Supplementary Online Content

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Supplement 1. Worldwide Variance in Brain Death/Death by Neurologic Criteria

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

Worldwide Variance in Brain Death/Death by Neurologic Criteria

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Abstract

Introduction Brain death/death by neurologic criteria (BD/DNC) is accepted as death throughout most of the world, but there is significant worldwide variability in both the definition and process of determining BD/DNC.

Methods We conducted a review of the literature and formulated recommendations with an expert panel on worldwide variability in determination of BD/DNC.

Results and Conclusions There is both inter- and intra-national variability in determination of BD/DNC. We provide recommendations and suggestions to manage this variability.

Brain death/death by neurologic criteria (BD/DNC) is accepted as death throughout most of the world, but there is significant worldwide variability in both the definition and process of determining BD/DNC.[1-4]

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.

Results of an international survey on determination of BD/DNC demonstrate that approximately 80% of nations have institutional protocols for BD/DNC determination. Protocols are less common in lower-income countries and countries that do not have a transplant network.[1]

Among the countries that have protocols for BD/DNC determination, there is general consensus on both the medical concept of BD/DNC and the minimum clinical standards required for determination of BD/DNC (namely, irreversible coma with an established etiology, absence of cortical or brainstem-mediated motor responses, brainstem areflexia and apnea in the setting of a hypercarbic respiratory challenge).[1] However, there is conceptual variability: most countries adhere to the "whole brain" concept of BD/DNC, but the United Kingdom, and some countries with past colonial links to the United Kingdom, follow the "brainstem" concept of BD/DNC.[5] Additionally, there is variability between countries in the qualifications for an examiner, prerequisite blood pressure, prerequisite temperature, prerequisite drug levels, number of examinations, timing of evaluations and the indications for use of ancillary testing.[1,6-8] Even within a given continent, practice is not uniform.[6,7,9] (See Tables 1 and 2)

There is also variability in BD/DNC determination within nations. The best data on variability in BD/DNC determination in a single country comes from the US (See Table 3). All 50 states in the US have recognized the legality of brain death, whether by statute, regulation, or judicial decision.[10] However, legal variability exists between states, particularly regarding accommodation for religious or moral objections to declaration of BD/DNC.[11,12] But below the state-level variability, variability also exists in hospital policies regarding how BD/DNC is determined and documented.[8,13] A recent French study of 763 intensivists also demonstrated variability of practice, with 97% ruling out drug intoxication prior to clinical testing, 63% doing a complete assessment of brainstem reflexes, and 90% performing apnea testing.[14]

The American Academy of Neurology (AAN) updated their practice parameter for determination of BD/DNC in adults in the US in 2010,[15] but studies of US hospital BD/DNC protocols indicate that fewer than 50% are in strict concordance with these guidelines.[8,13] Additionally, a single center retrospective analysis demonstrates variability in documentation.[13] However, it is worth mentioning that there has been some progress in ensuring that institutional BD/DNC policies conform with the AAN practice parameter in the top 50 US neurologic institutions in the last decade. In fact, hospital policies exhibited significantly improved compliance with respect to criteria related to apnea testing and appropriate ancillary testing in a study comparing 2006 with 2015.[16] Nonetheless, variability persists. The impact of variation in policies and documentation remains unclear, given that the fundamentals of the determination (coma, brainstem arreflexia, apnea, no reversible conditions) are relatively consistent. There is no evidence that, despite variability in policies and documentation, there is inappropriate determination of brain death taking place. Furthermore, although variability in policies could raise the concern for more lax criteria in one setting versus another, it is worth noting that sometimes the variability can lead to stricter, rather than more lax, criteria than what was outlined in the practice parameter.[17]

Outside of the US, the extent to which practice/policy varies in other nations, particularly developing world nations, is unclear. Additionally, it is unknown whether protocol variability leads to variability in actual practice. Ensuring that there is no variability in the practice of BD/DNC

determination would require strict instructions for proper testing, the incorporation of checklists and use of institutional quality improvement measures.

Recommendations and Suggestions

1. It is recommended that the minimum criteria for death determination be incorporated into brain death/death by neurological criteria (BD/DNC) determination protocols worldwide in order to harmonize practices and reduce variability to the fullest extent possible.
2. It is recommended that all hospital policies concerning BD/DNC worldwide adhere to the most up-to-date national guidelines.
3. It is recommended that clinical checklists for BD/DNC be implemented routinely.
4. It is suggested that training and credentialing be utilized for clinicians responsible for determining BD/DNC (as outlined in the Qualification and Education chapter).

Questions to Inform Research Agendas

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?

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Table 1. Variability in brain death determination

Reproduced from Wahlster et al[1] (2015)

WHO region/country	Country income level[a]	Law	Protocol	Exam[b]	Apnea test	Ancillary tests	No. of physicians	Time, h[c]	Pediatric criteria[d]	Transplant network[e]
African										
Botswana	3	A	A	NA	NA	NA	NA	NA	NA	A, NA
Burkina Faso	1	A	A	NA	NA	NA	NA	NA	NA	A, NA
Cape Verde	2	A	A	NA	NA	NA	NA	NA	NA	A, NA
Ethiopia	1	U	A	NA	NA	NA	NA	NA	NA	A, NA
Ghana	2	P[f]	P[f]	D	opt	Not used	2	ND	Same	A, N
Guinea	1	A	A	NA	NA	NA	NA	NA	NA	A, NA
Kenya	1	A	P	D	req	opt	2	ND	Same	A, N
Nigeria	2	A	A	NA	NA	NA	NA	NA	NA	A, NA
Rwanda	1	A	A	NA	NA	NA	NA	NA	NA	A, NA
Uganda	1	U	P	D	Not used	opt	2	ND	Same	A, N
Eastern Mediterranean										
Bahrain	4	A	P	C	req	opt	2	>25 (CA)	Same	P, Y
Iran	3	P[f]	P	D	req[g]	opt[g]	3	11-15[g]	Different	P, Y
Iraq	2	U	A	NA	NA	NA	NA	NA	NA	A, NA
Jordan	3	P[f]	P	D	req[g]	req	3[g]	ND	Same	P, Y
Kuwait	4	P	P	C	req	opt	3	ND	Different	P, Y
Lebanon	3	P	P	C	opt[g]	req	2	6-10	Different	P, Y
Pakistan	2	A	P[f]	C	req[g]	opt[g]	2[g]	6-10[g]	Different	A, N
Qatar	4	P	P	C	req	req	2[g]	6-10[g]	Same	P, Y
Saudi Arabia	4	P	P	D	req	req	2	ND[g]	Different	P, N
Syrian Arab Republic	2	U[g]	A	NA	NA	NA	NA	NA	NA	P, NA
United Arab Emirates	4	U[h]	P	D	req	opt	2[g]	>25[g]	Different	A, N
Yemen, Republic	2	A	A	NA	NA	NA	NA	NA	NA	A, NA
European										
Albania	2	A	A	NA	NA	NA	NA	NA	NA	P, NA
Armenia	2	P[f]	P[f]	D	req[g]	req[g]	3[g]	6-10[g]	Different	A, N
Austria	4	P	P	D	req	req[g]	2[g]	ND[g]	Different	P, N
Belgium	4	P	P	C	req	opt	3	ND	Different	P, N
Bulgaria	3	P	P	C	req	opt	3	11-15	Same	P, N
Croatia	4	A	P	D	req	opt[g]	3	11-15[g]	Same	P, Y
Czech Republic	4	P[f]	P	D	req	req	2	0-5[g]	Different	P, Y
Denmark	4	P	P	C	req	opt	2	6-10[g]	Different	P, N
Estonia	4	P	P	C	req	—	—	—	—	—
Finland	4	P	P	D	req	opt[g]	2	ND	Same	P, Y
France	4	P	P	C	req	req	2	ND	Same	P, N
Germany	4	P	P	C	req	opt	2	11-15	Different	P, N
Greece	4	P	P	D	req	opt	3	21-25[g]	Different	P, Y
Hungary	4	P	P	C	req	opt[g]	3[g]	11-15	Different	P, Y
Iceland	4	P	P	D	req	opt	2	ND	Same	P, N
Ireland	4	P	P	D	req	opt	2	>25[g]	Different	P, N
Israel	4	P	P	C	req	opt[g]	2[g]	6-10	Different	P, Y

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WHO region/country	Country income level[a]	Law	Protocol	Exam[b]	Apnea test	Ancillary tests	No. of physicians	Time, h[c]	Pediatric criteria[d]	Transplant network[e]
Italy	4	P	P	D	req	req	3[g]	6-10[g]	Different	P, Y
Lithuania	3	P	P	C	req	opt	3	21-25	Different	P, N
Macedonia	3	A	A	NA	NA	NA	NA	NA	NA	A, NA
Malta	4	P	P	C	req	Not used[g]	2[g]	ND[g]	Same	P, N
Netherlands	4	P	P	C	req	req	2[g]	ND	Different	P, N
Norway	4	P	P	C	req	req	2[g]	ND[g]	Same	P, N
Poland	4	P	P	D	req	opt	3[g]	6-10[g]	Different	P, N
Portugal	4	P	P	C	req	opt	2[g]	ND[g]	Same	P, Y
Romania	3	P	P	D	req	req	3[g]	6-10[g]	Different	P, Y
Russian Federation	3	P	P	D	req	req[g]	1[g]	0-5[g]	Same	A, N
Serbia	3	P[f]	P	D	opt[g]	opt[g]	3	ND	Same	P, N
Slovenia	4	P[f]	P	C	req	req	3	ND	Different	P, N
Spain	4	P	P	C	req	opt	3[g]	ND[g]	Different	P, N
Sweden	4	P	P	C	req	opt[g]	1	ND	Same	P, N
Switzerland	4	U[g]	P	D	req	req	2	21-25[g]	Different	P, N
Turkey	3	P	P	C	req	opt[g]	4	ND	Different	P, N
United Kingdom	4	P	P	D	req	Not used[g]	2	21-25[g]	Same	P, N
Pan-American										
Argentina	3	P	P	C	req	req	3[g]	ND[g]	Different	P, Y
Bolivia	2	P	P	D	req	opt	U	>25	Same	P, N
Brazil	3	P	P	C	req	req[g]	2[g]	6-10	Different	P, Y
Canada	4	P	P	C	req	opt	1	16-20[g]	Different	P, N
Chile	3	P	P	C	req	opt[g]	1[g]	ND[g]	Different	P, Y
Colombia	3	P	P	D	req[g]	opt	2	ND	Different	P, Y
Costa Rica	3	A[h]	A[h]	NA[g]	NA[g]	NA[g]	NA[g]	NA[g]	NA	P, NA
Cuba	3	P[f]	P	D	req	opt	2	ND[g]	Different	P, N
Dominican Republic	3	P	P	C	req	opt	2	6-10	Different	P, Y
Ecuador	3	P[f]	P[f]	D	req[g]	req[g]	3[g]	ND	Same	P, Y
Haiti	1	A	A	NA	NA	NA	NA	NA	NA	A, NA
Honduras	2	A	P[f]	D	req[g]	req[g]	2[g]	11-15[g]	Same	A, N
Jamaica	3	U[g]	P	D	req	Not used[g]	2	ND[g]	Same	A, N
Mexico	3	P	P	C	opt	req	1[g]	U	Same	P, Y
Panama	3	P	P	D	req	opt	1	ND	Same	P, Y
Peru	3	P	P	D	req	opt	2	6-10	Same	P, Y
Trinidad and Tobago	4	P[f]	P	D	req	Not used[g]	2	21-25[g]	Different	P, Y
United States	4	P, V	P	C	req	opt	V	6-10	Different	P, Y
Uruguay	3	P	P	C	req	opt	2[g]	21-25[g]	Different	P, N
Southeast Asian										
Bangladesh	1	P	A[h]	NA[g]	NA[g]	NA[g]	NA[g]	NA[g]	NA	A, N
Bhutan	2	A	A	NA	NA	NA	NA	NA	NA	A, NA
India	2	P	P	C	req	opt[g]	2[g]	6-10[g]	Different	P, N
Indonesia	2	A	P	D	req	—	—	—	—	—

Continued

WHO region/country	Country income level[a]	Law	Protocol	Exam[b]	Apnea test	Ancillary tests	No. of physicians	Time, h[c]	Pediatric criteria[d]	Transplant network[e]
Myanmar	1	U	A	NA	NA	NA	NA	NA	NA	A, NA
Sri Lanka	2	P	P	C	req	opt	2	ND	Same	P, N
Timor-Leste	2	U	A	NA	NA	NA	NA	NA	NA	A, NA
Western Pacific										
Australia	4	P, V	P	D	req	opt	2	0-5	Same	P, N
China	3	A	A	NA	NA	NA	NA	NA	NA	P, NA
Japan	4	P	A[h]	NA[g]	NA[g]	NA[g]	NA[g]	NA[g]	NA	P, N
Malaysia	3	P	P	D	req	opt[g]	2	16-20[g]	Different	P, N
New Zealand	4	P[f]	P	D	req	opt	2	0-5	Same	P, Y
Philippines	2	A	A[h]	NA	NA[g]	NA[g]	NA[g]	NA[g]	NA	P, NA
Singapore	4	P	P	D	req	opt	2	16-20[g]	Same	P, Y
South Korea	4	P	P	C	req	req[g]	2[g]	U[g]	Different	P, Y
Vietnam	2	P[f]	P[f]	D	req	req[g]	3[g]	ND[g]	Same	A, N

Abbreviations: A = absent; NA = not applicable (given absence of brain death provision); ND = not defined; opt = optional; P = present; req = required; U = respondent uncertain; V = variable between regions; WHO = World Health Organization.
Symbol: — = survey not completed.
[a] Country income level: According to World Bank Classification, based on 2012 gross national income per capita per year; 1 = lower income (≤$1,035), 2 = lower-middle income ($1,036-$4,085), 3 = upper-middle income ($4,086-$12,615), 4 = high income (≥$12,616).
[b] Examination: C = concordant with the contemporary American Academy of Neurology (AAN) guidelines[4]; D = discordant with the AAN guidelines.
[c] Time = minimum observation time until bran death declaration; CA = only in patients with cardiac arrest.
[d] Pediatric criteria: same/different in comparison to adult criteria.
[e] Transplant network: Y/N = yes/no (required to contact organ procurement organization before brain death declaration).
[f] Brain death law/protocol reported as present, absent in previously published data.[4]
[g] Brain death law/protocol reported as absent, but shown to be present in previously published data.
[h] Reported response different from previously published data.

Table 2. Variability in brain death determination in Asia

Reproduced from Chua et al[9] (2015)

	Brain death concept	Available brain death certificate guidelines?	Number of personnel needed for certification	Apnea Test – $PaCO_2$ threshold (mmHg)	Is repeat clinical testing required?	Time interval to repeat examination	Are ancillary tests required?	Consent for organ donation
China	Whole brain	Yes	At least 2	≥ 60 / ↑20 above baseline	Yes	12 h	Yes	Opt-in
Japan	Whole brain	Yes	At least 2	≥ 60	Yes	Depends on age; range of 6-24 hr	Yes	Opt-in
South Korea	Whole brain	Yes	4 to 6	Not specified	Yes	Depends on age; range of 6-48 hr	Yes	Opt-in
Taiwan	Brainstem	Yes	2	Not specified	Yes	Depends on age; range of 4-24 hr	No	Opt-in
Hong Kong	Brainstem	Yes	2	> 60 and pH < 7.3	Yes	Anytime after 1st examination	No	Opt-in
Philippines	Whole brain	Yes	2	≥ 60 / ↑20 above baseline	Yes	2 hr	No	Opt-in
Vietnam	Whole brain	No	2	Not specified	Yes	Not specified	No	Opt-in
Thailand	Whole brain	Yes	3	≥ 60 / ↑20 above baseline	Yes	6 hr	No	Opt-in
Myanmar	Whole brain	No	2	Not specified	Yes	Not specified	No	Opt-in
Malaysia	Whole brain	Yes	2	≥ 60 / ↑20 above baseline	Yes	Depends on age; range of 6-48 hr	2 EEGs required for children < 1 year old	Opt-in
Singapore	Brainstem	Yes	2	≥ 50 / ↑20 above baseline	No	Not applicable	No	Opt-in and opt-out
Indonesia	Whole brain	Yes	3	> 60	Yes	25 min-24 hr	No	Opt-in
India	Brainstem	Yes	4	≥ 60 / ↑20 above baseline	Yes	6 hr	No	Opt-in
Sri Lanka	Whole brain	Yes	2	Not specified	Yes	12 h	No	Opt-in

Table 3. Variability in brain death determination in the United States
Modified from Greer et al[8] (2016)

Criteria	%*	Elements
Expertise	33.1%	Require specific expertise in neurology or neurosurgery
Number of exams required	13.0%	1 exam
	65.9%	2 separate exams
	20.9%	More than 2 separate exams
Time between exams**	10.2%	< 6 hours
	71.1%	At least 6 hours
	2.6%	At least 12 hours
	1.1%	At least 24 hours
Prerequisites for clinical testing	11.2%	Absence of peripheral nerve electrical stimulation
	56.2%	Absence of hypotension
	73.9%	Absence of confounding medical conditions • Combination of severe electrolyte, acid-base and endocrine disorders specified (71.1%)
	82.9%	Established cause
	79.4%	Require patient's temperature to be at least 36°C
	94.3%	Absence of drugs
	25.1%	Specific drug levels mentioned
Specifics of clinical testing	92.9%	Absence of pupillary reflexes
	89.6%	Absence of corneal reflexes
	89.8%	Presence of coma
	89.2%	Absence of oculovestibular reflex
	88.2%	Absence of oculocephalic reflex
	87.2%	Absence of gag reflex
	84.3%	Absence of reaction to deep pain
	79.0%	Absence of cough reflex
	62.1%	Absence of spontaneous respirations (prior to apnea testing)
	22.6%	Absence of jaw jerk reflex
Requirement for apnea testing	97.4%	Require apnea testing • Liters per minute of oxygen specified (63.1%) • Absence of respiratory effort (88.0%) • Preoxygenation specified (79.0%) • Final $PaCO_2$ specified (83.5%) • ABG measurement required prior to testing (66.4%) • $PaCO_2$ level above baseline specified (59.1%) • Stop testing if patient unstable (63.5%)
Requirement for ancillary testing	6.5%	Required in all patients
	51.1%	Inability to complete examination
	48.5%	Inconclusive apnea test results
	32.0%	Toxic drug levels
	13.6%	Chronic carbon dioxide retention
	8.8%	Normal results of neuroimaging

*Hospital policies provided by 52 of 58 organ procurement organizations in the United States, with 492 policies providing adequate data for analysis.
**For policies that require more than one exam who specify a waiting period between exams [54.1% (266 of 492)]