

EVIDENCE-BASED GUIDELINE UPDATE: DETERMINING BRAIN DEATH IN ADULTS: REPORT OF THE QUALITY STANDARDS SUBCOMMITTEE OF THE AMERICAN ACADEMY OF NEUROLOGY

To the Editor: The Report of the American Academy of Neurology (AAN) Subcommittee,¹ issued 15 years after the AAN hallmark publication on determining brain death (BD) in adults,² has touched on several key points.

Wijdicks et al. concluded that there are no published reports of recovery of neurologic function after BD diagnosis. This is an important clinical, social, and ethical finding related to diagnosing death on neurologic grounds because irreversibility should be directly related to the determination of death.³ Furthermore, the Subcommittee did not find consensus on a minimally acceptable observation period for assuring that neurologic functions have permanently stopped.¹ Ancillary tests may play an important role in shortening periods of observation,^{3,4} but the panel of experts concluded that there are not enough data to show that newer tests confirm the termination of whole brain functioning.¹

It is widely accepted that BD is a clinical diagnosis and that confirmatory laboratory tests are recommended when specific components of the clinical testing cannot be evaluated.¹⁻³ An ideal confirmatory test should be safe, accurate, and inexpensive. Ancillary tests either show absent cerebral blood flow and brain metabolism or demonstrate loss of bioelectrical activity.^{3,4} The AAN Subcommittee examined 2 Class III studies in which somatosensory evoked potentials confirmed BD.¹ We used a test battery composed of multimodality evoked potentials (MEP) and electroretinography (ERG) to determine BD in a series of 72 patients.⁴

These tests are accessible in the intensive care unit (ICU) because they are portable machines. In addition, this test battery would permit the evaluation of several sensory pathways and the evaluation of brainstem and cerebral hemispheric functions. The period of observation is shortened and the examination of the primary brainstem lesions is also possible.^{3,4}

Unfortunately, these techniques are not routinely used in the ICU³ because neuromonitoring systems

need to be developed that would automatically record and process EEG and MEP.⁵

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To the Editor: The recent AAN Quality Standards Subcommittee authored by Wijdicks et al.¹ outlined several dilemmas facing practicing neurologists who must deal with the determination of BD. Unfortunately, by limiting the literature search to articles published after 1995, only 4 safety studies were identified and a large, earlier study was not included.

In June 1994, I coauthored a study of 70 apnea tests attempted on 61 comatose patients as part of the determination of BD.⁶ The technique we used for oxygenation in the 1990s was identical to the 2010 recommendations currently advocated. As an aside, the study was motivated by the death of one patient during apnea testing.

We found that 33% of patients developed marked hypotension (>15% drop in MAP) and 6% required prophylactic manipulation of vasopressors. We concluded that apnea testing can pose a significant risk of hypotension.² In a letter to the editor, Wijdicks⁷ wrote, "That hypotension develops during apnea testing in certain patients who otherwise fulfill the clinical criteria of brain death is well recognized." Over a decade later, in the largest safety study to date, Wijdicks et al.⁸ aborted apnea testing in 3% due to hypotension but 7% were judged medically unstable for the testing. The lower incidence of complications compared to our prior study was attributed to stricter, subsequently developed guidelines.

The legal and moral question of performing a potentially dangerous apnea test with no therapeutic implications for the individual has been discussed.⁹ Is informed consent needed—whether the risk is 3% or 33%? If time of death is the conclusion of the apnea test or ancillary test, as recently stated,¹ these comatose patients should be accorded all the moral and legal protections of any other living human being. It is a shame that these issues were not addressed in the recent review or similar policy statements.

Joseph S. Jeret, MD, FAAN, Rockville Centre, NY

Disclosure: Dr. Jeret serves on the speakers' bureau of Forest Pharmaceuticals, Inc.

To the Editor: The authors of the AAN's guideline update primarily set out to use evidence-based methodology to reduce variations in BD determination.¹ Although we agree with Wijdicks et al. that severe limitations remain in the scientific, evidence-based knowledge of this neurologic condition and its accurate diagnosis, classifying the guidelines as evidence-based raises the following concerns.

The Uniform Determination of Death Act (UDDA) states that death is to be determined in accordance with accepted medical standards. These standards must confirm that the UDDA brain criterion of death has been met. Wijdicks et al. should reliably establish the irreversible cessation of all functions of the entire brain including the brainstem, yet neither "irreversibility" nor "function of the brain" (or "of the entire brain") is defined. Both of these terms have engendered unresolved controversies. The Subcommittee does not identify the gold standard by which sensitivity, specificity, and predictive accuracy of the guidelines as a diagnostic tool are measured, with respect to either the irreversibility or the totality aspects. This gold standard does not and will never exist. Therefore, diagnostic guidelines for BD are inherently unable to be validated through an evidence-based methodology.

Critical elements in the guidelines received evidence level "U" including safety of apnea test, time interval necessary to ascertain irreversibility of clinical examination findings, and interpretation of complex coordinated movements of supraspinal vs spinal origin. Guidelines largely relying on expert consensus rather than empirical facts should respect diversity of views.¹⁰

The lack of reports showing BD recovery following BD determination is a spurious form of validation, given that in nearly all cases either support is stopped or organs are harvested upon the diagnosis. Medico-legal concerns may also hamper submission of recovery cases to medical journals. There have been calls for editorial censorship of articles that heighten public doubts about death criteria for organ donation.¹¹ Finally, the bias in selecting supporting vs opposing articles of similar evidence level and excluding non-English articles to answer the 5 critical questions can weaken the scientific authority of the guidelines.

We agree with Dr. Wijdicks' follow-up commentary¹²: "So, what are neurologists confirming? If documentation of a loss of all neuronal function is the ultimate goal for the definition of brain death, the

goal is not attainable because no confirmatory test can provide such documentation with certainty."

The same could be said about the clinical criteria, the "accuracy" of which is simply declared, not scientifically demonstrated. Concern regarding the validity of the clinical criteria has been reinforced by a recent report of 2 cases of well-documented clinical BD with return of spontaneous respiration during the period of preparation for organ harvesting.¹³

D. Alan Shewmon, Sylmar, CA; Joseph L. Verheijde, Mohamed Y. Rady, Phoenix, AZ

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Reply from the Authors: We generally agree with Dr. Machado that confirmatory tests should be "safe, accurate, and inexpensive." However, none are. His study of MEP and ERG adds little value because evoked potentials are absent in patients without meeting the criteria of BD. More ancillary tests only lead to more ambiguity.¹² Dr. Jeret continues to believe that the apnea test is a dangerous procedure, which has not been our experience. We have recently identified predictors for failing the apnea test and this may help in anticipating or even resolving problems.¹⁴

With our exhaustive review of the BD literature, we expected that those who reject brain death—even cardiac death—would use this opportunity to point out the lack of evidence regarding the clinical diagnosis of BD. Dr. Shewmon has completely rejected neurologic criteria for BD. He also recently suggested placing a warning on organ donor cards to indicate that transplant surgeons may take the cardholders' organs before the cardholder has died.¹⁵ Correspondents Drs. Verheijde and Rady have observed that organ donation has been "a concealed practice of physician assisted death."¹⁶

Drs. Shewmon et al. are mistaken. The gold standard is not the UDDA but a neurologic examination and irreversible loss of all brainstem function. We did not claim that the clinical examination of BD implies loss of all neuronal function. The medical community acknowledges that a permanently ventilated, apneic, poikilothermic, polyuric, comatose patient with no brainstem reflexes, loss of vascular tone, incremental need for vasopressors, and unstable cardiac rhythm resulting in cardiac arrest—often within days—is dead. After the diagnosis of BD, an amplified inflammatory response with apoptosis in multiple organs is rapidly compromising function. If that does not satisfy Drs. Shewmon, Verheijde, and Rady, then nothing else will.

BD can be justified both on empirical and biologic grounds. Moreover, there are over 50 years of patient data and clinical experience with no scientific

data to discount the clinical criteria of BD. All “recovered” adult cases reported in the literature and those in the media are suspect due to presence of confounders, no detailed description of testing, or no mention of the apnea test.¹⁷ Even the most recent cases had several glaring confounders which the authors from University of Calgary all recognize but not Drs. Shewmon, Rady, and Verheijde. It remains unclear whether the “return of respirations” was not simply ventilator autcycles, because repeat apnea tests were not done. Most importantly, no physician should determine BD in patients with a (possible reversible) septic shock or rapidly proceed with testing in patients seen soon after arrival in the emergency department.¹³ In addition, physician errors in neurologic assessment cannot be excluded. Moreover, for Shewmon et al. to imply that there are more and true cases of recovery that have difficulty getting published is a perplexing, new, and unsubstantiated claim.

Eelco F.M. Wijdicks, Rochester, MN; Panayiotis N. Varelas, Detroit, MI; Gary S. Gronseth, Kansas City, KS; David M. Greer, Boston, MA

Disclosure: See original article for full disclosure list.

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CORRECTION

Magnetic resonance spectroscopy biomarkers in premanifest and early Huntington disease

In the article “Magnetic resonance spectroscopy biomarkers in premanifest and early Huntington disease” by A. Sturrock et al. (*Neurology*® 2010;75:1702–1710), the author affiliations should have read as follows: “From the Centre for Molecular Medicine & Therapeutics (A.S., M.R.H., B.R.L.), Vancouver, BC, Canada; Department of Medical Genetics (J.D., R.D.S., A.J.C., S.C.) and UBC MRI Research Centre (C.L., A.L.M.), University of British Columbia, Vancouver, Canada; Department of Neurology (N.B., R.R.), University of Münster, Münster, Germany; and UCL Institute of Neurology (S.J.T.), University College London, Queen Square, London, UK.” The authors regret the error.

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