Chapter 6

Brain Death in Children

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Abstract

Brain death (BD) is a distinct mode of death in pediatric intensive care units, accounting for 16–23% of deaths. Coma, absent brainstem reflexes, and apnea in a patient with acute irreversible neurological insult should alarm the attending physician to start the appropriate actions to establish or refute the diagnosis for BD. BD diagnosis is clinical, starting with the preconditions that should be met, and based on the examination of all brainstem reflexes, including the apnea test. Apnea testing should be conducted according to standard criteria to demonstrate the absence of spontaneous respirations, in the case of an intense ventilatory stimulus, setting at increased $PaCO_2$ levels ≥60 and ≥20 mm Hg, compared to baseline. When elements of clinical examination and/or apnea test cannot be performed, ancillary studies to demonstrate the presence/absence of electrocerebral silence and/or cerebral blood flow are guaranteed. Two clinical examinations by qualified physicians at set intervals are required. Time of death is the time of second examination and ventilator support should stop at that time, except for organ donation. The use of check list in documentation of BD helps in the uniformity of diagnosis and fosters further trust from medical, family, and community personnel.

Keywords: brain death, pediatric intensive care unit, apnea testing, brainstem reflexes, coma

1. Introduction

The evolution of intensive care has led to circumstances that a human being could be artificially maintained in life through technological advancements even in the presence of

an irreversible neurological damage. Brain death (BD) in most instances occurs when an acute insult to the brain causes a neuropathologic viscious cycle of brain edema, increases intracranial pressure (ICP), and decreases cerebral blood flow that compromise blood supply to the brain and results in ischemia, a situation which resembles to "total brain infarction" according to Swedish Committee on defining death [1]. Severe traumatic head injury, infections, tumors, cerebral vascular accidents, or acute global anoxic/ischemic injury following severe respiratory failure, shock, or cardiac arrest are the main causes of BD in children [2]. Rarely, acute toxic neuronal injury as happened in fulminant hepatic failure or other metabolic diseases are the reasons, or cellular dysoxia, which prevents extraction or utilization of oxygen, as is the case in cyanide poisoning.

Brain death is a distinct mode of death both in adult and pediatric population; it is estimated that BD accounts for approximately 16–23% of deaths in the pediatric intensive care unit (PICU), while the corresponding values for adults are quite similar and depending on the nature of the unit, rising from 15% in multidisciplinary units up to 30% in neurocritical units [3–6]. Most research about BD involves adults; however, not all principles regarding BD could be transferred to children. The pediatric brain is immature; the development, plasticity, and maturation of central nervous system (CNS) ends by the 2 years of age according to the majority of researchers, while others believe to continue beyond the first decade of life [7]. Moreover, resilience to certain forms of injury could be found, due to the open fontanelles in infancy and the presence of certain forms of diseases that result in hydranencephalia and cerebral atrophy, and/or wide craniectomy, that could hasten the progress of intracranial hypertension. The above should be considered when interpreting diagnosis and confirming BD in infants and children [8].

The first effort to define BD as a new criterion for death was made in 1968 by a consensus report of the Ad Hoc Committee of the Harvard Medical School, without specific recommendations with respect to age [9]. Irreversible coma was defined as unresponsiveness to external stimuli, absent movements or breathing, absent reflexes, and a flat electroencephalograph (EEG).Later on, in 1975, on a review of the Harvard criteria by the American Academy of Neurology (AAN), they question the applicability of the consensus criteria to children stating that the above criteria may be inapplicable for children under 5 years of age since there are indications that the immature nervous system can survive significant periods of electrocerebral silence. In an effort to set a standard national definition on BD, in 1981, in the USA, the Uniform Determination of Death Act was adopted as part of the President's Commission [10]. Death was determined in accordance with accepted medical standards either as an irreversible cessation of circulatory and respiratory functions of a person, or irreversible cessation of all functions of the entire brain, including the brain stem. Age-specific guidelines were again not provided and medical standards were not described, and the commission recommended caution in applying neurological criteria to determine death in children younger than 5 years.

In 1995, the Quality Standards Subcommittee of the AAN published the practice parameters for determining brain death in adults to delineate the medical standards for the determination of BD in patients older than 18 years. The document emphasized the three cardinal clinical findings necessary to confirm irreversible cessation of all functions of the entire brain, including the brainstem: *coma or unresponsiveness* (with known cause), *absence of brainstem reflexes*,

and *apnea*. Future research in apnea testing, and the need for validation of confirmatory tests was recommended [11]. However, despite the published parameters, considerable practice variations were recorded, which led to the 2010 update that sought to use evidence-based methods to answer questions historically related to variations in BD determination, to promote uniformity in diagnosis [12].

The irreversible cessations of all functions of brain, including the brainstem, are not universally accepted; the definition of BD in each nation depends on jurisdiction. In the USA, Australia, and New Zealand for example, a whole brain death definition is accepted. On the contrary, in the UK, India, and Canada a brainstem-based definition of death is in place and the term "death by neurological criteria" (DNC) is adopted [13–16]. In the UK, the most recent definition for DNC was published in 2008 by the Academy of Medical Royal Colleges (AoMRC) in the code of practice for the diagnosis and confirmation of death. Consciousness and breathing capacity were recognized as essential characteristics of life and the irreversible loss of them were regarded equal to death [13]. The applicability of the criteria in infants younger than 2 months were questioned, in agreement with a report presented by the British Paediatric Association (BPA) in 1991, which stated also that the criteria of DNC cannot be applied in infants younger than 37 weeks of gestation [17]. Caution was relieved by the guidelines issued in 2015 by the Royal College of Paediatrics and Child Health (RCCHD) considering the diagnosis of DNC in infants from 37 weeks corrected gestation (postmenstrual) to 2 months (postterm) of age. RCCHD stated that the 2008 criteria of death could be applied to this population with precautionary measures regarding the apnea test due to immaturity of the newborn infant's respiratory system [18].

The first specific pediatric guidelines on BD were issued in 1987 by the American Academy of Pediatrics (AAP) to solve questions and give answers for this special topic. These guidelines were a consensus opinion regarding necessary clinical history, physical examination criteria, observation periods, and ancillary laboratory tests required to determine brain death in children[19]. An update followed in 2011, with emphasis given to two different age populations: the one from newborn 37 weeks gestation to 30 days of life and the other from 31 days of life to 18 years [20]. These guidelines could serve as a basis for the development of national guidelines at each nation, taking into account legal, cultural, and religious differences, and will be analyzed in this chapter, enriched by the experience of a single centre and the discussion of relevant references.

BD in most occasions is intertwined to organ harvesting and transplantation, and much research in the field has been done through national organ procurement databases [21, 22]. Nevertheless, the declaration of BD should be done by the patient physicians only, according to local national and institutional guidelines, irrespective from the transplantation team [23, 24]. The priority of the medical system is to save lives rather than to obtain organs and the public must feel confident that they would become organ donors only after all reasonable attempts to save their lives have failed. Maintenance of public trust is essential for the functioning of organ transplantation systems around the world [24]. BD is still a controversial issue for some physicians, and civilians as well, who deny the conceptual basis for equating an irreversibly nonfunctioning brain with a dead human being [25]. Though, the ethical, psychosocial, and

philosophical approach of BD is beyond the scope of this chapter which will concentrate on the biological and clinical approach only of pediatric patients dying from BD.

2. Dying from BD in the PICU

Regardless some terminology differences between the most widely USA definition of BD as the death of the whole brain, and the UK definition of death by DNC as the death of the brainstem, the concept that is universally accepted is that *the patient dying from BD suffered an acute irreversible CNS insult that resulted to coma, absent brainstem reflexes, and apnea* [7]. Although cases of confirmation of BD in children have been described outside the PICU, the proper place where the patients should be treated and diagnosis takes place is the PICU [22–24]. Frequently, the first indication by the bedside nurse is the lack of spontaneous awakening periods, the absence of cough during suctioning, and the fixed dilated pupils, which should alarm the attending physician that the patient deteriorates, and may be is going to BD. All sedative medications, including antiepileptic drugs and neuromuscular blocking agents, should stop at that time, the patient should continue to receive the maximum supportive intensive care treatment to preserve homeostasis, and the preparations should begin to establish or refute the diagnosis of BD. The diagnosis of BD is confirmed by clinical examination criteria only, based on the absence of neurologic function with a known irreversible cause of coma. Ancillary studies are not required except in cases where the clinical examination and apnea test cannot be completed [13, 14, 20].

3. Management of critically ill children dying from BD

For the better understanding of the evolution to BD in children, we will present the sequence of the events that happen in pediatric patients treated in a PICU after a severe neurological insult, step by step, in a timely manner. Our data were obtained from a retrospective study regarding all deaths that occurred between January 2011 and April 2016, in a multidisciplinary eight-bed PICU of Northern Greece. Among 275 deaths, 44 (16%) were defined as BD. The incidence was higher in boys (28/44 patients, 63.6%). Mean age was 68.75 ± 44.04 months (range 2 months to 13 years) and mean severity of illness as estimated with the pediatric risk of mortality (PRISM III-24 h) score at admission was 21.67 ± 9.98. Head injury was the most frequent cause of BD (29.41%) followed by CNS infection (23.52%), hypoxic/ischemic insults (23.52%), CNS tumors (11.76%), and intracranial bleeding (11.76%).

The management of the patients was done under the relevant for the diagnosis international protocols, under sedation, mechanical ventilation, chemoprophylaxis, gastric ulcer prophylaxis, and artificial nutrition. At admission, 88.6% of patients were already on mechanical ventilation and almost half of them (52.3%) were in shock. Central venous catheters and arterial lines were inserted in all patients. Nine patients (20.5%) had intracranial pressure (ICP) monitoring. Almost all received osmotherapy with either NaCl 3% (37 patients, 84.1%) and/or mannitol 20% (36 patients, 81.8%). Sedation was achieved with midazolam at mean max

dose of 0.93 ± 0.56 mg/kg/h and remifantanil at max dose of 0.09 ± 0.05 mcg/kg/min. Cis-attracurium was administered for neuromuscular blocking at a bolus dose of 0.2 mg/kg, as needed before interventions, e.g., suctioning to avoid inadvertent increase in ICP. Sodium thiopental at a max dose of 5 mg/kg/h was administered in 18 patients (40.9%) and four patients (9.1%) were treated with craniectomy, as a third tier therapy to refractory intracranial hypertention [26]. Diabetes insipidus was recorded in 33 patients (75%), and high sugar levels needed insulin therapy in 19 patients (43.2%). The higher serum Na and sugar levels that were recorded were 165 ± 15.39 mmol/l and 281 ± 159.07 mg/dl, respectively. During their stay, the majority of the patients (79.5%) needed inotropic and/or vasopressor support to preserve an acceptable hemodynamic status.

The clinical suspicion on BD was set on 3.59 ± 5.46 day through dilated unreacted pupils. Mean pupil size at admission was 4.07 ± 2.06 mm which was increased to the final size of 6.28 ± 1.13 mm. Following that all the prerequisites of BD were fulfilled, two clinical examinations were performed by a panel of three doctors registered for at least 2 years; one anesthetist, one neurologist or neurosurgeon, and the attending physician (pediatrician or pediatric surgeon), according to the Greek law. Mean sedation time was 4.02 ± 3.03 days. The first tests were done in 9.88 ± 6.50 days after admission and the second in 11.28 ± 6.53 days. Mean time between tests was 27.54 ± 11.80 h. Apnea testing was prepared according to national BD protocol, with preoxygenation with 100% oxygen for at least 10 min, and baseline mechanical ventilation aimed at 40 mmHg of $PaCO_2$ [11]. Oxygenation during apnea was done through a catheter tailored to endotracheal tube (ETT) size (size in CH doubled the ID size of ETT in mm), inserted in the endotracheal tube at a length corresponded to tracheal carina, with a flow of 1 l/min/age in years, initially, according to acute pediatric life support (APLS) recommendation for apneic oxygenation [27]. If oxygenation was inadequate, a gradually increase in O_2 flow in increments of 1 l/min up to max 12 l/min was performed [12]. For this purpose, we used a simple suction catheter of appropriate size as described above, with the valve occluded, and connected to an oxygen flow source, preferably a low pressure one (capable of giving oxygen at driving pressure of 1–2 bar). In the case of acute respiratory distress syndrome (ARDS), hypoxia, and need for high positive end expiratory pressure (PEEP), apnea testing was performed on continuous positive airway pressure (CPAP) modality. Duration of apnea was 10 min if feasible, or earlier if signs of hypoxia and/or hypotension appeared. Apnea testing was considered positive for BD if no spontaneous respiration occurred when the $PaCO_2$level was >60 and >20 mmHg compared to baseline, in accordance with international guidelines [11, 12, 14].

A total of 88 apnea tests were recorded. Incomplete data concerning the way of oxygenation during the apnea test were revealed in 50% of the tests, probably due to the retrospective data analysis and incomplete recordings. Thirty-six patients (81.81%) completed the test successfully. Eleven apnea tests (12.5%) were aborted, mainly due to hypoxia (8/11, 72.72%) and to a lesser degree due to shock (3/11, 27.27%). In detail, four patients did not manage to complete the first apnea test (three hypoxia, one shock), while seven patients aborted the second test (five hypoxia, two shock). The data of apnea testing are presented in **Table 1**. Ancillary study with magnetic resonance angiography (MRA) was carried out in eight patients (18.18%). Patients died 54.58 ± 59.64 h after the completion of the second apnea test. Three families (6.81%) gave consent for organ donation.

	Mechanical ventilation mode	FiO_2%	pH	PaO_2 (mmHg)	$PaCO_2$ (mmHg)
Baseline	IPPV (68.4%)	50.8 ± 20.6	7.44 ± 0.062	133.88 ± 33.90	33.36 ± 4.60
	PRVC (22.5%)				
	SIMV-PS (9.1%)				
A. prep.		100	7.33 ± 0.084	382 ± 97.59	45.46 ± 4.18
A. Apnea test	CPAP (20.4%)	100	7.10 ± 0.063	235 ± 107.18	84.15 ± 10.53
	Tracheal O_2 (29.6%)				
	NA (50%)				
B. Prep.		100	7.33 ± 0.073	354 ± 127	45.21 ± 5.20
B. Apnea test	CPAP (22.7%)	100	7.11 ± 0.063	223 ± 129.72	84.79 ± 13.99
	Tracheal O_2 (25%)				
	NA (52.3%)				

IPPV, intermittent postitive pressure ventilation; PRVC, pressure regulated volume control; SIMV-PS, synchronized intermittend mandatory ventilation-pressure support; CPAP, continuous positive airway pressure; Tracheal O_2, tracheal insufflation of oxygen at age-related flows of 1 l/min/age (max 12 l/min); NA, not applicable (lack of data).

Table 1. Data of apnea testing (n = 77) in pediatric BD patients (n = 44).

4. Guidelines for the determination of BD in infants and children

4.1. Definition of BD

In 2011, a multidisciplinary committee was formed by the Society of Critical Care Medicine (SCCM) and the AAP to update the 1987 Task Force Recommendations for the diagnosis of pediatric BD [12, 14, 20]. According to guidelines, *BD 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 DB. A complete neurologic examination is mandatory to determine BD with all components appropriately documented. An algorithm for the diagnosis of BD in children adapted from Ref. [20] is provided in Appendix 1.

4.2. Age definition

Two age definitions were set with an impact on the timing of first exam and the observation period between tests.

- Newborns 37 weeks gestation to 30 days of life.
- Infants 31 days of life to 18 years.

Because of insufficient data in the literature, recommendations for preterm infants less than 37 weeks gestational age were not included in this guideline.

4.3. Timing of first exam

- Twenty-four hours for patients aged from 37 weeks gestation to 30 days of life. Time is counted after birth, cardiac arrest with successful resuscitation or other severe neurological insult.
- Twelve hours for patients aged 31 days of life to 18 years. Time is counted after cardiac arrest with successful resuscitation or other severe neurological insult.

It is reasonable to defer neurologic examination to determine brain death for longer than 24 h, if dictated by clinical judgment of the treating physician. Neonates who probably suffered from hypoxic/ischemic insult during the neonatal period and had been put in therapeutic hypothermia deserve a longer observation time before the first examination. Hypothermia not only could interfere with brainstem reflexes interpretation but hastens drug metabolism as well. In addition, the first examination should be postponed beyond 24 h if residual drug effect is suspected. In general, the first examination cannot be performed unless all the preconditions of diagnosing BD are met.

4.4. Irreversible and identifiable cause of coma

A known and irreversible cause of coma should be established before the diagnosis of BD. In most instances, the evolution of a brain damage to BD is depicted with computed tomography (CT) or magnetic resonance imaging (MRI). Sometimes, neuroimaging if performed early enough in the course of the disease is without significant findings. Serial examinations in such occasions are helpful. CT and MRI are introductory studies and should not be relied on to make the determination of brain death. Additional data such as results from cerebrospinal fluid (CSF) analysis and/or other microbiological data are supportive [12]. In 2011 AAP guidelines, three major causes of coma were recognized: traumatic brain injury, anoxic brain injury, and known metabolic disorder. In cases that the cause of coma is not identifiable, the physician should specify the cause of coma as "Other." It is advisable to keep these major causes when recording BD, which will enable international comparisons, if needed.

4.5. Preconditions

The interpretation and validity of the clinical neurological examination and the apnea testing should not leave any space for concern. All the potentially influencing factors must be corrected in advance and the subsequent undeniable preconditions must be met:

- *Cardiovascular stability.* Mean or arterial systolic pressure should be normal for age (no less than two standard deviations from the mean age responding values). Inotropic and vasomotor support may be necessary for the treatment of shock. Direct arterial pressure measurement is strongly recommended, not only for the monitoring but for blood gases analysis and $PaCO_2$ evaluation as well, which is an integral part of the apnea testing that follow.

- *Normothermia.* Therapeutic hypothermia is increasingly used as an adjunctive therapy of the insulted brain and the physician should be aware of the potential hypothermia impact on the diagnosis of brain death. Hypothermia is a depressant to central nervous system activity and may lead to a false diagnosis of brain death. Metabolism and clearance of medications are retarded, which can interfere with brain death examination. Achieving normothermia with a core body temperature of 35°C (95°F) before the first exam and maintaining it throughout the observation period is essential.
- *Homeostasis.* The most common metabolic disturbance during BD is hypernatremia due to diabetes insipidus that should be corrected with the administration of antidiouretic hormone or desmopressin. Hyperglygemia is common too, and close monitoring of glucose levels and treatment with insulin when necessary is indicated. Hyponatremia, hypoglycemia, hypothyroidism, severe pH disturbances, severe hepatic or renal dysfunction or inborn errors of metabolism may also occur and cause a potentially reversible coma in pediatric patients. All the above should be excluded before moving on diagnostic tests for BD. A high index of clinical suspicion for metabolic disturbances should be especially raised in situations where the clinical history alone does not provide a reasonable explanation for the evolution of BD.
- *Neuromuscular blocking (NMB) agents*. Adequate clearance of these agents should be confirmed. In case there is a doubt for residual NMB action, a nerve stimulator with documentation of neuromuscular junction activity and twitch response should be used to demonstrate good neuromuscular activity with 4/4 responds in "train of four" testing [12, 23].
- *Drug intoxications.* Barbiturates, opioids, sedative and anesthetic agents, antiepileptic agents, and alcohols 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. 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 of 2011 AAP guidelines. Laboratory testing of drug levels should be performed if there is a concern regarding residual drug effect. Although there is evidence that therapeutic and subtherapeutic barbiturate levels (phenobarbital and pentobarbital at 15–40 ug/ml) did not interfere with the reliability of BD diagnosis, it is advised these drugs to be at the low to mid therapeutic range before neurological examination [28]. Unusual causes of coma such as neurotoxins and chemical exposure, e.g., organophosphates and carbamates, should be occluded in rare cases where an etiology for coma has not been established.

4.6. Physical examination: coma

The neurologic examination BD criteria in pediatrics have been adapted from 2010 American Academy of Neurology criteria for BD determination in adults [12]. Patients must exhibit complete loss of consciousness, vocalization, and volitional activity and should be in a profound state of coma. Flaccid tone is confirmed by passive range of motion in extremities given

there are no limitations to performing such an examination, e.g., previous trauma, and the patient is observed for any spontaneous or induced movements. Noxious stimuli in the cranial nerve distribution (deep supraorbital and/or condylomandibular pressure) and all four limbs (deep bed nail pressure), and trunk (sternal rub) should be applied and the responses, if any, should be carefully evaluated. Central (in the territory of cranial nerves, e.g., facial area) responsiveness to central and peripheral (outside the territory of cranial nerves) noxious stimuli must be absent, apart from spinally mediated reflexes. Complete absence of motion would equate a Clasgow Coma Scale (GCS) of 3. Observations such as decerebrate or decorticate posturing, true extensor or flexor motor responses to painful stimuli and seizures are not compatible with BD. Any motor response within the cranial nerve distribution, or any response in the limbs in response to cranial nerve stimulation, *precludes determination of brain death*. Spinal reflexes should be suspected in cases of motor responses in a somatic distribution after noncranial, e.g., peripheral nerve stimulus and not after stimulus in the cranial nerve territory [14].

4.7. Brainstem reflexes

The absence of all brain stem reflexes must be confirmed by the physical examination. Afferent and efferent pathways of cranial nerves are given in parentheses:

- *Oculomotor reflex (afferent II, efferent III).* Pupils must be >4mm up to 9 mm with absent pupillary response to bright light in both eyes. Fixed midsized or fully dilated pupils are common. In cases of uncertainty, a magnifying glass could be used. Interpret with caution pupil size less than 4 mm. Small constricted pupils should be suspected for drug intoxication [12, 14].
- *Corneal reflex (afferent V, efferent VII).* Special care should be taken not to damage the cornea during the examination. The absence of eyelid movements must be documented after touching the cornea with a cotton swab, a piece of gauze, paper, or water squirts.
- *Absence of facial or bulbar musculature movement in noxious stimulus (afferent V, efferent VII).* 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.
- *Oculovestibular reflex (caloric reflex, afferent VIII, efferent III, VI).* Check for patency of the external auditory canal with otoscopic examination. The eardrum should be visible, or it should be cleared before the test. Oculovestibular reflex is tested by irrigating each ear with ice water (caloric testing) after the head is elevated to 30° to place the horizontal semicircular canal in a horizontal position [14]. Each external auditory canal is irrigated (one ear at a time) with >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.
- *Oculocephalic reflex (eye doll reflex).* The same pathways as in the case of oculovestibular reflex are tested. Not required any more in AAP 2011 and ANZICS 2013 guidelines due to the fact that it is not considered strong enough stimuli to elicit a response and the risk of exacerbating possible cervical spinal trauma [14].

- *Gag reflex (afferent IX, efferent X).* The pharyngeal or gag reflex is tested after stimulation of the posterior pharynx using a tongue blade or suction device. The sucking and rooting reflexes are sought in neonates and infants [20].
- *Cough—tracheal reflex (afferent X).* 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. The efferent limbs for this reflex are the phrenic nerve and the thoracic and abdominal musculature. Therefore, it cannot be assessed in patients with high cervical cord injury [12].

4.8. Apnea test

Only if all the above reflexes are absent, proceed with testing for apnea. The apnea test should be conducted last so that a high $PaCO_2$ does not confound the testing of the other cranial nerves [14]. Apnea testing is the cornerstone for the diagnosis of BD both in adults and children and is conducted similar to adults. However, despite the consensus criteria published for adults and pediatrics, considerable variation has been described in performing the apnea test in both populations [2, 21, 22, 29]. In 1987 Task Force guidelines for pediatric BD is reported that apnea testing using standardized methods can be performed, but this is ordinarily done only after other examination criteria are met. Yet, the standardized methods are not described and the two associated references reported different ways of performing the apnea test. The former, by Outwaker and Rockoff, described apnea testing in 10 children aged 10 months to 13 years who met the conventional criteria for BD. In their study, oxygen 100% was provided for 5 min before the test, the ventilator rate was set to zero, and a continuous flow of oxygen was provided through the ETT. Arterial blood gases (ABG) were drawn at 0, 1, 2, 3, and 5 min. All patients completed the test successfully; mean $PaCO_2$ was 39.4 ± 7.4 mm Hg at the beginning and 59.5 ± 10.2 at the end of the test, with a mean rise of 4.0 ± 0.9 mm Hg/min [30]. The latter, by Rowland and coworkers, in 9 children aged 4 months to 13 years, mentioned that PCO_2 rise was faster than adults, and faster in the beginning of apnea test (4.4 ± 1.6, 3.4 ± 1.3 and 2.6 ± 1.2 mm Hg/min at 5, 10, and 15 min, respectively). $PaCO_2$ ranged from 60 to 116 mm Hg after 15 min of apnea. All apnea tests were accomplished uneventfully and no spontaneous respirations were observed in any of the patients after 15 min of apnea. The authors recommended that prevention of hypoxia can be reliably achieved with administration of 100% oxygen for 10 min before discontinuing ventilator support, and continuing oxygen (6 l/min) through a catheter into the length of the ETT for the duration of the test. An initial apnea test of 10 min was proposed, and if the desired levels of PCO_2 failed to achieve, then a repeated test with a longer duration of 15 min was advised. The study concluded that apneic oxygenation can be safely conducted in children as a component of the clinical evaluation of BD [31].

The above studies performed apnea testing differently. Even in the recent guidelines, there are no accurate instructions on how to perform a safe apnea test in children. Questions such as how much time is necessary for the preoxygenation period, which is the optimum baseline PCO_2 level, which is the best way for apneic oxygenation, how to prevent hypoxia and/or hypotention during the apnea test, which is the exact duration of apnea testing, remain blurred and left to the resolution of the attending physician. Physicians should always

remember that *apnea testing is the last element in clinical diagnosis of BD in suspected BD children*. There are references of prospective, retrospective studies, and case reports, in suspected BD children, mentioning that occasionally patients developed spontaneous breathing during apnea testing [2, 32–35]. These references not at all blunt the validity of apnea; on the contrary they confirm the value of the test on establishing pediatric BD. Not all parts of pediatric brain die simultaneously, especially in patients with preexisting neurologic disease. In cases that apnea is not positive for BD the patient is returned back to full support, until a following apnea test can be performed or an auxiliary test is pursued to establish or refute the diagnosis. It is worth mentioning that almost in all the aforementioned reports, most children died ultimately shortly afterwards, by a second apnea test that confirmed BD diagnosis or spontaneous cardiac arrest. One patient, who never fulfilled apnea testing, and therefore BD, remained in severe neurological impairment, keeping in life technology dependent, through tracheostomy, home mechanical ventilation, and gastrostomy [34]. Brain recovery of children that met all adult BD criteria based on neurologic examination has not been confirmed so far. The apparent reversibility of brain death reported by some authors through spontaneous respirations during apnea testing is questionable; further review of these cases would reveal that those children could not had fulfilled strict brain death criteria by currently accepted medical standards. There is no documented case of a person who *fulfils the preconditions and criteria for brain death* ever subsequently developing any return of brain function [8, 14, 18, 20, 23].

4.9. Performing apnea testing

The rationale behind the apnea test is that an intense ventilator stimulus, such as hypercapnia/respiratory acidosis is needed, to stimulate respiratory drive centers in the medulla to start respiratory efforts. During this procedure, concomitant hypoxemia should be avoided by the administration of 100% O_2. The levels of PCO_2 sufficient to stimulate the respiratory drive (PCO_2 threshold) was set at 60 mm Hg, based on the study of Scafer and Caronna, which report that three comatose, apparently BD adults, started to breath at PCO_2 levels of 44–56 mmHg [36]. According to AAP 2011 guidelines, if no respiratory effort is observed from the initiation of the apnea test to the time the measured $PaCO_2$ is ≥60 and ≥20 mm Hg above the baseline, the apnea test is consistent with brain death. Patients with chronic respiratory disease and chronic hypercapnia may need a higher respiratory stimulus, and in this case, the limit of ≥20 mm Hg above baseline is more appropriate.

Apnea testing should not pose risk in the patients tested; it should be safe, accurate, and reproducible [29]. In the literature, there is evidence that approximately 10% of all apnea tests are aborted (12.5% in our study), mainly due to hypoxia and to a lesser degree due to hypotension [22]. A preparation period is necessary; a fluid bolus, e.g., R/L 20 ml/kg (iv), may be helpful in the case of volume depletion in the context of diabetes insipidus that may be present; and inotropes and vasopressors should be ready and connected in line, even if they are not needed before apnea testing. The effects of raised PCO_2 levels in the circulatory system can vary. There could be an increase in heart rate and blood pressure due to sympathetic stimulation, or blood pressure may start falling due to the vasodilatation caused by the rising

PCO_2 levels and the myocardial depression caused by the acidosis; arterial line is necessary for a beat to beat evaluation of blood pressure and drug titration. Oxygenation is mostly maintained by the preoxygenation with 100% O_2 for 10 min, and through the apneic oxygenation during the test with the oxygen-diffusion technique, e.g., with tracheal insufflation of oxygen at a rate suitable for the age of the child (as described previously in our study). The catheter administrating oxygen should not be cut, the size should be appropriate to permit escaping for the excess oxygen through the ETT and prevent air trapping, and the oxygen rate should be appropriate; if these precautions are not met, there is a risk for inadvertent high oxygen pressures. Cases of barotrauma with pneumothoraces and/or pneumomediastinum have been described during apnea testing and should be avoided [37, 38]. In the case of hypoxia, CPAP could be applied through the application of the suitable valve in the T-piece. A Mapleson anesthesia bag attached to the ETT could also be used. There are reports of successfully performing the apnea test through a T-piece attached to the ET only; however, a question is arising if oxygen flowing simply at the end of ETT is capable of reaching the trachea to diffuse in the alveoli. Accomplishing apnea testing with the patient connected to ventilator should be avoided because all modern ventilators have built in apnea back up modes that do not allow zeroing the respiratory rate for a long time. Moreover, cardiac beating could trigger the ventilator if strong enough, and a false indication of spontaneous respiratory effort may appear. Maintenance of the homeostasis is of paramount importance for the safe and successful performance of the apnea test:

- Regular arterial blood gas (ABG) analysis should ensure normalization of the pH and $PaCO_2$; maintenance of core temperature above 35°C and normotension for age should be confirmed, even through dose adjustment of inotropic and vasopressor agents. Still in hemodynamic stable patients before the test, these drugs should be ready and connected to line for immediate hemodynamic support, in case hypotension occurs.

- Preoxygenation using 100% oxygen, aiming at nitrogen removal and oxygen enrichment, should be applied for at least 10 min [12]. Mechanical ventilation parameters could be modified as well at the same time, it is advisable to keep tidal volume and PEEP at the same level to avoid derecruitment and decrease only the respiratory rate aimed at eucapnia with baseline PCO_2 level of 35–45 mm Hg. This could facilitate the rise in $PaCO_2$ to the desired levels for a positive apnea testing [11, 12, 14].

- Intermittent mandatory mechanical ventilation is discontinued once the patient is well oxygenated and a normal $PaCO_2$ around 40 mm Hg has been achieved. Oxygenation should be accomplished with the apneic oxygenation method through the ETT as described earlier. The patient could also be changed to a T-piece attached to the ETT, or a self-inflating bag such as a Mapleson circuit connected to the ETT, or CPAP in cases of hypoxemia.

- Cardiac beating, blood pressure, and oxygen saturation should be continuously monitored while observing carefully for spontaneous respiratory effort (any respiratory muscle activity that results in abdominal or chest excursions or activity of accessory respiratory muscles) throughout the entire procedure [14].

- If the patient is well oxygenated ($SpO_2 > 85\%$) and hemodynamic stable, keep apnea duration to 10 min and then draw ABG for analysis. The longer the apnea times the more the

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possibilities for a positive apnea test. AAP 2011 guidelines suggest serial follow up ABG to monitor the rise in $PaCO_2$ while the patient remains disconnected from mechanical ventilation [20].

- Apnea test is consistent with brain death if no respiratory effort is observed for 10 min or the time (if earlier) that values of measured $PaCO_2$ ≥60 and ≥20 mm Hg above the baseline level are achieved. The patient should be placed back on mechanical ventilator support and medical management should continue until the confirmation of BD is completed by the second neurologic examination and the second apnea test.
- If oxygen saturations fall below 85% or hemodynamic instability limits completion of apnea testing draw ABG at this time, discontinue the test and return the patient to ventilator and full support. If $PaCO_2$ level of ≥60 and ≥20 mm Hg above the baseline has not been achieved at that time, 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.
- Observation of any respiratory effort is inconsistent with brain death and the apnea test should be aborted.
- Use of a capnograph to detect spontaneous respirations through end tidal $EtCO_2$ fluctuations is desirable.

4.10. Inability to perform elements of clinical examination and/or apnea

Clinical neurological examination and/or apnea test cannot be performed under some circumstances, especially during trauma. Ocular trauma, severe maxilofascial injuries, skull base fractures that are running through the external ear canal, and ear drum rupture limit the ability to perform and evaluate many of the brainstem reflexes. Cervical spinal trauma with possible participation of phrenic nerve limits the spontaneous breathing ability during apnea testing. Flaccid tone in patients with high spinal cord injury or neuromuscular diseases poses further concerns about the validity of clinical examination.

Furthermore, apnea testing cannot be performed in cases of severe hypoxia, e.g., in ARDS patients even under CPAP conditions, and/or in patients with severe hemodynamic instability. When concerns about the potentials and validity of elements of clinical examination and/or apnea testing are arisen, then continued observation is recommended. A valid neurologic evaluation and apnea test could be performed at a later time, as soon as all issues are resolved. If this is not possible, then an ancillary study is indicated to establish BD diagnosis.

4.11. Ancillary studies

The 2011 AAP BD guidelines recommends that ancillary studies (electroencephalogram and radionuclide cerebral blood flow) are not required to establish brain death and are not a substitute for the neurologic examination. The term "ancillary study" is preferred to "confirmatory study" since these tests assist the clinician in making the clinical diagnosis of brain death. Ancillary studies are not common in places where the DNC concept, as the death of

the brainstem, is accepted; on the contrary they are more common where the whole concept of BD, including the death of the brainstem, is acknowledged. Nevertheless, apart the above mentioned reasons that question the potential and safety of clinical examination, ancillary studies are sought also in suspected drug intoxication and to reduce the inter-examination observation period.

Before the use of ancillary studies, all the preconditions of BD that could be applied, and all parts of clinical examination, including apnea test, that could be performed, should be recorded. When an ancillary study supports the diagnosis of BD, a second clinical examination and apnea test must be done and components that can be completed must remain consistent with brain death. In this instance, the inter-examination observation interval may be shortened and the second clinical evaluation 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 [20].

4.11.1. EEG

Electroencephalograph (EEG) has been extensively studied in 485 suspected BD pediatric patients where signs of electrocerebral silence (ECS) were sought. In their first study, 76% of patients had ECS, which elevated to 89% in subsequent, if any, studies. Sixty-six patients had a second study that confirmed the ECS of the first study in 64/66 patients (97%). The two patients who showed EEG activity, in retrospect in depth analysis, would not have met the recent criteria for BD due to pharmacological agents present at the time of examination (a newborn with high phenobarbital levels of 30 μg/ml and a 5 years head trauma boy that received pentobarbital and pancuronium at the time of testing). In case that the first study showed EEG activity (85 patients), the second study showed ECS in 47/85 (55%) of patients. The rest 38/45 patients (45%), either did not have a second examination, or an ECG activity, as expected, were confirmed. It is worth mentioning that all the examined patients died (spontaneously or by withdrawal of support). Only one patient survived with severe neurological impairment from this entire group of 485 patients, the above-mentioned neonate with an elevated phenobarbital level, whose first EEG showed photic response [20].

4.11.2. CBF

Four-vessel cerebral angiography is the gold standard for determining the absence of cerebral blood flow (CBF). However, the technique is not always available, is very invasive and difficult to perform in young infants, and carry all the risk of transferring a potentially unstable patient outside the PICU. Thus, use of radionuclide CBF determinations to document the absence of CBF, with portable scanners where feasible, remains the most widely used methods to support the clinical diagnosis of brain death in infants and children. Evidence suggests that radionuclide CBF study can be used in patients with high dose barbiturate or other drugs therapy to demonstrate the absence of CBF. The classical appearance in a CBF scanning study positive for BD is the "hollow skull phenomenon" or "hot nose sign" due to the absence of circulation in the brain with relatively increased nasal region perfusion due to preserved external carotid artery flow [12, 20].

An extended study of CBF in 681 suspected BD patients showed that 86% of patients who met clinical BD criteria had absent CBF on first examination, a percentage that rose to 89% in case they had a following test. Among them, 26 patients had a second examination that confirm the absence of CBF in 24/26 patients (92%). The two exceptions with no flow in the first study that revealed some flow in the second study were two 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, and survived with severe neurologic impairment. Along with the 34 patients that had present flow in first study, 9/34 (26%) had no flow on the subsequent study, due to evolution to BD. The remaining 25/34 (74%) either had preserved flow or no further CBF studies were done, and all died (either spontaneously or by withdrawal of support). Interestingly, only one patient survived from this entire group (the one mentioned earlier) with severe neurologic deficit [20].

4.11.3. ECG versus CBF

There are 12 studies in the literature examining 149 suspected BD patients of any age with both initial EEG and CBF studies, which present special interest to compare one to another for their diagnostic yield. Data were stratified by three age groups: (i) all children (n = 149); (ii) newborns (<1 month of age, n = 30); and (iii) children aged >1 month to 18 years (n = 119). In the first EEG study, ECS was found in 70% in the whole cohort, 40% in newborns and 78% in older children. Similarly, the absence of flow in the first CBF study was documented in the same proportion in all age groups (70%), though performance was better in infants with absent flow in 63%, whereas in older children remained the same with absent flow in 71% of patients. Both studies were compatible with BD in 58% of all patients, only in 26% of newborns and 66% of older children. It seemed that for newborns, EEG with ECS was less sensitive (40%) than the absence of CBF (63%) when confirming the diagnosis of brain death, but even in the CBF group the yield was low. Performance was better for children older than 1 month of age and both of these ancillary studies remain accepted tests to assist with determination of brain death and are of similar confirmatory value. Radionuclide CBF techniques are increasingly being used in many institutions replacing EEG [20].

If the results of the ancillary study are equivocal, the patient cannot be pronounced BD. Observation under maximum supportive care is continued until a valid clinical examination and apnea testing is possible, or a subsequent ancillary study with definite results can be performed. A waiting period of 24 h is recommended before further radionuclide CBF study is performed, to allow for adequate clearance of Tc-99m. A waiting period of 24 h is reasonable and recommended before repeating EEG ancillary study as well.

There are reports of other newer ancillary studies performed in adults and children with suspected BD. Concerning the adult population, Transcranial Doppler is not included in adult AAN 2010 guidelines, whereas it is reported as a screening only test in ANZICS 2013 guidelines [12,14]. MRA angiography, CT angiography, somatosensory evoked potentials, and bispectral index are mentioned in adult 2010 guidelines but are not recommended due to insufficient evidence [12]. Correspondingly, pediatric AAP 2011 guidelines cannot

recommend any of the above studies as ancillary studies to assist with the determination of BD in children [20].

4.12. Number of examinations

Two examinations, including apnea testing with each examination, separated by an observation period, are required. The examinations should be performed by different attending physicians involved in the care of the child, or as specified by national law. The first examination determines the child has met neurologic examination criteria for brain death. The second examination, performed by a different attending physician, confirms brain death, based on an unchanged and irreversible condition.

4.13. Number of examiners

According to AAP 2011 guidelines, two physicians (one each time) must perform two independent examinations separated by specific intervals. Apnea testing, as an objective test, could be performed by the same physician, preferably the attending physician who is managing ventilator care of the child. The committee recommends that these examinations be performed by different attending physicians involved in the care of the child. Physicians should have experience with neonates, infants, and children and have specific training in neurocritical care. They must be competent to perform the clinical examination and interpret results from ancillary studies. Pediatric intensivists and neonatologists, pediatric neurologists and neurosurgeons, pediatric trauma surgeons, and pediatric anesthesiologists with critical care training could serve as examiners for BD diagnosis in children. Adult specialists should have the appropriate neurologic and critical care training to diagnose brain death in children. Junior doctors, residents, and fellows should be encouraged to learn how to properly perform brain death testing by observing and participating in BD diagnosis performed by senior experienced attending physicians.

The exact number, specialty, and the required qualifications of the examiners vary according to national law; e.g., in Greece, three physicians (anesthetist, neurologist/neurosurgeon, and attending physician such as pediatrician/pediatric surgeon), who should be board registered for their specialty at least for 2 years, are required. The same panel of doctors is mandatory to perform the second examination at the set observation period. No one must be potentially involved in the organ donation and transplantation team.

4.14. Observation period

The recommended observation periods are as follows:

- 24 h for neonates (37 weeks gestation to term infants 30 days of age).
- 12 h for infants and children (>30 days to 18 years).

Observation period could be shortened in case of an ancillary study compatible with BD. On this occasion, 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 [20].

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5. Special considerations for term newborns (37 weeks gestation to 30 days of age) by AAP 2011 guidelines

The younger the patient the greater the challenge of diagnosing BD in pediatric patients; the younger the patient the longer the observation period, unless clinical BD diagnosis is supported with ancillary studies whereas the observation period could be shortened [20]. Interestingly, the performances of ancillary studies which are supposed to help in the diagnosis are less accurate in very young infants. These reservations were recorded for the first time in AAP 1987 guidelines and are listed below for historical reasons [19]. Different diagnostic criteria were defined in those guidelines according three age categories starting from the 7th day of life; no recommendation was done then for neonates younger than 7 days of life due to insufficient data. Ancillary studies, especially EEG, were regarded an essential component of the diagnosis and were mandatory with different observation periods across age:

- Infants 7 days to 2 months: Two examinations and two EEG separated by at least 48 h.
- Children 2 months to 1 year: Two examinations and two EEG separated by at least 24 h. The second EEG was not necessary if a concomitant cerebral radionuclide scan or cerebral angiography demonstrated no flow or visualization of the cerebral arteries.
- Children older than 1 year: A shorter observation period of at least 12 h was recommended and ancillary testing was not required when an irreversible cause existed. However, with present ECS or absent CBF, the observation period in this age group could be further decreased.

In AAP 2011 guidelines, although some of the above precautions were revised, especially about the necessity of ancillary studies, there are still special considerations about the term newborns (37 weeks gestation to 30 days of life) in:

- *Clinical examination:* There is a concern about the maturation of brainstem reflexes on this age group and the difficulties arisen with the clinical examination. Therefore, a longer time of 24 h is recommended both before the initial evaluation for BD and for the observation period between tests. In cases of uncertainty, repeated clinical examinations are preferable to ancillary studies.
- *Apnea test:* Particularities of apnea testing in neonates are caused by the possibility that high oxygen pressures during preoxygenation may inhibit the potential stimulation of respiratory centers, and profound bradycardia may precede the gradual development of hypercapnia during apnea. The definition of a valid apnea test is the same as in older children.
- *Ancillary studies:* They are less sensitive in detecting brain electrical activity or cerebral blood flow than in older children. When both ancillary studies were conducted in 149 suspected BD neonates <1 month, absence of CBF (63%), although low, was more sensitive than demonstration of ECS (40%), which was even lower. Disparities were also recorded between studies; when the first examination showed ECS, the absence of CBF was confirmed in 66.7% of patients, while when the absence of flow was firstly recorded, ECS was present in only 42% of patients. Due to limitation of ancillary tests for this age, repeated clinical neurological examinations are indicated than relying on ancillary tests. However,

when ancillary tests are present and compatible with BD, the inter-examination interval could be shortened at the same way as happened to older children.

Similar recommendations for patients younger than 36 weeks to 1 month of age were issued by the ANZICS 2013 guidelines as well, stating that the initial evaluation for BD should defer for 48 h, with an interval of 24 h between the two tests [14].

6. Special considerations in patients younger than 2 months by RCCHD 2015 guidelines

Due to uncertainty about the validity of the 2008 AoMRC code of practice DNC criteria in young infants, in the UK, the RCCHD examined literature evidence for BD in very young patients from 37 weeks corrected gestation (postmenstrual) to 2 months postterm [18]. According to their guidelines, DNC is a clinical diagnosis with certain preconditions, and ancillary tests do not help in this diagnosis. They recommended that DNC for this age group should be made taking into account the following:

- *Preconditions:* The same preconditions are recommended as those detailed in the 2008 AoMRC code of practice and in the 1991 BPA report, with an additional prerequisite about the first clinical examination. Postasphyxiated infants or those receiving intensive care after resuscitation, having or not being treated with therapeutic hypothermia, should have a period of at least 24 h of observation. This observation period could be extended in the case of suspected residual drug-induced sedation.
- *Clinical diagnosis of DNC:* The same DNC clinical criteria are recommended as those used in the 2008 AoMRC code of practice for adults, children, and older infants, with special considerations on apnea. A stronger hypercarbic stimulus is used to establish respiratory unresponsiveness. Specifically, there should be a clear rise in $PaCO_2$ levels of >2.7 kPa (>20 mm Hg) *above a baseline of at least 5.3 kPa (40 mm Hg)* to >8.0 kPa (60 mm Hg) with no respiratory response at that level. Two clinical examinations are required with the same interval as in 2008 AoMRC code of practice.
- *Ancillary tests:* Ancillary tests were not found sufficiently robust to help confidently diagnose DNC in infants. They are required only in cases where a clinical diagnosis of DNC is not possible (for example because of extensive faciomaxillary injuries, or high cervical cord injury).
- *Examiners:* Two qualified pediatricians who have been registered for more than 5 years and are competent in the procedure are required. At least one should be a consultant. They should perform successfully two tests, including apnea.

7. Special considerations for premature newborns

Brainstem reflexes are not fully developed in premature babies, for example the pupillary response to light appears at 30 weeks, but is only consistently present at 32–35 weeks of gestation,

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and the central respiratory response to CO_2 is relatively poorly developed below 33 weeks of gestation. Due to the uncertainty surrounding this issue, there are not any international guidelines to address BD diagnosis in premature babies below 36–37 weeks postconceptual age [14, 20].

8. Declaration of death: documentation

Death is declared after the second neurologic examination and apnea test confirms an unchanged and irreversible condition. When there is a concern about the validity of the first clinical examination and 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. Documentation at each step of diagnosis is necessary, starting from the preconditions that should be met and finishing with the exact time of death, accompanied by the well written names and signatures of the responsible physicians. The use of a checklist provides standardized documentation to determine brain death ensuring that no step is missing and is highly recommended [20, 21, 24]. A checklist outlining essential examination and testing components is provided in Appendix 2.

The law, almost worldwide, recognizes that after DB declaration, preservation of technology-dependent life in modern ICUs is of no use, unless the patient is going to be an organ donor, whereas all the necessary actions should be undertaken. Time of clinical death after BD varies in different references according to national social, cultural, and religious preferences. In a preliminary announcement of our study, this time was approximately 2.74 days after the completion of the second apnea test, mainly attributed to the high emotional stress of the parents and the time needed by the family to accept the reality of BD for their children [39]. In one of the first relevant studies in children, it is reported that among 171 BD pediatric patients 47% had their ventilatory support withdrawn an average of 1.7 days after the diagnosis of BD, whereas in 46% support was continued until a cardiac arrest that happened an average of 22.7 days later [40]. The shorter period of 8.52 h is reported in Canada [2] and the longer period up to 4 years is recorded in Japan [7].

9. Parental support

The loss of a child is the most powerful emotional stress for a family. Moreover, there is evidence that parents cannot understand the concept of the brain death in a child that is apparently alive, connecting to ventilator with its heart beating. Good communication between the family and the medical team is necessary to make clear that, despite everything had been made for the recovery of their children, they will have a dismal outcome. The role of the bedside nurse who spent more time with the patients and the parents is fundamental in creating the trust to accept the reality of BD. From the very beginning of the admission of their child at the PICU, the parents should be fully informed of the disease, the treatments and the unfavorable prognosis. When parents are not well informed, they will take longer to understand the evolution to BD and accept the death of their child [7, 23].

Communication with families must be clear and concise, yet using a simple language without pompous medical terminology that they could not understand. Apart medical and nursing team, other medical workers could help families cope with the apparent death as well. The clerk and psychotherapists/psychologists may help them to take difficult end-of-life decisions and parents should be offered this possibility. The presence of family during the tests is questionable. Some families may find it helpful and relieving to see each diagnostic step and the complete loss of responsiveness, but a danger of severe emotional embarrassment lurks in case spinal reflexes are elicited [7]. The family must understand that after the confirmation of BD, their child meets legal criteria for death and continuation of medical therapies, including ventilator support, is no longer an option unless organ donation is planned [20].

10. Conclusions

Diagnosing BD in children is a challenging task and despite the existence of pediatric guidelines since 1987, great variation has been recorded. Strict adherence to published guidelines and medical standards for determining brain death is the minimum requirement for maintaining public trust. The neurological criteria, as outlined above, represent international practice in which the medical profession and the public can have complete confidence [16]. The use of checklist promotes the necessary documentation of each part of declaration of BD and is strongly recommended [2, 21, 24]. International guidelines should form a basis where national guidelines could be established, taking into account legal, ethical, cultural, and religious differences. Diagnosing BD is a medical duty and should be faced with the appropriate knowledge and responsibility.

Although it becomes more and more clear that BD is a clinical diagnosis, there are circumstances where ancillary studies are still necessary. Technology is rapidly evolving and newer methods assessing brain function are developed. Newer methods to assess CBF and neurophysiologic function comparing them to traditional ancillary studies is a forthcoming need, and they will be probably included in future guidelines to assist with determination of brain death in children. Additional information or studies are required to determine if a single neurologic examination is sufficient for neonates, infants, and children to determine brain death as currently recommended for adults over 18 years of age, by the 2010 AAN adult guidelines on BD [12, 20].

Appendices

Appendix 1. Brain death diagnosis algorithm (adapted from Ref. [20])

Appendix 2. Check list for determination of brain death (adapted from Ref. [20])

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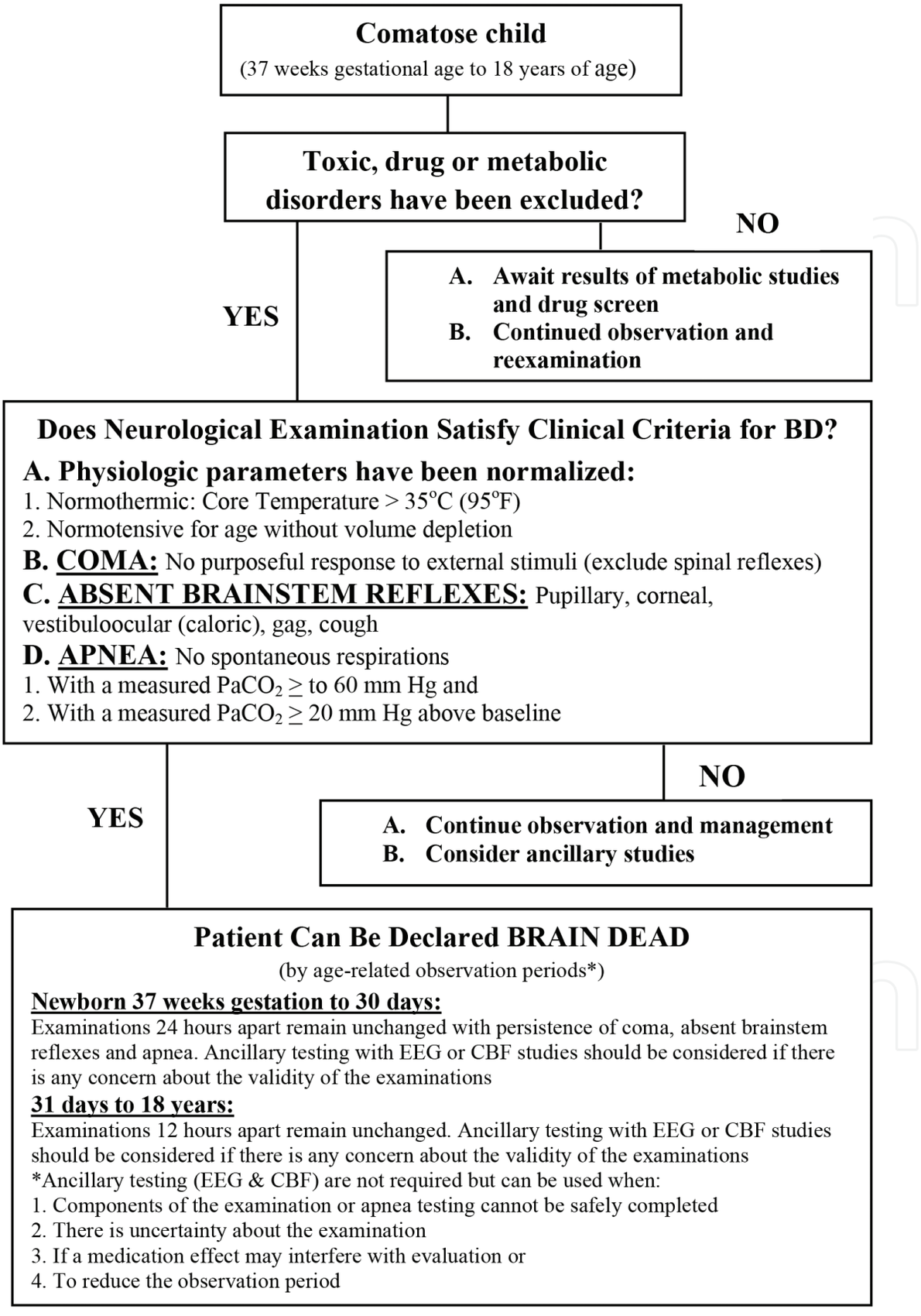

Brain Death Examination for Infants and Children
Two physicians must perform independent examinations separated by specified intervals

Patient name and age	Timing of first exam	Observation period
Term newborn 37 wks gestational age and up to 30 days old	□ 24h after birth OR following CPR or SBI	□ At least 24h □ Shortened due to ancillary study consistent with BD
31 days to 18 years	□ 24h after CPR or SBI	□ At least 12h □ Shortened due to ancillary study consistent with BD

Section 1. PRECONDITIONS for brain death examinations and apnea test

A. IRREVERSIBLE AND IDENTIFIABLE CAUSE OF COMA

□Traumatic brain injury □Anoxic Brain injury □Known metabolic disorder □Other (specify)

B. CORRECTION OF CONTRIBUTING FACTORS	Examination 1		Examination 2	
a. Core Body Temperature > 35°C	□ Yes	□ No	□ Yes	□ No
b. Systolic blood pressure or MAP at acceptable range	□ Yes	□ No	□ Yes	□ No
c. Sedative /analgesic drugs excluded	□ Yes	□ No	□ Yes	□ No
d. Metabolic intoxication/abnormalities excluded	□ Yes	□ No	□ Yes	□ No
e. Neuromuscular/antiepileptic drugs excluded	□ Yes	□ No	□ Yes	□ No

□ *If ALL preconditions are marked YES, then proceed to the next section, OR*

□…… *confounding variable was present. Ancillary study was performed to document BD.*

Section 2. PHYSICAL EXAMINATION ***Note: Spinal Cord Reflexes are Acceptable***	**Examination 1** **Date/time:**		**Examination 2** **Date/time:**	
a. Flaccid tone, unresponsive to deep painful stimuli	□ Yes	□ No	□ Yes	□ No
b. Pupils are midpositioned or fully dilated and non reactive	□ Yes	□ No	□ Yes	□ No
c. Corneal, cough, gag reflexes absent Sucking and rooting reflexes absent (infants/neonates)	□ Yes □ Yes	□ No □ No	□ Yes □ Yes	□ No □ No
d. Oculovestibular (caloric) reflexes absent	□ Yes	□ No	□ Yes	□ No
e. Spontaneous respirations on ventilator absent	□ Yes	□ No	□ Yes	□ No

The ……(specify) element could not be performed because of……

□ *Ancillary study (EEG or radionuclide CBF) was therefore performed to document BD.*

Section 3. APNEA TEST *Aim to baseline eucapnia $PaCO_2 \geq 40$ mm Hg*	**Examination 1** **Date/Time:**	**Examination 2** **Date/Time:**
No spontaneous respiratory efforts were observed despite final $PaCO_2 \geq 60$ mm Hg and a ≥ 20 mm Hg increase above baseline (examinations 1 & 2)	Pretest $PaCO_2$: Apnea (min): Pretest $PaCO_2$:	Pretest $PaCO_2$: Apnea (min): Pretest $PaCO_2$:

Section 4. ANCILLARY TESTING	**Date/Time:**	
□ Elecroencephalogram (EEG) report documents electocerebral silence (ECS) 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 the brainstem. Confirmatory examination to follow.

(Printed Name) (Signature)

(Specialty) (Lisence) (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 the brainstem. **The patient is declared dead at this time.**

Date/Time of Death:

(Printed Name) (Signature)

(Specialty) (Lisence) (Date mm/dd/yyyy) (Time)

CPR; Cardiopulmonary Resuiscitation, SBI; Severe Brain Injury

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