



## Proceedings from the Neurotherapeutics Symposium on Neurological Emergencies: Shaping the Future of Neurocritical Care

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PROCEEDINGS



# Proceedings from the Neurotherapeutics Symposium on Neurological Emergencies: Shaping the Future of Neurocritical Care

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## Abstract

Effective treatment options for patients with life-threatening neurological disorders are limited. To address this unmet need, high-impact translational research is essential for the advancement and development of novel therapeutic approaches in neurocritical care. “The Neurotherapeutics Symposium 2019—Neurological Emergencies” conference, held in Rochester, New York, in June 2019, was designed to accelerate translation of neurocritical care research via transdisciplinary team science and diversity enhancement. Diversity excellence in the neuroscience workforce brings innovative and creative perspectives, and team science broadens the scientific approach by incorporating views from multiple stakeholders. Both are essential components needed to address complex scientific questions. Underrepresented minorities and women were involved in the organization of the conference and accounted for 30–40% of speakers, moderators, and attendees. Participants represented a diverse group of stakeholders committed to translational research. Topics discussed at the conference included acute ischemic and hemorrhagic strokes, neurogenic respiratory dysregulation, seizures and status epilepticus, brain telemetry, neuroprognostication, disorders of consciousness, and multimodal monitoring. In these proceedings, we summarize the topics covered at the conference and suggest the groundwork for future high-yield research in neurologic emergencies.

**Keywords:** Conference proceedings, Diversity excellence, Team science, Translational research, Neurocritical care

## Introduction

High-impact translational research is essential for the development of novel therapeutic approaches in neurocritical care. Although it is well known that diversity improves productivity in team science [1–4], there is still a prominent imbalance in the representation of diverse backgrounds and gender in the neuroscience

workforce [5–7] and in scientific conferences [6, 8]. “The Neurotherapeutics Symposium 2019—Neurological Emergencies” was designed to address these challenges by creating a platform to facilitate the discussion of innovative translational approaches in acute neurologic illnesses, while specifically seeking the participation of women and underrepresented minorities in the conference planning and development processes. This 2-day conference was co-hosted by the University of Florida and University of Rochester and was funded by NINDS (R13 NS11956-01), the McKnight Brain Institute, and industry (detailed support is listed under

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funding section); no funding party provided input in the development of scientific content of the conference or in the proceedings. The symposium was endorsed by the Neurocritical Care Society and adds to the efforts promoting inclusion in the Neurocritical Care Research Network conferences [9]. A total of 90 participants from 25 institutions attended the conference, including 30 from under represented groups, and 42 women. The conference was comprised of 16 lectures, 6 discussion sessions, 2 workshops, a guided poster session, and 4 networking dinner/lunch gatherings. Each lecture was followed by interactive group sessions termed “Looking into the Future,” which sourced participants for next steps in the translational process and were facilitated by pairs of early and established investigators. Opportunities for mentoring and networking between scientists at various career stages were weaved into the curriculum throughout the conference. Digital technology, using an electronic conference ‘app,’ also promoted networking among attendees, while hosting a digital repository of e-posters, online discussions, and links to relevant manuscripts.

Another hallmark of the conference was the transdisciplinary participation of scientists from diverse backgrounds, including clinician-scientists, neuroscientists, bioengineers, rehabilitation experts, and trainees. Discussion topics within the conference included: early career development, funding strategies, diversity/team building, epilepsy and status epilepticus, neurotrauma, hypoxic pre-conditioning and neuroplasticity, cerebral edema and secondary brain injury, precision medicine in neurocritical care, neuroprognostication, advanced signal processing of neurophysiologic tests, disorders of consciousness, and neurogenic respiratory dysregulation.

We believe that facilitating such collaborative research has the potential to contribute to the development of long-term networking resources that nurture diversity in team science. Targeted fostering has shown initial success in an example of a women science database [10]. The talent represented by the high proportion of participants in this symposium from under represented groups, extended an opportunity to foster long-lasting mentorship relationships and career building for early career investigators. This is especially important as data support a persistent gap in racial and ethnic representation in the medical education pipeline [11]. Further, while the number of scholars of under represented background has grown, reflecting the establishment of an effective pipeline, attrition throughout their careers remains a significant factor that challenges the sustainability of inclusion efforts; this is supported by the lower proportion of grant funding and awards among these groups [7, 12, 13]. Our

goals were aligned with the Neurocritical Care Society’s stated goals for Diversity, Equity & Inclusion [14].

In addition to reviewing the discussed content, we provide a blueprint to shape the future directions of neurocritical care research focused on novel therapeutics. An executive summary of the conference proceedings is shown in Table 1. In the following sections, we summarize the key topics discussed in the conference, including disease-specific future directions for collaborative research.

### **Strategies for Promoting Success in New Research Initiatives in Neurocritical Care Through Team Science, Diversity, and Novel Funding Mechanisms**

The complexities and multifaceted sequela of neurological emergencies require novel strategies for scientific progress and the development of ground breaking therapies with the potential to change outcomes and mitigate disability. In the current era of advanced subspecialties, such as neurocritical care, transdisciplinary teams are critical for health care team functioning [1], as well as scientific discovery and translational research pursuits [2]. Capitalizing on the greater synergistic gains of team science will be an important asset in neurocritical care research. Transdisciplinary team science research often develops in phases, which are summarized in Table 2 [15]. Each phase has its own importance and function in a successful program. The impact of transdisciplinary team science engagement includes cross-disciplinary collaboration, work environments with positive team climate—a perceived set of norms, expectations, and attitudes of a team—[16], and novel approaches to conducting, analyzing, and disseminating research [15–17].

Transdisciplinary teams include members with resourcefulness, strong delegation skills, diverse backgrounds, and trust in the process of multidisciplinary collaboration. The latter includes the establishment of psychological safety: the notion of standing up to speak on bold concepts, without fear of retaliation or negative repercussions. Diverse teams are also more likely to resolve complex problems [16, 18]. Having team members from diverse backgrounds may be an effective way of altering behaviors of a social majority group and ultimately lead to more accurate group thinking, as diverse groups have an increased tendency to focus on facts and are less likely to make factual errors [19–21]. In addition to bringing more objectivity to the decision-making process and brainstorming activities [20], diverse teams are also more likely to explore novel approaches to problems [21, 22]. Diversity challenges conformity [23], and the resulting innovation and deeper information processing may enrich the potential of scientific progress [24]. Another important aspect of inclusive team science is

**Table 1 Future directions from the Neurotherapeutics Symposium 2019—Neurological Emergencies****Executive summary***Strategies for Promoting Success in New Research Initiatives Through Team Science, Diversity, and Novel Funding Mechanisms*

Intensify efforts in maintaining adequate representation of all stakeholders and backgrounds in future conference planning, speakers and attendees

Develop funding mechanisms that promote and facilitate team science approach

Expand the use of crowdsourcing funding mechanisms and advertisement of project campaigns across survivors and caregivers groups

Leverage the infrastructure provided by Strategies to Innovate Emergency Care Research Network (SIREN) with ancillary (“add-on”) study proposals to major ongoing clinical trials

Harmonization of multiple parametric data in future studies and creation of a centralized repository of curated data from clinical trials

*Stroke and Cerebrovascular Disease*

Work toward expanding evidence of safety within a broader eligibility criteria for reperfusion therapy in acute ischemic stroke

Optimization of systems of care for expeditious triage (imaging and clinical assessments) involving first responders, neurologists, radiologists, neurointerventionalists, and emergency medicine providers

Development of adjunctive therapies addressing secondary brain injury mechanisms that can be modulated by interventions targeting spreading depolarization, cerebral edema, white matter tract injury, seizures, and inflammation

*Therapeutic Intermittent Hypoxia and Neuroplasticity in Neurogenic Respiratory Dysregulation*

Refinement of acute intermittent hypoxia therapeutic protocols based on the weight of hypoxia depth and burden in competing mechanisms involved in neuroplasticity

Combination of acute intermittent hypoxia with pharmacologic modulation of adenosine- and/or serotonin-mediated pathways, with inflammation-targeted strategies

Refinement of acute intermittent hypoxia delivery and monitoring methods

*Brain Telemetry, Seizure Detection and Management in the Critically Ill*

Optimization of systems of care bypassing the lack of local critical care encephalography expertise, and capitalizing on the use of remote continuous EEG monitoring services

Automatic seizure detectors and real-time alarms using quantitative EEG should be developed and validated to expedite timely and accurate review

Expansion and refinement of continuous EEG use as well as standardization of algorithms for ischemia monitoring and brain dysfunction to direct individual hemodynamic goals

Expansion of status epilepticus international registries to overcome the challenges of examining patients with heterogeneity of disease processes

Expansion of antiseizure treatment algorithms to include nutritional therapies (ketogenic diet) and tailored immunomodulation

*Outcome Prediction in Disorders of Consciousness, Cognition, and Sepsis*

Objective characterization of gaps of knowledge and methodologic flaws in neuroprognostic studies

Unveiling endotypes using multimodality assessment of cerebral reserve and resilience coupled with longitudinal trajectories following critical illness

*Multimodal Monitoring (MMM) in the Neurocritically Ill*

Adaptation of strategies to show cost-effectiveness for multimodal monitoring, implement broadly applicable settings where possible, targeting overall clinical performance rather than single datapoints, and integrating various MMM elements and temporal trends

Incorporate standardized treatment algorithms, and assess their performance, in studies exploring the value of MMM

**Table 2 Phases of Team Science for Translational Research****Phases of Team Science [1, 2]**

Developmental phase—assembling team and developing roles

Conceptualization phase—developing a hypotheses framework and scientific approach

Implementation phase—conducting the research

Translational phase—collaborating to apply results to clinical trial study development

that diverse faculty members are more likely to engage in research aimed at reducing disparities in neurologic outcomes and spend more time mentoring diverse students and trainees [25, 26]. The Curing Coma Campaign, launched during the Neurocritical Care Society Annual Meeting in 2019, reflects the Neurocritical Care Society efforts in the establishment of longitudinal collaborations in a team science with the mission of addressing

disorders of consciousness and promoting awakening [27]. Nurturing diverse, early-career scholars, and trainees from under represented backgrounds is a crucial step to achieve inclusion excellence in neuroscience, as these promising scientists have the potential to become leaders in academic research and inspire future generations to explore innovative pathways to treat neurologic disorders. The Neurocritical Care Society’s Women in

Neurocritical Care (WINCC) section demonstrates the commitment toward diversity and equity and is a powerful resource to support early career scholars.

Several studies have demonstrated that knowledge gaps and lack of exposure to racially and ethnically diverse groups, as well as sexual and gender minorities, may lead to barriers in access to clinical care for disadvantaged populations. This may stem from unconscious decisions influenced by the implicit biases of providers [3, 4, 28] or system biases that limit accessibility for diverse populations. Neurodisparity is defined as the effect of disparities in neurologic care; [3] it does not only refer to barriers contributed by race and/or ethnicity, but includes disparities influenced by: sex, gender [7], age, neurodiversity, sexual orientation, religion, geographic origin, disability, weight, incarceration, and other social demographic factors [3]. For example, several publications highlight disparities in representation in the American Academy of Neurology recognition awards and of women in leadership roles in neurology [5, 6]. Neurocritical care, as a burgeoning discipline, is ripe to lead initiatives to increase awareness of knowledge gaps that will address the needs of diverse patient populations and foster adequate representation in clinical leadership and the neuroscience workforce.

Expanding funding mechanisms is essential to support diverse team science efforts [29]. Under represented groups have been reported to receive less support for research funding [13]. Also, the research funds that are provided are more likely to be limited to research topics that pertain to health disparities, disease prevention and intervention, socioeconomic factors, healthcare, lifestyle, psychosocial, adolescence, and risk management [26]. Specifically, funding was less likely to be awarded if these terms were used in comparison with studies that focused on topics linked to neuron, corneal, cell, and iron [26]. Several funding sources were discussed at the conference. Crowdfunding mechanisms are emerging funding opportunities that bring flexibility to support innovative scientific efforts while promoting a platform that bridges investigators and donors; the American Brain Foundation (ABF) Crowdfunding Grant Mechanism (<https://www.americanbrainfoundation.org/projects/>) is the first neuroscience crowdfunding platform and has received nearly 150 donations and funded 8 projects (as of 2019). The National Institute of Health (NIH) Strategies to Innovate Emergency Care Research Network (SIREN) [30] represents a new network established in 2017 with 11 regional centers and 50 satellite research sites, aimed to develop acute neurological emergency research across the disciplines of Neurology, Neurosurgery, Emergency Medicine and Critical Care, and leverage this infrastructure to support multicenter randomized clinical trials (RCT). This

multidisciplinary approach to clinical trials in the study of status epilepticus [31, 32] and stroke [33–35] have led to the identification of successful interventions. The Neurocritical Care Society has supported a growing grant funding portfolio that reflects its transdisciplinary mission and includes the Research Training—a 12-month research fellowship for physicians, nurses, scientists, advanced practitioners, among other specialties—and the INvesting in CLINical Neurocritical CarE Research (INCLINE) grant, which fosters multicenter outcome-focused research. The Neurocritical Care Research Central (NCRC) was developed to streamline research efforts within members of the Neurocritical Care Society. The Neurocritical Care Research Network (NCRN)—a subcommittee of the NCRC—was developed with the goal of bringing together a cohesive group of established researchers to facilitate successful implementation of patient-oriented research.

Further, efforts in harmonizing data collection in future trials of acute brain injuries, including curated multiple parametric and imaging data repositories, are urgently needed to facilitate subsequent data analyses and cohort discovery across populations.

### **Disease-Specific Knowledge Gaps and Future Directions**

The following represents a summary of topics discussed during the conference. Due to the nature of its format as a live conference with interactive presentations and critical debates, this summary highlights the major points of discussion and perceived future directions of research proposed by the Neurotherapeutics Symposium 2019 attendees.

#### **Stroke and Cerebrovascular Diseases**

Major advances in the treatment of ischemic stroke secondary to large-vessel occlusion have led to improved outcomes [33–35]. Patient selection mediated through advanced neuroimaging has expanded the eligibility of reperfusion therapies for patients outside the conventional treatment windows or with an unknown last-known-well time [36–38]. Novel strategies in stroke emphasize the role of neuroimaging to elucidate contributing mechanisms for neurologic recovery and further guide patient selection for acute therapy.

The current patient selection criteria for endovascular thrombectomy (EVT)—particularly late-window—are relatively strict, which deprives a significant proportion of patients from targeted revascularization [39]. Decision-making in acute therapy relies on the defined inclusion criteria from clinical trials. This may be best epitomized by decisions regarding EVT, which is dictated in large part by factors including time from symptom onset, the



presence of preexisting disability, and ischemic core volume estimates. The positive early- and late-windows EVT trials relied on neuroimaging markers for patient selection that varied in complexity from CT head and angiography (MR CLEAN [40]) and target mismatch on perfusion imaging (SWIFT PRIME [41] and DEFUSE-3 [34]). A relatively large ischemic burden reflected by Alberta Stroke Program Early CT Score (ASPECTS) scores of 5 or 6 is often used as a reason to not proceed with EVT within 6 h of last known well, though in some cases this score could reflect injury to areas of the brain that are less eloquent, and therefore, less likely to portend a poor outcome. Other limitations of using imaging as a strict criterion for therapy eligibility include early diffusion weighted image (DWI) reversibility [42–44] and CT perfusion “ghost” core [45]. Similarly, the presence of preexisting disability (e.g., inability to ambulate independently) is often used as an exclusion, yet providers should interpret preexisting disability from the perspective of the individual patient, not as an immutable construct. A paradigm shift was proposed, especially for the early window (<6 h), where considerations should be made to explore individualized decision-making such that the pool for those whom may benefit can be broadened. The goal would be to continue research efforts to determine which patients not included in published randomized control trials may still benefit from EVT without increasing the risk of harm.

Beyond reperfusion therapies, stroke-related therapeutics must expand to target white matter disease and cytotoxic edema pathways, and provide biologic biomarkers for patient individualized therapies [46, 47]. Premorbid white matter structural injury of presumed vascular origin can be characterized on MRI by diffusion tensor imaging (DTI) and inform functional outcomes [48, 49]. The characterization of white matter structural integrity could allow for a precision medicine-based prognostication and stroke outcome modeling, advancing knowledge on the critical white matter tracts involved in stroke recovery, increasing patient enrichment for clinical trials design, and potentially, leading to the future development of novel therapeutics. There are multiple ongoing early phase clinical trials testing lifestyle, behavior, and pharmacologic interventions aimed at reducing progression of white matter injury and cerebral small vessel disease [50].

Pathways leading to cytotoxic edema after stroke represent another target for novel therapeutics with promising findings in pre-clinical and early clinical trials. Glyburide—an inhibitor of the ATP-sensitive potassium channel regulatory subunit sulfonylurea receptor 1—is an emerging therapy with favorable results on metrics of edema in the phase II RCT of hemispheric strokes (GAMES-RP

[51, 52]). A phase III RCT testing the efficacy and safety of glyburide for severe cerebral edema after large hemispheric infarction (CHARM) has commenced enrollment (ClinicalTrials.gov Identifier: NCT02864953). This cytotoxic edema mechanism is probably shared by other acute brain injuries, and its modulation may represent a therapy with a role beyond acute ischemic stroke.

Deepening the understanding of mechanisms underpinning secondary brain injury in cerebrovascular disease is another important step toward neurotherapeutics. Cortical spreading depolarization and depression—self-propagating waves of near complete breakdown of ion gradient homeostasis—is a potential mechanism of secondary injury in traumatic brain injury, acute ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage (SAH) often triggered by extravasation of blood, trauma or focal ischemia [53]; however, a direct causal relationship remains to be demonstrated [54]. While the modulation of spreading depolarization as a potential therapeutic target in cerebrovascular diseases seems feasible given the wide range of available drugs that suppress its occurrence, there are important barriers to be overcome. There are no reliable noninvasive methods for spreading depolarization detection with high temporal resolution, and neurophysiologic invasive monitoring—the gold standard—has limited spatial resolution and requires violation of the cranial vault. In another angle, a novel filtration system (termed neuroapheresis) designed to rapidly remove blood and blood byproducts from cerebral spinal fluid in patients with SAH tackles the hypothesis that blood breakdown products in SAH are detrimental to outcomes. The feasibility study on this system has demonstrated that an automated lumbar catheter system can safely filter cerebral spinal fluid and remove blood byproducts [55], and may be associated with a positive impact in neuroinflammation.

These parallel avenues of translational research seek to improve long-term outcomes after cerebrovascular diseases through novel neurotherapeutics. Harmonizing existing clinical databases and standardizing neuroimaging and neurophysiology interpretations for the purpose of inter-institutional collaborations sharing advanced expertise (such as the application of machine learning to big datasets) will facilitate these efforts [46].

#### **Intermittent Hypoxia and Neuroplasticity in Neurogenic Respiratory Dysregulation**

Chronic respiratory failure is a common and extremely disabling complication of motor neuron disease and cervical spinal cord injury [56], rendering patients dependent on mechanical ventilation and prone to have respiratory tract infections. The mechanisms underlying respiratory motor neuron plasticity and resilience

to injury remain poorly understood, hindering advancement in neurotherapeutics focused on respiratory function rehabilitation [57].

Ischemic preconditioning through acute intermittent hypoxia (AIH) is a promising therapy with potential to prevent respiratory deconditioning and enhance rehabilitation in chronic respiratory failure [58, 59]. AIH promotes phrenic nerve long-term facilitation through carotid chemoreceptors and raphe nuclei modulation [57]. Respiratory motor neuron plasticity is mediated by balancing 5-HT receptor activation and adenosine (A2A) receptor antagonism at different levels of hypoxia depth and duration [60, 61]. The induction and maintenance of AIH follow different signaling pathways that allow for long-lasting phrenic motor facilitation to take place. In this context, 5-HT and A2A receptors can have both favorable and deleterious effects for neuron plasticity depending on the degree of activation or antagonism of these receptors. Serotonin can enhance synaptic transmission in motor neurons, while adenosine can be neurotoxic for phrenic motor neurons. Promising preliminary findings in human studies using AIH include improvement in exercise endurance by athletes and respiratory mechanics in patients who are ventilator dependent and had a phrenic diaphragm pacemaker (increase in maximal inspiratory pressure) [59, 62, 63]. Interestingly, increased muscle strength was not seen exclusively in diaphragmatic muscles in patients with chronic spinal cord injury. Forelimb function and walking ability were also improved when AIH was added to standard rehabilitation exercises [64]. These effects were dose dependent and varied according to the fraction of inspired oxygen level and number of AIH cycles per day.

These translational and pilot human studies highlight the complexity of the biological mechanisms involved in neuroplasticity. The high variability in respiratory mechanics improvement depending on AIH methods, and the depth and duration of hypoxic events, support the hypothesis that respiratory motor neuron plasticity relies on balancing several and often competing pathways. These methods can have beneficial, but also pathologic consequences to patients; therefore, the refinement of AIH therapies in future studies is imperative. Biomarkers of short-term and long-term respiratory function will be fundamental to guide the delivery and monitoring of these therapies. Future studies should combine AIH strategies with pharmacological interventions, such as adenosine antagonism with caffeine or autoinflammatory modulation with corticosteroids—an approach with the potential to enhance the already promising results of AIH in motor neuron disease and spinal cord injury.

### **Brain Telemetry, Seizure Detection and Management in the Critically Ill**

Continuous electroencephalography (cEEG) is an integral part of the evaluation of critically ill patients with encephalopathy as nonconvulsive seizures are common in the critically ill and may negatively impact outcomes [65, 66]. A cross-sectional analysis using the National Inpatient Sample database including over 7 million critically ill patients, 22,728 of whom underwent cEEG, suggested a positive impact of continuous monitoring on mortality in the subset of patients with intracerebral hemorrhage, SAH and those with encephalopathy, which may offset the increased cost of hospitalization associated with monitoring [67]. Recent studies indicate that epileptiform activity on EEG combined with changes in quantitative EEG measures, such as reduced alpha–delta ratio and relative alpha variability, can detect ischemia earlier than conventional modalities in patients with SAH [68, 69]. Despite these emerging benefits of cEEG beyond seizure detection, this tool is still under-utilized. Potential barriers to the expansion of its use as a brain telemetry instrument include the lack of resources for cEEG acquisition equipment and data storage, limited availability of trained EEG technologists, lack of experts in ICU EEG interpretation to provide timely review of the EEG to be meaningful to bedside clinicians, and the variability in interpretation of abnormal findings, and therapeutic management strategies.

Status epilepticus (SE) is a common neurologic emergency. Over the last decade, the role of pro-inflammatory mediators in seizure generation and propagation, and the search for novel therapeutic anti-inflammatory targets have been areas of intense research. Novel tailored immunotherapies targeting specific cytokines (e.g., interleukin-1 receptor antagonist—anakinra, and interleukin-6 receptor inhibitor—tocilizumab) have been shown to be effective in new-onset refractory status epilepticus (NORSE) and febrile-infection related epilepsy syndrome (FIRES) [70, 71]. In addition, the expansion of ketogenic diet to the critical care setting has been demonstrated to be feasible and effective with success rates in weaning anesthetics without recurrence of SE surpassing 70%, even when after 420 days from SE onset [72–74]. While these emerging therapies are promising novel treatment options, there remains a paucity of randomized controlled trials showing definitive safety, feasibility, and efficacy. Challenges that were identified as a first step in moving the needle toward the development of new treatment strategies and conducting clinical trials include: the heterogeneity of SE etiologies, lack of standardization of treatment protocols, and variations in the selected outcomes.

### **Outcome Prediction in Disorders of Consciousness, Cognition, and Sepsis**

Impairment in consciousness and cognition can occur in the setting of a primary neurologic disease (e.g., hypoxic-ischemic, hemorrhagic, or traumatic brain injury), or as a consequence of a systemic insult (e.g., toxic, metabolic, and/or infectious processes). Invariably, an interplay of multiple factors concurrently contributes to the development of encephalopathy. As a result, predicting the short- and long-term consequences of impaired consciousness and cognition remains a challenge, in which the self-fulfilling prophecy bias of premature pessimistic outcome predictions plays an important role [75, 76]. Key disease-specific knowledge gaps in neuroprognostication have been recently unveiled in a joint statement from the German Neurocritical Care Society and the Neurocritical Care Society [77]; future studies should account for these limitations. Population-derived disease severity scores are incorrectly used to ascertain long-term individual prognostic trajectories. Further, these scores are not dynamic and are frequently inaccurate. Accurate neuroprognostication is crucial to guide critical care resource allocation and to guide families in goals of care discussions; thus, it is imperative to improve tools for prognostication in neurocritically ill patients. cEEG monitoring provides dynamic information on brain physiology, and it can be used as a noninvasive biomarker that correlates with level of consciousness [78] and neurological recovery [79]. Machine learning has been demonstrated to be a promising tool to analyze EEG data and unveil patients with preserved awareness by means of electroencephalographic activation in patients with acute brain injury [78]. This state known as “cognitive motor dissociation” was previously demonstrated in chronically unresponsive patients [80], and more recently in acute brain injury [78, 81]. Similarly, the use of machine learning and quantitative analysis of longitudinal EEG signals shows promise in improving accuracy of commonly employed neurophysiologic predictors of outcome after cardiac arrest, such as background reactivity, epileptiform activity, and background continuity [79, 82].

Our understanding of the pathophysiology behind sepsis-associated encephalopathy (SAE) remains limited and is another area of much needed research in neurocritical care given the long-term disability associated with persistent cognitive deficits [83, 84]. A complex interplay of factors is involved in SAE pathophysiology and includes the release of damage associated molecular pattern (DAMP) molecules as potent activators of the innate immune system leading to the release of neuroinflammatory cytokines, which cause disruption of the brain blood barrier, activation of endothelial cells, mitochondrial dysfunction, cellular hypoxia, impaired

brain perfusion regulation, and apoptosis [85]. Methods to quantify the degree of neuronal injury associated with sepsis are urgently needed to characterize the spectrum of SAE, identify potential targeted therapies, and tailor rehabilitation. Chemical biomarkers of neuronal injury, such as serum neuron specific enolase (NSE), S-100 B and neurofilament (Nf), glial fibrillary acidic protein (GFAP), co-peptin, tau, and ubiquitin C-terminal hydrolase L1 (UCH-L1), are currently being investigated to fulfill this role (ClinicalTrials.gov Identifier: NCT03133208). In addition, there might be an association between elevations of certain biomarkers with specific microbiota. Currently, laboratory tests that can be ordered clinically are still not widely available at every institution and often may not result for several days to weeks, limiting its applicability in clinical practice.

### **Multimodal Monitoring (MMM) in the Neurocritical Care Unit**

Multimodal monitoring in neurocritical care includes, but is not limited to, cEEG, intracranial pressure (ICP) monitoring, and measurement of cerebral blood flow surrogates, cerebral oxygenation, and cerebral microdialysis. The employment of MMM is mainly targeted to detect factors associated with the development of secondary brain injury, often as a result of bioenergetic failure, and monitor responses to targeted therapies. Various MMM subtypes aim to evaluate tissue function by assessing individual measures of metabolism, blood supply, or oxygenation. Further, MMM allows for the reliable detection of spreading depolarizations and their metabolic toll in cerebral tissue. For each parameter being assessed by MMM, there are several drawbacks that limit the expansion of this modality in clinical practice. Targeting individual values from MMM is unlikely to improve clinical outcomes in isolation. The assessment of average values may miss transient changes that, cumulatively, may result in a higher injury burden. The lack of integral data analysis precludes the incorporation of time in relation to the brain injury and the duration of secondary insults. Additionally, not accounting for individual resilience to insults, and the morbidity of certain therapies (e.g., increased sedation or the use of vasopressors for hemodynamic augmentation), challenges the ability of MMM to demonstrate a positive impact in clinical outcomes.

### **Conclusions**

The Neurotherapeutics Symposium 2019 included a transdisciplinary participation of scholars from diverse backgrounds, research interest and fields, and subspecialty focus. The conference highlighted the perceived clinically relevant research needs in various acute brain injuries and outlined future strategies on how to expand



upon them while incorporating diversity and team science. We hope this format will also encourage continued mentorship and career building for early career investigators to help support and sustain a forward feeding pipeline of women and under represented minorities to advance translational research in neurologic emergencies. A focus on strong research networks, streamlined data sharing practices, and support for early investigators will increase the likelihood of important discoveries.

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