Real Cases from the NICU

Pediatric Grand Rounds
August 29th, 2014
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Objectives

At the end of the session, the participant will be able to…
1. Recognize a patient who would be a candidate for therapeutic hypothermia.
2. Discuss steps taken to minimize heat and fluid loss in an extremely preterm infant.
3. Delineate the approach to a patient in whom necrotizing enterocolitis is suspected.

OB calls…
• 35 y/o G5P4004 arrives in active labor, 41 0/7 weeks gestation. ROM at home, mother in active labor. Meconium present. FHR 140’s initially, then fetal bradycardia to 60’s.
• You are called to stat c-section.
• Team arrives and sets up for resuscitation.

Latest guidelines for neonatal resuscitation:

Summary:

• How is meconium handled in the delivery room???
• How much oxygen should be used for resuscitation of a term infant?
• How is meconium handled in the delivery room???
  - Is the patient vigorous?? (Vigorous is defined as HR>100, strong respiratory effort, good muscle tone).
    If not, intubate and suction with a meconium aspirator.
• How much oxygen should be used for resuscitation of a term infant?
  - Room air; adverse outcomes may result from even brief exposure to excessive oxygen during and following resuscitation. Hypoxia is not good either- more to follow on monitoring.

• Medical student catches the baby from OB.
• Infant covered with thick meconium. Infant is limp, cyanotic. Initial HR undetectable.
• You intubate with meconium aspirator and get meconium from below the cords. Repeat and get further meconium on suctioning.
• Intubate PPV. No heart sounds. Chest compressions. Epinephrine given via ETT, get ready for line. Good response. Pulse ox did not initially pick up, after epi, HR inc gradually to 180. O2 sat 90% at 6 minutes of life. APGARs 0, 3, 5.

• How do you use the pulse ox in the delivery room?
  - Where should the pulse ox be placed on the infant?
• What are your expectations?

Targeted Pre-Ductal SPO2 After Birth

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>SPO2</th>
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<tbody>
<tr>
<td>1</td>
<td>60-65%</td>
</tr>
<tr>
<td>2</td>
<td>65-70%</td>
</tr>
<tr>
<td>3</td>
<td>70-75%</td>
</tr>
<tr>
<td>4</td>
<td>75-80%</td>
</tr>
<tr>
<td>5</td>
<td>80-85%</td>
</tr>
<tr>
<td>10</td>
<td>85-95%</td>
</tr>
</tbody>
</table>

Resuscitate with room air if >32 weeks. Below use 30-60% O2, guide with pulse ox.

Our Patient

• Birthweight 3588g (50-75%), length 53.5 cm (95%), FOC 35 cm (50%).
• Cord gas: Not obtained
• Admission ABG 6.95/29/191/bicarb 6.4/BE -.25
• Gluc 191, iCal 1.43, hct 64 (spun).
• On admission: Limp, no reflexes noted, pupils did sluggishly react.
• Vent 21/5, R 30 FiO2 0.7.
Infant remains limp, little movement noted in arms. No dysmorphic features. Infant appears grossly normal. Pupils minimally reactive.

What do you do now?
What do you need to think about???

Therapeutic Hypothermia for Hypoxic Ischemic Encephalopathy

- Hypoxic-Ischemic Encephalopathy (HIE) cerebral dysfunction due to significant perinatal asphyxia.
- Essential Criteria: metabolic acidosis with a cord pH <7 or a base deficit at least 12 mmol/L, early onset of encephalopathy, multisystem organ dysfunction, exclusion of other causes. (AAP and ACOG 2013)

Pathophysiology – 2 phases

- Secondary energy failure
  - Presence and severity depends on extent of primary energy failure
  - Latent phase (therapeutic window)
  - Multiple pathophysiologic processes
    - Activation of microglia: inflammatory response
    - Activation of caspase proteins: trigger apoptosis
    - Reduction in growth factors, protein synthesis
    - Accumulation of excitatory neurotransmitters

Pathophysiology – 2 phases

- Primary energy failure
  - Reductions in cerebral blood flow and O₂/substrates leading to decrease ATP, phosphocreatine
  - Tissue acidosis
  - Acute intracellular derangements
    - Loss of ionic membrane homeostasis
    - Increased release & blocked reuptake of excitatory neurotransmitters, defective osmoregulation, inhibition of protein synthesis
    - Increase intracellular Ca triggering destructive pathways by activating lipases, protease, and endonucleases

Therapies

- Supportive intensive care
  - Correction of hemodynamic and pulmonary disturbances
  - Hypotension
  - Metabolic acidosis
  - Hypoventilation (do not want to hyperventilate)
  - Correction of metabolic disturbances
    - Glucose, Ca, Mg, electrolytes
  - Treatment of seizures
  - Monitoring for other end organ dysfunction

Photo from Dr. Alice Gong

Mechanism of Action of Hypothermia

- Reduces cerebral metabolism, prevents edema
- Decreases energy utilization
- Reduces/suppresses cytotoxic amino acid accumulation and nitric oxide
- Inhibits platelet-activating factor, inflammatory cascade
- Suppresses free radical activity
- Attenuates secondary energy failure
- Inhibits apoptosis (cell death)
- Reduces extent of energy


Adverse effects

- Increased blood viscosity
- Metabolic acidosis
- Decreased O2 availability
- Intracellular shift of K
- Cardiac arrhythmias
- Coagulation abnormalities
- Platelet dysfunction
- Chorea syndrome
- Exacerbation of Pulmonary Hypertension

Cochrane Updated Review 2013

- Increased to 11 randomized trials. N=1505 infants.
- Therapeutic hypothermia is beneficial in term and late preterm newborns with hypoxic ischaemic encephalopathy.
  - Cooling reduces mortality w/out inc in major disability in survivors.
  - The benefits of cooling on survival and neurodevelopment outweigh the short-term adverse effects.
  - Hypothermia should be instituted in term and late preterm infants with moderate-to-severe hypoxic ischaemic encephalopathy if identified before six hours of age.
  - Further trials to determine the appropriate techniques of cooling, including refinement of patient selection, duration of cooling and method of providing therapeutic hypothermia, will refine our understanding of this intervention.

Our Cooling Protocol

Inclusion Criteria (based on NICHD)

- Gestational age ≥ 36 weeks (some newer studies 35 wks)
- Postnatal age ≤ 6h
- Acidosis on cord gas or ABG w/in 1st hr of life
  - pH of 7.0 or a BE of -16 or greater OR
  - pH of 7.01-7.15 or a BE of -10 to -15.9 OR no blood gas
  - WITH an acute perinatal event AND 10 minute APGAR of 5 or less or assisted ventilation initiated at birth and cont for at least 10 minute
- ALSO presence of seizures or other evidence of moderate to severe encephalopathy based on Sarnat staging.
- Exclusion: inability to enroll w/in 6h, major chromosomal or congenital anomaly or severe IUGR (<1800g)

Modified Sarnat Staging

**Our Cooling Protocol**

- Once infant determined to be eligible:
  - Radiant warmer is turned off
  - Esophageal probe via nose after OG tube is placed (if too big, may place orally)
  - Placed on cooling blanket and core temp reduced to 33.5°C and maintained for 72h
- After 72h the set point of the cooling blanket is increased by 0.5°C per hour over a 6 hour period to 36.5°C
  - Temperature control is then returned to a radiant warmer and maintained via servocontrol with a temp probe placed on infant abdomen.

**Process - orders**

- VS per NICU protocol – q 15 min X 4, then q 1 h with hands on q 3 h
- NPO throughout cooling
- Need Venous and arterial access
- IVFs (TPN asap)
- Labs on admission
  - ABG, Lactate acid, Ammonia level
  - CBC with manual diff, Blood cx
  - Coagulation panel
  - UA and culture
  - Chem with magnesium, phosphorus and calcium, LFTs
  - Cardiac panel, CPK

**Our baby**

- Coagulation studies mildly out, but oozing early on so given FFP 10 ml/kg x2. Thrombocytopenia, received platelets transfusion x2.
- Required fluid resuscitation: normal saline bolus x 2.
- Given NaHCO3 x1.
- Lactate elevated, resolved within 24h
- Cardiac enzymes elevated, decreased over next weeks.
- LFTs were elevated, better by 1 wk of life.
- Renal: had oliguria first 48h, serum Cr not elevated, some blood on urinalysis. Likely mild acute tubular necrosis from hypoxia.

**Process - orders**

- Routine labs
  - At least Q 6 hrs ABG
  - Q 12 hrs Coags, CBC, BMP with Mg, Phos, Ca, ammonia level, lactate acid
  - Q 24 hrs T/D Bili
  - Q 48 hrs Cardiac panel (CK, CK-MB, Troponin T) LFT’s, CPK
  - HUS on admission, EEG-video
  - Sedation orders
  - Rewarm after 72 hrs, takes ~ 6 hours inc temp set point by 0.5°C q 1 hr using auto control mode until esophageal temperature reaches 36.5°C.

**Our baby cont**

- Neuro: Never had seizures, EEG’s x 24 h x 2 because had tremors, tremors improved on own. MRI bilateral frontoparietal echogenicity in deep white matter c/w HIE.
- Home at 27 d/o. Neuro exam normal per chart. Passed hearing screen.
- Has lg VSD and sm ASD- on furosemide 1 mg/kg bid and NaCl supplement.
- 27cal formula in order to gain wt.

**Selected References**

**Hypothermia for HIE**

Something a *little* different…

- You receive a call from OB…
- A 26 y/o woman is G4P1021 is in triage at 24 0/7 weeks. She has experienced some spotting and cramping. Found to be 4 cm dilated. Estimated Fetal Weight 696g, male infant.
- Mother is started on betamethasone.
- Parents have questions about survival and long term outcomes at this gestational age.
- How will you answer???

<table>
<thead>
<tr>
<th>Gestational Age (completed weeks)</th>
<th>Inborn UH (n)</th>
<th>2011 Inborn Network mean (first quartile; third quartile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>0% (5)</td>
<td>6.3% (0; 6)</td>
</tr>
<tr>
<td>23</td>
<td>30% (10)</td>
<td>32.5% (0; 50)</td>
</tr>
<tr>
<td>24</td>
<td>85.7% (14)</td>
<td>60.4% (23.3; 95.7)</td>
</tr>
<tr>
<td>25</td>
<td>93.3% (15)</td>
<td>76.2% (60; 100)</td>
</tr>
<tr>
<td>26</td>
<td>78.8% (14)</td>
<td>84.6% (75.0; 100)</td>
</tr>
<tr>
<td>27</td>
<td>81.8% (22)</td>
<td>89.6% (83.3; 100)</td>
</tr>
<tr>
<td>28</td>
<td>83.3% (30)</td>
<td>92.8% (86; 100)</td>
</tr>
</tbody>
</table>

National data vs local data.

http://www.nichd.nih.gov/about/org/der/branches/ppb/programs/epbo/Pages/epbo_case.aspx or Google: nichd calculator.
### Case cont

- Mother stopped having contractions after 24h, moved to the floor. Had more vaginal bleeding next night...
- Betamethasone treatment complete (2nd dose >24h prior to delivery).
- Labor progressed. Family counseled.
- Rupture of membranes 20 min prior to delivery. SVD at 0505 AM.
- Preparations????

### Single Course of Antenatal Steroids

- Decreased risk of neonatal death by 31%
- RDS reduced by 34%
- IVH by 46%
- NEC by 54%
- Infection in 48h by 44%
- Developmental Delay risk dec by 51%
- Trend towards decreased CP.

### Cold stress is a big problem for the extreme premie

- What are the proven ways to decrease cold stress?

### Thermal Control

- VLBW infants <1500g at higher risk for hypothermia.
- Pre-warmed delivery room to 26°C.
- Covering baby in plastic wrap, food grade.
- Placing the baby on exothermic mattress.
- Placing under radiant warmer.
- Slight chance for overheating. Larger babies, well infants Ok with pre-warmed blankets, skin-to-skin with mother. Drying.

### Preparations for delivery

- Neonatal resuscitation is a team sport. RT and nursing alerted to prepare.
- RT: warm surfactant. Prepare ETT. 2 equivalent surfactant products at our institution Survanta (4 ml/kg), Infasurf (3 ml/kg, more surfactant associated proteins). Set up vent.
- Nurse: prepare bed in NICU, giraffe omnibed. Double check exothermic mattress, polyethylene bag and hat.
- Physician: Communicate with family and team. Be ready to resuscitate; think ahead about orders.

### Infant is born

- The infant is born, HR 120, gives a brief cry- then does not breathe.
- Infant brought to preheated warmer and immediately placed on top of an exothermic mattress into a polyethylene bag, 2 hats placed on head. Connected to a pre-ductal pulse ox. HR 120, O2 sat 60%. Not breathing.
- Few breaths, BVM 30% O2, intubated, ETT position verified, and given 3 ml Survanta. APGARs 5/5/7
• Infant placed in transporter. Shown to family.
• Elevator: who goes?
• At the NICU, what to do?
• Vent settings?
• IVF?
• Orders?

Glucose infusion rate: GIR

\[ \text{GIR} = \text{IV rate (ml/h)} \times \text{glucose conc (g/dl)} \times 0.167 \]
\[ \times \text{weight (kg)} \]

usual 4-8 mg/kg/min

• Total fluid goal?
• AA and Calcium?

NICU Dextrose Fluids

Concerns…

• Concerns: catabolic state, hypo/hypernatremia, non-oliguric hyperkalemia, hypocalcemia. Adjustment of vent.
• At risk for hypotension. Volume status?
• If indicated… amp/gent.
• What will you feed? When?
• When to get a head ultrasound?
• When to check for ROP?
• Patent ductus arteriosus?

Giraffe Omnibed

• Our infant: wt 710g
• WBC 14.3, hgb 12.4, hct 37, plt 242. 43 segs, 6 bands.
• Mother: enterococcus UTI.
• ABG at 1 hol, 7.32/36/-7/18.5. Hct 32. gluc 42, iCal 1.11.
• Fibrinogen 385, INR 1, PTT 58.
• ABG 2 hol 7.25/56/-3/24.6
Our little man…

- Has done quite well. 2 months old. 2.5 x birthweight.
- All head ultrasounds normal.
- Has had lung disease, still requiring 2 LPM HFNC at 2 months of age.
- Patent ductus arteriosus, requiring indomethacin treatment x2.
- Growing well, tolerating good nutrition. Not old enough to po feed much yet…

Next…

- 27 wk male infant, 860 g, asymmetric IUGR infant born to mother with severe pre-eclampsia.
- Infant was given surfactant at delivery. Did well, extubated within next day. Except for initial neutropenia (likely associated with pre-eclampsia), did fairly well.
- Repeated bouts of feeding intolerance. Trophic feeds started as soon as breast milk available. Never had bovine milk protein.

DOL 27 developed abdominal distension, large residual, apnea.

What do you see?

What will you do now????
- What are you looking for?
- Orders?
• CBG 7.28/51/33/-3/18.3
• WBC 4.3, hgb 10.3, hct 29.6, plts 365K
  - 41 segs, 34 bands
• Chem OK
• Hypotensive, responded to volume bolus x1.
• How often follow-up? Physical exams? Labs? Xrays?

Next day

- WBC 2, hct 36, plts 215.
- 40 segs, 16 bands
- LP OK
- CBG: 7.2/57/26/-2
- Repeated apnea

Continued clinical worsening, thrombocytopenia, ascites

Surgery:
Perforation and necrotic bowel.

Initial Presentation of NEC
Key ➔ High suspicion!!!

<table>
<thead>
<tr>
<th>Sign</th>
<th>% of patients</th>
</tr>
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<tbody>
<tr>
<td>Abdominal distention</td>
<td>73</td>
</tr>
<tr>
<td>Bloody stool</td>
<td>28</td>
</tr>
<tr>
<td>Apnea, bradycardia</td>
<td>26</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>21</td>
</tr>
<tr>
<td>Retained gastric contents</td>
<td>18</td>
</tr>
<tr>
<td>Guaiac-positive stool</td>
<td>17</td>
</tr>
<tr>
<td>&quot;Septic appearance&quot;</td>
<td>12</td>
</tr>
<tr>
<td>Shock</td>
<td>11</td>
</tr>
<tr>
<td>Bilious emesis</td>
<td>11</td>
</tr>
<tr>
<td>Acidosis</td>
<td>10</td>
</tr>
<tr>
<td>Lethargy</td>
<td>9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
</tr>
<tr>
<td>Cellulitis of abd. wall</td>
<td>6</td>
</tr>
<tr>
<td>Rt. lower quadrant mass</td>
<td>2</td>
</tr>
</tbody>
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Clinical Presentation- NEC

Mild feeding intolerance - abdominal distension - shock and death

Pneumatosis intestinalis
70-80% of cases

Necrotizing Enterocolitis

Affects 1-8% of infants admitted to the NICU

- Incidence 5-15% in VLBW Infants
- Overall mortality 10-50%
- 1,000 deaths annually in the U.S
- Survivors- long term consequences
- Major Risk Factors:
  - Prematurity (consistent)
**PATHOLOGY**

- Inflammation of the intestine and/or coagulation necrosis
- Ileum and proximal colon are most often involved
- Skip areas are not uncommon
- Pneumatosis intestinalis occurs as submucosal gas

**Radiologic Evaluation**

- Findings may be non-specific: ileus, ascites, dilated loops
- Free air or portal venous air may be seen
- Perforation may occur with no free air evident on radiograph; obtain a left lateral decubitus or cross-table lateral

**Pathogenesis**

- Multifactorial
- No “single magic bullet”

**WHAT DO WE REALLY KNOW???
**Feeding**

- Feeding: key component
  - (90-95% cases exposed to recent enteral feeds or volume advancement)
  - NPO for prolonged periods: worse outcomes
  - How fast: large increases higher incidence of NEC (VLBW infants)
  - Type of feeding: maternal breast milk!!
  - Osmolality: theoretical….but pay attention to high osmolality formulas and medications (i.e. phenobarbital, 30 kcal/oz formulas)

**Bacteria**

- Intestinal microflora: good balance
- Cluster of cases: infection plays a role
- Bacteremia (35% cases)
- Pathogens: specific bacteria not consistent
- Interaction with immune responses
- Oral antibiotics: no role
- IV Abx: commensal microflora (good) \(\uparrow\) pathogenic bacteria

**Blood Transfusion/Anemia Clinical Trials**

- Case Reports associating with NEC
- Most clinical studies retrospective
  - Associations mostly a marker of severity of illness and gestational age
- RBC transfusions can trigger gut mucosal injury in patients with severe anemia during cardiopulmonary bypass
  - Reperfusion injury

**Treatment Goals**

1. Stabilize the infant
2. Prevent progression of NEC

**Treatment**

- Mainly supportive therapy
- X-rays – frequently in acute phase
- NPO and decompress
- Fluid and electrolyte needs
- IV abx
- Pressors, ventilatory support as needed

**Surgical Treatment**

Indications

- Perforation: single absolute indication!!!
- Worsening clinical and laboratory findings
- Portal air \(\rightarrow\) not definite indication
- Fixed loop for > 48 hrs
- Abnormal abdominal paracentesis
- Progressive erythema of the abdominal wall
Prevention

• Maternal Breast Milk!!!!!
  • Human milk is the best source of nutrition for neonates

Maternal Breast Milk

• Single modality shown to reduce the incidence of NEC consistently
  • Protection seems to be due to heightened immunity and defense against infection
  • Immunoglobulins, lactoferrin, neutrophils, lymphocytes, lysozyme
  • Protection due to avoidance of protein milk allergy (i.e. cow derived products)
  • Early introduction of enteral feedings is recommended
  • Prevents GI atrophy and likely decreases bacterial translocation

Probiotics- just confused

Meta-analysis 9 trials- only 5 reported NEC outcomes

• Enteral probiotics reduced the incidence of severe NEC on infants > 1000 grams [RR 0.32 (95%CI 0.17, 0.60)]
  • No reduction of sepsis or days on TPN
  • No cases of systemic infection with the probiotics supplemental organism
  • Not enough ELBW infants in studies

Probiotics- Pitfalls

• Studies enrolled a large number of late preterm infants
• Benefit only seen on those BW > 1,000 grams
• Incidence of NEC is highest on babies < 1,000 grams

Recommendations

• Look at the incidence in your center- hard data, avoid “perceptions”
• If hospital NEC rate is high then may implement “potential adjuvant therapies”
  • Donor Breast Milk or Probiotics if low MBM use
  • Human derived Fortifier if high MBM use
  • Strict Handwashing

Thank You!

• It takes a village…
• Dr. Gong
• Dr. Blanco
• Dr. Odom
• Dr. McGill
• Dr. Seidner