Published in final edited form as:

Arch Dis Child Fetal Neonatal Ed. 2018 July ; 103(4): F377–F382. doi:10.1136/archdischild-2017-313078.

Re-examining the Arterial Cord Blood Gas pH Screening Criteria in Neonatal Encephalopathy

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Abstract

Objective: Screening criteria for neonatal encephalopathy remain a complex combination of subjective and objective criteria. We examine the utility of universal cord blood gas testing and mandatory encephalopathy evaluation for infants with pH ≤ 7.10 on umbilical cord arterial blood gas (cABG) as a single screening measure for timely identification of moderate/severe encephalopathy.

Design, setting, patients: Infants born at a single center between 2008 and 2015, who were ≥ 36 weeks, had no congenital anomalies, and had a cABG pH ≤ 7.10 , were identified for a retrospective cohort study. Maternal/perinatal, and patient factors were collected.

Results: 27,028 infants were born during the study period, 412 met all inclusion criteria. Of those, 35/85 infants with pH < 7.00 and 34/327 infants with pH between 7.00 and 7.10 had moderate/severe encephalopathy. Encephalopathy was identified on the basis of pH and exam alone (no other perinatal criteria present) in 5/35 and 13/34 infants in the two pH groups, respectively.

A cABG pH threshold of ≤ 7.10 was associated with a sensitivity of 74.2% and a specificity of 98.7% for detection of moderate/severe encephalopathy. Based on these data, 25 infants with cABG pH between 7.00 and 7.10 will need to be screened to identify one neonate with moderate/severe encephalopathy, who might have otherwise been missed using conventional screening, a 15% increase in appropriate selection and treatment over current methods.

Conclusion: Universal cord blood gas screening with a pH threshold ≤ 7.10 and mandatory encephalopathy exam results in greater detection of infants with moderate/severe encephalopathy and timely initiation of TH.

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Conflict of interest and financial disclosure statement:

Conflicts of Interest: The authors have no conflicts of interest relevant to this article to disclose.

Presentation note: Poster presented at the Pediatric Academic Societies Annual Meeting; 8 May 2017; San Francisco, CA

INTRODUCTION

The effectiveness of therapeutic hypothermia (TH) to reduce secondary brain injury in the setting of hypoxic-ischemia has been demonstrated in both animal models [1–3] and randomized trials in humans [4–8], with subsequent meta-analysis showing a reduction in the composite outcome of mortality or major neurodevelopmental disability at 18 months [9]. Criteria for enrollment were generally consistent across these studies: birth at or beyond 36 weeks of gestation, evidence of perinatal acidosis (arterial cord blood pH < 7.00), low Apgar scores (< 5 at 10 minutes of life), and moderate/severe encephalopathy.

A significant challenge in timely initiation of TH is the need for rapid evaluation of the at-risk population. The ideal system would utilize an objective, universal screening test with high sensitivity, bringing high-risk infants to the attention of trained caregivers. The umbilical cord blood pH, a test which is easy to obtain, inexpensive, and completely objective is an excellent candidate. However, despite evidence that universal cord gas screening is cost-effective and may result in an improvement in perinatal outcomes [10,11], many obstetrical units do not routinely perform cord blood analysis or do so only in the case in the setting of “high-risk” deliveries, a practice in line with current ACOG recommendations [12]. Further complicating matters is the lack of a well-defined cord blood pH threshold that should trigger further evaluation.

While epidemiologic data suggest a mean±SD arterial cord blood pH of 7.25±0.07 [13–16] in healthy term infants, and an increase in the risk of morbidity or mortality in infants with a cord pH less than 7.00 [17–20], it is possible that a pH threshold of 7.00, while perhaps more specific for injury risk, may lack the sensitivity to be used as single screening criteria and may miss some infants with a higher pH. Indeed, there is likely a varying degree of resistance to hypoxia which has confounded the link between cord pH and outcome [21]. A threshold of < 7.10 (two standard deviations below the population mean) may represent an alternative level for screening which captures a greater proportion of the at-risk population; a notion supported in a recent paper by Yeh et al. [22].

In this study, we have leveraged our institution’s standard practice of universal cord blood gas testing for all live births and mandatory encephalopathy screening for all infants with an arterial pH < 7.10 in order to investigate the utility of this practice for the timely identification of candidates for TH. Specifically, we compared perinatal, patient, and outcome factors, between a group of infants with an arterial cord pH < 7.00 and a second group with a cord pH between 7.00 and 7.10. We also evaluated the performance of the arterial cord blood base deficit (using thresholds suggested by two major whole-body cooling trials: 12 mEq/L and 16 mEq/L [5,8]) as an alternative objective screening metric. We hypothesize that infants with cord pH values up to 7.10 are at risk for neonatal encephalopathy and an objective, expanded screening program using solely the arterial cord blood pH will enable superior identification of encephalopathic infants who may not have otherwise come to medical attention within the first six hours of life.

METHODS

Patient selection

Cases were selected using a searchable electronic medical record database (Clinical Investigation Data Exploration Repository, CIDER) maintained by Washington University's Center for Biomedical Informatics. Primary selection criteria were arterial cord blood pH 7.10 and delivery at Barnes-Jewish Hospital between 1 January 2008 and 31 December 2015. Screened infants underwent secondary selection to identify only those infants of term gestation (≥ 36 weeks EGA), lack of other known congenital anomalies, and to verify that selected infants had a complete clinical record.

Data collection

A comprehensive set of characteristics were collected for all infants identified. Perinatal factors included maternal age, sentinel event (if known), non-reassuring fetal heart tracing (i.e. category III tracing [23]), and need for operative delivery. Patient characteristics included gestational age, arterial cord blood base deficit (BD), sex, race, Apgar score (at one, five, and ten minutes), positive pressure ventilation at birth, and CPR at birth. Outcome factors included TH treatment, worst stage of encephalopathy [24], electrographic seizures, brain injury consistent with hypoxic-ischemia on MRI (defined as injury to the deep nuclear gray matter structures and/or watershed areas on diffusion, T1 and/or T2-weighted sequences) and death. Although initial case selection was automated, manual review of all selected charts was performed by one author (ZAV) to ensure accuracy and completeness of abstracted data.

Clinical practice

At our institution, universal paired umbilical cord gas sampling is performed at all deliveries. After delivery, a segment of the umbilical cord is doubly clamped, blood samples are drawn from the umbilical vein and one of the umbilical arteries, and then it is immediately brought to the clinical laboratory for blood gas analysis. If the arterial sample has a pH ≤ 7.10 , the on-call neonatologist is notified of the critical result, triggering standardized encephalopathy screening, performed hourly for the first six hours of life, by a single attending/fellow neonatologist team experienced in the performance of the standardized encephalopathy exam. All infants ≥ 36 weeks, with cord arterial cord blood pH ≤ 7.10 , who were found to be moderate or severely encephalopathic in the first 6 hours of life were transferred to the NICU at St. Louis Children's Hospital for presumptive treatment of hypoxic-ischemic encephalopathy with therapeutic hypothermia (TH).

All eligible infants underwent a standard whole-body TH protocol which included 72 hours of servo-controlled hypothermia at 33.5°C (followed by rewarming to 36.5°C, over 24 hours), conventional EEG monitoring for a minimum of 24 hours, and at least one non-sedated, non-contrast brain MRI in the first 14 days of life. Infants who did not undergo TH treatment underwent MRI examination at the discretion of the attending neonatologist.

Statistical approach

Perinatal, patient, and outcome factors were compared between infants with an arterial cord pH < 7.00 and those with a cord pH between 7.00 and 7.10 using the Mann-Whitney U-test for continuous variables or Fisher's Exact Test (two-sided) for categorical variables. The sensitivity and specificity of each candidate criteria (pH < 7.0, pH 7.10, BD > 12, BD > 16) for the diagnosis of moderate/severe encephalopathy was calculated. The C statistic was calculated for each candidate measure (pH and BD) to assess the degree of discrimination. Results were considered significant where $p < 0.05$. Statistical analysis was conducted using R version 3.2.4 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

Between 1 January 2008 and 31 December 2015, 27,028 infants were born at Barnes-Jewish Hospital. Of those, 560 (2%) met the primary selection criteria of an arterial cord pH 7.10. Upon secondary selection, 148 infants were excluded (EGA < 36 weeks and 0 days $n=127$; congenital anomalies $n=18$; incomplete record $n=3$) leaving 412 eligible infants who met all study criteria. Of those infants, 85/412 (20%) had an arterial cord pH < 7.00, 35/85 (41%) had moderate/severe encephalopathy, and 34/35 (97%) underwent TH treatment (one died prior to TH initiation). For the 327/412 (80%) infants who had an arterial cord pH between 7.00 and 7.10, 34/327 (10%) had moderate/severe encephalopathy, and 34/34 underwent TH treatment. An additional 33 term infants in the primary exclusion group were diagnosed with moderate/severe encephalopathy (pH > 7.1 $n=24$, missing pH data $n=9$). The clinical presentation of these infants was not subtle, with sentinel events identified in 33/33 infants, intubation in 21/33 (64%) infants, and CPR in 10/33 (30%) infants. A diagrammatic representation of patient selection is shown in Figure 1.

When comparing those infants with an arterial cord pH < 7.00 and those with a pH between 7.00 and 7.10, there were no differences in maternal age, base deficit, gestational age, need for assisted delivery, sex, or race. Infants with a cord pH < 7.00 were more likely to have a known sentinel event ($p<0.01$), non-reassuring fetal heart tracing prior to delivery ($p=0.02$), lower Apgar scores (at one, five, and ten minutes, $p<0.01$), receive positive pressure ventilation longer than five minutes ($p<0.01$), have moderate/severe encephalopathy ($p<0.01$), have electrographic seizures ($p<0.01$), and had a higher mortality rate ($p<0.01$). A complete overview of between group differences is shown in Table 1.

Evaluating the cohort as a whole, there was a significant difference between the pH groups in terms of the MRI outcome, although this was driven predominately by the greater proportion of infants with an arterial cord pH between 7.00 and 7.10 without MRI scans performed (49 vs. 76%). However, when considering only those infants who were moderately/severely encephalopathic (and thus receiving TH treatment), there was no statistical difference in rates of hypoxic-ischemic injury patterns between the two pH groups (Table 2).

5/85 (6%) of infants with an arterial cord pH < 7.00 were noted to have clinical encephalopathy in the first six hours of life without any identifiable clinical risk factors (sentinel event, Apgar score < 5 at ten minutes of life, need for chest compressions, or

positive pressure ventilation beyond 10 minutes of life) which would have otherwise prompted evaluation. All of these infants had moderate encephalopathy, all underwent therapeutic hypothermia treatment, 3/5 (60%) had electrographic seizures, and 2/5 (40%) had MRI evidence of hypoxic-ischemic brain injury.

While a smaller proportion of infants with an arterial cord pH between 7.00 and 7.10 were found to have moderate/severe encephalopathy as compared to those with an arterial cord pH < 7.0 (42% vs. 10%), more than one third (13/34) had no other identifiable clinical factors which would have otherwise prompted evaluation (sentinel event, Apgar score < 5 at ten minutes of life, need for chest compressions, or positive pressure ventilation beyond 10 minutes of life). All thirteen of these infants had moderate encephalopathy, all underwent therapeutic hypothermia, 2/13 (15%) had electrographic seizures, and 8/13 (62%) had MRI evidence of hypoxic-ischemic brain injury.

Sensitivity and Specificity Analysis

A pH threshold of ≥ 7.10 yields a sensitivity of 74.2% and specificity of 98.7% for detection of moderate/severe encephalopathy, while a threshold of < 7.00 yields a sensitivity of 37.6% and a specificity of 99.8%. In contrast, a base deficit threshold of 12 mEq/L yields a sensitivity of 30.1% and a specificity of 99.3%, while a threshold of 16 mEq/L yields a sensitivity of 10.8% and specificity of 98.9% for the detection of moderate/severe encephalopathy (Supplementary Table 1). The C statistics for pH and BD were 0.72 and 0.53, respectively (Figure 2).

DISCUSSION

These data shed light onto the most appropriate objective measure and threshold to *trigger an encephalopathy examination* by a qualified examiner. The arterial cord blood pH, with a threshold of ≥ 7.10 , is 74.2% sensitive and 98.7% specific for the diagnosis of moderate/severe encephalopathy. In contrast, the arterial cord blood base deficit misses the majority of qualifying infants, with a sensitivity between 11 and 30% (depending on which threshold is chosen). The value of the arterial cord pH as a single objective screening tool to identify at-risk infants was clearly demonstrated in this analysis, as 18/412 (4%) infants in this cohort went on to have moderate/severe encephalopathy with only the abnormal cord pH (≥ 7.10) as an indicator of risk.

Expanding the screening criteria to a threshold of ± 7.10 in this high-volume delivery center introduced the need for an additional 327 examinations over a seven-year period, equating to three additional patients examined every month. Furthermore, for every 25 patients with a cord pH between 7.00 and 7.10 who undergo encephalopathy examination, one patient is identified with clinical encephalopathy, who may otherwise have gone unnoticed. Given that all of the infants meeting these criteria had moderate encephalopathy and the majority (60%) had evidence of brain injury on subsequent imaging, this group represents one with significant potential for benefit from TH treatment. However, it is important to distinguish between mild acidosis from an acute perinatal event (thus one which might benefit from TH) and resolving severe acidosis from a more remote event (and unlikely to benefit from TH). A subgroup analysis, shown in Supplementary Table 2, suggests that encephalopathic infants

with a cord pH between 7.00 and 7.10 had identifiable sentinel events more frequently than the population of infants with a cord pH < 7.00 (47 vs. 35% of cases) and required positive-pressure ventilation and/or CPR in more than 50% of cases, support the supposition that the acidosis reflects recent compromise and that the infant might benefit from timely initiation of TH.

These data support two main conclusions. First, universal cord blood gas testing, in itself, is able to detect a greater number of infants at risk for moderate/severe encephalopathy. Second, using an arterial cord pH threshold of 7.10, as opposed to < 7.00, as the sole screening criteria, allows the pool of screened infants to be expanded, with greatly improved sensitivity and a relatively limited increase in workload. As the results of this study suggest, encephalopathic infants with a pH less than 7.00 or greater than 7.10, generally have clear presentations with identifiable perinatal risk factors and overt need for resuscitation, readily alerting providers to the possibility of encephalopathy. In contrast, those infants with a borderline pH (between 7.00 and 7.10) may be “silent” from the standpoint of traditional screening metrics, yet are at increased risk of encephalopathy, seizures, and brain injury. The screening approach outlined in this manuscript is well suited to identify these cases. The lack of difference in rates of hypoxic brain injury on MRI between the two pH groups further supports the use of a broad range for screening in order to increase detection.

Although setting the threshold in favor of high sensitivity is ideal for a screening tool, the cost, both financial and labor, should be considered. In the case of universal cord blood gas testing and mandatory encephalopathy examination of eligible babies, the cost is relatively minimal. Although cost of cord blood gas testing varies by region, several reports suggest that the expected cost per patient is on the order of US\$10–30 [25,26], quite small in comparison to the cost of providing most medical care. The additional cost of labor, namely the hourly encephalopathy examination by a neonatologist in eligible babies should also be considered, as these examinations may distract from other patient care responsibilities.

There are several caveats to this study. First, given the retrospective nature of the clinical data, it is possible that not all of the perinatal factors were recorded, potentially underestimating the incidence of sentinel events or other clinical data. Second, the retrospective nature of the study also limited the amount of information about those infants with a pH > 7.10. However, as all infants in the well-baby nursery undergo daily complete physical examination by both a resident and attending physician, it is reasonable to assume that all of those infants had essentially normal neurologic exams during their hospital stay. This assumption is subject to ascertainment bias however; these infants undergo a far less rigorous exam than those with arterial cord blood pH 7.10, potentially missing an unknown number of infants. This observation is of particular relevance given the recent increase in focus on adverse outcomes associated with mild encephalopathy [27,28]. Third, given that all infants meeting pH criteria underwent mandatory encephalopathy examination it is not possible to definitively state that the seventeen infants with an arterial cord pH between 7.00 and 7.10 would have gone unnoticed. Nevertheless, it is reasonable to state that the mandatory screening lead to timely identification and treatment initiation, an outcome which would not have been as certain under more stringent criteria.

We conclude that universal cord gas screening in conjunction with focused encephalopathy examinations on infants at or beyond 36 weeks with an arterial cord pH ≥ 7.10 may identify patients who can benefit from TH that would have otherwise gone untreated with the commonly used criteria of pH < 7.00 , a possibility that should be explored in a controlled clinical trial. Investigation should continue into the optimal method for screening infants to provide the best infant neurologic outcomes and the most cost-effective approach. Other cord blood biomarkers, such as lactate, should be explored as alternative or complementary quantitative markers of risk and may be more closely associated with outcome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding sources:

1. Washington University Institute of Clinical and Translational Sciences KL2 Training Program (NIH/NCATS KL2 TR000450)
2. Washington University in St. Louis Center for Biomedical Informatics, Clinical Investigation Data Exploration Repository (NIH/NCATS UL1 TR000448)

Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.

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What's known on this subject:

Universal cord blood gas screening with an expanded pH threshold of 7.10 may identify candidates for therapeutic hypothermia who might have otherwise gone unnoticed.

What this study adds:

In this retrospective cohort study, we examine the impact of universal cord blood gas screening with a pH threshold of 7.10 for the improved detection of moderate/severe encephalopathy and timely identification of infants who might benefit from therapeutic hypothermia.

Figure 1 –.
Case selection flowchart.

Figure 2 –.
ROC curves shown for the two pH thresholds (< 7.00 dashed line, ≤ 7.10 solid line)

Table 1.

Univariate comparison between pH groups

	Cord pH < 7.00 n=85	Cord pH 7.00–7.10 n=327	P value
Perinatal factors			
Maternal age, mean (SD), years	28.5 (6.2)	27.8 (6.4)	0.37
Sentinel Event			
Abruptio placentae, n (%)	14 (16)	16 (5)	<0.01 *
Eclampsia, n (%)	1 (1)	0 (0)	
Nuchal cord, n (%)	7 (8)	51 (16)	
Umbilical cord prolapse, n (%)	4 (5)	6 (2)	
Uterine rupture, n (%)	4 (5)	4 (1)	
Shoulder dystocia, n (%)	0 (0)	14 (4)	
Major trauma, n (%)	0 (0)	1 (0.3)	
None, n (%)	55 (65)	236 (72)	
Non-reassuring FHT, n (%)	55 (65)	165 (50)	0.02 *
Assisted delivery			
Vacuum device, n (%)	6 (7)	31 (9)	0.69
Forceps, n (%)	2 (2)	5 (2)	
None, n (%)	77 (91)	291 (89)	
Patient factors			
Gestational age, mean (SD), weeks	38.5 (1.3)	38.8 (1.4)	0.12
Base deficit, mean (SD), mEq/L	12.7 (4.1)	12.4 (4.5)	0.45
Male sex, n (%)	40 (47)	163 (49)	0.72
Race/Ethnicity			
Asian, n (%)	2 (2)	7 (2)	0.60
Black, n (%)	60 (71)	213 (65)	
Hispanic, n (%)	3 (4)	10 (3)	
Native American, n (%)	0 (0)	1 (0.3)	
Other	4 (5)	9 (3)	
White, n (%)	16 (19)	87 (27)	
Apgar score			
1-minute, median (range)	2 (0–8)	6 (0–9)	<0.01 *
5-minute, median (range)	6 (0–9)	8 (0–9)	<0.01 *
10-minute, median (range)	6 (0–9)	7 (0–9)	<0.01 *
Positive pressure ventilation			
<5 minutes, n (%)	23 (27)	59 (18)	<0.01 *
>5 minutes, n (%)	27 (32)	32 (10)	
None n (%)	35 (41)	236 (72)	

	Cord pH < 7.00 n=85	Cord pH 7.00–7.10 n=327	P value
CPR, n (%)	5 (6)	6 (2)	0.05
Outcome factors			
TH treatment, n (%) ^a	34 (40)	34 (10)	<0.01 *
Encephalopathy			
None, n (%)	45 (53)	274 (84)	<0.01 *
Mild, n (%)	5 (6)	20 (6)	
Moderate, n (%)	26 (31)	34 (10)	
Severe, n (%)	9 (11)	0 (0)	
Electrographic seizures, n (%)	11 (13)	9 (3)	<0.01 *
Died, n (%)	7 (8)	0 (0)	<0.01 *

Footnote:

* Denotes significance at $p < 0.05$. Comparisons were made using Mann–Whitney U-test for continuous variables or Fisher's Exact Test (two-sided) for categorical variables. Reported p values are unadjusted.

^a 1 infant in the pH <7.00 group died prior to initiation of TH.

Table 2.

MRI Injury, by groups

All infants (n=412)			
	Cord pH < 7.00 n=85	Cord pH 7.00–7.10 n=327	P value
Injury ^a	12 (14)	19 (6)	<0.01 [*]
No injury	31 (36)	62 (19)	
MRI not performed	42 (49)	246 (76)	
TH only (n=68)			
	Cord pH < 7.00 n=34	Cord pH 7.00–7.10 n=34	P value
Injury ^a	11 (32)	14 (41)	0.29
No injury	20 (59)	20 (59)	
MRI not performed	3 (9)	0 (0)	

Footnote:

* Denotes significance at $p < 0.05$.

^a Defined as injury to the deep nuclear gray matter structures or watershed areas noted on diffusion, T1 and/or T2 weighted MR imaging consistent with hypoxic-ischemic insult.