Neonatal Hypoglycemia: Update and recommendations

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Disclosures

• I have received consulting fees from TEVA Pharmaceuticals for the development of an educational slide deck regarding a medication used to treat hyperinsulinism.

• I receive speaker fees from TEVA Pharmaceuticals speaking regarding a medication used to treat hyperinsulinism.

• I will be discussing the use of Octreotide, which is not FDA approved for the treatment of hyperinsulinism and 18FDOPA which is an under an IND.
Objectives

- Understand the pathophysiology of the transition period
- Understand the normal range of glucose in the newborn
- Differentiate transitional hypoglycemia from pathological hypoglycemia
- Understand the weakness of the AAP and CPS guidelines
- Discuss the different forms of hyperinsulinism
Fetal glucose metabolism

- Glucose is transported across placenta by facilitated carrier mediated diffusion
- Placenta uses 50-60% of this glucose and fetus 40-50%
- As fetus grows and demands increased glucose, uterine blood flow increases
- Fetus can tolerate up to 50% reduction in uterine blood flow
- Any decrease in fetal blood flow will result in IUGR
Fetal glucose metabolism

• As gestation increases the materno-fetal gradient increases thus increasing diffusion and glucose supply to the fetus
• By term fetal glucose levels are lower than maternal by 0.5mmol/L (9mg/dl)
• This is accomplished by increasing fetal insulin secretion, driving anabolism
• 80% fetal energy comes from glucose metabolism, 20% lactate and amino acids
In-utero Materno-fetal metabolic state

• Placental secretion of lactogen, progesterone and estrogen cause maternal insulin resistance
  – Increase availability of glucose, lipids and amino acids
• Fetus has elevated insulin, with an inability to rapidly adjust levels and low glucagon
• Fetus is in a state of anabolism
  – Glycogen deposition peaking at term to 50 mg/g/liver
  – Fat deposition and protein buildup
Birth and Transition

• Abrupt cessation of glucose and AA supply with clamping of the cord
• In first minutes after birth Epi, Nore Epi and glucagon levels rise
• Glucose levels rapidly drop from intrauterine levels of approximately 70 mg/dl to 56 mg/dl by 2 hours of life, leading to inhibition of insulin secretion mediated by $K_{ATP}$ channel
• Natural food intake begins immediately at birth = colostrum = primarily fat
Transition 2

• Induction of PC and PEPCK leads to ability of newborn to start gluconeogenesis by 12 hours of age
• Falling insulin and rising glucagon levels lead to release of glycogen and fall in liver glycogen stores by 24 hours of life to <10 mg/g liver
• 50% of newborn glucose requirement comes from glycogen, 20-30% from gluconeogenesis of alanine/lactate, 20% from glycerol released by lipolysis and the remainder from recycled glucose carbon
• By 12-24 hrs fat metabolism starts to contribute to energy provision
Normal Glucose levels in the newborn

<table>
<thead>
<tr>
<th>Time</th>
<th>2 hours</th>
<th>24 hours</th>
<th>48 Hours</th>
<th>72 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>56</td>
<td>63</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>Calculated 5%</td>
<td>≤28</td>
<td>≤40</td>
<td>≤41</td>
<td>≤48</td>
</tr>
</tbody>
</table>

Lubchenco and Bard: 1971. Incidence of glucose < 30 mg/dl prior to first feeding in a normal newborn nursery

Fig. 1. Incidence of hypoglycemia in newborn infants, classified by birth weight and gestational age. Glucose levels <30 mg/100 ml prior to first feeding.
Are all neonates equal?

- When all babies were re-screened at 72 hours <1% or 2/374 babies had glucose ≤ 50 mg/dl
- Of the 55 babies in the study with hypoglycemia, 2 (3.6%) still had glucose <50 mg/dl by 72 hr

Lubchenko and Bard 1971
Brain glucose

• Glucose is transported across the BBB by Glut 1 transporter
• CSF glucose is typically 60% of plasma glucose
• As plasma glucose approaches 36mg/dl the CSF glucose approaches 0 mg/dl
• In patients with Glut 1 defects in whom brain damage occurs due to loss of brain fuel, the mean CSF glucose is 33mg/dl which in normal people equates to a plasma glucose of 56mg/dl
Thresholds for Responses to Acute Insulin-induced Hypoglycemia*

Arterialized venous plasma glucose

- Normal glucose concentration: 70 – 100 mg/dl
- Suppression of insulin secretion: 80 – 85 mg/dL
- Increased glucagon release: 65 – 70 mg/dL
- Increased epinephrine release: 65 – 70 mg/dL
- Increased cortisol and growth hormone: 65 – 70 mg/dL
- Awareness of symptoms: 50 – 55 mg/dL
- Impaired cognition: < 50 mg/dL

* Adapted from Table 2.1, pg 21 in Cryer PE 2009 Hypoglycemia in Diabetes: Pathophysiology, Prevalence, and Prevention. Alexandria, VA: American Diabetes Association
Conclusion regarding glucose levels in the first 72 hours of life

• Glucose levels <50mg/dl are very common in first 24 hours of life

• Glucose levels <50 mg/dl may be a normal physiological finding in first 24 hrs of life due to transition from fetal to extrauterine life

• By 72 hrs, glucose levels <50mg/dl are very rare <1%

• Metabolic profile / hormonal balance of the first 0-4 hrs is identical to hyperinsulinism
  – Low glucose, low FFA and low BOHB, low lactate
  – No utility in drawing critical sample in the first 4 hours of life
Conclusions 2

- The main source of glucose in the first 24 hrs is glycogen and glycerol (70%)
- Insulin inhibits glycogen release and lipolysis and thus hyperinsulinism states remove 70% of glucose availability
- Majority of non transitional hypoglycemia is secondary to hyperinsulinism or due to lack of glycogen reserves
How do we address glucose levels in the newborn period

• Cornblath and Swartz
• AAP guidelines
• CPS guidelines
• Breast feeding guidelines
AAP guidelines

• Check glucose 30 mins AFTER first feed

• IV glucose for
  – Symptoms and glu <40
  – Glu <25 first 4h
  – Glu <35 4-24 hrs
  – Goal is 40-50

• IDM and LGA screen for 12 H or maintain glucose >40 for 3 feeds

• SGA, preterm screen 24 hrs

• Babies with abn glucose homeostasis continue until 3 pre feed glucose >normal
AAP guidelines

• If unable to maintain glu >45mg/kg/day on 5-8mg/kg/min after 24 hours consideration should be given to Hyperinsulinemic states

• “Follow-up glucose measurements are always indicated to be sure an infant can maintain normal glucose concentrations over several feed-fast cycles.”
**CPS guidelines**

- Feed and check within 2h
- IV for glu <1.8 (32mg) @2h or <2 (36mg) >2h
- IV intervention for levels <2.6 (47mg) with symptoms or repeated asymptomatic <47mg
- Start iv glu at 5.5mg/kg/min (80ml/kg D10%)
- Target >2.6 >47mg
- If IV glu >10mg/kg/min needs investigation
- Screen until time or glucose remains >47
Hypoglycemia in at risk babies

- 514 at risk babies
  - 260 (51%) glucose \( \leq 47 \text{mg/dl} \) of which 81% occurred in the first 24 hours (48% in \( \leq 6 \text{H} \))
  - 97 (19%) glucose \( \leq 36 \text{mg/dl} \)
  - 31 (6%) required IV glucose to treat hypoglycemia
  - 98 (19%) had > 1 episode
  - 79% were asymptomatic, 15% poor feeding and 16% jittery

Harris et al 2012. J Pediatrics
Hypoglycemia in at risk babies

• Of the hypoglycemia babies
  – 95 (37%) had the first episode after 3 “normal” blood sugars.
  – 15 (6%) had the first hypoglycemia after 24 hours age.

Harris et al, J Pediatrics: 2012
AAP guidelines: Do they work

• 6% babies with first hypoglycemia >24H would have been missed.
• 37% babies had 3 “normal” glucose before 1st hypoglycemia and would have been missed
• 20 babies had glucose <48 mg/dl for >48 hours
• 31 babies needed IV glucose but we do not know the outcome
  – What should we do with them??
  – Wean slowly off IV and feed 2-3H and monitor glucose
What would you do

- AAP say if 3 glucose $> 40-45\, \text{mg/dl}$ in a row on Q 2-3 H feeds d/c testing
Nine hour fast Study
Cook Children’s Medical center

- To determine if a 6 or a 9 hour fast can differentiate patients with pathological hypoglycemia from transitional hypoglycemia presenting in the first days of life
Patients

- Evaluated 35 patients referred for hypoglycemia > 48 hours or hypoglycemia on IV fluids
  - 27 had PSHI requiring treatment with diazoxide
    - All required IV fluids
    - Mean age of test 17 days, range 2-62
    - 6 had dx made during wean from IV fluids
    - 11 diagnosed on Q3 H feeds
    - 10 required fasting study
  - 8 had PSHI that settled and did not require drug Rx
# Results

<table>
<thead>
<tr>
<th>Hours of fasting Glu &gt;50</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>On IV fluids at hypo</td>
<td>6</td>
</tr>
<tr>
<td>&lt;3 hours</td>
<td>5</td>
</tr>
<tr>
<td>3 hours</td>
<td>6</td>
</tr>
<tr>
<td>4 hours</td>
<td>5</td>
</tr>
<tr>
<td>5 hours</td>
<td>1</td>
</tr>
<tr>
<td>6 hours</td>
<td>1</td>
</tr>
<tr>
<td>7 hours</td>
<td>1</td>
</tr>
<tr>
<td>8 hours</td>
<td>1</td>
</tr>
<tr>
<td>9 hours</td>
<td>1</td>
</tr>
<tr>
<td>No hypoglycemia hour 9</td>
<td>8</td>
</tr>
</tbody>
</table>
No Hypoglycemia in 9 hour fast

- 8 patients had glu > 50 mg/dl for 9 Hours
  - Mean 9 hour glucose 78 mg/dl, range 60-100
  - Mean 6 hour glucose 77 mg/dl, range 62-94
    - Lowest range 62, 64,
Conclusions of 9 V 6 hour fast

- 7 of 10 (70%) patients who weaned off IV fluids were detected by 6 hour fast
- 3 patients “passed” by definition of >50 but had PSHI
- A 6 hour fast means skipping 1 feed and doing 3 finger stick and 1 lab glucose at 6h
How accurate are the AAP Guidelines

- Sensitivity of 3 glucose > 50 mg/dl
  - 63%
- Specificity of 3 glucose > 50 mg/dl
  - 100%
6 hour fast to 50 mg/dl

- **Sensitivity** (no of people who have disease who tested positive)
  - 70%

- **Specificity** (no of people who do not have disease who tested negative)
  - 100%
6 hour fast to 65 mg/dl

• Sensitivity  (no of people who have disease who tested positive)
  – 100%

• Specificity  (no of people who do not have disease who tested negative)
  – 75%
Conclusions

- The 6 hour fast to < 50 mg/dl with reflex to 9 Hour fast for those > 50 mg/dl but < 65 mg/dl will ensure all patients will be diagnosed and only 25% unaffected babies will need 9 hr fast

- Following the AAP guidelines would have missed 10 out of 27 affected babies.
  - 63 % Sensitivity and 100% specificity
Conclusions

• In the Harris paper 20 of 574 at risk babies had glucose < 48 after 48 hours of life, and based on the Sensitivity of 3 glu > 50 mg/dl being 63% this would imply that Harris had 32 infants with hypoglycemia >48 hours

• Of 514 at risk babies 32 (6.2%) need a 6 hour fast to determine if safe to go home

• Is this an acceptable burden of work?
Hyperinsulinism

- Hyperinsulinism is a condition in which there is a dissociation between glucose sensing and insulin secretion resulting in hypo-ketotic hypoglycemia.
- This combination of low glucose and low ketone bodies puts patients with HI at significant risk of brain damage or death.
- Rates of brain damage vary from 20-44%.
Etiology

• Hyperinsulinism may be
  – Congenital
  – Transient
  – Acquired
Congenital Hyperinsulinism

• Congenital Hyperinsulinism (HI) is the most common cause of persistent hypoglycemia in infancy

  ▪ Incidence is unclear in the USA
    – 1 : 50,000 in Belgium

• 9 known genetic defects cause HI and 50% of patients with diazoxide sensitive HI do not have mutations....... So there are more mutations out there
Diazoxide Unresponsive Congenital Hyperinsulinism

- AR mutations in genes encoding the $K_{ATP}$ channel
  - ABCC8 (SUR-1)
  - KCNJ11 (Kir6.2)
  - Focal or diffuse
Clinical features of Hyperinsulinism

- Hypoglycemia in babies
  - Seizures, twitching, jitteriness
  - Breathing difficulties in babies
  - Lethargy and unresponsiveness
- Hypoglycemia in older children and adults
  - Hunger, Pallor and sweatiness
  - Fatigue and lethargy
  - Crankiness and irritability
  - Poor concentration, slurred speech
  - Coma and seizures
Diagnosis of HI

- Persistent hypoglycemia
  - Plasma glucose < 50 mg/dL
  - Short fasting duration

- May have increased glucose utilisation
  - New-born - >4-6 mg/kg/min
  - Older child - >2-3 mg/kg/min

- Insulin > lower limit of detection

- Low plasma ketones <2.0 mmol/L

- Low FFA <1.5 mmol/L

- Glycemic response to glucagon >30 mg/dL when hypoglycemic
HI Treatment

- IV bolus 2 mls/kg D10% = 200 mg/kg glucose
- IV Dextrose 5ml/kg/hr = 8mg/kg/min
  - Recheck every 30 mins and rebolus and increase IV until glucose > 65 mg/dl
- Diazoxide 8-15 mg/kg/day po divided 2-3 times a day
- Octreotide 5 – 20 µg/kg/day
  - Not FDA approved for use in hyperinsulinism
  - 4-8 hourly sub q injection
Surgical Therapy

- When medical therapy can not safely and effectively keep glucose >70 mg/dl for 6 hours then surgery is indicated
  - Determine if focal or diffuse
    - 18 fluro-dopa PET scan
  - If focal
    - Localize lesion and remove with clear margins
  - If diffuse
    - 98% pancreatectomy
Focal HI Surgery

- Remove the lesion
  - 10 to 50% pancreatectomy
  - Leave as much normal tissue behind as possible
  - Frozen section to guide limits of surgery
- Cure rate is approx 80% with minimal diabetes risk
- Surgery for focal HI continues to require a multidisciplinary and skilled team approach. Two such referral centers in the US. (CHOP and CCMC)
Transient Neonatal Hyperinsulinism (TNHI)

- Infants of Diabetic mothers
- Perinatal Stress induced HI
  - Hypoglycemia caused by hyperinsulinism that lasts >3 days and resolves by 6 months.
  - Infants
    - AGA / SGA / LGA but no maternal diabetes
    - Pre eclampsia / Maternal hypertension
    - Evidence of fetal stress
  - Beckwith-Wiedeman Syndrome
Transient Neonatal HI

- Diazoxide 5 -10mg/kg/day
  - Patients tend to be very diazoxide responsive
  - May develop hyperglycemia on standard 15 mg/kg/day doses
  - Must do a fasting study to prove resolution off treatment before labeling transient
Transient Neonatal HI

- Although THI is easier to treat than $K_{\text{ATP}}$ HI
  - May still cause hypoglycemic brain damage
  - Requires careful follow up until resolution
Summary

• Hypoglycemia is not a diagnosis it is a biochemical finding
• If you do not know the cause, draw the critical sample at the time of hypoglycemia
• Critical sample
  – Insulin, Lactate and Beta-OH butyrate
  – Cortisol
  – GH
  – Ammonia
  – Urine organic acids
  – Acyl-carnitine profile
Summary

• Following the AAP guidelines on management of neonatal hypoglycemia will miss patients with pathological hypoglycemia

• Make sure your NICU has a well thought out plan