Clinical Guidelines for Routine Neuromonitoring in Neonatal and Pediatric Patients Supported on Extracorporeal Membrane Oxygenation

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Disclaimer: These guidelines for routine neuromonitoring in neonatal and pediatric patients supported on extracorporeal membrane oxygenation (ECMO) are intended for educational use to build the knowledge of physicians and other health professionals in assessing the conditions and managing the treatment of patients undergoing extracorporeal life support (ECLS)/ECMO and describe what are believed to be useful and safe practice for ECLS and ECMO but these are not necessarily consensus recommendations. The aim of clinical guidelines was to help clinicians to make informed decisions about their patients. However, adherence to a guideline does not guarantee a successful outcome. Healthcare professionals must make their own treatment decisions about care on a case-by-case basis, after consultation with their patients, using their clinical judgment, knowledge, and expertise. These guidelines do not take the place of physicians' and other health professionals' judgment in diagnosing and treatment of patients. These guidelines are not intended to and should not be interpreted as setting a standard of care or being deemed inclusive of all proper methods of care nor exclusive of other methods of care directed at obtaining the same results. The ultimate judgment must be made by the physician and other health professionals and the patient considering all the circumstances presented by the individual patient, and the known variability and biologic behavior of the clinical condition. These guidelines reflect the data at the time the guidelines were prepared; the results of subsequent studies or other information may cause revisions to the recommendations in these guidelines to be prudent to reflect new data, but ELSO is under no obligation to provide updates. In no event will ELSO be liable for any decision made or action taken in reliance upon the information provided through these guidelines.

Key Words: ECMO, neuromonitoring, guideline, pediatrics, neonatesFGROUPGuidelines

Neurologic injury is a major contributor to morbidity and mortality in children on extracorporeal membrane oxygenation (ECMO) support.[1–3] The incidence of neurologic complications in neonates and children on ECMO support has been reported to be between 12% and 52%.[2–5] Risk factors for neurologic injury during ECMO include underlying patient-related factors such as prematurity, lower body weight, congenital heart disease, cardiac failure, pre-ECMO cardiac arrest, acidosis, hypoxemia, hypocarbia, hypotension, and impairment of cerebral autoregulation. Mechanical risk factors related to ECMO include anticoagulation, alteration in blood flow, exposure of blood to artificial surfaces with systemic inflammatory response on initiation, nonpulsatile flow and venoarterial (VA) ECMO, and cannulation/manipulation of great vessels.[2,3,6–8] Acute neurologic injuries during ECMO include intracranial hemorrhage, hypoxic ischemic injury, ischemic stroke, cerebral edema, and seizures. Following acute neurologic injury during ECMO, 36–38% of children survive to hospital discharge.[3] A recent systematic review showed that children on ECMO support can have a wide range of short- and long-term neurologic disabilities, including motor impairment, cognitive delays, behavior abnormalities, and lower quality-of-life scores compared with age-matched normal and sick (non-ECMO) peers.[9] Neurologic disabilities increase with age, and neonatal ECMO survivors grow into their deficits and experience more motor disabilities and problems with academic achievement at an older age.[10–12] High-risk groups for neurologic injury include premature neonates, patients with extracorporeal cardiopulmonary resuscitation (ECPR) events, patients with congenital heart disease, recent cardiopulmonary bypass, cardiac arrest before and during ECMO, and patients with seizures. Timely recognition of a potentially high-risk event with adequate neuromonitoring during ECMO may lead to institution of neuroprotective measures and interventions to prevent or limit the injury.[3] Clinical neurologic examination can be difficult as many children are sedated and sometimes muscle relaxed during ECMO. Ideal neuromonitoring of neonatal and pediatric patients on ECMO support should be portable, easily accessible, cost-effective, easy to interpret, able to provide

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real-time interpretation, able to provide earlier diagnoses, and able to effectively change clinical management and improve outcomes.[13]

There is a lack of consensus about the most appropriate way for effective and reliable neuromonitoring in patients supported on ECMO.[3] Adequate neuromonitoring in patients supported on ECMO is likely to require a combination of different modalities such as neuroimaging with head ultrasound (HUS) in infants, cerebral oximetry, electroencephalography (EEG), transcranial Doppler ultrasound, plasma brain injury markers, and somatosensory evoked potentials (SSEP). A recent international survey of European ECMO centers showed significant variability in the use of different neuromonitoring modalities during and after ECMO.[14] Data on timing, frequency, and duration of monitoring using different modalities are limited to single-center observational studies and most studies only include infants.[1] Neuromonitoring methods described in this guideline are noninvasive and include neuroimaging methods such as HUS, head computed tomography (CT), transcranial Doppler, and neurophysiologic monitoring such as intermittent or continuous EEG (cEEG), SSEP, and cerebral oximetry. The aim of this clinical guideline for routine neuromonitoring in neonatal and pediatric patients supported on ECMO was to review current literature and provide guidance for healthcare professionals who manage neonatal and pediatric patients supported on ECMO.

Neuromonitoring Methods on Extracorporeal Membrane Oxygenation

Head Ultrasound

Head ultrasound should be obtained before and after ECMO initiation and can be considered daily for at least 3–5 days after cannulation in infants with abnormal HUS and high-risk infants with an open fontanel. Head ultrasound should be performed as needed in a case of clinical suspicion of neurologic injury, followed by a series of subsequent HUSs as required.

Intracranial hemorrhage and ischemic stroke can be detected by HUS in infants with an open fontanel. Head ultrasounds are portable, easy to obtain, low cost, and safe. Obtaining pre-ECMO HUS may help to establish preexisting intracranial hemorrhage, identify other abnormalities, and determine candidacy for ECMO cannulation.[13] Head ultrasound has several limitations including dependence on the skill and experience of the ultrasonographer; difficulty visualizing because of limited field of view; and inability to detect several abnormalities such as lesions in the periphery and posterior fossa, small hemorrhages, and ischemic changes.[13,15] Cerebellar hemorrhages can be difficult to identify by HUS *via* the anterior fontanel, and a transmastoid view or imaging *via* the posterior fontanel may improve the sensitivity of identifying these hemorrhages.[15] Head ultrasound findings do not always correlate with neurodevelopmental outcomes and cannot be used alone for prognostication.[13,16] Head ultrasound has high sensitivity and low specificity in detecting hemorrhages and ischemic changes.[17] Therefore, head CT is indicated for further evaluation of abnormalities found on HUS. In a recent single-center retrospective study, intra-ECMO ultrasounds detected worse injuries; however, injuries in the posterior fossa and ischemic injuries were likely to be missed when compared with post-ECMO CT/magnetic resonance imaging findings.[18] Most intracranial complications detected by HUS occur within 3–5 days of initiation of ECMO.[4,19,20] In high-risk infants and infants with abnormal initial HUS, daily HUS can be considered for 3–5 days depending on resource availability. Subsequent HUSs could be repeated every other day or based on clinical changes.

Computed Tomography Head

Head CT should be obtained in infants and children if there is a clinical concern of an acute neurologic injury or if abnormal findings are noted on other neuromonitoring modalities such as HUS or cerebral oximetry.

Acute changes in neurologic status such as changes in mental status, pupillary changes, seizures, weakness or focal neurologic deficit, vital signs changes such as changes in heart rate or blood pressure, bulging of the fontanel or cardiac arrest warrant further investigation and clinicians should consider obtaining a head CT. Approximately 23–32% of patients undergoing head CT require interventions such as a change in medical management, withdrawal of care, weaning from ECMO, or neurosurgical intervention.[21,22] A head CT is superior in detecting ischemic changes and hemorrhages when compared with HUS.[5] Although HUS is a good screening tool, head CT is the imaging modality of choice to accurately detect acute intracranial abnormalities during ECMO support.[5] A head CT should be considered within 24 hours in cardiac arrest and patients with ECPR for diagnostic purposes and to guide management.[23] Transport of patients supported on ECMO for CT scan can be logistically challenging and CT scan involves radiation exposure. Portable CT is as sensitive to detect injuries with comparable radiation exposure as standard CT. When available, portable CTs would help to avoid high-risk transports.[21]

Cerebral Oximetry

Continuous cerebral oximetry monitoring with near-infrared spectroscopy (NIRS) can be considered in all patients supported on ECMO to follow trends in cerebral tissue oxygenation. A decline in cerebral regional oxygen saturation of greater than 20% from baseline can be associated with neurologic injury and may warrant further workup.

Cerebral oximetry monitoring with NIRS has been studied in the pediatric cardiac population extensively. Few studies have been performed in patients supported on ECMO and most studies are descriptive, providing changes in regional cerebral oxygen saturation (rSO_2) without clinical correlation of neurologic injury.[1] Near-infrared spectroscopy studies on patients supported on ECMO have focused on relative and absolute changes in NIRS parameters during alterations in the ECMO flows. A multicenter, multinational survey of NIRS use in pediatric cardiac intensive care units (ICUs) showed that there was marked variability in the use of NIRS with very few centers having any protocol to guide intervention.[24] Despite this, NIRS is being increasingly used in children on mechanical circulatory support where it is believed to reflect the cerebral tissue oxygen saturation ($StcO_2$).[25] A recent prospective study with bifrontal probes showed that low mean $StcO_2$ in infants was associated with decreased survival and brain injury.[26] Likewise, another pediatric study showed a correlation of brain injury and high neuroimaging scores with loss of autoregulation

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determined by NIRS.[27] A recent pediatric retrospective study showed that a decline in rSO_2 to 50% or less and a 20% decline from baseline during ECMO was associated with unfavorable short-term neurologic decline and death.[28] Recent adult studies showed a correlation between low $StcO_2$ with mortality and brain injury.[29] Near-infrared spectroscopy is easy to use at the bedside and can be useful to monitor trends. A decline in cerebral oxygen saturation of greater than 20% from baseline from prior studies can be used as a threshold to suspect neurologic injury and further workup may be indicated.[28] More studies are required to determine interventions and changes in neurologic outcomes based on NIRS monitoring.[13]

Recent experimental studies have also evaluated multichannel NIRS and autoregulation in ECMO. A study in a small group of infants with a multichannel NIRS system (12 channels) using wavelet cross-correlation between cerebral oxyhemoglobin concentration and mean arterial pressure showed changes in cerebral autoregulation during ECMO flow changes.[30]

Electroencephalography

Continuous EEG monitoring initiation can be considered within 12–24 hours of ECMO cannulation for a duration of at least 24–48 hours. Prolonged EEG monitoring for at least 24 hours after seizure control can be considered in the presence of seizures or interictal abnormalities detected on cEEG. Intermittent EEG can be considered in resource-limited settings and extended to cEEG if there are abnormalities.

Clinical examination and detection of seizures during ECMO can be limited secondary to sedation or neuromuscular blockade. Extracorporeal membrane oxygenation support is associated with increased risk for seizures secondary to underlying risk factors such as hypoxia, hypoperfusion, acidosis, and intracranial hemorrhage. A study of the Extracorporeal Life Support Organization (ELSO) registry reported clinical seizures in 8.4% of children on ECMO support.[6] Seizures may be a risk factor for neurodevelopmental disorders, death, or severe outcome. The American Clinical Neurophysiology Society (ACNS) guidelines for adults, children, and neonates recommend cEEG monitoring during ECMO.[31,32] Most studies evaluated had intermittent EEG monitoring.[1] However, intermittent short-duration EEG monitoring can fail to detect seizures. Recent prospective and retrospective studies of cEEG in neonates and children during ECMO showed 18–23% incidence of seizures, of which 56–83% were subclinical seizures and 30–50% were status epilepticus.[33–35] The majority of seizures were detected within 24 hours[35] and approximately 75% were detected within 72 hours of ECMO cannulation.[34] Seizures during ECMO, status epilepticus in particular, are associated with unfavorable outcomes.[33] Continuous EEG monitoring used over an extended period may affect neonatal scalp integrity.[16] Very few studies evaluated amplitude-enhanced EEG (aEEG) with one to two channels in neonates and the sensitivity of aEEG to detect seizures is low.[1,16]

Doppler Ultrasound

Transcranial Doppler ultrasound as a measure of cerebral blood flow velocities (CBFVs) and pulsatility index (PI) can detect neurologic injuries; however, this has only been studied in a small group of patients supported on ECMO.

Transcranial Doppler ultrasonography is a noninvasive, portable method used to evaluate cerebral hemodynamics, including cerebral blood flow systolic, diastolic, and mean velocities and calculated PI ([systolic velocity – diastolic velocity]/mean velocity). Cerebral blood flow velocities can be measured in anterior, middle, and posterior cerebral circulation and the internal carotid artery.[36] Cerebral blood flow velocity appears to be decreased in patients supported on ECMO compared with sick and healthy control subjects and elevated after decannulation.[36–38] A prospective study in a small group (n = 18) showed that all four children who developed intracranial hemorrhage had a higher-than-normal cerebral flow velocity 2–6 days before the recognition of bleeding.[37] A recent prospective study showed increases in PI in the middle cerebral artery (MCA) in infants less than 90 days of age were predictive of ischemic injury.[38] Focal velocity elevations and velocity asymmetries were also associated with neurologic injury and were identified 1–4 days before injury.[36] Transcranial Doppler is operator-dependent and care must be taken to limit user variability during interpretation. Recently, an expert consensus guideline for the performance of transcranial Doppler in critically ill children was published to help with standardized data collection, interpretation, and reporting.[39] Larger trials are needed to establish references and differentiate venovenous and VA ECMO flow variabilities and association with outcomes.

Plasma Brain Injury Markers

Plasma brain injury markers are currently under research to detect neurologic injuries in patients supported on ECMO and are not available for rapid detection and clinical use.

Peak plasma values of brain injury markers including glial fibrillary acidic protein (GFAP), S-100 calcium-binding protein B (S-100B), neuron-specific enolase (NSE), and monocyte chemoattractant protein 1/chemokine (c-c motif) ligand 2 (MCP-1/CCL-2) have been reported to be significantly associated with an unfavorable outcome and mortality in patients with brain injury supported on ECMO.[1,40,41] S-100 calcium-binding protein B and GFAP were found to be increased 1–3 days before any signs of neurologic injury.[40] Another recent prospective observational study evaluated the combination of multiple plasma brain injury markers to increase the sensitivity and specificity for outcome prediction.[41] Some biomarkers are nonspecific markers of injury and can be elevated in other conditions such as shock and after cardiopulmonary bypass. Biomarkers can provide earlier detection of brain injury before signs of neuroimaging abnormalities and be useful in neuroprognostication. Plasma brain injury biomarkers are under investigation in ECMO populations for research; currently, there are no rapid tests available for clinical use to provide real-time interpretation and help with management and outcomes.

Somatosensory Evoked Potentials

Somatosensory evoked potential investigation studies to detect neurologic injuries are limited in patients supported on ECMO.

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Somatosensory evoked potentials may be used in children supported on ECMO to evaluate brain injury. Several studies have shown that mismatch negativity (MMN) is an auditory evoked potential (aEP) waveform with a high specificity to predict the record return of consciousness in patients in a coma from different etiologies.[42] However, it is unknown which characteristics of the MMN (*i.e.*, latency and amplitude) would be associated with a complete functional recovery. Recording of MMN early in the course of coma can predict awakening and the extended absence of certain waves in the brainstem aEPs suggests poor prognosis.[42] Absence of SSEP has been shown to identify poor neurologic outcomes in patients who had a history of cardiac arrest[43]; however, evidence for the usage of MMN and aEP in patients supported on ECMO is limited to several case reports.

Pupillometry

Automated pupillometry studies for neuromonitoring are limited in pediatric patients supported on ECMO.

Automated infrared pupillometers measure pupillary size and reactivity and are being used increasingly in ICUs. A recent single-center prospective study was performed in pediatric patients with brain injury under intracranial monitoring and pupillary reactivity was measured with neurologic pupil index (NPi). The study showed decrease in NPi was associated with increased intracranial pressure (ICP), but temporal association preceding elevated ICP was not consistently observed.[44] A recent adult single-center prospective study in patients supported on ECMO cannulated for refractory cardiac arrest and refractory cardiogenic shock showed NPi as a good neuroprognostication tool to predict mortality outcomes. Patients who died due to neurologic injury consistently had abnormal NPi.[45] Larger studies are required to study the correlation between brain injury and value as a neuromonitoring tool in pediatric patients supported on ECMO.

Combination Modalities

Combination of the above modalities including HUS, head CT, EEG, cerebral oximetry, and transcranial Doppler ultrasound should be used for neuromonitoring and for early identification of neurologic injury.

Neurologic injury in patients supported on ECMO is a frequent and potentially devastating event. Neurologic monitoring consists of an effective daily clinical neurologic assessment in combination with multimodality neuromonitoring methods. A well-defined combination of neuromonitoring modalities is likely to be successful in early detection of neurologic injury that will allow early institution of neuroprotective interventions and potentially improve outcomes.[1,3]

Summary

This guideline provides a combination of neuromonitoring modalities for neonatal and pediatric patients supported on ECMO. A well-defined combination of neuromonitoring modalities is likely to be successful in early detection of neurologic injury that will allow early institution of neuroprotective

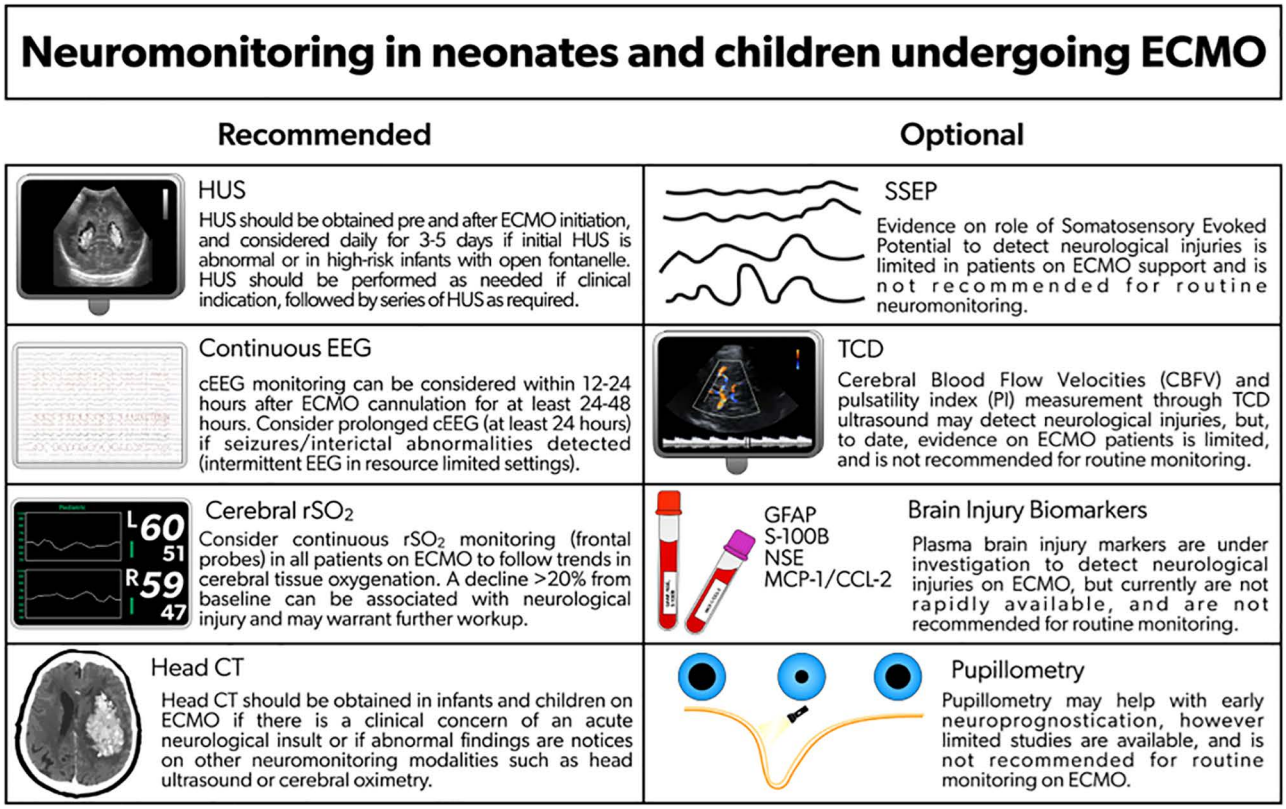

Figure 1. Summary of recommendations for neuromonitoring in neonatal and pediatric patients on ECMO support. CCL-2, chemokine ligand 2; cEEG, continuous electroencephalography; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; GFAP, glial fibrillary acidic protein; HUS, head ultrasound; MCP-1, monocyte chemoattractant protein-1; NSE, neuron-specific enolase; rSO_2, regional cerebral oxygen saturation; S-100B, S-100 calcium-binding protein B; SSEP, somatosensory evoked potentials; TCD, transcranial Doppler.

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interventions and potentially improve outcomes. This guideline provides recommendations based on currently available evidence. Figure 1 and the key recommendations below provide a summary of the recommendations for patients supported on ECMO and for specific high-risk groups. Limitations and barriers to implement the above recommendations may include resource constraints and training required for successful implementation. Additional research is required to investigate the relationship between specific combinations of different modalities and neurologic outcomes.

Key Recommendations for All Patients

Recommended

- Head ultrasound should be obtained before and after ECMO initiation and considered daily for at least 3–5 days after cannulation in infants with abnormal HUS and high-risk infants with an open fontanel. Head ultrasound should be performed as needed in a case of clinical suspicion of neurologic injury, followed by a series of subsequent HUSs as required.
- Head CT should be obtained in infants and children if there is a clinical concern of an acute neurologic injury or if abnormal findings are noted on other neuromonitoring modalities such as HUS or cerebral oximetry.
- Continuous cerebral oximetry monitoring with NIRS can be considered in all patients undergoing ECMO to follow trends in cerebral tissue oxygenation. A decline in cerebral regional oxygen saturation of greater than 20% from baseline can be associated with neurologic injury and may warrant further workup.
- Continuous EEG monitoring initiation can be considered within 12–24 hours of ECMO cannulation for a duration of at least 24–48 hours. Prolonged EEG monitoring for at least 24 hours after seizure control can be considered in the presence of seizures or interictal abnormalities detected on cEEG. Intermittent EEG can be considered in resource-limited settings and extended to cEEG if there are abnormalities.
- A combination of the aforementioned modalities including HUS, head CT, cEEG, cerebral oximetry, and transcranial Doppler ultrasound is recommended for neuromonitoring and for early identification of neurologic injury.

Optional

- Transcranial Doppler ultrasound as a measure of CBFV and PI can detect neurologic injuries; however, this has only been studied in small groups of patients supported on ECMO and is not recommended for routine neuromonitoring.
- Plasma brain injury markers are currently under research to detect neurologic injuries in patients supported on ECMO. They are not available for rapid detection and clinical use and are not recommended for routine neuromonitoring.
- Evidence on the role of SSEP to detect neurologic injuries is limited in patients supported on ECMO and is not recommended for routine neuromonitoring.
- Pupillometry may help with earlier neuroprognostication; however, limited studies are available, and it is not recommended for routine monitoring.

High-Risk Groups

- Patients undergoing ECPR have a history of cardiac arrest before or during ECMO, congenital heart disease, and recent cardiopulmonary bypass should ideally be monitored with cEEG, cerebral oximetry monitoring, and HUS in infants.
- Patients with new-onset clinical seizures should be monitored with cEEG and head CT can be considered.
- Patients who have an acute neurologic examination change should be evaluated with head CT and cEEG monitoring. Head ultrasounds should be considered for infants.

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