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Determination of Brain Death/Death by Neurologic Criteria in Countries in Asia and the Pacific

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Methods Between January 2018 and April 2019, we attempted to communicate with contacts in the 57 countries in Asia and the Pacific to determine if they had official national BD/ DNC protocols. We reviewed and compared the identified protocols.

Results We identified contacts for 40 (70%) of the 57 countries in Asia and the Pacific, and successfully communicated with 37 of them (93% of countries with contacts identified, 65% of countries in Asia and the Pacific). We found that 24 of the 37 countries had BD/DNC protocols. Two (13%) of the 16 protocols that provided a definition of death referred to brainstem death. Kazakhstan and Israel required only 1 examination to declare BD/DNC, while 10 (71%) of the other 14 protocols required 2 examinations separated by 6–48 hours. The prerequisites, clinical examination, apnea testing procedure, and indications for/selection of ancillary tests varied. Ancillary testing was required for all determinations of BD/DNC in five (21%) countries. Thirteen (54%) of the protocols included information about the time of death, while 12 (50%) of them provided instructions about discontinuation of organ support.

Conclusions The protocols for conducting a BD/DNC determination vary markedly among countries in Asia and the Pacific. Since it is optimal to have internationally and intranationally consistent BD/DNC protocols, efforts should be made to harmonize protocols both within this region and worldwide.

Key Words brain death, policy, death, Asia.

INTRODUCTION

During the 50 years since the publication of reports on the determination of brain death/ death by neurologic criteria (BD/DNC) by Harvard University and the World Medical Assembly in 1968, BD/DNC protocols have been developed in many countries around the world.¹⁻⁶ However, some countries still do not have medical standards for BD/DNC, and there is also international and intranational variability between the protocols that do exist.^{3,4,7-9}

The Asia-Pacific region is home to 60% of the global population and comprises 57 (29%) of the 197 countries in the world (the United Nations Asia-Pacific Group plus Israel and Taiwan).^{10,11} Since 1980, 367 (20%) of the 1,823 papers published in countries with 20 or more publications about BD/DNC were written by clinicians in countries in Asia and the Pacific.¹² Despite this, the review of worldwide BD/DNC protocols reported by Wijdicks in 2002 included only 22 countries in Asia and the Pacific (39% of the countries in this region), 18 of which had protocols for BD/DNC (83% of countries reviewed in the region, 35% of

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countries in Asia and the Pacific).⁴ Similarly, the international survey performed by Wahlster et al.³ in 2015 of physicians who are involved in declarations of BD/DNC included only 27 countries in Asia and the Pacific (47% of countries in the region), 17 of which had protocols for BD/ DNC (63% of countries reviewed in the region, 30% of countries in the region), while the review by Chua et al.⁹ in 2015 of Asian protocols included protocols from only 14 countries (25% of countries in Asia and the Pacific).

Wijdicks,4 Wahlster et al.,3 and Chua et al.9 all noted inconsistencies between protocols in the region in the criteria used for determining BD/DNC. However, these studies were all limited reviews, and while they addressed 1) the number of examiners, 2) observation time, 3) time between examinations, 4) concordance/discordance with the American Academy of Neurology (AAN) BD/DNC Practice Parameters, 5) target value and procedure of apnea testing, and 6) requirement for ancillary testing, they did not delve into the more-nuanced aspects of BD/DNC protocols, such as the 1) process used to rule out the effect of drugs on the evaluation, 2) minimum temperature and blood pressure for an evaluation to be performed, 3) technique used to assess each component of the examination and the findings of BD/DNC, 4) preparation for apnea testing, 5) reasons to end apnea testing, 6) accepted ancillary tests, 7) need for communication with a person's family, 8) time of death, and 9) discontinuation of organ support.

Our recent review of protocols for BD/DNC around the world found substantial variability.¹³ The existence of a BD/DNC protocol in a given country is dependent on acceptance of BD/DNC as death, access to resources (including experts in the neurosciences/critical care), the presence of a transplant network, and local laws.^{39,14} Religious beliefs markedly influence the acceptance of BD/DNC as death, and so it is noteworthy that there are various major religions in countries

in Asia and the Pacific region (Buddhism, Catholicism, Confucianism, Hinduism, Islam, Shintoism, and Taoism), some of which are unique to the region.9 Because of this, the perspectives on BD/DNC among residents of countries in Asia and the Pacific can differ from those among individuals in other parts of the world.¹⁵⁻¹⁷ Countries in Asia and the Pacific also exhibit extreme population variability, ranging from the most-populated countries in the world (China and India) to some of the least-populated countries (small island nations in the Pacific).10 Thus, although religious views in countries in Asia and the Pacific are distinct from those in the rest of the world, the diversity of political, economic, legal, social and religious climates throughout the region mirrors that globally. To better understand BD/DNC protocols in countries in Asia and the Pacific, we conducted an in-depth review of the protocols in this region that we had identified as part of our worldwide review.

METHODS

Protocol acquisition

We solicited official national BD/DNC protocols—or information that no protocol existed—from contacts in the 57 countries in Asia and the Pacific¹¹ between January 2018 and April 2019. After reaching out to personal connections, we emailed members of the 1) AAN, 2) World Federation of Societies of Intensive and Critical Care Medicine, and 3) International Society of Organ Donation and Procurement. We identified contacts for 40 (70%) of the 57 countries in Asia and the Pacific, and successfully communicated with contacts from 37 of these countries (93% of countries with contacts identified, 65% of countries in Asia and the Pacific) (Fig. 1).

Countries with protocols ($n=24$)		Countries without protocols (n=13)	Countries with unknown protocol status (n=20)	
Bangladesh	Mongolia	Afghanistan	Brunei*	Solomon Islands
China	Nepal	Bahrain	Fiji	Tajikistan
Cyprus	Philippines	Bhutan	Kiribati	Timor-Leste
India	Qatar	Cambodia	Kyrgyzstan	Tonga
Indonesia	Saudi Arabia	Iraq	Laos	Turkmenistan
Iran	Singapore	Maldives	Marshall Islands	Tuvalu
Israel	South Korea	Myanmar (Burma)	Micronesia	Uzbekistan*
Japan	Taiwan	Oman	Nauru	Vanuatu
Jordan	Thailand	Pakistan	North Korea	Yemen*
Kazakhstan	Turkey	Samoa	Palau	
Kuwait	Vietnam	Sri Lanka	Papua New Guinea	
Lebanon		Syria		
Malaysia		United Arab Emirates (UAE)		

Fig. 1. Status of protocols for the determination of brain death/death by neurologic criteria in countries in Asia and the Pacific. *Contact attempted, but was unsuccessful.

Protocol review

Protocols were reviewed and data on protocol year, definition of BD/DNC, examination/examiner, prerequisites, clinical examination technique, apnea testing, ancillary testing, and other considerations were extracted into a database, as described elsewhere.¹³ Protocols in languages other than English were either 1) reviewed by individuals fluent in that language or 2) translated into English using Internet translation tools.

Statistics

Data were reviewed using descriptive statistics. Because this study did not involve human subjects, there was no need to obtain IRB approval.

RESULTS

Protocols

We obtained protocols for the determination of BD/DNC from 24 of the 37 countries with contacts with whom we successfully communicated (65% of countries with contacts with whom we successfully communicated, 42% of all countries in Asia and the Pacific). The protocols had been published between 1983 and 2018, with a median of 2010. The AAN Practice Parameters were referenced in four protocols (17%).

Physiology

Fourteen (88%) of the 16 protocols that provided a definition of BD/DNC referred to "whole brain death," while the other 2 (13%; India and Cyprus) referred to "brainstem death." The need for damage to be "irreversible" was mentioned in 15/16 protocols that provided a definition of BD/DNC (94%), but 6 (38%) also noted that the damage must be "permanent." The need for "all functions" of the brain to be absent before declaring BD/DNC was included in 10 (63%) of the protocols that provided a definition of BD/DNC, and the need for "all activities" to cease was mentioned in 2 protocols (13%). No protocol required the absence of both "all functions" and "all activities" of the brain. Nearly all protocols that provided a definition of BD/DNC included the brain (88%) and the brainstem (81%) in the definition (Fig. 2).

Age groups

The age group to which the protocol applied was specified for 14 (58%) protocols, the lower limit of which varied, with 6 (43%) indicating that BD/DNC could be declared in a newborn without specifying a lower limit of age, while 1 (7%) had lower limits of 7 days, 1 month, 12 weeks, and 1 year, respectively. Ten (71%) of the 14 protocols that addressed age prescribed different guidelines for 2 to 5 age groups: in 7 (70%) of these, the time between examinations differed with age; in 3 (30%) the observation period before an examination differed with age; in 2 the ancillary testing indications differed



Fig. 2. Definitions of brain death/death by neurologic criteria in countries in Asia and the Pacific.

with age; and in 1 (10%) the number of examinations differed with age.

Examiner/examination

Twenty (95%) of the 21 protocols (88%) that provided information about the number of examiners required at least 2 examiners, of which 11 (55%) specified at least 1 examiner to be a neurosciences specialist. In 12 (50%) of all protocols it was stated that the examiner should not be a member of the transplant team.

Among the 14 protocols (58%) that indicated the number of examinations required to declare BD/DNC, only Kazakhstan and Israel required 1 examination, while 10 (71%) required 2 examinations separated by 6–48 hours, Vietnam required 3 examinations, and Mongolia required 4 examinations. The number of apnea tests was specified in 15 (62%) protocols, 8 (53%) of which required more than 1 test.

Prerequisites

Most protocols (n=21, 88%) indicated that it was necessary to identify a cause for catastrophic brain injury before conducting a determination of BD/DNC, but only six (25%) protocols required brain imaging. Conditions that mimic BD/ DNC were mentioned in 15 protocols (62%).

The observation period prior to conducting a BD/DNC determination was mentioned in 10 protocols (42%) and was less than 24 hours in all protocols except for in the one from India, which stated the need to wait 50–100 hours before a determination if there was suspicion for intoxication and a toxicology screen could not be performed.

The drugs that needed to be considered before conducting a BD/DNC determination and the time delay between drug administration and BD/DNC determination varied. Malaysia provided the most-detailed information about the assessment of drug clearance before a BD/DNC determination: the protocol included 17 drugs/classes of drugs to consider, most of which were accompanied by a detailed description of the half-life and therapeutic range.

The minimum temperature and blood pressure for performing a clinical assessment and apnea testing were not routinely provided, and were inconsistent between the protocols that did provide them. The need to rule out electrolyte, acid-base, and endocrine derangements before a determination varied (Table 1).

Clinical examination

The description of the components, technique, findings, and conditions that could affect the results of a clinical evaluation differed between protocols (Table 2). The protocols for Cyprus, Jordan, and Taiwan did not describe any components of the clinical assessment, while those for Mongolia and Singapore did not include an assessment of coma. The need to assess for movement induced by noxious stimulation to the cranium was noted in nine protocols (38%), while the need to assess for the response to noxious stimulation applied to the limbs was noted in seven of them (29%). The protocol from Iran did not describe the corneal, oculocephalic, or cough reflex; that from the Philippines did not include the oculocephalic or cough reflex; those from China and Vietnam did not mention the gag reflex; and that from Lebanon did not reference the gag or cough reflex. No country required the atropine test or an assessment of the oculocardiac reflex.

Apnea testing

The protocols from Cyprus, Lebanon, and Taiwan did not describe the technique for apnea testing. The description of the testing preparation, testing technique, reasons to abort testing, PaCO₂ target value, and next steps if testing is aborted varied across the protocols (Table 3). The oxygen flow rate varied among the 15 protocols that addressed its administration during apnea testing. No protocol discussed the apnea testing procedure for patients on extracorporeal membrane oxygenation.

Ancillary testing

Ancillary testing was required for all determinations of BD/ DNC in five (21%) protocols: China [required two ancillary tests including an electroencephalogram (EEG), and/or somatosensory evoked potentials (SSEPs), and/or transcranial ultrasound (TCD)]; Israel [required one of four-vessel angiogram, brainstem auditory evoked potentials, computed tomography angiogram (CTA), magnetic resonance angiogram, nuclear imaging study, SSEPs, or TCD]; Saudi Arabia [required an EEG (or if one cannot be performed or interpreted due to technical difficulties, a four-vessel angiogram]; South Korea (required an EEG); and Vietnam (required a four-vessel angiogram, CTA, EEG, nuclear imaging study, or TCD). The most-common indication for performing ancillary testing in the 19 countries where it was not required was the inability to complete apnea testing (n=9, 47%) (Fig. 3). No protocol recommended ancillary testing after treatment with targeted temperature management or in the setting of primary infratentorial pathology. Among the 24 protocols, the most commonly accepted ancillary test was the EEG (n=17, 71%) (Fig. 4). Acceptable ancillary tests were not indicated in the protocols from Bangladesh, Cyprus, Japan, Jordan, and Taiwan.

Communication

Only eight (33%) of the protocols mentioned the need for communication with a person's family prior to, during, or fol-

 Table 1. Prerequisites for the determination of BD/DNC in countries in

 Asia and the Pacific

Prerequisite	Number of protocols (n=24)
Observation period	
Not stated	14 (58)
General observation period	6 (25)
Anoxic brain injury without hypothermia	4 (17) [24 hours]
Hypothermia	2 (8) [not specified]
Intracerebral hemorrhage	2 (8) [6 hours]
Major neurosurgical procedure	1 (4) [4 hours]
Secondary brain injury	1 (4) [24 hours]
Suspicion of intoxication in the absence of screening	1 (4) [50–100 hours]
Traumatic brain injury	2 (8) [6 hours]
Tumor	1 (4) [6 hours]
Drugs to consider	
Not stated	5 (21)
Alcohol	4 (17)
Muscle relaxants/paralytics	15 (63)
Narcotics	9 (38)
Nonspecific central nervous system depressants	11 (46)
Sedatives	11 (46)
Other	4 (17)
Time between drug administration and determi	nation of BD/DNC
Not stated	16 (67)
6 hours	1 (4)
>24 hours	1 (4)
72 hours	1 (4)
120 hours	1 (4)
4 half-lives	1 (4)
5 half-lives	2 (8)
Depends on drug levels	1 (4)
Depends on renal function	1 (4)
Depends on hepatic function	1 (4)
Perform a train of four	2 (8)
Minimum temperature for performing a clinica apnea testing	l examination and
Not stated	7 (29), 14 (58)
Not hypothermic (no temperature specified)	2 (8), 1 (4)
Normothermic (no temperature specified)	0 (0), 1 (4)
32°C	6 (25), 2 (8)
32.5°C	1 (4), 0 (0)
34°C	2 (8), 0 (0)
35°C	2 (8), 1 (4)
36°C	3 (13), 2 (8)
36.5°C	1 (4), 3 (13)

 Table 1. Prerequisites for the determination of BD/DNC in countries in

 Asia and the Pacific (continued)

Prerequisite	Number of protocols (n=24)
Blood-pressure criterion for performing a clinical	examination and
apnea testing	
Not stated	15 (63), 11 (46)
MAP >60 mm Hg	0 (0), 3 (13)
Absence of shock or hemodynamic instability	1 (4), 1 (4)
Normal (no blood pressure specified)	1 (4), 2 (8)
SBP >90 mm Hg	4 (18), 6 (25)
SBP >100 mm Hg	3 (13), 2 (8)
Medical disturbances to rule out before the deter	mination
Not stated	6 (25)
Electrolyte derangements (general)	17 (71)
Electrolyte derangements (specific values noted)	0 (0)
Acid-base derangements (general)	10 (42)
Acid-base derangements (specific values noted)	0 (0)
Endocrine derangements (general)	17 (71)
Endocrine derangements (specific values noted)	0 (0)

Data are n (%) [range].

BD/DNC: brain death/death by neurologic criteria, MAP: mean arterial pressure, SBP: systolic blood pressure.

lowing a BD/DNC determination. Four (50%) of these protocols specified that it was necessary to communicate with a person's family before a determination of BD/DNC, while three (38%) indicated it was necessary to communicate with a person's family before the discontinuation of organ support.

Declaration, documentation, and discontinuation

Only 13 (54%) of the protocols included information about the time of death. The time of death was defined in the following different ways: 1) upon completion of the clinical examination (n=8, 62%), 2) upon completion of testing or the observation period (n=1, 8%), 3) after a waiting period in which there is no improvement following the establishment of a clinical examination consistent with BD/DNC (n=1, 8%), 4) after the BD/DNC judgement committee makes their determination (n=1, 8%), 5) at least 12 hours after the person has met criteria for BD/DNC (n=1, 8%), 6) 12 hours after the person has met the criteria for BD/DNC, unless there is secondary damage or ancillary testing is not used, in which case it is necessary to wait 24 hours to declare death (n=1, 8%), or 7) the time that the PaCO₂ reached the designated target value (n=1, 8%).

A checklist for documentation was included in 13 (54%)

 Table 2. Clinical examination for brain death/death by neurologic criteria determinations in countries in Asia and the Pacific

Examination component	Number of protocols (n=24)
Assessment of coma	
Not stated	5 (21)
Findings described	
Absence of consciousness	1 (4)
Absence of responsiveness	10 (42)
Glasgow Coma Scale score of 3	8 (33)
Technique described	
Nonspecific assessment of coma	4 (17)
Noxious stimulation (nonspecific)	1 (4)
Noxious stimulation to face	9 (38)
Noxious stimulation to limbs	7 (29)
Sternal rub	1 (4)
Assessment of pupillary reflex	
Not stated	3 (13)
Findings described	
No constriction to bright light	18 (75)
Enlarged (nonspecific)	1 (4)
Size ≥4 mm	5 (21)
Size ≥5 mm	1 (4)
Small or medium-size pupils may be present, so no specific size is required	1 (4)
Technique described	
Nonspecific assessment of pupillary reflex	4 (17)
Consensual assessment	1 (4)
Dim ambient lighting	1 (4)
Direct assessment	3 (13)
Household torches or ophthalmoscopes should not be used	1 (4)
Conditions that can impact the assessment	
Anticholinergic drugs can cause dilation	3 (13)
Cataracts preclude the assessment	2 (8)
Assessment of corneal reflex	
Not stated	4 (17)
Findings described	
Absence of blinking	4 (17)
Technique described	
Nonspecific assessment of corneal reflex	13 (54)
Cotton swab	8 (33)
Gauze	1 (4)
Conditions that can impact the assessment	
Facial weakness	1 (4)
Assessment of oculocephalic reflex	
Not stated	5 (21)
Findings described	
No eye movement	7 (29)

 Table 2. Clinical examination for brain death/death by neurologic criteria determinations in countries in Asia and the Pacific (continued)

Number	
Examination component	protocol
	(n=24)
Technique described	
Nonspecific assessment of oculocephalic reflex	10 (42)
Brisk horizontal head movement	5 (21)
Four seconds of movement	1 (4)
Conditions that can impact the assessment	
Rule out cervical injury	8 (33)
ssessment of oculovestibular reflex	
Not stated	3 (13)
Findings described	
No eye movement	8 (33)
Technique described	
Nonspecific assessment of oculovestibular reflex	10 (42)
20 mL of ice water	3 (13)
50 mL of ice water	7 (29)
100 mL of ice water	1 (4)
Elevate the head of the bed to 30°	5 (21)
Inspect the canal	6 (25)
Interval of several minutes between	
stimulating the two ears	4 (17)
Observe for 60 seconds	4 (17)
Utilize cold air if the tympanic membrane is	
not intact	1 (4)
Water temperature should be 5–6°C	1 (4)
Conditions that can impact the assessment	
Clotted blood/cerumen could reduce the response	1 (4)
Ruptured eardrum does not preclude	
the assessment	2 (8)
Ruptured eardrum precludes the assessment	5 (21)
Skull fracture can obliterate the response	3 (13)
Some drugs can obliterate the response	3 (13)
ssessment of cough and gag reflexes	
Cough reflex not stated	6 (25)
Gag reflex not stated	5 (21)
Technique described	
Nonspecific assessment of cough reflex	9 (38)
Nonspecific assessment of gag reflex	13 (54)
Pharyngeal wall	5 (21)
Suction catheter	9 (38)
Tongue depressor	1 (4)
Tracheobronchial wall	6 (25)
Conditions that can impact the assessment	5 (20)
	1 (4)
Rule out cervical injury ata are <i>n</i> (%).	1 (4)

Examination component	Number of protocols (n=24)
Preparation for testing	
Check for spontaneous breathing before conducting apnea testing	2 (8)
Complete the clinical examination for the determination of BD/DNC before conducting apnea testing	9 (38)
Obtain an arterial blood gas reading before apnea	13 (54)
Review the PaCO ₂ value before apnea testing	
$PaCO_2$ should be normal	1 (8)
$PaCO_2$ should be 35–45 mm Hg	7 (54)
$PaCO_2$ should be ~40 mm Hg	1 (8)
$PaCO_2$ should be ≥ 40 mm Hg	3 (23)
$PaCO_2$ should be 40–45 mm Hg	1 (8)
Review the pH value before apnea testing	(-)
Target not stated	12 (92)
pH should be normal	1 (8)
Factors that may preclude apnea testing	
Not stated	22 (92)
High-level spinal cord injury	1 (4)
Hypoxia	1 (4)
Preoxygenation	.,
Not stated	5 (21)
5 min of $FiO_2 = 100\%$	1 (4)
10 min of FiO ₂ =100%	15 (63)
15 min of FiO ₂ =100%	1 (4)
PaO₂ ≥200 mm Hg	5 (21)
Decrease respiratory rate by 2 breaths/min and increase FiO ₂ to 100 $\%$	1 (4)
Apnea testing procedure	
Not stated	3 (13)
Not described in detail	2 (8)
Administer oxygen (amount not specified)	1 (4)
Administer oxygen at 4–6 L/min	2 (8)
Administer oxygen at 6 L/min	11 (46)
Administer oxygen at 6–8 L/min	1 (4)
Administer oxygen at 10 L/min	1 (4)
Disconnect the ventilator	16 (67)
Place a catheter above the carina	8 (33)
Place a catheter 1 cm beyond the endotracheal tube	1 (4)
Turn off backup ventilation if testing is done on the ventilator	1 (4)
Utilize CPAP	3 (13)
Utilize a T-piece	5 (21)
Reasons to end apnea testing	. ,
Not stated	9 (38)
8 min has passed	2 (8)
· · ·	

Table 3. Apnea testing in countries in Asia and the Pacific (continued)

	Number of
Examination component	protocols
	(n=24)
10 min has passed	6 (25)
Dysrhythmia	7 (29)
Hemodynamic disturbance	3 (13)
Hypotension (general)	3 (13)
Hypotension with SBP <90 mm Hg	5 (21)
Hypoxia (general)	3 (13)
Hypoxia with saturation <85%	4 (17)
Hypoxia with saturation <90%	1 (4)
Hypoxia with saturation <91%	1 (4)
Spontaneous breathing	10 (42)
Target value of apnea testing	
Not stated	5 (21)
PaCO₂ ≥50 mm Hg	2 (8)
PaCO₂ ≥55 mm Hg	1 (4)
PaCO₂ >60 mm Hg	4 (17)
$PaCO_2 \ge 60 \text{ mm Hg}$	12 (50)
$PaCO_2$ increase of 10–15 mm Hg above baseline	1 (4)
$PaCO_2$ increase of ≥ 20 mm Hg above baseline	12 (50)
pH target provided	0 (0)
Next steps if apnea testing is aborted and no breaths we	re seen but
the $PaCO_2$ target value was not reached	
Not stated	13 (54)
Perform an ancillary test	9 (38)
Perform a blood flow	2 (8)
Repeat the test after 3 hours	1 (4)
Repeat the test with CPAP	2 (8)
Repeat the test for longer	1 (4)
Repeat the test with a higher oxygen flow rate	2 (8)

Data are *n* (%).

BD/DNC: brain death/death by neurologic criteria, CPAP: continuous positive airway pressure, SBP: systolic blood pressure.

protocols.

Instructions regarding the discontinuation of organ support were included in 12 (50%) protocols. Three (25%) of these protocols (Israel, Kazakhstan, and Qatar) stated that the objections of a family to the discontinuation of support should be considered. The protocol for Malaysia noted that input from religious authorities should be considered when determining BD/DNC, and also stated that 1) every person has a right to respect, even in death, and that continuing organ support after BD/DNC is an affront to a person's dignity, and 2) it is morally and economically unjustifiable to continue organ support after BD/DNC because this prevents patients with better prognoses from being admitted to the intensive care unit. In contrast, two (18%) protocols (Israel and Qatar) stated that the religious and moral beliefs of the per-



Fig. 3. Indications to electively perform ancillary testing in countries in Asia and the Pacific.



Fig. 4. Accepted ancillary tests in countries in Asia and the Pacific.

son should be considered when planning the time to discontinue support. That for Japan stated that reasonably respectful period should pass before discontinuing support, while that for Mongolia stated that support could be discontinued immediately after making a declaration. None of the protocols provided a separate description for what should be done after declaring BD/DNC in a pregnant person.

DISCUSSION

Among the 136 countries for whom we identified contacts during our review of protocols around the world on BD/ DNC, 61% (42% of the world) had BD/DNC protocols.¹³ Our contacts included representatives from 37 countries in Asia and the Pacific, 24 of whom provided us with their protocol

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for the determination of BD/DNC (65% of countries with contacts in this region with whom we successfully communicated, 42% of all countries in Asia and the Pacific). As far as we are aware, this study included more countries in Asia and the Pacific and a more in-depth analysis of protocols for BD/DNC than any previous study in the region; we successfully communicated with contacts in 65% of the countries in Asia and the Pacific, compared with 25%, 39%, and 47% for the protocol evaluations performed by Chua et al.,9 Wijdicks,⁴ and Wahlster et al.,³ respectively, in the same region. Our findings demonstrate that the percentage of countries in Asia and the Pacific with BD/DNC protocols is consistent with the percentage of countries worldwide with BD/DNC protocols.13 It is particularly notable that the number of countries in Asia and the Pacific with BD/DNC protocols appears to be increasing, since Wijdicks reported that China and Vietnam did not have protocols in 2002, whereas we found that both of these countries now have protocols.⁴

Like the results of our review of world protocols, we found that while some aspects of protocols from countries in Asia and the Pacific were consistent, overall there was marked variability in the criteria for BD/DNC.13 This situation can lead to inaccurate determinations or unsafe practices during such determinations. For example, some protocols did not indicate that the effects of hypothermia and drugs need to be excluded before conducting a BD/DNC determination. This is problematic given that hypothermia, alcohol, and both prescription and nonprescription drugs can transiently blunt brainstem reflexes.¹⁸⁻²⁰ Additionally, the instructions about the oxygen flow rate to apply during apnea testing were inconsistent. Moreover, two protocols recommended using an oxygen flow rate of more than 6 L/min, which is a safety issue since a high oxygen flow rate can result in barotrauma and lead to CO2 washout.21,22

Most of the protocols required two or more examiners and examinations, suggesting a common belief that a determination of BD/DNC is more likely to be accurate if multiple practitioners are involved at more than one point in time. Nonetheless, the mandatory credentials for the examiners varied. While it would be challenging—if not impossible—to ensure that the training background of practitioners responsible for declaring BD/DNC was identical throughout the region, or indeed worldwide, it would be reasonable to require mandatory training for all practitioners involved in such determinations in order to ensure safety and consistency, and thereby promote public trust in BD/DNC determinations.²³ Additionally, the use of detailed protocols and checklists could help ensure BD/DNC evaluations are performed correctly and meticulously.²⁴

Approximately one-fifth of BD/DNC protocols from coun-

tries in Asia and the Pacific referenced the AAN Practice Parameters, but there is no gold-standard protocol for BD/ DNC with which all BD/DNC protocols can be compared. However, it is evident that there is substantial protocol variability in both BD/DNC protocols from countries in Asia and the Pacific and worldwide, which could 1) conceivably lead to a person being considered alive in one place and dead in another, 2) promote unsafe practices, and 3) lead to inaccurate determinations of BD/DNC in a person who could recover. This situation makes it necessary to create formal guidelines regarding the minimum standards for determining BD/ DNC which individual countries can add to as they see fit according to their specific local practices and customs.

Limitations

The findings of this study are subject to a few limitations. Firstly, we were unable to establish communication with contacts for 20 countries (35% of the region), and hence could not establish whether or not they had a BD/DNC protocol. Two of these countries (Timor Leste and Yemen) were included in the studies of Wijdicks,⁴ Wahlster et al.,³ and Chua et al.,⁹ which found that neither country had a protocol. We believe that the inability of these studies to obtain information on the remaining 18 countries suggests that they have few (if any) clinicians that specialize in critical care or the neurosciences, making it unlikely that those countries have a protocol for BD/DNC. Secondly, it is possible that a contact provided us with a protocol that was not the most up-to-date accepted national protocol, or incorrectly told us that their country did not have a protocol for BD/DNC. For example, 1) Wijdicks⁴ reported that there were protocols in Oman and the United Arab Emirates, 2) Wahlster et al.³ noted that there were institutional protocols in Bahrain, Pakistan, and Sri Lanka, and 3) Chua et al.⁹ reviewed the protocols from Myanmar and Sri Lanka, whereas our contacts in these countries told us they did not have national protocols for the determination of BD/DNC. Thirdly, translating and interpreting protocols that are not in English can be imperfect and challenging, and so it is possible that we misconstrued the intended meaning of such protocols. It should also be noted that the presence of a national protocol for BD/DNC does not guarantee that the declaration of BD/DNC is universally accepted or that all institutions in the country strictly adhere to that protocol.7 It is particularly interesting that a global survey of neurocritical care found that hospitals in Asia and Oceania were the least likely to use clinical management protocols;25 however, that study did not focus on the use of or adherence to national BD/DNC protocols.

Conclusions

Because there is variability in BD/DNC protocols in both countries in Asia and the Pacific and worldwide, it is necessary to identify minimum standards for determination of BD/DNC. These minimum standards must include guide-lines on 1) the prerequisites for determining BD/DNC, 2) the technique for performing the clinical examination and the findings associated with BD/DNC, 3) the method used to perform apnea testing and the findings associated with BD/DNC, 4) the indications for and the selection of ancillary tests, and 5) communication and documentation about BD/DNC. Such minimum standards will ensure that BD/DNC determinations are performed in a consistent and reliable manner.

Author Contributions _

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Conflicts of Interest _

The authors have no potential conflicts of interest to disclose.

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REFERENCES

- A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death. *JAMA* 1968;205:337-340.
- 2. Gilder SS. Twenty-second World Medical Assembly. *Br Med J* 1968;3: 493-494.
- Wahlster S, Wijdicks EF, Patel PV, Greer DM, Hemphill JC 3rd, Carone M, et al. Brain death declaration: practices and perceptions worldwide. *Neurology* 2015;84:1870-1879.
- Wijdicks EF. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. *Neurology* 2002;58:20-25.
- Sprung CL, Truog RD, Curtis JR, Joynt GM, Baras M, Michalsen A, et al. Seeking worldwide professional consensus on the principles of endof-life care for the critically ill. The Consensus for Worldwide End-of-Life Practice for Patients in Intensive Care Units (WELPICUS) study. *Am J Respir Crit Care Med* 2014;190:855-866.
- Shemie SD, Hornby L, Baker A, Teitelbaum J, Torrance S, Young K, et al. International guideline development for the determination of death. *Intensive Care Med* 2014;40:788-797.
- Greer DM, Wang HH, Robinson JD, Varelas PN, Henderson GV, Wijdicks EF. Variability of brain death policies in the United States. *JAMA Neurol* 2016;73:213-218.
- Citerio G, Crippa IA, Bronco A, Vargiolu A, Smith M. Variability in brain death determination in Europe: looking for a solution. *Neurocrit Care* 2014;21:376-382.
- 9. Chua HC, Kwek TK, Morihara H, Gao D. Brain death: the Asian perspective. *Semin Neurol* 2015;35:152-161.
- United Nations Population Fund. Population trends [Internet]. New York, NY: United Nations Population Fund 2019 [cited 2019 Jul 25]. Available from: https://asiapacific.unfpa.org/en/node/15207.
- 11. Department for General Assembly and Conference Management, United Nations. United Nations regional groups of member states [Internet]. New York, NY: Department for General Assembly and Conference Management [cited 2019 Jul 19]. Available from: https://www. un.org/depts/DGACM/RegionalGroups.shtml.
- Doğan G, Kayır S. Global scientific outputs of brain death publications and evaluation according to the religions of countries. *J Relig Health* 2020;59:96-112.
- Lewis A, Bakkar A, Kreiger-Benson E, Kumpfbeck A, Liebman J, Shemie SD, et al. Determination of death by neurologic criteria around the world. *Neurology* 2020 June 23 [Epub]. Available from: https://doi. org/10.1212/WNL.00000000009888.
- Bernat JL. Comment: is international consensus on brain death achievable? *Neurology* 2015;84:1878.
- Asai A, Kadooka Y, Aizawa K. Arguments against promoting organ transplants from brain-dead donors, and views of contemporary Japanese on life and death. *Bioethics* 2012;26:215-223.
- Ding ZY, Zhang Q, Wu JW, Yang ZH, Zhao XQ. A Comparison of brain death criteria between China and the United States. *Chin Med J* (*Engl*) 2015;128:2896-2901.
- Dhanwate AD. Brainstem death: a comprehensive review in Indian perspective. *Indian J Crit Care Med* 2014;18:596-605.
- Geocadin RG, Eleff SM. Cardiac arrest resuscitation: neurologic prognostication and brain death. *Curr Opin Crit Care* 2008;14:261-268.
- XXXIV International Congress of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) 27–30 May 2014, Brussels. *Clin Toxicol (Phila)* 2014;52:419.
- López-Navidad A, Caballero F, Domingo P, Marruecos L, Estorch M, Kulisevsky J, et al. Early diagnosis of brain death in patients treated with central nervous system depressant drugs. *Transplantation* 2000; 70:131-135.
- Zisfein J, Marks SJ. Tension pneumothorax and apnea tests. Anesthesiology 1999;91:326.
- 22. Burns JD, Russell JA. Tension pneumothorax complicating apnea test-



ing during brain death evaluation. J Clin Neurosci 2008;15:580-582.

- 23. Cohen J, Steinberg A, Singer P, Ashkenazi T. The implementation of a protocol promoting the safe practice of brain death determination. *J Crit Care* 2015;30:107-110.
- 24. Delaney A, Angus DC, Bellomo R, Cameron P, Cooper DJ, Finfer S,

et al. Bench-to-bedside review: the evaluation of complex interventions in critical care. *Crit Care* 2008;12:210.

 Suarez JI, Martin RH, Bauza C, Georgiadis A, Venkatasubba Rao CP, Calvillo E, et al. Worldwide organization of neurocritical care: results from the PRINCE Study part 1. *Neurocrit Care* 2020;32:172-179.