



# Observation Time Prior to Determination of Death by Neurologic Criteria

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Medical standards on determination of death by neurologic criteria require demonstrating that, prior to commencing an evaluation, a patient has an established neurologic diagnosis, the nature and severity of which is capable of resulting in the irreversible loss of the capacity for consciousness, all brainstem reflexes, and the ability to breathe spontaneously [1–11]. In other words, the patient must have a neurologic diagnosis that could cause death by neurologic criteria and imaging or other data that suggests the injury is severe enough that it may have caused death by neurologic criteria. Additionally, prior to the evaluation, the presence of confounding factors must be excluded.

Establishing that a diagnosis is severe enough to lead to death by neurologic criteria is easiest when there is a structural injury and the damage is evident on imaging, such as after extensive head trauma, hemorrhage, or massive edema. In such cases, the time at which one begins the evaluation for death by neurologic criteria is not of major importance once confounding conditions have been ruled out. The structural damage is evident and clearly severe enough that the patient may be dead by neurologic criteria. Thus, the identification of an irreversible mechanism that has led to a severe injury and the elimination of all confounders are the relevant considerations prior to beginning an evaluation, rather than observation for a specific amount of time [12–29].

Contrastingly, there can be uncertainty about when to begin an evaluation for determination of death by neurologic criteria in the absence of imaging consistent with irreversible damage and edema, as may be the case after circulatory-respiratory arrest. Neurologic assessments may be unreliable in the acute post-resuscitative

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phase after circulatory-respiratory arrest, so many standards recommend that an evaluation for determination of death by neurologic criteria be delayed for at least 24 h post-arrest or an ancillary test be performed [3, 30, 31].

In this chapter, we examine the current standards and evidence for timing of the evaluation for determination of death by neurologic criteria after structural brain injury and hypoxic-ischemic brain injury (with consideration of the impact of targeted temperature management). We then review the advantages and disadvantages of delaying the evaluation for determination of death by neurologic criteria.

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## **1 Current Standards and Evidence for Timing of the Evaluation for Determination of Death by Neurologic Criteria After Structural Brain Injury**

### **1.1 Current Standards**

In general, there is very little controversy about the observation time required prior to evaluation for determination of death by neurologic criteria in patients with structural brain injuries [1–11, 30, 31]. Medical standards for determination of death by neurologic criteria indicate that an evaluation for determination of death by neurologic criteria can commence in the setting of coma and absence of motor function and brainstem reflexes if there is a known, proximate cause for the injury that is irreversible. Although there must be definite clinical or neuroimaging evidence of an acute event that has led to the irreversible loss of brain function, only 27% of international medical standards require neuroimaging prior to the evaluation [1]. Additionally, confounders must be ruled out, but there is variation in the factors that are considered across international standards such as: drug clearance (82%), temperature (78%), laboratory values (72%), and blood pressure (44%) [1]. After this step, the question is how much time must elapse in this state to be absolutely sure that the situation is irreversible?

In the United States [2, 5], Canada [8], and many other countries [1, 3, 4, 9–11, 30, 31], once these prerequisites have been met, the evaluation can begin; no minimum observation time is specified. Contrastingly, 24% of international standards require an observation period between 1 and 48 h for all determinations of death by neurologic criteria [1]. Further, a few standards specify the need for an observation period prior to evaluation for death by neurologic criteria after intracerebral hemorrhage (3 standards require a delay of 6 h), major neurosurgical procedures (2 standards require a delay of 4–6 h), secondary brain injury (6 standards require a delay of 12–72 h), or traumatic brain injury (5 standards require a delay of 6 h) [1].

The World Brain Death Project provides some guidance on the observation period prior to performance of an evaluation for determination of death by neurologic criteria that is relevant to patients with structural or hypoxic-ischemic brain

injury [30]. The authors note that the period of observation prior to an evaluation for determination of death by neurologic criteria for patients with structural brain injuries should be determined on a case-by-case basis and should be the time thought necessary to confidently exclude reversibility. They emphasize the need for caution. They further advise that prior to commencing an evaluation for determination of death by neurologic criteria, it must be demonstrated that the patient has an established neurologic diagnosis, the nature and severity of which is capable of resulting in the irreversible loss of the capacity for consciousness, all brainstem reflexes, and the ability to breathe spontaneously during a carbon dioxide and acidosis challenge. Additionally, they suggest that there be: (1) neuroimaging evidence of intracranial hypertension (severe cerebral edema and herniation) or (2) intracranial pressure measurements that equal or exceed the mean arterial pressure. In the absence of herniation on neuroimaging, it is suggested that caution be taken when considering performance of an evaluation for determination of death by neurologic criteria. Lastly, they note that confounders and/or reversible conditions that may mimic death by neurologic criteria must be excluded prior to commencing an evaluation for determination of death by neurologic criteria.

## 1.2 Evidence

There is insufficient evidence to determine the minimally acceptable observation period to ensure that neurologic functions have ceased irreversibly after structural brain injury. However, performance of serial evaluations to assess for evidence of return of function can be considered. The number of evaluations required to determine death by neurologic criteria is discussed elsewhere in this book. The appropriate observation period prior to evaluation for determination of death by neurologic criteria is the focus of a systematic review being conducted by a working group representing Canadian Blood Services, the Canadian Critical Care Society and the Canadian Medical Association A Brain-Based Definition of Death and Criteria for its determination After Arrest of Circulatory in Neurologic Function in Canada: A Clinical Practice Guideline.

## 1.3 Recommendation

As there is no firm evidence to dictate the observation time prior to evaluation for determination of death by neurologic criteria after structural brain injury, in accordance with most standards, we believe there is no minimal observation time necessary, as long as (1) there is an established cause for the patient's condition and the severity is sufficient to lead to irreversible loss of brain function and (2)

physiologic factors that may confound the evaluation have been screened for and excluded.

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## **2 Current Standards and Evidence for Timing of the Evaluation for Determination of Death by Neurologic Criteria After Hypoxic-Ischemic Brain Injury**

During circulatory-respiratory arrest, there is cessation of oxygen and glucose delivery to the entire body, including the brain. If this deprivation is not reversed, cessation of brain circulation will inevitably lead to permanent loss of brain function. When return of spontaneous circulation is achieved, it is not possible to evaluate the extent of recovery without a period of observation. Several studies on prognostication after circulatory-respiratory arrest demonstrate that a patient who is comatose and has absent brainstem reflexes immediately after return of spontaneous circulation can subsequently have return of brain function [32]. The role of targeted temperature management in survivors of cardiac arrest remains controversial in terms of outcome modification, but it is widely accepted that therapeutic hypothermia represents a potential confounder of accurate neurologic prognosis and should be resolved prior to definitive prognostic evaluation or neurologic determination of death [8, 29, 30, 33]. Imaging after hypoxic-ischemic brain injury may not show signs of intracerebral edema, herniation, or brain damage in the first 48 h post-arrest [34, 35].

### **2.1 Current Standards**

Guidance on the length of an observation period after hypoxic-ischemic brain injury vary both around the world and within the United States [6, 36]. In most countries, the observation time is not specified, but 17% of standards note that the evaluation should be delayed 24 h after hypoxic-ischemic brain injury in the absence of targeted temperature management, and 10% indicate there is a need for a delay when targeted temperature management is used [1]. The 2006 standard on determination of death by neurologic criteria in Canada noted that neurologic assessments may be unreliable in the acute post-resuscitation phase after circulatory-respiratory arrest, so evaluation for determination of death by neurologic criteria should be delayed for 24 h or an ancillary test should be performed [8]. The 2010 standard published by the American Academy of Neurology did not differentiate an observation time after hypoxic-ischemic brain injury as compared with structural brain injury; rather, it stated that there is insufficient evidence to determine the minimally acceptable observation period to ensure that neurologic functions have ceased irreversibly [5]. In European standards, timing prior to and between evaluations vary from 6–12 h, and many countries with a stipulated observation period recommend consideration of ancillary testing in lieu of waiting [37].

In addition to the aforementioned guidance provided by the World Brain Death Project about the observation time prior to performance of an evaluation for determination of death by neurologic criteria, the authors provide specific guidance that is relevant to patients with hypoxic-ischemic brain injury [30]. They recommend waiting a minimum of 24 h after hypoxic-ischemic brain injury before performing an evaluation. Further, after treatment with targeted temperature management, they advise waiting a minimum of 24 h after rewarming to  $\geq 36$  °C, taking clearance of medications that depress the central nervous system into consideration.

## 2.2 Evidence

There are no studies of the appropriate observation time after hypoxic-ischemic brain injury prior to evaluation for determination of death by neurologic criteria. The best surrogate for this data is the results of neuroprognostication studies. Sandroni et al. recently (2020) performed a systematic review of studies predicting poor neurologic outcome after circulatory-respiratory arrest [32]. They identified a 0% false-positive rate for prediction of poor outcome with bilateral absence of standard pupillary light reflex at 48 h after return of spontaneous circulation in some studies, which became consistent after 4 days, with sensitivities ranging from 18 to 36%. Similarly, they found a 0% false-positive rate for prediction of poor outcome at 48 h after return of spontaneous circulation or later (range 0–4%). Bilateral absence of the corneal reflex 4 days after return of spontaneous circulation consistently predicted a poor outcome; sensitivity ranged from 23 to 41%. Absence of pupillary light reflex in combination with the absence of corneal reflex on admission or within 72 h predicted poor neurologic outcome with false-positive rate ranging from 0 to 9% and sensitivity ranging from 27 to 28%. The absence of other brainstem reflexes, such as oculocephalic, gag, and cough reflexes, had 0% false-positive rate starting from 48 h after return of spontaneous circulation, but precision was low. An absent or extensor motor response to pain had high sensitivity, but low specificity, for poor outcome.

Although Sandroni's meta-analysis is helpful for neuroprognostication, death by neurologic criteria was not isolated from other poor outcomes, and there was no predictive value for absence of all brainstem reflexes. Nonetheless, we can extrapolate that the presence of coma, the absence of oculocephalic, gag and cough reflexes (false-positive rate = 0% at 48 h) combined with the absence of pupillary light reflex and corneal reflex at 48 h after return of spontaneous circulation is almost universally consistent with a poor neurologic outcome. However, while these findings are consistent with a poor neurologic outcome, Sandroni's study did not specifically address recovery of absent brainstem reflexes or motor responses.

## 2.3 Recommendation

Data is lacking on the appropriate time to observe a patient after hypoxic-ischemic brain injury, particularly if they are treated with targeted temperature management. However, extrapolating from the literature discussed above, we believe that unless there is clear evidence of severe hypoxic-ischemic damage on imaging after circulatory-respiratory arrest, it is probably best to wait at least 48 h before performing an evaluation for determination of death by neurologic criteria.

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## 3 Advantages and Disadvantages of Using a Longer Observation Period Before Evaluation for Determination of Death by Neurologic Criteria

### 3.1 Opportunity to Address Diagnostic Uncertainty

In cases where there is any uncertainty about whether it is appropriate to perform an evaluation for death by neurologic criteria, it is *always* appropriate to delay the evaluation for further monitoring and discussion with senior specialized clinicians.

### 3.2 Resolution of Confounders

It would seem logical that, the greater the time elapsed between neurologic injury and evaluation for determination of death by neurologic criteria, the greater the certainty that modifiable confounders have resolved. For example, the more time that passes after a patient received a medication that could depress the central nervous system, the more certain one can be that the effect of that medication has resolved. Common time-dependent confounders include sedative medications, neuromuscular blocking medications, intoxicants (i.e. alcohol, illicit substance ingestion), hypothermia, electrolyte derangements, and oxygenation or ventilation derangements [26–29, 38].

### 3.3 Availability of Senior Specialized Clinicians

Many healthcare systems operate using a model in which the most senior clinicians provide coverage and oversight of their patients with a combination of in-person presence and remote supervision of trainees. An accurate evaluation for determination of death by neurologic criteria is needed to avoid a false-positive determination (determination that a patient is dead when they are not) or a false-negative determination (determination that a patient is not dead when in fact, they are). Delaying an evaluation to ensure the most experienced clinician is available to perform an in-person assessment at the bedside facilitates the greatest degree of accuracy. Of course, any clinician performing this evaluation should have adequate training and

experience to do so with maximal accuracy. In some cases, it is necessary for a specialist with neurosurgical or neurological expertise to perform the evaluation or for a specialist with neuroradiology or electrophysiology training to interpret an ancillary test, so the evaluation should be delayed until they are available.

### **3.4 Communication and Education for Families**

Injuries that lead to death by neurologic criteria are generally unexpected. Further, as discussed elsewhere in this book, families often have a poor understanding of death by neurologic criteria. Therefore, it is necessary for clinicians to take the time to carefully educate them about the patient's condition before performing an evaluation for determination of death by neurologic criteria. Communication and education about death by neurologic criteria often requires time. A delay between brain injury and evaluation for determination of death can allow families to come to terms with the situation [39].

### **3.5 Respect for Patients and Their Families**

An unnecessary delay prior to an evaluation for determination of death by neurologic criteria can be considered disrespectful to both patients and families. It exposes patients to non-therapeutic interventions related to ongoing critical care and can lead to prolongation of suffering for families who may be anxiously awaiting a definitive answer about the patient's condition. Once it is believed that a patient may be dead by neurologic criteria and the prerequisites are met, it is incumbent on the medical team to perform an evaluation and communicate their findings to the patient's family in a timely fashion.

### **3.6 Resource Utilization**

Another potential harm of delaying the evaluation for determination of death by neurologic criteria is the unnecessary use of critical care resources. In healthcare systems with limited resources, this is particularly problematic. Inappropriate critical care increases cost and has the potential to negatively impact the quality of care for other patients who could benefit from critical care. Lustbader et al. found a substantial increase in intensive care unit costs with an increased time interval between evaluations for determination of death by neurologic criteria, and an increase in observation time undoubtedly also leads to increase in cost [40]. There is no doubt that a longer observation time means a longer ICU stay, and an increase in resource utilization. However, cost and resource utilization should not lead to rushed evaluations.

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### 3.7 Organ Donation

Although the primary purpose of an evaluation for determination of death by neurologic criteria is to distinguish alive from dead, it is important to note that patients who are determined to be dead by neurologic criteria have the potential to be organ donors. Allowing a period of observation prior to the evaluation can facilitate the engagement of organ donation organizations with families. Delaying the evaluation, however, can reduce organ donation. Lustbader et al. reported that performing a second evaluation for determination of death by neurologic criteria negatively affects organ donation [40]. In this series of 1229 adults and 82 pediatric patients declared dead by neurologic criteria, the mean interval between evaluations was 19.9 h in smaller hospitals compared to 16 h in larger centers. The authors noted an increase in rate of refusal, a decrease in consent, and an increase in organ loss due to circulatory-respiratory arrest between evaluations. No patient regained brainstem function between the evaluations. In another small study [41], the authors found that a delay of more than 6 h in the determination of death by neurologic criteria negatively affected consent for organ donation.

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## 4 Conclusion

Given the ramifications of an evaluation for determination of death by neurologic criteria and the risks of a false-positive determination, patients with devastating brain injuries should be admitted to an intensive care unit to allow sufficient time for a specialist to assess them, exclude confounders, and communicate with families before performance of an evaluation for determination of death by neurologic criteria [42]. The absolute duration of observation cannot be specified. We believe that in patients with a structural brain injury leading to edema and herniation, an evaluation for determination of death by neurologic criteria can be performed whenever confounders have been eliminated. In patients with hypoxic-ischemic brain injury, if imaging is done in the first hours after the event (or not at all) and does not demonstrate that the injury is irreversible and catastrophic, we believe the evaluation for determination of death by neurologic criteria should not be performed in the first 24 h post-arrest (or 24 h after rewarming if treated with targeted temperature management), and should probably be delayed for 48 h (noting that drugs are metabolized much more slowly in this situation, especially in the context of hypothermia). Clinicians should take individual circumstances into consideration on a case-by-case basis.

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