

# Anoxic Brain Injury: The Abominable Malady

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## Abstract

Anoxic brain injury (ABI) is an important cause of prolonged hospital stay and morbidity across the globe. It is a sequel of major systemic insults resulting from various etiologies, such as reduced oxygen availability, insufficient cerebral blood flow, reduced oxygen carriage, or any metabolic condition that can interfere with the utilization of oxygen. A varying combination of pathophysiologic mechanisms leads to a spectrum of clinical manifestations, the understanding of which will significantly help in prognostication of patients. Neuroprognostication helps both the clinician and the patient's family in planning future course and is further aided by various neuromonitoring modalities, biomarkers, and imaging. Targeted temperature management still remains a therapeutic tool in ABI and along with other neuroprotective measures may improve the survival. Continuing research in ABI may uncover more promising treatment strategies.

## Keywords

- ▶ anoxic brain injury
- ▶ neuroprognostication
- ▶ targeted temperature management
- ▶ hypothermia

## Introduction

Anoxic/hypoxic brain injury (ABI) results from reduced oxygen availability, insufficient cerebral blood flow, reduced oxygen carriage, or any metabolic condition that can interfere with the utilization of oxygen.<sup>1</sup> It commonly presents in the emergency departments and can result in prolonged hospitalization with an unfavorable prognosis.

## Etiology of Anoxic Brain Injury

The main etiologies that can lead to ABI in adults are:

1. Cardiac failure secondary to:
  - Massive blood loss
  - Traumatic or septic shock
  - Cardiac pathologies, for example, myocardial infarction and ventricular arrhythmia
2. Respiratory failure followed by cardiac arrest as a result of hypoxia due to:
  - Drowning/strangulation
  - Aspiration

- Oxygen-poor inspired gas during mechanical ventilation or anesthesia
  - Tracheal compression or obstruction
3. Carbon monoxide poisoning resulting in reduced oxygen carriage
  4. Cyanide poisoning, causing histotoxicity

## Pathophysiology of Anoxic Brain Injury in Adults

The presentation and pathophysiology of ABI differ depending on the underlying etiology. Ischemia as a result of low cerebral blood flow results in patchy infarctions at watershed zones that lie between the major cerebral arteries,<sup>1</sup> whereas hypoxia and reduced oxygen carriage by the blood cause neuronal death in the hippocampus, cerebellum (deep folia), and cerebral cortex.<sup>1</sup> In extreme cases of both ischemia and hypoxia, there is generalized neuronal damage of the cerebral cortex, deep nuclei, and cerebellum. The brain stem gray matter is resistant to anoxic neuronal injury and tends to survive even after severe and prolonged hypoxia, which has caused extensive cortical damage.<sup>1</sup>

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Neuronal injury in ABI is a progressive process, and at the cellular level, its magnitude depends on the duration and severity of the initial insult along with the combined effects of reperfusion injury and apoptosis.<sup>1,2</sup> The necrotic tissue swells rapidly, mainly because of excessive intra- and extracellular water content, and the tissue becomes pale as the arteries and arterioles become narrowed. Necrosis is not limited to neurons but also involves the oligodendroglial cells in the white matter.<sup>3</sup> An inflammatory response follows, activating endothelial cells to secrete proteases and cytokines.<sup>3</sup> At the molecular level, there is malfunction of the Krebs cycle, the electron transport system, accumulation of catabolic products, and excitatory neurotransmitters, such as glutamate, all leading to a massive intracellular influx of calcium and resulting in diffuse cell destruction.<sup>4,5</sup> After transient recovery of cerebral energy metabolism, the secondary phase of apoptotic neuronal death occurs causing demyelination and neuronal death sometime after the anoxic insult.<sup>4,5</sup> The pathophysiology of ABI is summarized in ►Fig. 1.

Carbon monoxide (CO) produces unique anoxia associated with delayed neurological deterioration and distinct histopathological patterns.<sup>6</sup> One pattern comprises the degeneration of the cortical laminae and basal ganglia occurring immediately after CO poisoning, and the other entails varying degrees of demyelination in the centrum semiovale, resulting in delayed encephalopathy. In cyanide (CN) toxicity, the cells are unable to utilize oxygen as cytochrome C oxidase is inhibited, resulting in neuronal death.

### Delayed Postanoxic Encephalopathy

Delayed postanoxic encephalopathy (DPE) can present in conditions where there is respiratory muscles weakness in neurological diseases, e.g., Guillain-Barré syndrome, amyotrophic lateral sclerosis, myasthenia gravis, or central nervous system injury (spinal cord injury). Clinicians should be aware of DPE, which is a delayed rare presentation that is difficult to diagnose in patients with ABI.<sup>6,7</sup>

Two main proposed hypotheses for the causation of DPE are neuronal apoptosis and demyelination.<sup>6,7</sup> In DPE, the

initial hypoxia is severe enough to trigger the apoptotic cascade leading to neuronal death. Demyelination is visible in cranial magnetic resonance imaging (MRI) and is caused due to oligodendroglial dysfunction and arylsulfatase A deficiency.<sup>8</sup>

### Clinical Presentation of ABI

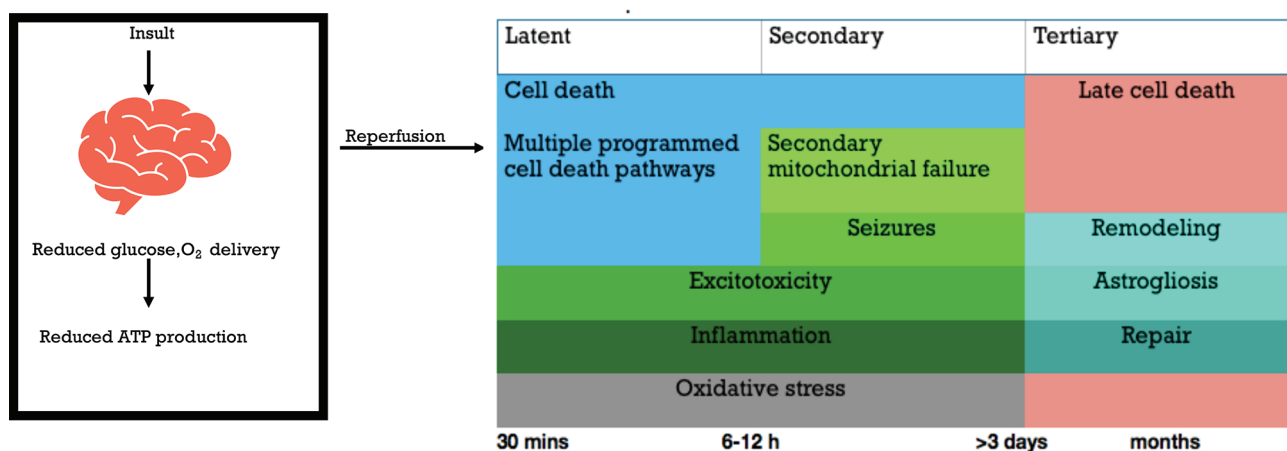
A plethora of clinical syndromes can occur in ABI, depending on the severity, the duration, and the underlying etiopathogenesis.<sup>9,10,11</sup> The clinical presentations of ABI are summarized in ►Table 1.

### Grading of Cerebral Hypoxia

The blood oxygen saturation (SpO<sub>2</sub>) is used as an objective measurement to grade the severity of cerebral hypoxia: 95 to 100% saturation is considered normal, 91 to 94% as mild, 86 to 90% as moderate, and anything < 86% as severe.<sup>1</sup> If CO poisoning is suspected, it should be borne in mind that the SpO<sub>2</sub> will not be not reliable and carboxyhemoglobin levels should be measured.

**Table 1** Clinical presentations of anoxic brain injury

1) Mild sustained hypoxia Cognitive impairment Confusional states Delirium
2) Brief anoxic-ischemic events Syncope Abortive or actual generalized seizure activity
3) Sustained severe hypoxia Coma with residual neurological deficits Dementia Vegetative state Brain death Seizure activity Watershed infarction of cerebrum, cerebellum, spinal cord Infarction distal to a pre-existing arterial stenosis or occlusion Postanoxic demyelination



ATP indicates adenosine triphosphate; O<sub>2</sub>, oxygen

**Fig. 1** Pathophysiology of anoxic brain injury.

When cerebral autoregulation is intact, a decrease in oxygen supply is countered by an increase in the cerebral blood flow. If this response is adequate to maintain the minimum oxygen required to meet the metabolic demand, the patient will remain asymptomatic.<sup>1</sup> When there is a demand delivery mismatch, symptoms of cerebral hypoxia will gradually manifest.<sup>1</sup> Mild hypoxia will have a less severe presentation, such as inattentiveness, difficulties with complex tasks, impaired short-term memory, and motor incoordination. Prolonged and severe oxygen deprivation can result in loss of consciousness, seizures, deep coma, cessation of brain stem reflexes, and ultimately, brain death. The duration of anoxia necessary to cause brain damage has not been clearly established. Critical factors, such as prearrest blood glucose levels, use of preischemic medications such as aspirin and calcium channel blockers, associated hypothermia, age as well as the secondary brain damage after reperfusion may determine the outcome of an anoxic episode.<sup>12,13</sup> It is generally accepted that more than 5 minutes of anoxia during a circulatory arrest can result in severe brain injury.<sup>13</sup>

Post-cardiac arrest, ABI patients remain in deep coma with associated brain stem dysfunction necessitating ventilation support. The duration of this state depends on the length of the anoxic insult; however, a majority of the patients regain brain stem function within 1 to 3 hours.<sup>12</sup> The initial flaccidity can progress to decerebrate or decorticate posturing before awakening.<sup>12</sup> Awakening of ABI patients is gradual and has different patterns. Patients who regain consciousness within 24 hours after cardiac arrest may have altered higher mental function and may remain agitated/confused for few hours to days until cognitive function recovers.<sup>13</sup> Arousal in some patients can be more prolonged, and in the interim period present with reflex motor posturing, grasping, eye-opening, and, finally, arousal. Diffuse cortical lesions mainly manifest as short-term memory loss, emotional lability, hallucinations, and inattention, whereas basal ganglia insult will manifest as chorea or parkinsonian syndrome.<sup>10,12,13</sup> Various seizure forms are encountered throughout this process, and asynchronous distal limb myoclonus or axial myoclonus are routinely encountered within the first 12 hours after cardiac arrest.<sup>10,12,14</sup> Generalized tonic-clonic seizures also occur occasionally. Simple or complex partial seizures can develop and may get misdiagnosed as a continuum of the patient's postanoxic stupor or confusional state.<sup>14</sup> Neurological syndromes that are manifested as a result of ABI are summarized in ► **Table 2**. When ischemia arising out of ABI is prominent, it can result in two rare clinical presentations namely, Bálint's syndrome and man-in-the-barrel syndrome (MBS).

### Bálint's Syndrome

Bálint's Syndrome is a rare syndrome, wherein the patient has a triad of neurological impairments: Simultanagnosia, that is, the individual is unable to perceive the visual field as a whole; oculomotor apraxia, that is, difficulty in fixating the eyes on an object; and optic apraxia, that is, difficulty in localizing an object with hand by using vision. It occurs after an anoxic insult to the brain, resulting in a bilateral infarction of the watershed area in the occipitoparietal

**Table 2** The neurological syndromes that are manifested as a result of anoxic brain injury

Neurological syndromes in anoxic brain injury
Cognitive impairment with or without extrapyramidal signs
Korsakoff syndrome
Parkinsonian syndrome with cognitive dysfunction
Choreoathetosis
Cerebellar ataxia
Intention myoclonus
Seizures
Persistent vegetative state
Brain death

region.<sup>15</sup> It can occur as a consequence of traumatic brain injury or multiple ischemic strokes resulting in ABI.<sup>15</sup>

### Man-in-the-Barrel Syndrome

The “man-in-the-barrel syndrome” is an unusual clinical condition characterized by weakness of bilateral upper limbs with intact motor power in the lower limbs.<sup>16</sup> In this condition, the patient is unable to move the upper limbs to any stimulus as if they are confined within a barrel. It is caused as a result of cerebral hypoperfusion, resulting in ABI of the watershed zones between the anterior and middle cerebral artery circulation that is responsible for brachial mobility.<sup>16</sup> Other reported etiologies include cerebral metastasis, and lesions involving pons, medulla, and spinal cord.<sup>16</sup>

### Cerebral Edema in ABI

More than one-third of patients who experience hypoxic insult during a cardiopulmonary arrest can have subsequent cerebral edema.<sup>17</sup> It is not associated with papilloedema and herniation is rare as opposed to edema encountered in post-ischemic stroke.<sup>17</sup> Postmortem studies have revealed that the edema is more commonly found in individuals who developed a comatose sequel, which indicates that it could be of postnecrotic etiology rather than a post-inflammatory one.<sup>17</sup> Intracranial hypertension is more likely to develop when the ABI and cardiac arrest are due to respiratory failure.<sup>17</sup> This could be due to the effects of hypercapnia and respiratory acidosis preceding the arrest in addition to hypoxia and cerebral hypoperfusion, but the efficacy of these parameters as predictors of poor outcome has not been validated. The incidence of raised intracranial pressure secondary to cerebral edema post-cardiopulmonary arrest is a marker of poor prognosis.<sup>17</sup> There is no evidence that treatment of this condition with hyperventilation, corticosteroids, osmotic diuretics, barbiturate-induced coma, or ventriculostomy might be beneficial.<sup>17</sup>

### Prognostication after Anoxic Brain Injury

#### Clinical Prognostication

Prognostication of ABI can be based on brain stem reflexes, motor response, Glasgow Coma Scale (GCS), electrocortico-

**Table 3** The clinical evaluation and prognostication of anoxic brain injury

Time since cardiac arrest	Patients with virtually no chance of regaining independence	Patients with best chance of regaining independence
Initial examination	No pupillary light reflex in the absence of other causes	Pupillary light reflexes present; motor response decorticate or decerebrate posturing; spontaneous eye movements conjugately roving or orienting
1 day	1-day motor response no better than decorticate posturing; spontaneous eye movements neither orienting nor conjugate; roving	1-day motor response withdrawal or better; 1-day eye opening to noise or spontaneously
3 days	3-day motor response no better than decorticate posturing	Motor response withdrawal or better; spontaneous eye movements or normal
1 week	Not obeying commands; spontaneous eye movements neither orienting nor conjugate	Obeying commands

-graphy, evoked potentials, and imaging. In patients with ABI post-cardiac arrest, 90% will wake up within the first 3 days. A delay in waking up after 72 hours is associated with persistent vegetative state (PVS).<sup>12</sup> The probability of awakening reduces by 50% after the first day, 20% after the third day, and 10% after the seventh day. The clinical evaluation and prognostication are summed up in **Table 3**.

### Brain Stem Reflexes and Motor Response

The absence of pupillary reflex immediately after cardiac arrest is not an indicator of poor prognosis; however, its presence is a sign of good prognosis. The absence of pupillary reflex 12 hours post-cardiac arrest is a predictor of poor prognosis, and persistence of fixed pupils on the third day suggests a PVS.<sup>13</sup> The presence of brain stem automatisms (blinking, swallowing, cough), myoclonus, and nystagmus suggests indemnity of the brain stem. It must also be borne in mind that blinking, myoclonus, and nystagmus are seen in patients with nonconvulsive epileptic states.

The presence of myoclonic status and conjugate vertical upward gaze deviation on the first day are signs of a poor prognosis. Ocular dipping is an involuntary conjugate eye movement, where there is a vertical deviation of the downward gaze persisting for several seconds and then returning to neutral position.<sup>12,13</sup> This is a unique presentation of ABI that signifies a poor outcome. Presence of withdrawal reflex is an indicator of good prognosis; but its absence is not synonymous with a poor prognosis. Absent pupillary reflexes, together with the absent motor response to pain on the third post-cardiac arrest day is associated with poor neurological prognosis with a specificity of 100%.<sup>12,13</sup>

### Glasgow Coma Scale

GCS has been used for prognostication in ABI. GCS < 5 within first 6 hours does not predict a poor prognosis; however, GCS > 10 is a predictor of good outcome. GCS < 8 with altered somatosensory evoked potentials (SSEPs) had a specificity of 97% to predict brain death. Isolated use of GCS as a prognosticating index is not viable.<sup>11</sup>

### Full Outline of UnResponsiveness Score

The Full Outline of UnResponsiveness (FOUR) score can be used to evaluate for clinical progression with serial examinations in patients with ABI. With an equal to higher interrater reliability

than the GCS, as well as validation in multiple patient populations, the FOUR score has proven to be an important initial tool in the evaluation of comatose patients. Perhaps because of its greater emphasis on brain stem reflexes and respiratory patterns, the FOUR score has also been shown to have greater predictive value in terms of eventual progression toward more severe injury, especially in patients with low GCS scores, or the relatively ubiquitous GCS score of 3 T, which is commonly reported by paramedics following intubation in the field after sedatives and paralytics have been given.<sup>12,13</sup> Brain stem damage and failure to maintain adequate ventilation are reflections of injury severity. The FOUR score does not contain a verbal component, and can be measured with equal accuracy in intubated and nonintubated intensive care unit patients. FOUR score has greater sensitivity than the GCS for detecting different levels of brain stem function, but because the FOUR score does not assess for visual fixation, it may not capture the transition from Vegetative State to Minimally Conscious State.<sup>11-13</sup>

### Electroencephalogram

Electroencephalogram (EEG) has a high sensitivity in the prognostication of ABI as it can provide continuous monitoring and is readily available in most centres.<sup>18</sup> The disadvantage being that its analysis can be confounded by the use of pharmacological agents such as barbiturates and benzodiazepines.<sup>18,19</sup> An EEG grading scale has been developed which when analyzed at 24 hours after successful cardiac resuscitation has a prognostic value of 98.4% (**Table 4**). Grades 1 and 2 predict a full recovery, whereas grades 4 and 5 predict a poor outcome.<sup>18</sup>

### Evoked Potentials

Evoked potentials for the prognostication of ABI have been extensively researched. The advantage of using evoked potentials is that they are noninvasive, can be done at the bedside, can be reproduced, and not affected by metabolic encephalopathy.<sup>20,21</sup> They also provide information on the location and severity of the ischemic insult in the central nervous system pathways. Altered evoked potentials are associated with poor neurological outcome, but the normality does not always predict recovery.<sup>21</sup> In SSEP, the N 70 that represents the corticocortical interactions has a more significant prognostic value than the conventional short latency responses (N13 and N20).<sup>20,21</sup> Bilateral absent median

**Table 4** Electroencephalography grading scale for prognosis of anoxic brain injury

Grade 1	Dominant alpha rhythm with some theta-delta activity, reactive
Grade 2	Theta-delta activity with some normal alpha activity, reactive
Grade 3	Predominantly theta-delta activity without normal alpha activity
Grade 4	Low voltage delta activity, nonreactive, alpha coma (generalized non-reactive alpha activity), paroxysm suppression pattern
Grade 5	Isoelectric

nerve SSEP 8 hours post insult has a mortality rate of 98%. Compared to SSEP, auditory evoked potentials have a poor predictive power.<sup>21</sup>

### Imaging in Anoxic Brain Injury

Computed tomography (CT) scan of the brain lacks sensitivity during the initial 24 hours, as a minimal to moderate degree of injury will be unnoticed but if any abnormality appears on the CT, it signifies severe neurological damage. The most common finding in the CT scan is the absence of gray-white differentiation and the absence of sulci and gyri denoting cerebral edema. Hypodense lesions involving the cerebral cortex, basal ganglia, and cerebellum are seen after 48 hours in the event of an ischemic injury. MRI has better sensitivity and specificity for detecting cerebral ischemia and edema.<sup>22</sup> The typical presentation being the absence of gray-white differentiation, diffusion restriction in diffusion-weighted imaging indicating cerebral infarction.<sup>23</sup> Seven days post-ABI, the cortical laminar necrosis of the affected regions will appear hyperintense in T<sub>1</sub>W, T<sub>2</sub>W, and fluid-attenuated inversion recovery sequences.<sup>23,24</sup> Single-photon emission computed tomography and MR spectroscopy have been sensitive in identifying ABI, but their prognostic capabilities are still being studied.

### Biomarkers of ABI

#### a. Creatinine kinase isoenzyme BB in CSF

An excellent correlation between the elevation of creatinine kinase isoenzyme in the cerebrospinal fluid (CSF) and the severity of neuronal damage has been established. A value of 50 IU/L at 48 to 72 hours has a sensitivity and specificity of 82% and 85%, respectively, and a positive predictive value of 0.96 for predicting PVS and a specificity of 100% with values > 205 IU/L.<sup>24</sup>

#### b. Serum neuron-specific enolase

Serum neuron-specific enolase levels reflect the degree of structural brain damage. A value of > 33 ng/mL predicts PVS or brain death with a specificity and sensitivity of 100% and 80%, respectively, the limitation being the absence of temporal correlation to confirm the prediction.<sup>24,25</sup>

#### c. Serum astroglial S100 protein

The S100 protein reflects the degree of structural brain damage. S100  $\geq$  0.2 ng/mL on the second day has a positive predictive value of 100% for mortality, and < 0.2 ng/mL in the initial 14 days has a survival prognosis of 89%. It is found that S100 protein values are significantly higher in

patients with persistent brain damage than in those who recover without neurological sequelae.<sup>25,26</sup>

### Guidelines on Neuroprognostication

Clinical findings and test results that can predict poor neurological outcome have been summarized in **Table 5**. In patients who are not treated with targeted temperature management (TTM), the earliest time to evaluate for prognostication of neurological outcome would be 72 hours after the cardiac arrest. If any residual effect of sedation or paralysis is suspected to confound the clinical examination, it is advised to wait for a more extended period as per the discretion of the clinician. In patients who have received TTM, it is advised to delay the clinical examination until 72 hours after the return of body temperature to normothermia before predicting the outcome.<sup>26-28</sup>

Rationale being that the clinical signs, blood markers, electrophysiological monitoring and imaging can be affected by hypothermia, sedation and neuromuscular blockade. Additionally, the comatose brain will be more sensitive to the effects of sedative medications, and the metabolism of these agents may take longer in the post-cardiac arrest period. No single clinical sign or testing modality can predict the neurological outcome with 100% sensitivity and specificity.<sup>27</sup> Thus, multiple modalities of clinical and ancillary testing should be used together to predict the outcome.<sup>27,28</sup>

**Table 5** Neuroprognostication of ABI: Clinical, imaging, and electrophysiological findings associated with poor neurological outcome

Red flags associated with poor neurologic outcome
Absence of pupillary reflex to light at 72 hours or more after cardiac arrest
Presence of status myoclonus (different from isolated myoclonic jerks) during the first 72 hours after cardiac arrest
Absence of the N20 somatosensory evoked potential cortical wave 24 to 72 hours after cardiac arrest or after rewarming
Presence of a marked reduction of the gray-white ratio on brain CT obtained within 2 hours after cardiac arrest
Extensive restriction of diffusion on brain MRI at 2 to 6 days after cardiac arrest
Persistent absence of EEG reactivity to external stimuli at 72 hours after cardiac arrest
Persistent burst suppression or intractable status epilepticus on EEG after rewarming
<b>Note:</b> Absent motor movements, extensor posturing, or myoclonus should not be used alone for predicting outcome

Abbreviations: ABI, anoxic brain injury; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging.

### Therapeutics in Anoxic Brain Injury

The therapeutic process starts once the patient has been successfully resuscitated from the causative etiology. Review of literature has shown that only 20% of the patients return to be entirely self-sufficient without any residual or minimal neurological deficit.<sup>29,30</sup> Approximately 80% of the patients will end up being partially or wholly dependent for their activities of daily living.<sup>29</sup>

The management of patients, post-ABI is exceptionally challenging and complex. The patient's medical history, the degree of self-sufficiency before the event, associated comorbidities, and the socioeconomic environment of the family have to be taken into account while making decisions.

A few decades ago, there was no means of prognosticating these patients and also specific neuroprotective therapies were unknown. This resulted in most patients who were successfully resuscitated gradually evolving into brain death, PVS, or total dependency.

In the recent past, few therapeutic measures have shown some degree of promising results such as the institution of hypothermia to the latest being TTM strategies.<sup>29,30</sup>

Therapeutic care starts with neuroprotective strategies such as:

- a. Ensuring adequate cerebral blood flow by maintaining a cerebral perfusion pressure > 60 mm Hg.
- b. Identification and prompt correction of hypotension (systolic blood pressure < 90 mm Hg) and maintaining a mean arterial pressure between 65 and 85 mm Hg.
- c. Maintenance of normoxia, normocarbia, normoglycemia, normovolemia, normonatremia.
- d. Prophylactic use of anticonvulsants as > 30% present with seizures.

### Targeted Temperature Management

In the past two decades, we have seen major landmark trials in the field of TTM for ABI. The initial two trials that popularized hypothermia for neuroprotection in post-cardiac arrest patients were published simultaneously in 2002.<sup>29,30</sup> The Australian study by Bernard et al randomized comatose survivors of ventricular fibrillation arrests into two groups: one receiving hypothermia of 33°C and the second receiving normothermia (no temperature intervention).<sup>29</sup> The paramedics initiated the cooling en route to the hospital and hypothermia was maintained for 12 hours, with the patients being sedated, paralyzed, and mechanically ventilated followed by active rewarming after 18 hours. Discharge to a rehabilitation facility or home was considered a good outcome. The study found that 49% of patients in the hypothermia group had a good outcome as compared to 26% in the normothermia group (relative risk [RR] of a good outcome, 1.85; 95% confidence interval [CI], 0.97–3.49; the number needed to treat [NNT] = 4). Mortality at discharge was 51% in the hypothermia group as compared to 68% in the normothermia group (RR, 0.76; 95% CI, 0.52–1.10; NNT = 6).<sup>29</sup>

This was followed immediately by the larger hypothermia after cardiac arrest by the European group where 273 comatose survivors of ventricular fibrillation arrests were randomized to mild therapeutic hypothermia (32–34°C) group versus the

normothermia group.<sup>31</sup> The patients were cooled with the aid of forced air blankets and mattresses and the temperature maintained for 24 hours. The patients underwent subsequent passive rewarming over the next 8 hours. They were sedated, paralyzed, and ventilated to prevent shivering. Fifty-five percent of the patients in the hypothermia group had a favorable neurological outcome, that is, they were able to live independently and work at least part-time at 6 months compared to 39% in the normothermia group. The mortality in the hypothermia group was 41% versus 55% in the normothermia group.<sup>31</sup>

Based on these trials, the International Liaison Committee on Resuscitation (ILCOR) recommended hypothermia at 32 to 34°C for 12 to 24 hours for patients who have been resuscitated from out-of-hospital cardiac arrest (OHCA).<sup>32</sup> A Cochrane meta-analysis by Holzer et al revealed that hypothermia at 33°C, when applied to patients who had survived an OHCA, had a favorable neurological recovery at discharge with an odds ratio of 1.68 (CI: 1.29–2.07) with an NNT of 4 to 13.<sup>33</sup>

One of the most significant and recent trials was the TTM 33 to 36 trial by Nielsen et al. This was a prospective multicenter trial done in Australia and Europe, where 939 OHCA survivors were randomized for cooling to 33 or 36°C along with protocol-based sedation, rewarming, and evaluation of prognosis. The cooling methods were not standardized and were left to the discretion of the study center with an intention to reach the target temperature as quickly as possible. After 28 hours, controlled rewarming (0.5°C per hour) was initiated. The investigators concluded that there was no difference in the outcome or complications between the two groups.<sup>34</sup>

In spite of this trial, the American Heart Association (AHA) in their 2015 guidelines recommended that comatose adult patients who had been resuscitated after cardiac arrest should undergo TTM (class I, level of evidence [LOE] B-R) for OHCA and non-ventricular fibrillation (VF)/pulseless ventricular tachycardia (VT) (nonshockable and in-hospital arrests [Class I, LOE-Expert opinion]).<sup>35</sup> The AHA recommended maintaining a constant temperature between 32 and 36°C during TTM (Class I, LOE B-R).<sup>35</sup> They recommended against the routine prehospital cooling of patients after return of spontaneous circulation (ROSC) with rapid infusion of cold IV fluids (Class III: no benefit, LOE A).<sup>35</sup> The ILCOR issued a statement after the TTM 33 to 36 trial urging clinicians to guide themselves with the existing recommendations as some institutions interpreted the results of the trial as evidence against therapeutic hypothermia.

In a study done by Chan et al, in patients who had in-hospital cardiac arrest, has reported that the use of therapeutic hypothermia compared to usual care was associated with lower survival likelihood and hospital discharge and a less favorable neurological outcome. Their findings warrant a randomized controlled trial to assess the efficacy of the application of therapeutic hypothermia for patients having in-hospital cardiac arrest.<sup>36</sup>

An international, investigator-initiated, blinded-outcome-assessor, parallel, pragmatic, multicenter, randomized clinical superiority trial was done by Kirkegaard et al in 10 critical care units at 10 university level hospitals across six European countries. They randomized post-cardiac arrest patients to TTM

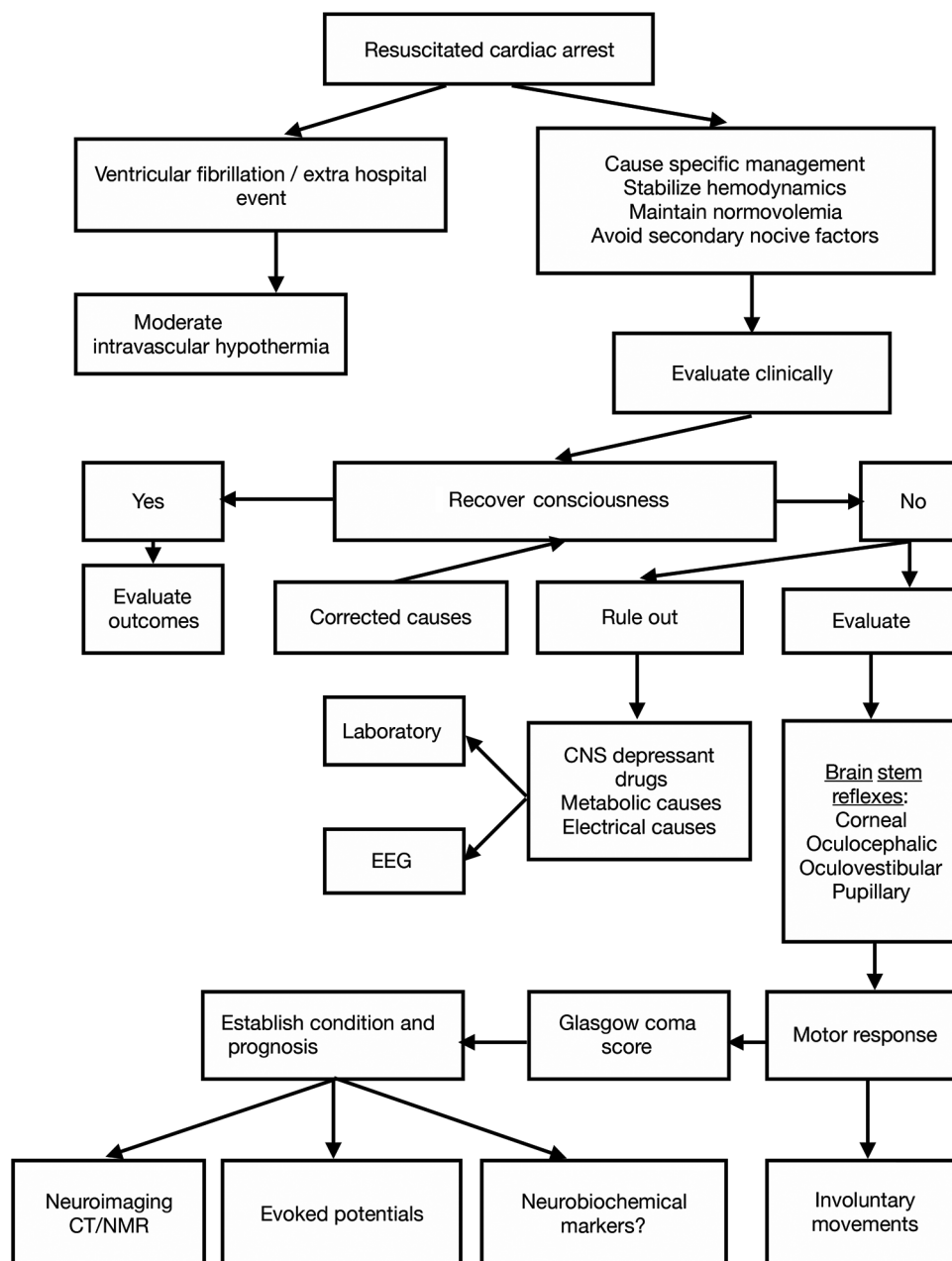
(33±1°C) for 48 hours (n=176) or 24 hours (n=179), followed by gradual rewarming of 0.5°C per hour until reaching 37°C. A Cerebral Performance Categories score of 1 or 2 was used to define favorable outcome at 6 months. Six-month mortality, including time to death, the occurrence of adverse events, and intensive care unit resource use were studied as secondary outcomes. They concluded that in patients who had survived OHCA, TTM at 33°C for 48 hours did not improve the 6-month neurologic outcome compared to those managed at 33°C for 24 hours. Their major limitation was that it was underpowered to detect clinically important differences.<sup>37</sup>

What remains unanswered is how the data and the results of these trials can be extrapolated to populations whose

quality and rate of bystander CPR are far inferior to the excellent rates reported in the TTM trials. This poor-quality CPR could result in more severe ABI, which may derive a more significant benefit from therapeutic hypothermia than in those with a milder injury.

Thus, the current consensus issued by AHA states that TTM between 32 and 36°C applied to post-cardiac arrest patients with prompt initiation and rapid achievement of the target temperature is ideal.<sup>35</sup> There should be controlled rewarming at 0.25 to 0.5°C per hour. There is evidence that initiation of TTM after 12 hours has no benefit.<sup>35</sup>

The comprehensive approach and management of a patient with ABI have been summarized in ►Fig. 2.



**Fig. 2** Comprehensive approach and management of a patient with anoxic brain injury. CNS, central nervous system; CT, computed tomography; EEG, electroencephalogram; NMR, nuclear magnetic resonance.

## Conclusion

ABI is an important cause of prolonged hospital stay and morbidity across the globe and is a sequel of major systemic insults resulting from various etiologies. Neuroprognostication is important in planning the future course of management of this complex neurological condition. TTM still remains a therapeutic tool in ABI and along with other neuroprotective measures, may improve the survival. Continuing research in ABI may uncover more promising treatment strategies in the future.

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None

### Conflict of Interest

None declared.

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