To Cool or Not to Cool?

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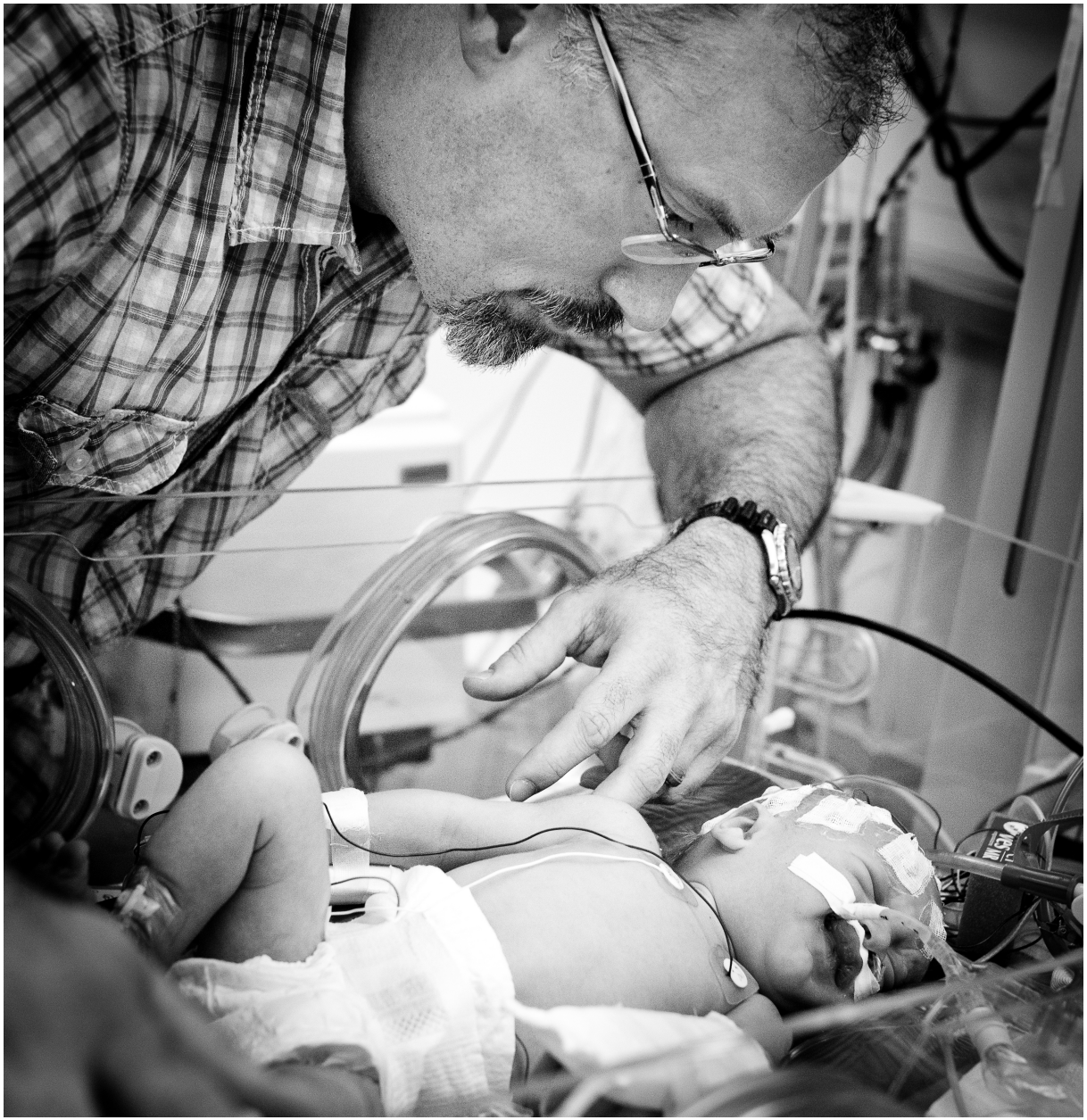


Neonatal Encephalopathy

- 2-6/1000 live term births
- 10-20% of infants die and 25% of survivors have significant disability
- Serial clinical examination necessary to identify and characterize evolution
- Hypoxic-ischemic injury accounts for 60-75% of etiologies

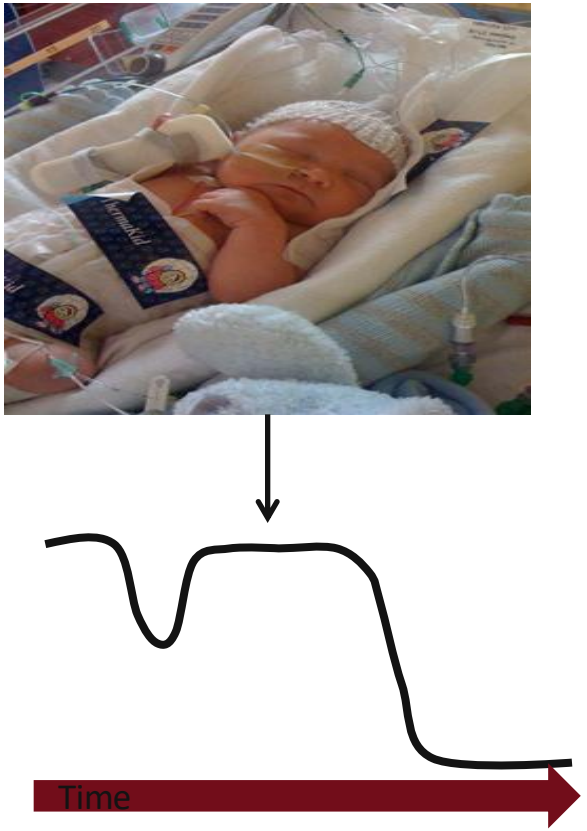
Hypoxic Ischemic Encephalopathy (HIE)

- Initial insult, and delayed energy failure

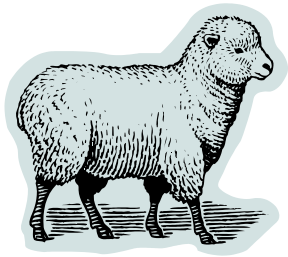
- Severity of insult clinically categorized by
  - Level of consciousness
  - Activity
  - Tone and posture
  - Autonomic function
  - Reflexes

- Defined as- Mild, Moderate, or Severe
  - *Note is a dynamic injury and exam*

- Therapeutic Hypothermia is only proven treatment



Neuroprotection – Hypothermia



Phases of Cerebral Injury

Cooling

Insult

Latent
- EEG low
- Oxidative metabolism OK
- Cytokines
- Intracytoplasmic Apoptosis

Secondary
- Cytotoxic edema
- Mitochondrial failure
- Seizures
- Excitotoxins

Cell Death
- Necrosis
- Apoptosis

Reperfusion

~30 min | 6-15 h | 3-7 days

Gunn J Perinat Med 2005

Inclusion Criteria for Hypothermia

AAP Committee Fetus and Newborn

- > 36 weeks Gestation

AND

- <u>One of the following</u>
  1. Sentinel event (e.g. Cord prolapse, fetal heart rate decelerations)
  2. Assisted ventilation required for 10 min after birth
  3. 10 min Apgar ≤ 5
  4. pH ≤7.0 (cord blood or 60 min infant)
  5. Base Deficit ≥16 mmol/L (cord blood or 60 min infant)

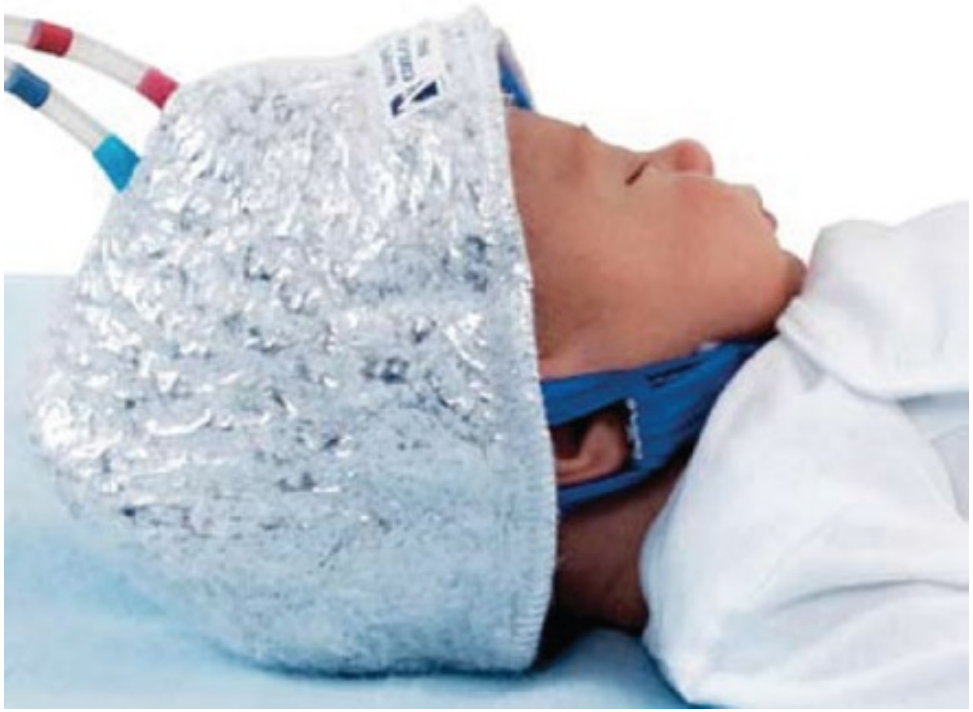
AND

- Moderate or Severe Neonatal Encephalopathy

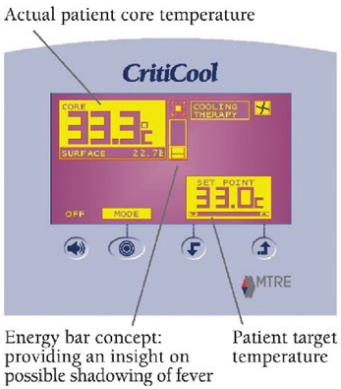
Degree of encephalopathy

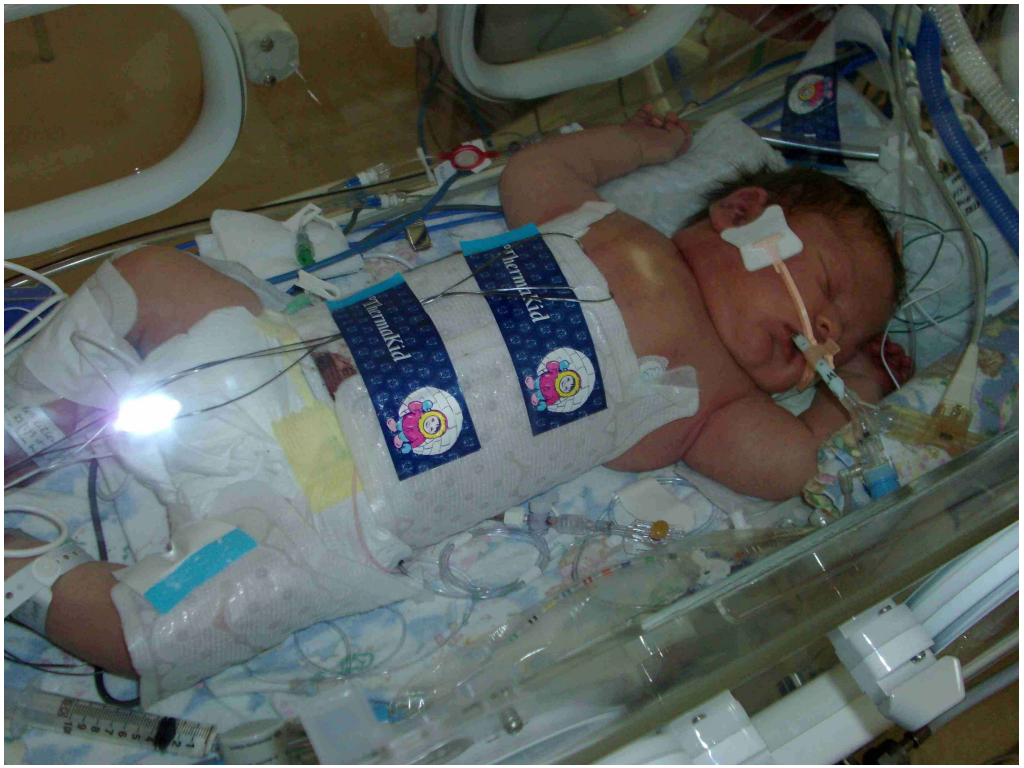
	Mild NE	Moderate NE	Severe NE
Level of Consciousness	Hyper-alert	Lethargic / obtunded	Stuporous
Spontaneous Activity	Normal	Decreased	Absent
Neuromuscular			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Decerebrate
Primitive Reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Autonomic Function			
Pupils	Mydriasis	Miosis	Variable; poor light reflex
Heart Rate	Tachycardia	Bradycardia	Variable
Respiration	Normal	Periodic Breathing	Apnea

How to cool? Cool Cap



Whole Body Cooling

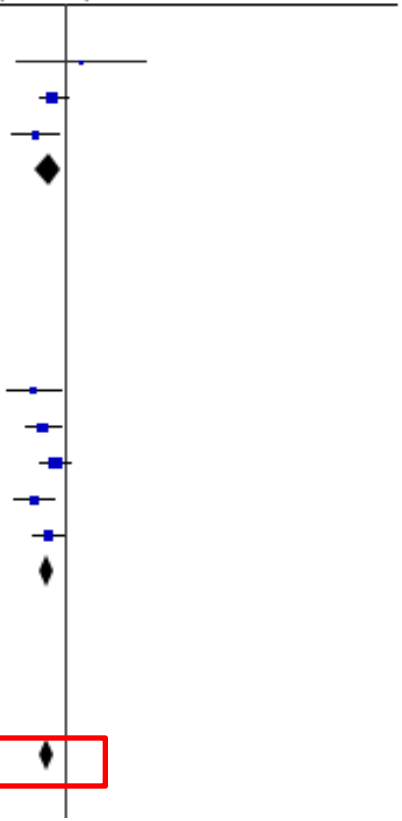




Hypothermia – Efficacy

- 13 randomized clinical trials

Study or Subgroup	Hypothermia Events	Hypothermia Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Selective head cooling with mild systemic hypothermia						
Gunn 1998	7	18	4	13	1.1%	1.26 [0.46, 3.44]
Cool Cap Study 2005	59	108	73	110	17.6%	0.82 [0.66, 1.02]
Zhou 2010	31	100	46	94	11.5%	0.63 [0.44, 0.91]
Subtotal (95% CI)		**226**		**217**	**30.3%**	**0.77 [0.64, 0.92]**
Total events	97		123			
Heterogeneity: Chi² = 2.46, df = 2 (P = 0.29); I² = 19%						
Test for overall effect: Z = 2.78 (P = 0.005)						
1.1.2 Whole body cooling						
Eicher 2005	14	27	21	25	5.3%	0.62 [0.41, 0.92]
NICHD Study 2005	45	102	64	103	15.5%	0.71 [0.54, 0.93]
TOBY Study 2009	74	163	86	162	21.0%	0.86 [0.68, 1.07]
neo.nEURO Study 2010	27	53	48	58	11.2%	0.62 [0.46, 0.82]
ICE Study 2011	55	107	67	101	16.8%	0.77 [0.62, 0.98]
Subtotal (95% CI)		**452**		**449**	**69.7%**	**0.75 [0.66, 0.84]**
Total events	215		286			
Heterogeneity: Chi² = 4.25, df = 4 (P = 0.37); I² = 6%						
Test for overall effect: Z = 4.80 (P < 0.00001)						
Total (95% CI)		**678**		**666**	**100.0%**	**0.75 [0.68, 0.83]**
Total events	312		409			



Hypothermia – Efficacy

Outcome	Number of studies/ number of participants	Relative risk
Mortality	12 / 1390	0.78 (0.65, 0.92)
ND disability in survivors	6 / 687	0.67 (0.54, 0.84)
Severe cerebral palsy	3 / 518	0.65 (0.48, 0.88)
MDI <70	4 / 522	0.70 (0.54, 0.90)
PDI <70	4 / 512	0.70 (0.54, 0.90)
Severe visual deficit	4 / 535	0.59 (0.35, 0.98)
Severe hearing deficit	4 / 510	0.75 (0.36, 1.55)
Epilepsy	5 / 413	0.80 (0.48, 1.31)
Life support withdrawn	6 / 746	0.93 (0.73, 1.18)

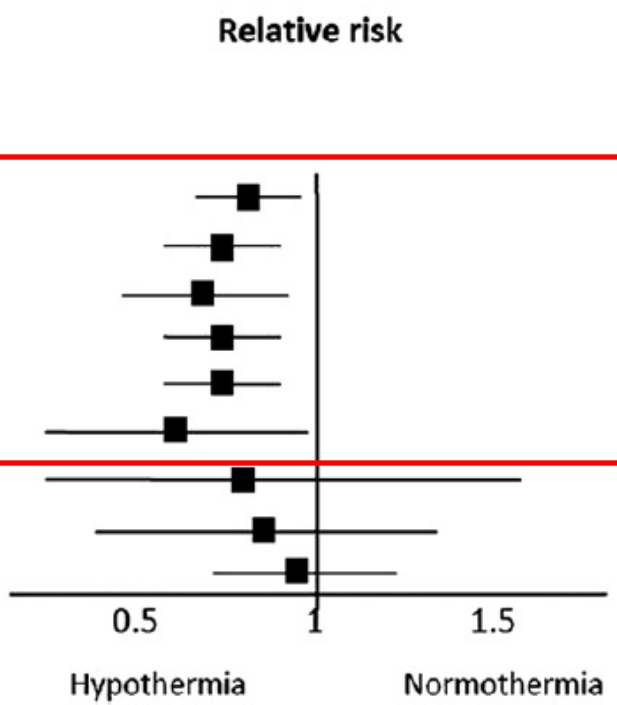


Fig. 3. Efficacy outcomes. ND, neurodevelopmental; MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index.

Benefits of Hypothermia in HIE

- International RCTs with entry at <6 hours in term infants with moderate-severe encephalopathy and acidemia/acute insult
- 25% reduction in death or disability (severe: MDI or PDI <70: cerebral palsy: sensorineural loss)
- NNT 5 to prevent one death or disabled child

Fetus and Newborn Committee Recommendations

1. Any center undertaking hypothermia should have access to all specialized neurological services including **EEG, MRI, neurological consultation and follow up.**
2. Eligibility – *term infant with moderate to severe encephalopathy and pH<7 BD>16; Apgar@10 <5; Resuscitation at 10 minutes of life and aEEG if head cooling.*
3. Protocols should be in place with **education** of in house and referring providers
4. Infants who do not reach these criteria should be treated with **informed parental consent and/or in a RCT**

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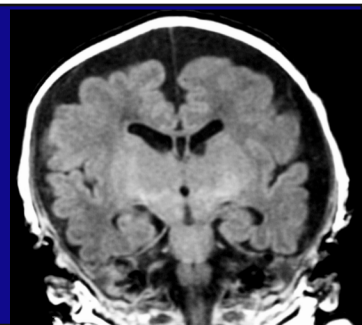
Do Infants with Mild NE benefit from Therapeutic Hypothermia



Outcome of Infants with Mild HIE

- Population of infants with mild HIE (n=34), followed to 9 years
  - Lower mean IQ in those with mild HIE v Controls; 98.6 v 109 (p=0.21)[1]
  - Increased thought problems with mild HIE v Controls (p=0.001)[2]
  - Worse motor assessment and manual dexterity (p=0.002)[3]

1. Van Handel M, et al. Dev Neuropsychol 2012
2. Van Handel M, et al. J Ped Psychology 2010
3. Van Kooij BJM, et al. Ped Research 2008

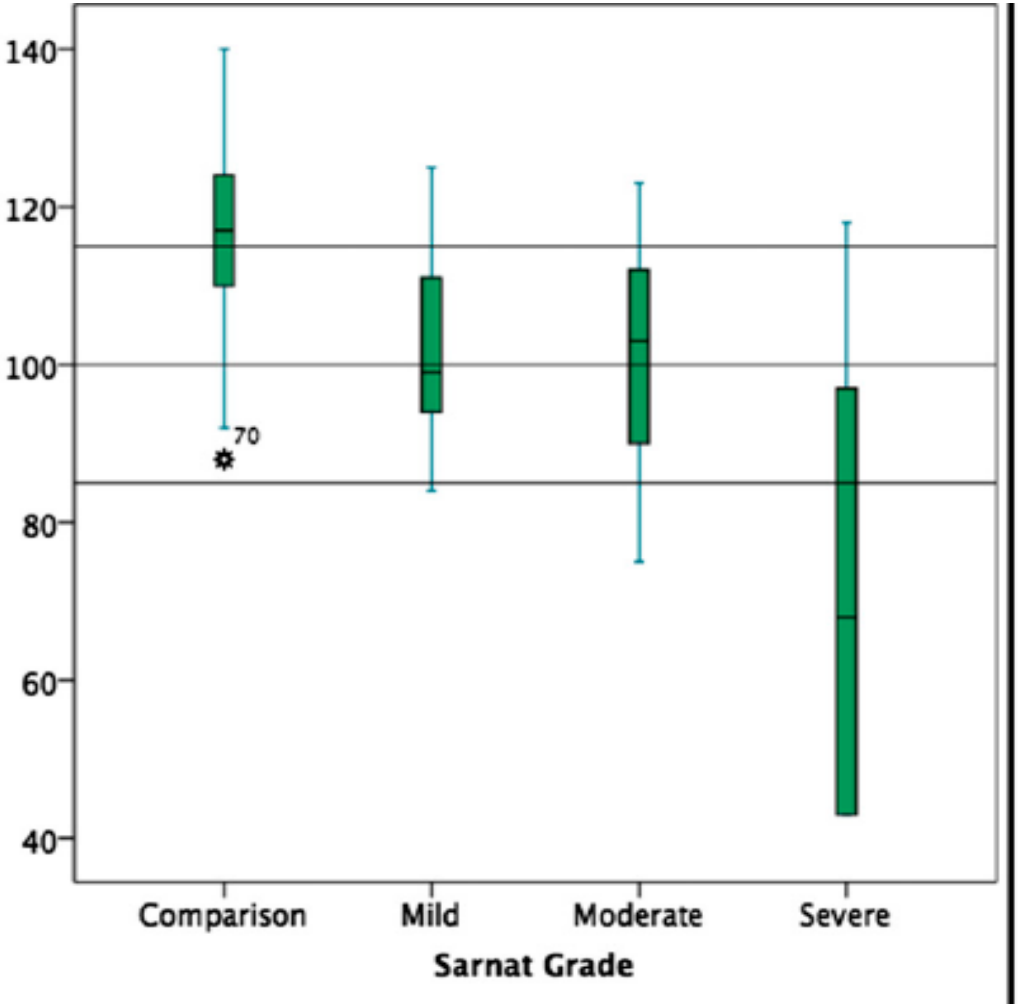
Early EEG Grade and Outcome at 5 Years After Mild Neonatal Hypoxic Ischemic Encephalopathy

Deirdre M. Murray, MD, PhD,[a,b] Catherine M. O'Connor, MSc, DPP(Clin),[a] C. Anthony Ryan, MB, MD, FRCPI,[a,b] Irina Korotchikova, MD, PhD,[a] Geraldine B. Boylan, PhD[a,b]

PEDIATRICS 2016 Volume 138, number 4,

Outcome was available in 53 infants with HIE and 30 controls at 5 years. Infants with mild HIE (n=22) had lower full scale IQ, FSIQ verbal IQ and performance IQ.

Infants with mild HIE did not differ from those with moderate HIE.



THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Short-Term Outcomes of Newborns with Perinatal Acidemia Who are Not Eligible for Systemic Hypothermia Therapy

Tara L. DuPont, MD[1], Lina F. Chalak, MD, MSCS[1], Michael C. Morriss, MD[2], P. Jeannette Burchfield, RN, BSN[1], Lucy Christie, RN[1], and Pablo J. Sánchez, MD[1]

- 89 did not meet HT criteria (per neuro exam)

	No Encephalopathy (n=29)	Mild encephalopathy (n=60)
Abnormal Discharge Exam	1	7
Seizures	0	5
Abnormal MRI	0	6
Death	0	1

- In this cohort 20% with mild HIE in first 6 hrs had abnormal short-term outcome

1. DuPont TL, et al. J Pediatr 2013

PRIME study

Any abnormality on examination = Mild Encephalopathy
>3 Abnormalities = Moderate-severe Encephalopathy

Category	Normal (0)	Mild(1)	Moderate (2)	Severe(3)
Level of consciousness	Alert(responsive to external stimuli)	Hyper-alert (responsive to minimal stimuli)	Lethargic	Stupor/Coma
Spontaneous activity	Normal	Normal or decreased	Decreased	None
Posture	Predominantly flexed	Mild flexion of distal joints	Distal flexion or complete extension	Decerebrate
Tone	Strong flexor tone in all extremities	Normal or slightly increased	a. Hypotonia (focal or general)	Flaccid
			b. Hypertonia	Rigid
Primitive reflexes				
Suck	Strong, easily illicit	Weak or Incomplete	Weak or incomplete and/or bite	Absent
Moro	Complete	Intact (low threshold)	Incomplete	Absent
Autonomic Nervous System (ANS)				
Pupils	Normal	Mydriasis	Myosis	Variable or Nonreactive
Heart rate	100–160 bpm	Tachycardia	Bradycardia	Variable
Respirations	Regular respirations	Hyperventilation	Periodic breath	Apnea or need ventilation

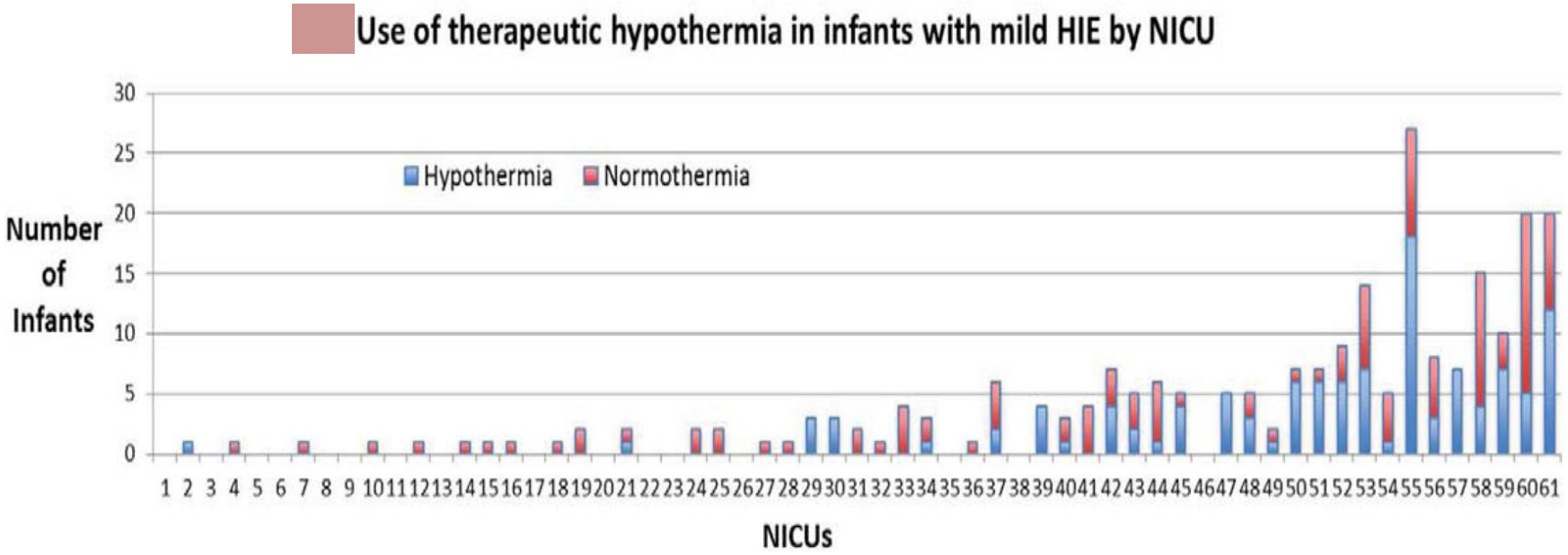
Outcomes

Results: Of the 63 infants enrolled, 51 (81%) were evaluated at 19 ± 2 months and 43 (68%) completed Bayley III. Of the 43 infants, 7 (16%) were diagnosed with disability including 1 cerebral palsy and 2 autism. Bayley scores <85 in either cognition, motor, or language were detected in 17 (40%): 14 (32%) language, 7 (16%) cognitive, and 6 (14%) motor domain. Infants with disability had more abnormalities on discharge examination and brain MRI, with longer hospital stay (p<0.001).

a. Cohort Results	(n=43)
Age at evaluation, months	19 [18–22]
Disability	7 (16 %)
Mild	4 (9%)
Moderate	0
Severe	3 (7%)
Cognitive score	95 [90 – 106]
≥ 85	36 (84%)
70–84	4 (9 %)
<70	3 (7%)
Language score	89 [79 – 100]
≥ 85	29 (67%)
70–84	10 (23%)
<70	4 (10%)
Language subtypes: Receptive communication	9 [7–10]
Expressive communication	8 [7–10]
Motor score *	100 [88 – 105]
≥85	37 (86%)
70–84	3 (7%)
<70	1 (2%)
Motor subtypes: Fine motor	10 [9–12]
Gross motor	9 [8–10]
Cerebral palsy	1 (2%)
Autism	2 (5%)

Therapeutic Hypothermia beyond the RCTs

- Increasing use of cooling beyond RCT parameters
- Significant variation in practice for mild HIE



Azzopardi Det al. PLoS One 2012
Massaro AN, et al. J Perinatol 2015

Kracer B, et al. J Pediatr 2014

Arch Dis Child Fetal Neonatal Ed. 2017 Sep 23.

Inclusion Criteria for Hypothermia

AAP Committee Fetus and Newborn

- > 36 weeks Gestation

AND

- One of the following
  1. Sentinel event (e.g. Cord prolapse, fetal heart rate decelerations)
  2. Assisted ventilation required for 10 min after birth
  3. 10 min Apgar ≤ 5
  4. pH ≤7.0 (cord blood or 60 min)
  5. Base Deficit ≥16 mmol/L (cord blood or 60 min)

AND

- Moderate or Severe Neonatal Encephalopathy

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  1. Sentinel event (e.g. Cord prolapse, fetal heart rate decelerations)
  2. Assisted ventilation required for 10 min after birth
  3. 10 min Apgar ≤ 5
  4. pH ≤7.0 (cord blood or 60 min)
  5. Base Deficit ≥16 mmol/L (cord blood or 60 min)

AND

- Moderate or Severe Neonatal Encephalopathy

Local Criteria

- > 34 weeks Gestation

AND

- One of the following
  1. Sentinel event (e.g. Uterine rupture, profound bradycardia or cord prolapse)
  2. Chest compressions and/or Intubation and/or PPV 10 min after birth
  3. 10 min Apgar ≤ 5
  4. pH <7.1 (cord blood or 60 min)
  5. Base Deficit (cord blood or 60 min)
     - ≥16 mmol/L – Provide hypothermia
     - 12 to 16 mmol/L – Recommend hypothermia
     - <12 mmol/L – Can consider hypothermia

AND

Any one of the following

- Seizure or concern for clinical seizure
- Neonatal Encephalopathy

Enrollment

- 136 infants screened for TH (90% 2013-2016)
- 95 infants received TH

- 6 excluded
  - 3 ECMO
  - 3 alternate pathology- Hydrocephalus, Genetic syndrome

- 89 infants included in this analysis
  - 6 Severe NE
  - 35 Moderate NE
  - 48 Mild NE

Demographic Details

Clinical Grade NE	Mild (n=48)	Moderate (n=35)	Severe (n=6)
Gestation (weeks)	39.5 (38.6-40.4)	38.8 (37.4-40.4)	38.6 (37.3-40.5)
Birth Weight (gm)	3268 (2968-3548)	3245 (2810-3555)	3247 (2775-3835)
Birth wt <10%ile	6 (12%)	3 (8%)	0
Gender (M/F)	26/22 (54/46)	19/16 (54/46)	5/1 (83/17)
Method of Delivery			
Spontaneous vaginal	13 (27)	9 (26)	2 (33)
Instrumental	11 (23)	2 (6)	0
Cesarean	24 (50)	24 (69)	4 (67)
Inborn	29 (60)	22 (63)	4 (67)

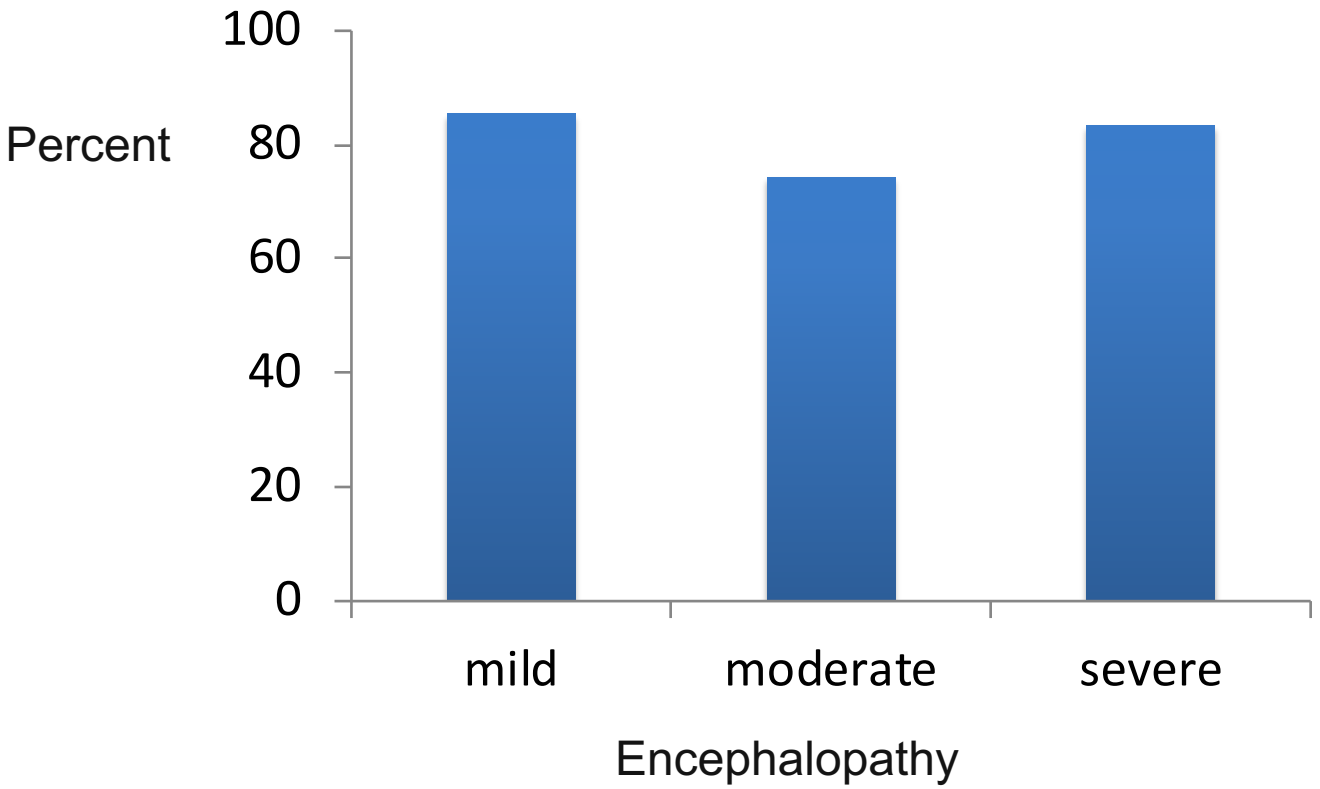
Median (IQR), n (%). *p<0.05, **p<0.01

Perinatal data

Clinical Grade NE	Mild (n=48)	Moderate (n=35)	Severe (n=6)	p value
Resuscitation required	41 (85)	31 (89)	6 (100)	0.60
Perinatal event	22 (47)	16 (46)	4 (67)	0.63
First pH	7.09 (6.98-7.27)	7.08 (6.96-7.22)	6.93 (6.66-7.06)	
First BE	-11.2 (-6.0 to -14.5)	-12.5 (-7.8 to -17.4)	-14.9 (-7.0 to -24.4)	0.22
Apgar at 10 min <5	6(13)	9 (26)	3 (50)	0.17
PPV required at 10 min	11 (23)	14 (40)	6 (100)	0.001
Met AAP criteria	0 (0)	25 (71)	5 (83)	<0.001

Median (IQR), n (%). *p<0.05, **p<0.01

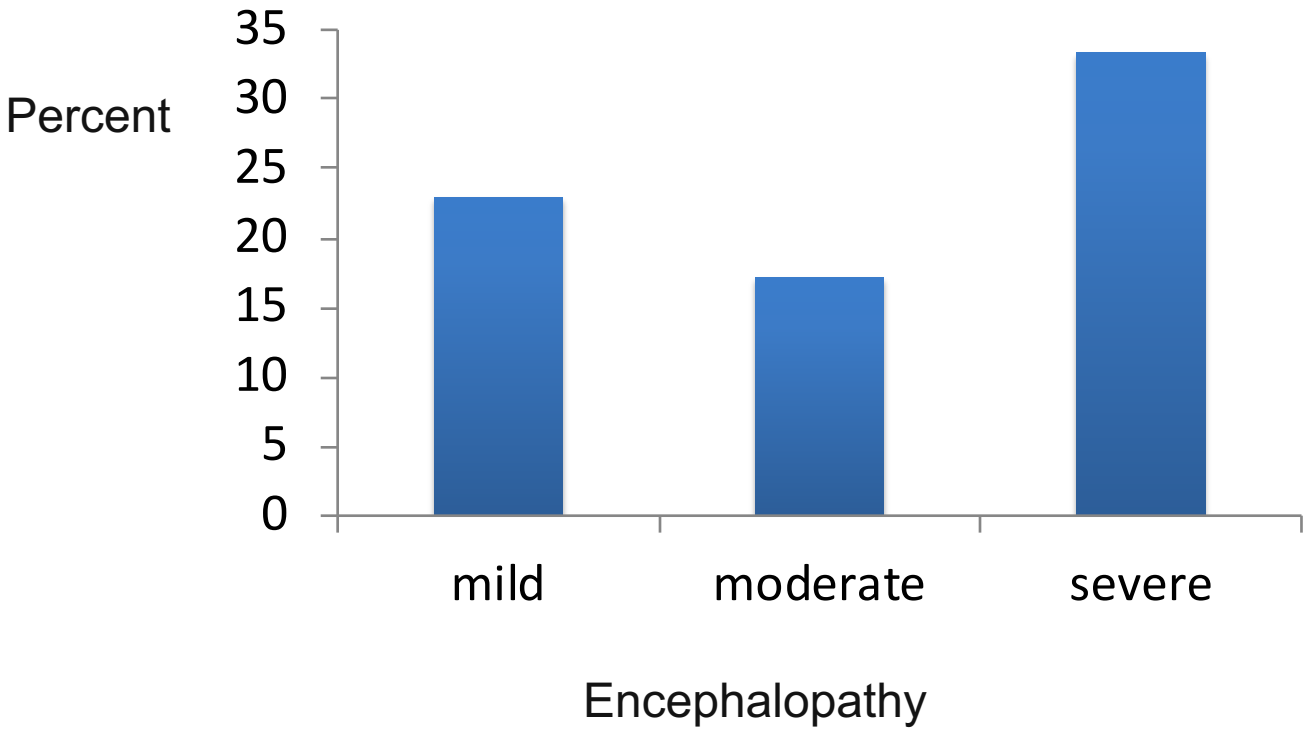
Fraction with any MRI abnormality

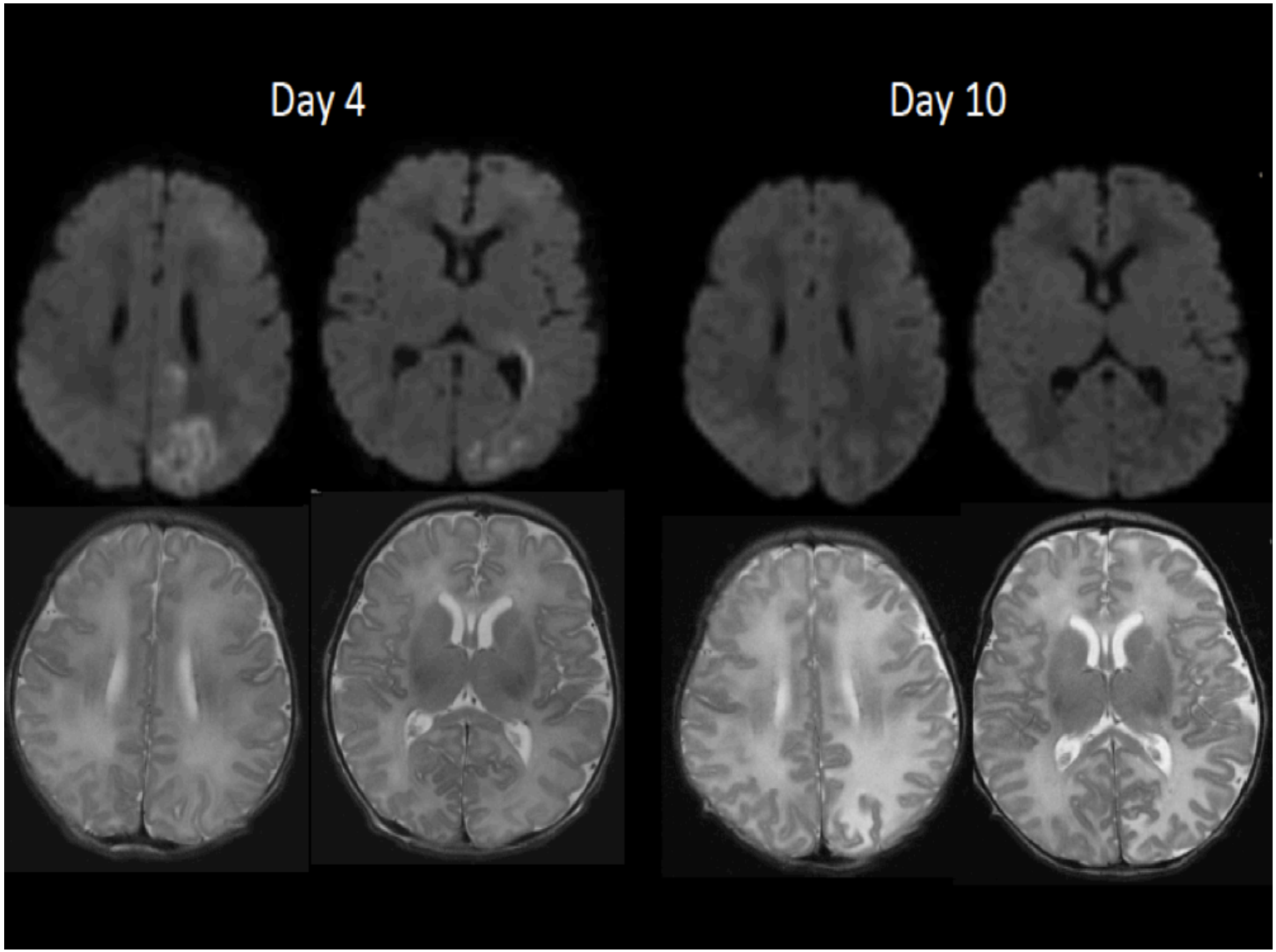


MRI Grading

Basal Ganglia /Thalamus		Watershed	
Score		**Score**	
0	Normal or isolated focal cortical infarct	**0**	Normal
1	Abnormal signal in the thalamus	**1**	Single focal infarction
		2	Abnormal signal in anterior or posterior watershed white matter
2	Abnormal signal in the thalamus and lentiform nucleus	**3**	Abnormal signal in anterior or posterior watershed cortex and white matter
3	Abnormal signal in the thalamus, lentiform nucleus, and perirolandic cortex	**4**	Abnormal signal in both anterior and posterior watershed zones
4	More extensive involvement	**5**	More extensive cortical involvement

Fraction with moderate/severe injury




Day 4
Day 10

Discussion

- Rate of Mod/Severe MRI injury among Mild HIE (30%) similar to outcome literature

	Mild HIE - (n)	Abnormal Outcome - %
Murray 2009	24	12.5%
Zhou 2010	39	33%
Jacob 2011	40	30%
Lally 2014	24	30%

Murray DM Pediatrics 2009
Jacob SE, et al. Arch Pediatr Adolesc Med 2011

Zhou W, et al. J Pediatr 2010
Lally PJ, et al. PlosOne 2014

Conclusion

- Retrospective observational single center study
- Half of infants with NE (mild, moderate, or severe) and treated with TH have an abnormal MRI.
- The incidence of moderate-severe cerebral injury is similar in infants with mild NE - 54% of these infants had an abnormality on cerebral MRI and 23% of them had moderate-severe cerebral injury.

Issues in application in mild NE

- Risk versus benefit of therapy
  - Separation of infant from mother
  - Only 30% of our infants are ventilated, does require UVC, TPN and morphine
  - 17% of mild NE received some blood product – mainly FFP
  - 1 infant had subcutaneous fat necrosis

Early cessation of hypothermia

- In a retrospective cohort of 10 babies with mild encephalopathy who had early cessation of cooling therapy. All babies had MRI and spectroscopy within 2 weeks after birth and neurodevelopmental assessment at 2 years. Cooling was prematurely discontinued at a median age of 9 hours (IQR 5-13) due to rapid clinical improvement. Five (50%) had injury on MRI or spectroscopy, and two (20%) had an abnormal neurodevelopmental outcome at 2 years.

- *Residual brain injury after early discontinuation of cooling therapy in mild neonatal encephalopathy. Lally PJ, et al S. Arch Dis Child Fetal Neonatal Ed. 2017 Sep 21.*

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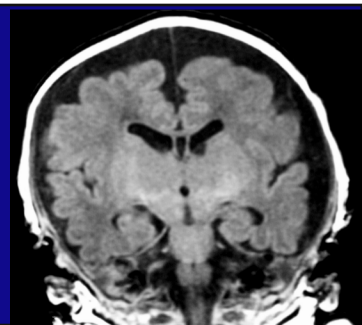
RISKS
Adverse Event Profile from Cochrane and Registries



Cooling for newborns with hypoxic ischaemic encephalopathy (Review)

Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG

THE COCHRANE COLLABORATION®

Involved System	n	Event Incidence [%(event/population)]		Relative Risk (95% CI)
Adverse Event		**HT**	**NT**	
Miscellaneous				
Renal Impairment	667	38.5 (126/327)	45 (153/340)	0.87 (0.74-1.02)
Oliguria	865	23 (100/435)	23 (101/430)	0.95 (0.76-1.19)
Hepatic Dysfunction	975	30 (147/485)	34 (169/490)	0.88 (0.74-1.05)
Sepsis	1221	7.5 (46/609)	8.6 (53/613)	0.87 (0.6-1.26)

1. Jacob SE, et al. Cochrane Database Syst Rev 2013

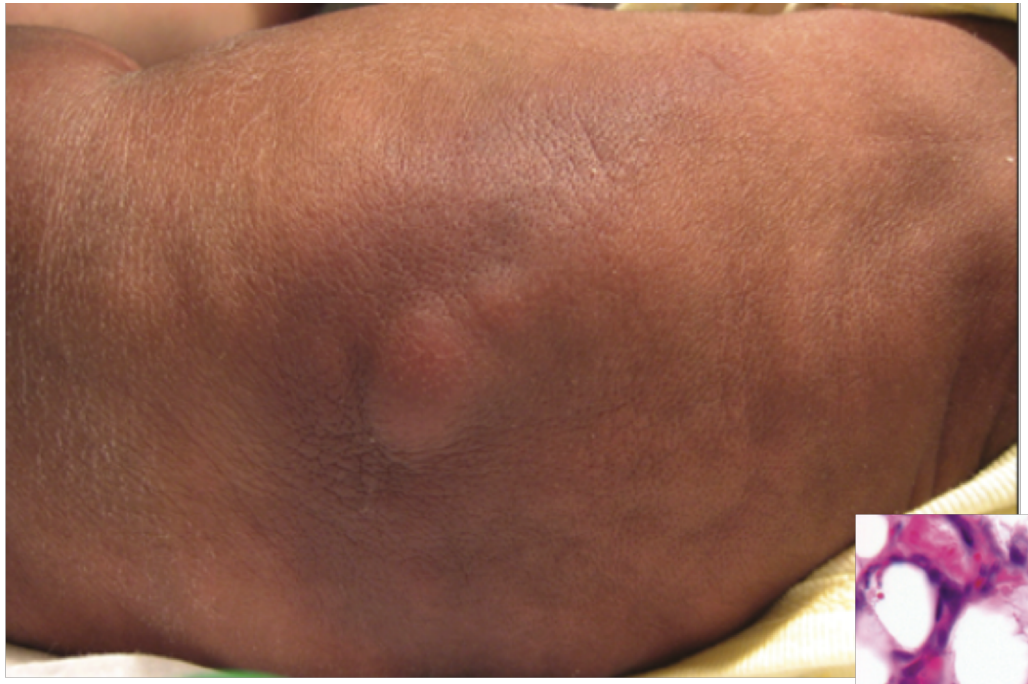
Involved System	n	Event Incidence [%(event/population)]		Relative Risk (95% CI)
Adverse Event		**HT**	**NT**	
Cardiovascular				
Sinus Bradycardia	**1292**	**9.5 (62/647)**	**0.5 (3/645)**	**11.59 (4.94-27.7)**
Major Arrhythmia	1292	0.3 (2/647)	0.6 (4/645)	0.55 (0.12-2.56)
Hypotension	1221	61 (369/608)	60 (373/618)	1 (0.92-1.09)
Hypotension requiring inotropes	768	53 (201/380)	49 (190/388)	1.09 (0.96-1.24)
Pulmonary HTN	616	17 (53/305)	13 (40/309)	1.36 (0.94-1.97)
Hematological				
Anemia Requiring RCC	749	13.5 (50/370)	13.4 (51/379)	1.01 (0.71-1.43)
Leukopenia	547	4 (11/266)	1.4 (4/271)	2.4 (0.85-6.79)
Thrombocytopenia	**1392**	**34.5 (241/698)**	**28 (197/694)**	**1.21 (1.05-1.4)**
Coagulopathy	1188	31 (184/589)	28 (170/599)	1.1 (0.93-1.29)

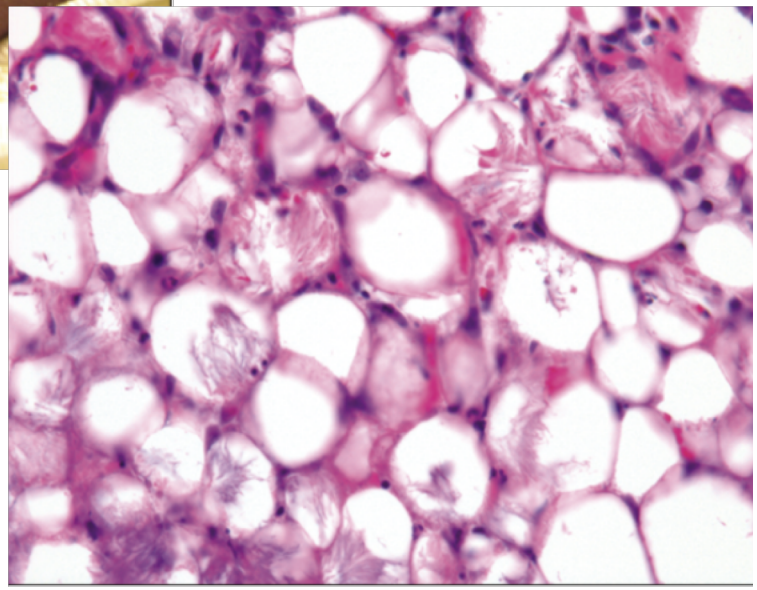
1. Jacob SE, et al. Cochrane Database Syst Rev 2013

Less Frequent Adverse Events

- Subcutaneous Fat Necrosis
  - Incidence 1-3.4%[1, 2]
  - TOBY reported incidence of 1% (n=12)[2]
    - Median age of appearance 6 days (4-42 days)
    - Hypercalcemia in 8 of 10 measured
    - Median Ca 11.92 mg/dL (6-20.4 mg/dL)

1. Chevallier M, et al. PLOS One 2013
2. Storhm B, et al Pediatrics 2011





1. Oza V, et al. Arch Dermatol 2010

RULES – OPTIMIZING HYPOTHERMIA

The Art of Hypothermia

- Method of cooling
  - Brain injured infants will drop their body temperature
  - No attention to temperature can lead to profound hypothermia
  - Resuscitation under overheads can increase body and brain temperature to inadvertent hyperthermia
  - Do not use 100% oxygen to resuscitate
  - Sedation with low dose morphine is not harmful and some evidence that it may help – No data on Fentanyl

Evaluating the high risk infant - neonatal seizures

- Should we monitor at high risk infants for neonatal seizures?
  - 30-90% of the seizures are subclinical – 2/3rds of abnormal movements do not have an EEG correlate
    - *Mizrahi and Kellaway 1987*
    - *Murray DM Archives of Dis Childhood 2007*
  - Electromechanical dissociation with anticonvulsant therapy
    - *Boylan GB. Et al Archives of Dis in Childhood 2002 86(3):F165-70*
    - *Scher M et al Pediatric Neurology 2003;28:277-80*

Considerations in neonatal seizures

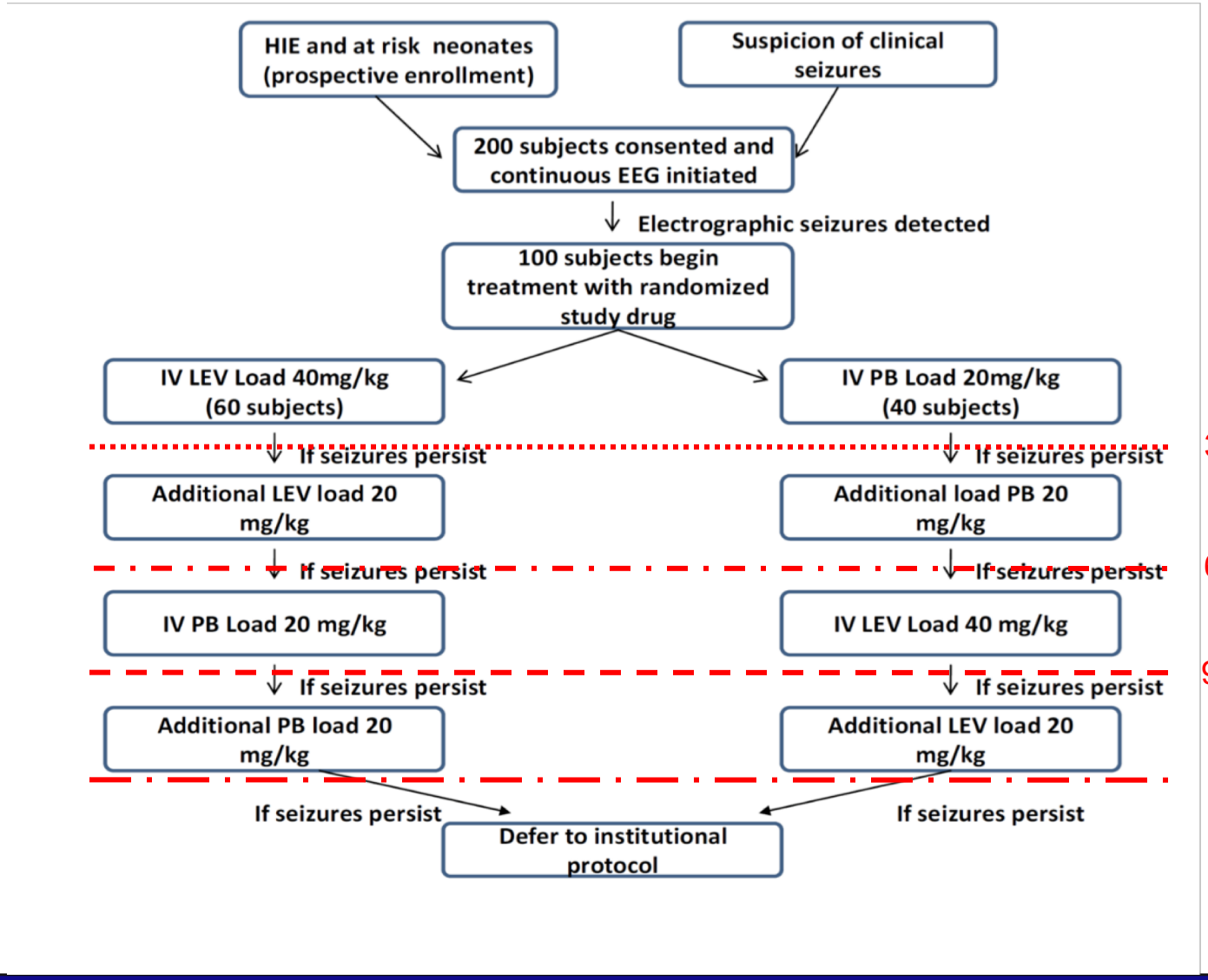
Murray DM et al Archives Dis Childhood 2007

- 51 infants encephalopathy and/or risk HIE
  - 12 infants with seizures and/or treated for seizures
  - Overall 48/526 EEG seizures (9%) clinically recognized (19% on video EEG)

- 3 infants "aggressively treated" for up to 31 clinical events with NO EEG seizures
- 2 infants did not receive any anticonvulsant therapy and had 38 & 56 EEG seizures.
- 5/12 infants (42%) received incorrect therapy

NEOLEV2

Protocol Flow



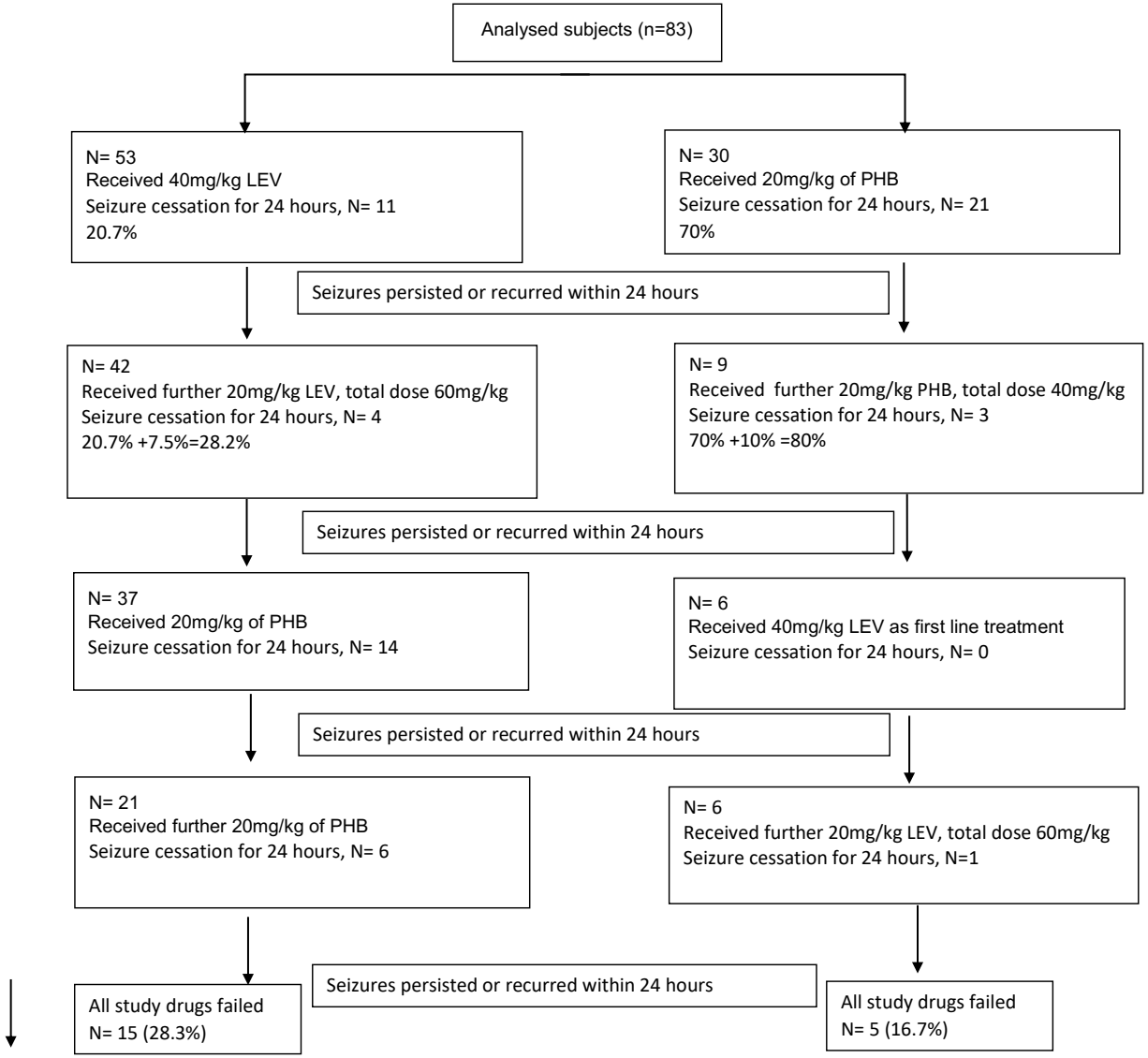
Primary Outcome:
Seizure Cessation to 24 hours

prim	Phenobarbital	Levetiracetam	Total	p.value
n	6 (20%)	38 (71.7%)	44 (53.01%)	<0.001
y	24 (80%)	15 (28.3%)	39 (46.99%)	
Total	30 (100%)	53 (100%)	83 (100%)	

Seizure cessation for 1 hour

sec	Phenobarbital	Levetiracetam	Total	p.value
n	2 (6.67%)	27 (50.94%)	29 (34.94%)	<0.001
y	28 (93.33%)	26 (49.06%)	54 (65.06%)	
Total	30 (100%)	53 (100%)	83 (100%)	

Figure 3: Seizure Efficacy Results



Seizures in the Newborn Therapy

- Monitor with aEEG or EEG – if no seizures in the first 24 hours then highly unlikely
- If second seizure occurs OR infant is severely affected then commence phenobarbitol 20mg/kg
- Second line phenobarbitol further 20mg/kg
- No maintenance may be needed – half life is 200-300 hours
- Coverage during the 72 hour storm
- Imaging reveals major brain injury and/or seizures recur then maintenance will be needed and Levetiracetam is appropriate

Why and how should we neuro-image?

- Confirm the diagnosis
- Define the nature and the extent of injury – prognosis and early intervention services

Imaging recommendations

- Head ultrasound is useful to detect major malformations and hemorrhages.
- CT shouldn't be used due to poor sensitivity and risk of injury.
- MRI on day 1 – 4 is useful for delineating injury on diffusion imaging and is helpful for estimating the timing of the injury.
- Follow up imaging between days 7 and 21 (preferably around day 10) is useful to show injury on conventional imaging (?15% false negative in TH).

D'Alton *et al*. Neonatal encephalopathy and neurologic outcome. American College of Obstetricians and Gynecologists. *Obstet Gyencol.* **123**, 896 (2014).

Accuracy of prediction of outcome by MRI following therapeutic hypothermia

Major MRI abnormalities	Cooled (95% Confidence intervals)	Non-cooled (95% Confidence intervals)
Sensitivity	0.88 (0.79-0.97)	0.94(0.88-1.0)
Specificity	0.82(0.72-0.92)	0.68(0.56-0.80)
Positive predictive value	0.76(0.65-0.87)	0.74(0.63-0.85)
Negative predictive value	0.91(0.83-0.99)	0.92(0.85-0.99)

Rutherford M, et al. Lancet Neurol. Jan 2010; 9(1): 39–45.

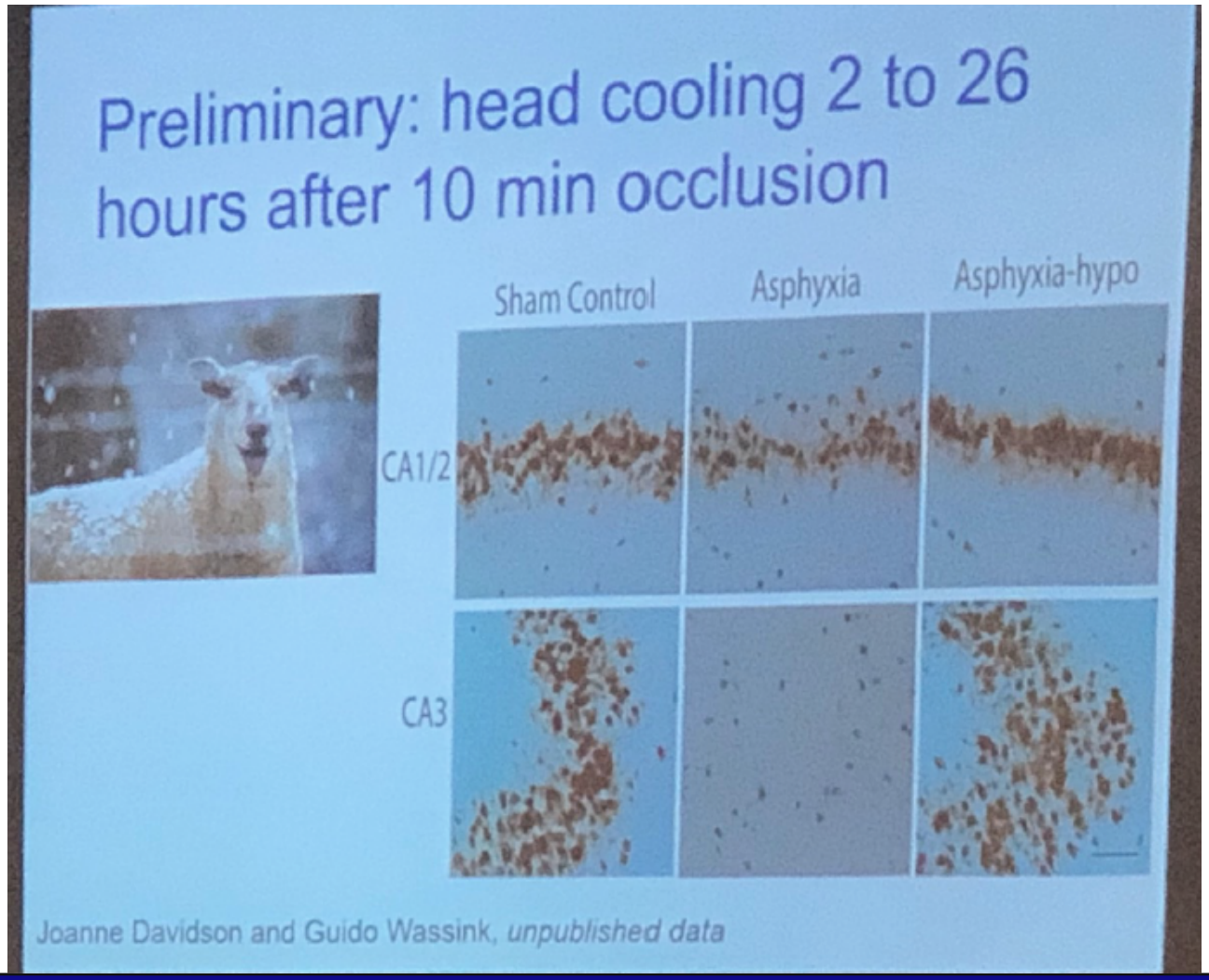
Mild NE – where to next?

- Randomized controlled trial
  - Selection based on neurological examination
  - Effect size/Number of infants
  - Length of follow up for cognitive outcomes

Mild NE – where to next?

- Randomized controlled trial
  - Selection based on neurological examination
  - Effect size/Number of infants
  - Length of follow up for cognitive outcomes
- Further investigations
  - Video of the neurological examination
  - MR imaging of all infants considered for hypothermia therapy who are not cooled
  - Registry data of who is being cooled
  - Investigation of impact on parents/anxiety in infants

Animal Experimental Data

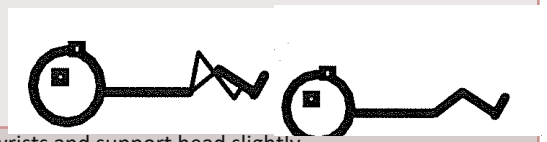
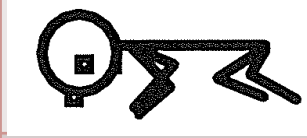
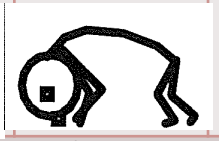
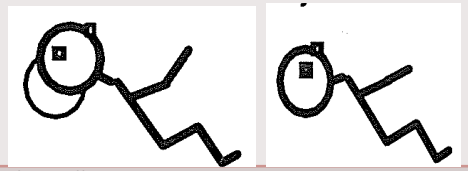


Mild NE – What should a clinician do today?

- Admit that we do not know if there is benefit from therapeutic hypothermia in mild NE
  - Animal data supports its efficacy
  - True risk exists
  - Document in chart discussion and consent from family
- Educate
  - Systematic neurological examination (video)
  - Community providers on identification
- Research and/or Monitor
  - Registry of infants being considered for hypothermia
  - Consider MRI in infants that are both cooled and not cooled

Date	NE Score	
1- Observe spontaneous activity	0	Normal
	2	Decreased = decreased frequency or amplitude of spontaneous facial and extremity movements
	3	Absent
2- Observe for Heart rate	0	Normal
	1	Tachycardia = resting HR 160-180. Only occasionally decreased to 120
	2	Bradycardia = resting HR 80-90. Only occasionally increases to 120
	3	Variable = resting HR varies considerably without a consistent baseline
3- Observe for respiration	0	Normal
	2	Periodic Breathing = 3 or more respiratory pauses ≥ 3 sec separated by normal breathing and < 20 sec. Often associated with shallow breathing
	3	Apnea = no breathing for ≥ 20 sec or < 20sec with HR changes or O2 desaturation
4- Observe for posture	0	Normal
	1	Mild Distal Flexion = fingers, toes in mild flexion, incomplete extension of fingers when stroked on dorsal surfaces. Thumbs flexed, adducted, opposed across palms "cortical thumb"
	2	Strong Distal Flexion = fingers and toes in strong flexion, incomplete extension of fingers when stroked on dorsal surfaces. Thumbs flexed, adducted, opposed across palms "cortical thumb"
	3	Decerebrate = Head, neck and back are arched in extension (opithotonus), elbows are extended, wrists are pronated and hips are abducted.
5- Observe for level of consciousness		Use Auditory stimulation, Visual stimulation and Tactile stimulation to assess level of consciousness
	0	Normal
	1	Hyperalert = full wakefulness with eyes open/staring but decreased frequency of blinking/tracking. Spontaneous motor activity normal or decreased with lowered threshold to all stimulus types
		Irritable = lowered threshold with excessive responses to all stimulus types. Can be seen with varied states including hyperalert, lethargy or obtundation
	2	Lethargic = slightly delayed but complete response to stimuli with slightly increased threshold for eliciting responses and decreased spontaneous activity
		Obtunded = delayed and incomplete response with marked increased threshold to all sensory stimuli and little or no motor activity.
	3	Stupor = no spontaneous eye opening to tactile stimulation elicits poorly sustained eye opening. Responds only to strong noxious stimuli. Absent gag and cornel reflex
		Coma = no eye opening with vigorous tactile stimulation

6- Tone Assessment	0	Normal
	2	Hypotonic = focal or generalized decreased resistance to passive movement. Associated with greater extension of extremities than normal
	3	Flaccid"Flat on the mat" appearance. Maybe associated with frog-leg posturing with arm and hips/legs lying in abduction

	Arm Recoil: Quickly extend (straighten) both arms; put next to body. Count to two. Let go. Repeat 3 times.		Leg Recoil: Take both ankles, bend hips+ knee. Quickly extend when infant not pushing. Let go. Repeat 3 times.	
	Normal- Arms flexes and remains flexed	Hypotonia	Normal: Complete Fast Flexion	Hypotonia:
				
	Ventral Suspension: Hold baby horizontal under the belly. Look at posture of back, arms, legs and head.		Head Lag: Pull baby to sit by the wrists and support head slightly.	
	Normal: Back straight, head in line with body, limb flexed	Hypotonia:	Normal: Lifts head in line with body	Hypotonia:
				
	Vertical Suspension: Hold baby upright by placing hands under axillae			
	Normal: No Slip through		Hypotonia: Slip Through	

7- Reflexes		
Sucking reflex	0	Normal
	1	Weak
	2	Weak/Incoordinated
	3	Absent
Moro Reflex	0	Normal
	1	Exaggerated
	2	Weak/Incomplete
	3	Absent
Light Reflex	0	Normal
	1	Dilated
	2	Constricted
	3	Unequal/ Fixed dilated

J Matern Fetal Neonatal Med. 2016 Mar;29(5):721-6.

Hypoxic ischemic encephalopathy in newborns linked to placental and umbilical cord abnormalities.

Nasiell J[1], Papadogiannakis N[2,3], Löf E[1], Elofsson F[1], Hallberg B[4].