level of consciousness or has clinical
 signs of respiratory compromise (low quality of evidence).
- Pulse oximetry to assess SpO₂ can accurately detect hypoxia although accuracy
 is reduced when SpO₂ is <90 % and in patients with hemodynamic instability,
 arrhythmias, hypothermia, peripheral vasoconstriction, darker skin or anemia
 (low quality of evidence).
- Optimal target values for systemic oxygenation have not been established in neurocritical care patients; at present aiming for normoxemia and avoiding hypoxemia and hyperoxemia are associated with better outcomes (low quality of evidence).
- There are at present insufficient data to demonstrate that systemic oxygen monitoring helps to improve neurocritical outcome (low quality of evidence).

Systemic Carbon Dioxide Monitoring

Routine systemic carbon dioxide monitoring, ideally by intermittent PaCO₂ and continuous ETCO₂, should be considered in every neurocritical patient that is ventilated, sedated, has a decline in level of consciousness or has respiratory compromise (low quality of evidence).

- Capnometry/capnography to assess ETCO₂ can be regarded as a reliable method
 to detect hyper- or hypocapnia in most patients, but is not equivalent to ABGderived PaCO₂ in all patients (e.g., in increased alveolar dead space); and so use
 of ETCO₂ should be validated against PaCO₂ (low quality of evidence).
- Monitoring of systemic CO₂ by PaCO₂ or ETCO₂ is a valuable aid to confirm
 correct tube positioning after intubation, to detect hypo- and hyperventilation,
 and to guide ventilator adjustment in neurocritical patients (low quality of
 evidence).
- Monitoring systemic CO₂, e.g., to maintain normocapnia may help improve TBI and SAH patient outcome (low quality of evidence).

Cerebral Blood Flow

- 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 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).

Additional Conclusions

What Neuromonitoring Threshold Best Identifies Risk for Ischemic Injury?

An anterior circulation, specifically middle cerebral artery (MCA) transcranial
Doppler ultrasonography mean velocity threshold of 120 cm/s can be used to
stratify patients at risk for angiographic vasospasm after aneurysmal
subarachnoid hemorrhage (moderate quality of evidence).

- An anterior circulation (MCA) transcranial Doppler ultrasonography mean velocity threshold of 200 cm/s can be used to identify patients at high risk for severe angiographic vasospasm and ischemic injury after aneurysmal subarachnoid hemorrhage (high quality of evidence).
- A posterior circulation transcranial Doppler ultrasonography mean velocity threshold of 85 cm/s can be used to identify patients at risk for angiographic vasospasm and ischemic injury after aneurysmal subarachnoid hemorrhage (low quality of evidence).

Does the Use of These Neuromonitors Improve Outcome for Those Patients at Risk for Ischemic Injury?

It is reasonable to use thermal diffusion flowmetry cerebral blood flow probes to
identify ischemic risk and guide implementation of therapeutics designed to
minimize secondary injury in select ABI patients where physical examination is
limited (very low quality of evidence).

Electrophysiology

- We recommend EEG in all patients with acute brain injury 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).

Additional Conclusions

Should All Acute Ischemic Stroke Patients Undergo EEG or Continuous EEG for the Detection of Cerebral Ischemia?

• EEG does not appear to be useful to detect cerebral ischemia and target CPP in AIS patients (very low quality of evidence).

Should Scalp EEG be Included for all Patients Undergoing Invasive Brain Monitoring?

• EEG should be considered for all patients undergoing invasive brain monitoring (low quality of evidence).

Should Intracranial EEG Monitoring be Part of Invasive Brain Monitoring?

• EEG monitoring may be used as a modality of invasive brain monitoring in select patients (low quality of evidence).

Cerebral Metabolism

- 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).

Additional Conclusions

Can Brain Chemistry be Used to Predict Clinical Outcome in Patients with Traumatic Brain Injury?

 Cerebral microdialysis may be used as a supplemental tool with other clinical indicators for clinical prognostication after acute traumatic brain injury (moderate quality of evidence).

Can Brain Chemistry be Used to Predict Clinical Outcome in Patients with Subarachnoid Hemorrhage?

 Cerebral microdialysis monitoring may be used with other clinical indicators in subarachnoid hemorrhage patients to help estimate clinical prognosis (low quality of evidence).

Can Brain Chemistry Measured by Cerebral Microdialysis be Used to Guide the Administration of Insulin?

 Cerebral microdialysis may be used to help guide systemic glycemic control, specifically to avoid cerebral hypoglycorrhachia (moderate quality of evidence).

Can Brain Chemistry be Used to Guide the Clinical Use of Therapeutic Hyperoxia or Hyperventilation?

 Cerebral microdialysis may help guide the application of therapeutic hyperoxia and hyperventilation to determine if the applied therapies result in normalization of abnormal metabolite values (very low quality of evidence).

Can Brain Chemistry be Used to Predict Secondary Deterioration in Patients with SAH?

• Cerebral microdialysis may be used to identify patients at risk for – or help diagnose delayed cerebral ischemia after SAH (moderate quality of evidence).

Can Brain Chemistry be Used to Predict Intracranial Hypertension in Patients with Traumatic Brain Injury?

• Cerebral microdialysis may be used early after TBI to predict which patients may develop elevated ICP (low quality of evidence).

Where Should Cerebral Microdialysis Probes be Placed?

• The location of cerebral microdialysis monitoring should be carefully selected to address the clinical question at hand, and may appropriately be in normal, perilesional or penumbral tissue; however, the information should be interpreted based on probe location identified on a post-insertion imaging study (moderate quality of evidence).

Glucose and Nutrition

Recommendations (and See Summary Statement)

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).

Additional Conclusions

With What Frequency or For How Long Should Blood Glucose be Monitored After Brain Injury?

• A specific frequency or duration for blood glucose monitoring after acute brain injury is still to be elucidated (very low quality of evidence).

Is There an Optimal Point of Care Testing Method that Should be Utilized for Setting Glycemic Targets?

- POC arterial blood testing is more accurate for monitoring blood glucose levels than POC capillary blood testing (low quality of evidence).
- POC testing during episodes of hypoglycemia or low perfusion states should be verified by central laboratory glucose measurement (low quality of evidence).

Hemostasis and Hemoglobin

Recommendations (and See Summary Statement)

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

- 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).

Additional Conclusions

 Serum pro-calcitonin may be helpful in discriminating EVD infection from noninfectious inflammation (very low quality of evidence).

Cellular Damage and Degeneration

Recommendations (and See Summary Statement)

- 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).
- We recommend against the routine use of molecular biomarkers for outcome prognostication in AIS, SAH, ICH, or TBI (strong recommendation, low quality of evidence).

Additional Conclusions

- Routine use of CSF biomarkers for prognostication in comatose post-cardiac hypoxic-ischemic encephalopathy (HIE) patients not treated with TH does not appear to provide valuable information (low quality of evidence).
- There is a limited role for routine use of blood or CSF molecular biomarkers to predict vasospasm and DCI in SAH (low quality of evidence).
- Plasma MMP-9 and c-Fn can be used in conjunction with clinical data to support
 prediction of hemorrhagic transformation in AIS patients treated with IV tPA
 within 3 h of onset (low quality of evidence).
- Routine use of molecular biomarkers does not help predict secondary deterioration after ICH or TBI (low quality of evidence).

ICU Processes of Care and Quality Assurance

Recommendations (and See Summary Statement)

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 Recommendations (and See Summary Statement)

- 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 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 intensive care unit to help address alarm fatigue (strong recommendation, low quality of evidence).

Additional Conclusions

Should Data from Specific Time Epochs of Clinical Interest be Reviewable to Improve Clinician Understanding of Patient Status?

 Data from specific time epochs of clinical interest should be reviewable by the clinician. The clinician is advised to work with data collection vendors to enable this feature (low quality of evidence).

Should Classical Statistical Methods (e.g., Mean, Variance, Correlation) and/or Advanced Analytic Methods (e.g., Signal Processing, Complex Systems Analysis) Methods be Applied to Physiological Data to Improve Clinician Understanding of Patient Status?

• A wide range of linear and nonlinear analytical methods should be applied to examine physiological data (moderate quality of evidence).

What Type of Data Should be Collected?

Collecting and archiving physiologic data (waveform signals and numeric data)
and phenotypic data (lab results, imaging, nursing notes) in a comprehensive data
warehouse is the crucial first step toward information management (low quality
of evidence).

At What Frequency Should Physiologic Data be Collected?

 Physiologic data should be collected at the highest possible frequency (low quality of evidence).

In What Format Should Data be Stored?

 All high-resolution physiological data should be stored in a non-relational open database format (low quality of evidence).

Is a Distributed Data Whole ICU Collection System or Kiosk-Type Cart that Moves Room to Room Better for Data Acquisition?

There are advantages and disadvantages to each approach and what is used will
depend on the specifications and needs of the intensive care unit (low quality of
evidence).

Should Data Monitoring be Centralized using Telemedicine Technology Such That One or Two Dedicated Clinicians Monitor Multiple Patients to detect problems?

• The infrastructure required for telemedicine is similar to what is needed in general and so ICUs should invest in an informatics infrastructure that supports care delivery whether the clinician is 3,000 miles away or 3 feet away from the patient (low quality of evidence).

What Parameters Should Devices Transmit?

Device manufacturers should enable devices to transmit all parameters that the
device generates including non-proprietary device status parameters to improve
clinical usability of its data (low quality of evidence).

At What Frequency Should Devices Transmit Data?

• Device manufacturers should provide data at the highest frequency generated by the device (low quality of evidence).

Should Devices Output Summary Measurements (e.g., Average Values) of its Measurements?

• Device manufacturers should provide raw measurements first and foremost, but also provide summary measurements as needed (low quality of evidence).

Monitoring in Emerging Economies

- 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).

References

1. Le Roux P, Menon DK, Citerio G, Vespa P, Bader MK, Brophy GM, Diringer MN, Stocchetti N, Videtta W, Armonda R, Badjatia N, Böesel J, Chesnut R, Chou S, Claassen J, Czosnyka M, De Georgia M, Figaji A, Fugate J, Helbok R, Horowitz D, Hutchinson P, Kumar M, McNett M, Miller C, Naidech A, Oddo M, Olson D, O'Phelan K, Provencio JJ, Puppo C, Riker R, Robertson C, Schmidt M, Taccone F. 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. Neurocrit Care. 2014. doi:10.1007/s12028-014-0041-5.

- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;2009(339):b2535.
- 3. Jaeschke R, Guyatt GH, Dellinger P, et al. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. BMJ. 2008;337:a744. [PubMed: 18669566]
- 4. Rochwerg B, Alhazzani W, Jaeschke R. Clinical meaning of the GRADE rules. Intensive Care Med. 2014;40(6):877–9. [PubMed: 24667920]
- Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, Rind D, Montori VM, Brito JP, Norris S, Elbarbary M, Post P, Nasser M, Shukla V, Jaeschke R, Brozek J, Djulbegovic B, Guyatt G. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726–35. [PubMed: 23570745]