

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

BRAIN DEATH DETERMINATION / APNEA TESTING

SUMMARY

Brain death occurs as a result of absent cerebral blood flow secondary to traumatic injury or critical illness. Brain death determination is most commonly confirmed by clinical neurologic examination in conjunction with a positive apnea test (lack of spontaneous respiratory efforts in the presence of an elevated PaCO₂) and requires independent brain death determinations by two licensed physicians. In specific clinical situations, confirmatory tests may be indicated.

RECOMMENDATIONS

- **Level 1**
 - **None**
- **Level 2**
 - **Brain death will be confirmed by two physicians licensed in the State of Florida.**
 - **The determination of brain death should be made by a combination of clinical neurologic examination and apnea test. Confirmatory tests may be performed at the discretion of the physicians involved.**
 - **Documentation of brain death should include the following information:**
 1. **Etiology and irreversibility of the patient's coma and overall clinical condition**
 2. **Absent pupillary light response**
 3. **Absent corneal reflexes**
 4. **Absent oculovestibular reflexes**
 5. **Absent gag reflex**
 6. **Absent motor response or grimace to a noxious pain stimulus**
 7. **Absent spontaneous respiration despite a PaCO₂ ≥ 60 mmHg**
 8. **Justification for and result of additional confirmatory test(s)**
 9. **Findings of repeat neurologic examination**
 - **Pre-oxygenation as well as correction of hypotension and metabolic acidosis should be performed prior to during apnea testing.**

INTRODUCTION

By the Uniform Determination of Death Act, "death" is defined as either "(1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brainstem..."(1). Brain death, defined as the absence of clinical brain function when the proximate cause is known and demonstrably irreversible, is commonly encountered in the ICU setting following severe traumatic brain injury, aneurysmal subarachnoid hemorrhage, blunt carotid injury, hypoxic-ischemic brain insults, fulminant hepatic failure, or severe hypoperfusion (2,3). Brain death occurs when intracranial pressure (ICP) exceeds cerebral perfusion pressure (CPP), resulting in cessation of cerebral blood flow and oxygen delivery. The determination of brain death has significant

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

legal and ethical implications, and should be performed and documented carefully. Guidelines for the determination of brain death have previously been published. In 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research recommended the use of confirmatory tests in addition to clinical neurologic examination and emphasized the requirement to rule out shock as a condition that might interfere with the accurate diagnosis of brain death (2). In 1995, the American Academy of Neurology conducted an evidence-based medicine review of the available literature and published clinical guidelines for brain death determination (3). Neither the State of Florida nor Orlando Health mandates the use of specific tests for determining brain death, but leaves this decision up to the physician (4,5). For a patient to be determined "brain dead" according to the Florida State Statutes, two licensed physicians must certify that the patient meets accepted criteria as mandated below:

382.009 Recognition of brain death under certain circumstances.—(4)

(1) For legal and medical purposes, where respiratory and circulatory functions are maintained by artificial means of support so as to preclude a determination that these functions have ceased, the occurrence of death may be determined where there is the irreversible cessation of the functioning of the entire brain, including the brain stem, determined in accordance with this section.

(2) Determination of death pursuant to this section shall be made in accordance with currently accepted reasonable medical standards by two physicians licensed under chapter 458 or chapter 459. One physician shall be the treating physician, and the other physician shall be a board-eligible or board-certified neurologist, neurosurgeon, internist, pediatrician, surgeon, or anesthesiologist.

CLINICAL NEUROLOGIC EXAMINATION

The clinical neurologic examination, supplemented in appropriate clinical situations by performance of one or more confirmatory tests, remains the standard for the determination of brain death (3,6,7). Declaration of brain death requires not only a careful clinical examination, but also:

- Establishment of the cause of coma
- Ascertainment of irreversibility
- Resolution of any misleading clinical neurologic signs
- Recognition of possible confounding factors
- Interpretation of neuroimaging studies
- Performance of any confirmatory laboratory tests deemed necessary

A clinical neurologic examination to determine the presence of brain death can only proceed if the following four prerequisites have been met:

1. Clinical or neuroimaging evidence of an acute central nervous system (CNS) catastrophe that is compatible with the diagnosis of brain death.
 - Typically, computed tomography (CT) of the brain demonstrates a catastrophic brain injury.
 - A normal CT scan should raise doubt as to the diagnosis of brain death and lead to further imaging studies.
2. Exclusion of complicating medical conditions that may confound clinical assessment such as:
 - Severe electrolyte, acid-base or endocrine disorders
 - Refractory shock (systolic blood pressure < 90 mmHg)
 - Guillain-Barré syndrome
 - "Locked-in" syndrome
 - A consequence of destruction of the pons, typically due to basilar artery thrombosis, in which the patient cannot move the limbs, grimace, or swallow, but retains consciousness, voluntary blinking, and vertical eye movements.
3. Absence of drug intoxication, poisoning, sedative, or neuromuscular blocking agents.
 - Drug screens may be needed when appropriate
 - Naloxone or flumazenil may be administered to document that no lingering effect of narcotics or benzodiazepines is present

4. Absence of severe hypothermia, defined as a core temperature < 32° C (90° F).
 - Pupillary response to light is lost at core temperatures of 28° to 32° C
 - Brainstem reflexes disappear when core temperature drops below 28° C
 - A core body temperature of ≥ 36° C is recommended

A comprehensive clinical neurologic examination includes documentation of the presence of coma, the absence of brainstem reflexes, and apnea. Each of these three components is described in further detail below:

1. **Coma or unresponsiveness**

- a. No cerebral motor response to pain in all extremities (nailbed pressure and supraorbital pressure)

2. **Absence of brainstem reflexes**

The examination of brainstem reflexes requires the assessment of reflex pathways in the mesencephalon, pons, and medulla oblongata. As brain death occurs, patients lose their brainstem reflexes in a rostral-to-caudal direction with the medulla oblongata being the last part of the brain to cease function. Complete cessation of all brainstem reflexes may require several hours to develop.

- **Pupils (CN II & III)**
 - Round or oval pupils measuring 4 to 9 mm with no response to bright light
- **Ocular movement (CN III, VI & VIII)**
 - No oculocephalic movements should be elicited by rapid turning of the head (performed only when no fracture or instability of the cervical spine is present)
 - No deviation of the eyes to cold caloric stimulation
 - i. Each tympanum should be irrigated with ice water after the head has been tilted 30 degrees.
 - ii. Allow 1 minute after injection and at least 5 minutes between testing on each side.
 - iii. The presence of clotted blood or cerumen within the external auditory canal may diminish the stimulatory response.
 - iv. There should be no tonic deviation toward the cold stimulus.
- **Facial sensation and facial motor response (CN V & VII)**
 - No corneal reflex to touch of the corneal edge by a swab
 - No jaw reflex
 - No grimacing to deep pressure on nail bed, supraorbital ridge, or temporomandibular joint
- **Pharyngeal and tracheal reflexes (CN IX & X)**
 - No response to stimulation of the posterior pharynx with a tongue blade
 - No cough response to bronchial suctioning (moving the endotracheal tube back and forth may not be an adequate stimulus)

3. **Apnea (see below)**

APNEA TEST

Apnea must be demonstrated as part of any brain death declaration. Apneic diffusion oxygenation is the procedure most commonly utilized to maintain oxygenation during apnea testing. Preoxygenation eliminates the respiratory nitrogen stores, accelerates the transport of oxygen, and significantly decreases the risk of hypoxic complications during the trial (7). The threshold of maximal stimulation of the respiratory centers in the medulla oblongata has been arbitrarily set in the United States at a partial pressure of arterial carbon dioxide (PaCO₂) of 60 mmHg (6-9). In patients with baseline hypercarbia (such as in chronic obstructive pulmonary disease), the criteria are modified to assume maximal stimulation at a PaCO₂ 20 mmHg above baseline (6-9). At these levels of hypercarbia, patients with an intact brainstem can be expected to demonstrate spontaneous respirations.

Once the patient has been found to have a clinical neurologic examination consistent with brain death, and assuming that there are no contraindications, an apnea test is performed. This test, by definition, is performed solely in patients who are critically ill with varying degrees of organ dysfunction. As a result, apnea testing is associated with a significant risk of complications including acidosis (63%), hypotension (24%), hypoxemia (12%), and cardiac arrhythmia (3%), most commonly due to inadequate preoxygenation and acidosis (10,11). Thus, contraindications to apnea testing include hemodynamic instability (SBP < 90 mmHg), acute respiratory failure requiring high-level ventilatory support and/or positive end-expiratory pressure (PEEP), metabolic acidosis, and requirement for increasing doses of vasopressors (8). If present, these abnormalities should be corrected before attempting an apnea test. By so doing, the risk of complications is significantly reduced. If an apnea test cannot be safely performed, one of the other confirmatory tests, most commonly technetium-99m cerebral blood flow imaging, should be utilized.

The apnea test is classically described as being performed after disconnecting the patient from the ventilator with 6-8 L/minute of oxygen being provided via the endotracheal tube through a catheter placed at the carina (3,6,7,8). Passage of the oxygen catheter through an end-tidal capnography detector placed on the end of the endotracheal tube provides a more sensitive method for detecting respiratory attempts than visual observation of the chest wall for movement alone. In a patient with an intact brainstem, spontaneous respiratory efforts are most likely to develop early in the test as the patient's carbon dioxide level rises. If the apnea test is performed with the patient on a mechanical ventilator (with the rate at zero), spinal reflex respiratory-like movements can occur despite brainstem failure and may, along with hyperdynamic cardiac contraction, trigger the patient's ventilator if the sensitivity is set too low, giving the false impression of spontaneous breathing efforts (12). Such movements, however, typically occur late in the test as a result of acidosis and/or hypoxemia, do not result in significant tidal volumes, and will show no change in the patient's end-tidal carbon dioxide waveform.

When appropriate, a 10 minute apnea test is performed according to the "Apnea Test Procedure" following pre-oxygenation for at least 10 minutes with a FiO₂ of 1.0 and normalization of the patient's PaCO₂ to 40 mmHg. Reducing the ventilatory rate to 10 breaths/minute for 5 minutes prior to the test is usually sufficient to normalize the patient's PaCO₂. The apnea test should be aborted if the patient becomes hemodynamically unstable or develops an SaO₂ <85% during the test. The certifying physician must be present throughout this study to document the presence of apnea as well as to be available to intervene should the patient become hemodynamically unstable during the test. Patients with an intact brainstem can be expected to breathe within the first few minutes of the test as hypercarbia typically develops at a rate of 3 mmHg per minute (6,7). Spontaneous body movements may be observed during the apnea test despite the absence of cerebral blood flow (8). These movements are generated by the spine, typically in response to physical stimulation. As a result, the patient should not be stimulated in any way during the apnea trial to avoid the development of spontaneous movements that might interfere with accurate interpretation of the test's results.

A patient is considered to meet apnea test criteria for brain death if:

1) No spontaneous respiratory efforts were witnessed during the test (as evidenced by physical attempts to inspire or documentation of end-tidal carbon dioxide by bedside waveform analysis)

AND

2) The patient's PaCO₂ is in excess of 60 mmHg (or at least 20 mmHg above baseline)

In the presence of these two findings, and in conjunction with an appropriate clinical examination, the patient meets accepted criteria for brain death and such documentation is made in the patient's medical record. Only one apnea test need be performed to confirm brain death. Once two independent determinations of brain death have been made and each physician has documented their findings and opinion in the medical record, discontinuation of life support may occur.

CONFIRMATORY LABORATORY TESTS

A confirmatory test is not mandatory, but is desirable in patients in whom specific components of clinical testing cannot be reliably performed or evaluated. The following confirmatory test findings are listed in order of the most sensitive test first.

1. Conventional angiography
No intracerebral filling at the level of the carotid bifurcation or circle of Willis. The external carotid circulation is patent, and filling of the superior longitudinal sinus may be delayed.
2. Electroencephalography
No electrical activity during at least 30 minutes of recording that adheres to the minimal technical criteria for EEG recording in suspected brain death.
3. Transcranial Doppler ultrasonography
Small systolic peaks in early systole without diastolic flow or reverberating flow, indicating very high vascular resistance associated with greatly increased intracranial pressure. Ten percent of patients may not have temporal insonation windows precluding use of this technique for determining brain death.
4. Technetium-99m cerebral blood flow scan
No uptake of isotope in brain parenchyma ("hollow skull phenomenon").
5. Somatosensory evoked potentials
Bilateral absence of N20-P22 response with median nerve stimulation.

CLINICAL CONDITIONS THAT MAY INTERFERE WITH THE DIAGNOSIS OF BRAIN DEATH

The following physical conditions may interfere with the clinical diagnosis of brain death (3). In such situations, confirmatory tests are recommended as clinical neurologic examination alone may not be accurate.

- Severe facial trauma
- Preexisting pupillary abnormalities
- Toxic levels of any sedative drugs, aminoglycosides, tricyclic antidepressants, anticholinergics, antiepileptic drugs, chemotherapeutic agents, or neuromuscular blocking agents (16)
- Sleep apnea or severe pulmonary disease resulting in chronic retention of carbon dioxide (PaCO₂)

CLINICAL OBSERVATIONS COMPATIBLE WITH THE DIAGNOSIS OF BRAIN DEATH

The following physical findings are occasionally seen and should not be misinterpreted as evidence for brainstem function (3):

- Spontaneous limb movements other than pathologic flexion or extension response
- Respiratory-like movements (shoulder elevation and adduction, back arching, intercostals expansion without significant tidal volumes)
- Sweating, blushing, tachycardia
- Normal blood pressure without pharmacologic support or sudden increases in blood pressure
- Absence of diabetes insipidus
- Deep tendon reflexes; superficial abdominal reflexes; triple flexion response
- Babinski reflex

MEDICAL RECORD DOCUMENTATION

Following the determination of brain death, appropriate documentation in the patient's medical record should be performed (3). This documentation should include the following components:

- Etiology and irreversibility of the patient's coma and overall clinical condition
- Absent pupillary light response and midsized pupils
- Absent corneal reflexes
- Absent oculovestibular reflexes
- Absent gag reflex

- Absent motor response or grimace to a noxious pain stimulus
- Absent spontaneous respiration despite a PaCO₂ ≥ 60 mmHg (when apnea testing can be safely or appropriately performed)
- Justification for and result of additional confirmatory tests (if indicated)
- Findings of repeat neurologic examination (performed by a second licensed physician)

LITERATURE REVIEW

Wijdicks et al. reviewed 228 patients (195 adults, 33 children) who were declared brain dead at the Mayo Clinic from 1996-2007 (13). All patients were hypotensive requiring vasopressor support. Diabetes insipidus requiring vasopressin was present in 61%. Brain death was declared within 24 hours of injury in 30% and within 72 hours of injury in 62%. An apnea test could not be performed in 7% of patients due to hemodynamic instability or poor oxygenation. Once begun, the apnea test was aborted in 3% due to hypotension or hypoxia. Hypotension was identified as a defining characteristic of the transition to brain death. Polyuria requiring vasopressin was similarly diagnostic. The authors concluded that the apnea test is a safe and effective method for determining the presence of brain death.

Greer et al. performed a review of the brain death determination guidelines of the top 50 neurology/neurosurgery institutions in the United States as identified by *US News and World Report* in 2006 (14). Although only one of the 38 institutions who provided their guidelines did not require performance of an apnea test, there was significant variation among the guidelines with respect to other aspects of the brain death determination process. The authors concluded that the lack of detail and consistency in the approach to brain death determination could lead to false positive declarations of brain death as well as delays in organ procurement. In response to this study, Powell et al. cite the New York State guidelines which advocate 1) two clinical examinations 6 hours apart followed by a single apnea test, 2) a confirmatory ancillary test when clinical examination is uncertain, and 3) involvement of at least one physician who is experienced and privileged in the determination of brain death (15).

Molina et al. report three patients who were declared clinically brain dead after being placed in a pentobarbital coma to treat elevated intracranial pressures (16). All three patients were found to have significantly elevated post-mortem pentobarbital levels that would have precluded use of a clinical examination to determine brain death. The authors caution against the use of clinical determination of brain death in such patients due to the prolonged half-life of pentobarbital and advocate the use of cerebral blood flow studies to confirm the absence of cerebral blood flow.

REFERENCES

1. Uniform Determination of Death Act, 12 Uniform Laws Annotated (U.L.A.) 589 (West 1993 and West Supp. 1997).
2. Guidelines for the determination of death: Report of the medical consultants on the diagnosis of death to the president's commission for the study of ethical problems in medicine and biomedical and behavioral research. *JAMA* 1981; 246:2184-2186.
3. Practice parameters: Determining brain death in adults. American Academy of Neurology. *Neurology* 1995; 45:1012-1014.
4. 2004 Florida State Statutes. <http://www.leg.state.fl.us/statutes>.
5. Withholding and Withdrawal of Life Sustaining Equipment: Patient with Brain Death for Adults and Minors. Orlando Regional Healthcare Policy #1725. Revision date 1/04.
6. Wijdicks EFM. Determining brain death in adults. *Neurology* 1995; 45:1003-1011.
7. Wijdicks EFM. The diagnosis of brain death. *NEJM* 2001; 344:1215-1221.
8. Wijdicks EFM. 10 questions about the clinical determination of brain death. *The Neurologist* 2007; 13: 380-381.
9. Belsh JM, Blatt R, Schiffman PL. Apnea testing in brain death. *Arch Intern Med* 1986; 146:2385-2388.
10. Goudreau JL, Wijdicks EFM, Emery SF. Complications during apnea testing in the determination of brain death: Predisposing factors. *Neurology* 2000; 55:1045-1048.
11. Sapsosnik G, Rizzo G, Vega A, Sabbatiello R, Deluca JL. Problems associated with the apnea test in the diagnosis of brain death. *Neurology India* 2004; 52:342-345.
12. Willatts SM, Drummond G. Brainstem death and ventilator trigger settings. *Anaesthesia* 2000; 55:676-677.
13. Wijdicks EFM, Rabinstein AA, Manno EM, Atkinson JD. Pronouncing brain death: Contemporary practice and safety of the apnea test. *Neurology* 2008; 71:1240-1244.
14. Greer DM, Varelas PN, Haque S, Wijdicks EFM. Variability of brain death determination guidelines in leading US neurologic institutions. *Neurology* 2008; 70:284-289.
15. Powell T, Zisfein J, Halerin J. Variability of brain death determination guidelines in leading US neurologic institutions (letter to the editor). *Neurology* 2008; 70:1839-1840.
16. Molina DK, McCutcheon JR, Rulon JJ. Head injuries, pentobarbital, and the determination of death. *Am J Forensic Med Path* 2009; 30:75-77.

APNEA TEST PROCEDURE

