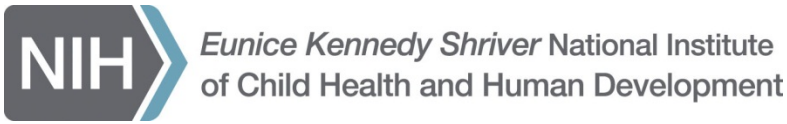
Study Eligibility Neurological Exam Certification for the Moderate-Severe HIE Trials

Seetha Shankaran MD

Abbot Laptook MD



Rationale for a Certification Process

- Majority of trials have objective inclusion criteria
  - Gestational age, birth weight, ventilator support etc
- Neuroprotection studies for HIE have a tiered inclusion criteria: objective markers followed by a neurological examination
- Examination is a subjective assessment
  - Many fellows get very little training in neurological exams
  - Relatively small percent of patients in NICUs need detailed neurological assessments
- Certification: minimizes examiner variability and promotes enrollment of appropriate infants

Neurological Examinations After Birth

- Challenging assessments
  - Transient effects of delivery, anesthesia, analgesia
  - Examination findings may improve or get worse
    - Severity and timing of hypoxia-ischemia
    - Compensatory hemodynamic changes
    - Endogenous CNS protective mechanisms
  - Associated conditions: Respiratory distress
  - Simultaneous mix of neurological findings
    - Components of none/mild, moderate or severe encephalopathy
- Dynamic nature of exam: certification exams should be done temporally close to each other

Neurological Examination

- Stage of HIE by exam is needed for study eligibility
- The Sarnat evaluation of stage of HIE correlates well with childhood outcome

Sarnat and Sarnat. 1976, Arch Neurol

Shankaran et al. 1991, Early Human Devel

Robertson CM. 2003, Fetal and Neonatal Brain Injury

Badawi et al. 2005, Dev Med Child Neurol

Ambalavanan et al, 2006 Pediatrics

Shankaran et al.2012, J Pediatr

Other Valuable Information from the Neurological Examination: Evolution of Encephalopathy

- Increased risk of death or disability after controlling for treatment group:
  - OR of 60 (15-246) if severe HIE persists at 72 hours after start of intervention
  - OR of 2.7 (1.1-6.7) if an abnormal neurological examination is present at discharge
    - Evidenced by abnormal tone, clonus, fisted hand, abnormal movements, absent gag, presence of asymmetric tonic neck reflex
  - OR of 8.6 (2.7-26.8) if gavage feeds or a G-tube is placed prior to discharge

Shankaran et al.2012, J Pediatr

The modified Sarnat exam

- Six Categories of assessment

- Signs to determine three potential Levels of encephalopathy

CATEGORY	MODERATE HIE	SEVERE HIE
1. Level of consciousness	2 = Lethargic	3 = Stupor/coma
2. Spontaneous Activity	2 = Decreased activity	3 = No activity
3. Posture	2 = Distal flexion, complete extension	3 = Decerebrate
4. Tone	2a = Hypotonia (focal or general) 2b = Hypertonia	3a = Flaccid 3b = Rigid
5. Primitive Reflexes Suck Moro	 2 = Weak or has bite 2 = Incomplete	 3 = Absent 3 = Absent
6. Autonomic System Pupils Heart rate Respiration	 2 = Constricted 2 = Bradycardia 2 = Periodic breathing	 3 = Deviation/dilated/ or nonreactive to light 3 = Variable HR 3a = on vent with spontaneous respirations 3b = on vent without spontaneous breaths

Study Eligibility: Moderate-Severe HIE

- The Modified Sarnat exam has 6 categories
  - Level of consciousness
  - Spontaneous activity
  - Posture
  - Tone
  - Primitive reflexes (has 2 signs---suck and Moro)
  - Autonomic nervous system (has 3 signs--pupils, heart rate, respiration)
- Each **category** contributes 1 point : there are 6 categories and 9 signs
  - Primitive reflexes and ANS have multiple signs, but these categories also contribute only 1 point even if more than one sign is coded as a 2 or a 3
    - In primitive reflexes and ANS, if > 1 sign is coded as a 2 or 3, choose the more severe code (3)
- To be eligible for study entry:
  - **3 of the 6 categories** have to be coded as either moderate or severe encephalopathy
  - **OR** Seizures

Points to consider

- Examine in 2 phases: Observation and active manipulation
- Score the awake state. Start with observation (activity, posture, HR, respiration)
- Active portion: Do the least noxious part of exam first (tone) and the most noxious part last (pupils)
- The stage of HIE has to be accurately assessed
- While seizures make an infant eligible—the certified neuro exam still needs to be done

The Observation Part of the Exam

- Spontaneous activity
- Posture
- Autonomic System (2 of 3 components)
  - Respiratory pattern
  - Heart rate

Active Manipulation Part of the Exam

- Level of consciousness
- Tone
- Primitive reflexes (2 components)
  - Suck
  - Moro
- Autonomic System (1 of 3 components)
  - Pupils

Spontaneous Activity

- Evaluate Spontaneous activity
  - Code 1 if infant is active
  - Code 2 if activity is decreased
  - Code 3 if no activity

If infant is sedated clinical judgment has to be used to decide whether the examination is reliable.

Paralysis will preclude a meaningful exam

The transport team and clinical team should be aware of need for this exam without sedation

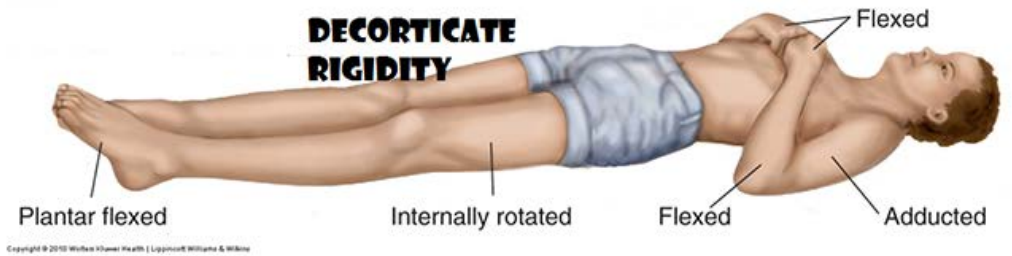
Posture

- Observe infant in awake state
  - Code 1 if infant is moving around and does not maintain one posture, should have flexion of lower extremity at hip and/or knees
  - Code 2 if strong distal flexion, complete extension or "frog-legged" position (complete abduction)
  - Code 3 if decerebrate with or without stimulation

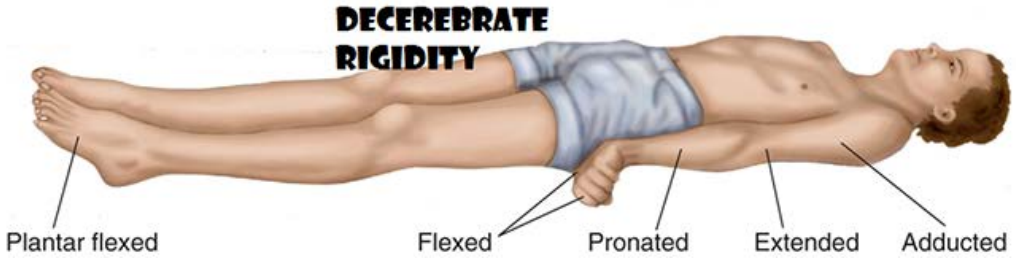
The frequency of decerebrate posture is rare, however it was documented in the first RCT

If posture is abnormal, but does not fit 2 or 3, code as 2

Decerebrate vs Decorticate Posture



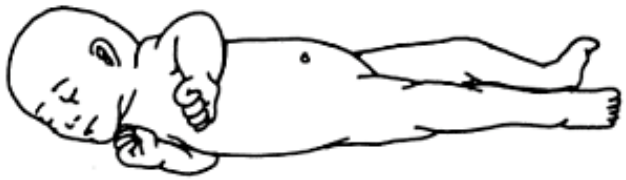
Adult



Infant

Decerebrate

Decorticate



B,C

Abnormal Posture
Opisthotonic, Decerebrate, Decorticate

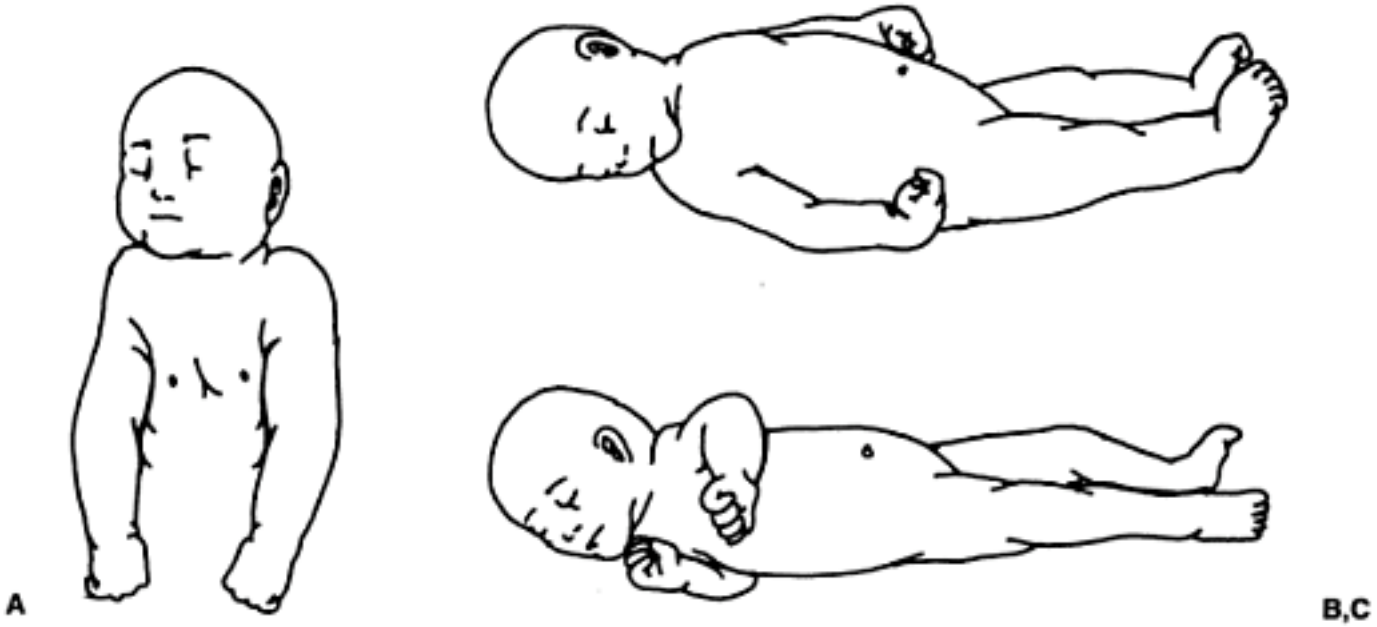


Figure 7. Abnormal posturing. **A:** Opisthotonic. The neck and arms are hyperextended. Legs and trunk may also be hyperextended. **B:** Decerebrate. The legs and arms are extended with the wrists flexed and hands fisted. **C:** Decorticate. The arms are flexed and legs extended.

Fletcher. *Physical Diagnosis of Neonatology*, p 468. 1998.

Autonomic System

Pupils, Heart Rate and Respiration

ANS - Respiration

- Code 1 if breathing spontaneously or if periodic breathing without desaturation
- Code 2 if periodic breathing associated with desaturations (SpO_2 < 80%) ± supplemental O_2
- Code 3 if apnea or requiring ventilator support:
  - 3a if spontaneous breaths above the ventilator
  - 3b if no spontaneous breaths above the vent

An intubated infant with spontaneous breaths is coded as 3: it cannot be ascertained if the spontaneous breaths can sustain respiration without ventilator support

ANS – Heart rate

- Code 1 if >100 per min consistently or tachycardia (>160)
- Code 2 if bradycardia (< 100/min) with only occasional increases to >120/min
- Code 3 if heart rate is not constant and varies widely between <100 and >120

Heart rate should be evaluated based on documented rate over the previous min/hrs

If assessing for study eligibility: Do not code heart rate if cooling has been initiated

If certifying examiners: code heart rate

Level of consciousness

- Code 1 if infant arouses to wakefulness, responds appropriately and promptly to external stimuli, or appears hyperalert or inconsolable/irritable
- Code 2 if lethargic: delayed but complete response to external stimuli (start with mild stimuli first then proceed to more noxious stimuli)
- Code 3 if stupor/coma: infant is not arousable and is non-responsive to external stimuli; may have a delayed but incomplete response to stimuli

LOC: is the deciding factor to assign HIE stage if # of moderate and severe categories are =

It is rare for LOC to be normal when rest of exam shows moderate/severe HIE

Tone

- Response to passive movement
  - Code 1 if there is normal resistance
  - Code 2:
    - 2a if hypotonic or floppy either focal or generalized
    - 2b if increased tone noted
  - Code 3:
    - 3a if flaccid (like a rag doll)
    - 3b if rigid (stiffness or inflexibility)

Evaluate extremities, trunk and neck tone and make clinical judgment of tone based on tone in these areas.

If responses differ in multiple areas, base code on the most common

Head Lag: Normal (A &B) Hypotonia (C)

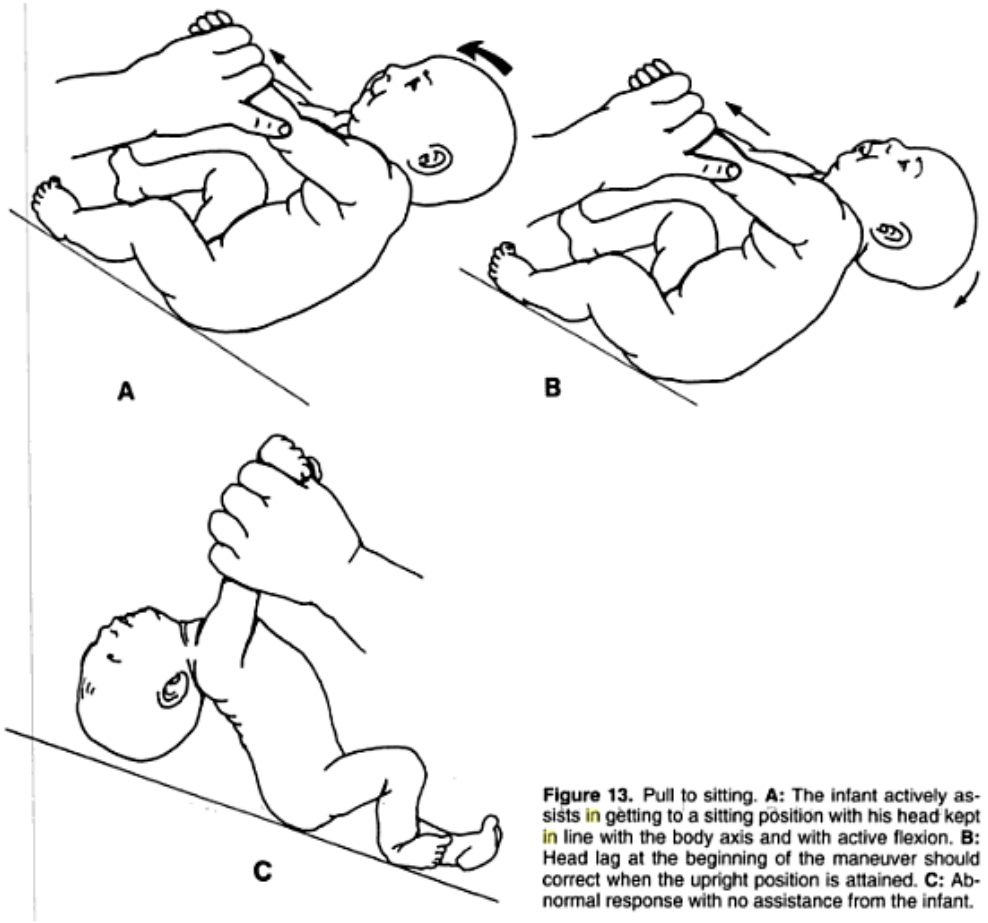


Figure 13. Pull to sitting. **A:** The infant actively assists in getting to a sitting position with his head kept in line with the body axis and with active flexion. **B:** Head lag at the beginning of the maneuver should correct when the upright position is attained. **C:** Abnormal response with no assistance from the infant.

Fletcher. *Physical Diagnosis of Neonatology*, p 477. 1998.

Ventral Suspension: Normal (A), Poor tone (B)

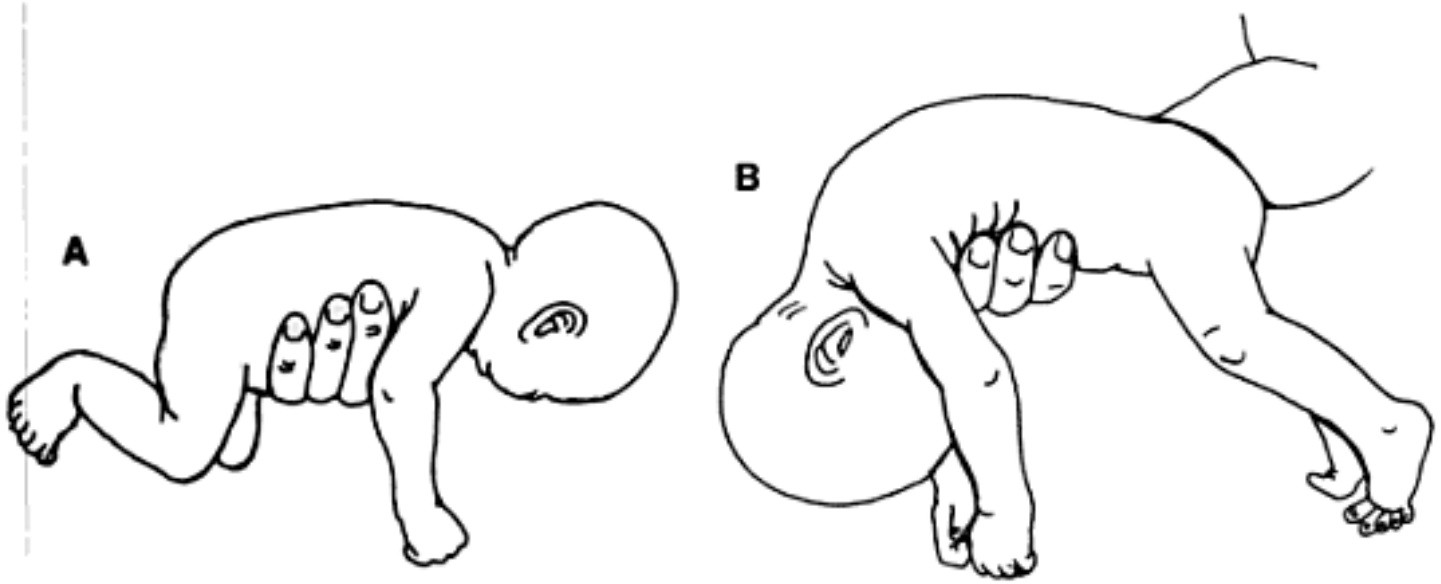


Figure 16. Ventral suspension. **A:** Good tone. **B:** Poor tone.

Fletcher. *Physical Diagnosis of Neonatology*, p 481. 1998.

Primitive Reflexes

Suck and Moro

Suck

–Code 1 if the infant vigorously sucks the examiners finger or the endotracheal tube

–Code 2 if suck is weak or if infant has a bite

–Code 3 if suck is absent

Moro

- Code 1 if, with stimulus, there is extension of limbs, opening of hands, extension with abduction of UE
- Code 2 if incomplete
- Code 3 if absent

If neonate has fracture of clavicle or brachial plexus injury, evaluate other extremity

Moro has to be done by gently raising and lowering the head when infant is intubated

ANS - Pupils

- Code 1 if normal in size and reactive to light
- Code 2 if constricted and reacting to light
- Code 3 if skew deviation of eyes, pupils are dilated or non-reactive to light
  - If pupils asymmetric, assign 3

Pupils are difficult to assess in the newborn infant with edema of eyelids---you will need to gently separate the eyelids while a second person shines light

Seizures

- Have to be documented in the chart or observed by MD or NNP
- Seizures can be subtle
  - Ocular deviation, sucking, lip smacking, swimming, rowing, bicycling movements
  - Seizures can be tonic/clonic, localized, multifocal or generalized

Requirements for Study Entry

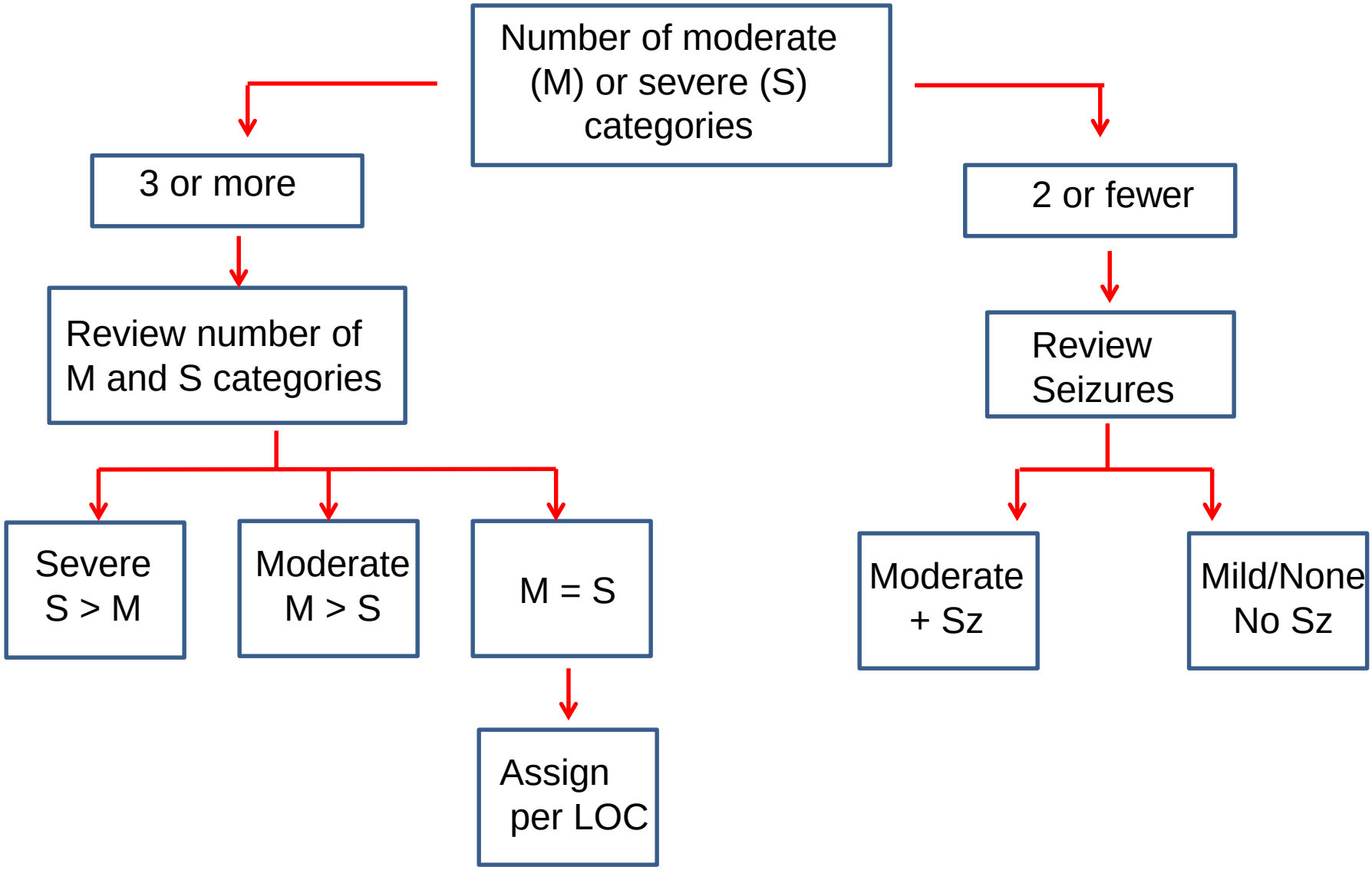
- 3 of 6 Categories need to be abnormal (either moderate or severe)
- **OR** Seizures

Moderate vs Severe Encephalopathy

Classification as moderate or severe HIE is based on the **predominant** number of categories that are level moderate or severe

Please note:

- 4 moderate and 2 severe categories = "Moderate" HIE
- 1 moderate and 2 severe categories = "severe" HIE
- 2 severe and 4 normal categories = NOT eligible for study


Number of moderate (M) or severe (S) categories
3 or more
2 or fewer
Review number of M and S categories
Review Seizures
Severe S > M
Moderate M > S
M = S
Moderate + Sz
Mild/None No Sz
Assign per LOC

Seizures and Study eligibility

- Moderate HIE by exam ± seizures
  = Moderate HIE
- Severe HIE by exam ± seizures = Severe HIE
- Seizures by history/observation
  = Moderate HIE
- Seizures by history/observation + mild/no HIE on exam = Moderate HIE

Subsequent exams

Serial exams are a good clinical predictor and biomarker of outcome

Although infrequent, the presence of hypertonia, fisted hand, abnormal movements, absent gag, asymmetric tonic neck reflex at discharge increased risk of death and disability at 18 months

Shankaran et al. J Pediatr 2012; 160:567-572

Additional components of exam: for subsequent and discharge exam

- Clonus
  - Code Yes if sustained (> 4-5 beats), No if not
- Fisted hand
  - Code Y if hand is fisted all the time (cortical thumb—thumb across the palm), N if hand open
- Abnormal movements
  - Code Y if excessive movements, either jerky, involuntary, bicycling, or myotonic

Additional components – cont'd.

- Gag reflex
  - Code Y if gag is absent
- Asymmetric tonic neck reflex

With infant supine, head is rotated to either side. A normal TNR is extension of arm and leg to side to which face is turned with flexion of arm and leg to opposite side (fencing position). Infant should spontaneously terminate this position. Code Y if position is maintained for > 30 seconds, N if not

- If support is being withdrawn, the neuro exam is required. (Not done in the first Hypothermia RCT)

Certification Process

- Screen for appropriate infants >36^0 weeks GA admitted to NICU or in observation/transition area
- Type of infant for examination
  - Hypoxia-ischemia (fetal acidemia, low Apgar scores)
  - Abnormal neurological state from non-HI conditions
  - Post-operative infants
- Number of examinations: 1
  - With neurological abnormalities

Certification Process (cont'd)

- Gold Standard examiner (site PI) and MD independently examine the infant
  - Exams performed within 1 hour of each other
  - Each examiner independently examines and completes a neurological exam form
    - Total the number of categories with abnormalities
    - Determine level of encephalopathy
    - Eligible to be hypothermia candidate
- GS examiner reviews exam with MD
  - Resolve any differences in exam, scoring and form completion

Processing Exam Forms

- If exams are discordant need to do more exams
  - Discordant: differences in more than **1 category**
- When exams appear concordant:
  - Forms should be legible and not have crossed outs
  - Exams will be centrally reviewed to determine certification
    - Need agreement between examiners on level of encephalopathy and differences in no more than one category
    - E-mail re Certification of examiners will be sent to GS examiners
- List of certified examiners maintained centrally
- Sites with>5000 deliveries/year may have 2 GS examiners

Here are some examples of examinations that are not coded appropriately re level of HIE that were submitted for review

The examiner counted multiple signs as categories associated with primitive reflexes and autonomic system (question 3).

For categories with multiple signs (primitive reflexes and autonomic system), code one value for each category; if the signs vary among levels of encephalopathy (normal/mild-1, moderate-2, and severe-3), code the most abnormal sign/level of encephalopathy.

It is a good practice to complete the right side of the table ("your determination") which reinforces one sign for each category.

THE 6 CATEGORIES:	SIGNS OF HIE IN EACH CATEGORY			Your Determination:	
	NORMAL / MILD HIE	MODERATE HIE	SEVERE HIE		
1. LEVEL OF CONSCIOUSNESS	1	2 = Lethargic	3 = Stupor/coma		= _____
2. SPONTANEOUS ACTIVITY	1	2 = Decreased activity	3 = No activity		= _____
3. POSTURE	1	2 = Distal flexion, complete extension	3 = Decerebrate		= _____
4. TONE	1	2a = Hypotonia (focal or general) 2b = Hypertonia	3a = Flaccid 3b = Rigid		= _____ _____ (Note a or b)
5. PRIMITIVE REFLEXES					Code highest level
Suck	1	2 = Weak or has bite	3 = Absent	= _____	} _____
Moro	1	2 = Incomplete	3 = Absent	= _____	
6. AUTONOMIC SYSTEM					Code highest level
Pupils	1	2 = Constricted	3 = Deviation/dilated/non-reactive to light	= _____	} _____ _____ (if vent. code a or b)
Heart rate	1	2 = Bradycardia	3 = Variable HR	= _____	
Respiration	1	2 = Periodic breathing	3 = Apnea or requires ventilator 3a=on vent with spont breaths 3b=on vent without spont breaths	= _____	

3. **Total # Categories should be NO MORE THAN 6 Total (Count Only the Highest Level in each sign)**

#5 Mild/Normal #4 Moderate #0 Severe

4. **Are there signs of moderate and/or severe HIE in at least 3 of the 6 categories above?** (Y) N (circle one)

There are multiple cross-outs which raise concerns about the confidence of the examiner in identifying signs.

Level of consciousness is circled as lethargic but under "your determination" is listed as a 1.

Question 3 is not answered with the number of categories as normal/mild, moderate or severe.

THE 6 CATEGORIES:	SIGNS OF HIE IN EACH CATEGORY			Your Determination:	
	NORMAL / MILD HIE	MODERATE HIE	SEVERE HIE		
1. LEVEL OF CONSCIOUSNESS	~~1~~	~~2~~ = Lethargic	3 = Stupor/coma		= 1
2. SPONTANEOUS ACTIVITY	1	~~2~~ = Decreased activity	3 = No activity		= 2
3. POSTURE	1	2 = Distal flexion, complete extension	3 = Decerebrate		= 1
4. TONE	1	2a = Hypotonia (focal or general) ~~2b~~ = Hypertonia	3a = Flaccid 3b = Rigid		= 2 b (Note a or b)
5. PRIMITIVE REFLEXES					Code highest level
Suck	~~1~~	~~2~~ = Weak or has bite	3 = Absent	= 1	2
Moro	1	~~2~~ = Incomplete	3 = Absent	= 2	
6. AUTONOMIC SYSTEM					Code highest level
Pupils	1	2 = Constricted	3 = Deviation/dilated/non-reactive to light	= 1	1 (if vent, code a or b)
Heart rate	1	2 = Bradycardia	3 = Variable HR	= 1	
Respiration	1	2 = Periodic breathing	3 = Apnea or requires ventilator 3a=on vent with spont breaths 3b=on vent without spont breaths	= 1	

3. Total # Categories should be NO MORE THAN 6 Total (Count Only the Highest Level in each sign)

#_____ Mild/Normal #__✓__ Moderate #_____ Severe

Similar to previous slide, there are multiple cross-outs which raise concerns about the quality of the examination.

Tone is circled as normal/mild but under "your determination" is listed as a 2b.

Suck is circled as weak but is listed under "your determination" as a 1 (normal/mild). This should be a 2 (moderate) to capture the most abnormal sign among categories with multiple signs.

Completion of the form needs to be carefully and accurately done since level of encephalopathy is a stratification variable

1. Does infant have seizures? Y (N)

2. Is the infant sedated/paralyzed? Y (N)

THE 6 CATEGORIES:	SIGNS OF HIE IN EACH CATEGORY			Your Determination:	
	NORMAL / MILD HIE	MODERATE HIE	SEVERE HIE		
LEVEL OF CONSCIOUSNESS	(1)	(2) = Lethargic	3 = Stupor/coma		= 2
SPONTANEOUS ACTIVITY	(1)	(2) = Decreased activity	3 = No activity		= 2
POSTURE	(1)	2 = Distal flexion, complete extension	3 = Decerebrate		= 1
TONE	(1)	2a = Hypotonia (focal or general) (2b) = Hypertonia	3a = Flaccid 3b = Rigid		= 2b (Note a or b)
PRIMITIVE REFLEXES					Code highest level
Suck	(1)	(2) Weak or has bite	3 = Absent	= 2	2
Moro	(1)	2 = Incomplete	3 = Absent	= 1	
AUTONOMIC SYSTEM					Code highest level
Pupils	(1)	2 = Constricted	3 = Deviation/dilated/non-reactive to light	= 1	1
Heart rate	(1)	2 = Bradycardia	3 = Variable HR	= 1	
Respiration	(1)	2 = Periodic breathing	3 = Apnea or requires ventilator 3a=on vent with spont breaths 3b=on vent without spont breaths	= 1	(if vent. code a or b)

3. Total # Categories should be NO MORE THAN 6 Total (Count Only the Highest Level in each sign)

#3 Mild/Normal #1 Moderate #_____ Severe

4. Are there signs of moderate and/or severe HIE in at least 3 of the 6 categories above? (Y) N (circle one)

5. Does this infant qualify for the Preterm Hypothermia Trial based on the exam findings? (Y) N (circle one)

6. What is the Level of HIE? MILD/NORMAL MODERATE SEVERE (circle one)

Refresher Session for Certified Examiners

- Conducted at each center: once per year
- GS examiner: review the neurological exam, definitions, assessment of eligibility with each certified examiner either individually or as a group
- Current presentation should be used as a refresher for GS and certified examiners
- Refresher completion centrally tracked
  - GS examiners should review and update list of examiners at their center

Certification Process

- GS examiners
  - Conduct annual training of review of slides
  - Please review protocol with examiners as part of certification
  - Be aware many mild HIE infants are being cooled
  - When doing certifications
    - Code patient 1 or 2 being examined
    - Ensure that examiners understand the difference between category (6) and signs (9)
    - Fill out every section of exam form
    - Please use current version of the form

Acknowledgments

- Please acknowledge the use of NICHD Neonatal Research Network materials in all relevant applications, presentations, and publications

- Include a disclaimer that: “The contents of this report represent the views of the authors and do not represent the views of the U.S. Department of Health and Human Services, National Institutes of Health, or the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network.”