Clinical Reasoning: Prognostication after cardiac arrest
What do we really know?

SECTION 1

A 43-year-old woman with a history of hypertension had a witnessed collapse while smoking crack cocaine. Immediate bystander cardiopulmonary resuscitation was performed for 15 minutes; total downtime was estimated at 30 minutes with return of spontaneous circulation (ROSC) achieved after defibrillation of ventricular fibrillation and a total of 5 mg IV epinephrine. Cardiac catheterization showed normal coronary vasculature. Initial neurologic examination 2 hours after fentanyl and vecuronium boluses was significant for nonreactive pupils, absent gag reflex, and no motor response to noxious stimulation, but intact corneal and oculocephalic reflexes. Head CT (obtained to rule out intracerebral hemorrhage in the setting of cocaine use) showed no acute abnormalities. Targeted temperature management (TTM) was initiated 3 hours after ROSC, targeting 32–34°C, and maintained for 24 hours. Continuous EEG initially showed a discontinuous pattern with widespread attenuation, followed by left temporal lateralized periodic discharges, and then by generalized spike and wave discharges. These EEG changes occurred during hypothermia and did not have any clinical correlate. The patient was treated with levetiracetam 55 mg/kg/d with improvement in hyperexcitable patterns. Ten hours after achieving normothermia, she developed frequent myoclonic jerking of her lower extremities, time-locked with epileptiform bursts, consistent with myoclonic status epilepticus (MSE) (figure 1A). Neurologic examination 48 hours after rewarming was unchanged, except for the development of 1–3 Hz myoclonic blinking and jerking of the upper and lower extremities.

Question for consideration:
1. Based on the American Academy of Neurology (AAN) guidelines for neuroprognostication in comatose cardiac arrest (CA) survivors, will this patient have a good or poor outcome?
Figure 1  EEG evolution from myoclonic status epilepticus (MSE) to resolution of diffuse hyperexcitability following treatment

All epochs demonstrate approximately 10 seconds of recording captured with high-pass filter at 1 Hz, low-pass filter at 70 Hz, Notch filter “off,” sensitivity set at 7 μV/mm, and paper speed of 10 mm/s in a longitudinal bipolar montage. (A) Post-cardiac arrest (CA) day 2: MSE characterized by highly epileptiform bursts of generalized 6–7 Hz activity lasting approximately 0.5 seconds (blue box) admixed with 1.5 Hz generalized midline predominant discharges (blue arrows). Bursts were in lockstep with myoclonic activity and underlying muscle artifact is demonstrated by red arrows. (B) Post-CA day 4 with resolution of MSE. Highly epileptiform bursts are no longer seen but persistent diffuse hyperexcitability is displayed with generalized midline predominant discharges (blue arrows) in a discontinuous attenuated delta/theta background despite continuous midazolam infusion at 20 mg/h. Note muscle artifact, which correlated with clinical myoclonus without electrographic correlate (red arrows) characterizing subcortical origin. (C) Post-CA day 11 with resolution of hyperexcitability. Burst suppression on continuous ketamine infusion at 6.8 mg/kg/h. Bursts of attenuated alpha/beta activity demonstrated with blue box. (D) Post-CA day 20 with improving background after anesthetic infusions were completely weaned off. Continuous background consisting of rich admixture of frequencies. Note 60-Hz artifact in the leads marked by green arrow.
SECTION 2
The 2006 AAN practice parameter suggests a poor prognosis in this case based on several criteria: (1) absent pupillary reflexes within 1–3 days of CA (Level A), (2) no motor response after 3 days post-CA (Level A), and (3) diffuse attenuation of background and generalized periodic discharges (Level C). However, these guidelines do not account for TTM treatment, which primarily or secondarily by delaying clearance of sedatives can introduce significant confounders affecting the accuracy of the clinical examination and EEG. In addition, the presence of MSE is traditionally considered pathognomonic of poor outcome.1,2 There is no uniform definition of MSE, which limits its accuracy when being used for prognostication. The AAN guidelines caution that when present in the first 24 hours, MSE is “invariably associated with poor outcomes.”1 It is well-known that Lance Adams syndrome is a separate clinical entity from MSE and has very different prognostic implications. One of the distinguishing features of Lance Adams syndrome is the early onset of MSE.3 With the use of TTM, myoclonus is often suppressed in the first 1–2 days due to administration of sedating agents and paralytics, as well as antiseizure effects of TTM, and may present after rewarming.4 The definitions of MSE range from a purely clinical diagnosis (multifocal myoclonus without EEG correlate) to electroclinical diagnosis (time-locked bursts).4 Without the use of EEG, it is impossible to decipher between cortical and subcortical myoclonus, which may have different effects on outcome. Finally, there is no uniform consensus in regards to treatment. Aggressive treatment of MSE is controversial, largely because it is unknown whether MSE is solely a marker of severe anoxic brain injury or if prolonged seizures themselves contribute to poor outcomes.5

Question for consideration:
1. Given her examination and EEG findings, would you have recommended withdrawal of life-sustaining therapy (WLST)?
SECTION 3
Based on prior literature regarding anoxic MSE and AAN guidelines, WLST would have been appropriate to consider. Nonetheless, supportive care was continued at that time as it is our institutional practice to refrain from early prognostic assessments, and 72 hours after rewarming, the patient regained pupillary and gag reflexes. Clinical and EEG MSE remained refractory to levetiracetam 2,000 mg every 12 hours, midazolam 20 mg/h, phenytoin 200 mg every 12 hours, phenobarbital 250 mg every 12 hours, and lacosamide 200 mg every 12 hours (figure 1B). Despite 9 days of continuous midazolam infusion and uptitration of antiseizure drugs, the patient did not achieve burst suppression until she was transitioned to a ketamine infusion, uptitrated to a maximum rate of 6.8 mg/kg/h (figure 1C). Burst suppression was maintained for 3 days, after which a successful complete wean of ketamine occurred over 18 hours and she was maintained on levetiracetam and phenobarbital (level 47; range 15–30 μg/mL). MRI (figure 2) was notable for subtle fluid-attenuated inversion recovery hyperintensities in the bilateral hippocampi on post-CA day 11. Despite early refractory MSE and a poor neurologic examination, MRI of the brain did not show signs of severe hypoxic-ischemic brain injury (HIBI). Family meetings discussing the prognostic uncertainty but high likelihood of a poor outcome were held daily; the family opted to pursue aggressive treatment of seizures and continuation of life-sustaining therapies. On post-CA day 18, the patient had percutaneous gastrostomy tube and tracheostomy placement due to her persistently poor neurologic status. EEG remained unreactive until post-CA day 14; on post-CA days 15 and 16, she developed stimulus-induced rhythmic, periodic, or ictal discharges as the only form of reactivity, and on post-CA day 17, her EEG became reactive (figure 1D). Shortly following EEG improvement, the patient demonstrated a slow recovery with the following milestones: eye opening on post-CA day 24, nonpurposeful spontaneous movement of the arms and legs on post-CA day 33, appendicular command-following on post-CA day 40, and intelligible speech on post-CA day 42. She was discharged to a rehabilitation center on post-CA day 52. At 6 months follow-up, she was able to care for herself and walk independently despite mild quadriplegia and choreiform movements of her arms, characterizing a Cerebral Performance Category scale score of 2.

Question for consideration:
1. Has the prognostic assessment of HIBI changed with the widespread use of TTM?

Figure 2  MRI brain on post-cardiac arrest (CA) day 11

(A) Axial diffusion-weighted imaging sequence at the level of the hippocampus. (B) Axial apparent diffusion coefficient sequence at the level of the hippocampus. (C) Axial fluid-attenuated inversion recovery (FLAIR) sequence at the level of the hippocampus. (D) Coronal FLAIR sequence at the level of the hippocampus.
Over the last 20 years, the management of HIBI has evolved, and the advent of TTM has led to an increase in survival and improvement in neurologic outcomes. Because hypothermia delays clearance of sedatives and directly interferes with the neurologic examination, it is important to challenge the validity of AAN guidelines. In the setting of hypothermia, the variables used for neurologic prognostication have unacceptably high false-positive rates. More recent guidelines suggest delaying prognostic assessments when TTM is used; however, time to awakening in HIBI varies and up to 1 in 7 patients may experience a delayed awakening with favorable neurologic outcome.

**DISCUSSION**

Given the complex relationship between TTM and neurologic prognosis, it is important to reevaluate previously ascribed indicators of poor prognosis. A meta-analysis of 37 studies of neuroprognostic tools used within 7 days from CA demonstrated that even predictors with a high positive predictive value were subject to a self-fulfilling prophecy bias. Moreover, the heterogeneity of the MSE definition across studies makes it difficult to uniformly evaluate its prognostic yield. The AAN guidelines define MSE as spontaneous, repetitive, unrelenting generalized multifocal myoclonus involving the face, limbs, and axial musculature in comatose patients; there is no mention of EEG correlate or requirement. Two distinct EEG patterns of postanoxic myoclonus were recently identified with equally distinct clinical significance: (1) high-amplitude polyspikes time-locked with myoclonic jerks in a suppression-burst background, which correlated with a poor outcome in 100% of cases; and (2) continuous background with narrow, vertex spike-wave discharges in lockstep with myoclonic jerks, which was associated with a favorable outcome in 50% of cases. Interestingly, our patient would have fell yet again in the MSE category with a dismal prognosis, demonstrating that although pattern distinction is important, it is not an infallible prognostic indicator.

We now add to the literature, describing the course of a patient with several poor prognostic signs who had a late but good recovery, highlighting the need for caution when giving definitive prognostic assessments. Our patient started following commands over 5 weeks post-CA; we speculate that this was multifactorial with the effect of prolonged and refractory seizures and sedating medications being the main factors. Importantly, she also underwent very aggressive treatment for her electrographic seizures, which is likely an uncommon practice. Despite aggressive management, she developed no iatrogenic complications except for mild scalp skin breakdown secondary to prolonged EEG monitoring. Evaluation of long-term prognosis and the incidence of late awakening is limited by WLST practices, thereby limiting the existing knowledge of the natural history of HIBI. Finally, all CA studies have been plagued by the self-fulfilling prophecy bias; therefore, no predictor should be used alone when assessing neurologic prognosis. In this patient, the clinical examination, EEG, and neuroimaging did not portend the same prognosis. Additional neuroprognostic tools such as somatosensory evoked potentials and biochemical markers such as neuron-specific enolase not available in our institution at the time this patient was treated should be used whenever able. We, along with others, advocate for performing neuroprognostication using a multimodal approach, and delaying definitive assessments if patients exhibit a dynamic examination towards improvement.

Our review of the literature stresses the importance of reevaluating prognostic signs post-TTM, the significance of WLST as a confounding variable, and the effect of seizure treatment in overall outcome. Prospective studies are needed using a standardized definition of MSE with electroclinical correlation, in addition to encouraging delayed assessments in the presence of any uncertainty or confounders.

**REFERENCES**


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