Supplementary Online Content

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Supplement 17. Questions That Address Knowledge Gaps to Facilitate Development of a Research Agenda About Brain Death/Death by Neurologic Criteria

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

Appendix 17. Questions That Address Knowledge Gaps to Facilitate Development of a Research Agenda About Brain Death/Death by Neurologic Criteria

There are still issues surrounding BD/DNC that remain unanswered or need clarification. Because of this, we generated a list of questions on each topic we addressed to inform a research agenda that can improve the evidence available to further guide practice in the future and address knowledge gaps.

1. Worldwide Variance in Brain Death
    1. What is the status of international consistency and variability in BD/DNC guidelines and protocols?
    2. How much variability in BD/DNC guidelines and protocols exists within countries?
    3. How does variability in BD/DNC guidelines and policies impact variability in actual bedside clinical procedures and medical record documentation?
    4. How does the variability in BD/DNC guidelines and policies influence current practice? What impact does it have on the reliability of determination and the risk of diagnostic error?
    5. What quality improvement measures can be put into place to ensure consistent and thorough determination of BD/DNC?

2. The Science of Brain Death
    1. What is the epidemiology (demographics, incidence, point prevalence) of BD/DNC with absent and preserved brain blood flow?
    2. What is the precise sequence of events in primary posterior fossa lesions that lead to BD/DNC?
    3. Do different primary brainstem pathologies have a different rate of progression to BD/DNC? What is the pathophysiology of this process?
    4. In post-anoxic BD/DNC with preservation of brain blood flow, how does one ensure that potentially reversible factors have been excluded? Is an observation period always necessary, and if so, how long should this period be?
    5. What is the clinical relevance of critical closing pressure (CrCP) of cerebral vessels?
    6. In the setting of decompressive craniectomy, what are the differences in pathophysiology of BD/DNC?
    7. Is there any relevant difference in pathophysiology of BD/DNC in children after full ossification of fontanelles and adults?
    8. What is the sequence of changes in heart rate variability during the development of BD/DNC? Is heart rate variability analysis predictive of progression to, or confirmation of, BD/DNC?

3. The Concept of Death by Neurologic Criteria
    1. When contrasting supratentorial pathology to infratentorial pathology (brainstem and/or posterior fossa):

a. What is the natural history for those who fulfil minimum clinical criteria for BD/DNC? Is there a risk of return of any brain function if BD/DNC is declared clinically in these populations?

b. What proportion of those who fulfil minimum clinical criteria for BD/DNC would have absence of cerebral blood flow on ancillary testing?

c. Should patients who have signs of BD/DNC because of brainstem compression first undergo decompression or ventriculostomy to assure irreversibility?

d. Are there additional tests that can exclude the possibility of clinically undetectable cerebral function in persons who fulfil the clinical criteria for BD/DNC?

e. What is the role of fMRI in persons with isolated brainstem pathology who fulfil the clinical criteria for BD/DNC?

2. What variables predict temporal evolution to intracranial hypertension and herniation in persons with isolated brainstem or posterior fossa pathology?

3. Are there tests that can confirm the complete and irreversible destruction of the entire brainstem?

4. Minimum Clinical Criteria for Determination of Brain Death

1. When the presence of drug intoxication is unclear and the pupils are not mid-position to dilated, should naloxone be routinely administered before conducting a BD/DNC determination? What dosing recommendations are reliable?

2. What is the impact of corneal transplant or cataract surgery on ocular examinations?

3. What method of performing apnea testing is associated with the lowest risk of complications?

4. What is the highest $PaCO_2$ and lowest pH at which a person has the potential to breathe?

5. Should there be a different $PaCO_2$ target at high altitudes?

6. Is neuroimaging evidence of severe intracranial hypertension, including the presence and severity of cerebral edema and pontomedullary herniation, predictive of, or correlated with:

a. Fulfillment of clinical criteria for BD/DNC prior to apnea testing?

b. Absence of spontaneous breathing during the apnea test?

c. Absence of brain blood flow on ancillary testing?

5. Beyond Minimum Clinical Determination of Brain Death

1. What is the validity of CTA, CT perfusion, MR angiography and MR perfusion in determination of BD/DNC?

2. How often and under what conditions does ancillary testing support or contravene a clinical determination of BD/DNC?

3. Does the presence and degree of cerebromedullary herniation on neuroimaging correlate with brain blood flow on ancillary testing?
4. When minimum clinical criteria for BD/DNC are fulfilled, does the absence of herniation on neuroimaging correlate with the presence of brain blood flow on ancillary testing?
5. What are the lower limits of brain blood flow and duration that are associated with cessation of brain function? Can physiologically irrelevant brain blood flow on ancillary testing be defined?
6. Can the lower limits of brain blood flow detection by ancillary testing, including radionuclide, be defined?
7. Can continuous TCD monitoring identify the moment of cessation of brain blood flow and does this correlate with loss of all brain function?
8. Are the findings on the second TCD ever different from the findings on the first TCD if a person meets clinical criteria for BD/DNC?
9. What is the natural history of clinical BD/DNC with preservation of brain blood flow by ancillary testing?
10. What are the potential roles of experimental approaches, including ultrasound of the retina, electrical impedance, transcranial magnetic stimulation, craniovascular flowmetry, and brain tissue oximetry in determination of BD/DNC?
11. What are the minimum requirements for training and expertise in the performance and interpretation of ancillary studies by neuroradiology experts?

6. Pediatric and Neonatal Brain Death
    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?

7. Determination of Brain Death in Patients on Extracorporeal Support: ECMO
    1. Are there different prerequisite hemodynamic targets for persons on V-A ECMO who are maintained on continuous blood flow?

2. Are the indications for ancillary tests different in patients on ECMO?
3. Does the addition of inhaled or sweep gas CO_2 mitigate the risks of apnea testing in ECMO patients?
4. Does non-pulsatile flow in patients on VA-ECMO impact the reliability of transcranial doppler as an ancillary test?

8. Determination of Brain Death after Treatment with Targeted Temperature Management
    1. For each population treated with TTM, what are the determinants that predict progression to BD/DNC?
    2. For patients treated with TTM who appear to fulfil clinical criteria for BD/DNC and do not have herniation on neuroimaging, what is the incidence and predictors of reversibility (resumption of brain function)?
    3. In the presence of neuroimaging evidence of cerebral edema and herniation, what is the minimum time period after rewarming that a clinical determination is reliable?
    4. When anoxic brain injury occurs under hypothermic conditions (e.g. cold-water drowning), should different observation times be considered?

9. Documentation of Brain Death

    None

10. Qualifications for and Education on Determination of Brain Death
    1. What is the best way to evaluate and validate BD/DNC training programs?
    2. How often should practitioners involved in determination of BD/DNC be required to complete certification?
    3. What are the most effective strategies to educate the public and health care professionals about the BD/DNC concept?
    4. What is the best model and frequency of certification?

11. Somatic Support After Brain Death for Organ Donation and Other Special Circumstances
    1. How often is somatic support continued in the setting of organ donation, pregnancy and requests to provide somatic support due to objection to the declaration of BD/DNC?
    2. How long can the body continue to function after BD/DNC with provision of aggressive somatic support?
    3. How does prolonged somatic support influence the degree, intensity and characteristics of spinal motor reflexes?

4. Does fluid, inotrope and/or vasopressor selection impact the length of time before cardiopulmonary arrest after BD/DNC?
5. Does timing to initiate vasopressin impact the length of time before cardiopulmonary arrest after BD/DNC?
6. Does thyroid hormone replacement impact the length of time before cardiopulmonary arrest after BD/DNC?
7. Does steroid replacement impact the length of time before cardiopulmonary arrest after BD/DNC?
8. What is the incidence of CPR use after BD/DNC?
9. What are the indications and optimal duration of CPR after BD/DNC?
10. What is the incidence of recovery of spontaneous circulation after CPR for circulatory arrest in brain dead decedents?
11. How often are pregnant brain dead decedents carried to gestation, and what are fetal outcomes?

12. Religion and Brain Death: Managing Requests to Forego a Brain Death Evaluation or Continue Somatic Support after Brain Death
    1. How frequently are requests to either forego a BD/DNC examination or continue somatic support after declaration of BD/DNC made and for what duration is support continued?
    2. What are common characteristics of families who request to either forego a BD/DNC examination or continue somatic support after declaration of BD/DNC?
    3. Are there international differences on requests to either forego a BD/DNC examination or continue somatic support after declaration of BD/DNC and how do health care systems manage these requests?
    4. What are the most effective strategies to address family or religion-based objections to BD/DNC and to educate local religious leaders?

13. Brain Death and the Law
    1. How frequently is legal action taken against practitioners/medical facilities after they've made a determination of BD/DNC?
    2. How frequently is legal action taken against practitioners/medical facilities to prevent determination of BD/DNC?
    3. What are common characteristics of families who take legal action against practitioners/medical facilities prior to or following determination of BD/DNC?
    4. Does legally stipulating the specific medical standard by which BD/DNC should be declared prevent inaccurate determinations?

5. Does legal provision for accommodation to objections to declaration of BD/DNC affect the number of objections to BD/DNC?
6. Does the absence of legal provisions for accommodation to objections to declaration of BD/DNC affect the number of objections?