Therapeutic Hypothermia

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Therapeutic Hypothermia
Declarations

• Curtis Dorn and Dawn Gosnell have no significant financial interests or other relationship with manufacturers of any of the products, processes or services that will be discussed.
• We will not present off-label use of any medication or medical device.

Therapeutic Hypothermia
Objectives

• Review the clinical findings and biochemical derangements in Hypoxic Ischemic Encephalopathy.
• Explain how therapeutic hypothermia blunts the secondary wave of damage after hypoxia/ischemia.
• Review the entry criteria and process of therapeutic hypothermia for infants and adults.
• Discuss complications and respiratory care issues related to therapeutic hypothermia.
Hypoxic-Ischemic Encephalopathy (HIE)

- HIE 3\textsuperscript{rd} leading cause of neonatal death (23\%).
  - Infection #1 (36\%), Preterm birth #2 (28\%).
- Brain insult from a lack of oxygen (hypoxia) and decreased blood flow (ischemia).
- Oxygen and glucose delivery is impaired, causing energy failure at the cellular level.

Etiology of Neonatal HIE

**Interruption of maternal-fetal exchange**
(asphyxia - impaired oxygen / carbon dioxide exchange)

- **Systemic (maternal):** cardiopulmonary arrest, eclampsia, hypovolemic shock, trauma.
- **Uterus:** Uterine rupture
- **Placenta:** Abruption
- **Cord:** compression, rupture, knot

Cellular Energy Failure

- Poor perfusion $\rightarrow$ rapid depletion of ATP (adenosine tri-phosphate), our cellular gasoline.
- **Krebs cycle:** Glucose + oxygen = 36 ATP
  - Glucose without $O_2$ = 2 ATP + lactic acid.
- **ATP** – needed: for synthesis, transport, ion pumps
  - Sodium (Na), calcium (Ca) constantly leak into the cell.
  - Potassium (K) constantly leaves out of cell
- Ion pumps use ATP to pump Na \& Ca out of cell, K into cell
  - No pump: Water follows Na into cell, cell swells and bursts.
- **No ATP** $\rightarrow$ cell death
Necrosis vs. Apoptosis

Two types of cell death:

- **Necrosis** (early cell death): Brief / severe insult, ATP-dependent Na+/K+ pumps fail, Na then H₂O influx, cell swelling, membrane fragmentation, inflammation.
- Neuron is destroyed. Post-event cooling **not** helpful.
- **Apoptosis** (delayed cell death): longer / milder insult, membrane depolarization, glutamate release, calcium influx, cell shrinks, no inflammation.
- Cascade of Apoptosis: **Starts 2-6hrs after event.** Window of opportunity for body cooling therapy.

Volpe Neurology of the Newborn

Apoptosis

  Our body makes too many cells, so pruning is needed.
- Programmed cell death – critical to life, but
  Too much apoptosis → Atrophy
  Not enough apoptosis → Cancer
- Multiple triggers of apoptosis: hormones, cytokines, medications, heat, radiation, hypoxia, hypoglycemia.
- **Trigger** stimulates production of Caspase by the targeted cell → leads to cascade of cellular shrinkage and digestion of organelles.
- Common event in cascade is too much intracellular calcium (\([Ca^{+2}]\)).

HIE – Power Failure at Cellular Level

- Intracellular calcium is critical intracellular second messenger.
- **Tiny** changes in intracellular calcium regulate cellular gene transduction, synthesis, transport and cell-to-cell signaling.
- Tiny changes in [Ca²⁺] are good.
- Triggers of Apoptosis cause **large influx** of calcium into the cell → with deadly effects.
**Effects of High Intracellular Calcium**

- Activates phospholipases (cell membrane injury)
- Activates proteases (disrupts cytoskeleton)
- Activates nucleases (nuclear injury)
- Disrupts ATP production (mitochondria)
- \(^\uparrow\) Excitatory neurotransmitter release (glutamate)
- Stimulates free radical production (membrane injury)
- All lead to cellular shrinkage and cellular death

→ **Clinical Effects**

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**Clinical Findings - 2 Stages**

**Early First Stage of HIE:**
- Stuporous - Stunned
- Periodic breathing
- Hypotonia, minimal movement
- Voltage suppression or seizures on EEG
  (electroencephalogram)
- After the First Stage, a brief recovery of cerebral metabolism and alertness may follow.

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**Clinical HIE - 2 Stages**

**Second Stage** Delayed (re-perfusion) stage:
- Starts 2-6 hrs after initial insult
- Worsens over next 24-48 hrs, then slow recovery
- Three levels of severity – Mild, Moderate, Severe
  (Sarnat’s Stages of Encephalopathy)
HIE – Clinical Findings

Mild HIE
- Mild hypertonia (increased tone).
- Brisk deep tendon reflexes.
- Sleepy, irritable, high-pitched cry.
- Poor feeding, sloppy, disorganized.
- CNS exam normal by day 3-4

Zanelli e-Medicine

HIE – Clinical Findings

Moderate HIE
- Marked hypotonia and Lethargy
- Pausing or mild apnea
- May have onset of seizures in 1st 24 hrs.
- Full recovery within 1-2 weeks possible
- Quicker recovery → better long-term outcome.

Zanelli e-Medicine

HIE – Clinical Findings

Severe HIE
- Minimal / no response to stimulus
- No gag reflex
- Pupils fixed/dilated
- Stuporous or comatose / floppy
- Irregular breathing / apnea → ventilator support
- Early seizures but often EEG goes flat

Zanelli e-Medicine
HIE – Clinical Findings

Severe HIE – Other organs
• Renal failure: oliguria → high output ATN (acute tubular necrosis)
• Gut: ileus, poor gastric emptying, diarrhea
• Stunned heart: Poor contractility, hypotension
• Pulmonary hypertension

HIE – Clinical Findings

Survivors of Severe HIE
• Level of alertness improves by day 4-5
• Spontaneous respiration by day 4-5
• Hypotonia / feeding difficulties persist
• Gastrostomy +/- fundoplication often needed

Outcome of HIE

Severe HIE: 50-75% mortality by 1 month. 80% survivors significant mental retardation, cerebral palsy, seizures.

Moderate HIE:
30-50% significant long term problems,
10-20% minor neurologic abnormalities.

Mild HIE:
Most escape long-term complications
HIE – Medical Care

Cardiovascular: Maintain normal BP
Fluids: Avoid hypoglycemia and hyperglycemia
Treat seizures: prevent additional damage
Ventilation: Keep carbon dioxide level normal (40-50)
Avoid Hyperoxia: 100% Oxygen toxic (goal 85-95% sat.)
In past, no effective treatment. Now →
Treatment: Therapeutic Hypothermia

HIE – Therapeutic Hypothermia

Mechanisms:
• Reduces metabolic rate (7-8% lower / 1°C)
• Reduces ion flux (calcium, sodium)
• Decreases excitatory transmitter release
• Reduces vascular permeability and edema
• Reduces apoptosis

Therapeutic Hypothermia for Infants

Types: Whole body (cooling blanket) vs. Selective head cooling (cool cap)
Timing: Within hour of injury ideal (up to 6hrs)
Maintain cooling for 72 hrs.
Re-warm over 6 – 8 hours
Head Cooling

Coolcap RCT 2005
- 234 infants, mod-sev HIE
- 72hrs of head cooling (rectal 34-35°C).

No difference in overall outcome.
(core of brain not adequately cooled?)
Subgroup analysis: Those with less severe aEEG had better neurologic outcome with head cooling.

Gluckman Lancet 2005

Whole Body Cooling

Trial 2005
208 babies, mod-sev. HIE
Whole body cooling 72hrs. (rectal temperature 33.5°C)
Decreased death or moderate-severe disability
44% - hypothermia group vs. 62% - control (RR: 0.72; 95% confidence interval 0.54-0.95; p<0.01)
Short-term side-effects decreased enthusiasm. (bleeding, acidosis, PHTN)

Shankaran NEJM 2005

Whole Body Cooling for HIE

Whole Body Cooling: Follow-up Study 18-22 months
No adverse effects of hypothermia at 20 months
Rehospitalization: 27% hypothermia / 42% control
Death: 24 hypothermia / 38 control
Severe disabilities: 19 hypothermia / 25 control

Body Cooling: Declared “Standard of Care”

Shankaran S: Pediatrics 2008
Wesley Medical Center
NICU Body Cooling Program

Started July 2009

- 1 - 2 infants per month
- 2 coolings stopped for bleeding, acidosis.
- Developmental Clinic: Much better than expected outcome - moderate-severe HIE.
- Not much improvement in Severe HIE
  (initial insult was devastating, cooling only helps decrease secondary/reperfusion injury)

HIE: Neuro-resuscitation

Ongoing intervention trials:

- **Allopurinol**: free radical scavenger
- **Xenon**: NMDA antagonist, less apoptosis
- **Erythropoietin**: ↑ vasculogenesis / neurogenesis,
  ↓ inflammation, ↓ oxidant damage ↓ apoptosis
- **Stem Cell Infusion** (umbilical cord blood)
  migrate to damage area → helps repair.
Suspect you have candidate for therapeutic hypothermia for HIE?

- Turn off warmer (goal 34-35°C for transport)
- Finish resuscitating and stabilizing infant
- Keep O2 saturations less than 95%
- Obtain cord gas or neonatal blood gas
- Call neonotologist to see if infant meets entry criteria, and arrange transfer or transport.

Body Cooling - Process

- Place UAC or UVC
- Cooling blanket – esophageal temp = 33.5 °C
- Cool for 72 hours
- Use morphine/nembutal – pain / sedation
- Increase temp by 0.5 C for complications: arrhythmias / acidosis / bleeding / pulm. HPTN
- Rewarm over 6 hours.
- Reset blood gas machine for infant’s temp.
Effect of Temperature: pH PCO₂ PO₂

- Decreased CO₂ production with cooling (low metabolic rate) and more CO₂ dissolved in cool blood (increased solubility).
- Partial pressure of a gas decreases as temperature decreases. (helium balloon → cold outside)
- So PO₂ and PCO₂ decrease with hypothermia (say 33° C) and as PCO₂ decreases, pH increases.
- BUT measurement chamber in BG machine heated to 37° C.
- As sample drawn at a body temp of 33° C warms to 37° C, PO₂ & PCO₂ will increase and pH will drop.
- So the PaO₂ and PCO₂ will appear higher and the pH lower than it really is in the hypothermic patient.
- Does it matter? Two blood gas strategies.

Bacher Intensive Care Med 2005

Effect of Temperature: pH PCO₂ PO₂

Patient 33° C true BG = pH 7.47 PCO₂ 32 PO₂ 92
BG machine 37° C = pH 7.40 PCO₂ 40 PO₂ 117

- **Alpha-stat method:** No correction for patient’s temperature. Argument: Intracellular pH doesn’t change much during cooling due to protein buffering.
- Some adult literature: better neuro outcome w/ α-stat, (probably due to inadvertent decrease in cerebral blood flow)
- Many centers doing adult and pediatric cardiac surgery use the α-stat method/strategy.

Groenedaal Pediatrics 2009

Effect of Temperature: pH PCO₂ PO₂

BG machine 37° C = pH 7.40 PCO₂ 40 PO₂ 117
Patient 33° C true BG = pH 7.47 PCO₂ 32 PO₂ 92

- **pH-stat method:** Correction for patient’s temperature. Reason: low PCO₂ decreases cerebral perfusion. If BG not corrected, you really don’t know what PCO₂ is.
- Low PCO₂ in infants asso./with PVL and deafness.
- Low PCO₂ infants after asphyxia → adverse outcome
- Improved cerebral recovery after hypothermic arrest in piglets using pH-stat method.
- NICHD neonatal cooling trials done w/ pH-stat method

Effect of Temperature: O2 saturation

- Oxy-hemoglobin Dissociation Curve shifted to the left with low temperature, low PCO2 and high pH
- At any pO2, saturation will be higher, especially when PO2 in the 30-50 range, BUT
- Leftward shift means Hb binds O2 more tightly and releases less O2 to the tissues. Additionally,
- Metabolism / O2 consumption decrease w/ cooling.
- Combined effect: low temperature on oxyhemoglobin and decreased O2 consumption (VO2) will lead to a large increase in mixed venous O2 saturation.

Bacher Intensive Care Med 2005
Therapeutic Hypothermia for PICU Patients

• No fully developed guidelines for pediatric patients. Still being studied. Most PICUs have developed protocols adapted from neonatal or adult protocols.

• Most protocols target patients with non-traumatic cardiac arrest with ROSC who remain comatose (GCS < 8), no response to pain, are intubated and mechanically ventilated.

• They exclude patients with active bleeding, coagulopathy, intracranial hemorrhage, sickle cell patients, cardiovascular instability from cardiac dysrhythmias or refractory hypotension, sepsis, MODS as a cause for the cardiac arrest.

Therapeutic Hypothermia for PICU Patients

• Target core temperature of 33°C (+/- 1°C) x 48 hours, instituted within 6 hours of ROSC, then gradual return to 36-37.5°C with avoidance of hyperthermia.

• Main issues: coagulopathy, hyperglycemia, arrhythmia, skin breakdown, hyperkalemia (upon rewarming).

• Neuromuscular blockade with sedation/analgesia for shivering.

• Typical respiratory issues include atelectasis, secretion clearance, and risk for VAP.

→ Therapeutic Hypothermia in adults

Dawn Gosnell, ARNP

HIE – Etiology in Adults

- Cardiac Arrest
  Coronary artery disease, cardiomyopathy, Long QT syndrome
  Respiratory failure – exacerbation, pneumonia
  - 265,100 out of hospital each year in the U.S.
  - 50% resuscitated
  - 14.6% survive

- Drownings
- Hangings
- Overdose
Post-cardiac arrest care
- Induced hypothermia generally recommended for adult survivors regardless of presenting rhythm.
  - Initiate as soon as possible after return of spontaneous circulation (ROSC) to a target temperature of 32°-34°C.
  - Ventricular Fib or Pulseless Ventricular Tach (Class I)
  - Pulseless Electrical Activity and Asystole (Class IIB)
- Urgent cardiac catheterization and percutaneous coronary intervention are recommended for ST Elevation MI patients.
  - There is support for other acute coronary syndrome patients.

Via Christi Exclusion Criteria
- Pulseless > 60 minutes
- > 12 hours since ROSC
- Uncontrolled GI bleeding, active bleeding, coagulopathy or bleeding diathesis
- Known terminal illness or pre-arrest impaired cognitive status
  - Unable to perform ADL independently, poor functional status
- Conflict with Advanced Directives or DNR status
- Follows commands
- Sepsis or multisystem organ failure as suspected cause of cardiac arrest
- Other reason for coma – intracranial pathology (intracranial hemorrhage, ischemic stroke, subarachnoid hemorrhage, sedation)
- Significant trauma, intra-abdominal such as splenic or liver laceration

Meaningful Neurological Response

<table>
<thead>
<tr>
<th>Eye Opening</th>
<th>Verbal</th>
<th>Motor</th>
<th>Brainstem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>Oriented</td>
<td>Obey</td>
<td>Pupils React</td>
</tr>
<tr>
<td>Deterior</td>
<td>Confused</td>
<td>Locomotor</td>
<td>Coma</td>
</tr>
<tr>
<td>Faint</td>
<td>Inappropriate</td>
<td>Withdraws (to pain)</td>
<td>Spontaneous Respiration</td>
</tr>
<tr>
<td>None</td>
<td>Insensible</td>
<td>Decorticate</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>Decelerate</td>
<td>Doll’s Eyes</td>
</tr>
<tr>
<td>Intubated</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Orange shaded areas are considered purposeful and if purposeful, the patient is NOT ELIGIBLE for therapeutic hypothermia.
Surface Cooling System

- There are many on the market, varying in price.
- Via Christi is utilizing the Gaymar wraps and blankets.

Intravascular Cooling System

- Via Christi is utilizing ICY Cath with the Alsius CoolGard
- Triple lumen CVC with two teal colored ports that attach to the Alsius tubing.

Cooling Process

- 2 liters of refrigerated (2-80°C) saline @ 500 mL/hr
- Ice packs around head, neck, axillary areas and groin for 20-25 minutes.
- Initiate cooling system
  - Set target to of 33°C (91.4°F)
  - Rapid cooling
- Keep at 33-34°C for 24 hours.
- No heated humidification on ventilator system
**Neurological Response**

- Decreased cerebral metabolic rate
  - 5-10% for every 1°C
- Reduced oxygen consumption in the ischemic brain
- Decreased intracranial pressure
- Decreased cerebral edema by maintaining integrity of the blood brain barrier
- Can decrease the frequency and amplitude of EEG studies

**Shivering**

- Assess
  - Overt shivering
  - Feel for “humming” of jaw
  - Look for an isolated muscle twitch
- Treatment
  - Neuromuscular blockade – Vecuronium
  - Dilaudid (hydromorphone)

**Cardiovascular Response**

- Decreased heart rate, contractility and cardiac output, increased systemic vascular resistance
  - 7% decrease in cardiac output for every 1°C decrease
- Hypotension
- ECG changes
  - Prolonged PR Interval, Widened QRS, Prolonged QT Interval, ST elevation or depression, T Wave inversion
- Delayed depolarization in pacemaker tissue
  - Bradycardia
  - Infants 80-90, Adults 40-50
  - Atropine is ineffective.
  - Treat with dopamine or Isuprel
**Cardiovascular Response**

- Decreased trans-membrane resting potential, fibrillation threshold, increased adrenergic stimulation secondary to catecholamine release
  - Increase in atrial fibrillation and ventricular fibrillation.
    - Amiodarone is less effective. Treat with Lidocaine.
  - For refractory or reoccurring arrhythmias or coding, must discontinue active cooling and begin re-warming.

**J Wave or Osborn Wave**

- Secondary to delayed K+ transport
- As J wave increases, the T wave may flatten
- Reversible, but can persist for 12-24 hours after core temperature is restored.

**Pulmonary Response**

- Blood gas values
  - pH increases 0.016 points for every 1°C decrease
  - PCO2 decreased due to increased dissolved CO2 and decreased CO2 production
  - Spontaneously breathing patients have decreased minute ventilation
- Temperature adjustment
  - Respiratory alkalosis at actual patient temperature
  - Uncorrected would show a lower pH and increased CO2
**Pulmonary Response**

- Decreased oxygen consumption
  - Shift to the left
    - O2 hangs onto the Hgb with less delivered to the tissues
- Increased pulmonary vascular resistance
- Bronchospasms
- Paralysis of mucociliary mechanism
  - Increased airway secretions
  - Impaired ciliary function
  - Increased risk for aspiration and pneumonia
  - Aggressive pulmonary therapy

**Renal Response**

- Impaired renal tubular transport and tubular dysfunction
- Cold diuresis
  - Decreased sodium and water reabsorption
  - Significantly reduced levels of potassium, magnesium, calcium and phosphorus
  - Decreased antidiuretic hormone response
- Fluid shift into the interstitial spaces
- Shift in potassium intracellularly when cooled, shift out when re-warmed

**Hematologic & Immunologic Response**

- Increased blood viscosity
  - Hct increase 2% for every 1°C decrease
- Delayed activation of the fibrinolytic system
  - Increased thrombus formation
- Leukocyte sequestration in the spleen
  - Increased bleeding risk
    - Delay in the clotting cascade
    - INR and PTT are prolonged
    - Platelet number and function decreases
- Decreased neutrophil function
  - Increased risk of infection
**Gastrointestinal & Metabolic Response**
- Impaired bowel function
  - Hypomotility
  - Stress ulceration
- Decreased hepatic metabolism
  - Increase liver enzymes
- Hyperglycemia
  - Decreased insulin secretion
  - Decreased insulin sensitivity
- Pancreatitis has been reported.

**Hypothermia & Medication Effect**

We don’t really know on most medications.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>No augmentation of platelet inhibition</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Plasma concentrations increased by 25%</td>
</tr>
<tr>
<td>GP IIb-IIIa Inhibitors</td>
<td>Augments eptifibatide (Integrisin) and tirofiban (Aggrastat) platelet inhibition</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Decreased metabolism by 60%, increased infusion rates</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>AUC (Area under the concentration time curve) increased 180%, elimination rate constant decreased 50%</td>
</tr>
<tr>
<td>Propofol</td>
<td>Decreased clearance, increased serum level by 25%</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>Decreased clearance by 11% per °C, doubled the duration of action</td>
</tr>
</tbody>
</table>

(Aspin & Green, 2008)

**Re-warming Process**
- Re-warm at 0.3°C per hour to a target of 36°C.
  - Slow over 12 hours
  - Thermoregulatory mechanisms will want to rebound or overcompensate.
  - Keep less than 37°C for 24 hours
Complications during Re-warming

- Seizures
- Ventricular fibrillation
- Hypovolemia
- Hypotension
  - Re-warming shock occurs when hypothermic vasoconstriction masks hypovolemia.
- Acidosis
- Hyperkalemia

Cerebral Performance Categories Scale

<table>
<thead>
<tr>
<th>CPC</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.</td>
</tr>
<tr>
<td>2</td>
<td>Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.</td>
</tr>
<tr>
<td>3</td>
<td>Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.</td>
</tr>
<tr>
<td>4</td>
<td>Coma or vegetative state; any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.</td>
</tr>
<tr>
<td>5</td>
<td>Brain death: apnea, areflexia, EEG silence, etc.</td>
</tr>
</tbody>
</table>

Safar (1981)

Via Christi Statistics

- N= 65 since June 2010
- Twice as many men than women (2:1)
- Average age of 63 years
- More external than internal cooling (1.7:1)
- Survival
  - Asystole 29%
  - PEA 63%
  - V Fib 61%
  - V Tach 100%
- CPC Scores of 1 or 2 that go HOME 59%, Rehab/SNU 13%
Mia’s Story

Maternal uterine rupture
Baby Mia had no heartbeat for 20 minutes
72 hours body cooling

Surprisingly good outcome
One year birthday follow-up

Bibliography - Neonatal Cooling

Bacher, A: Effects body temperature on blood gases. Int.CareMed 2005;31:24
Gluckman PD: Selective head cooling after HIE. Lancet 2005;365:665-70
Jacobs, S: Cooling for NB with HIE. Cochrane Review 2007
Robertson, N: Neuroprotective agents bedside ready? J.Peds 2011;169:544
Simhauner, G: Systemic Hypothermia. neonEURO.RCT Ped 2010;126:e771

Bibliography – Adult Cooling