

## Standardizing Brain Death Globally

Wade S. Smith, MD, PhD

**Neurologists**, neurointensivists, neurosurgeons, and intensivists worldwide at times are required to determine brain death/death by neurological criteria (BD/DNC). Variance in the practice of diagnosis is known to vary by country and region,



Viewpoint



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resulting in the uncomfortable status that a patient is considered deceased in one region but not in another. For example, within the US, a patient can be deceased yet transition to alive simply by crossing a state line.<sup>1</sup> Such variations multiply when considering the global scope. To better delineate the range of practice, custom, and legal considerations, more than 50 international medical professionals led a worldwide effort to document global practice to make consensus recommendations for BD/DNC declaration.<sup>2</sup> This consensus is summarized in the article,<sup>2</sup> which references a 193-page supplement detailing the basis for the recommendations ranging from “recommend” to “it is suggested to” to best deal with the vagaries of international practice. The scope of this review eclipses any prior synopsis on BD/DNC because of its global scope, attention to recent advances in critical care, and summary of how various cultures and religions view the diagnosis. The authors concluded that standard Grading of Recommendations Assessment, Development and Evaluation/ Appraisal of Guidelines for Research & Evaluation methods are not applicable given the lack of high-quality randomized studies in the field; therefore, many of the recommendations are based on consensus. Consensus was gained by having a review and endorsement of 5 world federations and 33 medical societies spanning 25 countries and regions and included expertise in adult and pediatric realms. These recommendations apply to the minimal standard for determination of BD/DNC and do not discourage additional practices.

If your practice includes determining BD/DNC, there are a few recommendations in this consensus statement to consider. First, it is comforting to learn that the global practice of determining BD/DNC is quite similar leading to a recommendation that BD/DNC be determined clinically. Namely, this requires (1) a clear diagnosis compatible with BD/DNC, (2) coma, (3) absent cerebral and brainstem reflexes, including apnea, and (4) an absence of factors that could cloud the diagnosis. Neurohormonal homeostasis and spinal reflexes are compatible with BD/DNC. The use of confirmatory tests is not needed unless confounding factors exist (eg, sedative medications). Any neurologist involved in determining BD/DNC should be competent in this process, and training courses exist online to refresh one’s knowledge.<sup>3</sup> The BD/DNC determination is a required component of neurology and neurosurgery training in

residency but not necessarily among critical care physicians. The consensus supplement details a standard for training.<sup>2</sup> Checklists are endorsed, as is standard documentation of the neurological examination supporting the diagnosis of BD/DNC. It is worthwhile to review local hospital protocols and guidelines to adhere to these recommendations.

There is international variance in the concept of brain death. For example, some regions endorse brainstem death while others endorse whole-brain death. The neurological examination used to support the diagnosis only tests brainstem function, leaving the rare possibility that the brainstem is destroyed but supratentorial structures could still function if the reticular activating system could be restored. This theoretical argument has no basis in published case example and the consensus statement recommends eliminating these terms and replacing them with BD/DNC. However, if a region still adheres to whole-brain death, it is recommended that some form of cerebral blood flow testing be used to confirm the destruction of supratentorial tissue.

A detailed list of ancillary tests was reviewed,<sup>2</sup> leading to the consensus recommendation that conventional cerebral angiography be the criterion standard, transcranial Doppler not be used in children, and electroencephalogram be abandoned but, if used, should be combined with brainstem-evoked and somatosensory-evoked potentials. Single-photon emission computed tomography (CT) is preferred over simple biplane radioscinigraphy to better separate blood flow in the scalp from brain blood flow. It is recommended that at least 24 hours elapse from the primary neurological insult before determining BD/DNC and the authors conclude that the minimum standard for making this diagnosis be at least 1 physician trained in the process. Depending on local laws, 2 physicians may be required, but in that case, this can be done concomitantly and the apnea test does not need to be repeated. The consensus does not recommend separating 2 examinations over 24 hours in children and recommends that the clinical examination in neonates, children, and adults be the same.

Recent advances in intensive care have added nuance to this practice. Specifically, instituting targeted temperature management with induced hypothermia for survivors of cardiac arrest in a coma is now universal.<sup>4-6</sup> Because the institution of hypothermia should begin quickly following the return of spontaneous circulation, it is not possible to declare a diagnosis of BD/DNC to a patient before targeted temperature management induction, leaving some patients who will die of hypoxia ischemia unable to be examined for 48 hours. This extends the window by 24 hours from prior recommendations for a 1-day waiting period. Based on case reports, performing the BD/DNC examination immediately after euthermia is es-

established can lead to false-positive declaration of death.<sup>7</sup> This new consensus recommends performing a head CT scan in patients in a persistent coma after rewarming and waiting longer to perform the clinical assessment of BD/DNC if the head CT results do not show marked cerebral edema and central herniation.

Extracorporeal membrane oxygenation (ECMO) adds challenges as well. Depending on the reason for instituting ECMO, some intensive care unit patients will lose neurological reflexes and demonstrate coma because of sedation or concomitant hypoxia-ischemia to the brain. The consensus document recommends that once sedative medications and neuromuscular junction-blocking drugs have been eliminated, the neurological examination to determine brain death should be the same. This includes performing an apnea test with modification. For patients for whom ECMO is used for primary respiratory failure, the ECMO circuit should be set to continue oxygen delivery but infuse carbon dioxide to lower the pH below 7.3 and/or raise the partial pressure of carbon dioxide above 60 mm Hg. Even though these patients cannot adequately breathe, they will still demonstrate respiratory effort if the medullary inspiratory neurons are functioning. In ECMO and non-ECMO patients, it is important to maintain adequate systolic blood pressure (>100 mm Hg or mean arterial pressure >60) during this apnea test to limit false positives. Using ancillary testing in ECMO patients is often necessary as it is hard to eliminate medication confounding the examination and cumbersome to transport these patients within the hospital to obtain diagnostic studies. Transcranial Doppler has not been validated in ECMO given the lack of pulsatile flow, so one should rely on radionuclide studies or cerebral angiography.

The consensus also reviews religious exemption to acceptance of BD/DNC. For example, in the US, some municipalities are exempted from allowing equivalency of BD/DNC and cardiopulmonary death based on religious beliefs (eg, New York City, New York, and New Jersey). Physicians who disagree with

this philosophy find themselves potentially unprotected by the US Universal Determination of Death act that absolves physicians of wrongdoing if they disconnect somatic support from a patient who has received a diagnosis of BD/DNC. It can lead to the unthinkable situation in which Jahi McMath was declared dead in California and when taken to New Jersey was no longer dead.<sup>1</sup> The consensus statement suggests that physicians consider local customs and laws when considering the finality of BD/DNC.

Lastly, the consensus challenges the evolving trend in which families may object to the administration of an apnea test. By doing so, families preclude the diagnosis of death, leading in some instances to prolonged somatic support that many physicians consider unethical. This is highlighted in the recent law under discussion in Michigan under which physicians will be required to gain consent from surrogates before testing for apnea.<sup>8</sup> Termed *Bobby's Law*, this proposed legislation is predicated on Simon's Law, which is now adopted in Missouri, Kansas, and Arizona. Simon's Law requires that physicians involve family members in end-of-life decisions, an ethic that is sensible. Bobby's Law in its final form may require parental consent for performing an apnea test. Ostensibly, families should be asked to provide consent because the apnea test may lead to cardiovascular collapse in some patients, classifying it as procedure with risk. Physicians have argued that apnea testing is part of the neurological examination and it should be performed to establish an important diagnosis (death), allowing them to communicate an honest prognosis. The consensus document recommends that consent not be required for apnea testing because of concerns over prolonged somatic support.<sup>2</sup>

For those with an academic interest in BD/DNC, the authors provide an extensive list of details worthy of study. The publication of this consensus marks an important beginning by establishing current practice and recommending international homogeneity in BD/DNC determination.

## ARTICLE INFORMATION

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## REFERENCES

1. Schmidt S. Jahi McMath, the Calif. girl in life-support controversy, is now dead. Accessed June 29, 2018. <https://www.washingtonpost.com/news/morning-mix/wp/2018/06/29/jahi-mcmath-the-calif-girl-declared-brain-dead-4-years-ago-is-taken-off-life-support/>

2. Sung GY, Greer DM, Shemie SD, et al. Determination of brain death/death by neurologic criteria: the World Brain Death Project. *JAMA*. Published online August 3, 2020. doi:10.1001/jama.2020.11586

3. Neurocritical Care Society. Brain death toolkit. Accessed April 1, 2020. <https://www.neurocriticalcare.org/education/digital-education/brain-death-toolkit>

4. Donnino MW, Andersen LW, Berg KM, et al; ILCOR ALS Task Force. Temperature management after cardiac arrest: an advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *Circulation*. 2015;132(25):2448-2456. doi:10.1161/CIR.0000000000000313

5. Duff JP, Topjian AA, Berg MD, et al. 2019 American Heart Association focused update on pediatric advanced life support: an update to the

American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Pediatrics*. 2020;145(1):145. doi:10.1542/peds.2019-1361

6. Geocadin RG, Wijdicks E, Armstrong MJ, et al. Practice guideline summary: reducing brain injury following cardiopulmonary resuscitation: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2017;88(22):2141-2149. doi:10.1212/WNL.0000000000003966

7. Webb AC, Samuels OB. Reversible brain death after cardiopulmonary arrest and induced hypothermia. *Crit Care Med*. 2011;39(6):1538-1542. doi:10.1097/CCM.0b013e3182186687

8. Harper R. Proposed 'Bobby's Law' would prevent minors from being removed from life support without a parent's consent. Accessed April 1, 2020. <https://www.wxyz.com/news/region/monroe-county/proposed-bobbys-law-would-prevent-minors-from-being-removed-from-life-support-without-a-parents-consent>

## Brain Death—Moving Beyond Consistency in the Diagnostic Criteria

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In this issue of *JAMA*, contributors to the World Brain Death Project present an international consensus report on criteria for the diagnosis of brain death, or determination of death by neurologic criteria (BD/DNC).<sup>1</sup> The report addresses inconsistencies in clinical guidelines across different countries and focuses attention on the need for better education and certification of clinicians who are authorized to make this clinical diagnosis.

Highlights of the summary report, along with the 13 in-depth reports provided in the accompanying supplemental material, include recommendations for the minimum clinical standards for determination of BD/DNC in adults and children, with helpful checklists and flowcharts. When the clinical examination cannot be completed, the Special Communication provides guidance for the use of ancillary diagnostic techniques. The report offers recommendations for testing patients who have received therapeutic hypothermia and for those supported with extracorporeal membrane oxygenation (ECMO). In addition, the report considers the importance of religious, cultural, and legal factors in making the diagnosis. The materials also include more than 70 questions to guide further research. The depth and scope of this project are reflected in the detailed and extensive content of the reports.

This Editorial aims to frame these recommendations within a larger context, by focusing on 2 key issues: the definition of death and the conceptual basis for defining death by neurologic criteria.

First, while consensus on the diagnostic standards is important, clinicians (and patients) must remember that the determination of death is not merely a scientific question to be answered by medical experts. Conceptions about what it means to be a living human being, and what it means for that life to end, rest on profound questions involving personal and foundational views in philosophy, religion, and culture. For example, the assumption that death can be defined in neurologic terms privileges a largely Western cartesian view above the more holistic views typical of Eastern cultures and religions.<sup>2</sup> Development of these consensus criteria should not be misinterpreted to imply that the concept of BD/DNC is universally accepted, and future research should include consideration of cross-cultural differences around these fundamental existential questions.

Second, even accepting the view that death can be defined in terms of neurologic functioning, no consensus exists on whether BD/DNC represents the death of the

whole brain, or just the brainstem. In the US (and most other countries), whole-brain death is the legal standard, requiring determination of the irreversible cessation of all functions of the entire brain, including the brainstem.<sup>3</sup> This view is founded on the premise that a functioning brain is required for the continued functioning of the organism as a whole.<sup>4</sup> Once brain functioning ceases, the body is no longer “integrated”—and literally disintegrates—such as after cardiac arrest. As one US expert suggested, “[physicians] now invariably equate brain death with death and do not distinguish it biologically from cardiac arrest.”<sup>5</sup>

In contrast, the standard in the UK and other countries and regions (such as India and Hong Kong) focuses exclusively on the loss of brainstem functions.<sup>6,7</sup> These include functioning of the reticular activating system (which is necessary for maintaining consciousness) and the respiratory centers (which are necessary for spontaneous respiration). Under the brainstem standard, BD/DNC is therefore conceptualized as a state of “irreversible apneic unconsciousness.” The UK standard does not claim that BD/DNC is equivalent to biological death, acknowledging that biological activity may persist, but rather asserts that brainstem death is death because it “entails the irreversible loss of those essential characteristics which are necessary to the existence of a living human person.”<sup>8</sup>

Over past decades, evidence has shown that the whole-brain concept has empirical flaws. First, experts now recognize that the diagnostic criteria for whole-brain death do not, in fact, diagnose the loss of all brain functions. Some patients correctly diagnosed by current criteria retain some brain functions, such as hypothalamic functions that regulate vital biological processes like temperature control and fluid homeostasis.<sup>9</sup> Second, the 2008 US President’s Commission concluded that patients correctly diagnosed with BD/DNC can maintain integrated biological functioning for months and even years.<sup>10,11</sup> In other words, whole-brain death fails on 2 counts: it is neither the complete loss of all brain function, nor is it synonymous with biological death.

In contrast, the UK concept of brainstem death, conceptualized by Pallis in the 1980s,<sup>12</sup> avoids both of these problems. Rather than requiring the loss of all brain function, it focuses on the irreversible loss of only 2 critical brain functions: consciousness and spontaneous respiration.

The distinction between whole-brain and brainstem death<sup>6</sup> is critically important, for 2 reasons. First, the US position characterizes BD/DNC as a scientific “fact” (biological death), implying that those who disagree with this concept are either uninformed or irrational. In contrast, the UK approach adopts a values-based position regarding the essential characteristics

of a living human being. The UK has therefore given the force of law to a particular set of values that it presumes to be widely shared within that society, even while accepting that some citizens may hold personal views not aligned with them.

The second reason that clarity about the meaning of BD/DNC is critical is because progress in improving and refining the criteria will be impossible without it. Under the US approach, the criterion standard for assessing the validity of the tests is whether they correlate with the loss of integrated functioning of the organism as whole, ie, biological death. But this reveals a fundamental problem: none of the tests fulfill the criterion for the US standard. In contrast, the UK standard provides clear diagnostic “targets” by which current and new tests can be assessed, ie, whether the patient is in a state of “irreversible apneic unconsciousness.”

*Is the patient unconscious?* Clinical assessment of the loss of consciousness requires that “there is no evidence of arousal or awareness to maximal external stimulation.”<sup>21</sup> For many decades, this was the same standard used for diagnosing unconsciousness in the persistent vegetative state. Advanced neuroimaging such as functional magnetic resonance imaging (fMRI) has shown this criterion to be incorrect in a substantial number of cases.<sup>13</sup> This is not to imply that every case of BD/DNC needs to have confirmatory fMRI evidence, but rather that the guidelines from the World Brain Death Project for establishing unconsciousness need additional empirical support, particularly for patients who have isolated brainstem pathology.

*Has the patient lost the capacity for spontaneous respiration?* Guidelines for the management of patients with increased intracranial pressure call for tight control of the PCO<sub>2</sub> (partial pressure of carbon dioxide) to the low normal range (35-40 mm Hg). Yet the procedures for performing the apnea test require allowing the patient’s PCO<sub>2</sub> to increase to 60 mm Hg or more, potentially causing the condition that the test is intended to diagnose. In addition to safety concerns, empirical questions remain about the threshold levels of PCO<sub>2</sub> necessary for a valid test, particularly in children, and how these may vary at different levels of oxygenation.<sup>14</sup>

Given these risks and uncertainties, future research should explore alternatives to the apnea test based on demonstrating irreversible destruction of the brainstem. While existing neurophysiologic and neuroimaging technologies are not sufficiently sensitive or specific, future research may

be successful in further refining these technologies or developing new tools to eliminate the need to perform the controversial apnea test.

*Are the conditions of unconsciousness and apnea irreversible?* Irreversibility can never be a certainty; it is always a refutable hypothesis contingent upon the absence of evidence to the contrary. This is further complicated because the diagnosis of BD/DNC is essentially a self-fulfilling prophecy, since biological death usually follows the diagnosis within a short period (by either organ donation or ventilator withdrawal), making it impossible to know if these patients might have shown some evidence of recovery had somatic support been continued.

Furthermore, empirical evidence of irreversibility would be difficult to establish. Large numbers of patients would have to be studied for prolonged periods to establish a false-positive rate that would be low enough to be deemed acceptable for the diagnosis of death. The fact that such studies are probably not feasible does not mean that irreversibility can never be assumed, only that the assumption will likely need to be based on theoretical considerations of the degree of neurologic injury, rather than on empirical studies.<sup>15</sup>

The World Brain Death Project guidelines represent an important contribution and serve as a foundational report for all clinicians involved in determining brain death. Scientific experts and representatives of numerous societies contributed to this process and were able to provide recommendations for the minimum clinical standards for determination of BD/DNC in adults and children, with clear guidance for various clinical circumstances. Bringing these recommendations to the entire international community will require a 2-pronged approach. First, evidence to support the existing tests needs to be bolstered, and this may require greater use of advanced neurodiagnostic techniques. A key question will be whether the whole-brain biological standard for defining BC/DNC will remain tenable, or whether this concept should be replaced by the values-based brainstem standard. Second, since much of the world does not have access to advanced technologies, the World Brain Death Project will need to focus on development and validation of tests that rely on the clinical examination and widely available diagnostic tools. This will be essential if the capacity for accurately diagnosing BD/DNC is to become accessible to all clinicians around the world.

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#### REFERENCES

- Greer DM, Shemie SD, Lewis A, et al. Determination of brain death/death by neurologic criteria: the World Brain Death Project. *JAMA*. Published online August 3, 2020. doi:10.1001/jama.2020.11586

- Lock M. *Twice Dead: Organ Transplants and the Reinvention of Death*. University of California Press; 2002.

- President’s Commission for the Study of Ethical Problems in Medicine and Biomedical Behavioral Research. *Defining Death: A Report on the Medical, Legal, and Ethical Issues in the Determination of Death*. President’s Council on Bioethics; 1981.

- Bernat JL, Culver CM, Gert B. On the definition and criterion of death. *Ann Intern Med*. 1981;94(3):389-394. doi:10.7326/0003-4819-94-3-389

- Wijdicks EFM. Deliberating death in the summer of 1968. *N Engl J Med*. 2018;379(5):412-415. doi:10.1056/NEJMp1802952

6. Wijdicks EF. The transatlantic divide over brain death determination and the debate. *Brain*. 2012; 135(pt 4):1321-1331. doi:10.1093/brain/awr282
7. Wijdicks EFM. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. *Neurology*. 2002;58(1):20-25. doi:10.1212/WNL.58.1.20
8. Academy of Medical Royal Colleges. A code of practice for the diagnosis and confirmation of death. 2008. Accessed July 27, 2020. [https://www.aomrc.org.uk/wp-content/uploads/2016/04/Code\\_Practice\\_Confirmation\\_Diagnosis\\_Death\\_1008-4.pdf](https://www.aomrc.org.uk/wp-content/uploads/2016/04/Code_Practice_Confirmation_Diagnosis_Death_1008-4.pdf)
9. Russell JA, Epstein LG, Greer DM, et al. Brain death, the determination of brain death, and member guidance for brain death accommodation requests: AAN position statement. *Neurology*. 2019;92(6):304.
10. The President's Council on Bioethics. Controversies in the Determination of Death: A White Paper of the President's Council on Bioethics. December 2008. <https://bioethicsarchive.georgetown.edu/pcbe/reports/death/>
11. Shewmon DA. Chronic "brain death": meta-analysis and conceptual consequences. *Neurology*. 1998;51(6):1538-1545. doi:10.1212/WNL.51.6.1538
12. Pallis CA. *ABC of Brainstem Death*. BMJ Books; 1983.
13. Giacino JT, Katz DI, Schiff ND, et al. Comprehensive systematic review update summary: Disorders of consciousness: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. *Neurology*. 2018;91(10):461-470. doi:10.1212/WNL.0000000000005928
14. Joffe AR, Anton NR, Duff JP. The apnea test: rationale, confounders, and criticism. *J Child Neurol*. 2010;25(11):1435-1443. doi:10.1177/0883073810369380
15. Shewmon DA. The probability of inevitability: the inherent impossibility of validating criteria for brain death or "irreversibility" through clinical studies. *Stat Med*. 1987;6(5):535-553. doi:10.1002/sim.4780060503

## VIEWPOINT

# Is There a Right to Delay Determination of Death by Neurologic Criteria?

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Editorial



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In September 2019, physicians at a Michigan hospital declared Bobby Reyes, a 14-year-old boy, dead by neurologic criteria. Nearly 3 weeks later, they took Bobby off of organ support, despite his parents' valiant attempts to prevent discontinuation of support by obtaining legal injunctions and seeking transfer to another facility. To provide other children who have severe brain injuries an extended opportunity to recover before pronouncement of death by neurologic criteria (DNC), Bobby's parents are working with a Michigan legislator to create "Bobby's Law." The proposal, if enacted, would allow parents/legal guardians to delay apnea testing (AT) for an unspecified period, thereby preventing determination of DNC and discontinuation of organ support.<sup>1</sup>

The controversy about whether families should have the right to delay AT is not unique to Bobby's case or to the state of Michigan. Over the past 4 years, families in California, Montana, and Virginia have publicly objected to AT.<sup>2</sup> However, this is the first legislative proposal that would allow families to delay AT. How did we get here, and what could this bill mean for clinicians?

In 1968, an ad hoc committee at Harvard proposed criteria by which death could be determined in the absence of brain activity: unreceptivity and unresponsivity, absence of movement or breathing, absence of brainstem reflexes, and, when performed, a flat electroencephalogram.<sup>3</sup> The impetus for these criteria was 2-fold. First, the advent of the ventilator allowed individuals, who previously would have died from the inability to breathe spontaneously, to survive for a protracted time. Second, there was a need to identify individuals who could serve as organ donors while complying with the dead donor rule.

To formally determine whether the concept of DNC should be accepted as the legal equivalent of death by cardiopulmonary criteria, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research analyzed DNC from medical, ethical, social, religious, and legal perspectives. Their review culminated in the Uniform Determination of Death Act (UDDA), which states: "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with accepted medical standards."<sup>4</sup> Death by neurologic criteria was subsequently incorporated into the legal standard for death in every state.<sup>5</sup>

Notwithstanding this very important legal innovation, there have been recurrent philosophical and religious objections to DNC.<sup>6</sup> Some have argued that continuing hormonal functions in an individual who is comatose, has absent brainstem reflexes, and is unable

to breathe spontaneously indicates that person is not dead under the UDDA, because they have not lost "all functions of the entire brain." However, the most common objection is that the only "true death" is "traditional" death by cardiopulmonary criteria. Therefore, if an individual's heart continues beating, even via support from a ventilator, they are not dead. These objections have led to conflicts between families and clinicians and have increasingly subjected clinicians to lawsuits and media scrutiny.

However, it is worth noting that clinicians have contributed to the growing controversy surrounding DNC by failing to ensure consistency among hospital DNC guidelines.<sup>7</sup> As a result, a person could be declared dead at one hospital yet alive at another. Additionally, clinicians do not universally comply with recognized medical standards for determination of DNC.<sup>8</sup> Consequently, there is an intolerable risk of error in these determinations, such that organ support could be discontinued from patients who do not meet accepted medical standards for determining DNC as required by the UDDA.

To ameliorate these concerns, clinicians are working to bolster trust in the use of neurologic criteria to declare death. The American Academy of Neurology, with support from multiple medical societies, vowed to tackle this challenge, and the Neurocritical Care Society developed a training module on DNC.<sup>7,9</sup>

Still, this is not enough. Ensuring that determinations of DNC are consistent from hospital to hospital and clinician to clinician does not eliminate all legal, philosophical, and religious objections to DNC. Therefore, we proposed a revised UDDA (RUDDA) to address several legal objections to DNC.<sup>10</sup> The RUDDA would make 3 changes to the UDDA. First, loss of hormonal function would not be required to declare DNC. Second, the 2010 American Academy of Neurology and 2011 Society of Critical Care Medicine/American Academy of Pediatrics/Child Neurology Society practice parameters on DNC, or subsequent versions of these documents recognized by the state board of medicine, would be declared the "accepted medical standards." Third, hospitals would be required to make reasonable efforts to notify an individual's legally authorized representative before a determination of DNC, but consent would not be mandated. If every state were to adopt the RUDDA as the legal standard for death, unseemly variation would be avoided.

At present, although only 2 states (Nevada and New York) explicitly note that consent is not legally required before a hospital may determine death, it is generally assumed that consent is not required even if the legislature has not said so explicitly.<sup>10</sup> "Bobby's Law" could change this.

Some have argued in favor of requiring consent for both adults and minors, noting that (1) consent is required for all medical procedures; (2) AT could be harmful; and (3) AT does not directly benefit a patient.<sup>2</sup> But the arguments against requiring consent are compelling, because doing so would (1) challenge the integrity of DNC; (2) increase the number of objections to DNC; (3) necessitate allocation of health care money and resources to patients who may be dead in lieu of those who are alive; and (4) create a double standard for death determination, given that **consent is not required for determination of death by cardiopulmonary criteria.**<sup>2</sup> Notably, 78% of adult neurologists and 72% of pediatric neurologists/intensivists believe that it should not be necessary to obtain consent before determination of DNC.<sup>2</sup>

So, how would clinicians be affected if state laws allowed families to delay AT for an unspecified period of time? Because most clinicians believe DNC is legal death, forcing them to delay AT and provide families with false hope would surely prompt objections about lack of transparency and deceitfulness. Additionally, under current practice, the medical team exercises informed clinical judgment to determine whether and when to initiate a formal determination of DNC, taking into consideration both medical and social circumstances. Under a rule that requires parental consent prior to AT, the

medical team would no longer have the prerogative to determine when it is appropriate to perform AT because grieving parents would be responsible for making this decision. Such an edict usurps traditional clinician responsibility and authority to distinguish life from death based on accepted medical standards.

It is conceivable that if clinicians were required to obtain consent for AT and a family objected to performance of this portion of the determination of DNC, clinicians might consider performing ancillary testing in lieu of AT. However, evading the consent requirement in this way would diminish the accuracy of a determination of DNC (**ancillary testing is neither 100% sensitive nor 100% specific**) and generate unnecessary expenses for no purpose other than bypassing a misguided legal requirement. Lastly, while facilitating organ donation is never the intent of a determination of DNC, it is important to keep in mind that delaying these determinations may adversely affect organ donation.

"Bobby's Law" is the most recent manifestation of the contentious political climate that has emerged over the past 50 years regarding the practice of declaring DNC. It is imperative to acknowledge and address these controversies and objections to DNC. However, allowing a negotiated standard for determination of death would be an ethically hazardous concession.

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#### REFERENCES

1. Durbin K. Monroe Co parents proposing "Bobby's Law" in honor of son taken off life support. *The Blade*. Published 2019. Accessed December 9, 2019. <https://www.toledoblade.com/local/suburbs/2019/12/02/bobbys-law-bobby-reyes-monroe-county-taken-off-life-support-university-of-michigan/stories/20191202150>

2. Lewis A, Greer D. Medicolegal complications of apnoea testing for determination of brain death. *J Bioeth Inq*. 2018;15(3):417-428. doi:10.1007/s11673-018-9863-8

3. A definition of irreversible coma: report of the ad hoc committee of the Harvard Medical School to Examine the Definition of Brain Death. *JAMA*. 1968; 205(6):337-340. doi:10.1001/jama.1968.03140320031009

4. Guidelines for the determination of death: report of the medical consultants on the diagnosis of death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *JAMA*. 1981; 246(19):2184-2186. doi:10.1001/jama.1981.03320190042025

5. Lewis A, Cahn-Fuller K, Caplan A. Shouldn't dead be dead? the search for a uniform definition of death. *J Law Med Ethics*. 2017;45(1):112-128. doi:10.1177/1073110517703105

6. Lewis A. Contentious ethical and legal aspects of determination of brain death. *Semin Neurol*. 2018; 38(5):576-582. doi:10.1055/s-0038-1668075

7. Lewis A, Bernat JL, Blosser S, et al. An interdisciplinary response to contemporary concerns about brain death determination. *Neurology*. 2018;90(9):423-426. doi:10.1212/WNL.0000000000005033

8. Braksick SA, Robinson CP, Gronseth GS, Hocker S, Wijdicks EFM, Rabinstein AA. Variability in reported physician practices for brain death determination. *Neurology*. 2019;92(9):e888-e894. doi:10.1212/WNL.0000000000007009

9. The Neurocritical Care Society. Brain Death Determination Course. Accessed December 9, 2019. <https://www.neurocriticalcare.org/higherlogic/s/p/cm/ld/fid=1101>

10. Lewis A, Bonnie RJ, Pope T, et al. Determination of death by neurologic criteria in the United States: the case for revising the Uniform Determination of Death Act. *J Law Med Ethics*. 2019;47(4\_suppl):9-24. doi:10.1177/1073110519898039

# Determination of Brain Death/Death by Neurologic Criteria

## The World Brain Death Project

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**IMPORTANCE** There are inconsistencies in concept, criteria, practice, and documentation of brain death/death by neurologic criteria (BD/DNC) both internationally and within countries.

**OBJECTIVE** To formulate a consensus statement of recommendations on determination of BD/DNC based on review of the literature and expert opinion of a large multidisciplinary, international panel.

**PROCESS** Relevant international professional societies were recruited to develop recommendations regarding determination of BD/DNC. Literature searches of the Cochrane, Embase, and MEDLINE databases included January 1, 1992, through April 2020 identified pertinent articles for review. Because of the lack of high-quality data from randomized clinical trials or large observational studies, recommendations were formulated based on consensus of contributors and medical societies that represented relevant disciplines, including critical care, neurology, and neurosurgery.

**EVIDENCE SYNTHESIS** Based on review of the literature and consensus from a large multidisciplinary, international panel, minimum clinical criteria needed to determine BD/DNC in various circumstances were developed.

**RECOMMENDATIONS** Prior to evaluating a patient for BD/DNC, the patient should have an established neurologic diagnosis that can lead to the complete and irreversible loss of all brain function, and conditions that may confound the clinical examination and diseases that may mimic BD/DNC should be excluded. Determination of BD/DNC can be done with a clinical examination that demonstrates coma, brainstem areflexia, and apnea. This is seen when (1) there is no evidence of arousal or awareness to maximal external stimulation, including noxious visual, auditory, and tactile stimulation; (2) pupils are fixed in a midsize or dilated position and are nonreactive to light; (3) corneal, oculoccephalic, and oculovestibular reflexes are absent; (4) there is no facial movement to noxious stimulation; (5) the gag reflex is absent to bilateral posterior pharyngeal stimulation; (6) the cough reflex is absent to deep tracheal suctioning; (7) there is no brain-mediated motor response to noxious stimulation of the limbs; and (8) spontaneous respirations are not observed when apnea test targets reach pH <7.30 and  $Paco_2 \geq 60$  mm Hg. If the clinical examination cannot be completed, ancillary testing may be considered with blood flow studies or electrophysiologic testing. Special consideration is needed for children, for persons receiving extracorporeal membrane oxygenation, and for those receiving therapeutic hypothermia, as well as for factors such as religious, societal, and cultural perspectives; legal requirements; and resource availability.

**CONCLUSIONS AND RELEVANCE** This report provides recommendations for the minimum clinical standards for determination of brain death/death by neurologic criteria in adults and children with clear guidance for various clinical circumstances. The recommendations have widespread international society endorsement and can serve to guide professional societies and countries in the revision or development of protocols and procedures for determination of brain death/death by neurologic criteria, leading to greater consistency within and between countries.

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The concepts of life and death have always been complicated, but ever more so as medical and technological advances continue to extend the limits to saving life and prolonging physiological function. For previous generations, cardiorespiratory death was the sole clinical definition of death, often without any standard criteria, leading to the risk of misdiagnosis. As resuscitation techniques and mechanical ventilation developed, a new definition of death was needed.

The idea of brain death/death by neurologic criteria (BD/DNC) was first recognized in 1959 as "coma dépassé"<sup>1</sup> and subsequently described as "brain death" with the first published clinical definition in 1968, commonly known as the Harvard Brain Death Criteria.<sup>2</sup> Since then, many other guidelines and protocols have been published, adopted, and revised throughout the world with general acceptance of the concept of BD/DNC among medical groups, major religions, and governments.<sup>3</sup>

However, there continues to be confusion and dilemmas that arise regarding BD/DNC. The wide variance in practice reflects this confusion and numerous other challenges. Inconsistencies in concept, criteria, practice, and documentation exist internationally and within countries.<sup>3,4</sup> Difficulties in conducting randomized clinical trials and large-scale studies on BD/DNC have resulted in a lack of robust data from which to develop evidence-based recommendations. Challenges to the validity of BD/DNC continue to promote controversy. These factors initiated this project to harmonize practice and improve the rigor of BD/DNC determination.

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## Methods

With the assistance of international professional societies including the World Federation of Intensive and Critical Care, World Federation of Pediatric Intensive and Critical Care Societies, World Federation of Neurology, World Federation of Neurosurgery, and the World Federation of Critical Care Nurses, experts in BD/DNC were recruited to develop and review recommendations on BD/DNC (n = 45). A topic list was created (n = 13) and section leaders (n = 18) were solicited from the writing committee to review the literature and draft recommendations on each topic. Section leaders were the primary authors for each topic. Those who did not wish to be section leaders reviewed the drafts at multiple points of development.

Authors conducted literature searches of the Cochrane, Embase, and MEDLINE databases to identify relevant articles published between January 1, 1992, and July 2017. Subsequent searches were performed to identify relevant articles published between July 2017 and April 2020. In total, more than 700 articles were identified and reviewed for the basis of recommendations and the supplements.

It was recognized that in this area, there is a lack of high-quality data from randomized clinical trials or large studies, so GRADE evaluation of the evidence was not performed. However, evidence was reviewed and recommendations were generated according to the following criteria.

Strong recommendations (*indicated as "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 were used when 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 pre-

cautionary, conservative approach, to prevent premature or erroneous determinations of death (false-positives).

Conditional or weak recommendations (*indicated as "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 interested parties.

For topics in which evidence was insufficient and the balance of benefits vs harms was neutral, no recommendations were made.

The findings of the literature review and preliminary recommendations were presented and discussed at an open pre-conference forum of the World Federation of Intensive and Critical Care 2017 meeting in Brazil, and then again at a plenary session of that conference. The text and recommendations for all sections were then reviewed by the steering committee members who provided the primary authors with comments and recommended revisions, and then distributed to the entire writing/review committee for comments and content consensus. The final draft was sent to international societies for final review and endorsement prior to submission for publication. The federations and societies that endorsed this project are listed at the end of the article under Additional Information.

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## Issues Addressed

This Special Communication provides the minimum standards for brain death/death by neurologic criteria (BD/DNC) and is intended to provide guidance to professional societies and countries in the development of their own protocols and procedures. See **Box 1** for an explanation of terms used throughout this document.

More in-depth reports on the different sections and other issues are included in the online supplement in the following appendixes: Worldwide Variance in Brain Death/Death by Neurologic Criteria ([Supplement 1](#)); The Science of Brain Death/Death by Neurologic Criteria ([Supplement 2](#)); The Concept of Brain Death/Death by Neurologic Criteria ([Supplement 3](#)); Minimum Clinical Criteria for Determination of Brain Death/Death by Neurologic Criteria ([Supplement 4](#)); Beyond Minimum Clinical Determination of Brain Death/Death by Neurologic Criteria ([Supplement 5](#)); Pediatric and Neonatal Brain Death/Death by Neurologic Criteria ([Supplement 6](#)); Determination of Brain Death/Death by Neurologic Criteria in Patients on Extracorporeal Support: ECMO ([Supplement 7](#)); Determination of Brain Death/Death by Neurologic Criteria after Treatment with Targeted Temperature Management ([Supplement 8](#)); Documentation of Brain Death/Death by Neurologic Criteria ([Supplement 9](#)); Qualification for and Education on Determination of Brain Death/Death by Neurologic Criteria ([Supplement 10](#)); Somatic Support after Brain Death/Death by Neurologic Criteria for Organ Donation and Other Special Circumstances ([Supplement 11](#)); Religion and Brain Death/Death by Neurologic Criteria: Managing Requests to Forego a Brain Death/Death by Neurologic Criteria Evaluation or Continue Somatic Support after Brain Death/Death by Neurologic Criteria ([Supplement 12](#)); Brain Death/Death by Neurologic Criteria and the Law ([Supplement 13](#)); Flow Diagram for Determination of Brain Death/Death by Neurologic Criteria ([Supplement 14](#)); A Checklist for Determination of Brain Death/Death by Neurologic Criteria ([Supplement 15](#)); Abbreviations Used in the Summary Document and

**Box 1. Glossary of Terms Related to Brain Death/Death by Neurologic Criteria (BD/DNC)**

BN/DNC terminology differs from country to country and it is not within the scope of this work to standardize terminology globally; however, to ensure consistency across documents, the following terms and definitions have been adopted.

**Ancillary test**

An alternative test to one that otherwise, for any reason, cannot be conducted or is unreliable

**Brain**

The cerebrum, brainstem, and cerebellum

**Brain function vs brain activity**

The term *brain function* refers to the more macro phenomena that are measurable on bedside neurological examination, that are also referred to as "signs." In contrast, the term *brain activity* refers to neuronal cellular micro phenomena recordable by technology. Thus, when discussing signs detectable on neurologic examination, the term *function* is used, whereas when discussing neuronal cellular measurements, the term *activity* is used

**Brain blood flow**

Blood flow to the cerebrum, brainstem and cerebellum. Also variably referred to as intracranial blood flow or cerebral blood flow

**Brain death/death by neurologic criteria**

BD/DNC is 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. "Brain death" is the traditional term adopted by both the public and health care professionals, but it is synonymous with "brain arrest," "brain circulatory arrest," "cerebral arrest," "cerebral circulatory arrest," "cerebral death," "coma dépassé," "irreversible coma," "neurologic death," "death by neurologic criteria," "death of the brain," "neurological determination of death" and "death by brain criteria." The term "death by neurologic criteria" describes the mode of determining death. To promote use of "death by neurologic criteria," which is more accurate terminology, while recognizing that it will be unwise to completely abandon the traditional terminology, this document uses the combined term BD/DNC

**Brain death/death by neurologic criteria, determination of**

The process of establishing, through neurologic criteria (clinical examination with or without ancillary testing) that a person is dead

**Brainstem death**

Diagnosis and confirmation of death based on the irreversible cessation of brainstem function

**Cellular-level neuronal and neuroendocrine activity**

Physiologic properties of cells and groups of cells that can be measured by laboratory means

**Cerebral perfusion pressure**

A measurement of the pressure gradient that results in cerebral blood flow. In brain injury, it is generally measured as MAP (mean arterial pressure) minus ICP (intracranial pressure):  $CPP = MAP - ICP$ . When  $ICP \geq MAP$ , there is no perfusion gradient for brain blood flow

**Clinical**

Based on direct, measurable observation or examination of the patient

**Clinical test**

A bedside test typically based on physical examination of the patient, but may include the use of a stethoscope and vital signs monitors

**CNS depressing medications**

Any medication, including but not limited to sedatives, anxiolytics, analgesics, and anesthetic agents, that may cause a depression of neurologic function and contribute to or exacerbate the level of coma. These medications may be associated with the primary cause of brain injury, eg, opiate overdose, or be used during the course of hospital treatment

**Coma**

Prolonged absence of wakefulness, awareness, and the capacity for sensory perception or responsiveness to the external environment

**Confirmatory test**

A test performed to confirm a previously conducted test

**Confounding conditions**

Circumstances during which a diagnostic test or clinical evaluation may become unreliable and require repetition over time or application of an alternative test

**Consciousness—loss of capacity for**

Lack of current or any future potential for awareness, wakefulness, interaction, and capacity for sensory perception or responsiveness to the external environment

**Craniovascular impedance**

An expression of the opposition to pulsatile blood flow in a cranial artery and includes the effects of elasticity, inertia, and viscosity in the vessels beyond

**Critical closing pressure**

The internal pressure at which a blood vessel collapses and closes completely. If blood pressure falls below critical closing pressure, then the vessels collapse

**Death declaration**

The point at which a health professional, having determined that an individual is dead, formally states this finding

**Death determination**

Processes and tests required to diagnose death in accordance with established criteria

**Devastating brain injury**

Brain injury in which there is an immediate threat to life, no effective treatments of disease remain, and early limitation of support is considered in favor of emphasis on end-of-life care and comfort measures. Etiologies of devastating brain injury leading to brain death include, but are not limited to, traumatic brain injury, ischemic or hemorrhagic stroke, and hypoxic-ischemic injury

**Irreversible**

Pertaining to a situation or condition that cannot return or resume. 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 does not require performance of nontherapeutic interventions to decrease intracranial pressure that are not judged to be clinically indicated

(continued)

**Box 1. (continued)****Isolated brainstem pathology**

A primary or secondary brainstem lesion due to infratentorial pathology, such as hemorrhagic stroke, that may fulfill clinical criteria for BD/DNC with or without supratentorial signs of intracranial hypertension

**Minimum criteria**

A set of criteria that satisfies the lowest acceptable standard for practice

**Oxygen insufflation method**

A form of apneic oxygenation achieved by continuous flow of oxygen delivered via cannula through an endotracheal tube or tracheostomy

**Preconditions/prerequisites**

Patient-related clinical, laboratory, or imaging requirements that should be fulfilled prior to application of diagnostic tests or clinical evaluation

**Recommendation—strong**

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). (Indicated by the phrase: "It is recommended that...")

**Recommendation—weak or conditional**

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. (Indicated by the phrase: "It is suggested that...")

**Somatic support**

Interventions used to maintain function of the body and organs, excluding the brain, after BD/DNC has been determined. Also referred to as physiological or organ support

**Spinal motor reflexes**

Spontaneous or reflex motor responses/movements that are based on spinal cord function alone without any transmission to and from brainstem and/or cerebrum. May include plantar flexor/extensor plantar responses, triple flexion response, abdominal reflex, cremasteric reflex, tonic-neck reflexes, isolated jerks of the upper extremities, unilateral extension-pronation movements, asymmetric ophisthotonic posturing of trunk, undulating toe flexion, myoclonus, respiratory-like movements, quadriceps contraction, and leg movements mimicking periodic leg movement

**Supplemental test**

A test performed in addition to an already conducted test

**Targeted temperature management**

An active treatment with the goal to achieve and maintain a specific body temperature below normothermia, ie, below 37 °C. Also referred to as therapeutic hypothermia

Appendixes (Supplement 16); and Questions That Address Knowledge Gaps to Facilitate Development of a Research Agenda About Brain Death/Death by Neurologic Criteria (Supplement 17).

**Recommendations****Worldwide Variance in BD/DNC**

There is both international and intranational variability in determination of BD/DNC.<sup>3,5-8</sup> For example, some countries require some type of ancillary test, while most do not, and in the US, California requires 2 examiners while most other states require only 1 examiner. See Supplement 1.

**Recommendations and Suggestions**

1. It is recommended that the minimum criteria for death determination be incorporated into BD/DNC determination protocols worldwide in order to harmonize practices and reduce variability to the fullest extent possible.
2. It is recommended that all hospital policies concerning BD/DNC worldwide adhere to the most up-to-date national guidelines.
3. It is recommended that clinical checklists for BD/DNC be implemented routinely.
4. It is suggested that training and credentialing be utilized for clinicians responsible for determining BD/DNC (as outlined in the Qualification for and Education on Determination of BD/DNC section).

**The Concept of BD/DNC**

There are 3 formulations of death by neurologic criteria: whole brain death, brainstem death, and higher brain death.<sup>9-12</sup> 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 (Supplements 2 and 3).<sup>13</sup>

**Recommendations and Suggestions**

1. It is recommended that 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 circulation to the brain, after devastating brain injury, or both. 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, medical standards, or both that use 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.

## Minimum Clinical Criteria for Determination of BD/DNC

See Supplement 4 for details about minimum clinical criteria for determination of BD/DNC.

### Prerequisites

The determination of BD/DNC is a clinical diagnosis, and given the implications and consequences of this diagnosis, a conservative approach and criteria are recommended. Initially, determination of BD/DNC must begin by establishing that (1) the clinical history, etiology, and neuroimaging demonstrate that the person has experienced an irreversible devastating brain injury leading to loss of all brain functions, and thus is compatible with BD/DNC; and (2) there are no confounders (circumstances during which a diagnostic test or clinical evaluation may become unreliable and require repetition over time or application of an alternative test) that could make the person appear to have irreversible brain injury, when, in fact, this is not the case. There have been several reports of reversible mimics of BD/DNC<sup>14-28</sup> and situations in which drug, metabolic, and hemodynamic derangements falsely suggest BD/DNC (eg, patients with residual sedation or treatment with hypothermia).<sup>29-33</sup>

### Recommendations and Suggestions

- It is recommended that pathological conditions, confounders, and/or reversible conditions that may mimic BD/DNC be excluded prior to commencing a determination of BD/DNC.
- It is recommended that, prior to commencing a determination of BD/DNC, it must be demonstrated that the person has an established neurologic diagnosis, the nature and severity of which is capable of resulting in the irreversible loss of the capacity for consciousness, the irreversible loss of all brainstem reflexes, and the irreversible loss of the ability to spontaneously breathe in the face of a carbon dioxide and acidosis challenge.
- It is suggested that prior to making a determination of BD/DNC, there be
  - neuroimaging evidence of intracranial hypertension (severe cerebral edema and herniation), or
  - intracranial pressure measurements that equal or exceed the mean arterial pressure.
- It is suggested that in the absence of herniation on neuroimaging, caution be taken when considering an evaluation for BD/DNC.
- It is suggested that the following prerequisites be met before an evaluation for determination of BD/DNC is performed:
  - The person should have a minimum core temperature of 36 °C, as defined by esophageal, bladder, rectal, or central venous or arterial catheter temperature measurements, with use of a warming blanket, automated temperature regulation device, thermal mattress, warmed fluids, and/or warmed oxygen as needed,
  - Adults should have a systolic blood pressure of at least 100 mm Hg, or a mean arterial pressure of at least 60 mm Hg, and there be age-appropriate targets in pediatrics, with use of vascular volume, vasopressors, and/or inotropes as needed.
- It is recommended that the following confounders be eliminated before an evaluation for determination of BD/DNC is performed:
  - Pharmacologic paralysis must be excluded through use of a train-of-four stimulator if available, or assessment of the presence of deep tendon reflexes if a train-of-four stimulator is not available.
  - The influence of central nervous system (CNS) depressing medications including toxins, taking into consideration the elimination half-life that may be prolonged by organ dysfunction and/or hypothermia, be excluded by:
    - use of a toxicology screen if there is concern for a toxic exposure, and
    - serially measuring drug levels to ensure they do not exceed the therapeutic range, and, even if within the therapeutic range, are not thought to confound the clinical examination, or
    - allowing 5 elimination half-lives to pass before an evaluation for BD/DNC be made (assuming normal hepatic and kidney function), or
    - performing ancillary testing in addition to the complete clinical examination and apnea test if there is concern about prolonged or unknown drug elimination.
  - If alcohol intoxication is suspected or confirmed, the alcohol blood level must be 80 mg/dL or lower.
  - Severe metabolic, acid-base, and endocrine derangements that could affect the examination must be corrected. If these derangements cannot be corrected and are judged to be potentially contributing to the loss of brain function while findings of the complete clinical examination and apnea test are consistent with BD/DNC, ancillary testing should be performed to confirm this determination.
- 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 therapeutic phases of care. It is recommended that if these types of interventions are not indicated for the treatment of devastating brain injury, they should not be performed simply for the purpose of demonstrating irreversibility of the clinical state.
- It is recommended that an adequate observation period take place prior to clinical testing for BD/DNC.
  - A minimum of 24 hours is recommended specifically for anoxic brain injury after resuscitated cardiac arrest. (See the section on Determination of BD/DNC After Treatment With Targeted Temperature Management.)
  - The period for other brain injuries has not been established and should be determined on a case-by-case basis. As a general rule, clinicians should be cautious, and if there is uncertainty about the potential reversibility of the clinical state, for any reason, the observation time should be the time thought necessary to exclude reversibility without any doubt.

## Clinical Testing

It is universally agreed that the clinical evaluation for determination of BD/DNC includes an assessment for coma and an evaluation for brainstem areflexia to demonstrate that (1) pupils are fixed in a midsize or dilated position and are nonreactive to light (as determined with the naked eye, magnifying glass, or a pupillometer); (2) the corneal, oculocephalic, and oculovestibular reflexes are absent; (3) there is no facial movement to noxious cranial stimulation; (4) the gag reflex is absent to bilateral posterior pharyngeal stimulation; (5) the cough reflex is absent to deep tracheal suctioning; and (6) there is no brain-mediated motor response to noxious stimulation of the limbs.<sup>7,34-38</sup>

## Recommendations and Suggestions

1. It is recommended that BD/DNC first and foremost be a clinical determination.
2. It is recommended that an assessment for determination of BD/DNC be made in all persons with devastating brain injuries who are believed to potentially meet criteria for BD/DNC, regardless of whether they are potential organ donors.
3. It is recommended that all of the neurologic assessments in Box 2 be performed as part of the minimum determination of BD/DNC. If a portion of the clinical examination cannot be done, it is recommended that the remainder be completed to the fullest extent possible. If any aspect of the clinical examination cannot be completed (except as stipulated in Box 2), but the examination, to the extent completed, is consistent with BD/DNC, ancillary testing is recommended.

## Apnea Testing

Apnea testing is part of nearly all protocols for determination of BD/DNC.<sup>7,35-38</sup> The goal of the apnea test is to allow the serum carbon dioxide to increase and the central nervous system pH to decrease to levels that would normally maximally stimulate the respiratory centers in a functioning medulla.<sup>39</sup> If there is no medullary function, the person will not make any respiratory effort in the setting of profound hypercarbia and acidosis. Although hypoxia depresses neuronal metabolism, it does not stimulate the central chemoreceptors to trigger respiration in adults.<sup>40</sup>

## Recommendations and Suggestions

1. Because there is concern that apnea testing may elevate intracranial pressure, it is recommended that
  - a. the apnea test be conducted last, after the rest of the clinical evaluation is completed and found to be consistent with BD/DNC, and
  - b. it has been determined that the person is not generating any spontaneous respirations when the ventilator is set on a spontaneous breathing mode in a normocarbic state, and
  - c. the test is performed by personnel with experience in resuscitation should the patient decompensate during testing.
2. It is recommended that ventilator requirements and pulmonary status be assessed before apnea testing to determine whether a person is likely to tolerate the evaluation.
3. In the setting of a high cervical cord injury, it is recommended that an apnea test not be performed and ancillary testing is indicated.
4. It is suggested that before commencing the apnea test
  - a. the systolic blood pressure be at least 100 mm Hg or mean arterial pressure be at least 60 mm Hg in adults (and above age-appropriate targets in pediatrics) with use of vascular volume, vasopressors, and/or inotropes as needed,
  - b. temperature be at least 36 °C, with use of a warming blanket, automated temperature regulation device, thermal mattress, warmed fluids, and/or warmed oxygen as needed,
  - c. the person be preoxygenated with 100% O<sub>2</sub> for at least 10 minutes.
5. It is suggested the minute ventilation be adjusted to establish normocarbica (Paco<sub>2</sub> of 35-45 mm Hg [4.7-6.0 kPa]) prior to apnea testing, confirmed by arterial blood gas testing prior to apnea testing.
6. It is suggested that a functioning arterial line be used to provide continuous blood pressure monitoring and to quickly draw blood gases during apnea testing.
7. It is suggested that the following techniques may be used for apnea testing:
  - a. the application of positive airway pressure with the use of CPAP/PEEP (continuous positive airway pressure/positive end-expiratory pressure) may prevent derecruitment and decrease the risk of cardiopulmonary instability, so 100% oxygen can be delivered to the lungs (i) via CPAP on the mechanical ventilator or (ii) via a resuscitation bag with a functioning PEEP valve,
  - b. oxygen can also be delivered via the oxygen insufflation method via placement of a tracheal cannula.
8. It is suggested that the apnea test targets during testing be pH less than 7.30 and Paco<sub>2</sub> of at least 60 mm Hg (8.0 kPa) unless a patient has preexisting hypercapnia, in which case it should be at least ≥20 mm Hg (2.7 kPa) above their baseline Paco<sub>2</sub>, if known.
9. It is recommended that apnea testing be aborted if
  - a. spontaneous respirations are witnessed during apnea testing,
  - b. systolic blood pressure becomes lower than 100 mm Hg or mean arterial pressure becomes lower than 60 mm Hg despite titration of fluids/inotropes/vasopressors,
  - c. there is sustained oxygen desaturation below 85%.
  - d. an unstable arrhythmia occurs.
10. It is recommended that arterial blood gas be tested 10 minutes after commencing apnea testing.
  - a. If point-of-care testing is available and the person is stable, they can be kept off the ventilator with repeated arterial blood gas sampling every 2 to 3 minutes until it is determined that the Paco<sub>2</sub> is at least 60 mm Hg (≥20 mm Hg above any known chronic baseline Paco<sub>2</sub> in persons with preexisting hypercapnia).
  - b. If point-of-care testing is not available, the person should be reconnected to the ventilator when the arterial blood gas is sent at 10 minutes.
11. It is suggested that, while noninvasive capnography may guide the duration of apneic observation, the arterial Paco<sub>2</sub> be used to confirm adequate elevation of CO<sub>2</sub> during apnea testing.
12. If the apnea test is inconclusive (does not reach Paco<sub>2</sub> goals) but the patient was stable during testing from pulmonary and hemodynamic standpoints, it is suggested that the test be repeated after reestablishing preoxygenation, normocapnea, and a normal pH, and extending the test by several minutes, using the same technique and parameters as above.

## Box 2. Clinical Examination for Determination of Brain Death/Death by Neurologic Criteria (BD/DNC)

1. Coma: there is no evidence of arousal or awareness to maximal external stimulation (including noxious visual, auditory, and tactile stimulation).
2. Pupillary reflexes
  - A. Test
    - Shine a bright light into each of the person's eyes, looking for pupillary constriction and measuring the diameter of the pupils. Use of a magnifying glass and/or pupillometer is suggested
  - B. Response consistent with BD/DNC
    - There should be absence of ipsilateral and contralateral pupillary response, with pupils fixed in a midsize or dilated position ( $\approx$ 4–6 mm), in both eyes
  - C. Considerations
    - Constricted pupils are not consistent with BD/DNC and suggest the possibility of drug intoxication or locked-in syndrome
    - Pupils can be any shape (round/oval/irregular)
    - Corneal trauma or prior ophthalmic surgery may influence pupillary reactivity and preclude adequate evaluation, necessitating ancillary testing
    - Ocular instillation of drugs may artificially produce transiently nonreactive pupils
    - In the setting of anophthalmia or inability to see the pupils, ancillary testing is recommended
3. Oculocephalic (OCR) and oculovestibular (OVR) reflexes
  - A. Test
    - OCR: Rotate the head briskly horizontally to both sides. There should be no movement of the eyes relative to head movement. Testing vertically is optional
    - OVR: Examine the auditory canal for patency and an intact tympanic membrane. Elevate the head to 30° to place the horizontal semicircular canals in the correct vertical position. Irrigate with at least 30 mL of ice water for at least 60 seconds using a syringe or a syringe attached to a catheter placed inside the canal. Test both sides separately, with a 5-minute interval between to allow the endolymph temperature to equilibrate
  - B. Response consistent with BD/DNC
    - There should be absence of extraocular movements. Detection of any extraocular movements is not compatible with BD/DNC
  - C. Considerations
    - Confirm the integrity of the cervical spine before proceeding with the OCR test. If the OCR cannot be performed, but the OVR is performed and there are no extraocular movements, ancillary testing is not required
    - Ensure the integrity of the tympanic membrane. Presence of a ruptured tympanic membrane does not negate the clinical testing but may risk introducing infections in the ear
    - A fracture of the base of the skull or petrous temporal bone may obliterate the response on the side of the fracture, and ancillary testing is recommended in this instance
    - Severe orbital or scleral edema or chemosis may affect the free motion of the globes, and ancillary testing is recommended in this instance
    - In the setting of anophthalmia, ancillary testing is recommended
4. Corneal reflex
  - A. Test
    - Touch the cornea of both eyes with a cotton swab on a stick at the external border of the iris, applying light pressure and observing for any eyelid movement
  - B. Response consistent with BD/DNC
    - No eyelid movement should be seen
  - C. Considerations
    - Care should be taken to avoid damaging the cornea
    - In the setting of anophthalmia, severe orbital edema, prior corneal transplantation, or scleral edema or chemosis, ancillary testing is recommended
5. Motor responses of the face and limbs
  - A. Test
    - Apply deep pressure to all of the following:
      - i. the condyles at the level of the temporomandibular joints
      - ii. the supraorbital notch bilaterally
      - iii. the sternal notch
      - iv. all 4 extremities, both proximally and distally
    - Insert a cotton swab on a stick in each nostril to perform "nasal tickle" testing
  - B. Response consistent with BD/DNC
    - Noxious stimuli should not produce grimacing, facial muscle movement, or a motor response of the limbs other than spinally mediated reflexes
    - Noxious stimuli above the foramen magnum should not produce any movement in the face or body. Noxious stimuli below the foramen magnum should not produce any movement in the face but may elicit spinally mediated peripheral motor reflexes
  - C. Considerations
    - The clinical differentiation of spinal from brain-mediated motor responses requires expertise. Consultation with an experienced practitioner is recommended if the origin of a response is unclear. Alternatively, if interpretation is unclear, ancillary testing is recommended
    - Ancillary testing is recommended if a person has a preexisting severe neuromuscular disorder, such as amyotrophic lateral sclerosis or a preexisting severe sensory neuropathy
    - Ancillary testing is not required if a person does not have all 4 limbs; absence of a limb does not preclude motor testing to pain on that side of the body
    - Severe facial trauma or swelling may preclude evaluation of facial motor response, so ancillary testing is recommended in this setting
6. Gag and cough reflexes
  - A. Test
    - Gag reflex: stimulate the posterior pharyngeal wall bilaterally with a tongue depressor or suction catheter
    - Cough reflex: stimulate the tracheobronchial wall to the level of the carina with deep endotracheal placement of a suction catheter
  - B. Response consistent with BD/DNC
    - Absence of gag and cough
  - C. Considerations
    - The efferent limb for the cough reflex includes the phrenic nerve, which may be injured in persons with high cervical cord injuries, so ancillary testing is recommended in this setting

13. It is suggested that while aborting the apnea test because of cardiorespiratory instability, an arterial blood gas be sent for testing. If the  $\text{Paco}_2$  target is met, the apnea test can be considered positive (consistent with BD/DNC).
14. It is suggested that if the apnea test has been aborted because spontaneous respirations are witnessed during testing, apnea testing should be repeated after 24 hours if the clinical evaluation otherwise remains consistent with BD/DNC.
15. If the apnea test is aborted and cannot be repeated safely, it is suggested that either an ancillary test be performed, or apnea testing be attempted after preapnea recruitment maneuvers, induction of hypercarbia with  $\text{CO}_2$  or carbogen before disconnecting from the ventilator, or utilizing CPAP to maintain oxygenation.

### Number of Examinations

The number of clinical examinations required to pronounce BD/DNC varies according to age, hospital, state, or country and generally ranges from 1 through 3.<sup>4,5,38</sup>

### Recommendations and Suggestions

1. It is suggested that a single examination, including apnea testing, is the minimum standard for determination of BD/DNC for adults.
2. If 2 evaluations are performed
  - a. it is suggested that an intervening period is unnecessary because if the prerequisite of irreversibility (which includes an observation period prior to initiating testing) has been satisfied, a second observation period is redundant,
  - b. it is suggested that the examinations be performed by 2 separate examiners,
  - c. it is suggested that only 1 positive apnea test be performed in adults.

### Beyond Minimum Clinical Determination of BD/DNC

Confounders (such as certain medications, metabolic abnormalities, or cardiopulmonary instability) may interfere with either completion or interpretation of the clinical examination for BD/DNC. Tests to assess for absence of brain blood flow or electrical activity may be necessary if the clinical examination (including the apnea test) cannot be completed. In some cases, these tests are mandated; a review from 2015 found that 22 of 70 countries with national protocols for the diagnosis of BD/DNC required the use of an ancillary test.<sup>5</sup> There are advantages and disadvantages to all ancillary tests (see Table 1 and Table 2 and Supplement 5).<sup>41-73</sup>

### Recommendations and Suggestions

#### Ancillary Testing

1. It is recommended that ancillary testing is required in the following circumstances:
  - a. inability to complete all aspects of the minimum clinical examination, including the apnea test,
  - b. confounding conditions that cannot be resolved,
  - c. uncertainty regarding interpretation of possible spinally mediated movements.
2. It is recommended that the clinical examination be completed to the fullest extent possible prior to conducting an ancillary test.

3. It is suggested that ancillary testing may be used to promote understanding of the clinical determination to families who express resistance or uncertainty.
4. It is recommended that the following brain blood flow-based methods be used for BD/DNC ancillary testing:
  - a. **Digital subtraction angiography (conventional 4-vessel cerebral angiography)**. It is recommended that if 4-vessel cerebral angiography is performed, the study demonstrates absent filling at the points where the internal carotid and vertebral arteries enter the skull base, with a patent external carotid circulation, in order to make a declaration of BD/DNC.
  - b. **Radionuclide studies**. It is suggested that if scintigraphic techniques are used as an alternative to digital subtraction angiography
    - I. diffusible radiopharmaceuticals be used preferentially,
    - II. SPECT (single-photon emission computed tomography) be chosen over planar imaging,
    - III. perfusion scintigraphy with anterior and lateral planar imaging be used, with appropriate time intervals to demonstrate static filling of the posterior fossa, if SPECT is not available,
    - IV. the study illustrates absence of intracranial isotope in order to make a determination of BD/DNC.
  - c. **Transcranial Doppler ultrasonography**. It is suggested that if transcranial Doppler is used as an alternative to conventional 4-vessel cerebral angiography or scintigraphy:
    - I. 2 examinations be performed at least 30 minutes apart,
      - Note that 10% of patients have no acoustic windows. Circulatory arrest can only be established in the presence of some preceding signal on earlier examination that indicated flow, establishing the presence of an adequate window. Consequently, 2 examinations are normally required to make a diagnosis of cerebral circulatory arrest with transcranial Doppler.
    - II. the examinations be performed bilaterally, anteriorly, and posteriorly to include both internal carotid arteries as well as the vertebrobasilar circulation,
    - III. the examinations illustrate biphasic oscillating flow and systolic spikes with reversal of flow in diastole in order to make a declaration of BD/DNC,
    - IV. transcranial Doppler should not be used in pediatrics in the absence of validation studies.
5. It is recommended that when ancillary testing is performed and demonstrates the presence of brain blood flow, BD/DNC cannot be declared at that time.
  - a. It is suggested that repeat examinations be conducted at another time if the clinical examination and apnea test continue to be consistent with BD/DNC, or that alternative end-of-life care be considered.
6. It is suggested that electrophysiologic testing with electroencephalography (EEG) no longer be used routinely as an ancillary test in adults, but that
  - a. it may be required if mandated by regional laws or policy, or craniovascular impedance has been affected by an open skull fracture, decompressive craniectomy, or an open fontanelle/sutures in infants,

Table 1. Tests of Brain Blood Flow

Test	Diagnostic criteria	Advantages	Disadvantages	Sensitivity/specificity, %	Comments
Digital subtraction angiography/conventional 4-vessel angiography	Absence of contrast within the intracranial arterial vessels	<ul style="list-style-type: none"> <li>Reference standard for ancillary tests</li> </ul>	<ul style="list-style-type: none"> <li>Requires transport to imaging suite</li> <li>Invasive (requires technical skills)</li> <li>Kidney susceptibility to contrast</li> <li>Stasis filling-false negative</li> </ul>	100/100 <sup>a,41,42</sup>	<ul style="list-style-type: none"> <li>Persistence of flow does not contradict comprehensive competent clinical diagnosis</li> <li>Equipment and operator dependence limits practical use; still used as calibration standard</li> </ul>
Radionuclide angiography	Absence of radiologic activity upon imaging of the intracranial vault	<ul style="list-style-type: none"> <li>Can be performed at bedside</li> <li>No kidney susceptibility to contrast</li> </ul>	<ul style="list-style-type: none"> <li>Limited evaluation of brainstem</li> <li>Limited availability</li> </ul>	98.5/56 <sup>43</sup>	<ul style="list-style-type: none"> <li>Persistence of flow does not contradict comprehensive competent clinical diagnosis</li> </ul>
Radionuclide perfusion scintigraphy	Absence of radiologic activity indicating metabolic uptake upon imaging of the intracranial vault	<ul style="list-style-type: none"> <li>Can be performed at bedside (planar imaging)</li> </ul>	<ul style="list-style-type: none"> <li>Limited availability</li> <li>Planar imaging may limit brainstem evaluation</li> <li>SPECT requires patient transport to scanner</li> </ul>	Planar: 77.8/100; SPECT: 88.4/100 <sup>a,44</sup>	<ul style="list-style-type: none"> <li>Uptake of isotope indicates metabolic activity</li> </ul>
Transcranial Doppler ultrasound	Biphasic (oscillating) flow or small systolic spikes on initial assessment of intracranial arterial supply, confirmed or proceeding to absent flow velocity signal on second assessment	<ul style="list-style-type: none"> <li>Easily performed at bedside</li> <li>No contrast required</li> <li>Can assess carotid and basilar circulations</li> </ul>	<ul style="list-style-type: none"> <li>Operator expertise required</li> <li>10% of patients have no acoustic windows</li> </ul>	90/98 <sup>45</sup>	<ul style="list-style-type: none"> <li>Persistence of flow does not contradict comprehensive competent clinical diagnosis</li> </ul>
Computed tomography angiography	No opacification of intracranial arterial circulation, or deep veins	<ul style="list-style-type: none"> <li>Widely available</li> <li>Relatively quick to perform</li> </ul>	<ul style="list-style-type: none"> <li>Requires transport to imaging suite</li> <li>Kidney susceptibility to contrast</li> <li>Stasis filling-false negative</li> </ul>	52-97/100 <sup>a,46-65</sup>	<ul style="list-style-type: none"> <li>Persistence of flow does not contradict comprehensive competent clinical diagnosis</li> <li>Limited consensus on required diagnostic criteria</li> <li>Small number of studies with lack of reference standard</li> <li>Not currently validated against above accepted tests</li> </ul>
Magnetic resonance angiography	No visualization of intracranial arterial circulation	<ul style="list-style-type: none"> <li>Not affected by stasis filling</li> <li>Visualization improved by gadolinium</li> </ul>	<ul style="list-style-type: none"> <li>Requires transport to imaging suite</li> <li>Specialized critical care equipment required in scanner</li> <li>Time of flight imaging affected by hematoma</li> </ul>	93-100 <sup>66-69</sup> /100 <sup>a,66,67</sup>	<ul style="list-style-type: none"> <li>Persistence of flow does not contradict comprehensive competent clinical diagnosis</li> <li>Small number of studies with lack of reference standard</li> <li>Uncertainty about risks of nephrogenic systemic fibrosis<sup>70</sup></li> <li>Not currently validated against above accepted tests</li> </ul>

Abbreviations: BD/DNC, brain death/death by neurologic criteria; SPECT, single-photon emission computed tomography.

<sup>a</sup> Specificity is assumed on basis of experimental data but should be interpreted

with caution<sup>71</sup> given the limitation of studies that reported only on clinically confirmed BD/DNC.

- b. if performed as an ancillary test, EEG should be used in conjunction with somatosensory and brainstem auditory evoked potentials given the limitations of EEG for evaluating brainstem function,
- c. it be interpreted in accordance with regional criteria. In the absence of regional criteria, guidance from the following may be considered: American Clinical Neurophysiology Society,<sup>74</sup> Bleck,<sup>75</sup> Korean Society of Clinical Neurophysiology,<sup>76</sup> or Société de Neurophysiologie Clinique de Langue Française.<sup>77</sup>
7. It is suggested that CTA (computed tomography angiography) and MRA (magnetic resonance angiography) not be used to support a diagnosis of cerebral circulatory arrest at present, pending further research into the sensitivity and specificity of these modalities.
8. It is recommended that no other modalities be used to support a diagnosis of cerebral circulatory arrest at present, pending further research.
9. It is suggested that conventional 4-vessel cerebral angiography remain the reference standard of ancillary testing, and that it be used for initial validation or research of newer techniques.
10. It is suggested that validation of new ancillary techniques will require assessment in patients fulfilling full and unconfounded clinical criteria for BD/DNC, as well as non-brain-dead patients as controls, and should include circumstances of infancy, craniovascular decompression, persistence of CNS depressing medications or intoxication, and hypothermia. Standardized methods of interpretation for each new technique should be developed, founded on principles of monitoring the whole brain, encompassing supratentorial and infratentorial integrity, flow, and function.
11. It is suggested that some priority be given to the further validation of CTA, given its increasing prevalence and usage. Integration with CT perfusion may prove valuable, given recent advances in CT technology.

#### Pediatric/Neonatal BD/DNC

For the purposes of this article, the age of a neonate ranges from 36 weeks' gestation to 30 days of age.<sup>78-84</sup> The upper age limit for a pediatric person may range from 14 to 18 years of age depending on pediatric intensive care unit (ICU) admission criteria and the mechanism of injury, eg, trauma.<sup>78,79</sup>

Table 2. Tests of Electrophysiological Function

Test	Diagnostic criteria	Advantages	Disadvantages	Sensitivity/specificity, %	Comments
EEG	No detectable electrical activity ( $\geq 2 \mu\text{V}$ ) over a 30-min period	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Can be performed at bedside</li> </ul>	<ul style="list-style-type: none"> <li>• Predominantly cortical assessment</li> <li>• Electromagnetic environmental noise can erroneously suggest cerebral electrical activity</li> <li>• Confounded by sedation, hypothermia, toxic states, metabolic disorders</li> </ul>	53-80.4/97 <sup>41,72</sup>	Concerns on confounding and interobserver variability limit use; may be more specific used in conjunction with multimodality evoked potential testing
Somatosensory evoked potentials	Bilateral absence of any electrical transmission through the brainstem and cerebrum in the setting of an intact signal in the brachial plexus and spinal cord	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Can be performed at bedside</li> <li>• Less susceptible to sedation than EEG</li> </ul>	<ul style="list-style-type: none"> <li>• Confounded by cervical spinal cord injury, isolated brainstem lesions, sedation, hypothermia</li> </ul>	100/78 <sup>73</sup>	Limited specificity as isolated test; may be helpful as component of multimodality evoked potential testing, used in conjunction with EEG
Auditory evoked potentials	Bilateral absence of waveforms through the brainstem to auditory cortex	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Can be performed at bedside</li> <li>• Less susceptible to sedation than EEG</li> </ul>	<ul style="list-style-type: none"> <li>• Confounded by sedation, profound hypothermia, isolated eighth cranial nerve or brainstem lesions</li> <li>• Limited to auditory cortex</li> </ul>		Not useful as isolated test; may be helpful as component of multimodality testing
Visual evoked potentials	Bilateral absence of waveforms through brainstem to visual cortex with preserved electroretinogram	<ul style="list-style-type: none"> <li>• Noninvasive</li> <li>• Can be performed at bedside</li> <li>• Less susceptible to sedation or hypothermia than EEG</li> </ul>	<ul style="list-style-type: none"> <li>• Confounded by sedation, retinal or optic nerve lesions</li> <li>• Limited to visual cortex</li> </ul>		Not useful as isolated test; may be helpful as component of multimodality evoked potential testing

Abbreviation: EEG, electroencephalography.

The definition of BD/DNC is the same for adults and children. BD/DNC is a clinical diagnosis based on the coexistence of unresponsive coma (loss of brain function), complete loss of brainstem reflexes, and apnea in a person with a known brain injury resulting in an irreversible condition.<sup>78-82</sup> Most countries use whole brain death criteria (brain and brainstem) to determine death in infants and children.<sup>78-82</sup> Ancillary studies are not usually mandatory,<sup>78-84</sup> but some protocols recommend them as they may be helpful when components of the physical examination or apnea test cannot be completed.<sup>78-82</sup> Criteria to determine BD/DNC are generally consistent across the age spectrum for children. However, because there is less evidence for determination of BD/DNC in the very young, a cautious approach is advocated when evaluating infants and younger children, resulting in variable age-based recommendations that often require serial examinations including apnea testing (Supplement 6).<sup>78-84</sup>

### Recommendations and Suggestions

1. It is recommended that the minimum criteria for a determination of BD/DNC in all pediatric age groups be the same as in adults, with an assessment of prerequisites, elimination of confounders, and performance of a clinical examination including apnea testing. Age-appropriate prerequisite hemodynamic targets should be applied.
2. It is suggested that BD/DNC can be determined in newborns as defined by age at least 36 weeks' gestation.
3. It is suggested that there is insufficient supporting evidence to accurately determine BD/DNC in newborns less than 36 weeks' gestation.
4. It is recommended that 2 examinations, including apnea testing, represent the minimum standard for determination of BD/DNC in the pediatric population. A cautious approach with serial examinations and consideration of an observation period is recommended to minimize the risk of diagnostic error.
5. It is recommended that those in the pediatric population be observed for unresponsive coma for a minimum of 24 hours prior to initial testing following birth asphyxia, resuscitation from cardiac arrest, and after rewarming from therapeutic hypothermia.
6. It is suggested that clinical criteria for determination of BD/DNC in newborns include the sucking and rooting reflexes.
7. It is suggested that recommendations for apnea testing targets in pediatrics are the same as in adults.
8. It is recommended that tracheal insufflation should not be used for apnea testing in newborns, infants, and young children.
9. It is suggested there are no pediatric-specific distinctions related to performing the apnea test during extracorporeal support.
10. It is recommended that ancillary studies are not routinely required to determine BD/DNC in the pediatric population.
11. It is recommended that indications for ancillary testing are the same as in adults.
12. It is recommended that, similar to adults, radionuclide cerebral blood flow study is an accepted and preferred ancillary study.
13. It is suggested at present that EEG, performed and interpreted in accordance with published guidelines, is also considered a valid ancillary study in infants and children and can be used in certain jurisdictions.
14. It is recommended that transcranial Doppler ultrasonography should not be used as an ancillary study in pediatrics until more studies determine the validity of this study in this population.
15. It is suggested that in a person with chronic hypoxemia due to cyanotic heart disease, apnea testing not be performed and instead an ancillary study be conducted to assist with determination of BD/DNC.
16. It is recommended that experienced pediatric clinicians with training and qualifications in pediatric critical care, neonatology, pediatric neurology, pediatric neurointensive care, neurosurgery, or traumatology perform testing to determine BD/DNC in pediatrics.

17. It is recommended that standardized checklists be incorporated into the practice of determining neurologic death in pediatrics to reduce operator variability and diagnostic error.

### Determination of BD/DNC in Patients Requiring Extracorporeal Membrane Oxygenation

Patients requiring extracorporeal membrane oxygenation (ECMO) and other forms of extracorporeal support are at high risk of complications leading to brain injury and BD/DNC. Brain-based determinations of death are increasingly relevant when circulatory support prevents arrest of circulation.

Performing an apnea test in persons receiving ECMO requires adherence to the same principles as in those not receiving ECMO, but it can sometimes be more challenging in this population, particularly because there is a lack of consistent guidance on how the test should be performed under these conditions (Supplement 7).

#### Recommendations and Suggestions

- It is recommended that the same fundamentals of the BD/DNC concept—etiology, prerequisites, minimum clinical criteria, apnea testing targets, and indications for ancillary testing—be applied to adults and children receiving ECMO.
  - It is recommended that performance of an apnea test be part of BD/DNC testing in persons receiving veno-venous or veno-arterial ECMO, unless contraindicated due to cardiopulmonary instability.
  - In persons receiving veno-arterial ECMO for circulatory and respiratory support, it is recommended that the extracorporeal blood flow be maintained during the clinical evaluation and apnea test in order to prevent hemodynamic instability and maintain a mean arterial pressure of at least 60 mm Hg in adults and age-appropriate targets in pediatrics. Veno-arterial ECMO flow rates may be increased to support the MAP if required before or during testing.
  - It is recommended that prior to apnea testing, a period of preoxygenation be provided for all persons receiving ECMO by administering 100% inspired oxygen via the mechanical ventilator and increasing the O<sub>2</sub> in the membrane lung from the ECMO machine to 100% for at least 10 minutes.
  - It is recommended that apnea testing in persons receiving ECMO be conducted by
    - delivering 100% oxygen to the lungs via CPAP on the mechanical ventilator, a resuscitation bag with a functioning PEEP valve, or oxygen flow via a tracheal cannula,
      - Similar to apnea testing in general, the application of positive airway pressure with the use of CPAP/PEEP may prevent derecruitment.
      - It is recognized that some patients may not be mechanically ventilated during ECMO and suspected BD/DNC. Under these conditions, while an apnea test can still be conducted, maintaining oxygenation during the apnea test may be challenging due to the inability to deliver oxygen to the lower airway. Oxygenation will depend on providing 100% oxygen in the sweep gas. If oxygenation cannot be maintained appropriately, the test will need to be aborted and ancillary testing will be required.
- In cases of veno-arterial ECMO with intrinsic cardiac output, blood gases should be measured simultaneously from the distal arterial line and postoxygenator ECMO circuit. The apnea tests targets for both sampling sites should be pH less than 7.30 and PaCO<sub>2</sub> of at least 60 mm Hg (20 mm Hg above the patient's baseline PaCO<sub>2</sub> for persons with preexisting hypercapnia).
  - maintaining oxygen in the membrane lung at 100% throughout the duration of the testing,
  - titrating the sweep gas flow rate to 0.5-1.0 L/min while maintaining oxygenation,
  - assessing for spontaneous breathing while targeting traditional apnea test targets via serial blood gases (as described in the Minimum Clinical Criteria for Determination of BD/DNC section), keeping in mind that achieving a pH less than 7.30 and PaCO<sub>2</sub> of at least 60 mm Hg (20 mm Hg above the patient's baseline PaCO<sub>2</sub> for persons with preexisting hypercapnia) may take longer than in a person without ECMO support,
  - terminating the test immediately if the person exhibits any kind of spontaneous respiratory movements or becomes unstable as described in the Minimum Clinical Criteria for Determination of BD/DNC section,
  - restarting mechanical ventilation and returning to the prior ECMO sweep gas flow rate when the pH reaches less than 7.30 and PaCO<sub>2</sub> reaches 60 mm Hg (20 mm Hg above their baseline PaCO<sub>2</sub> if there is pre-morbid hypercapnia).
- As described in the Minimum Clinical Criteria for Determination of BD/DNC section, it is suggested that if the apnea test cannot be safely conducted or completed, an ancillary test be considered.

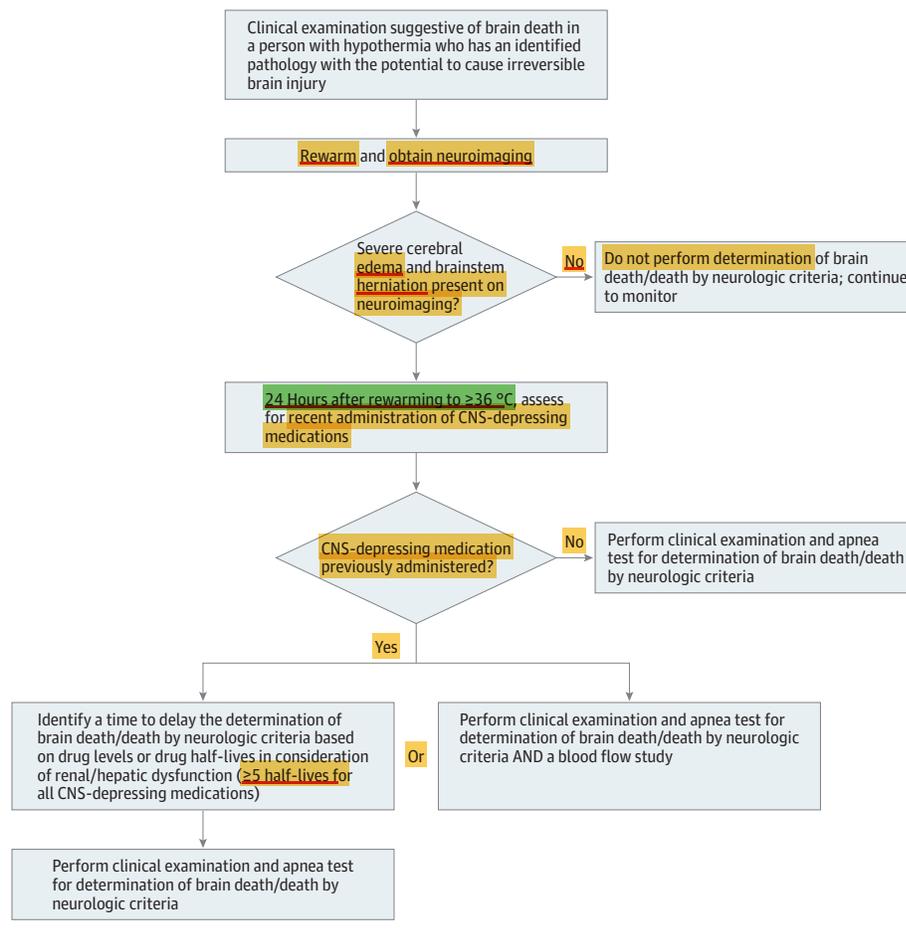
### Determination of BD/DNC After Treatment With Targeted Temperature Management

It can be challenging to identify BD/DNC after treatment with targeted temperature management (TTM). TTM is an evolving field and can mean different temperature goals for different situations; as regards to being a confounder of BD determination, this is specifically referring to therapeutic hypothermia because hypothermia can temporarily blunt brainstem reflexes.<sup>85,86</sup> This effect is particularly pronounced in persons treated with sedation prior to, or concurrent with, therapeutic hypothermia, due to altered pharmacokinetics and pharmacodynamics resulting in delayed drug elimination.<sup>35,87-91</sup> However, there is no standard on how long it is necessary to wait after treatment with therapeutic hypothermia before BD/DNC can be determined (Supplement 8).<sup>7,35,78,92</sup>

#### Recommendations and Suggestions

- It is recommended that practitioners be educated about the effects of hypothermia on both elimination of medications and determination of BD/DNC.
- If, after rewarming a person who was treated with TTM, the findings of their examination appear consistent with BD/DNC, it is recommended that neuroimaging be obtained to assess for both severe cerebral edema and brainstem herniation consistent with severe intracranial hypertension.

**Figure. Flow Diagram for Determination of Brain Death/Death by Neurologic Criteria in Persons Treated With Therapeutic Hypothermia**



3. If there are neuroimaging findings consistent with severe intracranial hypertension 24 hours after rewarming to at least 36 °C, it is recommended that an assessment for recent administration of CNS depressing medications or other confounders should be performed.
  4. If CNS depressing medications were recently administered to a person who (1) was treated with TTM, (2) has an examination results that appear consistent with BD/DNC, and (3) has neuroimaging evidence of severe intracranial hypertension, it is recommended that
    - a. the clinical examination be delayed until at least 5 elimination half-lives of the drug administered with the longest half-life pass before performing an evaluation for BD/DNC, taking into consideration that drug metabolism can be delayed in the setting of hepatic/kidney dysfunction, or
    - b. drug levels be obtained to ensure they are less than or equal to therapeutic levels before performing an evaluation for BD/DNC, or
    - c. an ancillary brain blood flow study be performed in addition to the clinical evaluation and apnea test to make a determination of BD/DNC.
  5. It is recommended that if an imaging study shows evidence of severe cerebral edema and brainstem herniation consistent with intracranial hypertension and no CNS depressing medications were recently administered and there are no other confounders, an examination for determination for BD/DNC be made 24 hours after temperature reaches at least 36 °C.
  6. It is recommended that, if an imaging study does not show evidence of severe cerebral edema and brainstem herniation consistent with intracranial hypertension, a determination for BD/DNC should not be performed because the injury may be reversible.
- The Figure provides a flow diagram for determination of BD/DNC in persons treated with therapeutic hypothermia.

#### Documentation of BD/DNC

Despite the fact that declaration and time of death have both significant medical (eg, organ/tissue donation) and nonmedical consequences, such as the initiation of mourning, estate administration and taxes, and preparation for burial,<sup>93</sup> multiple studies have shown documentation of BD/DNC is often incomplete or inaccurate.<sup>94-100</sup> Improving documentation of BD/DNC

determination may reduce any complications surrounding the nonmedical consequences of death and may also be used as a tool to help minimize the variations and inaccuracies of BD/DNC determination itself (Supplement 9).

### Recommendations and Suggestions

#### Documentation Required for Determination of BD/DNC

1. It is recommended that all phases of BD/DNC determination be clearly documented in the medical record, including:
  - etiology of the coma,
  - absence of confounders,
  - full details of clinical testing performed and results, including apnea testing and laboratory values,
  - neuroimaging results and timing in relation to clinical testing,
  - reason for and type of ancillary testing performed and results, if necessary,
  - time of death,
  - identity of practitioner(s) performing the evaluation.
2. It is recommended that a standardized checklist be used for death determination and its documentation.
3. It is suggested that the time of death be noted in accordance with regional legislation. If regional legislation does not dictate a standard for determining time of death, it is suggested that
  - a. in cases in which BD/DNC can be determined with a neurologic examination and ancillary testing is not needed, the time of death be documented as the time the arterial  $\text{Paco}_2$  reaches the target during the apnea test as reported by the laboratory,
  - b. if ancillary testing is performed, the time of death be documented as the time that the ancillary test results are formally interpreted and documented by the attending physician,
  - c. if 2 examinations are required to declare death, the time of death be the time that the second examination is completed.

Supplement 15 contains a checklist for BD/DNC.

### Qualifications for and Education on Determination of BD/DNC

Qualifications for performing a determination of BD/DNC vary around the world in terms of clinician specialty and length of time in practice. Determinations should be made by clinicians who are both licensed to practice medicine and trained in evaluation of BD/DNC. There are various training methods to educate practitioners about determination of BD/DNC, including online training videos and courses produced by academic institutions and simulation-based training.<sup>101-107</sup> Additionally, the Neurocritical Care Society offers a toolkit to teach both clinicians and the public about determination of BD/DNC.<sup>108</sup>

Clinicians should be educated during training and reeducated when they are in practice to ensure determinations are up-to-date with the latest medical standards (Supplement 10).

### Recommendations and Suggestions

1. It is recommended that BD/DNC determinations be performed by practitioners who have completed training and are licensed to independently practice medicine. These practitioners should be trained in determination of BD/DNC and in counseling fami-

- lies at the patient's end of life and have experience in the management of devastating brain injury.
2. It is suggested that practitioners be periodically certified in determination of BD/DNC.
3. It is recommended that trainees in fields that manage patients with devastating brain injuries be educated about BD/DNC and counseling families in end-of-life care.
4. It is suggested that students in all health care fields be educated about BD/DNC.
5. It is recommended that education about BD/DNC be comprehensive and include a discussion of prerequisites for testing, clinical testing procedures, indications for and performance of ancillary testing, management of complications, and techniques for effective communication with families/surrogates and religious and cultural viewpoints about death.

### Somatic Support After BD/DNC for Organ Donation and Other Special Circumstances

After declaration of BD/DNC, somatic support (also called physiological or organ support) should be discontinued unless (1) organ donation is planned, (2) the decedent is pregnant and the decision is made to continue support for the sake of the fetus, or (3) the family requests continuation of somatic support after BD/DNC due to religious or moral beliefs or other concerns about the use of neurologic criteria to declare death, and the hospital complies with this request for legal or social reasons (Supplement 11).<sup>109-111</sup>

### Recommendations and Suggestions

1. It is recommended that the decision of whether to continue somatic support after BD/DNC for the purposes of organ donation be made based on discussion between a local organ procurement representative and the family of the decedent, taking into consideration the decedent's known or presumed wishes about donation.
2. It is recommended that the decision of whether to continue somatic support after BD/DNC in a pregnant decedent be made after a multidisciplinary discussion with the decedent's family about potential fetal outcome, taking into consideration the decedent's advanced medical directives or expressed wishes and local laws on continuation/discontinuation of support in this setting.
3. It is recommended that the decision of whether to continue somatic support to accommodate an objection to the use of neurologic criteria to declare death or discontinuation of somatic support be made in accordance with local guidelines, as discussed in the section on Religion and Brain Death: Managing Requests to Forgo a BD/DNC Evaluation or Continue Somatic Support After BD/DNC.
4. If organ support is being continued after BD/DNC for the purposes of organ donation, if a decedent is pregnant, or to accommodate an objection to the use of neurologic criteria to declare death or discontinuation of somatic support,
  - a. In an effort to prevent and manage arrhythmias after BD/DNC, it is suggested that
    - i. hypokalemia and hypomagnesemia be avoided/corrected,

- II. amiodarone or lidocaine be used to treat ventricular arrhythmias,
  - III. amiodarone be used to treat supraventricular arrhythmias,
  - IV. atropine not be used to treat bradyarrhythmias because the vagus nerve is nonfunctional after BD/DNC,
  - V. dopamine, dobutamine, epinephrine, or isoproterenol be used to treat bradyarrhythmias in the setting of decreased cardiac output,
  - VI. pacing be considered to manage bradyarrhythmias in the setting of organ donor management or pregnancy, but not in the setting of requests to provide somatic support due to objection to the declaration of BD/DNC,
  - VII. the health care team and decedent's family discuss the potential for cardiopulmonary arrest and the use of cardiopulmonary resuscitation if/when cardiac arrest occurs.
- b. In an effort to prevent and manage perfusion derangements after BD/DNC, it is suggested that
    - I. traditional measures of hemodynamic function and cardiac output be monitored,
    - II. blood pressure be targeted based on individual patient characteristics to maintain adequate organ perfusion,
    - III. boluses of fluid and maintenance fluid be started immediately after BD/DNC to target euvolemia,
    - IV. crystalloids and/or colloids be used to achieve volume goals, but hydroxyethyl starch be avoided,
    - V. vasopressin be used to treat hypotension in the setting of diabetes insipidus,
    - VI. dopamine, norepinephrine, or phenylephrine be started at the lowest dose necessary to maintain hemodynamic stability if a decedent remains hypotensive despite fluids,
    - VII. if cardiopulmonary instability is refractory to the above interventions, initiation of ECMO or placement of an intra-aortic balloon pump be considered in the setting of donor management or pregnancy, but not in the setting of requests to provide somatic support due to objection to the declaration of BD/DNC,
    - VIII. short-acting medications such as nicardipine, labetalol, or esmolol be used to treat hypertension.
  - c. In an effort to maintain normothermia after BD/DNC, it is suggested that
    - I. room temperature be kept at least 24 °C,
    - II. warming blankets, automated temperature regulation devices, thermal mattresses, warmed fluids, and/or warmed oxygen be used, but heat lamps, immersion in hot water, or infusion of warm fluids into the bladder, stomach, pleural, or peritoneal cavity not be used to treat hypothermia,
    - III. cooling blankets or automated temperature regulation devices be used to treat hyperthermia.
  - d. In an effort to prevent and manage respiratory complications after BD/DNC, it is suggested that
    - I. ventilator settings be adjusted as needed to provide the minimum ventilator support to achieve normal pH, eucapnia, and normoxemia,
    - II. a tidal volume of 6 to 8 mL/kg be targeted,
  - III. aggressive suctioning, corticosteroids, PEEP, nebulizers, prone positioning, recruitment maneuvers, or high-frequency oscillation be considered to improve oxygenation,
  - IV. diuretics may be considered to treat pulmonary edema if the patient is hemodynamically stable.
- e. In an effort to prevent and manage endocrine complications after BD/DNC, it is suggested that
    - I. urine output, serum sodium, and urine specific gravity be closely monitored for evidence of diabetes insipidus,
    - II. vasopressin be used if a decedent with diabetes insipidus is hypotensive, or desmopressin be used to treat diabetes insipidus in the absence of hypotension,
    - III. thyroid hormone replacement and/or steroids be considered in the setting of hemodynamic instability,
    - IV. insulin and dextrose be given as needed to target euglycemia.
  - f. In an effort to prevent and manage hematologic complications after BD/DNC, it is suggested that
    - I. an INR (international normalized ratio) and platelet goal be established based on the clinical situation,
    - II. red blood cells be transfused as needed in the setting of active bleeding or symptomatic anemia, such as in the setting of hypotension.
5. When the decision is made to continue somatic support for a brain dead pregnant decedent, it is recommended that
    - a. a multidisciplinary team of intensivists, obstetricians, and neonatologists be involved,
    - b. medications be selected based on their safety profile in pregnancy,
    - c. the fetus be monitored routinely with at least daily heart rate checks and nonstress testing, weekly ultrasounds, and monthly biophysical profiles, as well as performance of amniocentesis on an as-needed basis, given that fetal health may affect decision-making regarding continuation of somatic support,
    - d. antenatal corticosteroids be administered to facilitate lung maturation,
    - e. tocolytics (preference for calcium channel blockers and prostaglandin inhibitors over  $\beta$ -mimetic agents) be utilized as needed to prevent preterm uterine contractions,
    - f. preparations be made for cesarean delivery between 26 and 33 weeks when fetal lung maturity is reached, with the understanding that it may be necessary to perform a delivery earlier in the setting of maternal somatic instability or fetal distress,
    - g. nutritional requirements be calculated based on maternal serum alimentary values, maternal weight and growth of the fetus, and nutrition be provided enterally if the decedent is able to tolerate tube feeds, or parenterally if they are not,
    - h. a tracheostomy be placed if long-term ventilation is anticipated,
    - i. infection prevention practices be rigorous, and infections be treated aggressively,
    - j. precautions be taken to prevent catheter-associated urinary tract infections, corneal abrasions, deep vein thrombosis, line infections, skin ulceration, and ventilator-associated pneumonia.

Table 3. Perspectives of Major Religions on Brain Death/Death by Neurologic Criteria (BD/DNC)

Religion	Perspective on BD/DNC
Buddhism	BD/DNC is <b>accepted</b> as death by some scholars, but this position is <b>not universally</b> held
Christianity	<p><i>American Baptists</i>: there is no official statement on the criteria to declare death, but no opposition to use of neurologic criteria to determine death</p> <p><i>Anglicanism</i>: BD/DNC is accepted as death</p> <p><i>Eastern Orthodoxy</i>: BD/DNC is neither accepted nor rejected</p> <p><i>Evangelicalism</i>: it is accepted that no medical treatment can reverse BD/DNC and noted that "life support" should be removed in the case of BD/DNC to "facilitate the process of dying"</p> <p><i>Jehovah's Witnesses</i>: there is <b>no official statement</b> on the criteria to declare death, but <b>no opposition</b> to use of neurologic criteria to determine death</p> <p><i>Lutheranism</i>: there are mixed opinions on use of neurologic criteria to determine death</p> <p><i>Presbyterianism</i>: BD/DNC is acknowledged to be widely accepted as death</p> <p><i>Roman Catholicism</i>: BD/DNC is generally <b>accepted</b> as death</p> <p><i>Seventh-day Adventists</i>: there is no official statement on the criteria to declare death, but no opposition to use of neurologic criteria to determine death</p> <p><i>Southern Baptists</i>: there is no official statement on the criteria to declare death, but no opposition to use of neurologic criteria to determine death</p> <p><i>United Methodists</i>: there is no official statement on the criteria to declare death, but no opposition to use of neurologic criteria to determine death</p> <p><i>Unitarian Universalists</i>: there is no official statement on the criteria to declare death, but no opposition to use of neurologic criteria to determine death</p>
Hinduism	BD/DNC is <b>accepted</b> as death by some authorities, but this position is <b>not universally</b> held
Islam	<p><i>Shiism</i>: BD/DNC is generally <b>accepted</b> as death</p> <p><i>Sunnism</i>: <b>mixed</b> opinions on BD/DNC</p>
Judaism	<p><i>Conservative Judaism</i>: BD/DNC is <b>accepted</b> as death</p> <p><i>Orthodox Judaism</i>: <b>mixed</b> opinions on BD/DNC</p> <p><i>Reform Judaism</i>: BD/DNC is <b>accepted</b> as death</p>

### Religion and BD/DNC: Managing Requests to Forgo a BD/DNC Evaluation or Continue Somatic Support After BD/DNC

Although BD/DNC is accepted throughout much of the world,<sup>5-7</sup> when a person is declared brain dead, or when a BD/DNC evaluation is planned, families sometimes object and request to either forgo a BD/DNC examination and await cardiopulmonary death or continue somatic support after declaration of BD/DNC (for an indication other than organ donation or maintenance of support for a fetus). These requests affect individual persons, their families, health care teams, and other critically ill patients who require admission to an ICU.<sup>109,112</sup> Two surveys of health care professionals involved in BD/DNC declaration in the US found these requests are made for a variety of reasons, including belief that a person who is brain dead could regain neurologic function, desire to await arrival of additional family members prior to discontinuation of support, and lack of acceptance that a person can be dead if their heart is beating.<sup>109,112</sup> Religious objections, however, are the foundation for the majority of these requests.<sup>113-128</sup> BD/DNC is generally accepted in most religions, but the frequency of this acceptance varies both between and within religions (Table 3 and Supplement 12).<sup>129-142</sup>

#### Recommendations and Suggestions

1. In an effort to preemptively avoid conflict with families regarding determination and declaration of BD/DNC, it is suggested that
  - a. hospitals work with local religious and cultural leaders to learn about their communities and proactively discuss the management of decedents with BD/DNC,
  - b. health care teams be trained in cultural sensitivity and communication, and treat all persons and families with respect,
  - c. family support and education be provided when it is suspected that a person with devastating brain injury may progress to BD/DNC,
  - d. a multidisciplinary support team (ethics, nursing, social work, palliative care, spiritual care, religious officials) be included in discussions about BD/DNC,

- e. health care organizations proactively create guidance on the management of requests for accommodation, including indications for provision of accommodation and notation of specific interventions that can be initiated, continued, or withheld after brain death in the setting of accommodation requests,
  - f. families should be provided with support and education before, during, and after discontinuation of somatic support,
  - g. families be invited to observe the BD/DNC determination.
2. It is recommended that reasonable efforts should be made to notify a person's next-of-kin before performing a BD/DNC determination.
  3. It is recommended that there is no need for consent for performance of the clinical evaluation, apnea testing, or ancillary testing for determination of BD/DNC.
  4. It is recommended that health care teams seek guidance and support from their local ethics and legal teams and hospital administration if a family requests to either forgo a BD/DNC examination or continue somatic support after declaration of BD/DNC.
  5. It is recommended that attempts should be made to handle requests to either forgo a BD/DNC examination or continue somatic support after declaration of BD/DNC within a given hospital system before turning to the legal system.
  6. It is suggested that, while it is reasonable to continue somatic support after BD/DNC for a finite period of time, assuming that the specific time frame for doing so is brief and uniform, and that a family is informed of the time frame in advance, this should ordinarily should not be done for a period greater than 48 hours, and policies should clearly stipulate the time that support will be continued, rather than using a phrase such as "a reasonable amount of time."
  7. It is suggested that if BD/DNC has been declared, but a family voices religious objection to this declaration, the family should be informed that escalation of existing levels of treatment, including cardiopulmonary resuscitation, will not be provided.

8. It is suggested that if only one physician was involved in determination of BD/DNC, an additional clinician in the hospital should provide the family with a second opinion regarding determination of BD/DNC if it is thought that this may assist the family in accepting the decedent's death.
  9. It is suggested that, in the setting of a request to either forgo a BD/DNC examination or continue somatic support after declaration of BD/DNC, a family should be provided with a finite period of time to seek to arrange transfer to another facility (should they wish to do so) and the health care team should speak to a potential accepting institution if requested to do so.
  10. It is suggested that, even in the setting of requests to continue somatic support after declaration of BD/DNC, support should be discontinued if a hospital bed is required for a living patient and no other bed is available.
6. It is suggested that legislation, regulations, judicial formulations, executive orders, decrees, or legal guidelines about BD/DNC address management of objections to use of neurologic criteria to declare death.
  7. It is suggested that legislation, regulations, judicial formulations, executive orders, decrees, or legal guidelines about BD/DNC indicate that there is no need for consent for performance of the clinical evaluation, apnea testing, or ancillary testing for determination of BD/DNC.
  8. It is suggested that legislation, regulations, judicial formulations, executive orders, decrees, or legal guidelines indicate that once BD/DNC has been confirmed in accordance with regional medical criteria, consent should not be required for the discontinuation of somatic support.

### BD/DNC and the Law

In 1968, expert committees from Harvard and the 22nd World Medical Assembly published reports stating that advances in resuscitative and supportive measures necessitated the ability to determine the death of a person based on identification of a permanently nonfunctioning brain.<sup>2,143</sup> Changing the requirements for death, however, was not straightforward, as it is well acknowledged that declaration of death has personal and societal consequences such as initiation of mourning, preparation for burial, estate administration, taxes, and criminal prosecution. Because of this, the US President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research determined that death must be defined by law, both to ensure public acceptance of determination of BD/DNC and to protect practitioners from being prosecuted for discontinuing somatic support after BD/DNC.<sup>144</sup> This report became the basis for the Uniform Determination of Death Act, which provided a legal determination of brain death and was adopted by most of the US. In the 50 years since the Harvard and World Medical Assembly reports, many countries have established a definition of death through legislation, regulation, judicial formulation, executive order, decree, or legal guidelines ([Supplement 13](#)).

### Recommendations and Suggestions

1. It is recommended that all countries recognize BD/DNC as legal death.
2. It is recommended that practitioners be protected from legal action for making determinations of BD/DNC.
3. It is recommended that it should be legally stipulated that while practitioners involved in determination of BD/DNC can be involved in provision of somatic support of potential organ donors, they should not be involved in organ procurement or transplantation.
4. It is suggested that it should be legally stipulated that when there are multiple practitioners who are qualified to determine BD/DNC and care for potential transplantation recipients, the practitioner(s) involved in determination of BD/DNC not concurrently be involved in the care of a potential transplantation recipient.
5. It is suggested that legislation, regulations, judicial formulations, executive orders, decrees, or legal guidelines about BD/DNC specify the locally accepted medical criteria written by experts involved in the process of determination of BD/DNC to be employed when making a determination of BD/DNC while allowing latitude for future versions of such criteria generated by the medical community.

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## Discussion

This is the first international consensus document that reviews the basic and complex clinical aspects and the social and legal aspects of BD/DNC determination. Although countries or professional societies may choose to adopt stricter criteria for BD/DNC, the criteria outlined herein are the minimum criteria as determined by expert consensus and endorsed by 5 world federations and a number of national and regional professional societies.

One important limitation to this consensus document is that a lack of high-quality data from randomized clinical trials or large studies prevented the use of GRADE, AGREE, or other formal analytic techniques. While the authors have attempted to make the recommendations as pragmatic as possible and applicable to all types of hospitals, not all nations will necessarily be able to adopt these recommendations in total. In some cases, economic, technological, or personnel constraints may result in limited ancillary testing choices; in other circumstances, existing laws may restrict adoption of all recommendations. The determination of BD/DNC will always be influenced by local factors including, but not limited to, religious, societal, and cultural perspectives, legal requirements, and resource availability. Another limitation is that these recommendations were developed without inclusion of patient partners, and with sensitivity to, but without direct input from, diverse social/religious groups.

Questions about BD/DNC still remain. Because of this, a list of questions was generated for each topic that was addressed to inform a research agenda ([Supplement 17](#)).

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## Conclusions

This report provides recommendations for the minimum clinical standards for determination of brain death/death by neurologic criteria in adults and children with clear guidance for various clinical circumstances. The recommendations have widespread international society endorsement and can serve to guide professional societies and countries in the revision or development of protocols and procedures for determination of brain death/death by neurologic criteria, leading to greater consistency within and between all countries.

## ARTICLE INFORMATION

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Critical Care Medicine (ISCCM); 12. Intensive Care Society (ICS), UK; 13. Intensive Care Society of Ireland; 14. International Pan Arab Critical Care Medicine Society (IPACCMS); 15. International Society for Donation and Procurement (ISODP); 16. Japanese Society of Intensive Care Medicine (JSICM); 17. Korean Neurocritical Care Society (KNCS); 18. Latin American Brain Injury Consortium (LABIC); 19. National Association of Specialists in Neuroanesthesia and Neurocritical Care, Russia; 20. Nepalese Society of Critical Care Medicine (NSCCM); 21. Neurocritical Care Society (NCS); 22. Sociedad Argentina de Terapia Intensiva (SATI-Argentine Society of Intensive Care); 23. Sociedad Española de Anestesiología, Reanimación y Terapéutica del Dolor (SEDAR); 24. Sociedad Española de Neurocirugía (SENEC-Spanish Society of Neurosurgery); 25. Sociedad Española de Neurología (SEN-Spanish Society of Neurology); 26. Society for Neuroscience in Anesthesiology and Critical Care (SNACC); 27. Society of Critical Care Medicine (SCCM). The following societies reserve the term *endorsement* only for those guidelines that adhere to clinical practice guideline methodologies such as GRADE/JAGREE; for guidelines that are evidence-based consensus-driven, other terminology are used. "The American Academy of Neurology has affirmed the value of this statement as an educational tool for neurologists." "The American Association of Neurological Surgeons/Congress of Neurosurgical Surgeons Joint Section for Neurotrauma and Critical Care affirms the educational benefit of this document." "Although the Canadian Critical Care Society reserves societal endorsement for clinical practice guidelines that have been developed through comprehensive guideline methodology (1) such as GRADE, the CCCS, the CCCS recognizes the importance of this document and looks forward to working with local, provincial, and national bodies to adapt the concepts that are presented in the World Brain Death Document to our national context."

## REFERENCES

- Mollaret P, Goulon M. Le coma depasse. *Rev Neurol (Paris)*. 1959;101:3-15.
- A definition of irreversible coma: report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. *JAMA*. 1968;205(6):337-340. doi:10.1001/jama.1968.03140320031009
- Lewis A, Bakkar A, Kreiger-Benson E, et al. Determination of death by neurologic criteria around the world. *Neurology*. 2020;95(3):e299-e309. doi:10.1212/WNL.0000000000009888
- Greer DM, Wang HH, Robinson JD, Varelas PN, Henderson GV, Wijdicks EF. Variability of brain death policies in the United States. *JAMA Neurol*. 2016;73(2):213-218. doi:10.1001/jamaneurol.2015.3943
- Wahlster S, Wijdicks EFM, Patel PV, et al. Brain death declaration: practices and perceptions worldwide. *Neurology*. 2015;84(18):1870-1879. doi:10.1212/WNL.0000000000001540
- Sprung CL, Truog RD, Curtis JR, et al. Seeking worldwide professional consensus on the principles of end-of-life care for the critically ill: the Consensus for Worldwide End-of-Life Practice for Patients in Intensive Care Units (WELPICUS) study. *Am J Respir*

- Crit Care Med.* 2014;190(8):855-866. doi:10.1164/rccm.201403-0593CC
7. Shemie SDHL, Hornby L, Baker A, et al; the International Guidelines for Determination of Death phase 1 participants, in collaboration with the World Health Organization. International guideline development for the determination of death. *Intensive Care Med.* 2014;40(6):788-797. doi:10.1007/s00134-014-3242-7
  8. Da Silva IR, Frontera JA. Worldwide barriers to organ donation. *JAMA Neurol.* 2015;72(1):112-118. doi:10.1001/jamaneurol.2014.3083
  9. Bernat JL. How much of the brain must die in brain death? *J Clin Ethics.* 1992;3(1):21-26.
  10. Gervais KG. *Redefining Death.* Yale University Press; 1987.
  11. Conference of Royal Colleges and Faculties of the United Kingdom. Diagnosis of brain death. *Lancet.* 1976;2(7994):1069-1070.
  12. Mohandas A, Chou SN. Brain death: a clinical and pathological study. *J Neurosurg.* 1971;35(2):211-218. doi:10.3171/jns.1971.35.2.0211
  13. Smith M, Citerio G. Death determined by neurological criteria: the next steps. *Intensive Care Med.* 2017;43(9):1383-1385. doi:10.1007/s00134-017-4676-5
  14. Kung NH, Dhar R, Keyrouz SG. Diffuse leptomeningeal carcinomatosis mimicking brain death. *J Neurol Sci.* 2015;352(1-2):132-134. doi:10.1016/j.jns.2015.03.045
  15. Rigamonti A, Basso F, Stanzani L, Agostoni E, Lauria G. Guillain-Barré syndrome mimicking brain death. *J Peripher Nerv Syst.* 2009;14(4):316-319. doi:10.1111/j.1529-8027.2009.00244.x
  16. Vargas F, Hilbert G, Gruson D, Valentino R, Gbikpi-Benissan G, Cardinaud JP. Fulminant Guillain-Barré syndrome mimicking cerebral death: case report and literature review. *Intensive Care Med.* 2000;26(5):623-627. doi:10.1007/s001340051213
  17. Moussouttas M, Chandry D, Dyro F. Fulminant acute inflammatory demyelinating polyradiculoneuropathy: case report and literature review. *Neurocrit Care.* 2004;1(4):469-473. doi:10.1385/NCC.1.4.469
  18. Young GB. De-efferentation and de-afferentation in fulminant polyneuropathy: lessons from the isolated brain. *Can J Neurol Sci.* 2003;30(4):305-306. doi:10.1017/S0317167100002997
  19. Liik M, Puksa L, Luus SM, Haldre S, Taba P. Fulminant inflammatory neuropathy mimicking cerebral death. *BMJ.* 2012.
  20. Bakshi N, Maselli RA, Gospe SM Jr, Ellis WG, McDonald C, Mandler RN. Fulminant demyelinating neuropathy mimicking cerebral death. *Muscle Nerve.* 1997;20(12):1595-1597. doi:10.1002/(SICI)1097-4598(199712)20:12<1595::AID-MUS17>3.0.CO;2-#
  21. Martí-Massó JF, Suárez J, López de Munain A, Carrera N. Clinical signs of brain death simulated by Guillain-Barré syndrome. *J Neurol Sci.* doi:10.1016/0022-510X(93)90034-V
  22. Ravikumar S, Poysophon P, Poblete R, Kim-Tenser M. A case of acute motor axonal neuropathy mimicking brain death and review of the literature. *Front Neurol.* 2016;7:63. doi:10.3389/fneur.2016.00063
  23. Bernard V, Van Pesch V, Hantson P. Guillain-Barré syndrome mimicking brain death pattern: a poorly reversible condition. *Acta Neurol Belg.* 2010;110(1):93-96.
  24. Hantson P, Guérit JM, de Tourchaninoff M, et al. Rabies encephalitis mimicking the electrophysiological pattern of brain death. *Eur Neurol.* 1993;33(3):212-217. I doi:10.1159/000116939
  25. John J, Gane BD, Plakkal N, Aghoram R, Sampath S. Snake bite mimicking brain death. *Cases J.* 2008;1(1):16. doi:10.1186/1757-1626-1-16
  26. Dayal M, Prakash S, Verma PK, Pawar M. Neurotoxin envenomation mimicking brain death in a child: a case report and review of literature. *Indian J Anaesth.* 2014;58(4):458-460. doi:10.4103/0019-5049.139008
  27. Freund B, Hayes L, Rivera-Lara L, et al. Adult intestinal colonization botulism mimicking brain death. *Muscle Nerve.* 2017;56(4):E27-E28. doi:10.1002/mus.25689
  28. Joffe AR, Anton N, Blackwood J. Brain death and the cervical spinal cord: a confounding factor for the clinical examination. *Spinal Cord.* 2010;48(1):2-9. doi:10.1038/sc.2009.115
  29. Felton D, Carey, JL, Boyer, E, Neavyn, MJ. Brain death and overdose. *Clinical Toxicology* 2014;52:419
  30. López-Navidad A, Caballero F, Domingo P, et al. Early diagnosis of brain death in patients treated with central nervous system depressant drugs. *Transplantation.* 2000;70(1):131-135.
  31. Morrow SA, Young GB. Selective abolition of the vestibular-ocular reflex by sedative drugs. *Neurocrit Care.* 2007;6(1):45-48. doi:10.1385/NCC.6:1:45
  32. Schmidt JE, Tamburro RF, Hoffman GM. Dilated nonreactive pupils secondary to neuromuscular blockade. *Anesthesiology.* 2000;92(5):1476-1480. doi:10.1097/00000542-200005000-00039
  33. Webb AC, Samuels OB. Reversible brain death after cardiopulmonary arrest and induced hypothermia. *Crit Care Med.* 2011;39(6):1538-1542. doi:10.1097/CCM.0b013e3182186687
  34. Larson MD, Muhiudeen I. Pupillometric analysis of the "absent light reflex". *Arch Neurol.* 1995;52(4):369-372. doi:10.1001/archneur.1995.00540280051018
  35. Wijdicks EFM, Varelas PN, Gronseth GS, Greer DM; American Academy of Neurology. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2010;74(23):1911-1918. doi:10.1212/WNL.0b013e3181e242a8
  36. Academy of Medical Royal Colleges. *A code of Practice for the Diagnosis and Confirmation of Death.* 2008.
  37. Australian and New Zealand Intensive Care Society. *The ANZICS Statement on Death and Organ Donation.* ANZICS; 2013.
  38. Wijdicks EF. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. *Neurology.* 2002;58(1):20-25. doi:10.1212/WNL.58.1.20
  39. Bruce EN, Cherniack NS. Central chemoreceptors. *J Appl Physiol (1985).* 1987;62(2):389-402. doi:10.1152/jappl.1987.62.2.389
  40. Lust RM. Chemical regulation of respiration. In: Caplan M, ed. *Reference Module in Biomedical Sciences.* Elsevier; 2007.
  41. Paolin A, Manuali A, Di Paola F, et al. Reliability in diagnosis of brain death. *Intensive Care Med.* 1995;21(8):657-662. doi:10.1007/BF01711544
  42. Braum M, Ducrocq X, Huot JC, Audibert G, Anxionnat R, Picard L. Intravenous angiography in brain death: report of 140 patients. *Neuroradiology.* 1997;39(6):400-405. doi:10.1007/s002340050432
  43. Flowers WM Jr, Patel BR. Radionuclide angiography as a confirmatory test for brain death: a review of 229 studies in 219 patients. *South Med J.* 1997;90(11):1091-1096. doi:10.1097/00007611-199711000-00007
  44. Joffe AR, Lequier L, Cave D. Specificity of radionuclide brain blood flow testing in brain death: case report and review. *J Intensive Care Med.* 2010; 25(1):53-64. doi:10.1177/0885066609355388
  45. Chang JJ, Tsvigoulis G, Katsanos AH, Malkoff MD, Alexandrov AV. Diagnostic accuracy of transcranial Doppler for brain death confirmation: systematic review and meta-analysis. *AJNR Am J Neuroradiol.* 2016;37(3):408-414. doi:10.3174/ajnr.A4548
  46. Combes JC, Chomel A, Ricolfi F, d'Athis P, Freysz M. Reliability of computed tomographic angiography in the diagnosis of brain death. *Transplant Proc.* 2007;39(1):16-20. doi:10.1016/j.transproceed.2006.10.204
  47. Sawicki M, Sotek-Pastuszka J, Jurczyk K, et al. Original protocol using computed tomographic angiography for diagnosis of brain death: a better alternative to standard two-phase technique? *Ann Transplant.* 2015;20:449-460. doi:10.12659/AOT.893808
  48. Şahin H, Pekçevik Y. CT angiography as a confirmatory test in diagnosis of brain death: comparison between three scoring systems. *Diagn Interv Radiol.* 2015;21(2):177-183. doi:10.5152/dir.2014.14241
  49. Sawicki M, Bohatyrewicz R, Safranow K, et al. Computed tomographic angiography criteria in the diagnosis of brain death: comparison of sensitivity and interobserver reliability of different evaluation scales. *Neuroradiology.* 2014;56(8):609-620. doi:10.1007/s00234-014-1364-9
  50. Dupas B, Gayet-Delacroix M, Villers D, Antonioli D, Veccherini MF, Soullou JP. Diagnosis of brain death using two-phase spiral CT. *AJNR Am J Neuroradiol.* 1998;19(4):641-647.
  51. Quesnel C, Fulgencio JP, Adrie C, et al. Limitations of computed tomographic angiography in the diagnosis of brain death. *Intensive Care Med.* 2007;33(12):2129-2135. doi:10.1007/s00134-007-0789-6
  52. Rieke A, Regli B, Mattle HP, et al. Computed tomography angiography (CTA) to prove circulatory arrest for the diagnosis of brain death in the context of organ transplantation. *Swiss Med Wkly.* 2011;141:w13261. doi:10.4414/smw.2011.13261
  53. Shankar JJ, Vanderpe R. CT perfusion for confirmation of brain death. *AJNR Am J Neuroradiol.* 2013;34(6):1175-1179. doi:10.3174/ajnr.A3376
  54. Garrett MP, Williamson RW, Bohl MA, Bird CR, Theodore N. Computed tomography angiography as a confirmatory test for the diagnosis of brain death. *J Neurosurg.* 2018;128(2):639-644. doi:10.3171/2016.10.JNS161042
  55. Frampas E, Videcoq M, de Kerviler E, et al. CT angiography for brain death diagnosis. *AJNR Am J Neuroradiol.* 2009;30(8):1566-1570. doi:10.3174/ajnr.A1614
  56. Leclerc X, Taschner CA, Vidal A, et al. The role of spiral CT for the assessment of the intracranial circulation in suspected brain-death. *J Neuroradiol.* 2006;33(2):90-95. doi:10.1016/S0150-9861(06)77237-6
  57. Bohatyrewicz R, Sawicki M, Walecka A, et al. Computed tomographic angiography and perfusion in the diagnosis of brain death. *Transplant Proc.* 2010;42(10):3941-3946. doi:10.1016/j.transproceed.2010.09.143

58. Welschehold S, Kerz T, Boor S, et al. Computed tomographic angiography as a useful adjunct in the diagnosis of brain death. *J Trauma Acute Care Surg*. 2013;74(5):1279-1285. doi:10.1097/TA.0b013e31828c46ba
59. Lanfermann H, Schober O. Imaging of irreversible loss of brain function. *Rofo*. 2016;188(1):23-26.
60. Welschehold S, Boor S, Reuland K, et al. Technical aids in the diagnosis of brain death: a comparison of SEP, AEP, EEG, TCD and CT angiography. *Dtsch Arztebl Int*. 2012;109(39):624-630.
61. Welschehold S, Boor S, Reuland K, et al. CT angiography as a confirmatory test in brain death. *Acta Neurochir Suppl*. 2012;114:311-316.
62. Welschehold S, Kerz T, Boor S, et al. Detection of intracranial circulatory arrest in brain death using cranial CT-angiography. *Eur J Neurol*. 2013;20(1):173-179. doi:10.1111/j.1468-1331.2012.03826.x
63. Marchand AJ, Seguin P, Malledant Y, Taleb M, Raoult H, Gauvrit JY. Revised CT angiography venous score with consideration of infratentorial circulation value for diagnosing brain death. *Ann Intensive Care*. 2016;6(1):88. doi:10.1186/s13613-016-0188-7
64. Orban JC, El-Mahjoub A, Rami L, Jambou P, Ichai C. Transcranial Doppler shortens the time between clinical brain death and angiographic confirmation: a randomized trial. *Transplantation*. 2012;94(6):585-588. doi:10.1097/TP.0b013e3182612947
65. MacDonald D, Stewart-Perrin B, Shankar JJS. The role of neuroimaging in the determination of brain death. *J Neuroimaging*. 2018;28(4):374-379. doi:10.1111/jon.12516
66. Karantanas AH, Hadjigeorgiou GM, Paterakis K, Sfiras D, Komnos A. Contribution of MRI and MR angiography in early diagnosis of brain death. *Eur Radiol*. 2002;12(11):2710-2716. doi:10.1007/s00330-002-1336-z
67. Sohn CH, Lee HP, Park JB, et al. Imaging findings of brain death on 3-tesla MRI. *Korean J Radiol*. 2012;13(5):541-549. doi:10.3348/kjr.2012.13.5.541
68. Luchtman M, Beuing O, Skalej M, et al. Gadolinium-enhanced magnetic resonance angiography in brain death. *Sci Rep*. 2014;4:3659. doi:10.1038/srep03659
69. Ishii K, Onuma T, Kinoshita T, Shiina G, Kameyama M, Shimosegawa Y. Brain death: MR and MR angiography. *AJNR Am J Neuroradiol*. 1996;17(4):731-735.
70. FDA Drug Safety Communication: FDA warns that gadolinium-based contrast agents (GBCAs) are retained in the body; requires new class warnings. Updated May 2018. Accessed August 13, 2018. <https://www.fda.gov/Drugs/DrugSafety/ucm589213.htm>
71. Mitchell OC, De La Torre E, Alexander E Jr, Davis CH Jr. The nonfilling phenomenon during angiography in acute intracranial hypertension: report of 5 cases and experimental study. *J Neurosurg*. 1962;19:766-774. doi:10.3171/jns.1962.19.9.0766
72. Grigg MM, Kelly MA, Celesia GG, Ghobrial MW, Ross ER. Electroencephalographic activity after brain death. *Arch Neurol*. 1987;44(9):948-954. doi:10.1001/archneur.1987.00520210048018
73. Su Y, Yang Q, Liu G, et al. Diagnosis of brain death: confirmatory tests after clinical test. *Chin Med J (Engl)*. 2014;127(7):1272-1277.
74. American Clinical Neurophysiology Society. Guideline 3: minimum technical standards for EEG recording in suspected cerebral death. *J Clin Neurophysiol*. 2006;23(2):97-104. doi:10.1097/00004691-200604000-00004
75. Bleck TP. Electrophysiologic evaluation of brain death: a critical appraisal. In Aminoff M, ed. *Electrodiagnosis in Clinical Neurology*. 6th ed. Elsevier; 2012:789-811. doi:10.1016/B978-1-4557-0308-1.00035-2
76. Lee SY, Kim WJ, Kim JM, Kim J, Park S. The Korean Society of Clinical Neurophysiology Education Committee. Electroencephalography for the diagnosis of brain death. *Ann Clin Neurophysiol*. 2017;19:118-124. doi:10.14253/acn.201719.2.118
77. Szurhaj W, Lamblin MD, Kaminska A, Sediri H; Société de Neurophysiologie Clinique de Langue Française. EEG guidelines in the diagnosis of brain death. *Neurophysiol Clin*. 2015;45(1):97-104. doi:10.1016/j.neucli.2014.11.005
78. Nakagawa TA, Ashwal S, Mathur M, Mysore M; Committee for Determination of Brain Death in Infants and Children. Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations—executive summary. *Ann Neurol*. 2012;71(4):573-585. doi:10.1002/ana.23552
79. Nakagawa TA, Ashwal S, Mathur M, Mysore M; Society of Critical Care Medicine, Section on Critical Care and Section on Neurology of American Academy of Pediatrics; Child Neurology Society. Clinical report—guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations. *Pediatrics*. 2011;128(3):e720-e740. doi:10.1542/peds.2011-1511
80. Shemie SD, Doig C, Dickens B, et al; Pediatric Reference Group; Neonatal Reference Group. Severe brain injury to neurological determination of death: Canadian forum recommendations. *CMAJ*. 2006;174(6):S1-S13. doi:10.1503/cmaj.045142
81. *The ANZICS Statement on Death and Organ Donation*. Edition 3.2. ANZICS; 2013.
82. Spanish Royal Decree 1723/2012 regulating the activities of recovery, clinical use and territorial coordination of human organs intended for transplantation and setting quality and safety standards. 2012. Accessed January 3, 2018. <https://www.boe.es/boe/dias/2012/12/29/pdfs/BOE-A-2012-15715.pdf>
83. Royal College of Paediatrics and Child Health. Diagnosis of death by neurological criteria (DNC) in infants less than 2 months old: clinical guideline. April 2015. Accessed July 17, 2020. [https://www.rcpch.ac.uk/sites/default/files/2019-03/2015\\_dnc\\_-\\_full\\_clinical\\_guideline.pdf](https://www.rcpch.ac.uk/sites/default/files/2019-03/2015_dnc_-_full_clinical_guideline.pdf)
84. Academy of Medical Royal Colleges. A Code of Practice for the Diagnosis and Confirmation of Death. 2008. <https://bts.org.uk/information-resources/publications/>
85. Wijdicks EFM. Determining brain death in adults. *Neurology*. 1995;45(5):1003-1011. doi:10.1212/WNL.45.5.1003
86. Mathur M, Ashwal S. Pediatric brain death determination. *Semin Neurol*. 2015;35(2):116-124. doi:10.1055/s-0035-1547540
87. Cronberg T, Brizzi M, Liedholm LJ, et al. Neurological prognostication after cardiac arrest: recommendations from the Swedish Resuscitation Council. *Resuscitation*. 2013;84(7):867-872. doi:10.1016/j.resuscitation.2013.01.019
88. Geocadin RG, Eleff SM. Cardiac arrest resuscitation: neurologic prognostication and brain death. *Curr Opin Crit Care*. 2008;14(3):261-268. doi:10.1097/MCC.0b013e3282fd68ea
89. Rady MY, Verheijde JL. Determining brain death after therapeutic hypothermia on nonpulsatile continuous-flow mechanical circulatory support devices. *J Cardiothorac Vasc Anesth*. 2013;27(2):e8-e9. doi:10.1053/j.jvca.2012.08.014
90. Lang CJ. There is no reversible brain death. *Crit Care Med*. 2011;39(9):2205-2206. doi:10.1097/CCM.0b013e318222727c
91. Wijdicks EFM, Varelas PN, Gronseth GS, Greer DM. There is no reversible brain death. *Crit Care Med*. 2011;39(9):2204-2205. doi:10.1097/CCM.0b013e318222724e
92. Sampson BG, Datson LD, Bihari S. Use of imaging studies for determination of brain death in South Australian intensive care units. *Crit Care Resusc*. 2017;19(1):57-63.
93. Lewis A, Greer D. Point: should informed consent be required for apnea testing in patients with suspected brain death? *No. Chest*. 2017;152(4):700-702. doi:10.1016/j.chest.2017.05.030
94. Wang MY, Wallace P, Gruen JP. Brain death documentation: analysis and issues. *Neurosurgery*. 2002;51(3):731-735. doi:10.1097/O0006123-200209000-00021
95. Mathur M, Petersen L, Stadler M, et al. Variability in pediatric brain death determination and documentation in southern California. *Pediatrics*. 2008;121(5):988-993. doi:10.1542/peds.2007-1871
96. Shappell CN, Frank JI, Husari K, Sanchez M, Goldenberg F, Ardelit A. Practice variability in brain death determination: a call to action. *Neurology*. 2013;81(23):2009-2014. doi:10.1212/01.wnl.0000436938.70528.4a
97. Puttinger G, Gruber F, et al. Documentation of brain death diagnostics in Upper Austria 2011-2013: an audit. *Eur J Neurol*. 2016;(suppl 2):165.
98. Kashkoush A, Weisgerber A, Dharaneeswaran K, Agarwal N, Shutter L. Medical training and the brain death exam: a single institution's experience. *World Neurosurg*. 2017;108:374-378. doi:10.1016/j.wneu.2017.08.185
99. Pandey A, Sahota P, Nattanmai P, Newey CR. Variability in diagnosing brain death at an academic medical center. *Neurosci J*. 2017;2017:6017958. doi:10.1155/2017/6017958
100. Krawiec C, Ceneviva GD, Thomas NJ. Assessing and improving documentation of pediatric brain death determination within an electronic health record. *Neuropediatrics*. 2019;50(2):80-88. doi:10.1055/s-0038-1676661
101. Araki T, Yokota H, Ichikawa K, et al. Simulation-based training for determination of brain death by pediatric healthcare providers. *Springerplus*. 2015;4:412. doi:10.1186/s40064-015-1211-4
102. MacDougall BJ, Robinson JD, Kappus L, Sudikoff SN, Greer DM. Simulation-based training in brain death determination. *Neurocrit Care*. 2014;21(3):383-391. doi:10.1007/s12028-014-9975-x
103. Cleveland Clinic. Death by neurological criteria course. Accessed July 16, 2020. [https://www.lifesharing.org/wp-content/uploads/2016/02/Neurological\\_Criteria\\_Course.pdf](https://www.lifesharing.org/wp-content/uploads/2016/02/Neurological_Criteria_Course.pdf)
104. University of Chicago. Brain death simulation workshop. January 2016. Accessed July 16, 2020. <https://cme.uchicago.edu/bdsw2016>
105. University of Cape Town. Organ donation: from death to life. Accessed July 15, 2020. <https://www.coursera.org/learn/organ-donation>

106. NHS Blood and Transplant. Diagnosing death using neurological criteria. Accessed July 16, 2020. <https://www.odt.nhs.uk/deceased-donation/best-practice-guidance/donation-after-brainstem-death/diagnosing-death-using-neurological-criteria/>
107. Canadian Blood Services. Neurological determination of death. <https://cbs.online-compliance.com/default.php>
108. Neurocritical Care Society. Brain death toolkit. Accessed July 16, 2020. <https://www.neurocriticalcare.org/education/digital-education/brain-death-toolkit>
109. Lewis A, Adams N, Varelas P, Greer D, Caplan A. Organ support after death by neurologic criteria: results of a survey of US neurologists. *Neurology*. 2016;87(8):827-834. doi:10.1212/WNL.0000000000003008
110. Field DR, Gates EA, Creasy RK, Jonsen AR, Laros RK Jr. Maternal brain death during pregnancy: medical and ethical issues. *JAMA*. 1988;260(6):816-822. doi:10.1001/jama.1988.03410060086033
111. Escudero D, Valentín MO, Escalante JL, et al. Intensive care practices in brain death diagnosis and organ donation. *Anaesthesia*. 2015;70(10):1130-1139. doi:10.1111/anae.13065
112. Lewis A, Adams N, Chopra A, Kirschen MP. Organ support after death by neurologic criteria in pediatric patients. *Crit Care Med*. 2017;45(9):e916-e924. doi:10.1097/CCM.0000000000002452
113. In re Long Island Jewish Medical Center. *West's NY Suppl*. 1996;641:989-992.
114. Flamm AL, Smith ML, Mayer PA. Family members' requests to extend physiologic support after declaration of brain death: a case series analysis and proposed guidelines for clinical management. *J Clin Ethics*. 2014;25(3):222-237.
115. Johnson LSM. The case for reasonable accommodation of conscientious objections to declarations of brain death. *J Bioeth Inq*. 2016;13(1):105-115.
116. Kahn PA. Bioethics, religion, and public policy: intersections, interactions, and solutions. *J Relig Health*. 2016;55(5):1546-1560. doi:10.1007/s10943-015-0144-0
117. Lewis A, Greer D. Current controversies in brain death determination. *Nat Rev Neurol*. 2017;13(8):505-509. doi:10.1038/nrneuro.2017.72
118. Lewis A, Pope TM. Physician power to declare death by neurologic criteria threatened. *Neurocrit Care*. 2017;26(3):446-449. doi:10.1007/s12028-017-0375-x
119. Luce JM. The uncommon case of Jahi McMath. *Chest*. 2015;147(4):1144-1151. doi:10.1378/chest.14-2227
120. Paris JJ, Cummings BM, Moore MP Jr, Moore MP. "Brain death," "dead," and parental denial—the case of Jahi McMath. *Camb Q Healthc Ethics*. 2014;23(4):371-382. doi:10.1017/S0963180114000048
121. Pope TM. Legal briefing: brain death and total brain failure. *J Clin Ethics*. 2014;25(3):245-257.
122. Burkle CM, Pope TM. Brain death: legal obligations and the courts. *Semin Neurol*. 2015;35(2):174-179. doi:10.1055/s-0035-1547537
123. Choong KA, Rady MY, Re A (A Child) and the United Kingdom Code of Practice for the Diagnosis and Confirmation of Death: should a secular construct of death override religious values in a pluralistic society? *HEC Forum*. 2018;30(1):71-89. doi:10.1007/s10730-016-9307-y
124. Bosek MS, Anderson JA, Vernaglia LW, Morrigan SP, Bard TR. Refusal of brain death diagnosis. *JONAS Health Law Ethics Regul*. 2007;9(3):87-94. doi:10.1097/O1.NHL.00000287972.28806.42
125. Smith ML, Flamm AL. Accommodating religious beliefs in the ICU: a narrative account of a disputed death. *Narrat Inq Bioeth*. 2011;1(1):55-64. doi:10.1353/nib.2011.0003
126. Berner D, Gaeta S. Religion based non-acceptance of brain death, an end-of-life ethical dilemma. *Crit Care Med* 2012;40:304. doi:10.1097/O1.ccm.0000425404.78820.1b
127. Olick RS, Braun EA, Potash J. Accommodating religious and moral objections to neurological death. *J Clin Ethics*. 2009;20(2):183-191.
128. Shanawani H, Bazy N. Non-acceptance of neurologic criteria of death in a minority ethnic/religious community in southeast Michigan: the challenge when accepted medical guidelines are in conflict with local religious beliefs. *Am J Respir Crit Care Med*. 2010;181:A6698. doi:10.1164/ajrccm-conference.2010.181.1.MeetingAbstracts.A6698
129. Veith FJF, Fein JM, Tendler MD, Veatch RM, Kleiman MA, Kalkines G. Brain death, I: a status report of medical and ethical considerations. *JAMA*. 1977;238(15):1651-1655. doi:10.1001/jama.1977.03280160045026
130. Setta SM, Shemie SD. An explanation and analysis of how world religions formulate their ethical decisions on withdrawing treatment and determining death. *Philos Ethics Humanit Med*. 2015;10:6. doi:10.1186/s13010-015-0025-x
131. Campbell C. Fundamentals of life and death: Christian fundamentalism and medical science. In: Youngner S, Arnold RM, Schapiro R, ed. *The Definition of Death: Contemporary Controversies*. John Hopkins University Press; 1999.
132. Furton EJ. Brain death, the soul, and organic life. *Natl Cathol Bioeth Q*. 2002;2(3):455-470. doi:10.5840/nbcq20022332
133. Haas JM. Catholic teaching regarding the legitimacy of neurological criteria for the determination of death. *Natl Catholic Bioethics Q*. 2011;11:279-299. doi:10.5840/nbcq20111254
134. Pontifical Academy of Sciences. *The Signs of Death*. Pontifical Academy of Sciences; 2007.
135. Rosner F. The definition of death in Jewish law. In: Youngner S, Arnold RM, Schapiro R, ed. *The Definition of Death: Contemporary Controversies*. Johns Hopkins University Press; 1999.
136. Halachic Organ Donor Society. Accessed August 19, 2017. <https://www.hods.org>
137. Miller AC, Ziad-Miller A, Elamin EM. Brain death and Islam: the interface of religion, culture, history, law, and modern medicine. *Chest*. 2014;146(4):1092-1101. doi:10.1378/chest.14-0130
138. Qazi F, Ewell JC, Munawar A, Asrar U, Khan N. The degree of certainty in brain death: probability in clinical and Islamic legal discourse. *Theor Med Bioeth*. 2013;34(2):117-131. doi:10.1007/s11017-013-9250-8
139. Padelá AI, Arozullah A, Moosa E. Brain death in Islamic ethico-legal deliberation: challenges for applied Islamic bioethics. *Bioethics*. 2013;27(3):132-139. doi:10.1111/j.1467-8519.2011.01935.x
140. Albar MA. Islamic ethics of organ transplantation and brain death. *Saudi J Kidney Dis Transpl*. 1996;7(2):109-114.
141. Khalid I, Hamad WJ, Khalid TJ, Kadri M, Qushmaq I. End-of-life care in Muslim brain-dead patients: a 10-year experience. *Am J Hosp Palliat Care*. 2013;30(5):413-418. doi:10.1177/1049909112452625
142. Jain S, Maheshwari, MC. Brain death: the Indian perspective. In: Machado C, ed. *Brain Death*. Elsevier; 1995.
143. Gilder SS. Twenty-second World Medical Assembly. *Br Med J*. 1968;3(5616):493-494. doi:10.1136/bmj.3.5616.493
144. President's Commission for the Study of Ethical Problems in Medicine and Biomedical Behavioral Research. *Defining Death: A Report on the Medical, Legal and Ethical Issues in the Determination of Death*. President's Council on Bioethics; 1981.