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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, oculocephalic, 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 $Paco_2$ ≥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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Editorial

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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 depassé"[1] and subsequently described as "brain death" with the first published clinical definition in 1968, commonly known as the Harvard Brain Death Criteria.[2] 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.[3]

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.[3,4] 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.

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 precautionary, 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.

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 depassé," "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 is ≥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 of 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.[3,5-8] 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.[9-12] 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).[13]

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[14-28] and situations in which drug, metabolic, and hemodynamic derangements falsely suggest BD/DNC (eg, patients with residual sedation or treatment with hypothermia).[29-33]

Recommendations and Suggestions

1. 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.
2. 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.
3. It is suggested that prior to making a determination of BD/DNC, there be
   a. neuroimaging evidence of intracranial hypertension (severe cerebral edema and herniation), or
   b. intracranial pressure measurements that equal or exceed the mean arterial pressure.
4. It is suggested that in the absence of herniation on neuroimaging, caution be taken when considering an evaluation for BD/DNC.
5. It is suggested that the following prerequisites be met before an evaluation for determination of BD/DNC is performed:
   a. 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,
   b. 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.
6. It is recommended that the following confounders be eliminated before an evaluation for determination of BD/DNC is performed:
   a. 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.
   b. 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:
      I. use of a toxicology screen if there is concern for a toxic exposure, and
      II. 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
      III. allowing 5 elimination half-lives to pass before an evaluation for BD/DNC be made (assuming normal hepatic and kidney function), or
      IV. performing ancillary testing in addition to the complete clinical examination and apnea test if there is concern about prolonged or unknown drug elimination.
   c. If alcohol intoxication is suspected or confirmed, the alcohol blood level must be 80 mg/dL or lower.
   d. 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.
7. 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.
8. It is recommended that an adequate observation period take place prior to clinical testing for BD/DNC.
   a. 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.)
   b. 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 pupilometer); (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.[7,34-38]

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.[7,35-38] 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.[39] 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.[40]

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_2 for at least 10 minutes.
5. It is suggested the minute ventilation be adjusted to establish normocarbia ($PaCO_2$ 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 $PaCO_2$ 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 $PaCO_2$, 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 $PaCO_2$ is at least 60 mm Hg (≥20 mm Hg above any known chronic baseline $PaCO_2$ 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 $PaCO_2$ be used to confirm adequate elevation of CO_2 during apnea testing.
12. If the apnea test is inconclusive (does not reach $PaCO_2$ 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 (≈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 $Paco_2$ 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 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.[4,5,38]

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.[5] There are advantages and disadvantages to all ancillary tests (see **Table 1** and **Table 2** and Supplement 5).[41-73]

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	• Reference standard for ancillary tests	• Requires transport to imaging suite • Invasive (requires technical skills) • Kidney susceptibility to contrast • Stasis filling–false negative	100/ 100[a,41,42]	• Persistence of flow does not contradict comprehensive competent clinical diagnosis • Equipment and operator dependence limits practical use; still used as calibration standard
Radionuclide angiography	Absence of radiologic activity upon imaging of the intracranial vault	• Can be performed at bedside • No kidney susceptibility to contrast	• Limited evaluation of brainstem • Limited availability	98.5/ 56[43]	• Persistence of flow does not contradict comprehensive competent clinical diagnosis
Radionuclide perfusion scintigraphy	Absence of radiologic activity indicating metabolic uptake upon imaging of the intracranial vault	• Can be performed at bedside (planar imaging)	• Limited availability • Planar imaging may limit brainstem evaluation • SPECT requires patient transport to scanner	Planar: 77.8/ 100; SPECT: 88.4/100[a,44]	• Uptake of isotope indicates metabolic activity
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	• Easily performed at bedside • No contrast required • Can assess carotid and basilar circulations	• Operator expertise required • 10% of patients have no acoustic windows	90/98[45]	• Persistence of flow does not contradict comprehensive competent clinical diagnosis
Computed tomography angiography	No opacification of intracranial arterial circulation, or deep veins	• Widely available • Relatively quick to perform	• Requires transport to imaging suite • Kidney susceptibility to contrast • Stasis filling–false negative	52-97/ 100[a,46-65]	• Persistence of flow does not contradict comprehensive competent clinical diagnosis • Limited consensus on required diagnostic criteria • Small number of studies with lack of reference standard • Not currently validated against above accepted tests
Magnetic resonance angiography	No visualization of intracranial arterial circulation	• Not affected by stasis filling • Visualization improved by gadolinium	• Requires transport to imaging suite • Specialized critical care equipment required in scanner • Time of flight imaging affected by hematoma	93-100[66-69]/ 100[a,66,67]	• Persistence of flow does not contradict comprehensive competent clinical diagnosis • Small number of studies with lack of reference standard • Uncertainty about risks of nephrogenic systemic fibrosis[70] • Not currently validated against above accepted tests

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

[a] Specificity is assumed on basis of experimental data but should be interpreted with caution[71] 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,[74] Bleck,[75] Korean Society of Clinical Neurophysiology,[76] or Société de Neurophysiologie Clinique de Langue Française.[77]

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.[78-84] 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.[78,79]

Table 2. Tests of Electrophysiological Function

Test	Diagnostic criteria	Advantages	Disadvantages	Sensitivity/ specificity, %	Comments
EEG	No detectable electrical activity (≥2 μV) over a 30-min period	• Noninvasive • Can be performed at bedside	• Predominantly cortical assessment • Electromagnetic environmental noise can erroneously suggest cerebral electrical activity • Confounded by sedation, hypothermia, toxic states, metabolic disorders	53-80. 4/97[41,72]	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	• Noninvasive • Can be performed at bedside • Less susceptible to sedation than EEG	• Confounded by cervical spinal cord injury, isolated brainstem lesions, sedation, hypothermia	100/78[73]	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	• Noninvasive • Can be performed at bedside • Less susceptible to sedation than EEG	• Confounded by sedation, profound hypothermia, isolated eighth cranial nerve or brainstem lesions • Limited to auditory cortex		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	• Noninvasive • Can be performed at bedside • Less susceptible to sedation or hypothermia than EEG	• Confounded by sedation, retinal or optic nerve lesions • Limited to visual cortex		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.[78-82] Most countries use whole brain death criteria (brain and brainstem) to determine death in infants and children.[78-82] Ancillary studies are not usually mandatory,[78-84] but some protocols recommend them as they may be helpful when components of the physical examination or apnea test cannot be completed.[78-82] 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).[78-84]

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

1. 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.
2. 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.
3. 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.
4. 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_2 in the membrane lung from the ECMO machine to 100% for at least 10 minutes.
5. It is recommended that apnea testing in persons receiving ECMO be conducted by
   a. 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 $Paco_2$ of at least 60 mm Hg (20 mm Hg above the patient's baseline $Paco_2$ for persons with preexisting hypercapnia).
   b. maintaining oxygen in the membrane lung at 100% throughout the duration of the testing,
   c. titrating the sweep gas flow rate to 0.5-1.0 L/min while maintaining oxygenation,
   d. 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 $Paco_2$ of at least 60 mm Hg (20 mm Hg above the patient's baseline $Paco_2$ for persons with preexisting hypercapnia) may take longer than in a person without ECMO support,
   e. 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,
   f. restarting mechanical ventilation and returning to the prior ECMO sweep gas flow rate when the pH reaches less than 7.30 and $Paco_2$ reaches 60 mm Hg (20 mm Hg above their baseline $Paco_2$ if there is premorbid hypercapnia).
6. 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.

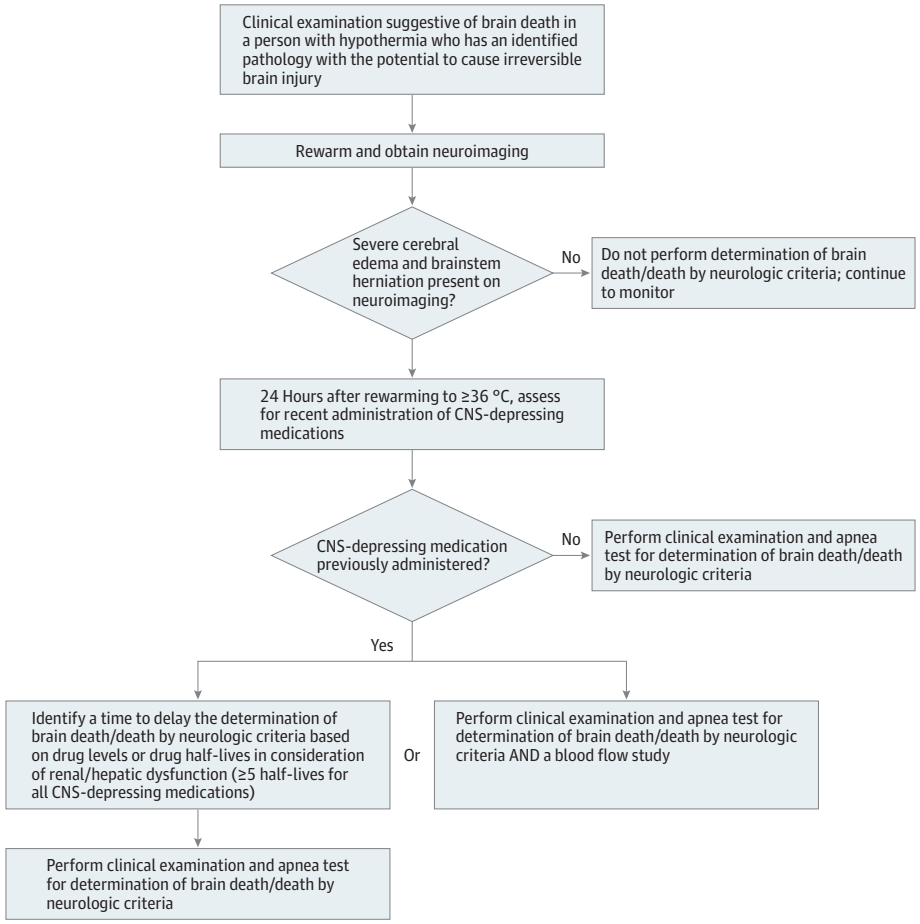
Determination of BD/DNC After Treatment With Targeted Temperature Management

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.[85,86] 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.[35,87-91] 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).[7,35,78,92]

Recommendations and Suggestions

1. It is recommended that practitioners be educated about the effects of hypothermia on both elimination of medications and determination of BD/DNC.
2. 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 a 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,[93] multiple studies have shown documentation of BD/DNC is often incomplete or inaccurate.[94-100] 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 $Paco_2$ 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.[101-107] Additionally, the Neurocritical Care Society offers a toolkit to teach both clinicians and the public about determination of BD/DNC.[108]

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 families 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).[109-111]

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 β-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 accepted as death by some scholars, but this position is not universally held
Christianity	*American Baptists:* there is no official statement on the criteria to declare death, but no opposition to use of neurologic criteria to determine death *Anglicanism*: BD/DNC is accepted as death *Eastern Orthodoxy*: BD/DNC is neither accepted nor rejected *Evangelicalism*: 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" *Jehovah's Witnesses*: there is no official statement on the criteria to declare death, but no opposition to use of neurologic criteria to determine death *Lutheranism*: there are mixed opinions on use of neurologic criteria to determine death *Presbyterianism*: BD/DNC is acknowledged to be widely accepted as death *Roman Catholicism*: BD/DNC is generally accepted as death *Seventh-day Adventists*: there is no official statement on the criteria to declare death, but no opposition to use of neurologic criteria to determine death *Southern Baptists:* there is no official statement on the criteria to declare death, but no opposition to use of neurologic criteria to determine death *United Methodists*: there is no official statement on the criteria to declare death, but no opposition to use of neurologic criteria to determine death *Unitarian Universalists*: there is no official statement on the criteria to declare death, but no opposition to use of neurologic criteria to determine death
Hinduism	BD/DNC is accepted as death by some authorities, but this position is not universally held
Islam	*Shiism*: BD/DNC is generally accepted as death *Sunnism*: mixed opinions on BD/DNC
Judaism	*Conservative Judaism*: BD/DNC is accepted as death *Orthodox Judaism*: mixed opinions on BD/DNC *Reform Judaism*: BD/DNC is accepted as death

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,[5-7] 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.[109,112] 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.[109,112] Religious objections, however, are the foundation for the majority of these requests.[113-128] 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).[129-142]

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.

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.[2,143] 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.[144] 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.
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.

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).

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.

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