Supplementary Online Content

Greer DM, Shemie SD, Lewis A, et al. Determination of brain death/death by neurologic criteria: The World Brain Death Project. *JAMA*. doi:10.1001/jama.2020.11586

Supplement 6. Pediatric and Neonatal Brain Death/Death by Neurologic Criteria

This supplementary material has been provided by the authors to give readers additional information about their work.

Pediatric and Neonatal Brain Death/Death by Neurologic Criteria

Thomas A. Nakagawa, MD[1], Stephen Jacobe, MD, MHL, FRACP, FCICM[2], David Greer, MD, MA[3], Ariane Lewis, MD[4], Gene Sung, MD, MPH[5] Sylvia Torrance, BSc[6], Sam D. Shemie, MD[7]

1) University of Florida, Jacksonville, USA; 2) University of Sydney; The Children's Hospital of Westmead, Westmead, Australia 3) Boston University School of Medicine, Boston, USA; 4) NYU Langone Medical Center, New York, USA; 5) University of Southern California, Los Angeles, USA; 6) Canadian Blood Services, Ottawa, Canada; 7) McGill University, Montreal Children's Hospital, Montreal, Canada

Key words: brain death, neurologic death, pediatrics, apnea, neonatal, coma

Abstract

Introduction This article reviews current global practices for the determination of brain death/death by neurologic criteria (BD/DNC) in infants and children.

Methods Medical literature focusing on BD/DNC for infants and children was reviewed including factors influencing determination of death. Recommendations were developed based on literature review, consensus opinion, and expert commentary.

Results/Conclusions Although less evidence exists compared with adult practice, BD/DNC can be determined in infants and children 36 weeks gestational age and older. No evidence is currently available to guide accurate determination of BD/DNC in preterm neonates less than 36 weeks gestational age. Determination of BD/DNC is a clinical process based on specific criteria consistent across the age spectrum for children, but caution is advised in younger infants. The clinical criteria, indications for and types of ancillary testing for pediatric patients are similar to those for adults. Distinctions between adults and children include variability in pre-test observation periods, number of tests and inter-examination observation periods. The incidence of BD/DNC in children and in particular infants and newborns is much lower than in adults. The process for determination of BD/DNC in infants and children should: outline minimum requirements necessary to determine BD/DNC; identify qualified professionals to determine BD/DNC; and stipulate requirements for documentation of death. Determination of death should occur in a timely manner by qualified individuals with pediatric training. The process of determining BD/DNC should be carefully explained to parents to maximize understanding and confidence in determination of death.

Introduction

The definition of brain death/death by neurologic criteria (BD/DNC) is the same for adults and children. BD/DNC is a clinical diagnosis based on the coexistence of unresponsive coma (loss of brain function), complete loss of brainstem reflexes, and apnea in a person with a known brain injury resulting in an irreversible condition.[1-5] Most countries use whole brain death criteria (brain and brainstem) to determine death in infants and children.[1-5] Ancillary studies are not usually mandatory [1-7], but some protocols recommend them as they may be helpful to the clinician to make a determination of BD/DNC

when components of the physical examination or apnea test cannot be completed.[1-5] Criteria to determine BD/DNC are generally consistent across the age spectrum for children. However, because there is less evidence for determination of BD/DNC in the very young, a cautious approach is advocated when evaluating infants and younger children, resulting in variable age-based recommendations that often require serial examinations including apnea testing.[1-7]

Authors conducted the initial literature searches of the Cochrane, Embase and MEDLINE databases for the time period between January 1, 1992 and July 2017. Subsequent searches were performed to capture relevant articles between July 2017 and April 2020. Because of the significant lack of data from randomized controlled trials or large studies, GRADE evaluation of the evidence was not performed. However, evidence was reviewed by a multidisciplinary group of clinicians (see Introduction chapter) and recommendations were generated according to the following criteria. Strong recommendations ("It is recommended that") were based on expert consensus that clinicians should follow the recommendation unless a clear and compelling rationale for an alternative approach was present, and where actions could be adopted as policy. Even though most evidence in this area is limited and of low-quality, strong recommendations were made as a precautionary, conservative approach, to prevent premature or erroneous determinations of death (false positives). Conditional or weak recommendations ("It is suggested that") were generated when there were potentially different options and the best action may differ depending on circumstances, patients, resources or societal values, or where there is a need for further evidence or discussion among clinicians and stakeholders. In cases where there was insufficient evidence and the balance of benefits versus harms was neutral, no recommendations were made.

Much of the currently available evidence for determination of death in infants and children is from case reports, case series, and limited studies. This information forms the basis for current guidelines that are primarily consensus or expert committee recommendations. A comparison of international guidelines is provided in Table 1. This review discusses determination of BD/DNC for infants and children, assesses currently accepted ancillary studies, and highlights important differences between children and adults that can create challenges when determining death for this population. This review focuses on circumstances where there are unique pediatric considerations and is intended to augment the descriptions of minimum criteria for determination of BD/DNC and use of ancillary testing when compared with the adult population, which are discussed elsewhere in this series.

Definition of a Pediatric Person

The definition of a pediatric person varies by disease process and country. A 'term newborn' ranges from 36-37 weeks gestation, with Australia, Canada and other countries using 36 weeks gestation and the United States, United Kingdom, and Spain defining 37 weeks gestation as the lower age limit for determination of BD/DNC in children. The age of a neonate ranges from 36-37 weeks gestation to 30 days of age.[1-7] The upper age limit for a pediatric person may range from 14-18 years of age depending on mechanism of injury, i.e. trauma.[1,2]

Frequency of BD/DNC in the Pediatric Population

BD/DNC in infants and children is a relatively rare occurrence as the majority of pediatric deaths occur after planned withdrawal of life-sustaining medical therapies.[8-11] Despite this, there is good experience determining BD/DNC in older children; however, far fewer younger children are declared dead by neurologic criteria. In the United States, where there is significant experience determining BD/DNC, the ratio of children (30 days to 18 years of age) declared dead by neurologic criteria compared to adults is 1:100.[8] This ratio increases to 1:1000 for infants less than 30 days of age.[8] BD/DNC accounted for 20.7% of 15,344 deaths in US pediatric intensive care units, with a linear association between PICU size and the number of brain deaths per year.[12] The etiology of neurologic injury leading to BD/DNC in pediatric patients differs from adults, with hypoxic ischemic injury being the most common in infants and younger children, while trauma accounts for most cases of neurologic injury in older children.[8] Cerebrovascular events or spontaneous intracranial hemorrhage are relatively rare when compared with adults.

Physiologic and Anatomic Differences in Children

For the most part, pediatric patients have similar physiology and anatomy as adult patients. However, neonates and infants have patent sutures and open fontanelles that can result in less dramatic increase in intracranial pressure, which can cause ancillary studies, such as radionuclide cerebral blood flow study, to be less reliable.[1,2] The presence of patent sutures and open fontanelles modifies the initial compensation of intracranial hypertension, resulting in a distortion of cerebral hemodynamic patterns that are different from children and adults with a rigid skull. Additionally, there may be subtle, but important, differences in neonatal brain metabolism, blood flow, and response to injury. Pupillary examination can be difficult in neonates or smaller infants, and small airways can affect apnea testing if tracheal insufflation is used. Lastly, in considering unique pediatric populations, it is important to note that anencephalic newborns retain some degree of brainstem function and in the absence of a secondary cause of brainstem injury (e.g. cardiorespiratory arrest) cannot fulfill BD/DNC.

Prerequisite Criteria

Preconditions for the pediatric age group are similar to adults, but it is universally recommended that prerequisite blood pressure for determinations of BD/DNC in pediatric persons must be determined based on age-appropriate physiologic parameters. Unusual causes of coma such as neurotoxins and chemical exposure (i.e. organophosphates and carbamates) should be considered in rare cases where an etiology for coma has not been established.[1,2] Additionally, protocols for determination of BD/DNC frequently specify that inborn errors of metabolism, which could affect hepatic or renal function, need to be considered. Assessment of neurologic function may be unreliable immediately following a catastrophic neurologic injury or cardiopulmonary arrest, requiring an observation period of 12-24 hours or more before initiating testing for neurologic death.[1-7]

Examination Criteria

Physical examination criteria are generally the same for children and adults. Patency of the auditory canal should be assessed for tortuosity, foreign body or cerumen obstruction. Some protocols include the assessment of the rooting and/or sucking reflex in the newborn age group.

Testing for Apnea

The preconditions, testing parameters, CO_2 targets and complications for apnea testing are similar in adults and children. The rate of CO_2 rise is approximately 3-5 mmHg per minute.[1,2] Procedurally, protocols for determination of BD/DNC in pediatric persons generally recommend maintenance of oxygenation during the apneic period using either a T-piece circuit connected to the endotracheal tube or a flow-inflating anesthesia bag with titration of end expiratory pressure. Tracheal insufflation is less favored, particularly in younger children/infants/newborns due to carbon dioxide washout and risk of barotrauma if the catheter is advanced too distally into the airway.[1,2,4] A $PaCO_2$ of $\geq$ 60 mmHg (8.0 kPa) is generally considered adequate to stimulate respiration although some authors have suggested the threshold might be higher in neonates and infants [1-5,7], while others have suggested the immature medulla may in fact be more sensitive to hypoxemia.[13] An increase in the $PaCO_2$ of at least 20 mmHg (2.7 kPa) above the baseline is recommended in many jurisdictions to ensure there is an adequate stimulus for respiration [1-3,7]. This is especially true for children with pre-existing lung disease and chronic CO_2 retention. Some guidelines also include a pH threshold.[3,4,7] Although a single apnea test is performed in many jurisdictions [3-7], some guidelines consider apnea testing part of the examination for BD/DNC and recommend performing an apnea test with each neurologic examination, providing this can be done safely.[1,2,4] Case reports of respiratory effort occurring with higher $PaCO_2$ levels during apnea testing have been published, however, the currently available evidence is not compelling enough to suggest increasing the threshold.[14] There are no pediatric specific distinctions related to performing the apnea test during extracorporeal support.

One unique aspect of apnea testing in infants and children is management of children with cyanotic congenital heart disease who have obligatory intracardiac right-to-left shunting leading to chronic hypoxemia and polycythemia based on their cardiac physiology. Baseline oxygen saturations generally range from 65-90%.[15] There are no published reports to guide the clinician tasked with safely performing an apnea test to determine BD/DNC in this population. The inability to perform an apnea test in this population would mandate an ancillary study to determine BD/DNC.

Number of Examinations and Observation Periods

A more cautious approach to determining BD/DNC has been recommended in children and most jurisdictions require more examinations (a minimum of two) and a longer observation period than is required in adults.[1-7] Rare, case reports of false positive testing have been reported[16] emphasizing the continued need for a cautious and conservative approach when determining BD/DNC, especially for young infants with open sutures and children with skull fractures or decompressive craniotomy that can alter intracranial pressure dynamics. In some countries, such as the UK, 2 physicians are required to be present for 2 separate evaluations to determine BD/DNC in children.[6,7] In the USA, UK, Australia, Canada, and New Zealand, apnea testing is regarded as part of the examination criteria, and is recommended with each examination.[1-6]

Assessment of brain function following a devastating neurologic injury or cardiopulmonary arrest may be unreliable immediately following the event and therefore many guidelines recommend a period of observation ranging from 24-48 hours or greater to allow stabilization of a pediatric person and to ensure that prerequisite criteria have been met prior to testing for BD/DNC.[1-7] The evidence guiding

determination of BD/DNC in the neonatal population is sparse compared with that for older children and adults.[1,2] For term newborns, many jurisdictions recommend a minimum observation period of 24-48 hours or longer before considering neurologic testing for death.[3-6]

Observation periods between examinations for infants and children have been arbitrarily defined. There are no studies to indicate that a longer or shorter observation period is more sensitive when determining BD/DNC in children. Reports of diagnostic error have been noted in children. In these case reports, prerequisite criteria, including appropriate observation periods, were not met, thereby invalidating the determination of BD/DNC.[17] A conservative approach requiring an observation period between examinations has been recommended for younger infants and children because of limited experience compared with adults.[1-5] Consecutive examinations without an inter-examination observation period are used in some countries while most other countries have pre-defined inter-examination observation period with some jurisdictions recommending a 12-hour inter-examination observation for children older than 30 days of age and older.[1,2,7] A 24-hour inter-examination observation period is recommended for neonates and infants 37 weeks gestation to 30 days of age in many current pediatric guidelines.[1,2,4,5]

Ancillary Studies

Similar to adults, ancillary studies are neither mandated to make a determination of BD/DNC in infants and children, nor are they sufficient on their own to determine BD/DNC. Ancillary studies are used to 'compliment' the clinical examination with continued emphasis that BD/DNC is a clinical diagnosis. The use of ancillary studies is usually reserved for situations where a full clinical examination and apnea test cannot be completed and where there is a high probability that the person is, in fact, dead by neurologic criteria. A recent survey of US pediatric intensivists and neurologists showed that while most respondents only performed ancillary testing if the clinical examination and apnea test could not be completed, variability exists, with 20% of 195 respondents performing ancillary testing for other reasons, including: to convince a family that objected to the brain death determination that a patient is truly dead, personal preference, and institutional requirement.[18] Currently recommended ancillary testing in children includes cerebral blood flow (CBF) studies including 4 vessel angiography and nuclear perfusion studies, and electroencephalography (EEG). Notably, ancillary testing in very young pediatric patients is unique because there can be persistence of blood flow in the context of BD/DNC due to the presence of an open fontanelle.[19] Intracranial pressure dynamics can also be altered with cranial fractures or decompressive craniotomy. While 4 vessel digital subtraction angiography has long been the gold standard for determination of absent CBF, the limited availability of interventional neuroradiology and technical challenges involved in performing angiography in infants and small children has led to this procedure now being rarely if ever performed in pediatric patients. Nuclear medicine cerebral perfusion studies are probably the most common ancillary studies currently performed in children in most jurisdictions [1-7], and while EEG and CBF are of similar confirmatory value for infants older than 30 days of age, they are both less sensitive in newborns. [1,2]

Perfusion CT, MR spectroscopy, and transcranial Doppler sonography (TCD) have been proposed as potential ancillary studies; however, operator dependency and lack of validation compared with traditionally accepted ancillary studies limit their reliability in children. Studies using somatosensory evoked potentials and brainstem auditory evoked potentials as a reliable ancillary study for determination

of BD/DNC in infants and children are limited and also lack validation. More research is needed in this area and none of these studies can be recommended at this time as a suitable ancillary study to assist with BD/DNC in infants and children.

Special Considerations:

Hypothermia

Targeted temperature management and hypothermia protocols are being used more frequently following cardiac arrest and traumatic brain injury. This is especially true in the neonatal population where hypothermia protocols are commonly used for neonatal asphyxia.[20] Adequate time following rewarming after a period of hypothermia is crucial prior to initiating testing for BD/DNC. Additionally, delayed drug metabolism and end organ function must be considered when hypothermia protocols have been instituted, and an observation period of 72 hours or longer may be required in some cases. [21-23] Please refer to the chapter on determination of brain death and targeted temperature management for further discussion and recommendations.

Documentation of BD/DNC

Many pediatric guidelines for determination of BD/DNC in infants and children incorporate a checklist to ensure standardization of the process and documentation.[1-4,6,7] Documentation is described in further detail in the Documentation of Brain Death chapter.

Additional considerations

It is well-acknowledged that the neurological examination to determine death in pediatric patients should only be performed by clinicians with training in pediatric critical care, neonatology, pediatric neurology or neurosurgery, or trauma, who are suitably qualified to perform the clinical examination including apnea testing and interpret the results of ancillary studies. Clear and concise communication with the child's parents to explain the process to determine BD/DNC and ensure they have confidence in this process is critical.[10] Many protocols advise utilization of palliative care specialists and other support services such as social workers and spiritual care providers to assist the grieving family following the death of their child.[10,24,25]

Recommendations and Suggestions

1. It is recommended that the minimum criteria for a determination of BD/DNC in all pediatric age groups be the same as in adults, with an assessment of prerequisites, elimination of confounders, and performance of a clinical examination including apnea testing. Age-appropriate prerequisite hemodynamic targets should be applied.
2. It is suggested that BD/DNC can be determined in newborns as defined by age ≥ 36 weeks gestation.
3. It is suggested that there is insufficient supporting evidence to accurately determine BD/DNC in newborns < 36 weeks gestation.
4. It is recommended that two examinations, including apnea testing, represent the minimum standard for determination of BD/DNC in the pediatric population. A cautious approach with

serial examinations and an adequate observation period is recommended to minimize the risk of diagnostic error.

5. It is recommended that those in the pediatric population be observed for unresponsive coma for a minimum of 24 hours prior to initial testing following birth asphyxia, resuscitated cardiac arrest and after rewarming from therapeutic hypothermia.
6. It is suggested that clinical criteria for determination of BD/DNC in newborns include the sucking and rooting reflexes.
7. It is suggested that recommendations for apnea testing targets in pediatrics are the same as in adults.
8. It is recommended that tracheal insufflation should not be used for apnea testing in newborns, infants and young children.
9. It is suggested there are no pediatric specific distinctions related to performing the apnea test during extracorporeal support.
10. It is recommended that ancillary studies are not routinely required to determine BD/DNC in the pediatric population.
11. It is recommended that indications for ancillary testing are the same as in adults.
12. It is recommended that similar to adults, radionuclide cerebral blood flow study is an accepted and preferred ancillary study.
13. It is suggested at the present time that EEG, performed and interpreted in accordance with published guidelines, is also considered a valid ancillary study in infants and children and can be used in certain jurisdictions.
14. It is recommended that transcranial Doppler should not be used as an ancillary study in pediatrics at this time until more studies determine the validity of this study.
15. It is suggested that in a person with chronic hypoxemia due to cyanotic heart disease, apnea testing not be performed and instead an ancillary study be conducted to assist with determination of BD/DNC.
16. It is recommended that experienced pediatric clinicians with training and qualifications in pediatric critical care, neonatology, pediatric neurology, pediatric neurointensive care, neurosurgery or traumatology perform testing to determine BD/DNC in pediatrics.
17. It is recommended that standardized checklists be incorporated into the practice of determining neurologic death in pediatrics to reduce operator variability and diagnostic error.

Questions to Inform Research Agendas

1. Can guidelines for pediatric and adult BD/DNC be harmonized?
2. Is a single examination practical and safe to determine BD/DNC for children?
3. What is the incidence of diagnostic error with current practice of determination of BD/DNC in infants and children, and what measures must be adopted to eliminate such error?
4. Despite differences in etiology of pediatric traumatic brain injury, after full ossification of the skull by the age of two, is the pathophysiology of BD/DNC the same as in adults?
5. Is the validity of the $PaCO_2$ threshold for apnea testing in infants and children similar to adults?
6. Can transcranial Doppler, perfusion CT, MR spectroscopy, somatosensory evoked potentials be prospectively studied and validated as ancillary studies in the pediatric age group?
7. Are there ancillary studies that might be more reliable in neonates?

References

1. Nakagawa TA, Ashwal S, Mathur M, Mysore M, Committee For Determination Of Brain Death In Infants C. Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations-executive summary. *Ann Neurol.* 2012;71(4):573-585.
2. Nakagawa TA, Ashwal S, Mathur M, et al. Clinical report-Guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations. *Pediatrics.* 2011;128(3):e720-740.
3. Shemie SD, Doig C, Dickens B, et al. Severe brain injury to neurological determination of death: Canadian forum recommendations. *CMAJ.* 2006;174(6):S1-13.
4. Society AaNZIC. The ANZICS Statement on Death and Organ Donation (Edition 3.2) 2013.
5. Spanish Royal Decree 1723/2012 regulating the activities of recovery, clinical use and territorial coordination of human organs intended for transplantation and setting quality and safety standards. 2012; https://www.boe.es/boe/dias/2012/12/29/pdfs/BOE-A-2012-15715.pdf. Accessed January 3, 2018.
6. Royal College of Pediatrics and Child Health. The diagnosis of death by neurological criteria in infants less than 2 month old. https://www.rcpch.ac.uk/improving-child-health/clinical-guidelines/find-paediatric-clinical-guidelines/published-rcpch/diagn Accessed February 6, 2018. 2015.
7. Academy of Medical Royal Colleges. A Code of Practice for the Diagnosis and Confirmation of Death. 2008. https://bts.org.uk/information-resources/publications/). 2008.
8. OPTN: Organ Procurement and Transplantation Network. https://optn.transplant.hrsa.gov/data/view-data-reports. Accessed February 2, 2017.
9. Burns JP, Sellers DE, Meyer EC, Lewis-Newby M, Truog RD. Epidemiology of death in the PICU at Five U.S. teaching hospitals. *Critical Care Medicine.* 2014;42(9):2101-2108.
10. Martin DE, Nakagawa TA, Siebelink MJ, et al. Pediatric Deceased Donation-A Report of the Transplantation Society Meeting in Geneva. *Transplantation.* 2015;99(7):1403-1409.
11. Workman JK, Myrick CW, Meyers RL, Bratton SL, Nakagawa TA. Pediatric organ donation and transplantation. *Pediatrics.* 2013;131(6):e1723-e1730.
12. Kirschen MP, Francoeur C, Murphy M, et al. Epidemiology of Brain Death in Pediatric Intensive Care Units in the United States. *JAMA Pediatr.* 2019.
13. Joffe AR, Anton NR, Duff JP. The Apnea Test: Rationale, Confounders, and Criticism. *Journal of Child Neurology.* 2010;25:1435-1443.
14. Sosa T, Berrens Z, Conway S, Stalets EL. Apnea Threshold in Pediatric Brain Death: A Case with Variable Results Across Serial Examinations. *J Pediatr Intensive Care.* 2019;8(2):108-112.
15. Desai K, Rabinowitz EJ, Epstein S. Physiologic diagnosis of congenital heart disease in cyanotic neonates. *Curr Opin Pediatr.* 2019;31(2):274-283.
16. Shewmon DA. False-Positive Diagnosis of Brain Death Following the Pediatric Guidelines: Case Report and Discussion. *J Child Neurol.* 2017;32(14):1104-1117.

17. Joffe AR, Kolski H, Duff J, deCaen AR. A 10-month-old infant with reversible findings of brain death. *Pediatr Neurol.* 2009;41(5):378-382.
18. Lewis A, Adams N, Chopra A, Kirschen MP. Use of Ancillary Tests When Determining Brain Death in Pediatric Patients in the United States. *J Child Neurol.* 2017;32(12):975-980.
19. Flowers WM, Jr., Patel BR. Persistence of cerebral blood flow after brain death. *South Med J.* 2000;93(4):364-370.
20. Newborn CoFa, Papile LA, Baley JE, et al. Hypothermia and neonatal encephalopathy. *Pediatrics.* 2014;133(6):1146-1150.
21. Mulder M, Gibbs HG, Smith SW, et al. Awakening and withdrawal of life-sustaining treatment in cardiac arrest survivors treated with therapeutic hypothermia*. *Crit Care Med.* 2014;42(12):2493-2499.
22. Gold B, Puertas L, Davis SP, et al. Awakening after cardiac arrest and post resuscitation hypothermia: are we pulling the plug too early? *Resuscitation.* 2014;85(2):211-214.
23. Grossestreuer AV, Abella BS, Leary M, et al. Time to awakening and neurologic outcome in therapeutic hypothermia-treated cardiac arrest patients. *Resuscitation.* 2013;84(12):1741-1746.
24. Owens D. The role of palliative care in organ donation. *Journal of Hospice and Palliative Nursing.* 2006;8:75-76.
25. Boss R, Nelson J, Weissman D, et al. Integrating palliative care into the PICU: a report from the Improving Palliative Care in the ICU Advisory Board. *Pediatr Crit Care Med.* 2014;15(8):762-767.
26. Takeuchi K, Iinuma K, Ogawa Y, et al. Report on the criteria for the determination of brain death in children. Part II: Determination of brain death in children in Japan. *Japan Medical Association Journal.* 2002;45(8):336-357.

Table 1. Comparison of pediatric guidelines to determine neurologic death

	United States[1,2]	Canada[3]	United Kingdom[7]	United Kingdom[6]	Australia/ New Zealand[4]	Spain[5]	Japan[26]
Year of publication	2011	2006	2008	2015	2013	2012	2002
Pediatric specific	Yes	Yes	No	Specific to children <2 months of age	No	No	Yes for children <6 years of age
Definition	Whole brain	Whole brain	Brainstem	Brainstem	Whole brain	Whole brain	Whole brain
Lower age limit	37 weeks	36 weeks	2 months	37 weeks	36 weeks	37 weeks	12 weeks from (estimated) birth date
Minimum temperature	>35°C	≥34°C ≥36°C for newborns	>34°C	>34°C	>35°C	>35°C for children <24 months of age	≥35°C
Observation period before testing for neurologic death	Min. 24 hrs post arrest or catastrophic injury	24 hrs post arrest	24 hrs post HIE	24 hrs post asphyxiation or resuscitation	24 hrs post arrest	48 hrs	Not mentioned
Neonatal observation period after birth	24 hrs	48 hrs	N/A	Not specified. 24 hours post asphyxiation or resuscitation	24-48 hrs	Not specified	Not mentioned
Number of examinations	2	2	2	2	2	2	2
Inter-examination observation period (hours)	24 hrs <30 days 12 hrs >30 days	24 hrs <30 days Not specified >30 days; No required inter-examination period for age >1 year	Not specified	Not specified	24 hrs <30 days None >30 days	48 hrs <37wk 12 hrs 37 wk-30 days 12 hrs >30 days-24 months 6 hrs >24 months	≥24 hrs
Number of apnea tests	1 with each exam	1 - 2	1	1	1 with each exam	1	2
$PaCO_2$ threshold	≥60 mmHg	≥60 mmHg	≥48 mmHg	>60 mmHg	≥60 mmHg	≥60 mmHg	≥60 mmHg
$PaCO_2$ rise above baseline	20 mmHg	20 mmHg		20 mmHg			
pH threshold	None	≤7.28	<7.4	None	7.3	None	None
Ancillary studies required	No	No	No	No	No	No unless hypothermia, drug intoxication, hypothermia, or severe cranio-cephalic injury affecting brain death testing	Yes
Period of normothermia after therapeutic hypothermia	Recommend 24 hrs	Not mentioned	Not mentioned	24 hrs	24 hrs	Not mentioned	Not mentioned
Who declares death	Attending physician	Physician	Physician	Physician	Physician	Physician	Physician

- HIE = hypoxic ischemic encephalopathy
- Definition of death was incorporated into all guidelines
- Confounding variable or preconditions were discussed in each guideline
- Spain requires an atropine test to determine neurologic death. Heart rate should not increase by >10% over baseline in the patient who is neurologically dead.