

ORIGINAL ARTICLE

Cooling in neonatal hypoxic-ischemic encephalopathy: practices and opinions on minimum standards in the state of California

CJ Wusthoff^{1,2}, CL Clark¹, HC Glass³, TK Shimotake⁴, J Schulman⁵ and SL Bonifacio²

OBJECTIVE: Although hospitals increasingly offer therapeutic hypothermia (TH), there is variable implementation of related services. We assessed current practices and opinions regarding what services should be required of centers providing TH in California.

STUDY DESIGN: We surveyed neonatal intensive care unit physicians statewide regarding practices and opinions about services related to TH.

RESULTS: Of the 50 participating centers (47% response rate), 66% offer TH. Most TH centers reported using: an evidence-based protocol (92%), neurology consultation (92%), amplitude-integrated electroencephalography (aEEG) or EEG (88%), magnetic resonance imaging (MRIs) interpreted by pediatric neuroradiologists (71%) and developmental follow-up (93%). TH centers reported treating a median of 11 patients annually (interquartile range (IQR) 4 to 24). Respondents considered it 'critical' that TH centers offer: aEEG monitoring (70%), MRI (69%), occupational and physical therapy (67%) and developmental follow-up (94%). Over 70% thought TH centers should treat a minimum volume annually (median = 10, IQR 5 to 12).

CONCLUSION: Physicians across practice settings in California endorsed minimum standards for TH centers to promote quality of care.

Journal of Perinatology (2018) **38**, 54–58; doi:10.1038/jp.2017.153; published online 19 October 2017

INTRODUCTION

Therapeutic hypothermia (TH) is the first treatment demonstrated to be effective for reducing the risk of neurodisability from hypoxic-ischemic encephalopathy (HIE). In 2010, the Neonatal Task Force of the International Liaison Committee on Resuscitation issued an advisory statement recommending TH be offered to term or near-term infants with moderate to severe HIE.¹ That statement advised that cooling be conducted using protocols consistent with published randomized controlled trials, that TH be performed in neonatal intensive care units (NICUs) with the capacity 'of providing multidisciplinary care including electroencephalographic (EEG) monitoring' and that treated infants receive serial neurodevelopmental follow-up. This recommendation was affirmed in the 2015 American Heart Association Guidelines for Neonatal Resuscitation.² Similarly, in 2014 the American Academy of Pediatrics Committee on Fetus and Newborn published a clinical report noting that TH is an effective therapy, and that centers offering TH should be 'capable of providing comprehensive clinical care.'³ In particular, this report indicated centers offering TH should adhere to written protocols based on published trials, undertake training and outreach to those involved in identifying patients for cooling and should be able to provide magnetic resonance imaging (MRI), seizure detection and monitoring with amplitude-integrated EEG (aEEG) or EEG, neurologic consultation and neurodevelopmental follow-up. Over recent years, TH has become standard of care for

neonatal HIE in term newborns treated before 6 h of age. In addition, although controversial, some centers use TH in other populations, including those of lower gestational age or after 6 h. At the same time, it is increasingly recognized that centers providing TH should be able to provide comprehensive clinical services related to HIE and TH. In a recent national survey, 99% of respondents reported that TH is now standard of care, increased from 67% 6 years prior. However, respondents also indicated there remained variability in care practices such as brain imaging after rewarming and in the use of brain monitoring.⁴ Although the need for comprehensive services has been outlined in guidance statements as above, until recently, there were no minimum standards required in order for centers to offer TH. Establishing such standards is challenging, and entails examining the presumed benefits of care at a high-volume comprehensive TH center in comparison with the presumed benefits of promoting access to as many patients as possible by avoiding excessively stringent requirements. Similarly, the benefits of TH at a high-volume center might be offset by the costs of transport and separation of the infant from parents. In addition, although simple in concept, providing TH requires close attention to detail in order to provide care in a safe manner. Safety concerns such as sinus bradycardia, pulmonary hypertension, coagulopathy and excessive cooling were reported in TH-treated neonates in the randomized trials. A recent study characterized the implementation of TH across California, and highlighted an increase in TH use and the need to explore practice-site variation.⁵ As part of the

¹Division of Child Neurology, Stanford University School of Medicine, Palo Alto, CA, USA; ²Division of Neonatal and Developmental Medicine, Stanford University School of Medicine, Palo Alto, CA, USA; ³Department of Neurology, Pediatrics and Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA; ⁴Department of Neonatology, University of California, San Francisco, San Francisco, CA, USA and ⁵California Department of Health Care Services, Sacramento, CA, USA. Correspondence: Dr CJ Wusthoff, Division of Child Neurology, Stanford University School of Medicine, 750 Welch Road, Suite 317, Palo Alto, CA 94304, USA. E-mail: wusthoff@stanford.edu

Received 5 April 2017; revised 6 July 2017; accepted 11 August 2017; published online 19 October 2017

process of developing new statewide requirements of TH centers,⁶ we surveyed neonatologists and neurologists practicing at California Children's Services (CCS) -approved NICUs to describe current practices, and assessed opinions regarding what resources and services should be required of centers providing TH.

METHODS

Email invitations to participate in an online survey about TH practices and opinions were sent to neonatologists and neurologists practicing at the 107 CCS-approved NICUs between May and October 2014. In California, CCS-approved NICUs are designated as intermediate, community and regional (highest level of care) and all intermediate- and community-level facilities must have a cooperation agreement with a regional center. Units designated as intermediate are units that can provide care for sick neonates and infants who do not require critical care but require care at a higher level than that of a 'well baby' nursery. An intermediate NICU generally corresponds to an AAP (American Academy of Pediatrics) level II designation. These units may provide intravenous medications and nutrition, tube feedings, oxygen and short-term ventilator support (≤4 h). Community NICUs can provide intensive care with continuous cardiopulmonary monitoring and other specialized care technology for multisystem problems. Community-level NICUs would most closely resemble level II to III NICUs per the AAP criteria. Regional NICUs can provide a full range of neonatal care services including surgery for severely ill patients and must support community and intermediate NICUs. Regional NICUs would most closely resemble level III to IV NICUs per the AAP designation. The survey was closed with a final sample of 64 responses captured through the REDCap data management system. The survey included questions about clinicians' roles, clinical practice settings and self-report of practices currently used at TH centers (for example, neuromonitoring defined as aEEG and/or continuous EEG). Respondents were also asked to provide their opinions about the types of services TH centers should offer, to ensure safe and high-quality care, regardless of their centers' current actual practice. When providing opinions regarding which practices are important, respondents were asked to classify each practice as: 'critical', meaning it is an essential service that should be required at all cooling centers; 'recommended', meaning it is important or advisable but a center could perform cooling without the service; or 'optional', meaning the service may be desirable, but is not at all required for every cooling center. The majority of the analyses report the calculation of counts and proportions. To test for differences in opinions comparing regional/intermediate vs community nurseries, a multivariate analysis of variance was conducted. Survey data were analyzed with SPSS 23 (IBM SPSS, Armonk, NY, USA). This project was approved by the University of California, San Francisco and Stanford institutional review boards.

RESULTS

A total of 64 individual responses were received from 50 individual centers (47% response rate). Surveys were sent to 107 total centers that included 71 community, 22 regional and 13 intermediate NICUs. Response rates varied across the center types: 44% for community, 95% for regional and 15% for intermediate. Individual invitations to complete the survey were successfully sent to 220 neonatologists and neurologists, who were designated by their centers as being clinical leads or most knowledgeable about TH at their center. Table 1 characterizes the respondents who were primarily neonatologists. Of those responding, 66% reported that they currently offer TH. In reporting current practices related to HIE (regardless of whether the center currently offered TH), there was a wide range of estimated HIE cases annually, from 2 to 70, with a mean of 18 and a median of 12.

Respondents from centers offering TH (TH centers) were asked questions related to their current practices related to TH. Results are shown in Table 2. At these centers offering TH, there was a range of estimated TH cases annually, from 1 to 55, with a mean of 14 and a median of 11 (interquartile range (IQR) 4 to 24). All respondents reported use of a written TH protocol at their center. The majority of clinicians at centers providing TH indicated that

Table 1. Demographic characteristics of sample

Category	Characteristic	N	%
<i>All respondents (n = 64)</i>			
Practice role	Neonatologist	54	84.4
	Neurologist	10	15.6
Clinical practice setting	Academic affiliated with university ^a	12	18.8
	Academic in university-based hospital	11	17.2
	Community	27	42.2
	Kaiser Permanente or HMO	13	20.0
Size of primary nursery	Other	1	1.6
	< 11 Beds	3	4.7
	11–20 Beds	14	21.9
	21–35 Beds	20	31.3
	36–60 Beds	11	17.2
	61–80 Beds	4	6.3
Offer therapeutic hypothermia?	> 80 Beds	2	3.1
	No	22	34.4
Nursery certification ^b	Yes	42	65.6
	Community	31	48.4
	Intermediate	2	3.1
	Regional	21	32.8

Abbreviation: HMO, Health Maintenance Organization. ^aAcademic neonatologists whose main practice is at a hospital other than a university-based hospital, such as a community or private hospital. ^bResponses only from neonatologists, n = 54.

Table 2. Therapeutic hypothermia centers^a

Category	Characteristic	N	%
Type of TH	Selective head cooling	1	2.4
	Whole body cooling	37	88.1
	Both	4	9.5
TH protocol used	Yes	42	100.0
TH protocol based on one used in a randomized controlled trial	Yes	39	92.9
	No	1	2.4
	Don't know	2	4.8
Neurology consulted for neonates who receive TH ^b	Yes	39	92.9
	Depends	1	2.4
Brain monitoring used	No	0	0.0
	Yes	37	88.1
	No	5	11.9
Type of brain monitoring ^c	aEEG	13	31.0
	EEG	4	9.5
	Both aEEG and EEG	21	50.0
	Don't know	1	2.4
Percent of MRIs reviewed by pediatric neuroradiologist	None	7	16.7
	< 50%	5	11.9
	50–99%	4	9.5
	100%	26	61.9
Percent of neonates treated with TH referred for follow-up	< 50%	0	0.0
	50–99%	3	7.1
	100%	39	92.9

Abbreviations: aEEG, amplitude-integrated electroencephalography; EEG, electroencephalography; TH, therapeutic hypothermia. ^aTotal respondents from 50 centers include some centers with responses from both a neonatologist and a neurologist. ^bTwo respondents did not answer. ^cThree respondents did not answer.

Table 3. Opinions about providing therapeutic hypothermia

	Community/ intermediate centers ^a		Regional centers ^b		Total	
	N	%	N	%	N	%
<i>Pediatric neurologist available to consult</i>						
Critical	19	57.6	10	47.6	29	53.7
Recommended	10	30.3	10	47.6	20	37.0
Optional	3	9.1	0	0.0	3	5.6
<i>Nursing staff trained in TH</i>						
Critical	29	87.9	16	76.2	45	83.3
Recommended	3	9.1	5	23.8	8	14.8
<i>aEEG monitoring throughout TH</i>						
Critical	22	66.7	16	76.2	38	70.4
Recommended	5	15.2	4	19.0	9	16.7
Optional	5	14.2	0	0.0	5	9.3
No opinion	0	0.0	1	4.8	1	1.9
<i>Continuous video EEG monitoring</i>						
Critical	7	21.2	5	23.8	12	22.2
Recommended	12	36.4	10	47.6	22	40.7
Optional	13	39.4	5	23.8	18	33.3
No opinion	0	0.0	1	4.8	1	1.9
<i>Continuous video EEG monitoring available 24/7</i>						
Critical	7	21.2	3	14.3	10	18.5
Recommended	8	24.2	10	47.6	18	33.3
Optional	15	45.5	7	33.3	22	40.7
No opinion	1	3.0	1	4.8	2	3.7
<i>Pediatric neuroradiologist review MRI</i>						
Critical	13	39.4	6	28.6	19	35.2
Recommended	15	45.5	10	47.6	25	46.3
Optional	3	9.1	5	23.8	8	14.8
No opinion	1	3.0	0	0.0	1	1.9
<i>Access to developmental follow-up</i>						
Critical	32	97.0	21	100.0	53	98.1
Recommended	0	0.0	0	0.0	0	0.0
Optional	0	0.0	0	0.0	0	0.0
<i>Palliative care team</i>						
Critical	11	33.3	3	14.3	14	25.9
Recommended	13	39.4	14	66.7	27	50.0
Optional	7	21.2	3	14.3	10	18.5
No opinion	1	3.0	1	4.8	2	3.7
<i>Occupational/Physical Therapy available to consult</i>						
Critical	24	72.7	15	71.4	39	72.2
Recommended	6	18.2	6	28.6	12	22.2
Optional	2	6.1	0	0.0	2	3.7
<i>From a safety perspective, is there a minimum number of neonates to be treated</i>						
No	13	39.4	4	19.0	17	31.5
Yes	19	57.6	17	81.0	36	66.7
<i>From quality perspective, is there a minimum number of neonates to be treated</i>						
No	10	30.3	5	23.8	15	27.8
Yes	22	66.7	16	76.2	38	70.4

Abbreviations: aEEG, amplitude-integrated electroencephalography; EEG, electroencephalography; MRI, magnetic resonance imaging; TH, therapeutic hypothermia. Some totals differ because of missing data. ^aTotal number of respondents from community/intermediate centers = 32. ^bTotal number of respondents from regional centers = 21.

they adhere to a set protocol based on published evidence for TH, consult a neurologist for the majority of neonates receiving TH, use either aEEG or EEG brain monitoring, have the majority of MRIs interpreted by pediatric neuroradiologists and refer all neonates receiving TH for developmental follow-up after hospital discharge.

Next, survey respondents were asked to provide their opinions regarding services that should be available at centers providing TH. Table 3 summarizes responses. In terms of opinions about the services that should be required of TH centers, there was no significant difference among clinicians from community-, intermediate- and regional-approved NICUs, suggesting that there is some consistency in opinions about minimum standards for TH centers across practice settings. There were also no significant differences between responses from centers that currently provide hypothermia and those that do not (multivariate analysis of variance $F(11, 48) = 1.15$). Overall, the majority of respondents considered it critical that TH centers: have pediatric neurologists available to consult, train nursing staff in TH, conduct at least aEEG monitoring throughout TH, have access to inpatient MRI, have access to developmental follow-up and have occupational and physical therapy consultation available. Additional services and resources, including continuous video EEG monitoring, pediatric neuroradiologist review of MRIs and a palliative care team were considered at least recommended by a majority of respondents.

Over 70% overall thought that, to ensure quality of care, a cooling center should treat a minimum number of patients with TH annually. For those who thought a minimum number of patients should be treated to ensure quality of care, when asked opinions regarding what minimum number of neonates should receive TH at a site annually to ensure quality care, respondents suggested a wide range from 1 to 60, with a median suggested number of 10 and mean of 10.4 (IQR 5.0 to 12.0). Current TH centers suggested a median of 10, and mean of 9.5 (IQR 5.0 to 12.0) and non-TH centers suggested a median of 9 and mean of 11.9 (IQR 5.3 to 11.5). There was no significant difference between current TH centers and non-TH centers in their response to this question ($t(42) = 0.8$, not significant).

DISCUSSION

TH is currently standard of care for neonatal HIE, but care practices surrounding the provision of TH for HIE are still evolving. Variation has existed over which practices and resources are considered essential of a TH center, despite guidelines offering some specific recommendations regarding care surrounding TH.¹⁻³ We found that the majority, but not all, of surveyed TH centers provide services in accordance with these guidelines. Over 90% offer neurodevelopmental follow-up to all neonates receiving TH, in line with the guidelines offered by ILCOR (International Liaison Committee on Resuscitation), the AHA (American Heart Association) and AAP Committee on Fetus and Newborn. Similarly, over 90% adhere to a protocol for providing TH that is based on a published clinical trial, and have pediatric neurology consultation available for all neonates receiving TH. Of note, just over half of centers use EEG monitoring (either alone or in conjunction with aEEG) as advised by ILCOR, though 88% report using some form of brain monitoring (either EEG or aEEG monitoring), as advised by the AAP Committee. These findings suggest that the vast majority of centers in California currently offering TH do so in accordance with published recommendations for comprehensive care of these neonates.

We also queried respondents regarding their opinions regarding minimum standards of cooling centers. Again, the services and resources identified by most respondents as 'critical' were consistent with those delineated in the AAP Committee guidance.

We found that opinions regarding what should be offered at a TH center did not differ between respondents at different practice settings. This suggests that there exists a minimum set of standards that might be acceptable statewide that does not vary by level of care. Specific training in TH of nursing staff was endorsed as critically important across levels of care, highlighting the critical role of the bedside nurse in providing safe and quality care.

There was a wide range of responses regarding a minimum number of cases annually that should be required of a TH center. The majority of respondents agreed a minimum should be required, with a median of 10 cases annually and the IQR of 5 to 12. Although the range overall was wide, the IQR of minimum cases was relatively narrow, with a difference of only 7 patients. Of note, these numbers aligned closely to what was reported as annual volumes by current TH centers, who reported treating a median of 14 cases each year (IQR 4 to 24). Again, this suggests that there exists a minimum case volume that might be expected to maintain competence at TH centers. In California, over a recent 3-year period, 10 'low-volume' centers began providing TH treating between 1 and 9 patients over a 1- to 2-year period.⁵ Although simple in concept, TH requires accurate and consistent implementation practices, such as frequent monitoring of core temperature and evaluation for hemodynamic complications. Neonates who require TH can be critically ill and complications such as clinically significant bradycardia due to excessive hypothermia may occur and may complicate hemodynamics. Treatment of a low number of patients may not be sufficient to assure and maintain competence. Assurance of competence in implementing TH is needed as more low-volume centers begin to provide this therapy.

Our findings are in agreement with a previous survey of NICUs across the entire United States. Although that study similarly must be interpreted in the context of a survey with a 42% response rate, the overall responses were congruent. In the Harris survey, over 80% reported 'always' performing brain imaging after TH, with over 90% stating the preferred method of imaging was MRI. Regarding brain monitoring, 41% reported use of continuous EEG monitoring. Respondents were split regarding preferred method of brain monitoring, with about half preferring aEEG and half preferring EEG.⁴ Our findings also build upon previous reports of actual practices through multicenter TH registries. The Vermont Oxford Network published registry data from 2006 to 2010 describing their practices associated with encephalopathy in both cooled and non-cooled neonates.⁷ They reported only 38% received TH. Overall, 65% were imaged with MRI. Two-thirds received any EEG and 33% had aEEG. Differences in our findings from these results may reflect changes in practice over the past several years since that study, and that our survey asked just about practices related to TH, whereas that data included both cooled and non-cooled neonates. Finally, the Children's Hospitals Neonatal Consortium HIE Focus Group reported data on actual practices from 2010 to 2013 among all severities of HIE in both cooled and non-cooled neonates.⁸ They reported MRI was performed in 80% of patients overall. EEG or aEEG was performed in the first 24 h of admission for 61% and 31% of patients, respectively. These data assessing actual practice are in accordance with the reported practices from our survey respondents in this study. We found a higher reported rate of referral to follow-up after discharge, with 93% stating all neonates were referred for follow-up, but the CHN consortium reporting only 62% overall follow-up. This difference may reflect referral practices specific to California in our survey population.

A strength of this study was the inclusion of responses from a variety of practice settings across California, including both community and regional NICUs. We sought to include input from diverse settings, and thus extended the invitation to participate to all NICUs certified by CSS, the main credentialing body of the

California Department of Health Care Services for NICUs in the state. Furthermore, responses were anonymous in an effort to ensure honest opinions, particularly where opinions regarding what services should be offered might differ from those currently offered at a center. At the same time, this voluntary survey is subject to limitations. All responses regarding current practices were by self-report, without other confirmation. Despite being anonymous, responses may have been biased, with the possibility of overreporting a volume of treated patients to meet a perceived minimum standard. To achieve the most accurate self-reports possible, respondents were those designated by their NICU as clinical leads or most knowledgeable about TH at their center. Similarly, because this was a voluntary survey, it cannot comprehensively account for all viewpoints that would be important in establishing minimum standards for TH centers. Further work would be needed to evaluate the impact of any proposed minimum standards on access to TH, including economically and upon availability and quality of care.

This study did not address the issue of increasing training and outreach to ensure as many eligible patients as possible are referred for TH. It has previously been described that there remain neonates with HIE who are not identified or referred in time for TH, creating a missed opportunity for care.^{5,9} These issues are clearly important and warrant further attention, particularly to ensure that TH is available to as many neonates as possible, even if minimum standards are required of TH centers. In California, the CPQCC (California Perinatal Quality Care Collaborative) has developed and published a toolkit to facilitate identification and treatment of neonates who may meet criteria for TH and expanded its data collection to capture all neonates treated with TH. This toolkit is freely available to all hospitals and aims to address the important issue of ensuring that all eligible patients are identified and provided treatment in a timely manner.¹⁰

In sum, survey respondents across practice settings in California described a core set of practices currently offered at TH centers, and endorsed a set of minimum requirements of cooling centers to ensure quality of care. These data informed the recently enacted CCS Program Requirements for Providing Neonatal Therapeutic Hypothermia.⁶ Further work is required to evaluate the impact of implementing these standards.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- 1 Perlman JM, Davis P, Wyllie J, Kattwinkel J. Therapeutic hypothermia following intrapartum hypoxia-ischemia. An advisory statement from the Neonatal Task Force of the International Liaison Committee on Resuscitation. *Resuscitation* 2010; **81**: 1459–1461.
- 2 Wyckoff MH, Aziz K, Escobedo MB, Kapadia VS, Kattwinkel J, Perlman JM *et al*. Part 13: neonatal resuscitation: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2015; **132**(Suppl 2): S543–S560.
- 3 Committee on Fetus and Newborn, Papile LA, Baley JE, Benitz W, Cummings J, Carlo WA *et al*. Hypothermia and neonatal encephalopathy. *Pediatrics* 2014; **133**: 1146–1150.
- 4 Harris MN, Carey WA, Ellsworth MA, Haas LR, Hartman TK, Lang TR *et al*. Perceptions and practices of therapeutic hypothermia in American neonatal intensive care units. *Am J Perinatol* 2014; **31**: 15–20.
- 5 Kracer B, Hintz SR, Van Meurs KP, Lee HC. Hypothermia therapy for neonatal hypoxic ischemic encephalopathy in the state of California. *J Pediatr* 2014; **165**: 267–273.
- 6 Dimand R. Program requirements for providing therapeutic hypothermia. Available at: <http://www.dhcs.ca.gov/services/ccs/Documents/ccsn061116.pdf> (Accessed 2017).
- 7 Pfister RH, Bingham P, Edwards EM, Horbar JD, Kenny MJ, Inder T *et al*. The Vermont Oxford Neonatal Encephalopathy Registry: rationale, methods, and initial results. *BMC Pediatrics* 2012; **12**: 84.

- 8 Massaro AN, Murthy K, Zaniletti I, Cook N, DiGeronimo R, Dizon M *et al*. Short-term outcomes after perinatal hypoxic ischemic encephalopathy: a report from the Children's Hospitals Neonatal Consortium HIE focus group. *J Perinatol* 2015; **35**: 290–296.
- 9 Khurshid F, Lee KS, McNamara PJ, Whyte H, Mak W. Lessons learned during implementation of therapeutic hypothermia for neonatal hypoxic ischemic encephalopathy in a regional transport program in Ontario. *Paediatr Child Health* 2011; **16**: 153–156.
- 10 California Perinatal Quality Care Collaborative (CPQCC). Early Screening and Identification of Candidates for Neonatal Therapeutic Hypothermia Toolkit. Available at: <https://www.cpqcc.org/qi-tool-kits/early-screening-and-identification-candidates-neonatal-therapeutic-hypothermia-toolkit> (Accessed 2016).