

Supplementary Online Content

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Supplement 3. The Concept of Death by Neurologic Criteria/Death by Neurologic Criteria

This supplementary material has been provided by the authors to give readers additional information about their work.

The Concept of Death by Neurologic Criteria/Death by Neurologic Criteria

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Abstract **Key Words:** brain death, brainstem death

Introduction Prior to the 1950s, death was determined solely by cardiopulmonary criteria. The concept of brain death/death by neurologic criteria (BD/DNC) was developed in the 1950s in response to the advent of cardiopulmonary resuscitation and positive pressure ventilation.

Methods We conducted a review of the literature and formulated recommendations with an expert panel on the concept and determination of death by neurologic criteria.

Results and Conclusions There are three formulations of death by neurologic criteria: whole brain death, brainstem death, and higher brain death. The “whole brain death” and “brainstem death” formulations are both used today in different countries. Their clinical application usually leads to the same conclusion, differing only in the rare case of isolated primary brainstem or posterior cerebral circulation pathology.

This section reviews historical concepts of death by neurologic criteria, with emphasis on rationale and conceptual models of brain-based determinations of death.

Methods

Authors conducted the initial literature searches of the Cochrane, Embase and MEDLINE databases for the time period between January 1, 1992 and July 2017. Subsequent searches were performed to capture relevant articles between July 2017 and April 2020. Because of the significant lack of data from randomized controlled trials or large studies, GRADE evaluation of the evidence was not performed. However, evidence was reviewed by a multidisciplinary group of clinicians (see Introduction chapter) and recommendations were generated according to the following criteria. Strong recommendations (“It is recommended that”) were based on expert consensus that clinicians should follow the recommendation unless a clear and compelling rationale for an alternative approach was present, and where actions could be adopted as policy. Even though most evidence in this area is limited and of low-quality, strong recommendations were made as a precautionary, conservative approach, to prevent premature or erroneous determinations of death (false positives). Conditional or weak recommendations (“It is

suggested that”) were generated when there were potentially different options and the best action may differ depending on circumstances, patients, resources or societal values, or where there is a need for further evidence or discussion among clinicians and stakeholders. In cases where there was insufficient evidence and the balance of benefits versus harms was neutral, no recommendations were made.

Development of the Concept of Death by Neurologic Criteria

Prior to the 1950s – when positive-pressure ventilation (PPV) and cardiopulmonary resuscitation (CPR) were developed – death was conceptually a unitary phenomenon and its bedside determination was straightforward and uncontroversial. Death was the permanent cessation of the three “vital functions” of respiration, circulation, and brain function. Because of their mutual interdependence, once any one vital function ceased, the others inevitably ceased within a few minutes because no technologies existed to reverse ventricular fibrillation/asystole or to support ventilation to compensate for complete apnea.

The development of CPR and PPV forever severed the mutual interdependence of the vital functions. Timely CPR could restore circulation in formerly fatal ventricular fibrillation/asystole, and PPV could support respiration in formerly fatal apnea. Complete cessation of all brain functions could occur, but technological support could maintain respiration and circulation, at least temporarily. The traditional concept of death could not answer the question of whether such a person was alive or dead because they retained two of the traditional vital signs (respiration and circulation) but had permanently lost the third vital sign (brain function). It was to resolve this enigma that neurologists first proposed that, because brain function was the most essential vital function, its complete and permanent absence indicated death, irrespective of the continued technological support of respiration and circulation.

Clinical descriptions of such cases were first reported in the late 1950s by Mollaret and Goulon, called “le coma dépassé” (a state beyond coma), an irreversible state of apneic coma with absent brainstem reflexes and absence of electroencephalographic (EEG) activity.¹ In 1968, a Committee of Harvard University faculty proposed clinical and EEG criteria to diagnose this state that they called “brain death,”² now also called death by neurologic criteria (BD/DNC), terms that have been subject to misinterpretation. They asserted that, despite the presence of mechanically supported respiration and consequent circulation and visceral organ functioning, people with permanent loss of all functions of the entire brain were dead. The Harvard report had a powerful influence on medical practices in hospitals throughout the world.³

Rationales to Support Use of Neurologic Criteria to Declare Death

BD/DNC proponents cite several arguments to justify its equivalence with human death. The most compelling argument is that, in our technological era, death is the permanent cessation of function of the organism as a whole. The organism as a whole is not synonymous with the whole organism (the sum of its parts), but refers instead to a higher order concept encompassing the unique emergent functions of the organism.⁴ According to this argument, technological support can maintain life in the parts of a human organism, despite the organism’s death, once there has been permanent cessation of function of the organism as a whole. The brain is primarily responsible for the set of emergent functions defining the organism as a whole.⁵ A related justification is that the brain is the thermodynamic anti-entropic “critical system” governing the organism.⁶ The argument that the brain is the organism’s principal functional

integrator, while true in the 1970s when it was developed, has been shown to be inadequate now that intensive care unit technology can replace some of these integrating functions.⁷

Today, there is widespread acceptance, especially in the Western world, that human death is the permanent cessation of function of the brain. This idea is generally taken to mean the permanent loss of capacity for consciousness combined with the permanent loss of capacity to breathe.

Opponents of BD/DNC cite several arguments to deny the equivalency of BD/DNC and human death. First, they claim that BD/DNC is not what we mean by death and that it should be abandoned as an anachronism.⁸ Some scholars claim that BD/DNC is merely a “legal fiction” contrived by doctors and society to permit organ donation.⁹ Other opponents cite the fact that some persons diagnosed as brain dead can be physiologically maintained for months or years, and in some cases, can grow, achieve puberty, or gestate infants – all capacities that are incompatible with being dead.¹⁰ Debate persists around distinctions between the absence of brain function, such as capacity for consciousness or ability for unassisted breathing, and the potential for persistence of cellular activities, such as posterior pituitary antidiuretic hormone release or residual nests of neuronal electrical function. Some scholars argue that BD/DNC is simply incoherent on both conceptual and physiological grounds.^{11,12} The debate over the conceptual validity of BD/DNC has largely been confined to academic circles.¹³ However, recent high profile media cases of family refusals to accept BD/DNC based on religious objections have brought this debate to wider society. Given the technological ability to provide prolonged somatic support and the mounting frequency of requests for religious accommodation, this debate remains ongoing. The current societal status of BD/DNC was aptly but ironically described by one public policy leader in the BD/DNC movement as “well settled yet still unresolved.”¹⁴

Three Conceptual Models for Death by Neurologic Criteria

The Harvard report championed the “whole brain” formulation for BD/DNC, i.e. that BD/DNC requires the permanent cessation of function of the cerebral hemispheres, diencephalon, brainstem, and cerebellum. This approach was ultimately accepted throughout the United States and most other countries,¹⁵ and it is the foundation of a successful public policy.⁶ Within a few years, however, two other distinct brain-based concepts of death were developed.¹⁶

Firstly, in the United States in the 1970s, the “higher brain” formulation was described and became popular in academic circles. This approach to BD/DNC requires only the permanent cessation of bilateral cerebral hemispheric function. The higher brain formulation was rationalized based on the fact that consciousness and cognition, not brainstem function, are unique defining attributes in humans.¹⁷ Notably, this formulation does not meet the generally accepted definition of BD/DNC, i.e., the permanent loss of capacity for consciousness combined with the permanent loss of capacity to breathe, as a person with loss of only cerebral hemispheric functions can still breathe. This formulation classifies patients in permanent vegetative states as dead. As a result, despite many academic proponents, the “higher brain” formulation never has achieved sufficient traction to influence any medical societies or jurisdictions in the United States to change from the prevailing whole-brain formulation, and it was not embraced anywhere else in the world.

The second alternative to the “whole brain” formulation is the “brainstem” formulation of death, which requires only total brainstem failure. This concept became popular in the United Kingdom after

Mohandas and Choi conducted an autopsy study that showed that the state of irreversible coma and apnea was associated with autolysis of the brainstem.^{18,19} This approach is defended on the grounds that the brainstem houses the seats of consciousness, respiration, and circulation, and is a through station for nearly all cerebral hemispheric input and output. Cognitive processing is therefore incompatible with cessation of midbrain function, and higher centers cannot become activated without the brainstem.²⁰ The United Kingdom and a few other countries currently accept the brainstem death formulation.

“Whole Brain” Death Versus “Brainstem” Death

The transatlantic debate over whether the “whole brain” or “brainstem” formulation should be used to determine BD/DNC has undermined both public and professional confidence in the credibility of BD/DNC.²¹ Attempting to define BD/DNC based on anatomical structures is the root of this controversy. A move to base BD/DNC on permanent loss of brain function would help decrease variability and promote international consensus and provide a more consistent, standardized approach to the diagnosis. This move requires consensus on the extent of loss of brain functions that is necessary to make the clinical diagnosis, and when, and which, ancillary tests are required. Calls for international consensus on this issue and attempts to achieve this by standardizing practice and reducing variability have been made and remain ongoing.^{22,23}

In clinical practice, there is little difference in how death is determined using the “whole brain” or the “brainstem” death formulation. Both “brainstem death” and “whole brain death” are generally the result of infratentorial damage resulting from a devastating supratentorial injury with transtentorial herniation such as from intracerebral hemorrhage, traumatic brain injury or subarachnoid hemorrhage. While the two formulations may differ conceptually, the process and clinical procedures for making the determination are nearly always synonymous.²⁴ In both formulations, the determination of BD/DNC requires a three-staged clinical approach that identifies: (1) an established cause for the condition; (2) the exclusion of confounders and reversible causes; and (3) the absence of all brainstem reflexes and the capacity to breathe. In some countries, there is also a requirement to use ancillary tests to confirm whole brain death via demonstration of absent brain blood flow or an isoelectric EEG.

The difference between the “whole brain” and “brainstem” formulations is most evident in the presence of an isolated brainstem injury.²⁴ This situation is highly unusual; a recent observational study estimated that “primary brainstem death” comprised only 1.9% of all BD/DNC clinical examinations in a single hospital over a period of 88 months (3/161 adult patients with isolated brainstem death in a single US center).²⁵ Nonetheless, a patient could have a devastating brainstem injury, yet retain supratentorial blood flow and evidence of electrical activity including EEG activity, visual evoked potentials or somatosensory evoked potentials, at least transiently.²⁶⁻³⁴ In principle, if brainstem function is completely lost, then transmission of evoked potentials through the brainstem should also be absent. Theoretical concerns have been expressed regarding infratentorial lesions with loss of clinical brainstem function with the possibility of sparing the reticular activating system and preservation of some form of undetected consciousness.³⁵ The detection of persisting supratentorial flow or electrical activity does not infer brain function – the relationship between persistence of electrical activity and brain function in posterior fossa lesions consistent with brainstem death has not been well studied. In a single center study, four patients with primary brainstem or cerebellar injuries had clinical findings consistent with BD/DNC, but had

supratentorial blood flow on computed tomographic (CT) angiography that disappeared on repeat cerebral blood flow testing in all four cases.²⁵ Similarly, in a retrospective Spanish study, 2.4% of 289 patients clinically diagnosed as BD/DNC after a posterior fossa injury had preserved EEG activity that was subsequently lost on repeat testing. In two of these cases, which were both caused by basilar artery thrombosis, the EEG activity only abated after 100 hours.³² Both of these studies suggest that “primary brainstem death” progresses over time to entire BD/DNC. Yet, a 2008 White Paper on Controversies in the Determination of Death by The United States’ President’s Council on Bioethics noted that a determination of BD/DNC requires destruction of both the brainstem and the structures above it and emphasized that the condition of the brainstem is not a reliable indicator of the condition of the higher brain centers.³⁶

Should Absence of Brain Blood Flow be Required to Make a Determination of BD/DNC?

According to a recent meta-analysis, preservation of supratentorial blood flow with CT angiography evidence of filling of the cortical branches of the middle cerebral artery, the internal cerebral veins, or both, is seen in 15%–16% of all patients diagnosed clinically as BD/DNC, not solely those who have isolated brainstem lesions.³⁷ Recent studies have shown that patients with supratentorial pathology, ancillary test (EEG or CT angiography) confirmed clinical assessment 98% of the time.³⁸ For the cases in which the ancillary test did not confirm the clinical exam, the ancillary test was performed within the first 2 hours after the clinical assessment. A maximum observation of 25.5 hours was required before the ancillary test supported the clinical exam. The relevance of persistent perfusion is debatable. Some argue that the opacification of larger supratentorial vessels may be due to stasis filling, because the loss of flow starts at the capillary level, and its presence does not necessarily preclude the diagnosis of BD/DNC. This perspective is supported by a recent study that demonstrated non-viable brain using CT perfusion, despite the presence of flow in the larger cerebral vessels on CT angiography.³⁹

The existing limitations in the ability to distinguish between flow, perfusion and function support that BD/DNC remains a clinical determination based on loss of function. (For an in-depth discussion of the validity of ancillary brain blood flow testing in BD/DNC, refer to the Beyond Minimum Clinical Criteria chapter). However, in principle, the most reliable method to determine the absence of flow, perfusion and function is after the permanent loss of oxygenated circulation to brain subsequent to a confirmed cardiac arrest resulting in cessation of circulation. The prevalent dual conceptions of death, brain-based versus heart-based, may therefore be harmonized into a single brain-based definition of death subsequent to devastating brain injury or after a circulatory arrest.^{23,40}

Irreversibility

The meaning of the terms irreversible and permanent (cannot be reversed under any conditions versus will not be reversed under existing conditions) has been debated extensively in death after circulatory-respiratory formulations of death.⁴¹ Death after cardiac arrest is contingent on the access and decision to deploy cardiopulmonary resuscitation and/extracorporeal resuscitation.⁴⁰ The permanent cessation of circulatory arrest has been widely accepted, based on acceptance that the circulation will not, rather than cannot, be resumed.

Recent animal studies have shown the ability to restore brain circulation and cellular function, without electrographic activity, hours post mortem with ex vivo normothermic perfusion to a decapitated

pig brain removed from the cranium.⁴² Studies of this experimental nature challenge the outer limits of the ability to resuscitate brain function with resumption of circulation. While they may inform improvements in brain resuscitation after resuscitated cardiac arrest, they do not inform nor confound existing concepts of BD/DNC.

Brain death determination is almost always a retrospective determination showing that an event has previously occurred. Therefore, its delineation always has required irreversible cessation of brain function. In the context of BD/DNC, it is recognized that interventions to decrease intracranial pressure, such as hyperosmolar therapy, ventricular drainage and decompressive craniectomy, should be applied when clinically indicated during neuroprotective phases of care. Ensuring irreversibility of a person's clinical state in BD/DNC does not require performance of non-therapeutic interventions to decrease intracranial pressure that are not judged to be clinically indicated.

There are no recorded instances in the literature of a recovery of neurologic function after a correctly performed neurological examination diagnosing BD/DNC.⁴³ Shewmon describes the McMath case as such an example but this report is unsubstantiated at this time.⁴⁴

Recommendations and Suggestions

1. It is recommended that brain death/death by neurologic criteria (BD/DNC) be defined as the complete and permanent loss of brain function as defined by an unresponsive coma with loss of capacity for consciousness, brainstem reflexes and the ability to breathe independently. This may result from permanent cessation of oxygenated circulation to the brain and/or after devastating brain injury. Persistence of cellular level neuronal and neuroendocrine activity does not preclude the determination. In the context of death determination, 'permanent' refers to loss of function that cannot resume spontaneously and will not be restored through intervention.
2. It is recommended that ensuring irreversibility of a person's clinical state in BD/DNC does not require performance of interventions to decrease intracranial pressure that are not judged to be clinically indicated.
3. It is recommended that persistence of hormonal regulatory function does not preclude the diagnosis of BD/DNC.
4. It is suggested that the terms "whole brain death" and "brainstem death," should be abandoned and replaced with BD/DNC. However, it is recognized that many jurisdictions have laws and/or medical standards using the 'whole brain' or 'brainstem' terminology. As such, it is recommended that clinicians be guided by the laws and standards in their jurisdictions.
5. It is suggested that if an assessment for BD/DNC is being made in a region that equates "whole brain death" with BD/DNC, in the setting of an isolated brainstem lesion or posterior circulation vascular lesion, ancillary testing should be performed. In these circumstances, it is suggested that BD/DNC should not be diagnosed until supratentorial and infratentorial blood flow is lost, even if the clinical examination and apnea test are suggestive of BD/DNC.

Questions to Inform Research Agendas

1. When contrasting supratentorial pathology to infratentorial pathology (brainstem and/or posterior fossa):
 - a. What is the natural history for those who fulfil minimum clinical criteria for BD/DNC? Is there a risk of return of any brain function if BD/DNC is declared clinically in these populations?
 - b. What proportion of those who fulfil minimum clinical criteria for BD/DNC would have absence of cerebral blood flow on ancillary testing?
 - c. Should patients who have signs of BD/DNC because of brainstem compression first undergo decompression or ventriculostomy to assure irreversibility?
 - d. Are there additional tests that can exclude the possibility of clinically undetectable cerebral function in persons who fulfil the clinical criteria for BD/DNC?
 - e. What is the role of fMRI in persons with isolated brainstem pathology who fulfil the clinical criteria for BD/DNC?
2. What variables predict temporal evolution to intracranial hypertension and herniation in persons with isolated brainstem or posterior fossa pathology?
3. Are there tests that can confirm the complete and irreversible destruction of the entire brainstem?

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