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REVIEW

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Diagnosis of brain death

Pawarisa Chaisuthikun[1], Kittikorn Kittirukwarakorn[1], Nattanon Pornchaisakuldee[2]

[1]Intensive Care Unit, Department of Medicine, Ramathibodi Hospital, Bangkok, Thailand, 10400;
[2]Neurology Unit, Department of Medicine, Ramathibodi Hospital, Bangkok, Thailand, 10400

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Corresponding author:
Kittikorn Kittirukwarakorn
Intensive Care Unit, Department of Medicine, Ramathibodi Hospital, Bangkok, Thailand, 10400
Tel: (+66) 2-201-1301
E-mail: pp_pangpond_03@hotmail.com

ABSTRACT:

Brain death (BD), or death by neurological criteria (DNC), defined as the irreversible cessation of all cerebral and brainstem activities, has been a medically and legally accepted formulation of death. This review article summarizes the clinical criteria and diagnostic protocols for determining brain death. Emphasis is placed on the integration of clinical examination findings, such as the absence of brainstem reflexes and apnea testing, alongside ancillary tests when required. Key guidelines are discussed to ensure a standardized and legally sound diagnosis, including approaches to confounding factors such as drug intoxication, metabolic disturbances, or hypothermia. Furthermore, the article highlights advancements in imaging techniques and electrophysiological monitoring that supplement traditional assessments. This review aims to provide a comprehensive understanding of brain death diagnosis, ensuring accuracy and consistency in clinical and legal practices worldwide.

Keywords: Brain death; Death by neurological criteria; Apnea test; Ancillary tests; Clinical criteria.

INTRODUCTION

In 1959, Mollaret and Goulon first described this state as “coma de´passe´” or irretrievable coma. A more precise definition of brain death was issued in 1968 in the report of the Ad Hoc Committee of Harvard Medical School[1] and adult guidelines were put forth in the 1995 (and revised 2010) American Academy of Neurology (AAN) guidelines on the determination of BD/DNC. In 1987, the American Academy of Pediatrics task force on brain death in children published guidelines for the pediatric population, which was updated in 2011[2].

In 2023, in collaboration with the American Academy of Pediatrics (AAP), Child Neurology Society (CNS), and Society for Critical Care Medicine (SCCM), the AAN formulated an updated, evidence-informed, consensus-based guideline for pediatric and adult brain death/death by neurologic criteria (BD/DNC) determination. This 2023 guideline builds on the minimum standards for BD/DNC determination established through international expert consensus in the World Brain Death Project (WBDP) and reflects the multidisciplinary expertise of US adult and pediatric neurologists, intensivists, and neurosurgeons. It replaces the 2010 AAN guideline for adult BD/DNC determination and the 2011 AAP, CNS, and SCCM guideline for pediatric BD/DNC determination (referred to here as "the prior guidelines"). These prior guidelines followed earlier standards: the 1995 AAN guideline for adult BD/DNC determination and the 1987 Task Force guideline for pediatric BD/DNC determination. Although the prior pediatric and

adult guidelines were largely similar, a few key differences existed. The publication of this unified 2023 guideline for both pediatric and adult BD/DNC determination marks a significant achievement, addressing one of the goals set at the 2016 multi-society summit organized by the AAN- to improve public trust in BD/DNC determination. While recommendations for both pediatric and adult BD/DNC determination in the 2023 guideline are largely identical, the document provides age-specific guidance to account for physiological differences between children and adults, as well as historical considerations.

While the prior pediatric and adult guidelines were largely similar, there were some notable differences. The 2023 guideline represents a significant achievement, aligning both pediatric and adult BD/DNC recommendations while also addressing age-specific physiological differences and historical considerations. This unified approach helps improve public trust in BD/DNC determination, a goal set at the 2016 multi-society summit organized by the AAN.

KEY MESSAGES:

- Brain death (BD), or death by neurological criteria (DNC), has been a medically and legally accepted formulation of death.
- Guideline updates are intended to strengthen the methods and practice of BD/DNC determination; these include the World Brain Death Project (WBDP) in 2020, the Canadian guideline update in 2023, and the US combined pediatric and adult guidelines from multiple societies in 2023.
- Diagnosing brain death in patients on ECMO is a complex process due to the nature of ECMO itself. The apnea test, a crucial component of brain death determination

Incidence of brain death in Thailand

Analysis of the 2023 annual report from the Organ Donation Center of the Thai Red Cross Society reveals a significant increase in organ donors following brain death. [3] Between January 1, 2019, and December 31, 2023, a total of 418 brain-death organ donors were recorded. This figure demonstrates a substantial rise in 2023, with 120 donors compared to 81 in 2022, representing a 48% increase. The primary causes of death leading to organ donation were accidents (56%), encompassing traffic injuries, assaults, homicides, and suicides, while natural causes, predominantly hemorrhagic strokes, accounted for the remaining 44%.[3]

In Thailand, the determination of BD is governed by guidelines established by the Thai Medical Council. These guidelines outline the criteria and procedures for declaring BD, ensuring consistency and adherence to medical standards. The Thai Medical Council's guidelines are informed by international standards and are periodically updated to reflect advancements in medical knowledge and practices. The incidence of BD in Thailand is influenced by various factors, including the prevalence of conditions leading to severe brain injury, such as traumatic brain injuries, cerebrovascular accidents, and other neurological events. Accurate data on the exact incidence of BD in Thailand is limited; however, the establishment of clear guidelines by the Thai Medical Council aims to standardize the determination process and enhance the reliability of BD declarations across the country. The Thai Medical Council's recommendations are periodically reviewed and updated to incorporate the latest medical research and international best practices. This ensures that the determination of BD in Thailand remains consistent with global standards and is aligned with the evolving understanding of neurological conditions. For healthcare professionals in Thailand, adherence to the Thai Medical Council's recommendation is essential for the ethical and accurate determination of BD, thereby upholding the integrity of medical practice and ensuring respect for patients and their families.

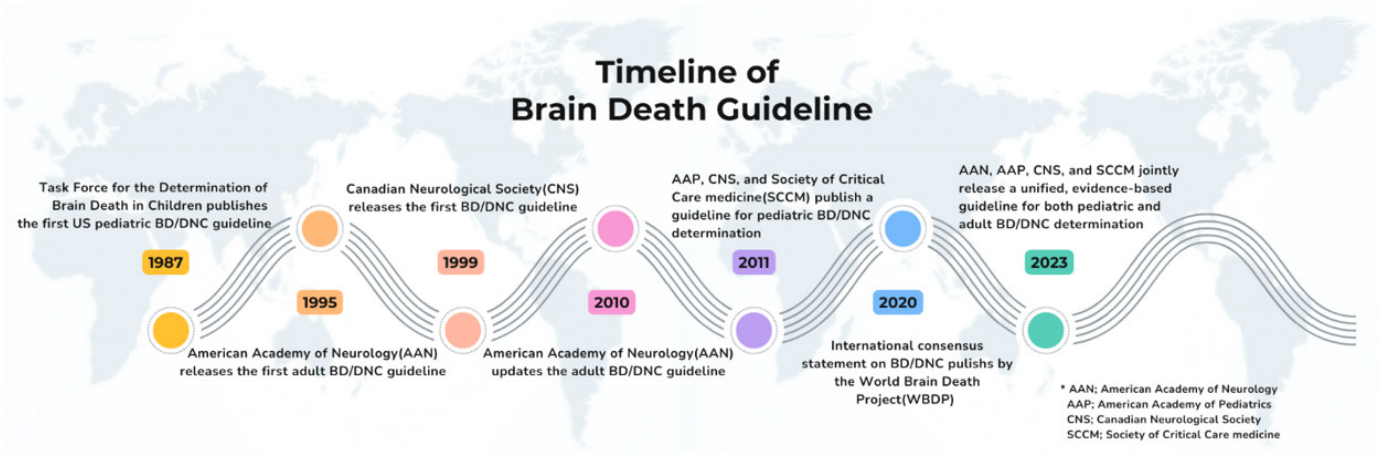

Figure 1. Timeline of brain death guideline.

MAIN BODY

Brain death, defined as the irreversible cessation of all brain functions, including those of the brainstem[4], represents a clinical entity largely shaped by advancements in mechanical ventilation. Before widespread access to such technology, neurological crises typically resulted in apnea, subsequently causing hypoxia and culminating in cardiac arrest.

Today, BD is widely accepted conceptually and legally worldwide[5]. While diagnostic protocols exhibit variability both within and between nations[6, 7]. BD results from either primary cerebral insults (e.g., subarachnoid hemorrhage, traumatic brain injury, intracerebral hemorrhage, ischemic stroke, or rarely, neoplasm) or secondary insults, most commonly anoxic brain injury following cardiac arrest. Regardless of etiology, the terminal pathway involves elevated intracranial pressure, precipitating the arrest of cerebral circulation. Brain function deterioration generally follows a rostral-to-caudal pattern, with brainstem function being the last to decline due to its relative resistance to anoxic injury. Within the brainstem, the medulla is the final region to lose function, as evidenced by the cessation of respiratory drive[8].

Declare brain death

Before conducting a BD/DNC evaluation (Figure 2), establishing the etiology of the acute central nervous system (CNS) injury is paramount. This requires demonstrating clinical evidence of a catastrophic neurological insult consistent with profound brain function loss. While neuroimaging[9] is a crucial component of this assessment, it is important to acknowledge that initial imaging studies may not consistently reveal significant structural abnormalities, particularly in the early stages of injury. In such instances, serial neuroimaging is strongly recommended to document the evolution and severity of the acute brain injury, thereby substantiating the clinical findings and supporting the subsequent BD/DNC evaluation.

Confirmation of irreversible brain injury necessitates a sufficient observation period, guided by the specific injury's pathophysiology[10], despite the absence of definitive temporal guidelines[11]. Before brain death/determination of neurological criteria (BD/DNC) evaluation, optimal management of intracranial pressure (ICP) is required to exclude potential neurological recovery[12] and exclude confounding factors that can mimic brain death (Table 1). To mitigate conflicts of interest, clinicians involved in organ recovery for transplantation must be independent of the BD/DNC evaluation team. Establishing irreversibility typically involves a waiting period determined by the underlying etiology. In cases of global anoxic brain injury following cardiac arrest, a minimum 24-hour waiting period after rewarming to ≥ 36 °C for TTM[13] or core temp ≤ 35.5 °C [12]. Among the metabolic derangements that can lead to coma, abnormal brainstem reflexes, and respiratory arrest are hyponatremia, hyperammonemia associated with acute liver failure, hypermagnesemia, and hypophosphatemia[14]. In BD-diagnosed patients, thyroid function is frequently altered but typically remains partially preserved. However, patterns of low TSH, T3, and T4 are consistent with both euthyroid sick syndrome and, in some cases, true central neuroendocrine failure. Euthyroid sick syndrome is commonly observed in critically ill patients and generally does not require treatment. Nonetheless, if hypothyroid-related symptoms interfere with physiological functions, hormonal supplementation may be warranted[15].

The Medical Council of Thailand's legal document recommends a two-stage examination process for determining BD in adults, with a minimum six-hour interval between assessments[18]. This protocol aims to enhance diagnostic reliability and confirm the irreversible cessation of all brain functions.

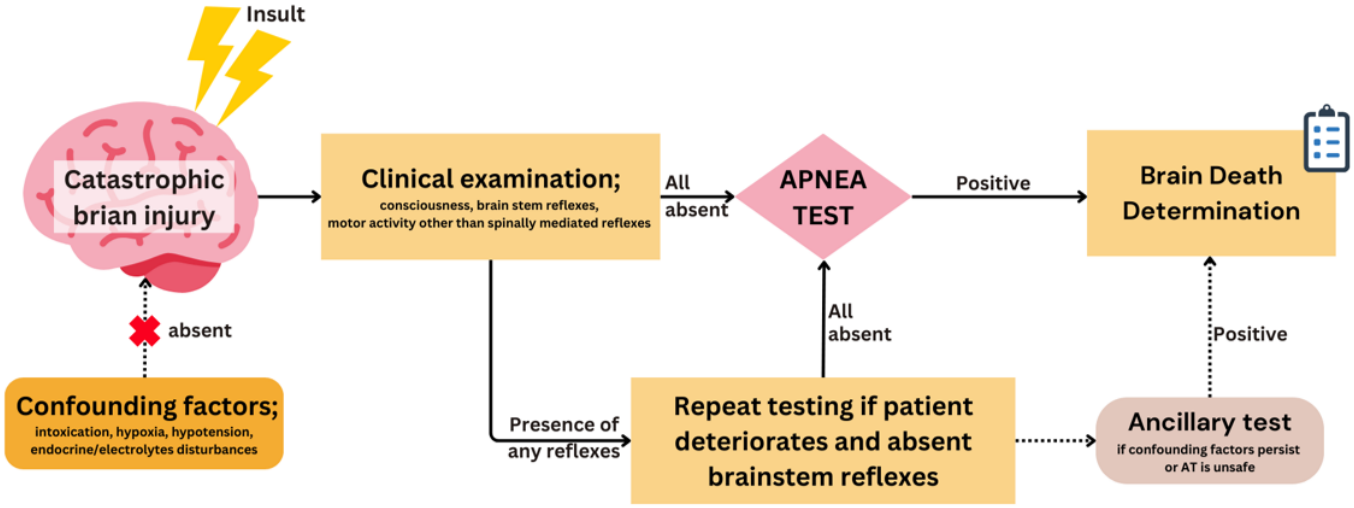

Figure 2. Diagnosis of brain death.

Table 1. Reversible conditions that may mimic brain death [12, 16, 17].

Confounding factors for determining brain death	Target before BD evaluation
Hypothermia	core temperature ≥ 36 °C
Unresuscitated shock	• SBP ≥ 100 mmHg and • MAP ≥ 60 mmHg (only MAP goal is applicable on VA ECMO)
Hyper/hyponatremia	serum Na 130 - 155 mmol/L
Hypermagnesemia	serum Mg 1.5 - 4 mg/dL
Hypophosphatemia	serum PO4 ≥ 1 mg/dL
Hypoglycemia	serum glucose 70 - 300 mg/dL
Liver and renal dysfunction	• serum ammonia < 150 umol/L • BUN < 75 mg/dL
Acid/base derangements	pH 7.3 - 7.5
Thyroid dysfunction	• Total T4 3 - 30 mg/dL • FT4 0.4 - 5 ng/dL
Sedatives and other medications that suppress CNS function	• Waiting at least five half-lives, taking hepatic or renal dysfunction, BMI, body temperature, and age (consideration pharmacokinetic) • Ensure pentobarbital level < 5 ug/mL
Intoxication	• Keep blood alcohol level ≤ 80 mg/dL • Negative blood and urine drug screens should be obtained when clinically indicated
Pharmacologic paralysis	Utilization of a train-of-four stimulator (eliciting twitches with maximal ulnar nerve stimulation) or assessment of deep tendon reflexes

Abbreviations: SBP: Systolic Blood Pressure; MAP: Mean Arterial Pressure; VA ECMO: Veno-Arterial Extracorporeal Membrane Oxygenation; Na: Sodium; Mg: Magnesium; PO4: Phosphate; BUN: Blood Urea Nitrogen; T4: Total Thyroxine; FT4: Free Thyroxine; BMI: Body Mass Index; CNS: Central Nervous System

Clinical examination

Before initiating a brain death evaluation, neuroimaging (Figure 3) is essential to confirm both the mechanism and severity of the brain injury. Subsequently, a comprehensive assessment of brainstem reflexes is performed to further delineate the extent of neurological impairment[19].

In Thailand, a committee of no fewer than three physicians is required to diagnose brain death. These physicians must not include the surgeon performing the organ transplant or the doctor caring for the patient in need of the organ transplant. Additionally, the hospital director or a designated representative, in writing, must be involved in certifying the brain death diagnosis and must sign to confirm the death. Any clinician participating in death determination must have the requisite skills, training, and knowledge of death determination processes and procedures[18].

The clinical examination conducted for the determination of brain death required meticulous technique and maximal stimulation (Table 2). A coma is established by the absence of responsiveness to noxious auditory, visual, and tactile stimulation. Pressure should be applied to the trunk, arms, legs, supraorbital notch, and temporomandibular joint, which are important in a person with a high cervical cord injury or severe peripheral neuropathy. Quantitative pupillometry (QP) has been increasingly applied in neurocritical care as an easy-to-use and reliable technique for evaluating the pupillary light reflex (PLR) for the BD evaluation[20].

The Neurological Pupil index (NPi) algorithm provides an objective, quantitative assessment of PLR by integrating key reactivity variables. These variables include baseline pupil size, latency to constriction, constriction velocity, percentage change in pupil diameter during constriction, and dilation velocity[21]. The algorithm generates a numerical NPi value, with a score of 0 signifying the absence of PLR. Consistently, an NPi of 0 has been demonstrated in patients meeting criteria for BD[22], reflecting the complete loss of brainstem function.

In Canada, it is recommended against the addition of oculocephalic reflex testing to oculovestibular reflex testing as part of the clinical assessment for patients undergoing DNC because "doll's eyes sign" has much lower specificity than the oculovestibular reflex[9].

Apnea test

The apnea test (AT) (Figure 4) constitutes the final diagnostic procedure following a comprehensive neurological examination for BD/DNC diagnosis in adult patients. This test aims to assess the patient's respiratory drive by observing their ability to spontaneously breathe during a controlled rise in CO_2 levels. The absence of spontaneous respiratory efforts under these conditions strongly indicates the absence of brainstem function. Before performing the apnea test, certain precautions must be taken to ensure cardiovascular and pulmonary stability.

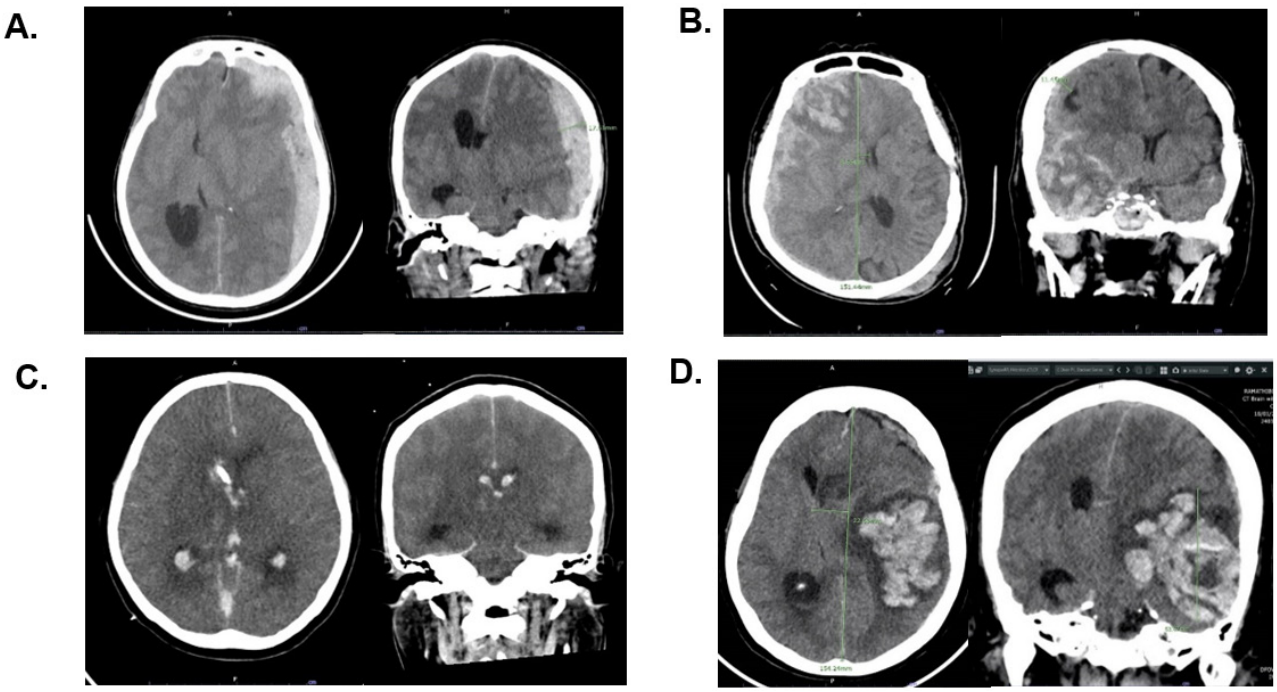

Figure 3. Neuroimaging in BD/DNC reveals consistent evidence of catastrophic injury.
A. Extensive acute SDH along left cerebral convexity associated with pressure effect as midline shift, transtentorial, and bilateral uncal herniation.
B. Acute SAH and SDH along the right front-parietal-temporal lobe and intraparenchymal hemorrhage associated with pressure effect as midline shift, right to left subfalcine, and bilateral uncal herniation.
C. Extensive CVST with diffuse brain edema and descending transtentorial herniation.
D. Acute ICH (about 95 ml in volume) with descending transtentorial herniation and obstructive hydrocephalus.

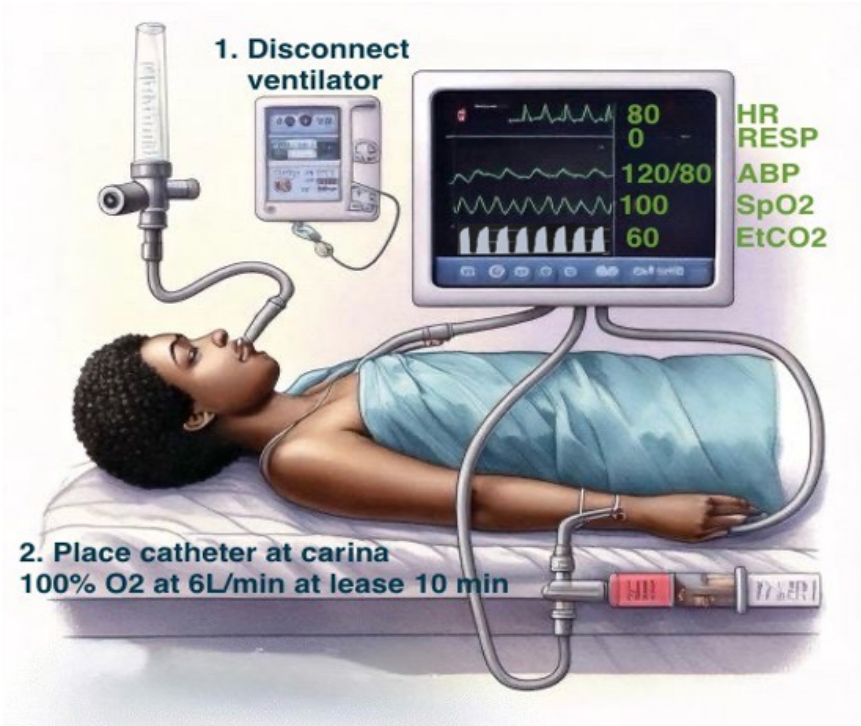

Figure 4. Apnea test.

Table 2. Clinical examination to determine brain death [1, 4, 13, 17].

Test	Description	Region of brain as-sessed	Caution
Consciousness			
Absence of respon-siveness to all noxious stimulation	Apply a painful stimulus to the trunk, arms, legs, supraorbital notch and temporoman-dibular joint. Use of adequate stimulation is important	Bilateral cerebral cortex and brain-stem	High cervical cord injury or severe peripheral neuropathy that might preclude a response due to disrupted sensory or motor pathways
Brainstem reflexes			
• Pupillary light reflex/ Pupillometry	Shine a light in each eye to check for pupil constriction. Quantitative pupillometry may be a useful adjunct for detection of subtle reactivity - **Abnormal:** absent pupil constriction	Midbrain (brainstem)	Use of medications may affect pupil-lary reactivity. History of corneal trauma or oph-thalmic surgery may affect reactivity.
• Corneal reflex	Apply pressure at corneal limbus with a cot-ton swab on a stick - **Abnormal:** no blinking of the eyelids	Pons (brainstem)	Avoid the lateral conjunctiva, as it is less sensitive than the proximal con-junctiva
• Oculocephalic reflex ("doll's eye" maneuver)	Rotate the head while keeping the patient's eyes open and observe eye movement - **Abnormal:** no eye movement with head-turning	Midbrain and Pons (brainstem)	Avoid in patients with an unstable cervical spine injury.
• Oculovestibular reflex ("cold caloric" reflex test)	Inject cold water into the ear canal. Head should be elevated to an angle of 30 degrees and wait 5 minutes between testing of each ear - **Abnormal:** no eye movement within 60 sec-onds of instillation of ice water	Pons and Medulla (brainstem)	Confirm the tympanic membrane is intact before testing. A fractured base of skull resulting in blood, CSF or brain tissue in the ex-ternal auditory canal is a contra-in-dication
• Gag (pharyngeal) reflex	Stimulate bilateral of the posterior pharynx with a tongue depressor or suction catheter - **Abnormal:** no gagging	Medulla oblongata (brainstem)	
• Cough (laryngeal) reflex	Suction or stimulate the airway through an endotracheal tube - **Abnormal:** no coughing	Medulla oblongata (brainstem)	
• Motor response with-in the cranial nerve distribution	Apply deep pressure to condyles of TMJ, su-praorbital notch bilaterally, sternal notch, and both proximal and distal of all 4-extremities - **Abnormal:** Noxious stimuli should not elic-it grimacing, facial muscle movement, or any motor response of the limbs other than spi-nally mediated reflexes	Brainstem, cerebral hemispheres	May be difficult to distinguish spi-nally mediated responses from cere-brally mediated responses; expertise and, in some instances, ancillary testing may be required
Apnea test			
Apnea test	Remove the patient from the ventilator and observe for any spontaneous breathing - **Abnormal:** no respiratory effort after 10 min, with $pCO_2 \geq 60$ mmHg or CO_2 retainer (20 mmHg above baseline)	Medulla	Should be undertaken when all other brain-stem reflexes are found to be absent.

Abbreviations: CSF: Cerebrospinal Fluid; TMJ: Temporomandibular Joint; pCO_2: Partial Pressure of Carbon Dioxide; CO_2: Carbon Dioxide

The patient must be adequately preoxygenated with 100% oxygen, which is crucial to mitigate the risk of hypoxia and obtain a PaO_2 of ≥ 200 mmHg [19], which can increase the potential for cardiac dysrhythmias and hypotension[23]. Subsequently, the patient's $PaCO_2$ should be normalized to a range of 35 - 45 mmHg or their known baseline in cases of chronic hypercapnia. Additionally, the arterial blood pH should be within the normal range of 7.35 – 7.45.

During the apnea test, the threshold for BD/DNC determination is a $PaCO_2$ level of ≥ 60 mmHg (or 20 mmHg above baseline in cases of chronic elevated baseline CO_2) in the absence of respiratory movements[4] following disconnection from the ventilator and the administration of 100% oxygen at 6 L/min through a catheter placed just above the carina or delivering 100% oxygen using CPAP on the ventilator that may prevent derecruitment and decrease the risk of cardiopulmonary instability. Conducting ABG measurements at regular intervals of 3-5 minutes has been shown to result in a shorter test duration, a smaller increase in PCO_2, and a less pronounced reduction in pH compared to intervals determined at the discretion of the attending physician[24]. Additionally, utilizing an $EtCO_2$ target of 60 mmHg[25] as a guideline has been demon-

strated to effectively shorten the duration of the apnea test and stabilize systolic blood pressure[26].

The apnea test must be conducted for a minimum of 10 minutes. However, relying solely on fixed durations, which are based on the expected $PaCO_2$ rise of 3-4 mmHg/min under normal physiological conditions, may lead to inconsistent results. This is because the relationship between $PaCO_2$ and CO_2 production can be significantly altered in the context of terminal illness and brain death[27].

A slight extension of the apnea test duration (e.g., up to 15 minutes) may be warranted in instances where a non-linear relationship is observed between the rate of $PaCO_2$ increase and time. This scenario may arise in the presence of a hyperdynamic cardiac state, a physiological phenomenon frequently encountered during apnea. This hyperdynamic state may result in a delayed $PaCO_2$ rise, potentially mediated by robust cardiac pulsations that induce intermittent compression and relaxation of adjacent alveolar units[28].

The apnea test should be aborted under the following conditions: 1) the presence of spontaneous respiratory effort, which indicates that the patient does not meet the criteria for brain death; 2) hemodynamic instability, evidenced by SBP < 100 mmHg or MAP < 75 mmHg, despite optimization with vasopressors, inotropes, and/or intravenous fluids; 3) progressive hypoxemia, defined as a decrease in oxygen saturation lower to 85%; and 4) development of cardiac arrhythmias associated with hemodynamic instability[12, 19].

Ancillary test

Despite global consensus on the concept of brain death, there is considerable variability in the application of ancillary testing. Ancillary tests are primarily used when confounding factors interfere with the accurate completion of a clinical assessment, physiological instability precludes performance of an apnea test, or there is uncertainty in the interpretation of spinally mediated reflexes[5], such as the triple flexion reflex (TFR)[29], which is defined as flexion of the thigh and leg, accompanied by dorsiflexion of the foot, in response to a noxious stimulus applied to the foot and is considered a complex spontaneous spinal cord reflex. In some regions, however, confirmatory ancillary tests are routinely mandated before a diagnosis of brain death can be made. These tests evaluate cerebral blood flow through methods like cerebral angiography, transcranial doppler (TCD), or radionuclide brain perfusion studies[30].

Four-vessel cerebral angiography is a diagnostic procedure in which the contrast medium is administered at a rate of 8 mL/s for the common carotid arteries and 5 mL/s for the vertebral arteries to visualize both the anterior and posterior cerebral circulations. A 20-second scan series is recommended for optimal imaging. The absence of intracranial blood flow beyond the carotid bifurcation or the circle of Willis is considered the "gold standard" ancillary test[31] for diagnosing brain death. The utility of the test is constrained by the availability of specialized expertise and equipment, its invasive nature, and the potential for false-positive results in hypotensive patients. However, computed tomography angiography (CTA) has become more widely available as an alternative, although it is not as universally accepted as four-vessel angiography for this purpose.

TCD and radionuclide imaging[1, 30] are also acceptable ancillary tests for the BD diagnosis. TCD, performed using a 2 MHz probe,[31] evaluates blood flow velocity and spectral waveforms in the MCA through the bitemporal window above the zygomatic arch and in the vertebrobasilar arteries through the suboccipital window. The examination is conducted twice, with a 30-minute interval between assessments. A finding of complete absence of signal may not be reliable. Reverberating or oscillatory flow or small systolic peaks at the early systole are considered positive for BD. Radionuclide brain perfusion studies demonstrate high sensitivity and specificity (100%) for diagnosing brain death when using scintigraphic imaging with 99mTc-labeled HMPAO or ECD.[31] These lipophilic tracers enable the technetium isotope to cross the blood-brain barrier. In cases of BD, characteristic findings include the "hollow skull sign"[4] or "empty light bulb sign," indicating the absence of tracer uptake in all vascular territories. Additionally, tracer activity in the superior sagittal sinus is absent. The "hot nose sign,"[30] characterized by increased tracer accumulation in the nose due to perfusion from the external carotid arteries, may also be observed.

The most notable change is the designation of EEG as an unacceptable test for all patients; it was previously considered acceptable for both pediatric and adult BD/DNC determination. This designation is consistent with the guidance from the World Brain Death Project (WBDP), which no longer supports EEG as an ancillary test[5, 19, 32] for adult BD/DNC determination[10]. The decision to classify EEG as an unacceptable ancillary test is based on concerns that, while EEG assesses the function of the cerebral hemispheres, it does not evaluate brainstem function. This is problematic, as ancillary testing is often used when there is difficulty in fully assessing brainstem function[11].

BD/DNC communication and declaration

Before BD/DNC evaluation, clear communication is essential regarding consent, time of death, post-mortem steps, and hospital policies on managing family disagreements[12]. BD confirmation must adhere to medical and legal standards, with thorough documentation and respect for advance directives. Addressing family denial and cultural concerns with sensitivity fosters informed decision-making. Emphasizing education for surrogate decision-makers and empathetic communication ensures a transparent and supportive process[19].

Special considerations

- **Brain death determination after treatment with TTM**

Hypothermia reduces cerebral metabolism and oxygen demand, potentially delaying irreversible neuronal injury and prolonging brainstem dysfunction, complicating the distinction between transient post-anoxic

suppression and brain death[5]. TTM may mask neurological function, necessitating rewarming to normothermia (≥36°C), eliminating confounders, and delaying evaluation for at least 24 hours post-rewarming to allow neurological recovery before BD assessment[5]. Additionally, TTM alters pharmacokinetics, prolonging the effects of sedatives and neuromuscular blockers, which may confound clinical evaluation. In cases where CNS-depressing drugs were administered, a cerebral blood flow study may be considered alongside examination and apnea testing[13].

- **Brain death on ECMO**

The determination of brain death is based on the presence of devastating brain injury, as evidenced by imaging, neurological examination, and the apnea test after excluding any confounding factors. A systematic review indicated that the apnea test can be incorporated into the criteria for diagnosing brain death in patients on extracorporeal membrane oxygenation (ECMO). When performing the apnea test is difficult due to hemodynamic or cardiopulmonary instability, cerebral angiography or nuclear imaging (radionuclide brain scan) is preferred as an alternative confirmatory test[33, 34]. However, in the absence of consensus, legal criteria must be followed for brain death diagnosis if apnea testing cannot be performed.

In patients on ECMO, guidelines recommend preoxygenation by increasing both the fraction of oxygen in the sweep gas flow and FiO_2 to 100% for at least 10 minutes. Additionally, CO_2 removal should be reduced by gradually decreasing the sweep gas flow to no less than 500-1000 mL/min, while the respiratory rate on the mechanical ventilator should be reduced to 1-2 breaths per minute, and positive end-expiratory pressure (PEEP) should be maintained with 100% FiO_2. Alternatively, oxygen can be insufflated through a T-piece with a PEEP valve to maintain continuous positive airway pressure (CPAP)[33]. Both blood samples must meet the $PaCO_2$ and pH thresholds to confirm that cerebral circulation, influenced by both native cardiac output and the ECMO circuit, adequately stimulates the medullary chemoreceptors. In venoarterial ECMO patients, arterial blood should be sampled from both the distal arterial line and post-oxygenator ECMO circuit. Values from both sites should be consistent and meet the recommended targets of pH < 7.3, $PaCO_2 \geq 60$ mmHg and $PaCO_2$ ≥20 above baseline values[2].

CONCLUSION

BD is a legally and clinically recognized determination of death, defined by the irreversible loss of all brain activity, including both cerebral and brainstem functions. Accurate diagnosis is critical for ethical, legal, and organ donation considerations. Before evaluation, physicians must confirm a diagnosis of a permanent, severe brain injury known to cause BD despite appropriate treatment, with supporting evidence of significant brain damage on imaging.

Diagnosis relies on a comprehensive neurological examination demonstrating the absence of cerebral and brainstem reflexes and the inability to sustain spontaneous respiration, confirmed by an apnea test. Ancillary tests, such as cerebral angiography or radionuclide brain scans, may be necessary when clinical assessment is inconclusive or when confounding factors like drug intoxication, hypothermia, or neuromuscular blockade are present. Special considerations apply to patients on extracorporeal membrane oxygenation (ECMO), requiring protocol adjustments to the apnea test. Despite consensus on brain death criteria, variability exists in the use of ancillary testing across different regions.

A thorough understanding of BD determination protocols is essential for clinicians, particularly in complex cases, to ensure an accurate diagnosis and appropriate management within clinical, ethical, and legal frameworks.

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