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Clinical Report—Guidelines for the Determination of Brain Death in Infants and Children: An Update of the 1987 Task Force Recommendations

abstract

FREE

OBJECTIVE: To review and revise the 1987 pediatric brain death guidelines.

METHODS: Relevant literature was reviewed. Recommendations were developed using the GRADE system.

CONCLUSIONS AND RECOMMENDATIONS: (1) Determination of brain death in term newborns, infants and children is a clinical diagnosis based on the absence of neurologic function with a known irreversible cause of coma. Because of insufficient data in the literature, recommendations for preterm infants less than 37 weeks gestational age are not included in this guideline.

(2) Hypotension, hypothermia, and metabolic disturbances should be treated and corrected and medications that can interfere with the neurologic examination and apnea testing should be discontinued allowing for adequate clearance before proceeding with these evaluations.

(3) Two examinations including apnea testing with each examination separated by an observation period are required. Examinations should be performed by different attending physicians. Apnea testing may be performed by the same physician. An observation period of 24 hours for term newborns (37 weeks gestational age) to 30 days of age, and 12 hours for infants and chi (> 30 days to 18 years) is recommended. The first examination determines the child has met the accepted neurologic examination criteria for brain death. The second examination confirms brain death based on an unchanged and irreversible condition. Assessment of neurologic function following cardiopulmonary resuscitation or other severe acute brain injuries should be deferred for 24 hours or longer if there are concerns or inconsistencies in the examination.

(4) Apnea testing to support the diagnosis of brain death must be performed safely and requires documentation of an arterial $Paco_2$ 20 mm Hg above the baseline and ≥ 60 mm Hg with no respiratory effort during the testing period. If the apnea test cannot be safely completed, an ancillary study should be performed.

(5) Ancillary studies (electroencephalogram and radionuclide cerebral blood flow) are not required to establish brain death and are not a substitute for the neurologic examination. Ancillary studies may be us d to assist the clinician in making the diagnosis of brain death (i) when components of the examination or apnea testing cannot be completed safely due to the underlying medical condition of the patient; (ii) if there is uncertainty about the results of the neurologic examination; (iii) if a medication effect may be present; or (iv) to reduce the inter-examination observation period. When ancillary studies are used, a second clinical examination and apnea test should be performed and components that can be completed must remain consistent with brain death. In this instance the observation interval may be shortened and the second neurologic examination and apnea test (or all components that are able to be completed safely) can be performed at any time thereafter.

(6) Death is declared when the above criteria are fulfilled. *Pediatrics* 2011;128: e720–e740

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KEY WORDS

apnea testing, brain death, cerebral blood flow, children, electroencephalography, infants, neonates, pediatrics

ABBREVIATIONS

EEG—electroencephalogram
CBF—cerebral blood flow
CT—computed tomography
MRI—magnetic resonance imaging
ETT—endotracheal tube
CPAP—continuous positive airway pressure
ICP—intracranial pressure
ECS—electrocerebral silence

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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INTRODUCTION

In 1987, guidelines for the determination of brain death in children were published by a multi-society task force.[1,2] These consensus based guidelines were developed because existing guidelines from the President's Commission failed to adequately address criteria to determine brain death in pediatric patients. They emphasized the importance of the history and clinical examination in determining the etiology of coma so that correctable or reversible conditions were eliminated. Additionally, age-related observation periods and the need for specific neurodiagnostic tests were recommended for children younger than 1 year of age. In children older than 1 year, it was recommended that the diagnosis of brain death could be made solely on a clinical basis and laboratory studies were optional. Little guidance was provided to determine brain death in neonates less than 7 days of age because of limited clinical experience and lack of sufficient data.

These guidelines generally have been accepted and used to guide clinical practice; however they have not been reviewed nor revised since originally published. Several inherent weaknesses have been recognized including: (1) limited clinical information at the time of publication; (2) uncertainty concerning the sensitivity and specificity of ancillary testing; (3) biological rationale for the use of age-based criteria; and (4) little direction as to whether, when and how the diagnosis of brain death could be made in neonates. Despite national and legal acceptance of the concept of brain death, these limitations have resulted in the lack of a standardized approach to determining brain death in children.[3–9] These issues are not unique to infants and children[10] nor limited to the United States. The American Academy of Neurology published guidelines to determine brain death in adults in 1995 which have been revised in 2010.[11,12] Additionally, guidelines to determine brain death in adults and children have been published in Canada.[13]

The Society of Critical Care Medicine (SCCM) and the Section on Critical Care and Section on Neurology of the American Academy of Pediatrics (AAP), in conjunction with the Child Neurology Society (CNS), formed a multidisciplinary committee of medical and surgical subspecialists under the auspices of the American College of Critical Care Medicine (ACCM) to review and revise the 1987 guidelines. Its purpose was to review the neonatal and pediatric literature from 1987, including any prior relevant literature, and update recommendations regarding appropriate examination criteria and use of ancillary testing to diagnose brain death in neonates, infants and children. The committee was also charged with developing a checklist to provide guidance and standardization to document brain death. Uniformity in the determination of brain death should allow physicians to pronounce brain death in pediatric patients in a more precise and orderly manner and ensure that all components of the examination are performed and appropriately documented.

Tables 1–3 of this publication contain the committee's updated recommendations, the GRADE classification system, and clinical and neurologic examination criteria for brain death. Appendices 1–7 provide additional information concerning the diagnosis of brain death in children. Appendix 1 (check list) and Appendix 2 (pharmacological data for the time interval to testing after medication discontinuation) provide additional resources to aid the clinician in diagnosing brain death. Appendix 3 summarizes data regarding apnea testing. Appendices 4–6 provide data on the diagnostic yield of ancillary testing, specifically electroencephalography (EEG), and radionuclide cerebral blood flow (CBF) studies. Appendix 7 compares the 1987 guideline's criteria to the revised recommendations. Appendix 8 provides an algorithm for the determination of brain death in infants and children.

This update affirms the definition of death as stated in the 1987 pediatric guidelines. This definition had been established by multiple organizations including the American Medical Association, the American Bar Association, the National Conference of Commissioners on Uniform State Laws, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research and the American Academy of Neurology as follows: "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with accepted medical standards."[1]

METHODS

A multidisciplinary committee composed of physicians and nurses with expertise in pediatrics, pediatric critical care, neonatology, pediatric neurology and neurosurgery, nuclear medicine, and neuroradiology was formed by the SCCM and the AAP to update the guidelines for the diagnosis of pediatric brain death. The committee was divided into three working groups, each charged with reviewing the literature on brain death in neonates, infants and children for the following specific areas: (1) examination criteria and observation periods; (2) ancillary testing; and (3) declaration of death by medical personnel including legal and ethical implications.

A Medline search of relevant literature published from January 1987 to June

TABLE 1 Summary Recommendations for the Diagnosis of Brain Death in Neonates, Infants, and Children

Recommendation	Evidence Score	Recommendation Score
1. Determination of brain death in neonates, infants and children relies on a clinical diagnosis that is based on the absence of neurologic function with a known irreversible cause of coma. Coma and apnea must coexist to diagnose brain death. This diagnosis should be made by physicians who have evaluated the history and completed the neurologic examinations.	High	Strong
2. Prerequisites for initiating a brain death evaluation		
a. Hypotension, hypothermia, and metabolic disturbances that could affect the neurological examination must be corrected prior to examination for brain death.	High	Strong
b. Sedatives, analgesics, neuromuscular blockers, and anticonvulsant agents should be discontinued for a reasonable time period based on elimination half-life of the pharmacologic agent to ensure they do not affect the neurologic examination. Knowledge of the total amount of each agent (mg/kg) administered since hospital admission may provide useful information concerning the risk of continued medication effects. Blood or plasma levels to confirm high or supratherapeutic levels of anticonvulsants with sedative effects that are not present should be obtained (if available) and repeated as needed or until the levels are in the low to mid therapeutic range.	Moderate	Strong
c. The diagnosis of brain death based on neurologic examination alone should not be made if supratherapeutic or high therapeutic levels of sedative agents are present. When levels are in the low or in the mid-therapeutic range, medication effects sufficient to affect the results of the neurologic examination are unlikely. If uncertainty remains, an ancillary study should be performed.	Moderate	Strong
d. Assessment of neurologic function may be unreliable immediately following cardiopulmonary resuscitation or other severe acute brain injuries and evaluation for brain death should be deferred for 24 to 48 hours or longer if there are concerns or inconsistencies in the examination.	Moderate	Strong
3. Number of examinations, examiners and observation periods		
a. Two examinations including apnea testing with each examination separated by an observation period are required.	Moderate	Strong
b. The examinations should be performed by different attending physicians involved in the care of the child. The apnea test may be performed by the same physician, preferably the attending physician who is managing ventilator care of the child.	Low	Strong
c. Recommended observation periods:		
(1) 24 hours for neonates (37 weeks gestation to term infants 30 days of age)	Moderate	Strong
(2) 12 hours for infants and children ($>$ 30 days to 18 years).		
d. The first examination determines the child has met neurologic examination criteria for brain death. The second examination, performed by a different attending physician, confirms that the child has fulfilled criteria for brain death.	Moderate	Strong
e. Assessment of neurologic function may be unreliable immediately following cardiopulmonary resuscitation or other severe acute brain injuries and evaluation for brain death should be deferred for 24 to 48 hours or longer if there are concerns or inconsistencies in the examination.	Moderate	Strong
4. Apnea testing		
a. Apnea testing must be performed safely and requires documentation of an arterial $Paco_2$ 20 mm Hg above the baseline $Paco_2$ and $\geq$ 60 mm Hg with no respiratory effort during the testing period to support the diagnosis of brain death. Some infants and children with chronic respiratory disease or insufficiency may only be responsive to supranormal $Paco_2$ levels. In this instance, the $Paco_2$ level should increase to $\geq$ 20 mm Hg above the baseline $Paco_2$ level.	Moderate	Strong
b. If the apnea test cannot be performed due to a medical contraindication or cannot be completed because of hemodynamic instability, desaturation to $<$ 85%, or an inability to reach a $Paco_2$ of 60 mm Hg or greater, an ancillary study should be performed.	Moderate	Strong
5. Ancillary studies		
a. Ancillary studies (EEG and radionuclide CBF) are not required to establish brain death unless the clinical examination or apnea test cannot be completed	Moderate	Strong
b. Ancillary studies are not a substitute for the neurologic examination.	Moderate	Strong
c. For all age groups, ancillary studies can be used to assist the clinician in making the diagnosis of brain death to reduce the observation period or when (i) components of the examination or apnea testing cannot be completed safely due to the underlying medical condition of the patient; (ii) if there is uncertainty about the results of the neurologic examination; or (iii) if a medication effect may interfere with evaluation of the patient. If the ancillary study supports the diagnosis, the second examination and apnea testing can then be performed. When an ancillary study is used to reduce the observation period, all aspects of the examination and apnea testing should be completed and documented.	Moderate	Strong
d. When an ancillary study is used because there are inherent examination limitations (ie, i to iii), then components of the examination done initially should be completed and documented.	High	Strong
e. If the ancillary study is equivocal or if there is concern about the validity of the ancillary study, the patient cannot be pronounced dead. The patient should continue to be observed until brain death can be declared on clinical examination criteria and apnea testing, or a follow-up ancillary study can be performed to assist with the determination of brain death. A waiting period of 24 hours is recommended before further clinical reevaluation or repeat ancillary study is performed. Supportive patient care should continue during this time period.	Moderate	Strong
6. Declaration of death		
a. Death is declared after confirmation and completion of the second clinical examination and apnea test.	High	Strong
b. When ancillary studies are used, documentation of components from the second clinical examination that can be completed must remain consistent with brain death. All aspects of the clinical examination, including the apnea test, or ancillary studies must be appropriately documented.	High	Strong
c. The clinical examination should be carried out by experienced clinicians who are familiar with infants and children, and have specific training in neurocritical care.	High	Strong

The "evaluation score" is based on the strength of the evidence available at the time of publication.
The "recommendation score" is the strength of the recommendations based on available evidence at the time of publication. Scoring guidelines are listed in Table 2.

TABLE 2 Grading of Recommendations Assessment, Development and Evaluation (GRADE) System[14-18]

1. Classification of evidence	
Grade	
A. High	Further research is very unlikely to change our confidence in the estimate of effect
B. Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
C. Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
D. Very low	Any estimate of effect is very uncertain
2. Recommendations: The strength of a recommendation reflects the extent to which we can be confident that desirable effects of an intervention outweigh undesirable effects.	
Strong	When the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not. (a) For patients—most people in your situation would want the recommended course of action and only a small proportion would not (b) For clinicians—most patients should receive the recommended course of action (c) For policy makers—the recommendation can be adopted as a policy in most situations
Weak	Evidence suggests that desirable and undesirable effects are closely balanced or the quality of evidence is low. (a) For patients—most people in your situation would want the recommended course of action, but many would not (b) For clinicians—you should recognize that different choices will be appropriate for different patients and you must help each patient to arrive at a management decision consistent with his or her values and preferences. (c) For policy makers—policy making will require substantial debate and involvement of many stakeholders
No specific recommendations	The advantages and disadvantages of the recommendations are equivalent or where there is insufficient evidence on which to formulate a recommendation

2008 was conducted. Key words included: brain death, neurologic death, neonatal, pediatric, cerebral blood flow, electroencephalography, apnea test, and irreversible coma with the subheading, "children." Additional articles cited in the post 1987 literature that were published prior to 1987 were also reviewed if they contained data relevant to this guideline. Abstracts and articles were independently reviewed and summarized by at least two individuals on each committee. Data were summarized into five categories: clinical examination, apnea testing, observation periods, ancillary tests, and other considerations.

Methodological issues regarding analysis of evidence warrant further discussion as they directly affected the decision of how information and recommendations about brain death are presented. No randomized control trials examining different strategies regarding the diagnosis of brain death exist. Standard evidence-based approaches for guidelines used by many organizations attempting to link the "strength of the evidence" to the "strength of the recommendations" therefore cannot be used in this instance. There is, however, considerable experiential consensus within observational studies in the pediatric population. Grading of Recommendations Assessment, Development and Evaluation (GRADE), a recently developed standardized methodological consensus-based approach, allows panels to evaluate the evidence and opinions and make recommendations.[14–17] GRADE uses 5 domains to judge the balance between the desirable and undesirable effect of an intervention. *Strong recommendations* are made when there is confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects. *Weak recommendations* indicate that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is less confident. *No specific recommendations* are made when the advantages and disadvantages of alternative courses of action are equivalent or where there is insufficient evidence on which to formulate a recommendation.[15,18] Table 2 outlines the GRADE methodology used in formulating recommendations for this guideline. Each committee member assigned a GRADE score for (i) the strength of evidence linked to a specific recommendation and (ii) indicated (*a*) "yes," (*b*) "no" or (*c*) "uncertain" for each of the six recommendations listed at the end of this report. By a priori consensus, the committee decided that a "strong" recommendation could only be made if greater than 80% of the committee members voted "yes"

TABLE 3 Neurologic Examination Components to Assess for Brain Death in Neonates, Infants and Children* Including Apnea Testing

Reversible conditions or conditions that can interfere with the neurologic examination must be excluded prior to brain death testing.
See text for discussion

1. **Coma. The patient must exhibit complete loss of consciousness, vocalization and volitional activity.**
   - Patients must lack all evidence of responsiveness. Eye opening or eye movement to noxious stimuli is absent.
   - Noxious stimuli should not produce a motor response other than spinally mediated reflexes. The clinical differentiation of spinal responses from retained motor responses associated with brain activity requires expertise.
2. **Loss of all brain stem reflexes including:**

Midposition or fully dilated pupils which do not respond to light.
Absence of pupillary response to a bright light is documented in both eyes. Usually the pupils are fixed in a midsize or dilated position (4–9 mm). When uncertainty exists, a magnifying glass should be used.

Absence of movement of bulbar musculature including facial and oropharyngeal muscles.
Deep pressure on the condyles at the level of the temporomandibular joints and deep pressure at the supraorbital ridge should produce no grimacing or facial muscle movement.

Absent gag, cough, sucking, and rooting reflex
The pharyngeal or gag reflex is tested after stimulation of the posterior pharynx with a tongue blade or suction device. The tracheal reflex is most reliably tested by examining the cough response to tracheal suctioning. The catheter should be inserted into the trachea and advanced to the level of the carina followed by 1 or 2 suctioning passes.

Absent corneal reflexes
Absent corneal reflex is demonstrated by touching the cornea with a piece of tissue paper, a cotton swab, or squirts of water. No eyelid movement should be seen. Care should be taken not to damage the cornea during testing.

Absent oculovestibular reflexes
The oculovestibular reflex is tested by irrigating each ear with ice water (caloric testing) after the patency of the external auditory canal is confirmed. The head is elevated to 30 degrees. Each external auditory canal is irrigated (1 ear at a time) with ~10 to 50 mL of ice water. Movement of the eyes should be absent during 1 minute of observation. Both sides are tested, with an interval of several minutes.

3. **Apnea. The patient must have the complete absence of documented respiratory effort (if feasible) by formal apnea testing demonstrating a $Paco_2$ ≥ 60 mm Hg and ≥ 20 mm Hg increase above baseline.**
   - Normalization of the pH and $Paco_2$, measured by arterial blood gas analysis, maintenance of core temperature > 35°C, normalization of blood pressure appropriate for the age of the child, and correcting for factors that could affect respiratory effort are a prerequisite to testing.
   - The patient should be preoxygenated using 100% oxygen for 5–10 minutes prior to initiating this test.
   - Intermittent mandatory mechanical ventilation should be discontinued once the patient is well oxygenated and a normal $Paco_2$ has been achieved.
   - The patient's heart rate, blood pressure, and oxygen saturation should be continuously monitored while observing for spontaneous respiratory effort throughout the entire procedure.
   - Follow up blood gases should be obtained to monitor the rise in $Paco_2$ while the patient remains disconnected from mechanical ventilation.
   - If no respiratory effort is observed from the initiation of the apnea test to the time the measured $Paco_2$ ≥ 60 mm Hg and ≥ 20 mm Hg above the baseline level, the apnea test is consistent with brain death.
   - The patient should be placed back on mechanical ventilator support and medical management should continue until the second neurologic examination and apnea test confirming brain death is completed.
   - If oxygen saturations fall below 85%, hemodynamic instability limits completion of apnea testing, or a $Paco_2$ level of ≥ 60 mm Hg cannot be achieved, the infant or child should be placed back on ventilator support with appropriate treatment to restore normal oxygen saturations, normocarbia, and hemodynamic parameters. Another attempt to test for apnea may be performed at a later time or an ancillary study may be pursued to assist with determination of brain death.
   - Evidence of any respiratory effort is inconsistent with brain death and the apnea test should be terminated.
4. **Flaccid tone and absence of spontaneous or induced movements, excluding spinal cord events such as reflex withdrawal or spinal myoclonus.**
   - The patient's extremities should be examined to evaluate tone by passive range of motion assuming that there are no limitations to performing such an examination (eg, previous trauma, etc) and the patient observed for any spontaneous or induced movements.
   - If abnormal movements are present, clinical assessment to determine whether or not these are spinal cord reflexes should be done.

* Criteria adapted from 2010 American Academy of Neurology criteria for brain death determination in adults (Wijdicks et al, 2010).

for a recommendation and that a "weak" recommendation was made if greater than 60% but less than 80% voted "yes." "No recommendation" was made if less than 60% of the committee voted "yes" for a specific recommendation. Table 1 summarizes GRADE recommendations and evidence scores.

The committee believes these revised diagnostic guidelines, summarized in Table 1 and a standardized checklist form (Appendix 1), will assist physicians in determining and documenting brain death in children. This should ensure broader acceptance and utilization of such uniform criteria. The committee recognizes that medical judgment of involved pediatric specialists will direct the appropriate course for the medical evaluation and diagnosis of brain death. The committee also recognizes that no national brain death law exists. State statutes and policy may restrict determination of brain death in certain circumstances. Physicians should become familiar with laws and policies in their respective institution. The committee also recognizes that variability exists for the age designation of pediatric trauma patients. In some states, the age of the pediatric trauma patient is defined as less than 14 years of age.

Trauma and intensive care practitioners are encouraged to follow state/local regulations governing the specified age of pediatric trauma patients. The committee believes these guidelines to be an important step in protecting the health and safety of all infants and children. These revised guidelines and accompanying checklist are intended to provide a framework to promote standardization of the neurologic examination and use of ancillary studies based on the evidence available to the committee at the time of publication.

TERM NEWBORNS (37 WEEKS GESTATIONAL AGE) TO CHILDREN 18 YEARS OF AGE

Definition of Brain Death and Components of the Clinical Examination (*Recommendation 1, Table 1 and Table 3*)

Brain death is a clinical diagnosis based on the absence of neurologic function with a known diagnosis that has resulted in irreversible coma. Coma and apnea must coexist to diagnose brain death. A complete neurologic examination that includes the elements outlined in Table 3 is mandatory to determine brain death with all components appropriately documented.

Prerequisites for Initiating a Clinical Brain Death Evaluation (*Recommendations 2a–d, Table 1*)

Determination of brain death by neurologic examination should be performed in the setting of normal age-appropriate physiologic parameters. Factors potentially influencing the neurologic examination that must be corrected before examination and apnea testing include: (1) shock or persistent hypotension based on normal systolic or mean arterial blood pressure values for the patient's age. Systolic blood pressure or MAP should be in an acceptable range (systolic BP not less than 2 standard deviations below age appropriate norm) based on age; (2) hypothermia; (3) severe metabolic disturbances capable of causing a potentially reversible coma including electrolyte/glucose abnormalities; (4) recent administration of neuromuscular blocking agents; and (5) drug intoxications including but not limited to barbiturates, opioids, sedative and anesthetic agents, antiepileptic agents, and alcohols. Placement of an indwelling arterial catheter is recommended to ensure that blood pressure remains within a normal range during the process of diagnosing brain death and to accurately measure $Paco_2$ levels during apnea testing.

Hypothermia is used with increasing frequency as an adjunctive therapy for individuals with acute brain injury.[19–22] Hypothermia has also been used following cardiac arrest to protect the brain because it reduces cerebral metabolic activity.[23–26] The clinician caring for critically ill infants and children should be aware of the potential impact of therapeutic modalities such as hypothermia on the diagnosis of brain death. Hypothermia is known to depress central nervous system function[27–29] and may lead to a false diagnosis of brain death. Hypothermia may alter metabolism and clearance of medications that can interfere with brain death testing. Efforts to adequately rewarm before performing any neurologic examination and maintain temperature during the observation period are essential. The 1987 guidelines stated that the patient must not be significantly hypothermic however no definition was provided.[1] It is reasonable that the core body temperature at the time of brain death examination be as close to normal to reproduce normal physiologic conditions. A core body temperature of $>35°C$ (95°F) should be achieved and maintained during examination and testing to determine death. This temperature is consistent with current adult guidelines and is relatively easy to achieve and maintain in children.[11,13]

Severe metabolic disturbances can cause reversible coma and interfere with the clinical evaluation to determine brain death. Reversible conditions such as severe electrolyte imbalances, hyper or hyponatremia, hyper or hypoglycemia, severe pH disturbances, severe hepatic or renal dysfunction or inborn errors of metabolism may cause coma in a neonate or child.[28,29] These conditions should be identified and treated before evaluation for brain death, especially in situations where the clinical history does not provide a reasonable explanation for the neurologic status of the child.

Drug intoxications including barbiturates, opioids, sedatives, intravenous and inhalation anesthetics, antiepileptic agents, and alcohols can cause severe central nervous system depression and may alter the clinical examination to the point where they can mimic brain death.[28,29] Testing for these drugs should be performed if there is concern regarding recent ingestion or administration. When available, specific serum levels of medications with sedative properties or side effects should be obtained and documented to be in a low to mid therapeutic range before neurologic examination for brain death testing. Longer acting or continuous infusion of sedative agents can also interfere with the neurologic evaluation. These medications should be discontinued. Adequate clearance (based on the age of the child, presence of organ dysfunction, total amount of medication administered, elimination half-life of the drug and any active metabolites) should be allowed before the neurologic examination. In some instances this may require waiting several half-

lives and rechecking serum levels of the medication before conducting the brain death examination. If neuromuscular blocking agents have been used, they should be stopped and adequate clearance of these agents confirmed by use of a nerve stimulator with documentation of neuromuscular junction activity and twitch response. Other unusual causes of coma such as neurotoxins, and chemical exposure (ie, organophosphates, and carbamates) should be considered in rare cases where an etiology for coma has not been established. Recommendations of time intervals before brain death evaluation for many of the commonly used medications administered to critically ill neonates and children are listed in Appendix 2.

Clinical criteria for determining brain death may not be present on admission and may evolve during hospitalization. Assessment of neurologic function may be unreliable immediately following resuscitation after cardiopulmonary arrest[30–33] or other acute brain injuries and serial neurologic examinations are necessary to establish or refute the diagnosis of brain death. Additionally, initial stabilization may take several hours during which time correcting metabolic disturbances and identifying and treating reversible conditions that may imitate brain death can be accomplished. It is reasonable to defer neurologic examination to determine brain death for 24 hours or longer if dictated by clinical judgment of the treating physician in such circumstances. If there are concerns about the validity of the examination (eg, flaccid tone or absent movements in a patient with high spinal cord injury or severe neuromuscular disease) or if specific examination components cannot be performed due to medical contraindications (eg, apnea testing in patients with significant lung injury, hemodynamic instability, or high spinal cord injury), or if examination findings are inconsistent, continued observation and postponing further neurologic examinations until these issues are resolved is warranted to avoid improperly diagnosing brain death. An ancillary study can be pursued to assist with the diagnosis of brain death in situations where certain examination components cannot be completed.

Neuroimaging with either computed tomography (CT) or magnetic resonance imaging (MRI) should demonstrate evidence of an acute central nervous system injury consistent with the profound loss of brain function. It is recognized that early after acute brain injury, imaging findings may not demonstrate significant injury. In such situations, repeat studies are helpful in documenting that an acute severe brain injury has occurred. CT and MRI are not considered ancillary studies and should not be relied on to make the determination of brain death.

Number of Examinations, Examiners and Observation Periods (*Recommendations 3a–e, Table 1*)

Number of Examinations and Examiners

The 1987 guidelines recommended observation periods between brain death examinations based on age and the results of neurodiagnostic testing.[1] Two examinations and EEG's separated by at least 48 hours were recommended for infants 7 days to 2 months. Two examinations and EEG's separated by at least 24 hours were recommended for children 2 months to 1 year. A repeat EEG was not necessary if a cerebral radionuclide scan or cerebral angiography demonstrated no flow or visualization of the cerebral arteries. For children older than 1 year, an observation period of 12 hours was recommended and ancillary testing was not required when an irreversible cause existed. The observation period in this age group could be decreased if there was documentation of electrocerebral silence (ECS) or absent cerebral blood flow (CBF).[1] The general consensus was the younger the child, the longer the waiting period unless ancillary studies supported the clinical diagnosis of brain death and if so, the observation period could be shortened.

The current committee supports the 1987 guideline recommending performance of two examinations separated by an observation period. The committee recommends that these examinations be performed by different attending physicians involved in the care of the child. Children being evaluated for brain death may be cared for and evaluated by multiple medical and surgical specialists. The committee recommends that the best interests of the child and family are served if at least two different attending physicians participate in diagnosing brain death to ensure that (i) the diagnosis is based on currently established criteria, (ii) there are no conflicts of interest in establishing the diagnosis and (iii) there is consensus by at least two physicians involved in the care of the child that brain death criteria are met. The committee also believes that because the apnea test is an objective test, it may be performed by the same physician, preferably the attending physician who is managing ventilator care of the child.

Duration of Observation Periods

A literature review of 171 children diagnosed as brain dead found that 47% had ventilator support withdrawn an average of 1.7 days after the diagnosis of brain death was made.[34] Seventy-nine children (46%) in whom support was continued after declaration of brain death suffered a cardiac arrest an average of 22.7 days later. The re-

maining children died by an unknown mechanism (5%), or made an incomplete (1%) or complete recovery (0.5%). Review of the children who survived indicates they did not fulfill brain death criteria by accepted medical standards. The age range of the children in this study included preterm and term neonates and older infants and children up to 18 years of age. These data and the reports of more recent studies[35,36] suggest that there is likely no biological justification for using different durations of observation to diagnose brain death in infants greater than one month of age. In fact, there are no reports of children recovering neurologic function after meeting adult brain death criteria based on neurologic examination findings.[37] Although some authors have reported apparent reversibility of brain death, further review of these cases reveals these children would not have fulfilled brain death criteria by currently accepted US medical standards.[38]

Based on the above data, currently available literature and clinical experience, the committee recommends the observation period between examinations should be 24 hours for neonates (37 weeks up to 30 days), and 12 hours for infants and children (> 30 days to 18 years). The first examination determines the child has met neurologic examination criteria for brain death. The second examination confirms brain death based on an unchanged and irreversible condition. Timing of the first clinical brain death examination, reduction of the observation period, and use of ancillary studies are discussed in separate sections of this guideline.

Apnea Testing (*Recommendations 4a,b, Table 1*)

Apnea testing should be performed with each neurologic examination to determine brain death in all patients unless a medical contraindication exists. Contraindications may include conditions that invalidate the apnea test (such as high cervical spine injury) or raise safety concerns for the patient (high oxygen requirement or ventilator settings). If apnea testing cannot be completed safely, an ancillary study should be performed to assist with the determination of brain death.

The normal physiologic threshold for apnea (minimum carbon dioxide tension at which respiration begins) in children has been assumed to be the same as in adults with reports demonstrating that $Paco_2$ levels in the normal range (24–38 mm Hg) may be adequate to stimulate ventilatory effort in children with residual brainstem function.[39] Although expert opinion has suggested a range of $Paco_2$ levels from 44 to 60 mm Hg for apnea testing in adults, the general consensus in infants and children has been to use 60 mm Hg as a threshold.[40–42] Appendix 3 summarizes data from 4 studies (3 being prospective) on 106 apnea tests in 76 children 2 months old to 17 years with suspected brain death.[39–42] 73 of 76 children had no spontaneous ventilatory effort. In 3 of these studies mean $Paco_2$ values were 59.5 ± 10.2, 68.1 ± 17.7, and 63.9 ± 21.5 mm Hg; in the fourth study, mean $Paco_2$ values were not reported, only the range (ie, 60–116 mm Hg).[39–42] Three children exhibited spontaneous respiratory effort with measured $Paco_2$ levels < 40 mm Hg.[39,42] Serial measurements of $Paco_2$ were done in most studies and 15 minutes was the usual end point of testing although patients may have had apnea for longer periods. The maximum rate of $Paco_2$ increase usually occurred within 5 minutes. Sixty five children had no ventilatory effort during the apnea test. After completion of apnea testing, support was withdrawn in all of these patients. Patient outcome was not reported for one study although these 9 children all had absent brainstem reflexes for a period of > 72 hours.[41] In one study 4/9 patients had phenobarbital levels that were interpreted as not affecting the results of apnea testing.[41]

There are three case reports discussing irregular breaths or minimal respiratory effort with a Pco_2 > 60 mm Hg in children who otherwise met criteria for brain death.[43–45] Two children died, one after meeting all criteria for brain death including a second apnea test. The remaining child survived and was supported in a chronic care facility with a tracheostomy, chronic mechanical ventilation and a gastrostomy tube. One other report describes a 3-month-old who met all criteria for brain death including 2 apnea tests with serial Pco_2's of 69.3 mm Hg and 62.1 mm Hg respectively. This infant was declared dead on hospital day 5. This infant developed irregular spontaneous respirations at a rate of two to three breaths per minute 38 days later which continued while receiving mechanical ventilator support until death on day 71.[46] Review of this case and others remind us to be cautious in applying brain death criteria in young infants. However, these cases should not be considered to represent reversible deficits or failure of current brain death criteria.[47]

Technique for Apnea Testing

Apnea testing in term newborns, infants, and children is conducted similar to adults. Normalization of the pH and $Paco_2$, measured by arterial blood gas analysis, maintenance of core temperature > 35°C, normalization of blood pressure appropriate for the age of the child, and correcting for factors that could affect respiratory effort are a prerequisite to testing. The patient must be preoxygenated using 100% oxygen for 5–10 minutes before initiating this test. Intermittent manda-

tory mechanical ventilation should be discontinued once the patient is well oxygenated and a normal $Paco_2$ has been achieved. The patient can then be changed to a T piece attached to the endotracheal tube (ETT), or a self-inflating bag valve system such as a Mapleson circuit connected to the ETT. Tracheal insufflation of oxygen using a catheter inserted through the ETT has also been used, however caution is warranted to ensure adequate gas excursion and to prevent barotrauma. High gas flow rates with tracheal insufflation may also promote CO_2 washout preventing adequate $Paco_2$ rise during apnea testing. Continuous positive airway pressure (CPAP) ventilation has been used during apnea testing. Many current ventilators automatically change from a CPAP mode to mandatory ventilation and deliver a breath when apnea is detected. It is also important to note that spontaneous ventilation has been falsely reported to occur while patients were maintained on CPAP despite having the trigger sensitivity of the mechanical ventilator reduced to minimum levels.[48] Physician(s) performing apnea testing should continuously monitor the patient's heart rate, blood pressure, and oxygen saturation while observing for spontaneous respiratory effort throughout the entire procedure. $Paco_2$, measured by blood gas analysis, should be allowed to rise to $\geq$ 20 mm Hg above the baseline $Paco_2$ level and $\geq$ 60 mm Hg. If no respiratory effort is observed from the initiation of the apnea test to the time the measured $Paco_2 \geq 60$ mm Hg and $\geq$ 20 mm Hg above the baseline level, the apnea test is consistent with brain death. The patient should be placed back on mechanical ventilator support and medical management should continue until the second neurologic examination and apnea test confirming brain death is completed. If oxygen saturations fall below 85%, hemodynamic instability limits completion of apnea testing, or a $Paco_2$ level of $\geq$ 60 mm Hg cannot be achieved, the infant or child should be placed back on ventilator support with appropriate treatment to restore normal oxygen saturations, normocarbia, and hemodynamic parameters. In this instance, another attempt to test for apnea may be performed at a later time or an ancillary study may be pursued to assist with determination of brain death. Evidence of any respiratory effort that is inconsistent with brain death and the apnea test should be terminated and the patient placed back on ventilatory support.

Ancillary Studies (*Recommendations 5a–e, Table 1*)

The committee recommends that ancillary studies are not required to establish brain death and should not be viewed as a substitute for the neurologic examination. Ancillary studies may be used to assist the clinician in making the diagnosis of brain death (i) when components of the examination or apnea testing cannot be completed safely due to the underlying medical condition of the patient; (ii) if there is uncertainty about the results of the neurologic examination; (iii) if a medication effect may be present; or (iv) to reduce the inter-examination observation period. The term "ancillary study" is preferred to "confirmatory study" since these tests assist the clinician in making the clinical diagnosis of brain death. Ancillary studies may also be helpful for social reasons allowing family members to better comprehend the diagnosis of brain death.

Four-vessel cerebral angiography is the gold standard for determining absence of CBF. This test can be difficult to perform in infants and small children, may not be readily available at all institutions, and requires moving the patient to the angiography suite potentially increasing risk of exacerbating hemodynamic and respiratory instability during transport of a critically ill child outside of the intensive care unit. Electroencephalographic documentation of electrocerebral silence (ECS) and use of radionuclide CBF determinations to document the absence of CBF remain the most widely used methods to support the clinical diagnosis of brain death in infants and children. Radionuclide CBF testing must be performed in accordance with guidelines established by the Society of Nuclear Medicine and the American College of Radiology.[49,50] EEG testing must be performed in accordance with standards established by the American Electroencephalographic Society.[51] Interpretation of ancillary studies requires the expertise of appropriately trained and qualified individuals who understand the limitations of these studies to avoid any potential misinterpretation.

Similar to the neurologic examination, hemodynamic and temperature parameters should be normalized before obtaining EEG or CBF studies. Pharmacologic agents that could affect the results of testing should be discontinued (Appendix 2) and levels determined as clinically indicated. Low to mid therapeutic levels of barbiturates should not preclude the use of EEG testing.[48] Evidence suggests that radionuclide CBF study can be used in patients with high dose barbiturate therapy to demonstrate absence of CBF.[52,53]

Diagnostic Yield of the EEG in Suspected Brain Dead Children

Appendix 4 summarizes EEG data from 12 studies in 485 suspected brain dead children in all age groups.[34,54–65] The data show that 76% of all children who were evaluated with EEG for brain death on the first EEG had ECS. Multiple EEGs increased the yield to 89%. For those children who had ECS on their

first EEG, 64/66 patients (97%) had ECS on a follow-up EEG. The first exception was a neonate who had a phenobarbital level of 30 μg/mL when the first EEG was performed.[65] The second exception was a 5 year old head trauma patient who was receiving pentobarbital and pancuronium at the time of the initial EEG.[62] This patient also had a CBF study performed demonstrating flow. In retrospect, these two patients would not have met currently accepted standards for brain death based on pharmacologic interference with EEG testing. Additionally, of those patients with EEG activity on the first EEG, 55% had a subsequent EEG that showed ECS. The remaining 45% either had persistent EEG activity or additional EEGs were not performed. All died (spontaneously or by withdrawal of support). Only one patient survived from this entire group of 485 patients, a neonate with an elevated phenobarbital level whose first EEG showed photic response and survived severely neurologically impaired.

Diagnostic Yield of Radionuclide CBF Studies in Suspected Brain Dead Children

Appendix 5 summarizes CBF data from 12 studies in 681 suspected brain dead children in all age groups.[36,54,55,57,59,60,63,64–68] Different but well standardized and conventional radionuclide cerebral angiography methods were used. Absent CBF was found in 86% of children who were clinically brain dead and the yield did not significantly change if more than one CBF study was done (89%). Appendix 5 also summarizes follow-up data on children whose subsequent CBF study showed no flow. 24/26 patients (92%) had no flow on follow-up CBF studies when the first study showed absent flow. The two exceptions where flow developed later were newborns. The first newborn had minimal flow on the second study and ventilator support was discontinued. The other newborn developed flow on the second study and had some spontaneous respirations and activity. A phenobarbital level two days after the second CBF study with minimal flow was 8 μg/mL.[65]

In those patients with preserved CBF on the first CBF study, 26% (9/34) had a second CBF study that showed no flow. The remaining 74% either had preserved flow or no further CBF studies were done and all but one patient died (either spontaneously or by withdrawal of support). Only one patient survived with severe neurologic impairment from this entire group of patients—the same neonate as noted previously with no CBF on the first study but presence of CBF on the second study.

Diagnostic Yield of the Initial EEG Versus Radionuclide CBF Studies in Brain Dead Children

Appendix 6 summarizes the comparative diagnostic yield of EEG versus CBF determinations in children who had both studies done as part of the initial brain death evaluation. Data from the 12 studies cited in Appendices 4 and 5 were stratified by 3 age groups: (i) all children ($n = 149$); (ii) newborns (< 1 month of age, $n = 30$); and (iii) children age > 1 month to 18 years ($n = 119$).[36,54–56,58–68]

The data in Appendices 4 and 5 show that the yield from the initial CBF studies was higher (86%) than from the initial EEG (76%) but no differences were present for any CBF study (89%) vs any EEG study (89%). In contrast the data in Appendix 6 for all children show that when both studies are initially performed, the diagnostic yield is the same (70% had ECS; and 70% showed absent CBF). The diagnostic yield for children greater than 1 month of age was similar for both tests (EEG with ECS, 78%; no CBF, 71%). For newborns, EEG with ECS was less sensitive (40%) than absence of CBF (63%) when confirming the diagnosis of brain death but even in the CBF group the yield was low.

In summary, both of these ancillary studies remain accepted tests to assist with determination of brain death in infants and children. The data suggest that EEG and CBF studies are of similar confirmatory value. Radionuclide CBF techniques are increasingly being used in many institutions replacing EEG as an ancillary study to assist with the determination of brain death in infants and children.[5,69] Other ancillary studies such as the Transcranial Doppler study and newer tests such as CT angiography, CT perfusion using arterial spin labeling, nasopharyngeal somatosensory evoked potential studies, MRI-MR angiography, and perfusion MRI imaging have not been studied sufficiently nor validated in infants and children and cannot be recommended as ancillary studies to assist with the determination of brain death in children at this time.

Repeating Ancillary Studies

If the EEG study shows electrical activity or the CBF study shows evidence of flow or cellular uptake, the patient cannot be pronounced dead at that time. The patient should continue to be observed and medically treated until brain death can be declared solely on clinical examination criteria and apnea testing based on recommended observation periods, or a follow-up ancillary study can be performed to assist and is consistent with the determination of brain death, or withdrawal of life-sustaining medical therapies is made irrespective of meeting criteria for brain death. A waiting period of 24 hours is recommended before further ancillary testing, using a radionuclide CBF study, is performed allowing adequate clearance of Tc-99m.[49,50] While no evidence exists for a recommended

waiting period between EEG studies, a waiting period of 24 hours is reasonable and recommended before repeating this ancillary study.

Shortening the Observation Period

If an ancillary study, used in conjunction with the first neurologic examination, supports the diagnosis of brain death, the inter-examination observation interval can be shortened and the second neurologic examination and apnea test (or all components that can be completed safely) can be performed and documented at any time thereafter for children of all ages.

SPECIAL CONSIDERATIONS FOR TERM NEWBORNS (37 WEEKS GESTATION) TO 30 DAYS OF AGE (*RECOMMENDATIONS 1–5, TABLE 1*)

Preterm and term neonates younger than 7 days of age were excluded from the 1987 Task Force guidelines. The ability to diagnose brain death in newborns is still viewed with some uncertainty primarily due to the small number of brain-dead neonates reported in the literature[54,65,70] and whether there are intrinsic biological differences in neonatal brain metabolism, blood flow and response to injury. The newborn has patent sutures and an open fontanelle resulting in less dramatic increases in intracranial pressure (ICP) after acute brain injury when compared with older patients. The cascade of events associated with increased ICP and reduced cerebral perfusion ultimately leading to herniation are less likely to occur in the neonate.

Clinical Examination

Limited data are available regarding the clinical examination for brain death in preterm and term infants.[70] It has been recognized that examination of the preterm infant less than 37 weeks gestation to determine if they meet brain death criteria may be difficult because of the possibility that some of the brainstem reflexes may not be completely developed and that it is also difficult to assess the level of consciousness in a critically ill, sedated and intubated neonate. Because of insufficient data in the literature, recommendations for preterm infants less than 37 weeks gestational age were not included in this guideline. However, as discussed in the following section on observation periods, the available data suggest that recovery of neurologic function is unlikely when a term newborn is diagnosed with brain death. Based on review of the literature, the task force supports that brain death can be diagnosed in term newborns (37 weeks gestation) and older, provided the physician is aware of the limitations of the clinical examination and ancillary studies in this age group. It is important to carefully and repeatedly examine term newborns, with particular attention to examination of brainstem reflexes and apnea testing. As with older children, assessment of neurologic function in the term newborn may be unreliable immediately following an acute catastrophic neurologic injury or cardiopulmonary arrest. A period of 24 hours or longer is recommended before evaluating the term newborn for brain death.

Apnea Testing

Neonatal studies reviewing $Paco_2$ thresholds for apnea are limited. However, data from 35 neonates who were ultimately determined to be brain dead revealed a mean $Paco_2$ of 65 mm Hg suggesting that the threshold of 60 mm Hg is also valid in the newborn.[35] Apnea testing in the term newborn may be complicated by the following: (1) Treatment with 100% oxygen may inhibit the potential recovery of respiratory effort.[71,72] (2) Profound bradycardia may precede hypercarbia and limit this test in neonates. A thorough neurologic examination must be performed in conjunction with the apnea test to make the determination of death in any patient. If the apnea test cannot be completed as previously described, the examination and apnea test can be attempted at a later time, or an ancillary study may be performed to assist with determination of death. Ancillary studies in newborns are less sensitive than in older children. There are no reported cases of any neonate who developed respiratory effort after meeting brain death criteria.

Observation Periods in Term Newborns

There is some experience concerning the duration of observation periods in neonates being evaluated for brain death. A review of 87 newborns revealed that the duration of coma from insult to brain death was 37 hours and the duration of time from the initial neurologic examination being indicative of brain death to final confirmation was 75 hours. The overall average duration of brain death in these neonates was about 95 hours or almost 4 days.[37] 53 neonates less than 7 days of age donating organs for transplantation had a total duration of brain death including time to transplantation that averaged 2.8 days; for neonates 1–3 weeks of age, the duration of brain death was approximately 5.2 days.[37] None of these patients recovered any neurologic function. These data suggest that once the diagnosis of brain death is made in newborns, recovery is unlikely. Based on data extracted from available literature and clinical experience the committee recommends the observation period between examinations should be 24 hours for term newborns (37 weeks) to 30 days of age.

Ancillary Studies

Ancillary studies performed in the newborn $<$ 30 days of age are limited.[70] As summarized in Appendix 6, ancillary studies in this age group are less sensitive in detecting the pres-

ence/absence of brain electrical activity or cerebral blood flow than in older children. Of the two studies, detecting absence of CBF (63%) was more sensitive than demonstration of ECS (40%) in confirming the diagnosis of brain death, however even in the CBF study group the sensitivity was low.[70]

EEG activity is of low voltage in newborns raising concerns about a greater chance of having reversible ECS in this age group. In a retrospective review of 40 newborns with ECS, 9/10 with ECS on the initial EEG showed ECS on repeated studies.[70] The remaining patient had a phenobarbital level of 30 μg/mL at the time of the initial EEG, probably accounting for the initial ECS. Several other cases have been reported with initial ECS but careful review found that the patients were not clinically brain dead. Based on available data it is likely that if the initial EEG shows ECS (assuming an absence of correctable conditions) in a newborn who meets all clinical criteria for brain death, then it is an accurate and reliable predictor of brain death and repeat EEG studies are not indicated.

CBF in viable newborns can be extremely low because of the decreased level of brain metabolic activity.[50] However earlier studies using stable xenon computed tomography measurements of CBF have shown that the level of CBF in brain dead children is much lower than that seen in viable newborns.[73,74]

The available data suggest that ancillary studies in newborns are less sensitive than in older children. This can pose an important clinical dilemma in this age group where clinicians may have a greater level of uncertainty about performing a valid neurologic examination. There is a greater need to have more reliable and accurate ancillary studies in this age group. Awareness of this limitation would suggest that longer periods of observation and repeated neurologic examinations are needed before making the diagnosis of brain death and also that as in older infants and children, the diagnosis should be made clinically and based on repeated examinations rather than relying exclusively on ancillary studies.

DECLARATION OF DEATH (FOR ALL AGE GROUPS) (*RECOMMENDATIONS 6a–c, TABLE 1 AND APPENDIX 8 ALGORITHM*)

Death is declared after the second neurologic examination and apnea test confirms an unchanged and irreversible condition. An algorithm (Appendix 8) provides recommendations for the process of diagnosing brain death in children. When ancillary studies are used, documentation of components from the second clinical examination that can be completed, including a second apnea test, must remain consistent with brain death. All aspects of the clinical examination, including the apnea test, or ancillary studies must be appropriately documented. A checklist outlining essential examination and testing components is provided in Appendix 1. This checklist also provides standardized documentation to determine brain death.

ADDITIONAL CONSIDERATIONS (FOR ALL AGE GROUPS)

In today's modern pediatric and neonatal intensive care units, critical care practitioners and other physicians with expertise in neurologic injury are routinely called on to declare death in infants and children. Because the implications of diagnosing brain death are of great consequence, examination should be conducted by experienced clinicians who are familiar with neonates, infants and children and have specific training in neurocritical care. These physicians must be competent to perform the clinical examination and interpret results from ancillary studies. Qualified clinicians include: pediatric intensivists and neonatologists, pediatric neurologists and neurosurgeons, pediatric trauma surgeons, and pediatric anesthesiologists with critical care training. Adult specialists should have appropriate neurologic and critical care training to diagnose brain death when caring for the pediatric patient from birth to 18 years of age. Residents and fellows should be encouraged to learn how to properly perform brain death testing by observing and participating in the clinical examination and testing process performed by experienced attending physicians. It is recommended that both neurologic examinations be performed and documented by an attending physician who is qualified and competent to perform the brain death examination.

These revised pediatric brain death diagnostic guidelines are intended to provide an updated framework in an effort to promote standardization of the neurologic examination and use of ancillary studies. A standardized checklist (Appendix 1) will help to ensure that all components of the examination, and ancillary studies if needed, are completed and documented appropriately. Pediatric specialists should be invited to participate in the development of institutional guidelines to ensure that the brain death examination is conducted consistently each time the diagnosis is being considered. A comparison of the 1987 pediatric brain death guidelines and 2011 update for neonatal and pediatric brain death guidelines are listed in Appendix 7.

Diagnosing brain death must never be rushed or take priority over the needs of the patient or the family. Physicians are obligated to provide support and guidance for families as they face difficult end-of-life decisions and attempt to understand what has happened to their child. It is the responsibility of the physician to guide and direct families during the treatment of their child. Communication with families must be clear and concise using simple termi-

nology so that parents and family members understand that their child has died. Permitting families to be present during the brain death examination, apnea testing and performance of ancillary studies can assist families in understanding that their child has died. The family must understand that once brain death has been declared, their child meets legal criteria for death. Families may otherwise become confused or angry if discussions regarding withdrawal of support or medical therapies are entertained after declaration of death. It should be made clear that once death has occurred, continuation of medical therapies, including ventilator support, is no longer an option unless organ donation is planned. Appropriate emotional support for the family should be provided including adequate time to grieve with their child after death has occurred. Consultation or referral to the medical examiner or coroner may be required by state law in certain situations when death occurs.

FUTURE DIRECTIONS

Development of a national database to track infants and children who are diagnosed as brain dead should be strongly considered. Information compiled from this database would increase our knowledge about brain death, especially in neonates.

1. Studies comparing traditional ancillary studies to newer methods to assess CBF and neurophysiologic function should be pursued. Further information about ancillary studies, waiting periods, and research regarding validity of newer ancillary studies is needed for future recommendations to assist with determination of brain death in children.
2. Cerebral protective therapies such as hypothermia may alter the natural progression of brain death and their impact should be reviewed as more information becomes available. The clinician caring for critically ill infants and children should be aware of the potential impact of new therapeutic modalities on the diagnosis of brain death.
3. While each institution and state may have specific guidelines for the determination of brain death in infants and children, we should work with national medical societies to achieve a uniform approach to declaring death that can be incorporated in all hospital policies.[75] This will help eliminate confusion among medical personnel thereby fostering further trust from the community of patients and families that we serve.
4. Additional information or studies are required to determine if a single neurologic examination is sufficient for neonates, infants, and children to determine brain death as currently recommended for adults over 18 years of age.[12,76]

ENDORSEMENTS AND APPROVALS

This document has been reviewed and endorsed by the following societies:

American Academy of Pediatrics

Sub sections:

Section on Critical Care

Section on Neurology

American Association of Critical Care Nurses

Child Neurology Society

National Association of Pediatric Nurse Practitioners

Society of Critical Care Medicine

Society for Pediatric Anesthesia

Society of Pediatric Neuroradiology

World Federation of Pediatric Intensive and Critical Care Societies

American Academy of Neurology affirms the value of this manuscript.

The following societies have had the opportunity to review and comment on this document

American Academy of Pediatrics

Sub sections:

Committee on Bioethics

Committee on Child Abuse and Neglect

Committee on Federal Government Affairs

Committee on Fetus and Newborn

Committee on Hospital Care

Committee on Medical Liability and Risk Management

Committee on Pediatric Emergency Medicine

Committee on Practice and Ambulatory Medicine

Committee on State Government Affairs

Council on Children With Disabilities

Section on Anesthesiology and Pain Medicine

Section on Bioethics

Section on Child Abuse and Neglect

Section on Critical Care

Section on Emergency Medicine

Section on Hospital Medicine

Section on Neurology

Section on Perinatal Pediatrics

Section on Neurological Surgery

Section on Pediatric Surgery

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APPENDIX 1 Check List for Documentation of Brain Death

Brain Death Examination for Infants and Children

Two physicians must perform independent examinations separated by specified intervals.

Age of Patient	Timing of first exam	Inter-exam. interval
Term newborn 37 weeks gestational age and up to 30 days old	☐ First exam may be performed 24 hours after birth OR following cardiopulmonary resuscitation or other severe brain injury	☐ At least 24 hours ☐ Interval shortened because ancillary study (section 4) is consistent with brain death
31 days to 18 years old	☐ First exam may be performed 24 hours following cardiopulmonary resuscitation or other severe brain injury	☐ At least 12 hours OR ☐ Interval shortened because ancillary study (section 4) is consistent with brain death

Section 1. PREREQUISITES for brain death examination and apnea test

A. IRREVERSIBLE AND IDENTIFIABLE Cause of Coma (Please check)

☐ Traumatic brain injury ☐ Anoxic brain injury ☐ Known metabolic disorder ☐ Other (Specify) _____

B. Correction of contributing factors that can interfere with the neurologic examination	Examination One		Examination Two	
a. Core Body Temp is over 95° F (35° C)	☐ Yes	☐ No	☐ Yes	☐ No
b. Systolic blood pressure or MAP in acceptable range (Systolic BP not less than 2 standard deviations below age appropriate norm) based on age	☐ Yes	☐ No	☐ Yes	☐ No
c. Sedative/analgesic drug effect excluded as a contributing factor	☐ Yes	☐ No	☐ Yes	☐ No
d. Metabolic intoxication excluded as a contributing factor	☐ Yes	☐ No	☐ Yes	☐ No
e. Neuromuscular blockade excluded as a contributing factor	☐ Yes	☐ No	☐ Yes	☐ No

☐If ALL prerequisites are marked YES, then proceed to section 2, OR
☐ _____confounding variable was present. Ancillary study was therefore performed to document brain death. (Section 4).

Section 2. Physical Examination (Please check) NOTE: SPINAL CORD REFLEXES ARE ACCEPTABLE	Examination One Date/ time: _____		Examination Two Date/ Time: _____	
a. Flaccid tone, patient unresponsive to deep painful stimuli	☐ Yes	☐ No	☐ Yes	☐ No
b. Pupils are midposition or fully dilated and light reflexes are absent	☐ Yes	☐ No	☐ Yes	☐ No
c. Corneal, cough, gag reflexes are absent	☐ Yes	☐ No	☐ Yes	☐ No
Sucking and rooting reflexes are absent (in neonates and infants)	☐ Yes	☐ No	☐ Yes	☐ No
d. Oculovestibular reflexes are absent	☐ Yes	☐ No	☐ Yes	☐ No
e. Spontaneous respiratory effort while on mechanical ventilation is absent	☐ Yes	☐ No	☐ Yes	☐ No

☐The _____ (specify) element of the exam could not be performed because_____.
Ancillary study (EEG or radionuclide CBF) was therefore performed to document brain death. (Section 4).

Section 3. APNEA Test	Examination One Date/ Time_____	Examination Two Date/ Time_____
No spontaneous respiratory efforts were observed despite final $PaCO_2 \geq 60$ mm Hg and a ≥ 20 mm Hg increase above baseline. (Examination One) No spontaneous respiratory efforts were observed despite final $PaCO_2 \geq 60$ mm Hg and a ≥ 20 mm Hg increase above baseline. (Examination Two)	Pretest $PaCO_2$: _____ Apnea duration: _____min Posttest $PaCO_2$: _____	Pretest $PaCO_2$: _____ Apnea duration: _____min Posttest $PaCO_2$: _____

Apnea test is contraindicated or could not be performed to completion because_____.
Ancillary study (EEG or radionuclide CBF) was therefore performed to document brain death. (Section 4).

Section 4. ANCILLARY testing is required when (1) any components of the examination or apnea testing cannot be completed; (2) if there is uncertainty about the results of the neurologic examination; or (3) if a medication effect may be present. **Ancillary testing can be performed to reduce the inter-examination period however a second neurologic examination is required. Components of the neurologic examination that can be performed safely should be completed in close proximity to the ancillary test**	**Date/Time:** _____
☐ Electroencephalogram (EEG) report documents electrocerebral silence OR	☐ Yes ☐ No
☐ Cerebral Blood Flow(CBF) study report documents no cerebral perfusion	☐ Yes ☐ No

Section 5. Signatures

Examiner One

I certify that my examination is consistent with cessation of function of the brain and brainstem. Confirmatory exam to follow.

_____ _____
(Printed Name) (Signature)

_____ _____ _____ _____
(Specialty) (Pager #/License #) (Date mm/dd/yyyy) (Time)

Examiner Two

☐I certify that my examination☐ and/or ancillary test report ☐confirms unchanged and irreversible cessation of function of the brain and brainstem. The patient is declared brain dead at this time.
Date/Time of death: _____

_____ _____
(Printed Name) (Signature)

_____ _____ _____ _____
(Specialty) (Pager #/License #) (Date mm/dd/yyyy) (Time)

APPENDIX 2 Medications Administered to Critically Ill Pediatric Patients and Recommendations for Time Interval to Testing After Discontinuation

Medication	Infants/Children Elimination ½ life	Neonates Elimination ½ life
Intravenous induction, anesthetic, and sedative agents		
Thiopental	Adults: 3–11.5 hours (shorter ½ life in children)	
Ketamine	2.5 hours	
Etomidate	2.6–3.5 hours	
Midazolam	2.9–4.5 hours	4–12 hours[77–80]
Propofol	2–8 minutes, Terminal ½ life 200 minutes (range 300–700 minutes)	
Dexmedetomidine	Terminal ½ life 83–159 minutes[79–81]	Infants have faster clearance[81–83]
Antiepileptic drugs		
Phenobarbital	Infants: 20–133 hours* Children: 37–73 hours*	45–500 hours*[79,84,85]
Pentobarbital	25 hours*	
Phenytoin	11–55 hours*	63–88 hours*
Diazepam	1 month–2 years: 40–50 hours 2 years–12 years: 15–21 hours 12–16 years: 18–20 hours	50–95 hours[79,86,87]
Lorazepam	Infants: 40.2 hours (range 18–73 hours) Children: 10.5 hours (range 6–17 hours)	40 hours[86]
Clonazepam	22–33 hours	
Valproic Acid	Children > 2 months: 7–13 hours* Children 2–14 years: Mean 9 hours; range 3.5–20 hours	10–67 hours*
Levetiracetam	Children 4–12 years: 5 hours	
Intravenous narcotics		
Morphine sulfate	Infants 1–3 months: 6.2 hours (5–10 hours) 6 months–2.5 years: 2.9 hours (1.4–7.8 hours) Children: 1–2 hours	7.6 hours (range 4.5–13.3 hours)[79,89–91]
Meperidine	Infants < 3 months: 8.2–10.7 hours (range 4.9–31.7 hours) Infants 3–18 months: 2.3 hours Children 5–8 years: 3 hours	23 hours (range 12–39 hours)
Fentanyl	5 months–4.5 years: 2.4 hours (mean) 0.5–14 years: 21 hours (range 11–36 hours for long term infusions)	1–15 hours
Sufentanil	Children 2–8 years: 97 ± 42 minutes	382–1162 minutes
Muscle relaxants		
Succinylcholine	5–10 minutes Prolonged duration of action in patients with pseudocholinesterase deficiency or mutation	
Pancuronium	110 minutes	
Vecuronium	41 minutes	65 minutes
Atracurium	17 minutes	20 minutes
Rocuronium	3–12 months: 1.3 ± 0.5 hours 1 to < 3 years: 1.1 ± 0.7 hours 3 to < 8 years: 0.8 ± 0.3 hours Adults: 1.4–2.4 hours	

Modified from Ashwal and Schneider.[57]

Metabolism of pharmacologic agents may be affected by organ dysfunction and hypothermia.

Physicians should be aware of total amounts of administered medication that can affect drug metabolism and levels.

* Elimination ½ life does not guarantee therapeutic drug levels for longer acting medications or medications with active metabolites. Drug levels should be obtained to ensure that levels are in a low to mid therapeutic range prior to neurologic examination to determine brain death. In some instances this may require waiting several half-lives and rechecking serum levels of the medication before conducting the brain death examination.

APPENDIX 3 Apnea Testing in Pediatric Brain Death

Author	*n*	Age Range	$Paco_2$	Comments
Rowland (1984)[41]	9 children, 16 apnea tests performed	4 months–13 years	Range: 60–116 mm Hg after 15 minutes of apnea	No spontaneous respiratory effort noted in any patient during testing. Phenobarbital levels of 10,11.6,18,25 mg/dL were measured in 4 patients,
Outwater & Rockoff (1984)[40]	10 children	10 months–13 years	Mean 59.5 ± 10.2 mm Hg after 5 minutes of apnea	No spontaneous respiratory effort noted in any patient during testing or after support was withdrawn
Riviello (1988)[39]	19 children	2 months–15 years	Mean 63.9 ± 21.5 mm Hg	2 children with Pco_2 levels of 24 mm Hg and 38 mm Hg had spontaneous respirations during the apnea test. All other children had no spontaneous respiratory effort noted after support was withdrawn.
Paret (1995)[42]	38 children, 61 apnea tests performed	2 months–17 years	Mean 68.07 ± 17.66 after 5 minutes Mean 81.8 ± 20.2 after 10 minutes Mean 86.88 ± 25.6 after 15 minutes	1 child had spontaneous respiratory effort with a $Paco_2$ of 49 mm Hg. This patient was retested 24 hours later and had no respiratory effort.

APPENDIX 4 EEG in Pediatric Brain Death: Diagnostic Yield From First Versus Any Study

Study	Total # Pts in Study	% Patients With ECS on EEG#1	% Patients With ECS on Any EEG	% Pts With ECS on f/u EEG When First EEG Had ECS	% Pt With ECS on Later EEGs When First EEG Had Activity
Ruiz-Garcia et al, 2000 (60)	125	72% (88/122)	91% (111/122)	NA	68% (23/34)
Drake et al, 1986[55]	61	70% (33/47)	91% (43/47)	100% (17/17)	71% (10/14)
Parker et al, 1995[36]	60	100% (9/9)	100% (9/9)	NA	NA
Alvarez et al, 1988[56]	52	100% (52/52)	100% (52/52)	100% (28/28)	NA
Ashwal, 1993[54]	52	85% (28/33)	85% (28/33)	100% (3/3)	0% (0/1)
Ruiz-Lopez et al, 1999[61]	51	48% (14/29)	72% (21/29)	NA	47% (7/15)
Ashwal & Schneider, 1989[65]	18	50% (9/18)	78% (14/18)	88% (7/8)	56% (5/9)
Holzman et al, 1983[62]	18	61% (11/18)	67% (12/18)	67% (2/3)	14% (1/7)
Ashwal et al, 1977[58]	15	67% (10/15)	73% (11/15)	100% (2/2)	20% (1/5)
Coker et al, 1986[59]	14	100% (11/11)	100% (11/11)	100% (5/5)	NA
Furgiuele et al, 1984[63]	11	100% (10/10)	100% (10/10)	NA	NA
Okuyaz et al, 2004[64]	8	100% (8/8)	100% (8/8)	NA	NA
Total	485	76% (283/372)	89% (330/372)	97% (64/66)	55% (47/85)

EEG Electroencephalogram.
ECS Electrocerebral silence.

APPENDIX 5 CBF in Pediatric Brain Death: Diagnostic Yield From First Versus Any Study

Study	Total # of Pts in Study	CBF#1: % Patients With Absent CBF*	% Patients With Absent CBF on Any Study**	% Pts With No CBF on f/u Study When First Study Had Shown No CBF	% Pt With No CBF on Later Study When First Study Had CBF Present
Shimizu et al, 2000[66]	228	100% (27/27)	100% (27/27)	NA	NA
Ruiz-Garcia et al, 2000[60]	125	92% (83/90)	92% (83/90)	NA	NA
Drake et al, 1986[55]	61	68% (32/47)	81% (38/47)	100% (17/17)	40% (6/15)
Parker et al, 1995[36]	60	87% (26/30)	87% (26/30)	NA	NA
Coker et al, 1986[59]	55	100% (55/55)	100% (55/55)	NA	NA
Ashwal, 1993[54]	52	86% (19/22)	86% (19/22)	NA	NA
Ahmann et al, 1987[67]	32	83% (6/6)	83% (6/6)	NA	NA
Ashwal &Schneider, 1989[65]	18	65% (11/17)	65% (11/17)	71% (5/7)	0% (0/3)
Holzman et al, 1983[62]	18	39% (7/18)	44% (8/18)	100% (2/2)	9% (1/11)
Ashwal et al, 1977[58]	15	100% (11/11)	100% (11/11)	NA	NA
Schwartz et al, 1984[68]	9	100% (9/9)	100% (9/9)	NA	NA
Okuyaz et al, 2004[64]	8	75% (6/8)	100% (8/8)	NA	100% (2/2)
Total	681	86% (292/340)	89% (301/340)	92% (24/26)	26% (9/34)

* # pts with no CBF on first study/# pts with first CBF study.
** # pts with no CBF on any study/# pts with any CBF.
CBF Cerebral blood flow.

APPENDIX 6 EEG and CBF Diagnostic Screening Yield by Age Groups

	ECS	EEG$^+$	Total	Diagnostic Screening Yield
All children ($n = 149$)*				
No CBF	86	18	104	% pt with ECS = 70%
CBF$^+$	19	26	45	% pts with no CBF = 70%
Total	105	44	149	
Just newborns (< 1 month of age; $n = 30$)**				
No CBF	8	11	19	% pt with ECS = 40%
CBF$^+$	4	7	11	% pts with no CBF = 63%
Total	12	18	30	
Children (> 1 month of age; $n = 119$)***				
No CBF	78	7	85	% pt with ECS = 78%
CBF$^+$	15	19	34	% pts with no CBF = 71%
Total	93	26	119	

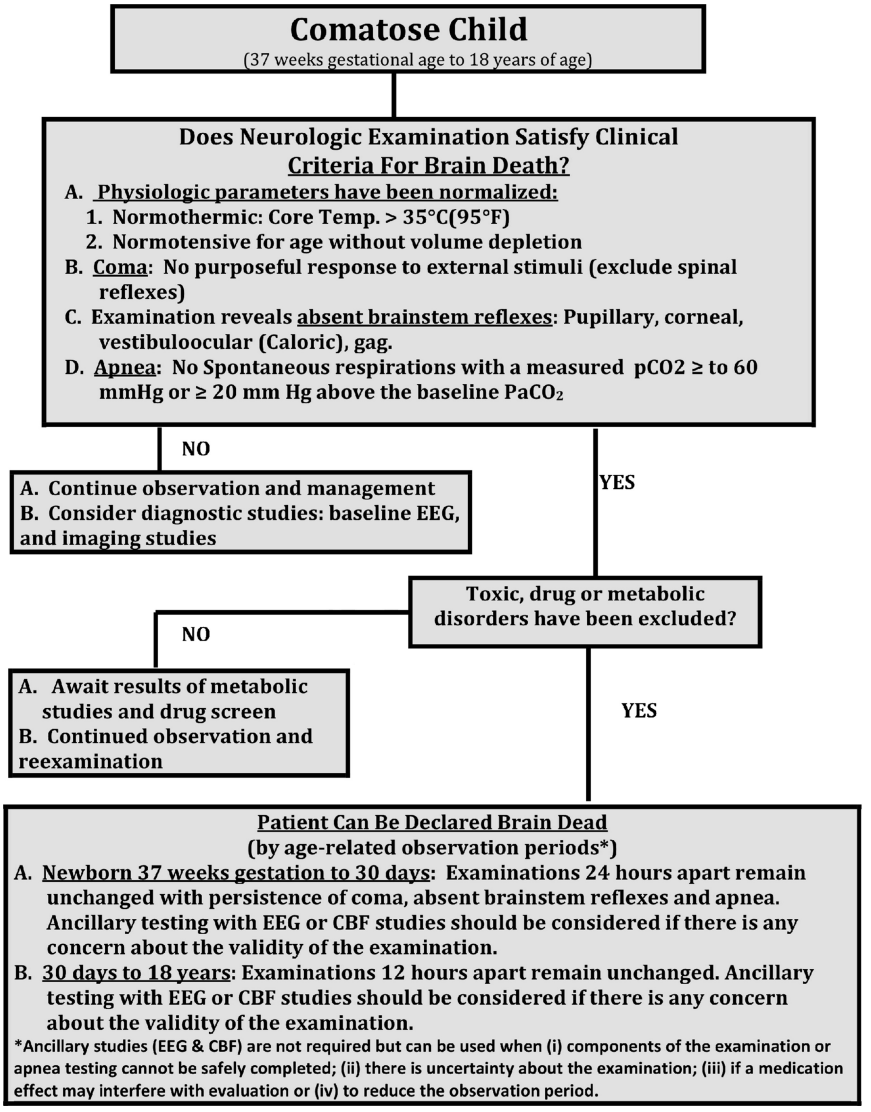
* Data extracted from references cited in Appendix 4,5.
** Data extracted from references cited in Ashwal S.[35]
*** Data represent the differences between "All children" and "just newborns" groups.
ECS Electrocerebral silence.
CBF Cerebral blood flow.
EEG$^+$ Activity on EEG.
CBF$^+$ Cerebral blood flow present.

APPENDIX 7 Comparison of 1987 Pediatric Brain Death Guidelines and the Updated Guideline for Determination of Brain Death in Infants and Children

	1987	Updated Guidelines
Waiting period before initial brain death examination	Not specified	24 hours following cardiopulmonary resuscitation or severe acute brain injury is suggested if there are concerns about the neurologic examination or if dictated by clinical judgment
Clinical examination	Required	Required
Core body temperature	Not specified	> 35°C (95°F)
Number of examinations	Two exams 2nd examination not necessary in 2 months–1 year age group if initial examination, EEG and concomitant CBF consistent with brain death	Two exams, irrespective of ancillary study results (if ancillary testing is being done in lieu of initial examination elements that cannot be safely performed, the components of the second examination that can be done must be completed)
Number of examiners	Not specified	Two (Different attending physicians must perform the first and second exam)
Observation interval between neurologic examinations	Age dependent ● 7 days–2 months: 48 hours ● 2 months–1 year: 24 hours ● >1 year: 12 hours (24 hrs if HIE)	Age Dependent ● Term newborn (37 weeks gestation) to 30 days of age: 24 hours ● 31 days–18 years: 12 hours
Reduction of observation period between exams	Permitted only for > 1 year age group if EEG or CBF consistent with brain death	Permitted for both age groups if EEG or CBF consistent with brain death
Apnea testing	Required, number of tests ambiguous	Two apnea tests required unless clinically contraindicated
Final Pco_2 threshold for apnea testing	Not specified	≥60 mm Hg and ≥20 mm Hg above the baseline $Paco_2$
Ancillary study recommended	● Age dependent 7 days–2 months: 2 EEGs separated by 48 hrs ● 2 months–1 year: 2 EEG's separated by 24 hours. CBF can replace the need for 2nd EEG ● >1 year: No testing required	Not required except in cases where the clinical examination and apnea test cannot be completed ● Term newborn (37 weeks gestation) to 30 days of age: EEG or CBF are less sensitive in this age group. CBF may be preferred. ● >30 days–18 years: EEG and CBF have equal sensitivity
Time of death	Not specified	Time of the second examination and apnea test (or completion of ancillary study and the components of the second examination that can be safely completed)

EEG Electroencephalogram.
CBF Cerebral blood flow.
HIE Hypoxic ischemic encephalopathy.

APPENDIX 8 Algorithm to Diagnose Brain Death in Infants and Children



APPENDIX 9 Taskforce Organization

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Guidelines for the Determination of Brain Death in Infants and Children: An Update of the 1987 Task Force Recommendations

Thomas A. Nakagawa, Stephen Ashwal, Mudit Mathur, Mohan Mysore and the Society of Critical Care Medicine, Section on Critical Care and Section on Neurology of the American Academy of Pediatrics, and the Child Neurology Society

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