Guidelines for the determination of brain death in infants and children: An update of the 1987 Task Force recommendations*

Thomas A. Nakagawa, MD, FAAP, FCCM; Stephen Ashwal, MD, FAAP; Mudit Mathur, MD, FAAP; Mohan R. Mysore, MD, FAAP, FCCM; Derek Bruce, MD; Edward E. Conway, Jr, MD, FCCM; Susan E. Duthie, MD; Shannon Hamrick, MD; Rick Harrison, MD; Andrea M. Kline, RN, MS, FCCM; Daniel J. Lebovitz, MD; Maureen A. Madden, MSN, FCCM; Vicki L. Montgomery, MD, FCCM; Jeffrey M. Perlman, MBChB, FAAP; Nancy Rollins, MD, FAAP; Sam D. Shemie, MD; Amit Vohra, MD, FAAP; Jacqueline A. Williams-Phillips, MD, FAAP, FCCM; Society of Critical Care Medicine; the Section on Critical Care and Section on Neurology of the American Academy of Pediatrics; and the Child Neurology Society

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

Methods: **Relevant literature was reviewed. Recommendations were developed using the Grading of Recommendations Assessment, Development and Evaluation (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 <37 wks 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 hrs for term newborns (37 wks gestational age) to 30 days of age and 12 hrs for infants and children (>30 days to 18 yrs) 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 after cardiopulmonary resuscitation or other severe acute brain injuries should be deferred for ≥24 hrs 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 used to assist the clinician in making the diagnosis of brain death a) when components of the examination or apnea testing cannot be completed safely as a result of the underlying medical condition of the patient; b) if there is uncertainty about the results of the neurologic examination; c) if a medication effect may be present; or d) to reduce the interexamination 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 these criteria are fulfilled. (Crit Care Med 2011; 39:2139–2155)**

KEY WORDS: apnea testing; brain death; cerebral blood flow; children; electroencephalography; infants; neonates; pediatrics

***See also p. 2197.**

Professor (TAN), Anesthesiology and Pediatrics, Wake Forest University School of Medicine, Director, Pediatric Critical Care, Brenner Children's Hospital at Wake Forest University Baptist Medical Center, Winston-Salem, NC; Professor of Pediatrics (SA), Department of Pediatrics, Chief, Division of Child Neurology, Loma Linda University School of Medicine, Loma Linda, CA; Associate Professor of Pediatrics (MM), Division of Pediatric Critical Care, Loma Linda University School of Medicine, Loma Linda, CA; Professor of Pediatrics (MRM), University of Nebraska College of Medicine, Director, Pediatric Critical Care, Children's Hospital and Medical Center, Omaha, NE; Professor of Neurosurgery and Pediatrics (DB), Children's National Medical Center, Washington, DC; Professor of Pediatrics (EEC), Beth Israel Medical Center, Hartsdale, NY; Pediatric Critical Care (SED), Rady Children's Hospital–San Diego, San Diego, CA; Assistant Professor of Pediatrics (SH), Emory University, Children's Healthcare of Atlanta, Atlanta, GA; Professor of Pediatrics (RH), David Geffen School of Medicine UCLA, Mattel Children's Hospital, UCLA, Los Angeles, CA; Nurse Practitioner (AMK), Riley Hospital for Children, Indianapolis, IN; Associate Professor of Pediatrics (DJL), Cleveland Clinic Lerner College of Medicine, Cleveland Clinic Children's Hospital, Cleveland, OH; Assistant Professor of Pediatrics (MAM), Robert Wood Johnson Medical School, Pediatric Critical Care Nurse Practitioner, Bristol-Myers Squibb Children's Hospital, New Brunswick, NJ; Professor of Pediatrics (VLM), University of Louisville, Chief, Division of Pediatric Critical Care Medicine, Medical Director, Patient Safety Officer, Norton Healthcare Kosair Children's Hospital, Louisville, KY; Professor of Pediatrics (JMP), Weill Cornell Medical College, New York, NY; Professor of Pediatrics and Radiology (NR), Children's Medical Center, Southwestern University, Dallas, TX; Professor of Pediatrics (SDS), Montreal Children's Hospital, Montreal, Canada; Assistant Professor of Pediatrics (AV), Wright State University, Pediatric Critical Care, Children's Medical Center, Dayton, OH; Associate Professor of Pediatrics (JAW-P), UMDNJ-Robert Wood Johnson Medical School, Director, Pediatric Intensive Care Unit, Bristol-Myers Squibb Children's Hospital, New Brunswick, NJ.

The American College of Critical Care Medicine (ACCM), which honors individuals for their achievements and contributions to multidisciplinary critical care medicine, is the consultive body of the Society of Critical Care Medicine (SCCM) that possesses recognized expertise in the practice of critical care. The College has developed administrative guidelines and clinical practice parameters for the critical care practitioner. New guidelines and practice parameters are continually developed, and current ones are systematically reviewed and revised.

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For information regarding this article, E-mail: tnakagaw@wfubmc.edu

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In 1987, guidelines for the determination of brain death in children were published by a multisociety 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 <1 yr of age. In children >1 yr, 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 <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) biologic 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 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 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 through 3 of this publication contain the committee's updated recom-

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 Critical Care

Section on Anesthesiology and Pain Medicine

Section on Bioethics

Section on Child Abuse and Neglect

Section on Emergency Medicine

Section on Hospital Medicine

Section on Neurology

Section on Perinatal Pediatrics

Section on Neurological Surgery

Section on Pediatric Surgery

The Pediatric Section of the American Association of Neurosurgeons and the Congress of Neurologic Surgeons have been provided the opportunity to review this document.

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 neurologic examination must be corrected before 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 midtherapeutic 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 midtherapeutic 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 after cardiopulmonary resuscitation or other severe acute brain injuries and evaluation for brain death should be deferred for ≥24–48 hrs 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. Twenty-four hrs for neonates (37 wks gestation to term infants 30 days of age) 2. Twelve hrs for infants and children (>30 days to 18 yrs)	Moderate	Strong
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 after cardiopulmonary resuscitation or other severe acute brain injuries and evaluation for brain death should be deferred for ≥24–48 hrs 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 ≥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 ≥20 mm Hg above the baseline $Paco_2$ level.	Moderate	Strong
b. If the apnea test cannot be performed as a result of 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, an ancillary study should be performed.	Moderate	Strong
5. Ancillary studies:		
a. Ancillary studies (electroencephalography and radionuclide cerebral blood flow) 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 1) components of the examination or apnea testing cannot be completed safely as a result of the underlying medical condition of the patient; 2) if there is uncertainty about the results of the neurologic examination; or 3) 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 (i.e., 1–3 in 5c), 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 hrs is recommended before further clinical re-evaluation or repeat ancillary study is performed. Supportive patient care should continue during this time period.	Moderate	Strong

Table 1. —*Continued*

Recommendation	Evidence Score	Recommendation Score
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 "evidence 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)

Grade	Description
1. Classification of evidence	
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 policymakers—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 policymakers—policymaking 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

mendations, the Grading of Recommendations Assessment, Development and Evaluation (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. Appendices 1 (checklist) and 2 (pharmacologic 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 guidelines' criteria with 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, nu-

Table 3. Neurologic examination components to assess for brain death in neonates, infants, and children[a] including apnea testing

Reversible conditions or conditions that can interfere with the neurologic examination must be excluded before 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 one or two 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°. Each external auditory canal is irrigated (one ear at a time) with approximately 10–50 mL of ice water. Movement of the eyes should be absent during 1 min 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 mins before 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 <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 (e.g., previous trauma, etc.) and the patient observed for any spontaneous or induced movements.
   - If abnormal movements are present, clinical assessment to determine whether these are spinal cord reflexes should be done.

[a]Criteria adapted from 2010 American Academy of Neurology criteria for brain death determination in adults (12).

clear medicine, and neuroradiology was formed by the Society of Critical Care Medicine and the American Academy of Pediatrics 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 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 before 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.

Methodologic issues regarding analysis of evidence warrant further discussion because 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 evidenced-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. GRADE, a recently developed standardized methodologic consensus-based approach, allows panels to evaluate the evidence and opinions and make recommendations (14–17). GRADE uses five 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 1) the strength of evidence linked to a specific recommendation and 2) 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 >80% of the committee members voted "yes" for a recommendation and that a "weak" recommendation was made if >60% but <80% voted "yes." "No recommendation" was made if <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 use 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 <14 yrs 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, Tables 1 and 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 physiological 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 mean arterial pressure should be in an acceptable range (systolic blood pressure not <2 SDS 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 after 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 physiological 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, infant, or child (28, 29). These conditions should be identified and treated before evaluation for brain death, especially in situations in which 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 midtherapeutic 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 (i.e., organophosphates and carbamates) should be considered in rare cases in which 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 after 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 hrs if dictated by clinical judgment of the treating physician in such circumstances. If there are concerns about the validity of the examination (e.g., 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 as a result of medical contraindications (e.g., apnea testing in patients with sig-

nificant 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 in which certain examination components cannot be completed.

Neuroimaging with either computed tomography or magnetic resonance imaging 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. Computed tomography and magnetic resonance imaging 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 EEGs separated by at least 48 hrs were recommended for infants 7 days to 2 months. Two examinations and EEGs separated by at least 24 hrs were recommended for children 2 months to 1 yr. 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 >1 yr, an observation period of 12 hrs 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 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 1) the diagnosis is based on currently established criteria; 2) there are no conflicts of interest in establishing the diagnosis; and 3) 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 sustained cardiac arrest an average of 22.7 days later. The remaining 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 yrs of age. These data and the reports of more recent studies (35, 36) suggest that there is likely no biologic justification for using different durations of observation to diagnose brain death in infants >1 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 U.S. medical standards (38).

Based on these data, currently available literature, and clinical experience, the committee recommends the observation period between examinations should be 24 hrs for neonates (37 wks up to 30 days) and 12 hrs for infants and children (>30 days to 18 yrs). 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 physiological 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 four studies (three being prospective) on 106 apnea tests in 76 children age 2 months to 17 yrs with suspected brain death (39–42). Seventy-three of 76 children had no spontaneous ventilatory effort. In three 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 (i.e., 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 mins 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 mins. 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 nine children all had absent brainstem reflexes for a period of >72 hrs (41). In one study, four of nine 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 two apnea tests with serial PCO_2s of 69.3 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 mins before 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 can then be changed to a T-piece attached to the endotracheal tube or a self-inflating bag valve system such as a Mapleson circuit connected to the endotracheal tube. Tracheal insufflation of oxygen using a catheter inserted through the endotracheal tube 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 ventilation has been used during apnea testing. Many current ventilators automatically change from a continuous positive airway pressure 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 continuous positive airway pressure 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 ≥20 mm Hg above the baseline $Paco_2$ level and ≥60 mm Hg. 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. 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 1) when components of the examination or apnea testing cannot be completed safely as a result of the underlying medical condition of the patient; 2) if there is uncertainty about the results of the neurologic examination; 3) if a medication effect may be present; or 4) to reduce the interexamination observation period. The term "ancillary study" is preferred to "confirmatory study" because 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 the 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 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 midtherapeutic levels of barbiturates should not preclude the use of EEG testing (48). Evidence suggests that a 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 of 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-yr-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 who 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. Twenty-four of 26 patients (92%) had no flow on follow-up CBF studies when the first study showed absent flow. The two exceptions in which 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 2 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% (nine of 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 the presence of CBF on the second study.

Diagnostic Yield of the Initial EEG vs. Radionuclide CBF Studies in Brain-Dead Children

Appendix 6 summarizes the comparative diagnostic yield of EEG vs. 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 three age groups: 1) all children (n = 149); 2) newborns (<1 month of age, n = 30); and 3) children age >1 month to 18 yrs (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 >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 computed tomography angiography, computed tomography perfusion using arterial spin labeling, nasopharyngeal somatosensory evoked potential studies, magnetic resonance imaging–magnetic resonance angiography, and perfusion magnetic resonance 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 hrs is recommended before further ancillary testing, using a radionuclide CBF study, is performed allowing adequate clearance of Tc-99m (49, 50). Although no evidence exists for a recommended waiting period between EEG studies, a waiting period of 24 hrs 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 interexamination 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 <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 as a result of the small number of brain-dead neonates reported in the literature (54, 65, 70) and whether there are intrinsic biologic 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 after acute brain injury when compared with older patients. The cascade of events associated with increased intracranial pressure and reduced cerebral perfusion ultimately leading to herniation is 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 <37 wks gestation to determine whether 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 <37 wks 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 wks 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. Like with older children, assessment of neurologic function in the term newborn may be unreliable immediately after an acute catastrophic neurologic injury or cardiopulmonary arrest. A period of ≥24 hrs 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); and 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 hrs and the duration of time from the initial neurologic examination being indicative of brain death to final confirmation was 75 hrs. The overall average duration of brain death in these neonates was approximately 95 hrs or almost 4 days (37). Fifty-three neonates <7 days of age donating organs for transplantation had a to-

tal duration of brain death including time to transplantation that averaged 2.8 days; for neonates 1–3 wks 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 hrs for term newborns (37 wks) 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 presence/absence of brain electrical activity or CBF 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, nine of ten 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 in which 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 like 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 carried out 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; and 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 yrs 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 carried out consistently each time the diagnosis is being considered. A comparison of the 1987 pediatric brain death guidelines and 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 terminology 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.

Studies comparing traditional ancillary studies to newer methods to assess CBF and neurophysiological 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.

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.

Although 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.

Additional information or studies are required to determine whether a single neurologic examination is sufficient for neonates, infants, and children to determine brain death as currently recommended for adults >18 yrs of age (12, 76).

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Appendix 1. Checklist for documentation of brain death in infants and children—two physicians must perform independent examinations separated by specified intervals

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 Half-Life	Neonates Elimination Half-Life
Intravenous induction, anesthetic, and sedative agents		
Thiopental	Adults: 3–11.5 hrs (shorter half-life in children)	
Ketamine	2.5 hrs	
Etomidate	2.6–3.5 hrs	
Midazolam	2.9–4.5 hrs	4–12 hrs (77–80)
Propofol	2–8 mins, terminal half-life 200 mins (range, 300–700 mins)	
Dexmedetomidine	Terminal half-life 83–159 mins (79–81)	Infants have faster clearance (81–83)
Antiepileptic drugs		
Phenobarbital	Infants: 20–133 hrs[a]; children: 37–73 hrs[a]	45–500 hrs[a] (79, 84, 85)
Pentobarbital	25 hrs[a]	
Phenytoin	11–55 hrs[a]	63–88 hrs[a]
Diazepam	1 month to 2 yrs: 40–50 hrs 2–12 yrs: 15–21 hrs 12–16 yrs: 18–20 hrs	50–95 hrs (79, 86, 87)
Lorazepam	Infants: 40.2 hrs (range, 18–73 hrs) Children: 10.5 hrs (range, 6–17 hrs)	40 hrs (88)
Clonazepam	22–33 hrs	
Valproic acid	Children >2 months: 7–13 hrs[a] Children 2–14 yrs: mean 9 hrs; range, 3.5–20 hrs	10–67 hrs[a]
Levetiracetam	Children 4–12 yrs: 5 hrs	
Intravenous narcotics		
Morphine sulfate	Infants 1–3 months: 6.2 hrs (5–10 hrs) 6 months to 2.5 yrs: 2.9 hrs (1.4–7.8 hrs) Children: 1–2 hrs	7.6 hrs (range, 4.5–13.3 hrs) (79, 89–91)
Meperidine	Infants <3 months: 8.2–10.7 hrs (range, 4.9–31.7 hrs); infants 3–18 months: 2.3 hrs Children 5–8 yrs: 3 hrs	23 hrs (range, 12–39 hrs)
Fentanyl	5 months to 4.5 yrs: 2.4 hrs (mean); 0.5–14 yrs: 21 hrs (range, 11–36 hrs for long–term infusions)	1–15 hrs
Sufentanil	Children 2–8 yrs: 97 ± 42 mins	382–1,162 mins
Muscle relaxants		
Succinylcholine	5–10 mins; prolonged duration of action in patients with pseudocholinesterase deficiency or mutation	
Pancuronium	110 mins	
Vecuronium	41 mins	65 mins
Atracurium	17 mins	20 mins
Rocuronium	3–12 months: 1.3 ± 0.5 hrs 1 to <3 yrs: 1.1 ± 0.7 hrs 3 to <8 yrs: 0.8 ± 0.3 hrs Adults: 1.4–2.4 hrs	

[a]Elimination half-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 midtherapeutic range before 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.

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.

Appendix 3. Apnea testing in pediatric brain death

Author	No.	Age Range	$Paco_2$	Comments
Rowland (1984) (41)	9 children, 16 apnea tests performed	4 months to 13 yrs	Range, 60–116 mm Hg after 15 mins 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 and Rockoff (1984) (40)	10 children	10 months to 13 yrs	Mean 59.5 ± 10.2 mm Hg after 5 mins of apnea	No spontaneous respiratory effort noted in any patient during testing or after support was withdrawn
Riviello (1988) (39)	19 children	2 months to 15 yrs	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 to 17 yrs	Mean 68.07 ± 17.66 after 5 mins; mean 81.8 ± 20.2 after 10 mins; mean 86.88 ± 25.6 after 15 mins	1 child had spontaneous respiratory effort with a $Paco_2$ of 49 mm Hg; this patient was retested 24 hrs later and had no respiratory effort

Appendix 4. Electroencephalography in pediatric brain death: Diagnostic yield from first vs. any study

Study	Total No. of Patients in Study	Percent Patients With ECS on EEG 1	Percent Patients With ECS on Any EEG	Percent Patients With ECS on Follow-Up EEG When First EEG Had ECS	Percent Patients 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 and 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)

ECS, electrocerebral silence; EEG, electroencephalogram; NA, not available.

Appendix 5. Cerebral blood flow in pediatric brain death: Diagnostic yield from first vs. any study

Study	Total No. of Patients in Study	CBF 1: Percent Patients With Absent CBF[a]	Percent Patients With Absent CBF on Any Study[b]	Percent Patients With no CBF on Follow-Up Study When First Study Had Shown no CBF	Percent Patients 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 and 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)

CBF, cerebral blood flow; NA, not available.

[a]No. of patients with no CBF on first study/no. of patients with first CBF study; [b]no. of patients with no CBF on any study/no. of patients with any CBF.

Appendix 6. Electroencephalography and cerebral blood flow diagnostic screening yield by age groups

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

CBF, cerebral blood flow; ECS, electrocerebral silence.

[a]Data extracted from references cited in Appendices 4 and 5; [b]data extracted from references cited in Ashwal (35); [c]data represent the differences between "all children" and "just newborns" groups.

Appendix 7. Comparison of 1987 pediatric brain death guidelines and the updated guidelines for determination of brain death in infants and children

	1987	Updated Guidelines
Waiting period before initial brain death examination	Not specified	24 hrs after 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 examination; second examination not necessary in 2 months to 1 yr age group if initial examination, electroencephalography and concomitant cerebral blood flow consistent with brain death	Two examinations 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 to 2 months: 48 hrs 2 months to 1 yr: 24 hrs >1 yr: 12 hrs (24 hrs if hypoxia–ischemia encephalopathy)	Age-dependent Term newborn (37 wks gestation) to 30 days of age: 24 hrs 31 days to 18 yrs: 12 hrs·
Reduction of observation period between examinations	Permitted only for >1 yr age group if electroencephalography or cerebral blood flow consistent with brain death	Permitted for both age groups if electroencephalography or cerebral blood flow 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 to 2 months: 2 electroencephalograms separated by 48 hrs 2 months to 1 yr: 2 electroencephalograms separated by 24 hrs; cerebral blood flow can replace the need for second electroencephalogramhrs >1 yr: no testing required	Not required except in cases in which the clinical examination and apnea test cannot be completed Term newborn (37 wks gestation) to 30 days of age: electroencephalography or cerebral blood flow are less sensitive in this age group; cerebral blood flow may be preferred >30 days to 18 yrs: electroencephalography and cerebral blood flow 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)