

# Hypoxic Ischemic encephalopathy

## HIE AND THE TREATMENT OF THERAPEUTIC HYPOTHERMIA

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# What is Hypoxic Ischemic Encephalopathy? (HIE)

- Acute or subacute perinatal asphyxia
- Evidenced by neurologic examination and laboratory data
- Decreased fetal cerebral blood flow and /or hypoxemia
- One of the primary causes of severe, long term neurological deficits
- Incidence in the USA 1-3 per 1000 births

# Definitions Relating to HIE

## Definition of terms

**Hypoxic-ischaemic Encephalopathy:** Lack of sufficient oxygen to the brain and a diminished amount of blood perfusing the brain. This results in suppression of electrical activity and cortical depression.

**Primary Neuronal Death:** immediate death if the insult is severe. This is related to cellular hypoxia leading to primary energy failure and cellular depolarisation.

**Secondary Neuronal Death:** after a latent period (6-100 hrs) neuronal death may be initiated by a cascade of pathologic processes and is associated with marked encephalopathy. This involves cytotoxic oedema, mitochondrial failure, accumulation of excitotoxins, active cell death, nitric oxide synthesis and cytotoxic actions of activated microglia. Seizure activity is increased during this phase

**Encephalopathy:** Brain disease, damage or malfunction. In general encephalopathy is manifested by an altered mental state that may be accompanied by physical manifestations e.g abnormal limb movements.

**Apoptosis:** Programmed cell death. Cells die in response to a variety of stimuli and during apoptosis they do so in a controlled, regulated manner. Apoptosis is a process in which cells play an active role in their own death and is often referred to as cell suicide.

**Medi-Therm III hyper/hypothermia system:** Provides a means for regulating patient temperature by supplying temperature controlled water via a blanket placed under the patient.

# What This Lecture Will Focus On

**Secondary Neuronal Death:** after a latent period (6-100 hrs) neuronal death may be initiated by a cascade of pathologic processes and is associated with marked encephalopathy. This involves cytotoxic oedema, mitochondrial failure, accumulation of excitotoxins, active cell death, nitric oxide synthesis and cytotoxic actions of activated microglia. Seizure activity is increased during this phase

and the treatment of Therapeutic Hypothermia for neonates



# Intrapartum Risks for HIE

- Fetal distress
  - Cord prolapse/placental compression
  - Acute hemorrhage: abruption, uterine rupture
  - Maternal fever
- Traumatic delivery
  - Shoulder dystocia
  - Tight nuchal cord
  - Breech delivery
  - Emergent C/section

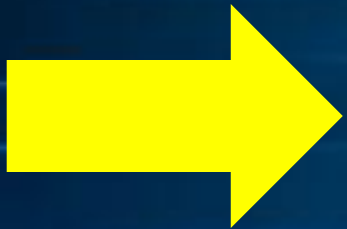


# Asphyxia and HIE

- Asphyxia is the result of reduced oxygen and compromised circulation in the fetus
- May occur before, during, or after labor
- Hypoxic ischemic encephalopathy (HIE) is the indirect consequence of systemic asphyxia

# Patho-Physiology of HIE Brain Injury

- 2 phases
  - primary and Secondary
- Primary
  - characterized by reductions in cerebral blood flow and oxygen substrates
- Secondary involves continuation of the excitotoxic –oxidation injury
  - cell death, inflammation, altered growth factors and protein synthesis



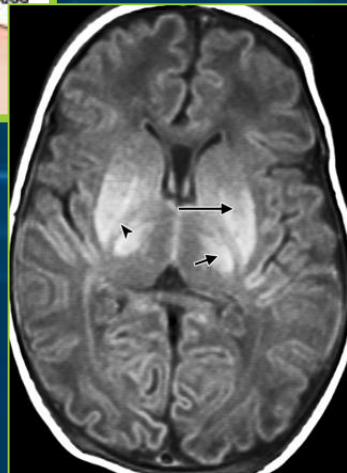
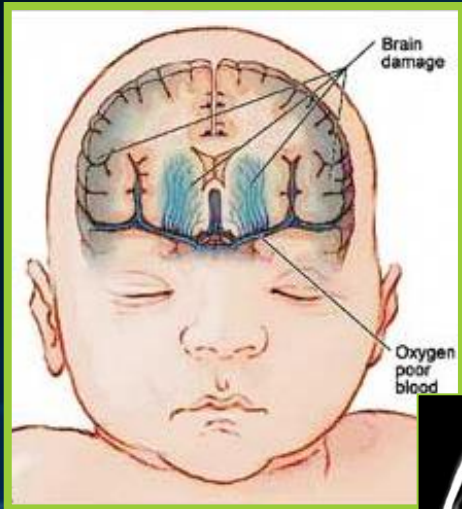
# What Happens to the Infant Brain with HIE

- Neonatal injury evolves over time
- First few hours
  - fluctuations in blood flow result in excitotoxicity, free radical generations and edema
- 6 hours to days
  - results in neuroinflammation,
  - mitochondrial permeabilization
  - loss of cerebral autoregulation



# Neurologic Impact of HIE

- Effects of moderate to severe HIE
  - seizure activity
  - cerebral palsy
  - varying degrees of developmental delays
  - increased risk of death
    - early and Late



# What is The Treatment of Therapeutic Hypothermia for HIE?

A neuroprotective intervention that can reduce the severity of secondary reperfusion brain injury associated with HIE, if induced hypothermia is begun during the latent phase.



# Why Therapeutic Hypothermia?

- HIE is estimated to be responsible for 23% of neonatal mortality worldwide
- Apart from supportive care, the only proven treatment for HIE is therapeutic hypothermia.
- Actively lowering body temperature has been shown to
  - reduce the extent of brain injury after an ischemic event
  - has a favorable effect on multiple biochemical pathways contributing to brain injury.

# Window of Opportunity

- The **latent period** represents a therapeutic “**window of opportunity**” between asphyxial event and secondary phase of impaired energy metabolism and injury.





# What's with the 6 hour window?

## Primary injury

- Loss of electrolyte homeostasis
- Sodium and calcium are retained in brain cells, wrecking havoc!
- sodium attracts water - the glial cells swell
- calcium triggers cell destruction

## Secondary injury

- Occurs 6 - 48 hours after the initial insult
- Cascade of destruction results in neuronal cell death by
  - apoptosis
  - necrosis



# How Does Cooling Work for HIE ?

- Decreases
  - Excitatory neurotransmitter release
  - Free radical production
  - Cerebral metabolic rate for glucose and oxygen
  - Toxic nitric oxide production
  - Apoptosis of neural cells
  - Inflammation

# Meta-analysis

Jacobs, et al. Cochrane Reviews 2013



- 11 Randomized Trials analyzed
- Combines n = 1505 FT and LPT neonates w/HIE (mod-severe) from birth asphyxia
- Benefits of therapeutic hypothermia still outweigh the short-term adverse effects and should be instituted before 6 hours of age.
- Improved survival and development at 18 to 24 months for term and late preterm infants at risk for brain damage from HIE

# What Do We Do In California?

- Whole body cooling or head cooling
- Standardized protocols with expert healthcare members
- Initiate cooling within 6 hours
- Temperature lowering to 33c-34c (plus or minus 0.5c)
- Maintain hypothermic temperature for 72 hours
- Neurological follow up for at least 18 months
- Data is entered into CPQCC website



# CPQCC-California Perinatal Quality Care Collaborative

- Data is the heart of the program
- Collect critical information on the care provided in over 90% of CA NICU

	A	B	C	D	E	F	G	H
1	Birth Year	Gestational Age (weeks)	Center Cases	Center Denom	Center Percent	CPQCC Network Cases	CPQCC Network Denom	CPQCC Network Percent
2	2010-2017	≤34 6/7	1	470	0.2%	59	26,896	0.2%
3	2010-2017	35 0/7 - 36 6/7	25	289	8.7%	436	15,024	2.9%
4	2010-2017	37 0/7 - 38 6/7	39	458	8.5%	954	20,847	4.6%
5	2010-2017	39 0/7 - 41 6/7	107	749	14.3%	2,104	32,015	6.6%
6	2010-2017	≥42 0/7	6	13	46.2%	41	357	11.5%
7	2010-2017	Total	178	1,979	9.0%	3,594	95,139	3.8%

# Some of The Data Points Captured in California

	Cases		PreTerm		Inborn		Seizures		Deaths	
	<b>239</b>		<b>31</b>	<b>15.1%</b>	<b>105</b>	<b>43.9%</b>	<b>59</b>	<b>24.7%</b>	<b>20</b>	<b>8.4%</b>
2009	<b>1</b>	0.4%	--		<b>0</b>	0.0%	<b>0</b>	0.0%	<b>0</b>	0.0%
2010	<b>16</b>	6.7%	--		<b>5</b>	4.8%	<b>6</b>	10.2%	<b>1</b>	5.0%
2011	<b>17</b>	7.1%	--		<b>5</b>	4.8%	<b>4</b>	6.8%	<b>2</b>	10.0%
2012	<b>19</b>	7.9%	<b>2</b>	6.5%	<b>9</b>	8.6%	<b>4</b>	6.8%	<b>3</b>	15.0%
2013	<b>16</b>	6.7%	<b>4</b>	12.9%	<b>4</b>	3.8%	<b>6</b>	10.2%	<b>2</b>	10.0%
2014	<b>14</b>	5.9%	<b>2</b>	6.5%	<b>7</b>	6.7%	<b>5</b>	8.5%	<b>1</b>	5.0%
2015	<b>28</b>	11.7%	<b>5</b>	16.1%	<b>16</b>	15.2%	<b>3</b>	5.1%	<b>5</b>	25.0%
2016	<b>31</b>	13.0%	<b>2</b>	6.5%	<b>14</b>	13.3%	<b>7</b>	11.9%	<b>0</b>	0.0%
2017	<b>49</b>	20.5%	<b>7</b>	22.6%	<b>24</b>	22.9%	<b>14</b>	23.7%	<b>2</b>	10.0%
2018	<b>46</b>	19.2%	<b>9</b>	29.0%	<b>20</b>	19.0%	<b>9</b>	15.3%	<b>4</b>	20.0%
<b>YTD</b>	<b>2</b>	0.8%	<b>0</b>	0.0%	<b>1</b>	1.0%	<b>1</b>	1.7%	<b>0</b>	0.0%

# Therapeutic Hypothermia Clinical Team Members

- Neonatologists
- Neurologists/EEG
- Educated clinical bedside RNs, RCPs
- Social Workers, OT, PT, Speech
- Palliative Care Team
- Diagnostic Imaging
- High Risk Infant Follow up



# What Can You Do To Impact The Lives Of California Infants





# Know Your Cooling Criteria and Centers

- Early intervention and identification
- Important 6 hour window-(prior to secondary reperfusion injury)
- Better outcomes for neonates identified with moderate to severe HIE



# Birth to Treatment and Beyond



- Perinatal event
- Stabilization
- Notify cooling center
- Infant meets criteria

Birth

- Within 6 hour window
- Transport to cooling center
  - Start cooling for 72 hours at 33.5c

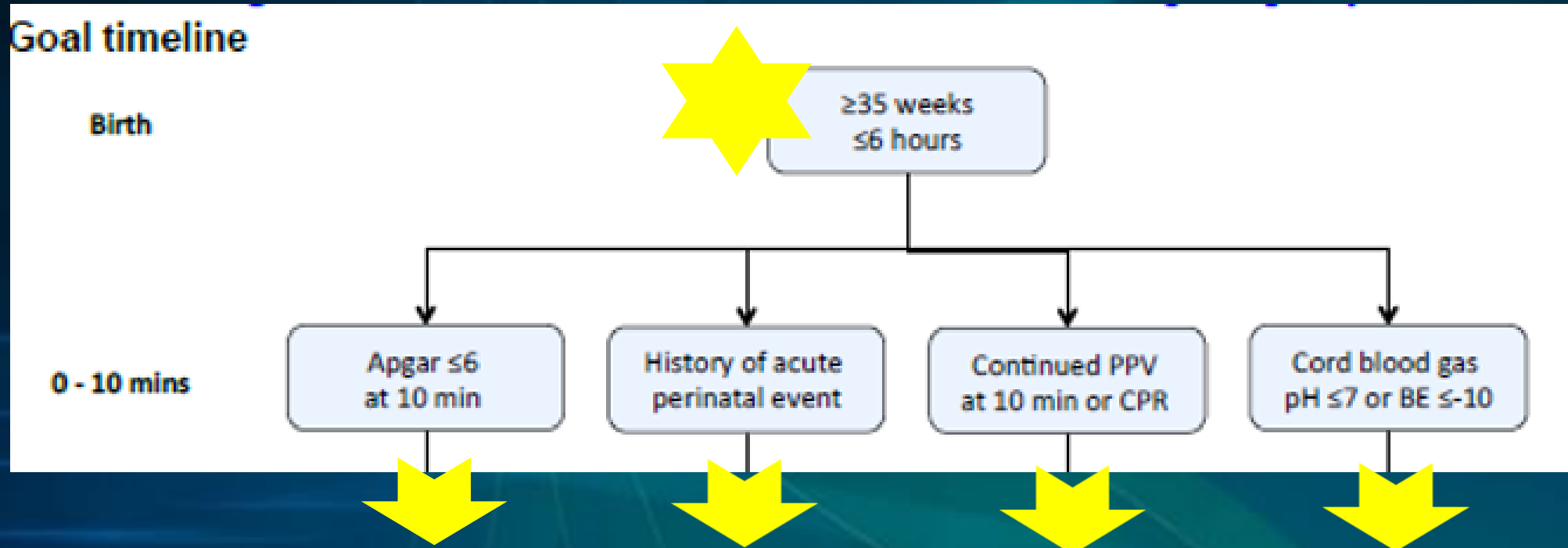
- Infant undergoes MRI
- High Risk Infant follow up
- Neurological follow up times 18 months at least.

Post 72 hours

# How Can You Help?

- Be aware of the **cooling criteria**
- resuscitation of a infant occurs
  - Is this infant a cooling candidate?
- ★ • Did we do **cord gases**?
- Is your facility a cooling center
- **Birth time** is forefront in your brain -**6 hours**
- Quickly include the **decision makers** ( Pediatricians/transfer centers...)
- **Speak up** if you feel the infant may meet criteria and benefit

# Screening Criteria for Cooling Candidate



# Do You Know Your Closest Cooling Center?

10 - 60 mins

- Request cord blood gas
- Obtain blood gas at  $\leq 1$  hour of age
- Perform targeted neurologic exam using chart below
- Observe for seizures



60 - 120 mins

Call cooling center at ( \_\_\_ ) \_\_\_ - \_\_\_  
to discuss the need for transfer and  
cooling



# Neurologic Exam for HIE Candidate

4. Clinically defined moderate or severe HIE (stage 2 or 3 based on modified Sanart Classification). The presence of moderate/severe HIE is defined as seizures OR presence of signs in at least three of the six categories below:

	Moderate encephalopathy	Severe encephalopathy
Level of consciousness	Lethargic	Stupor/coma
Spontaneous activity	Decreased activity	No activity
Posture	Distal flexion, full extension	Decerebrise
Tone	Hypotonia	Flaccid
Primitive reflexes	Weak suck, incomplete Moro	Absent suck, absent Moro
Autonomic system		
Pupil	Constricted	Dilated/non-reactive
Heart rate	Bradycardia	Variable heart rate
respirations	Periodic breathing	apnoea

cpqcc.org

Neonatal Therapeutic  
Hypothermia Toolkit  
All cooling centers in  
California are  
CPQCC members

Appendix J  
Screening for Hypothermia Therapy for Infants with HIE  
QJ Form

Birth Hospital: \_\_\_\_\_ Patient ID: \_\_\_\_\_

DOB/TOB: \_\_\_\_\_ GA \_\_\_\_\_ BW \_\_\_\_\_ Apgar@1 \_\_\_\_\_ Apgar@5 \_\_\_\_\_

Criteria for screening:  Apgar <6 at 10 minute  pH <7  BD >10  PPV at 10 minutes of life  CPR  use of epi/resuscitation drugs/blood?  Perinatal event (Abruptio, Fetal distress, Cord prolapse, Uterine rupture, maternal trauma)

Cord gas UA/unmarked: pH \_\_\_\_\_ pCO<sub>2</sub> \_\_\_\_\_ Base deficit \_\_\_\_\_

Cord gas UV/unmarked: pH \_\_\_\_\_ pCO<sub>2</sub> \_\_\_\_\_ Base deficit \_\_\_\_\_

1<sup>st</sup> Baby gas: date/time: \_\_\_\_\_ pH \_\_\_\_\_ pCO<sub>2</sub> \_\_\_\_\_ Base deficit \_\_\_\_\_

Heat sources removed: date/time: \_\_\_\_\_ Temp monitoring began: date/time: \_\_\_\_\_

Lowest temp: °C/F \_\_\_\_\_ rectal / axilla / skin (please circle one) date/time: \_\_\_\_\_

Highest temp: °C/F \_\_\_\_\_ rectal / axilla / skin (please circle one) date/time: \_\_\_\_\_

Time to reach temp 33-34°C: \_\_\_\_\_

Seizure:  Yes  No  suspected/unsure If yes, date/time: \_\_\_\_\_

Lowest Glucose value in the 1<sup>st</sup> 6 hours of life: \_\_\_\_\_ date/time: \_\_\_\_\_

Called cooling center?  Yes  No If yes, date/time: \_\_\_\_\_

Cooling center: \_\_\_\_\_

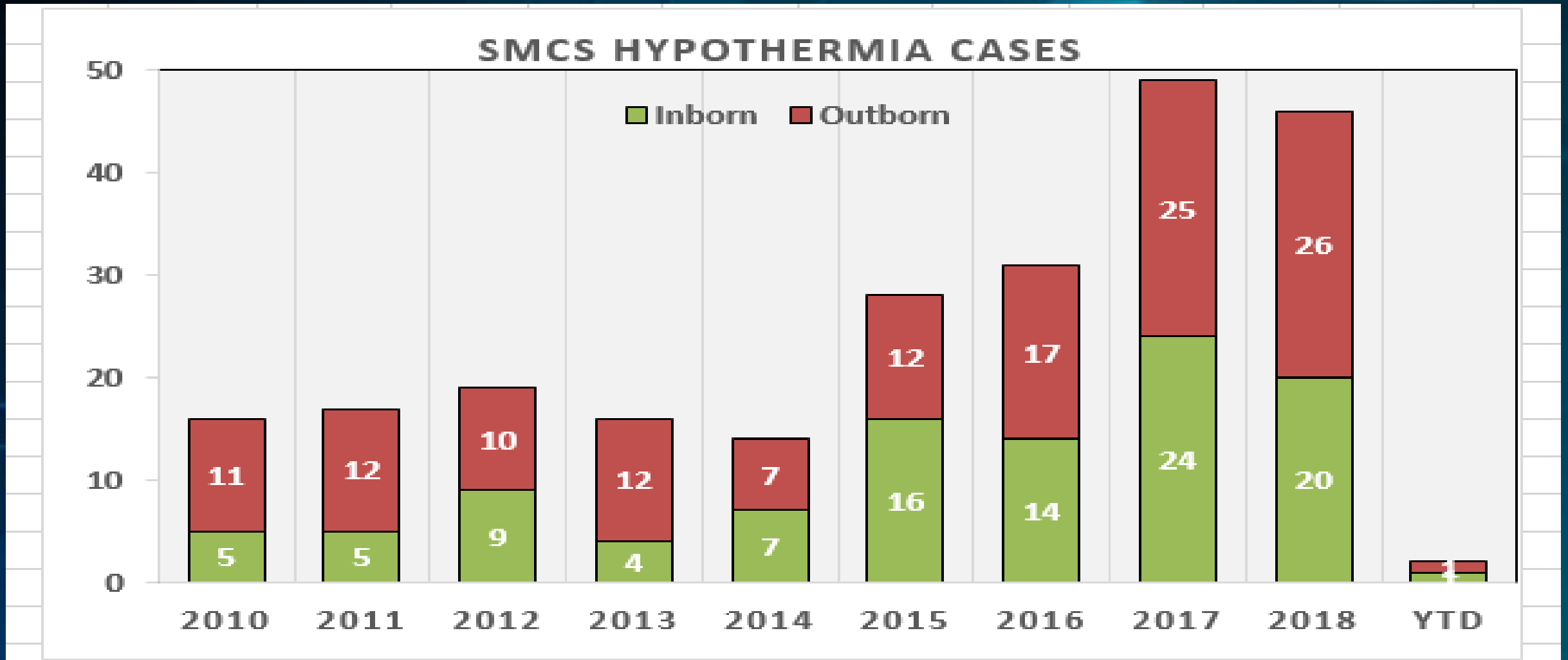
Advice given about cooling: observe / passive / active / intermediate (explain): \_\_\_\_\_

Transferred?  Yes  No If yes, date/time: \_\_\_\_\_

Cooled on transport? (explain)  Yes  No  intermediate

Cooled at the cooling center?  Yes  No If yes, date/time: \_\_\_\_\_

# Outborn vs Inborn at a Cooling Center



# Initiation of Cooling at the Birth Hospital



- cooling during transport are necessary given the limited therapeutic window,
- travel distances between the birth hospital and cooling center
- cases of late referral.
- the Tecotherm Neo (Inspiration Healthcare, Leicester, UK)
- Criticool (MTRE, Southampton, PA, USA),.



# Whole Body Cooling Systems

e.g., CSZ Blanketrol III®





# What do We Say to Parents? Cochrane Review 2013

- Damage from a lack of oxygen during birth can destroy cells in a newborn baby's brain.
- This damage continues for some time afterward.
- One way to try to stop this damage from continuing is to cool the baby for several days.
- Expect that cooling will decrease their baby's chance of dying,
- If their baby survives, cooling will decrease his/her chance of major disability.

# Family Care During Therapeutic Hypothermia

- Provide education
- Assist communication
- Encourage infant touching
- Speak in clear terms-factual
- Support



# Follow Up for HIE Infants

## MRI (Magnetic Resonance Imaging)

- The method of choice for investigation of neonatal anatomy
- Cortex and basal ganglia damaged during the initial hypoxic ischemic injury
  - is directly predictive of language and motor outcome in childhood

## MRS( Magnetic Resonance Spectroscopy)

- allows brain metabolism to be imaged in real time


# What is Not Evidence Based (yet?)

- The benefit initiated beyond 6 hours demonstrated,
  - randomized clinical trial in newborns presenting at 6 to 24 hours is currently underway (NCT0 0614744)
- Starting Therapeutic Hypothermia in the delivery room
- Therapeutic Hypothermia treatment for <35 weeks
- Stopping Therapeutic Hypothermia before 72 hours
- Restarting Therapeutic Hypothermia after seizures have started ( after 6 hours)



# What's New and Upcoming

- Erythropoietin treatment with cooling



High doses of Epo given with hypothermia resulted in less MRI brain injury and improved one-year motor outcomes following HIE.

High-Dose Erythropoietin and  
Hypothermia for Hypoxic-Ischemic  
Encephalopathy: A Phase II Trial



# Other Trials that are Ongoing

- Darbepoetin and cooling
- Xenon and cooling
- Human Cord Blood is being investigated
- Topiramate with cooling

# QUESTIONS

