Published Ahead of Print on October 11, 2023 as 10.1212/WNL.0000000000207740

SPECIAL ARTICLE

Pediatric and Adult Brain Death/Death by Neurologic Criteria Consensus Guideline

Report of the AAN Guidelines Subcommittee, AAP, CNS, and SCCM

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Neurology® 2023;101:1-21. doi:10.1212/WNL.0000000000207740

Abstract

Background and Objectives

The purpose of this guideline is to update the 2010 American Academy of Neurology (AAN) brain death/death by neurologic criteria (BD/DNC) guideline for adults and the 2011 American Academy of Pediatrics, Child Neurology Society, and Society of Critical Care Medicine guideline for infants and children and to clarify the BD/DNC determination process by integrating guidance for adults and children into a single guideline. Updates in this guideline include guidance related to conducting the BD/DNC evaluation in the context of extracorporeal membrane oxygenation, targeted temperature management, and primary infratentorial injury.

Methods

A panel of experts from multiple medical societies developed BD/DNC recommendations. Because of the lack of high-quality evidence on the subject, a novel, evidence-informed formal consensus process was used. This process relied on the panel experts' review and detailed knowledge of the literature surrounding BD/DNC to guide the development of preliminary recommendations. Recommendations were formulated and voted on, using a modified Delphi process, according to the 2017 AAN Clinical Practice Guideline Process Manual.

Major Recommendations

Eighty-five recommendations were developed on the following: (1) general principles for the BD/DNC evaluation, (2) qualifications to perform BD/DNC evaluations, (3) prerequisites for BD/DNC determination, (4) components of the BD/DNC neurologic examination, (5) apnea testing as part of the BD/DNC evaluation, (6) ancillary testing as part of the BD/DNC evaluation, and (7) special considerations for BD/DNC determination.

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Approved by the Guidelines Subcommittee on January 23, 2023, by the Quality Committee on February 11, 2023, and the American Academy of Neurology Institute Board of Directors on July 20, 2023. The Neurocritical Care Society affirmed the value of this consensus guideline on September 28, 2023.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AAN = American Academy of Neurology; **AAP** = American Academy of Pediatrics; **ABG** = arterial blood gas; **AEP** = auditory evoked potential; **APP** = advanced practice provider; **BBB** = blood-brain barrier; **BD/DNC** = brain death/death by neurologic criteria; **COI** = conflict of interest; **CPAP** = continuous positive airway pressure; **CV** = curriculum vitae; **ECMO** = extracorporeal membrane oxygenation; **ETT** = endotracheal tube; **HIBI** = hypoxic-ischemic brain injury; **MAP** = mean arterial pressure; **OCR** = oculocephalic reflex; **OVR** = oculovestibular reflex; **PEEP** = positive end-expiratory pressure; **SBP** = systolic blood pressure; **SCCM** = Society of Critical Care Medicine; **SEP** = somatosensory evoked potential; **UDDA** = Uniform Determination of Death Act; **VA** = venoarterial.

Introduction

Determination that a patient meets neurologic criteria for death is a medical responsibility that leads to a legal declaration. The purpose of this guideline is to clarify the brain death determination process for integration of guidance for adults and children into a single guideline. Updates in this guideline also include addressing issues related to determination of death by neurologic criteria in the setting of extracorporeal membrane oxygenation (ECMO), targeted temperature management, and primary infratentorial injury.

Death by neurologic criteria, commonly referred to as *brain death*, occurs in individuals who have sustained catastrophic brain injury, with no evidence of function of the brain as a whole, a state that must be permanent. The process of this determination always begins with the presumption that the patient does *not* meet brain death/death by neurologic criteria (BD/DNC), a presumption that must then be disproved. BD/DNC determination must be accurate and consistent. As stated in the report of the 1968 Harvard Committee, reaffirmed by subsequent presidential reports and prior adult and pediatric guidelines, the essential underlying concept that defines BD/DNC is permanent coma and loss of all brainstem function, coupled with the inability to breathe in the setting of an adequate stimulus (i.e., hypercarbia and acidosis). Because complete loss of the brainstem's reticular activating system is the most robust predictor of the permanence of a comatose state, most of the neurologic assessment focuses on demonstrating the loss of all brainstem reflexes. Of importance, BD/DNC determination is based on clinical assessment; ancillary testing is required only if the clinical assessment cannot be safely or fully completed.

The Uniform Determination of Death Act (UDDA), the legal foundation for the declaration of BD/DNC in the United States, stipulated that determination of BD/DNC must be made in accordance with accepted medical standards.[1] In 2018, multiple medical societies agreed that the accepted medical standards for determination of BD/DNC were the 2010 AAN guideline for adults and the 2011 Society of Critical Care Medicine (SCCM)/American Academy of Pediatrics (AAP)/Child Neurology Society guideline for infants and children.[2-4] These guidelines stipulate that BD/DNC should be declared when a patient with a known cause of catastrophic brain injury has permanent loss of function of the entire brain, including the brainstem, resulting in (1) coma, (2) brainstem areflexia, and (3) apnea in the setting of an adequate stimulus.

In concert with the Ethics, Law, and Humanities Committee, a joint committee of the AAN, the American Neurological Association, and the Child Neurology Society and with the support of AAN leadership and the AAN Quality Committee, the AAN Guidelines Subcommittee (eAppendices 1 and 2, links.lww.com/WNL/D73) formed a multidisciplinary panel with members from multiple medical societies to make updated formal consensus recommendations about the process of BD/DNC determination. The panel considered that the process for diagnosing death, either cardiopulmonary or neurologic, should to the fullest extent possible be independent of patient age, making note of where child-specific principles apply. This document combines adult and pediatric recommendations to ensure accurate, consistent determination of BD/DNC in persons of all ages. Most aspects of BD/DNC evaluation are the same, regardless of age, with a few exceptions. By unifying recommendations into 1 document, there is consistent guidance to clinicians in various practice settings.

Author Panel Formation and Methodology

Leadership from the AAN Guidelines Subcommittee (A.R.-G., J.J.H.) and the AAN Brain Death Working Group (D.M.G., M.P.K., A.L.), a subgroup of the AAN Ethics, Law, and Humanities Committee, engaged a broad panel of stakeholders from multiple medical societies to collaborate on an updated BD/DNC guideline. Panel members were invited from the following organizations: AAP, American College of Radiology, Child Neurology Society, Congress of Neurological Surgeons, Neurocritical Care Society, and SCCM. Clinicians with expertise in BD/DNC were also invited. The author panel included BD/DNC experts (D.M.G., M.P.K., A.L., G.S.G., S.A., M.A.B., D.F.B., L.B., A.C., S.P., M.A.R., L.S., C.T., R.C.T., P.N.V., and E.W.), process facilitators (A.R.-G., J.J.H.), and a methodologist (G.S.G.). Each potential author was required to submit an AAN relationship disclosure form and a copy of his or her curriculum vitae (CV). The panel leadership (A.R.-G., J.J.H., G.S.G., D.M.G., M.P.K., A.L.) and AAN staff reviewed the relationship disclosure forms and CVs for financial and intellectual conflict of interest (COI). These documents were

specifically screened to exclude those individuals with a clear financial conflict and those whose profession and intellectual bias would diminish the credibility of the guideline in the eyes of the intended users. Before the formation of the author panel, it was determined that a financial link with organ procurement organizations in the prior 5 years would preclude participation as a direct conflict to participation. As required by the AAN, most (51%) of the members (A.L., G.S.G., A.R.-G., S.A., M.A.B., D.F.B., L.B., A.C., S.P., M.A.R., C.T., R.C.T., E.W., and J.J.H.) of the author panel and the lead authors (D.M.G., M.P.K., and A.L.) are free of COI relevant to the subject matter of this practice guideline.

The author panel met in person on October 11, 2019, to define the methodology and develop initial rationales and recommendations. Because of the lack of high-quality evidence on the subject, a novel, evidence-informed formal consensus process was used. This process relied on the panel experts' detailed knowledge of the literature surrounding BD/DNC to guide the development of preliminary recommendations, followed by 3 iterative rounds of anonymous voting on each rationale and recommendation (modified Delphi process), with prespecified rules for determining consensus attainment and the strength of each recommendation. The intent was for recommendations to be conservative to minimize the risk of a false-positive determination of BD/DNC (determining BD/DNC in a patient who does not have permanent catastrophic brain injury with no evidence of brain function), yet practical.

A subset of the panel (D.M.G., A.R.-G., M.P.K., A.L., and J.J.H.) drafted recommendations with input from the methodologist (G.S.G.). Panel members answered a series of questions for each recommendation to determine the cogency of the rationale supporting the recommendation and the strength of the recommendation (eAppendix 3, links.lww.com/WNL/D73).

Recommendations were formulated according to the 2017 AAN Clinical Practice Guideline Process Manual.[5] Each recommendation statement includes an action verb of must, should, or may reflecting the strength of the recommendation. The action verb corresponds to the level of consensus reached. Level A voting consensus resulted in a must statement. Level B voting consensus resulted in a should statement. Level C voting consensus resulted in a may statement.

Before initiation of voting, each recommendation draft statement action verb was anchored at must, should, or may, as deemed appropriate by the panel. This anchoring prevented the statement from reaching a higher strength of recommendation. Because of this anchoring, there are recommendation statements that have reached a high level of consensus with a lower action verb. For example, Recommendation statement 7b states, "Clinicians should conduct further diagnostic evaluation and not undertake evaluation for BD/DNC if a patient is comatose, apneic and has absent brainstem reflexes, and there is not an identified mechanism of brain injury that is known to lead to BD/DNC" with Level A consensus. The recommendation statements with anchored action verbs are 7b, 11b, 11c, 13d, 18c, 24c, 25b, 25i, 25j, 25k, 25l, 25m, 26, 27b, 29, 30, 31, 35, 37a, 37b, 38, and 39.

After the first round of voting, the preliminary manuscript and initial rationales and recommendations were reviewed by the AAN Guidelines Subcommittee for comment on January 11, 2020, and revised by panel members. After the second round of voting, the document was distributed for public comment (December 14, 2020, through January 12, 2021), and all comments were analyzed and incorporated where appropriate. The panel met virtually on January 13, 2022, to review public comment revisions and discuss plans for the third round of voting. Because of concerns for potential ambiguity in the questions used to determine the strength of recommendations, panel members revised the questions for the recommendations related to increasing the accuracy of BD/DNC determination.

The panel also added a question so that panel members would self-identify the primary population (adult or children) they treated. This was done in case it was necessary to stratify recommendations by adult and pediatric populations to attain consensus.

The author panel met virtually on April 28, 2022, to finalize the revised voting questions and instructions (eAppendix 4, links.lww.com/WNL/D73). After the third round of voting, it was determined that differences between pediatric and adult recommendations warranted separate considerations, with voting for each by the panel members with relevant self-identified expertise. After multiple rounds of voting and revisions to attain consensus, the rationales and recommendations were finalized for the manuscript.

Terminology

The term *brain death* has been used in common parlance, but the panel chose to use *brain death/death by neurologic criteria* or BD/DNC to both embrace the colloquial term and emphasize that a determination means more than death of the brain and that, rather, death of the person has occurred, equivalent to death by cardiopulmonary criteria. This terminology was also used in the World Brain Death Project.[6]

The terms *irreversible* and *permanent* have both been used to describe the extent of loss of function that must be present to determine BD/DNC. The panel chose to use the term *permanent* to mean function was lost and (1) will not resume spontaneously, and (2) medical interventions will not be used to attempt restoration of function. This terminology was also used in the World Brain Death Project.

The term *child* has been defined for purposes of this document as any patient who is at least 37 weeks old, corrected gestational age, and younger than 18 years old. There are several individual recommendations that detail specific age ranges.

Recommendations

eAppendix 5 (links.lww.com/WNL/D73) provides a checklist for the following recommendations. The eFigure (links.lww.com/WNL/D74) illustrates this process through a flowchart.

General Principles for the BD/DNC Evaluation

Recommendation 1 Rationale

The UDDA states that BD/DNC is declared when there is irreversible cessation of all functions of the entire brain, including the brainstem. In this document, "all functions of the entire brain" is interpreted as permanent loss of function of the brain as a whole, including the brainstem, resulting in (1) coma, (2) brainstem areflexia, and (3) apnea in the setting of an adequate stimulus. Lack of meticulous attention to stringent guidelines could lead to inappropriate or inaccurate diagnosis of BD/DNC. Consistently following a standardized process for BD/DNC determination will guard against inappropriate or inaccurate diagnosis or variability in the diagnosis. The following recommendations have been developed based on a critical review of the available evidence, using a formal consensus-developing methodology (modified Delphi) among adult and pediatric neurologists, neurosurgeons, and intensivists with expertise in the field, with input from the AAP, SCCM, Child Neurology Society, Neurocritical Care Society, American College of Radiology, and Congress of Neurologic Surgeons, have undergone extensive peer review, and can provide the basis for determination of BD/DNC in US institutions.

Recommendation Statement 1

Unless otherwise legislated by local, regional, or federal authorities, clinicians at institutions in the United States should follow the standardized process in this document for determination of BD/DNC (Level B).

Recommendation 2 Rationale

Clinical determination of BD/DNC is likely less reliable in infants younger than 37 weeks, corrected gestational age, because some brainstem reflexes may not be completely developed.[7]

Recommendation Statement 2

BD/DNC cannot be determined in infants younger than 37 weeks, corrected gestational age, during BD/DNC evaluation; therefore, clinicians should not evaluate infants younger than 37 weeks, corrected gestational age, for BD/DNC (Level B).

Recommendation 3 Rationale

The purpose of BD/DNC evaluation is to determine whether a patient meets criteria for BD/DNC. The clinician's primary responsibility is to the interests of that patient. A patient who meets criteria for BD/DNC may be a candidate for organ/tissue donation, which affects the interests of other patients. These interests may conflict.

Recommendation Statement 3a

To avoid COI, clinicians involved in BD/DNC determination must only consider the interests of their patient and avoid any direct involvement in decision-making regarding organ donation (Level A).

Recommendation Statement 3b

To avoid COI, any clinician involved with surgical recovery of organs for transplantation must not be involved with BD/DNC evaluation (Level A).

Recommendation 4 Rationale

Before performing the BD/DNC evaluation, patients must be observed for sufficient time to determine the severity and permanency of the brain injury and exclude confounders. During this time, patients require mechanical ventilation and often hemodynamic support. The BD/DNC evaluation requires apnea testing, which may lead to hypoxemia and hemodynamic compromise.[8] Apnea testing must be performed in a setting with staff with appropriate expertise in managing the potential cardiopulmonary complications of the test.

Recommendation Statement 4

Patients undergoing BD/DNC evaluation must be cared for in an environment that allows adequate observation, to ensure the severity and permanency of the brain injury and exclude confounders, and has staff with appropriate expertise in managing the potential cardiopulmonary complications of apnea testing (Level A).

Recommendation 5 Rationale

Spontaneous breathing, absence of coma, any intact brainstem reflexes, or motor activity other than spinally mediated reflexes indicate brain function and are inconsistent with BD/DNC.

Recommendation Statement 5

Patients with any evidence of consciousness or preservation of any brainstem reflex or who display motor movements that are mediated by the brain or brainstem or are spontaneously breathing do not meet established criteria and must not undergo BD/DNC testing (Level A).

Clinicians Who Perform BD/DNC Evaluations

Previous AAN guidelines did not address qualifications for clinicians performing BD/DNC evaluations. The 2011 pediatric guidelines noted that 2 attending clinicians, each of whom is a pediatric intensivist, neonatologist, pediatric neurologist, pediatric neurosurgeon, pediatric trauma surgeon, pediatric anesthesiologist with critical care training, or an adult specialist trained in neurology and/or critical care, are needed for an evaluation of BD/DNC.[2,3,9]

Recommendation 6 Rationale

Clinician competency in performing a BD/DNC evaluation is important to optimize the accurate and consistent application of this process to avoid erroneous BD/DNC determination. There may be different mechanisms by which clinicians can acquire and demonstrate this competency.

Recommendation Statement 6a

Attending clinicians performing BD/DNC examinations must be appropriately credentialed members of the hospital's

medical staff and be adequately trained and competent in the evaluation of BD/DNC in children or adults, as applicable (e.g., intensivists, neurologists, neurosurgeons, etc.) and in accordance with local laws and institutional standards (Level A).

Recommendation Statement 6b

In settings where acute and critical care advanced practice providers (APPs) are performing BD/DNC evaluations independently in accordance with local laws and institutional standards, they must be appropriately credentialed and adequately trained and competent in the evaluation of BD/DNC in children or adults, as applicable (Level A).

Recommendation Statement 6c

Trainees and acute and critical care APPs, in settings where they are not permitted to perform BD/DNC evaluations independently in accordance with local laws and institutional standards, must be directly supervised by an attending clinician who meets Recommendation 6a criteria who should be present at the patient's bedside for the entirety of the evaluation (Level A).

Recommendation Statement 6d

Clinicians performing BD/DNC examinations should have specific education in training on performing BD/DNC evaluation and demonstrate competency in the BD/DNC evaluation of child or adult patients, as appropriate, by such means as completion of a supervised BD/DNC evaluation in a clinical environment (Level B). Supplementary education on BD/DNC can include completion of a well-designed online or in-person training course (Level B).

Recommendation Statement 6e

Clinicians should provide support and guidance for families as they face difficult end-of-life decisions for their loved one who has sustained a catastrophic brain injury (Level B). Communication should be clear, concise, and supportive and include simple terminology that families can understand. Appropriate emotional support for the family should be provided (Level B).

Prerequisites for Determination of BD/DNC

Identification of the Etiology of Brain Injury

BD/DNC can result from injuries such as traumatic brain injury, cerebrovascular events (subarachnoid hemorrhage, intracerebral hemorrhage, ischemic stroke), space-occupying lesions, hypoxic-ischemic brain injury (HIBI), intracranial infection, toxin ingestions, or metabolic disorders leading to malignant cerebral edema.[9-11] However, there have been numerous reports of reversible mimics of BD/DNC caused by other pathologies, including, but not limited to, Guillain-Barré syndrome, leptomeningeal carcinomatosis, snake bites, botulism, and high cervical cord injuries.[6]

The 2010 AAN guidelines noted the necessity of neuroimaging to explain the etiology of coma, and the 2011 pediatric BD/DNC guidelines stated that neuroimaging "should demonstrate evidence of an acute CNS injury consistent with the profound loss of brain function," acknowledging that "early after acute brain injury, imaging findings may not demonstrate significant injury, (so) in such situations, repeat studies are helpful in documenting that an acute severe brain injury has occurred."[2,3]

Recommendation 7 Rationale

BD/DNC evaluation can only be initiated when a patient has sustained a catastrophic, permanent brain injury, and the mechanism of the brain injury is known to lead to BD/DNC. When a patient is comatose, apneic, and has absent brainstem reflexes but there is not an identified mechanism of brain injury that is known to lead to BD/DNC, there is a risk that the clinical findings may be caused by a reversible process. Neuroimaging can assist with identifying the mechanism of brain injury and determining the severity of the brain injury.

Recommendation Statement 7a

Clinicians must ascertain that a patient has sustained a catastrophic, permanent brain injury caused by an identified mechanism that is known to lead to BD/DNC before initiating a BD/DNC evaluation (Level A).

Recommendation Statement 7b

Clinicians should conduct further diagnostic evaluation and not undertake evaluation for BD/DNC if a patient is comatose, apneic, and has absent brainstem reflexes, and there is not an identified mechanism of brain injury that is known to lead to BD/DNC (Level A).

Recommendation 7c

Clinicians should determine that neuroimaging is consistent with the mechanism and severity of brain injury (Level B).

Observation for Permanency

The UDDA requires that BD/DNC determination only be made if an individual has sustained "irreversible cessation of all functions of the entire brain, including the brainstem."[1] It was noted in the 2010 AAN guidelines that there is insufficient evidence to determine the minimally acceptable observation period to ensure permanent loss of function of the brain.[2] The 2011 pediatric guidelines recommended that BD/DNC evaluation be deferred for 24–48 hours or longer if there are concerns or inconsistencies in the examination after cardiopulmonary resuscitation or other severe acute brain injuries. The 2011 pediatric guidelines also recommended an age-based observation period between the first and second clinical examinations for BD/DNC (24 hours for term newborns 37 weeks gestational age up to 30 days of life, 12 hours for infants and children 31 days to 18 years).[3] A conservative observation period after brain injury and before evaluation for BD/DNC helps ensure the brain injury is permanent. Around the world, there is no standard observation period before the initiation of the evaluation for BD/DNC.

Recommendation 8 Rationale

Infants and young children with open fontanelles and unfused sutures can experience different physiologic consequences of acute brain injury from those of older children and adults. The anterior fontanelle usually closes between 13 and 24 months gestational age, but closure may be delayed beyond this period in patients with certain genetic or metabolic conditions.[7,12] In patients with open fontanelles and unfused sutures, the distensibility of the calvarium and dura may prevent the rise in intracranial pressure and subsequent herniation syndromes caused by cerebral edema. In addition, the brainstem in infants is more resistant to HIBI than other brain regions.[13-15] Thus, infants and younger children may retain some brainstem function that only becomes apparent when cerebral edema subsides, particularly after HIBI, which accounts for nearly two-thirds of the brain injuries that lead to BD/DNC in pediatric populations.[10]

Recommendation Statement 8

For infants and children younger than 24 months, clinicians should wait at least 48 hours after the acute brain injury before initiating the BD/DNC evaluation (Level B).

Recommendation 9 Rationale

The determination of BD/DNC requires that the catastrophic brain injury is permanent. A conservative observation period after the brain injury occurs and before the initiation of the BD/DNC evaluation helps ensure that there is no potential for recovery of brain function. In patients older than 2 years with HIBI, an observation period of at least 24 hours is reasonable. There is no evidence to support a specific observation period between brain injury of other etiologies and performance of the BD/DNC evaluation.

Recommendation Statement 9a

Clinicians must wait a sufficient amount of time after the brain injury occurs before initiating the BD/DNC evaluation to ensure there is no potential for recovery of brain function (Level A). This observation period must be based on the pathophysiology of the brain injury leading to the neurologic state of the patient (Level A).

Recommendation Statement 9b

Clinicians should wait a minimum of 24 hours after acute HIBI in patients aged 24 months and older before initiating the BD/DNC evaluation (Level B).

Recommendation 9c Rationale

There are medical and surgical interventions that may be used to treat elevated intracranial pressure before BD/DNC. BD/DNC may occur despite medical and surgical interventions to treat elevated intracranial pressure. The determination of BD/DNC requires that the catastrophic brain injury is permanent. A conservative observation period after interventions to treat elevated intracranial pressure and before the initiation of the BD/DNC evaluation helps ensure that there is no potential for recovery of brain function.

Recommendation Statement 9c

After medical or surgical interventions to treat elevated intracranial pressure, clinicians must wait a sufficient amount of time to ensure there is no recovery of brain function before initiating the BD/DNC evaluation (Level A). This observation period must be based on the pathophysiology of the brain injury leading to the neurologic state of the patient and the findings on neuroimaging (Level A).

Avoiding Inaccurate Determination of BD/DNC Caused by Hypothermia

Hypothermia can affect the neurologic examination because of blunting of brainstem reflexes.[11] This is particularly problematic when patients took or received medications that depress the CNS before being, or while, hypothermic because hypothermia alters drug pharmacokinetics and pharmacodynamics, leading to delayed elimination.[16-19] The minimum temperature for BD/DNC evaluation around the world varies from 32 to 36°C.[20] The 2010 AAN BD/DNC guidelines recommended a minimum temperature of 36°C, but the 2011 pediatric BD/DNC guidelines recommended 35°C.[2,3] It is unknown how long hypothermia can affect the neurologic examination, so there is no standard period to delay evaluation for BD/DNC after achieving normothermia.[20,21] There are 2 cases in the literature in which BD/DNC was determined prematurely after rewarming from therapeutic hypothermia, with subsequent recovery of some neurologic function.[22,23]

Recommendation 10 Rationale

Hypothermia may suppress brain function, resulting in a comatose patient with brainstem areflexia and apnea, potentially leading to an inaccurate determination of BD/DNC.[22,23] Hypothermia may result from either environmental exposure or be induced as a neuroprotective therapy in some patients after cardiac arrest or other types of acute brain injury. Hypothermia delays the clearance of medications that depress the CNS.[16-19] There is no evidence to support a specific observation period between establishment of a minimum appropriate core body temperature and performance of the BD/DNC evaluation. Providing a conservative observation period for patients who have been hypothermic before initiating the BD/DNC evaluation should help ensure that there is no potential for recovery of brain function after restoring and maintaining normothermia and medications that depress the CNS have had adequate time to be cleared.

Recommendation Statement 10a

Clinicians must ensure that patients' core body temperatures are maintained ≥36°C before performing a BD/DNC evaluation (Level A).

Recommendation Statement 10b

In patients whose core body temperature has been ≤35.5°C, clinicians should wait a minimum of 24 hours after the patient has been rewarmed to ≥36°C before evaluating for BD/DNC (Level B).

Avoiding Inaccurate Determination of BD/DNC Caused by Hypotension

Hypotension may suppress brain function and lead to a false-positive BD/DNC determination. The 2010 AAN BD/DNC guidelines recommended that systolic blood pressure (SBP) be ≥ 100 mm Hg, and the 2011 pediatric BD/DNC guidelines recommended that systolic or mean arterial blood pressure be not less than 2 SDs below age-appropriate norms.[2,3]

There are no data to suggest a lowest allowable blood pressure level to ensure that a brain-injured patient's unresponsiveness could not be partly due to inadequate cerebral perfusion. Published reference ranges for children are influenced by many factors, including age, sex, height, ethnicity, and measurement method. Individual variability in blood pressure and underlying medical conditions (e.g., chronic kidney disease, endocrinopathies, and chronic cardiac or vascular conditions) can also affect baseline blood pressure.

Recommendation 11 Rationale

Hypotension may suppress brain function, which can result in an impermanent coma, brainstem areflexia, and apnea and lead to an inaccurate determination of BD/DNC.

Recommendation Statement 11a

Clinicians must ensure that the patient is not hypotensive before performing a BD/DNC evaluation (Level A). Intravenous administration of volume (crystalloid or colloid), with vasopressors or inotropes as needed for management of blood pressure, before and during BD/DNC evaluation, may facilitate this.

Recommendation Statement 11b

In adults, clinicians should maintain SBP ≥100 mm Hg and mean arterial pressure (MAP) ≥75 mm Hg; and in children, clinicians should maintain SBP and MAP ≥fifth percentile for age (Level A). The same values are applicable for patients supported with venovenous ECMO.

Recommendation Statement 11c

For adults supported by venoarterial (VA) ECMO, clinicians should target an MAP ≥75 mm Hg; and for children supported by VA ECMO, clinicians should target MAP ≥fifth percentile for age (Level A).

Recommendation Statement 11d

If an individual has a baseline blood pressure that varies significantly from their age-based normal range, clinicians should target an SBP and MAP that approximate the known chronic baseline for that individual patient (Level B).

Avoiding Inaccurate Determination of BD/DNC Caused by Drugs/Medications and Metabolic Derangements

Regarding drugs/medications and metabolic derangements, the 2010 AAN BD/DNC guidelines (1) recommended exclusion of "CNS-depressant drug effect by history, drug screen, calculation of clearance using 5 times the drug's half-life (assuming normal hepatic and renal function), or, if available, drug plasma levels below the therapeutic range"; (2) noted that a determination of BD/DNC could not be performed after recent administration of neuromuscular blocking agents, which could be ruled out by the presence of a train of 4 twitches with maximal peripheral nerve stimulation; (3) noted that the legal alcohol limit of 0.08% was a practical threshold below which determination of BD/DNC could be performed; and (4) required exclusion of "severe electrolyte, acid-base, or endocrine disturbance (defined by severe acidosis or laboratory abnormalities markedly deviated from the norm)."[2] Similarly, the 2011 pediatric BD/DNC guidelines (1) recommended exclusion of drug or alcohol intoxication by checking levels, when available, to ensure they were in the low to mid-therapeutic range before determination of BD/DNC or waiting several half-lives; (2) noted that adequate clearance of neuromuscular blocking agents should be confirmed through demonstration of a twitch response to nerve stimulator; and (3) noted that severe electrolyte, hyperglycemia or hypoglycemia, severe pH disturbances, severe hepatic or renal dysfunction, or inborn errors of metabolism may cause reversible coma and should be identified and treated before evaluation for BD/DNC.[3] The American College of Medical Toxicology provided a position statement regarding BD/DNC determination after drug overdose in 2017.[24]

While we noted that there is no scientific rationale to define specific laboratory results that are/are not acceptable in BD/DNC and that a paucity of protocols around the world stipulate such values,[20] we recognized that the acceptability of a given value is commonly questioned. Acknowledging that a multitude of derangements could result in coma and even impair brainstem reflexes, and that determination of cutoff values is arbitrary, we proposed general guidance on specific laboratory result abnormalities which, if identified through clinically indicated testing, warrant correction before the clinical evaluation for BD/DNC and/or performance of ancillary testing (eTables 1 and 2, links.lww.com/WNL/D76). It should be noted that while most of the noted laboratory results are obtained routinely, ammonia levels or thyroid function tests are not routinely measured.[25]

Recommendation 12 Rationale

Conditions such as metabolic derangements, intoxication, or medications can depress the CNS and result in a comatose patient with brainstem areflexia and apnea, which may lead to an inaccurate determination of BD/DNC.[6]

Recommendation Statement 12a

Clinicians must ensure that metabolic derangements, intoxication, and medications that depress the CNS are excluded, adequately corrected, or eliminated before evaluating patients for BD/DNC, as clinically appropriate. Specifically, clinicians must:

1. Ensure a toxicology (urine and blood) screening result, if clinically indicated, is negative.
2. Ensure the alcohol blood level, if clinically indicated, is ≤80 mg/dL.
3. Ensure drug levels for medications that are or may be present and that suppress CNS function, if available, are in the therapeutic or subtherapeutic range and not considered to contribute to the neurologic state. If levels are unavailable:
   - Allow at least 5 half-lives for all CNS-depressing medications or intoxicants to pass and longer if there is renal or hepatic dysfunction or if the patient is obese or was hypothermic (eTable 2, links.lww.com/WNL/D76).
   - Account for age-dependent metabolism of potentially depressing medications in infants and young children and older patients (eTable 2, links.lww.com/WNL/D76).
   - If the patient has received pentobarbital, the level must be <5 μg/mL or below the lower limit of detection for that laboratory before evaluation for BD/DNC.
4. Exclude severe metabolic, acid-base, and endocrine derangements.
5. Exclude the effect of pharmacologic paralysis, if administered or suspected, through use of a train-of-four stimulator or demonstration of deep tendon reflexes (Level A).

Recommendation Statement 12b

If metabolic derangements are unable to be adequately corrected, but the neurologic examination(s) and apnea test(s) are consistent with BD/DNC, the clinician must perform ancillary testing (Level A).

Performing the BD/DNC Neurologic Examination

Number of Examinations

In the first AAN practice parameter on BD/DNC (1995), after the initial examination for determination of BD/DNC, a repeat clinical examination 6 hours later was advised, but no firm recommendation could be provided, and it was acknowledged that the interval is arbitrary.[9] The 2010 AAN guideline noted a single examination was the minimum standard for BD/DNC determination in adults.[2] By contrast, 2 examinations with an age-dependent observation period between them were recommended for BD/DNC determination in children in the 1987 and 2011 pediatric guidelines.[3,26]

Recommendation 13a Rationale

Review of the medical record before examination is standard medical care. BD/DNC can only be determined in a patient with a catastrophic, permanent brain injury due to a mechanism that is known to lead to BD/DNC. It is necessary to exclude confounders before performance of a BD/DNC examination.

Recommendation Statement 13a

Before performing a BD/DNC examination, clinicians must review the medical record to determine that the patient has sustained a catastrophic, permanent brain injury with a mechanism of brain injury that is known to lead to BD/DNC and that confounders to the examination have been excluded (Level A).

Recommendation 13b Rationale

A neurologic examination is a required component of the BD/DNC examination.

Recommendation Statement 13b

Clinicians must perform a minimum of 1 examination for BD/DNC (Level A).

Recommendation 13c and 13d Rationale

The neurologic examination is a required component of the BD/DNC examination. Performance of 2 independent BD/DNC examinations may decrease the risk of a false-positive determination due to diagnostic error.

Recommendation Statement 13c

In adults, a second clinician may perform a separate and independent examination for BD/DNC (Level C).

Recommendation Statement 13d

In children, 2 clinicians must each perform a separate and independent examination for BD/DNC. In consideration of the stipulated observation period between the 2 examinations in the 1987 and 2011 pediatric guidelines, a minimum interval of 12 hours should separate the 2 examinations (Level A).

Recommendation 14 Rationale

Accurate assessment of head, neck, and limb motor responses can be confounded by severe neuromuscular disorders, sensory neuropathies, spinal cord injuries, and/or consequences of facial trauma or swelling. Accurate assessment of the pupillary light reflex can be impeded by corneal trauma, severe orbital/scleral edema/chemosis, ophthalmic surgery, anophthalmia, and/or use of ocular or systemic anticholinergic medications. Accurate assessment of the oculocephalic reflex (OCR) and/or oculovestibular reflex (OVR) can be

impeded by anophthalmia, severe orbital/scleral edema/chemosis, skull fracture, cervical spine fracture, or a ruptured tympanic membrane. Accurate assessment of the corneal reflex can be impeded by anophthalmia or severe orbital/scleral edema/chemosis. Accurate assessment of the gag and cough reflexes can be confounded by high cervical cord injury. Other injuries or confounders may also interfere with the accurate evaluation of the neurologic examination for BD/DNC.[6]

Recommendation Statement 14a

When the accurate evaluation of a component of the BD/DNC neurologic examination cannot be assessed safely, clinicians must perform ancillary testing to complete BD/DNC determination (Level A).

Recommendation Statement 14b

All elements of the BD/DNC neurologic examination included here that can be assessed must be assessed, and findings must be consistent with BD/DNC (Level A). If any components of the neurologic examination are inconsistent with BD/DNC, the patient does NOT meet criteria for BD/DNC.

Components of the BD/DNC Neurologic Examination

The clinical examination findings supporting BD/DNC described in this guideline are consistent with those included in prior guidelines, both in the United States and around the world (eTable 3, links.lww.com/WNL/D76).[2,3,20]

Assessment for Unresponsiveness

Recommendation 15 Rationale

The presence of coma with no response to noxious stimulation is a key component of the BD/DNC neurologic examination.

Recommendation Statement 15

Clinicians performing the BD/DNC neurologic examination must ensure that the patient is comatose and unresponsive to visual, auditory, and tactile stimulation. Evidence of responsiveness precludes a diagnosis of BD/DNC (Level A).

Assessment for Motor Response

Recommendation 16 Rationale

The absence of cerebrally mediated motor responses to noxious stimuli is a key component of BD/DNC neurologic examination. Retained spinally mediated reflexes can be seen in the setting of BD/DNC and do not invalidate the diagnosis of BD/DNC (eTable 4, links.lww.com/WNL/D76).[27] It can sometimes be challenging to determine whether a movement is cerebrally or spinally mediated based solely on the clinical examination. When such difficulties arise, review with more experienced clinicians may be helpful.

Recommendation Statement 16a

Clinicians performing the BD/DNC neurologic examination must ensure that the patient has no motor responses, other than spinally mediated reflexes, of the head/face, neck, and extremities after application of noxious stimuli to the head/face, trunk, and limbs (Level A).

Recommendation Statement 16b

If it is unclear whether observed limb movements are spinally mediated, determination of BD/DNC should include an ancillary test (Level B).

Assessment of the Pupillary Light Reflex

Recommendation 17 Rationale

The pupillary light reflex is a brainstem reflex and part of the BD/DNC neurologic examination.

Recommendation Statement 17

Clinicians performing BD/DNC neurologic examinations must determine that there are no pupillary responses to bright light bilaterally (Level A).

Assessment of the OCR and the OVR

Recommendation 18 Rationale

The OCR and OVR are brainstem reflexes that test the same cranial nerves and are part of the BD/DNC neurologic examination. The OCR can be harmful to a patient with cervical spine injury or absence of skull base integrity. The OVR provides a stronger vestibular stimulus than the OCR and therefore may be a more sensitive test of the involved brainstem pathways.[28]

Recommendation Statement 18a

Clinicians performing the BD/DNC neurologic examinations must determine that there is no OCR unless there is concern for cervical spine or skull base integrity (Level A).

Recommendation Statement 18b

If the OCR is absent bilaterally or if the OCR cannot be tested because of concern for cervical spine or skull base integrity, OVR must be performed bilaterally (Level A).

Recommendation Statement 18c

If the OCR cannot be tested because of concern for cervical spine or skull base integrity, clinicians may diagnose BD/DNC

without ancillary testing provided that the OVR can be tested and is absent bilaterally and all other BD/DNC criteria are satisfied (Level A).

Assessment of the Corneal Reflex

Recommendation 19 Rationale

The corneal reflex is a brainstem reflex and part of the BD/DNC neurologic examination.

Recommendation Statement 19

Clinicians performing the BD/DNC neurologic examination must determine that there are no corneal reflexes bilaterally (Level A).

Assessment of the Gag and Cough Reflexes

Recommendation 20 Rationale

Medullary function in the BD/DNC neurologic examination is clinically assessed by the cough and gag reflexes and the apnea test. The gag reflex is a brainstem reflex. The cough reflex is a brainstem reflex.

Recommendation Statement 20

Clinicians performing the BD/DNC neurologic examination must determine that both the gag and cough reflexes are absent (Level A).

Assessment of the Sucking and Rooting Reflexes

Recommendation 21 Rationale

The sucking reflex is a centrally mediated primitive reflex in infants that becomes a voluntary response at approximately 4 months of age. The rooting reflex is a centrally mediated primitive reflex in infants that disappears between 3 and 6 months of age.

Recommendation Statement 21

In infants younger than 6 months, clinicians performing the BD/DNC neurologic examination must determine that there is no sucking or rooting reflex (Level A).

Apnea Testing as Part of the BD/DNC Evaluation

Number of Apnea Tests Required

Both the 1995 AAN practice parameter and 2010 AAN guideline for adults recommended performance of a single apnea test.[2,9] By contrast, the 1987 and 2011 pediatric guidelines recommended performance of 2 apnea tests.[3,26] In seeking to determine the appropriate number of apnea tests to recommend, the panel considered (1) the desire to err on the side of being conservative and (2) the fact that there is potential for cardiopulmonary instability during apnea testing.

Recommendation 22 Rationale

Apnea testing is a required component of the BD/DNC evaluation. Apnea testing may lead to hypoxemia and hemodynamic compromise.[8] There are no physiologic reasons or empiric evidence to support performing more than 1 apnea test to determine BD/DNC.[8]

Recommendation Statement 22a

Clinicians must perform at least 1 apnea test after the final BD/DNC neurologic examination in adults (Level A).

Recommendation Statement 22b

Clinicians must perform 2 apnea tests in children, 1 after each BD/DNC neurologic examination (Level A).

Procedure for Performing the Apnea Test

Safe performance of apnea testing after patients meet all other BD/DNC clinical criteria is of paramount importance and can be achieved by numerous means (eTable 5, links.lww.com/WNL/D76).[6,8,20] Apneic oxygen diffusion is the most commonly used technique in adults, with disconnection from the ventilator and providing oxygen through a catheter placed just above the carina. Alternative methods for testing include delivering 100% oxygen through a flow-inflating resuscitation bag with a functioning positive end-expiratory pressure (PEEP) valve. The level of PEEP using these methods is often set to the same PEEP as the ventilator before disconnection. Atelectasis from the drop in mean airway pressure while disconnecting the ventilator can cause shunting and hypoxemia. Lower rates of hypoxemia are described in adults using continuous positive airway pressure (CPAP) vs tracheal insufflation, although CO_2 rise and premature termination of the apnea test are similar between the different methods of apneic oxygenation.[29-32] Apnea testing using CPAP has also been performed safely and successfully in children. The use of CPAP in children can prevent hypoxemia and early termination of the apnea test.[33] Tracheal insufflation is not recommended in children because this technique can result in complications such as barotrauma and CO_2 washout that can complicate and/or prolong apnea testing.[1] Other methods of apneic oxygenation include bulk diffusion[34] and CO_2 augmentation,[35] although the latter may not affect pH and thus is not preferred. Performing apnea testing on the ventilator can be complicated by autocycling caused by cardiac pulsations or condensation in the tubing, leading to difficulty distinguishing between patient-initiated and autocycle-initiated breaths.

Although the 2010 AAN BD/DNC guideline indicated that the $PaCO_2$ threshold for determination of BD/DNC during apnea testing was ≥60 mm Hg (or 20 mm Hg over baseline for patients with elevated baseline), the 2011 pediatric BD/DNC guidelines specified a threshold of ≥60 and ≥20 mm Hg over baseline.[2,3] The distinction between whether "baseline" referred to premorbid $PaCO_2$ or $PaCO_2$ before commencement

of apnea testing was not specified in either BD/DNC guideline. Selection of targets for this challenge is arbitrary because no scientific data demonstrate specific $PaCO_2$ above which medullary chemoreceptors would prompt respiration if they were functional. However, much of the world uses $PaCO_2$ target of ≥60 mm Hg for determination of BD/DNC.[20]

Neither the 2010 AAN BD/DNC guideline nor the 2011 BD/DNC guideline dictate a pH target; similarly, there is only a pH target for apnea testing in a few countries around the world.[2,3,20] However, the triggers for medullary chemoreceptors to initiate respiration are both hypercarbia and acidosis.[36,37] The procedure described in this guideline is consistent with that which is included in prior guidelines, both in the United States and around the world.[2,3,20]

Recommendation Rationale 23

Respiration is stimulated in the medullary chemoreceptors by hypercarbia and secondary acidosis. The BD/DNC evaluation requires an evaluation for spontaneous respiratory effort in response to a hypercarbic and acidotic challenge by apnea testing. Spontaneous respirations are a sign of brainstem function and are not compatible with BD/DNC. Apnea testing can lead to complications, including hypoxemia and hemodynamic compromise with cardiovascular collapse requiring cardiopulmonary resuscitation.[38-42] These complications can usually be prevented through preoxygenation, fluid repletion, and medications as appropriate. Hypoxemia and hypotension before apnea testing are associated with a higher risk of cardiopulmonary decompensation during apnea testing.[8] Patients with severe respiratory and/or cardiovascular failure may be at higher risk of cardiopulmonary decompensation during apnea testing.

Recommendation Statement 23

Before attempting apnea testing, clinicians must ensure that the patient's risk of cardiopulmonary decompensation during apnea testing is assessed and is acceptable (Level A). Specifically, clinicians must ensure that the patient is not hypoxemic, hypotensive, or hypovolemic before starting the apnea test (Level A).

Recommendation 24 Rationale

The apnea test evaluates for spontaneous respiratory effort in response to a hypercarbic and acidotic challenge. Before apnea testing, patients who are not known to have chronic hypercarbia need to have normal $PaCO_2$ and pH values. In patients with chronic hypercarbia (e.g., chronic obstructive pulmonary disease), medullary chemoreceptors can develop a diminished response to CO_2 over time, especially at CO_2 concentrations below the patient's baseline level. Patients with chronic hypercarbia need to have their preapnea testing $PaCO_2$ level be at their chronic baseline level before apnea testing.

Recommendation Statement 24a

Clinicians must ensure that patients have normal $PaCO_2$ (35–45 mm Hg) and pH (7.35–7.45) levels before apnea testing, provided the patient is not known to be hypercarbic at baseline (Level A).

Recommendation Statement 24b

If a patient is known to have chronic hypercarbia, and the patient's chronic baseline level is known, the $PaCO_2$ level before apnea testing should be at the patient's chronic baseline level (Level B).

Recommendation Statement 24c

If a patient is known or suspected to have chronic hypercarbia but the patient's chronic baseline $PaCO_2$ level is not known, the $PaCO_2$ level before apnea testing should be at the patient's estimated chronic baseline. However, in this circumstance, if apnea is present, clinicians should perform ancillary testing in addition (Level A).

Recommendation 25 Rationale

Apnea testing can lead to hypoxia, hypotension, arrhythmias, and pneumothorax.[8] Adherence to a protocol ensures the proper performance of the apnea test and helps avoid potential complications. A person who demonstrates spontaneous respiratory effort during apnea testing does not meet criteria for BD/DNC. In the absence of respirations, the $PaCO_2$ level increases by approximately 2–3 mm Hg per min in normothermic individuals.[8] Failure to abort the apnea test in the event of hemodynamic instability or hypoxemia could lead to cardiovascular collapse and cardiopulmonary arrest.[8]

Recommendation Statement 25a

Clinicians should preoxygenate the patient with 100% oxygen for at least 10 minutes before apnea testing to achieve a PaO_2 level >200 mm Hg (Level B).

Recommendation Statement 25b

To allow multiple arterial blood gas (ABG) measurements and reliably monitor the patient's hemodynamic status during apnea testing, clinicians should ensure that the patient has an invasive arterial catheter whenever possible (Level A).

Recommendation Statement 25c

Clinicians should perform ABG measurement after preoxygenation and before disconnecting the ventilator to determine the baseline PaO_2, $PaCO_2$, and pH levels (Level B).

Recommendation Statement 25d

Clinicians must ensure adequate oxygenation during apnea testing. In adults, this can be accomplished through (1) stopping intermittent mandatory ventilation and disconnecting the ventilator from the patient's endotracheal tube (ETT)/tracheostomy and delivering 100% oxygen at a rate of 4–6 L/min through a catheter that is <70% of the diameter of the ETT/tracheostomy (to avoid barotrauma), placed inside the ETT/tracheostomy just above the level of the carina; (2) stopping intermittent mandatory ventilation and delivering 100% oxygen through CPAP on the ventilator; or (3) stopping intermittent mandatory ventilation and disconnecting the ventilator from the patient's ETT/tracheostomy and delivering 100% oxygen through a flow-inflating resuscitation bag with a functioning PEEP valve. In children, this can be accomplished through (1) stopping intermittent mandatory ventilation and delivering 100% oxygen through CPAP on the ventilator or (2) stopping intermittent mandatory ventilation and disconnecting the ventilator from the patient's ETT/tracheostomy and delivering 100% oxygen through a flow-inflating resuscitation bag with a functioning PEEP valve (Level A).

Recommendation Statement 25e

Clinicians should perform an ABG measurement after 8–10 minutes of apnea (Level A). The patient may be kept off the ventilator until it is confirmed that the arterial pH and $PaCO_2$ level criteria for BD/DNC determination are met if the patient is hemodynamically stable. Because the physiologic threshold for BD/DNC determination may be reached before 8–10 minutes of apnea, point-of-care blood gas testing may be used to perform ABG measurements earlier and more frequently. If the patient has cardiopulmonary instability, blood gas measurements might be necessary sooner.

Recommendation Statement 25f

Clinicians must conclude that the apnea test is consistent with BD/DNC criteria if:

1. In patients who are known NOT TO HAVE chronic CO_2 retention, if (1) no respirations occur, (2) the arterial pH level is <7.30, and (3) the $PaCO_2$ level is ≥60 and ≥20 mm Hg above the patient's preapnea test baseline level.
2. In patients who are KNOWN TO HAVE chronic CO_2 retention, and the baseline $PaCO_2$ level is KNOWN, clinicians must conclude that the apnea test is consistent with BD/DNC criteria if (1) no respirations occur, (2) the arterial pH level is <7.30, and (3) the $PaCO_2$ level is ≥60 and ≥20 mm Hg above the patient's known chronic elevated premorbid baseline level.
3. In patients who are SUSPECTED TO HAVE chronic CO_2 retention, but the baseline $PaCO_2$ level is UNKNOWN, clinicians must conclude that the apnea test is consistent with BD/DNC criteria if (1) no respirations occur, (2) the arterial pH level is <7.30, and (3) the $PaCO_2$ level is ≥60 and ≥20 mm Hg above the patient's baseline (pretest) level, AND ancillary testing must be performed (Level A).

Recommendation Statement 25g

Clinicians must abort apnea testing if the patient takes 1 or more spontaneous respirations because the patient does not meet criteria for BD/DNC (Level A).

Recommendation Statement 25h

Clinicians must abort apnea testing if the patient experiences hemodynamic instability or hypoxemia at any point during the apnea test as identified by:

1. SBP <100 mm Hg or MAP <75 mm Hg in adults or SBP or MAP <fifth percentile for age in children despite titration of vasopressors, inotropes, and/or intravenous fluids, or
2. Progressive decrease in oxygen saturation below 85%, or
3. A cardiac arrhythmia with hemodynamic instability (Level A).

Recommendation Statement 25i

If the patient develops a decrease in blood pressure or oxygen saturation and the need to abort the apnea test seems imminent, clinicians should obtain an ABG measurement before placing the patient back on the ventilator (Level A).

Recommendation Statement 25j

If the $PaCO_2$ and pH level criteria are not reached, and the patient did not experience hemodynamic instability or hypoxemia during apnea testing, clinicians should either continue the apnea test beyond 10 minutes with ABG measurements checked at least every 2 minutes or if the test was discontinued but the patient was hemodynamically stable and did not desaturate, repeat apnea testing for a longer period after again preoxygenating to a PaO_2 level >200 mm Hg and reestablishing normal $PaCO_2$ and pH levels (Level A).

Recommendation Statement 25k

If the patient experienced hypoxemia during apnea testing and the pH and $PaCO_2$ level criteria were not reached, clinicians should either repeat the apnea test using an alternative apneic oxygenation method that maintains functional residual capacity (e.g., CPAP through a flow-inflating resuscitation bag), repeat the apnea test when it can be safely completed, or perform an ancillary test (Level A).

Recommendation Statement 25l

If the patient experienced hypotension during apnea testing and the pH and $PaCO_2$ level criteria were not reached, clinicians should either repeat apnea testing after augmenting the blood pressure, repeat the apnea test when it can be safely completed, or perform an ancillary test (Level A).

Recommendation Statement 25m

If the patient developed a cardiac arrhythmia with hemodynamic instability during apnea testing, and the pH and $PaCO_2$ level criteria were not reached, clinicians should repeat the apnea test when it can be safely completed or perform an ancillary test (Level A).

Procedure for Performing the Apnea Test in Patients on ECMO

The methodology for apnea testing on ECMO was not included in the prior adult or pediatric BD/DNC guidelines.[2,3] Despite this, apnea testing is performed regularly in patients on ECMO.[32,43-49] The physiologic principles when apnea testing is performed while on cardiopulmonary mechanical support with ECMO are identical to when apnea testing is performed off ECMO—respiration is stimulated in the medullary chemoreceptors by hypercarbia and secondary acidosis.

When not on VA ECMO, the $PaCO_2$ and pH levels obtained from a distal arterial catheter approximate the values in the cerebral circulation. Similarly, when a patient on VA ECMO has an absence of cardiac contractility, blood sampled from a distal arterial line will approximate the cerebral circulation. However, for a patient on VA ECMO who has some native myocardial function, blood flow from the native heart and lungs mixes with blood from the ECMO circuit at a point in the aorta called the "watershed" or "mixing point."[50,51] Gas tensions measured from a distal arterial line in this situation do not approximate the cerebral circulation. Thus, ECMO arterial cannula position and the potential contributions to cerebral blood flow from both the ECMO circuit and the patient's native cardiac output affect decision-making about the location of ABG sampling.[51] Adjusting the sweep gas flow rate or titrating exogenous CO_2 into the ECMO circuit lead to increased $PaCO_2$ levels.[32,45,47,48]

Recommendation 26 Rationale

Patients on ECMO may progress to BD/DNC, and modifications to apnea testing are necessary because of differences in cardiopulmonary support. Preoxygenation through the membrane lung and ventilator minimizes hypoxia for patients on ECMO. The $PaCO_2$ level for patients on ECMO can be increased through the addition of exogenous CO_2 in the ECMO circuit or a decrease in the sweep gas flow. Locations of ABG sampling from the patient must consider ECMO arterial cannula position and the potential contributions to cerebral blood flow from both the ECMO circuit and the patient's native cardiac output.

Recommendation Statement 26

Clinicians should adhere to the following protocol for apnea testing on ECMO:

1. Preoxygenate by using 100% FiO_2 on the ventilator and through the membrane lung.
2. To achieve an adequate increase in $PaCO_2$ level, either titrate exogenous CO_2 into the ECMO circuit or adjust the sweep gas flow rate to 0.2–1 L/min.
3. Sample ABG measurements from both the patient's distal arterial line and the ECMO circuit postoxygenator for patients on VA ECMO. $PaCO_2$ and pH levels from both locations are required to meet BD/DNC criteria for the apnea test to be consistent with BD/DNC. This ensures that, independent of the mixing point, the $PaCO_2$ and pH levels in the cerebral circulation meet BD/DNC criteria. For patients on venovenous ECMO, sample ABG measurements only from the patient's distal arterial line.
4. Avoid hypotension during apnea testing on ECMO by increasing ECMO flows, intravenous fluid administration, or vasopressor/ionotropic support (Level A).

Ancillary Testing as Part of the BD/DNC Evaluation

Indications for Ancillary Testing

Evaluation for BD/DNC remains a clinical evaluation, and under most circumstances, ancillary testing is not required. Under some circumstances, the BD/DNC clinical examination and apnea test cannot be completed in their entirety, such as in patients with injuries to the head and neck that preclude evaluation of cranial nerve reflexes or when apnea testing cannot be completed safely because of the patient's underlying medical condition. Both the 2010 AAN and 2011 pediatric guidelines state that ancillary tests can be used when uncertainty exists about the reliability of parts of the neurologic examination or when the apnea test cannot be performed because of the underlying medical condition of the patient.[2,3] The pediatric guidelines further state that ancillary testing can be used if a medication effect may be present or to shorten the duration of the interexamination observation period.[3]

Recommendation 27 Rationale

In most circumstances, the diagnosis of BD/DNC is based on the clinical demonstration of coma, absent brainstem reflexes, and apnea and does not require ancillary testing. There are some situations where a component of the BD/DNC neurologic examination or the apnea test cannot be completed or the findings cannot be interpreted adequately. Although ancillary tests have previously been used in the setting of confounding factors such as hypothermia or high levels of sedating medications, the effects of these factors on ancillary tests and cerebral perfusion particularly are poorly defined,

confounding interpretation of cerebral perfusion studies. The presence of an open fontanelle, skull fracture, skull defect (e.g., craniectomy), or CSF diversion device does not preclude performance of a complete clinical assessment and apnea test but can affect ancillary testing. Hospital or state policies may dictate indications for ancillary tests and ancillary test selection.

Recommendation Statement 27a

Clinicians should only perform ancillary testing to assist with the diagnosis of BD/DNC when the BD/DNC neurologic examinations or apnea test cannot be completed or the findings cannot be interpreted adequately (Level B).

Recommendation Statement 27b

Clinicians should use ancillary testing in the following circumstances:

1. Injuries such as fractures of the cervical spine, skull base, or orbits, severe facial injuries or abnormalities that preclude accurate assessment of any components of the neurologic examination (with the exception of the OCR if untestable due to concern for C-spine or skull base integrity), or injuries to the cervical spinal cord that limit the adequate assessment of extremity movement or spontaneous respirations, or
2. The inability to perform or complete the apnea test safely because of the patient's risk of cardiopulmonary decompensation or the inability to interpret the $PaCO_2$ levels in a patient with chronic hypercarbia for whom the chronic baseline $PaCO_2$ level is unknown, or
3. Neurologic examination findings that may be difficult to interpret, such as limb movements that may or may not be spinally mediated, or
4. Metabolic derangements that are unable to be adequately corrected (Level A).

Recommendation Statement 27c

Clinicians must not use ancillary tests to assist in the diagnosis of BD/DNC in the setting of hypothermia or high levels of sedating medications or to avoid performing otherwise testable elements of the BD/DNC assessment (Level A).

Recommendation Statement 27d

If ancillary testing is needed to diagnose BD/DNC, before proceeding to an ancillary test, BD/DNC neurologic examination(s) and apnea test(s) still need to be performed to the fullest extent possible, and findings must be consistent with BD/DNC (Level A).

Recommendation Statement 27e

If any findings on the BD/DNC neurologic examination or apnea test are consistent with brain-mediated activity, the patient does not meet criteria for BD/DNC, and ancillary testing must not be performed (Level A).

Recommendation Statement 27f

In patients who meet all clinical criteria for BD/DNC, clinicians should not perform ancillary testing solely because of the presence of an open fontanelle, skull fracture, skull defect (e.g., craniectomy), or CSF diversion device (Level B).

Performance of Ancillary Tests

Several different modalities are available to evaluate for electrophysiologic function or perfusion of the brain. However, all ancillary tests have shortcomings, and as discussed further, none are 100% sensitive and specific (eTable 6, links.lww.com/WNL/D76). In identifying the tests that could be used when ancillary testing is indicated, specificity is paramount because a false-positive result (i.e., patient is alive and ancillary test is consistent with BD/DNC) could lead to an inaccurate diagnosis of BD/DNC.

Tests of Electrophysiologic Function: EEG

The 2010 AAN and 2011 pediatric BD/DNC guidelines include EEG as an acceptable ancillary test, but they do not include evoked potentials.[2,3] Although the EEG was the only ancillary test included in the first US delineation of the BD/DNC construct by a group at Harvard Medical School in 1968,[52] and it has consistently been recommended ever since, it has at least 1 fundamental limitation—it assesses the function of the cerebral hemispheres and not deeper structures, notably the brainstem. Even the absence of any detectable EEG activity is not informative about the presence or absence of brainstem function, which is problematic because one of the more common reasons for performing an ancillary test is the inability to fully assess a patient's brainstem function.

Recommendation 28 Rationale

Neurophysiologic tests, including EEG, auditory evoked potentials (AEPs), and somatosensory evoked potentials (SEPs) have historically been used as ancillary tests to assist with BD/DNC determination. EEG assesses the function of the cerebral hemispheres and not the brainstem. Thus, the absence of any detectable EEG activity does not provide information about the presence or absence of brainstem function. Yet, one of the primary indications for ancillary testing is when the clinical evaluation of brainstem function, including apnea testing, cannot be completed. Studies of anatomically limited somatosensory and brainstem auditory pathways provide incomplete information about the entire brainstem. Thus, the addition of AEPs and SEPs cannot completely compensate for this inherent limitation of EEG for the purpose of assisting with BD/DNC determination.

Recommendation Statement 28

Clinicians should not use EEGs, AEPs, or SEPs as ancillary tests to assist with the diagnosis of BD/DNC (Level B).

Tests of Cerebral Perfusion: 4-Vessel Catheter Angiography

Recommendation 29 Rationale

Catheter angiography has long been considered the gold standard perfusion study because it allows direct and dynamic assessment of intracranial flow through intra-arterial injection under pressure with the catheter positioned in the great vessels leading to the brain.[53] Flow arrests at the point of entry of the vessels to the dura in both the anterior and posterior circulation, the result of tamponade from highly elevated intracranial pressure. The absence of intracranial perfusion is because of intracranial pressure that has increased beyond MAP and is consistent with BD/DNC.

Recommendation Statement 29

Clinicians may use conventional 4-vessel catheter angiography as an ancillary test to aid in the diagnosis of BD/DNC (Level A).

Tests of Cerebral Perfusion: Radionuclide Perfusion Scintigraphy

Recommendation 30 Rationale

Radionuclide cerebral scintigraphy is practical and widely used in adults and children to assist with BD/DNC determination. Standards established by the Society of Nuclear Medicine and Molecular Imaging and the American College of Radiology must be followed when applicable to ensure appropriate interpretation of images.[54,55] Tc 99m hexamethyl propylene amine oxime and Tc 99m ethyl cysteinate dimer[54] are lipid soluble and brain-specific agents, which allow vascular and delayed planar imaging to demonstrate absence of intracranial blood flow and cerebral perfusion. SPECT imaging can also be helpful because it provides better visualization of posterior fossa and brainstem structures but requires longer imaging time. Nonspecific, nonlipophilic agents such as Tc 99m diethylene triamine penta-acetic acid use planar imaging and can be performed at the bedside but provide only vascular imaging and do not assess tissue perfusion.[54] Notably, findings on vascular imaging with nonbrain-specific agents are more susceptible to technique-related challenges.[55]

Recommendation Statement 30

Clinicians may use either SPECT radionuclide perfusion scintigraphy with a blood-brain barrier (BBB)–crossing agent or planar radionuclide angiography, preferably with a BBB-crossing agent or, if necessary, a non–BBB-crossing agent, as an ancillary test to aid in the diagnosis of BD/DNC (Level A).

Tests of Cerebral Perfusion: Transcranial Doppler Ultrasonography

Recommendation 31 Rationale

Transcranial doppler ultrasonography is widely available and relatively easy to perform at the bedside. In approximately 10% of adults, skull thickness precludes adequate insonation.[56] Detection of oscillating flow or systolic spikes in proximal large intracranial arteries (internal carotid, middle and anterior cerebral, posterior cerebral, basilar, and vertebral arteries) is consistent with BD/DNC in adults.[56,57] It is not difficult to differentiate between the absence of any signal for technical reasons and the flow pattern seen in patients with absent cerebral perfusion, thereby meeting criteria for BD/DNC. It has not been validated in children.

Recommendation Statement 31

Clinicians may use transcranial doppler ultrasonography in adult patients as an ancillary test to aid in the diagnosis of BD/DNC and should not use transcranial doppler ultrasonography as an ancillary test for children (Level A).

Tests of Cerebral Perfusion: CT and Magnetic Resonance Angiography

Recommendation 32 Rationale

Because of the widespread availability of CT angiography, this technique has been used with increasing frequency to assist with BD/DNC diagnosis.[58,e1] However, the available data demonstrate a lack of validation and the potential for false positives.[58,e2] Variations in protocols with different sensitivities and specificities, contrast injection parameter variation, and limited data that compare this technique with other tests of cerebral blood flow currently relegate CT angiography as only investigational as an ancillary test to assist with BD/DNC determination.[e1,e3]

Recommendation Statement 32

Clinicians should not use CT angiography as an ancillary test to aid in the diagnosis of BD/DNC (Level A).

Recommendation 33 Rationale

Because of the widespread availability of magnetic resonance angiography, this technique has been used to assist with BD/DNC diagnosis.[e4,e5] It can be challenging to perform in critically ill patients, and the available data do not demonstrate adequate validation.[e4-e6]

Recommendation Statement 33

Clinicians should not use MRI or magnetic resonance angiography as an ancillary test to aid in the diagnosis of BD/DNC (Level B).

Special Considerations

There are several special considerations not included in the prior adult and pediatric guidelines for BD/DNC, which we address here.[2,3,9,26] These include (1) consent before evaluation for BD/DNC, (2) time of death and discontinuation of organ support, (3) evaluation of BD/DNC in a patient who is pregnant, (4) preservation of neuroendocrine function, and

(5) evaluation of BD/DNC in a patient with primary posterior fossa injury.

Obtaining Consent for BD/DNC Evaluation

In recent years, the question of whether consent is needed before evaluation for BD/DNC has been debated in medical, legal, ethical, and philosophical forums.[e7-e12] This discussion is often focused on apnea testing particularly. The risks of apnea testing are minimized through adherence to guidelines. According to the UDDA, which was written in 1981 by the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, the American Bar Association, and the American Medical Association, death can be declared if there is irreversible cessation of cardiopulmonary function or irreversible cessation of whole brain function.[1] The need for consent before evaluation for either BD/DNC or death by cardiopulmonary criteria is not addressed in the UDDA. However, some states (New York and Nevada) legally stipulate that consent is not required before evaluation for BD/DNC.[e13,e14] When this matter has been adjudicated in court, some courts determined that consent is not required before evaluation for BD/DNC or discontinuation of organ support,[e12,e15] while others ruled that a person's surrogate decision maker has the right to choose whether any medical procedure, including evaluation for BD/DNC, is performed.[e16]

A 2015 survey of adult neurologists in the AAN found that 78% of respondents believed clinicians should not need to obtain consent before an evaluation for BD/DNC.[e17] Similarly, a 2016 survey of pediatric neurologists and intensivists found that 72% believed clinicians should not need to obtain consent before an evaluation for BD/DNC.[e18] Accordingly, in a 2019 position statement, the AAN noted that clinicians should inform a patient's surrogate decision makers about the intent to perform an evaluation for BD/DNC, but that there was no obligation to obtain informed consent before performing the evaluation.[e19] However, institutional policies and state laws may govern rules and regulations regarding consent.

Recommendation 34 Rationale

Death by BD/DNC criteria is equivalent medicolegally to death by cardiopulmonary criteria. Evaluating a patient for death in a timely and accurate manner is a necessary part of clinicians' professional responsibilities. Consent is not required to evaluate a patient for death. The decision to initiate an evaluation for BD/DNC after catastrophic, permanent brain injury is a clinical decision made by the attending clinician in accordance with the institution's policy.

Recommendation Statement 34

Clinicians do not need to obtain consent before an evaluation for BD/DNC unless otherwise stipulated by the institution's policy or state laws or regulations (Level A).

Recommendation 35 Rationale

Loss of a family member is a traumatic event for families. Being informed of the BD/DNC process before its initiation and having the opportunity to witness the BD/DNC evaluation may aid in acceptance of BD/DNC.

Recommendation Statement 35a

Clinicians planning to evaluate a patient for BD/DNC should make a reasonable attempt to inform the patient's family of the plan to perform a BD/DNC examination (Level A).

Recommendation Statement 35b

Clinicians evaluating a patient for BD/DNC should provide the option for the family to observe the clinical evaluation, including apnea testing (Level B). Clinicians should inform families that patients may have reflexive movements caused by activity from the spinal cord, muscles, or nerves during the BD/DNC evaluation and that these movements do not preclude determination of BD/DNC (Level B).

Time of Death

Recommendation 36 Rationale

Death certificates require that the time of death be recorded. Death, either cardiopulmonary or neurologic, can be determined once the patient has met the necessary testing requirements. The process of assigning the time of death for patients who meet criteria for BD/DNC should be consistent.

Recommendation Statement 36a

For patients who meet clinical criteria for BD/DNC, clinicians must assign the time of death as the time during the final apnea test (if more than 1 is performed) that the ABG results are reported and demonstrate that the $PaCO_2$ and pH levels are consistent with BD/DNC criteria (Level A).

Recommendation Statement 36b

For patients in whom an ancillary test is required and performed, clinicians determining BD/DNC must assign the time of death as the time an attending clinician (e.g., nuclear medicine physician or angiographer) documents in the medical record that the ancillary test results are consistent with BD/DNC (Level A).

Recommendation 37 Rationale

Once BD/DNC has been determined, the mechanical or pharmacologic support that is maintaining respiratory or cardiac function is generally discontinued unless organ donation is being considered. However, it is reasonable for this organ support to be continued for a period, providing the family with a reasonable but limited amount of time with the deceased patient. Some US states legally require accommodation of

requests to continue organ support after BD/DNC determination under specifically defined circumstances.

Recommendation Statement 37a

Organ support may be continued for a period after BD/DNC, the length of which is based on the judgment of the attending clinician of record in accordance with the institution's policy, to provide the family with a reasonable but limited amount of time with the deceased patient before the discontinuation of this support (Level B).

Recommendation Statement 37b

Hospital policies should include consideration of providing a reasonable period to accommodate families after the death of a family member and should provide a process to resolve disagreements when families do not agree with the medical team about initiation of the BD/DNC evaluation and/or termination of organ support after determination of BD/DNC (Level B).

Evaluation of BD/DNC in a Patient Who Is Pregnant

People who are pregnant can develop catastrophic, permanent brain injuries requiring determination of BD/DNC.[e20-e22] It is feasible to continue organ support in a pregnant person after BD/DNC with the goal of delivery of a viable infant. This has been attempted in people with a fetus of gestational age ranging from 1 to 40 weeks, but aggressive medical management was needed to address the multiorgan dysfunction that developed before and after BD/DNC, and there is risk of cardiopulmonary arrest at any time after BD/DNC; thus, although some cases of continuation of organ support after BD/DNC in a pregnant person resulted in delivery of a developmentally normal infant, others resulted in spontaneous abortion or intrauterine death.[e20,e22] In a 2019 position statement, the AAN noted that if a pregnant person is found to be BD/DNC, the family should be "educated by knowledgeable professionals about relevant law as well as fetal outcome, which is often uncertain," and that decision-making regarding continuation vs discontinuation of organ support should be based on consideration of the viability of the fetus, fetal brain injury incurred in the setting of their parent's catastrophic brain injury, and the law in addition to the prior wishes of the patient, loved ones, and the patient's surrogate decision-maker.[e19]

Recommendation 38 Rationale

Patients who are pregnant can develop catastrophic, permanent brain injuries and may be determined to meet BD/DNC criteria. In these situations, the fetus may still be viable. Continued organ support in a pregnant person after BD/DNC determination may lead to the delivery of a viable newborn.[e20,e22] The ethical analysis of whether to continue organ support in a pregnant person determined BD/DNC should largely focus on the welfare of the fetus.[e19]

Recommendation Statement 38a

Pregnancy in and of itself is not a contraindication to BD/DNC evaluation. Clinicians should assess and diagnose pregnant persons with catastrophic, permanent brain injuries for BD/DNC (Level A).

Recommendation Statement 38b

After the determination of BD/DNC in a pregnant person, the clinicians providing care, assisted by clinicians knowledgeable in maternal-fetal medicine, child neurology, and neonatology, as needed, should educate and discuss with surrogate decision-makers the risks and benefits to the fetus of continuing maternal organ support (Level B).

Neuroendocrine Function

The hypothalamic-hypophyseal axis may remain intact after BD/DNC, partly because of variable extracranial vascular supply, reducing the effect of ischemia.[e23,e24] Thus, diabetes insipidus is reported to develop in BD/DNC (9%–90% in adults and 38%–41% in children).[e25-e30] In a 2019 position statement, the AAN noted that neuroendocrine function can persist in patients with permanent injury to the brain[e19] and "is not inconsistent with the whole brain standard of death."

Recommendation 39 Rationale

The concept of BD/DNC has its legal origin in the United States in the UDDA, which in turn is rooted in the Harvard criteria.[1] The UDDA states, "an individual who has sustained…irreversible cessation of all functions of the entire brain, including the brainstem, is dead. The determination of brain death must be made in accordance with accepted medical standards." Since the publication of the Harvard criteria, the accepted medical standards to evaluate loss of function of the brain as a whole have been anchored in "unreceptivity and unresponsiveness, absent breathing or movements," and absent brainstem function—standards reaffirmed in the 1995 and 2010 AAN brain death guidelines and the 1987 and 2011 AAP, SCCM, and Child Neurology Society pediatric brain death guidelines.[3,26] Neuroendocrine function may persist in patients with catastrophic, permanent brain injury who meet the criteria for BD/DNC established in the 1995 and 2010 AAN and 1987 and 2011 AAP, SCCM, and Child Neurology Society brain death guidelines.[e25-e30]

Recommendation Statement 39

Clinicians may initiate a BD/DNC evaluation and determine a patient BD/DNC despite evidence of neuroendocrine function (Level B).

Primary Posterior Fossa Injury

Permanent loss of function of the entire brain, including the brainstem, usually begins with supratentorial injury followed by downward transtentorial herniation, leading to infratentorial

injury. In rare cases, the primary injury takes place in the posterior fossa, and edema, obstructive hydrocephalus, and upward herniation subsequently lead to injury of the supratentorial structures.[e31]

Recommendation 40 Rationale

Patients with primary posterior fossa injury may be clinically comatose with brainstem areflexia and apnea; however, they may retain some cortical function.[e31]

Recommendation Statement 40

To avoid determining BD/DNC in patients with primary posterior fossa injury and retained supratentorial function, clinicians should ensure that the posterior fossa process has also led to catastrophic supratentorial injury as demonstrated on a conventional neuroimaging study before initiating the BD/DNC evaluation (Level B).

Suggestions for Future Research

There are several topics related to BD/DNC that warrant further research and attention, including but not limited to:

- Importance of number of examinations and qualifications of examiners
- Appropriate observation periods to ensure permanency
- Further development and validation of ancillary testing, with particular attention to advances in and standardization of CT cerebral blood flow imaging to validate its use as an additional ancillary test
- Further efforts to harmonize guideline recommendations, hospital policies, and state and federal laws to provide optimal care
- Further development of registries for reporting BD/DNC determinations to foster process improvement

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Acknowledgment

The panel thanks the leadership of the AAN, the staff of the AAN, and the multiple societies who engaged in this collaborative process. The panel also thanks Karla Resendiz, PharmD, BCPPS, and Bridget Blowey, PharmD for assistance with eTable 2 (links.lww.com/WNL/D76).

Study Funding

This consensus practice guideline was developed with financial support from the American Academy of Neurology (AAN). Authors who participated at the in-person meeting where drafts were developed were offered reimbursement by the AAN for expenses related to travel. Authors who serve or served as AAN subcommittee members or as methodologists (G.S.G., A.R.-G., L.B., C.T., and J.J.H.) or who are or were AAN staff (A.B., S.R.W.) were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

Disclosure

D.M. Greer has received travel funding from Boston University, serves as Editor-in-Chief for *Seminars in Neurology*, receives publishing royalties for 50 Studies Every Neurologist Should Know and Successful Leadership in Academic Medicine, has received honoraria from the American Academy of Neurology (AAN), has received research funding from Becton, Dickinson, and Company, and has served as expert witness in legal proceedings. M.P. Kirschen has received funding for travel from AAN/Child Neurology Society and has received research support from Masimo, Infrascan, and the Neurocritical Care Society. A. Lewis has received honoraria from AAN and Neurodiem, serves as *Neurology*® Deputy Editor of Disputes and Debates, and serves as Deputy Editor

of *Seminars in Neurology*. G.S. Gronseth has received personal compensation in the range of $10,000 for serving as an Editor, Associate Editor, or Editorial Advisory Board Member for *Neurology*, has received personal compensation in the range of $0–$499 for serving as an Editor, Associate Editor, or Editorial Advisory Board Member for *Brain & Life*, and has received personal compensation in the range of $0–$499 for serving as a member/evidence-based medicine consultant on the AAN Guidelines Subcommittee. A. Rae-Grant has received royalties for editing or coediting multiple textbooks with Springer Publishing and Wolters-Kluwer publisher and works part time for Ebsco Industries editing point-of-care evidence-based information for DynaMed, a subscription-based point-of-care tool for clinicians. S. Ashwal serves on the medical advisory board of the Tuberous Sclerosis Association and receives publishing royalties as coeditor of Pediatric Neurology: Principles and Practice. M.A. Babu has testified at a grand jury hearing relating to brain injury. D.F. Bauer has received research funding from the NIH and Park-Reeves collaborative. L. Billinghurst reports no disclosures relevant to the manuscript. A. Corey has performed blinded case review of MRI and CT scans for RadMD LLC, has received travel funding from Georgia Radiological Society, and is employed by the Department of Veterans Affairs. S. Partap has received honoraria from AAN and the American Academy of Pediatrics, has served on advisory boards for Bayer and GLG, and has received research support from the National Cancer Institute. M.A. Rubin has received travel funding from AAN and the Neurocritical Care Society, serves on the editorial board for *Neurology Today*, and has received honoraria from the University of Texas Tyler and Cooper Clinic. L. Shutter serves on a scientific advisory board for SENSE NeuroDiagnostics, serves on the ACCM Board of Regents, has received travel funding from SENSE NeuroDiagnostics, has received honoraria from the AAN, has received research support from the Chuck Noll Foundation, receives publishing royalties as coeditor of Pittsburgh Critical Care Medicine: Neurocritical Care, and has served as an expert witness and counsel in legal proceedings. C. Takahashi reports no disclosures relevant to the manuscript. R.C. Tasker has served as an NIH grant reviewer, serves as Senior Associate Editor for Archives of Disease in Childhood, serves as ad hoc reviewer for *Intensive Care Medicine*, serves as editor of the pediatric neurology section of *Current Opinions in Pediatrics*, serves as Editor-in-Chief of the Society of Critical Care Medicine journal *Pediatric Critical Care Medicine*, receives publishing royalties from *Nelson's Textbook of Pediatrics, edition 21*, *Oxford Handbook of Paediatrics and Child Health, edition 2*, *Roger's Textbook of Pediatric Intensive Care, edition 5*, UpToDate, 2 chapters: ICP treatment and ICP recognition, and has received research support from NIH and Boston Children's Hospital. P.N. Varelas serves on a scientific advisory board for Portola, has received honoraria from Portola, serves on a speakers' bureau for Portola, serves on an advisory board for UBC, serves on the editorial board of *Neurocritical Care*, has received royalties for the book *Seizures in Critical Care*, and has received research funding from Marinus and Bard. E. Wijdicks receives publishing royalties from Oxford Press for Brain Death. A. Bennett reports no disclosures relevant to the manuscript. S.R. Wessels reports no disclosures relevant to the manuscript. J.J. Halperin has received personal compensation in the range of $500–$4,999 for serving as an Expert Witness for Tri-Century Insurance Company, has received intellectual property interests from 3 publications relating to health care, and has received personal compensation in the range of $0–$499 for serving as a medical consultant with TelaDoc, and Dr. Halperin's institution has received research support from the NIH. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* March 27, 2023. Accepted in final form June 28, 2023. Submitted and externally peer reviewed. The handling editor was Editor-in-Chief José Merino, MD, MPhil, FAAN.

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Continued

Appendix *(continued)*

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Neurology published online October 11, 2023
DOI 10.1212/WNL.0000000000207740