Neonatal Glucose Disorders: “The highs and the lows”.

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Conflicts of interests

- I have no conflicts of interest
Objectives

- Try to define hypoglycemia
- Learn how infants manage their blood sugar
- How to diagnose and treat hypoglycemia
- Discuss the diagnosis and management of hyperglycemia
What is a normal blood glucose (mg/dl)?

- A survey of 26 pediatric textbooks and 178 pediatric consultants produced a range from 18 to 72 mg/dl.

Hypoglycemia as Commonly Defined
The Confusion and Contradiction Remains

• “No evidence to support hypothesis . . . that the newborn has a unique physiologic adaptation to low blood glucose. The optimal range for plasma glucose should be considered to be 70 – 100 mg/dl.” Stanley and Pallotto, In Taeusch, Ballard & Gleason, Avery’s Diseases of the Newborn, 8th ed., 2005.

• “Although a consensus regarding cutoff values for hypoglycemia have not been reached, most investigators would consider a plasma glucose of lower than 36 mg/dl to be low and require intervention.” Kahlan and Parimi, in Fanaroff & Martin, Neonatal-Perinatal Medicine, 8th ed. 2005

• <40 mg/dl, Ogata, Avery’s Neonatology, MacDonald, Mullett & Seshia, eds, 6th ed. 2005

• <36-40, <40-45 mg/dl plasma, McGowan and Hay, Handbook of Neonatal Intensive Care (Merenstein & Gardner), 6th Ed, 2006

• “. . . The experimental and human clinical data are clear that hypoglycemia (blood glucose level < 45 mg/dl), isolated or combined with mild hypoxia-ischemia, is injurious to the newborn brain . . .” Inder T, Pediatrics, 2008

None of these definitions is supported by any objective measures or experimental evidence.

**Slide is borrowed from Dr. David Adamkin**
At present there is no rational basis to identify any specific value or even range of plasma glucose concentrations at any one time that is sufficient to define “hypoglycemia” as a pathologic entity (NICHD 2008)

SO WHAT IS HYPOGLYCEMIA!!!!!!
The definition of clinically significant hypoglycemia remains one of the most confused and contentious issues in contemporary neonatology.
Working Definition

• The “classic standard” is **40 mg/dl**. (Cornblath, Journal of Peds 1959)

• Using a statistical approach would place a “normal” blood glucose in a healthy infant >45 mg/dl

• However, this does not define below what level would cause permanent neurologic insult to a newborn’s brain

• No absolute correlation between serum glucose and acute symptoms or long-term effects
Don’t Panic . . . time for a little glucose metabolism slides
Glucose Storage/Metabolism

- During gestation, the fetus has a high insulin to glucagon ratio, which causes glucose storage... not consumption
- Fetus cannot make glucose, crosses the placenta
- Cord is clamped... surge of catecholamines... glucose utilization (glycogenolysis, gluconeogenesis)

Baby is born
Glucose metabolism

- High blood glucose
  - Insulin
  - Glycogen storage
  - Gluconeogenesis
  - Glycogenolysis
  - Glucose uptake/storage
  - Low blood glucose
  - Glucagon/glucocorticoids
  - Glucose production
In the beginning . . .

- Blood glucose falls during first hours of life
- Reaches nadir >40mg/dl at 2 hours of life
- 40-80mg/dl by 4-6 hours of life
Do babies need to consume 1-2 ounces of milk in first 24 hours of life to maintain euglycemia?
Let’s not forget what is normal

- A study published in *The Journal of Pediatrics* (2010) examined the range of colostrum intake in 90 normal, term infants during the first 24 hours.
- A total of 307 feedings were evaluated using scales with 0.5 g sensitivity.
- The results identified the “mean weight gain per breastfeeding was 5.0 ± 3.6 g. (range 0 to 6.6 g)” on Day 1.
Breastfeeding and blood glucose

- Up to 14% of healthy term babies may have blood glucose less than 47 mg/dl in the first three days of life. Lowest concentrations are more likely on day 1

Nicholl, R. Arch Dis Child 2003;88:238-239
Suckling Ketogenesis

- Ketones are an alternative fuel for the brain during a fast or periods of hypoglycemia.
- Produced from breakdown of fatty acids in the colostrum (high fat content), peaks on 3rd day.
- Response is blunted with formula.
- May protect newborn brain for injurious affects of hypoglycemia.

Who is at risk?

Who do we worry about the most?

- Premature babies (< 37 wks)
  
  *Low storage pool because not enough time*

- SGA/IUGR
  
  *Low storage pool because of chronic intrauterine malnutrition*

- LGA/Infants of DM

  *Hyperinsulinemic state*
Asymptomatic to severe CNS abnormalities.

Symptoms include:
- jittery/tremors
- apathy
- cyanosis
- seizure
- apnea
- lethargic
- poor feeding
Should we care?

- Neurodevelopment outcome
  - Few well done studies evaluating this topic
  - Level or duration of hypoglycemia and risk of harm is still unknown

  - 661 preterm neonates evaluated at 18 months
  - 2/3 had BG <47mg/dl for 3-30 days
  - If >5 days, consecutive or separate
    - Significant increased risk of ND deficit

- However this was not sustained at 7.5 to 8 yrs follow up. . . Important?
CNS symptoms

- Since we are so concerned with the long term implications from untreated or unrecognized hypoglycemia, should we place a higher value on the central nervous system signs?
- Ex: lethargy, poor tone and seizures

- Reality is that most cases of diagnosed hypoglycemia occur with asymptomatic infants
Etiologies

Decreased Production/Impaired mobilization

Versus

Increased Utilization
Decreased Production

- **Limited storage pool**
  - Prematurity (third trimester predominately stores)
  - IUGR
  - SGA

http://www.telegraph.co.uk
Impaired mobilization

- Inborn errors of metabolism (ie glycogen storage disease, FAO)
- Hormone deficiency (ie congenital adrenal hyperplasia)
- Maternal beta blocker usage (impairs infant catecholamine response)
Increased Utilization

- Increased utilization
  - hypothermia (increased glucose use for ATP production)
  - polycythemia (increased consumption from inc RBC mass)
  - sepsis (decrease caloric intake, inc insulin sensitivity, inc metabolic rate, decreased gluconeogenesis)
Increased Utilization

- Hyperinsulinemia
  - Transient (infants of DM, Beckwith-Wiedemann Syndrome)
  - Congenital hyperinsulinemia

Beckwith-Wiedemann Syndrome

Microcephaly  Macroglossia  Umbilical hernia
Work up

- Don’t wait to treat!
- I-stat/accu check/chemstrip/whatever
- Confirm with serum blood glucose
Work Up (refractory hypoglycemia)

- Insulin level (should be low!)
- Cortisol (more variable but less than 1 is significant)
- Growth hormone (more useful in neonates)
- Serum Amino acids, plasma free and total carnitine
- Urine ketones and organic acids
OH CRAP!!
Hypoglycemia protocol

Hypoglycemia screening in first 24 hours of age:

- **Symptomatic** infants all need screening blood sugar and if <40 mg/dl confirm stat glucose. If <40 mg/dl transfer to the NICU for possible IV treatment.

- **Asymptomatic** infants:
  - IDM, LGA (90%) or > 4500g for first 12 hours of life
  - LPI (34-36 6/7 wks), SGA (<10%) or < 2500 g for 24 hours
Feeding within 1 hour after delivery (Breast/Bottle)

Chemstrip glucose: check 30 minutes after feed

<25
Confirm stat glucose
Re-feed (formula 15-20ml)
Rescreen in 30 minutes

25-40
Re-feed (breast + bottle)
Rescreen in 3 hours

< 25 confirm stat glucose
Transfer to NICU for IV

25-40
Re-feed every 3 hours
Repeat strip glucose q 3 hours

If < 40 at > 6hrs of life send to NICU
How much glucose is baby getting?

- GIR (glucose infusion rate) normally is to maintain adequate glucose supply to the brain is 4-6mg/kg/min (5-8 for premature)

- GIR equation: \[ \text{[Dextrose]} \times \text{Rate (cc/hr)} \times \text{Wt (kg)} \times 6 \text{ (factor)} \]
IV Treatment

- Avoid large boluses to prevent insulin rebound
- Give 2ml/kg of D10W over 5-10 minutes
- Keep blood sugars >50-55mg/dl
- Start continuous dextrose infusion 4-8mg/kg/min
Treatment for refractory hypoglycemia

- Hydrocortisone if GIR >12-15 mg/kg/min
- Glucagon (won’t work if has decreased stores/GSD but if increased BG by 20-30mg/dl in first 20 minutes suggestive of hyperinsulinemia)
- If GIR>15, then consider Endocrine consult
- Diazoxide
- Octreotide
- Calcium channel blockers (nifedipine)
- Surgery
HYPERGLYCEMIA
Hyperglycemia

- Arbitrarily defined as blood glucose > 125 ml/dl or plasma glucose > 150 mg/dl irrespective of gestational age\(^1\)

- Although in clinical setting the definition amongst neonatologists would vary

How common is hyperglycemia

- Difficult to get good numbers but low birth weight is primarily the largest risk factor
- Preterm birth ranks second
- Therefore incidence is inversely related to birthweight in the preterm infant
- Can range from 2% in >2kg, 45% <1kg and close to 80% in <750g

Hemachandra, A and Cowett, R. Neonatal Hyperglycemia. Peds in Review, 1999;20;e16
Risks for Hyperglycemia

- Preterm infants
- Intrauterine growth restriction (IUGR)
- Increased stress hormones (ie exogenous catecholamine infusions and glucocorticoid administration)
- Excessive IV lipid infusions
- Excessive IV glucose infusion rates
- Lack of enteral nutrition (ie diminished “incretin” secretion)
Pathophysiology

- Preterm birth/IUGR
  - appear to have lower capacity for insulin secretion
  - have less muscle mass therefore less capacity for insulin to promote peripheral glucose utilization.

- IUGR infants can also have decreased hepatic insulin sensitivity (ie glucose production from liver continues despite elevated blood glucose levels)
Pathophysiology

Increased “stress” hormones
- catecholamines inhibit both insulin secretion and action (happens in both term and preterm infants)

-glucocorticoids facilitate protein breakdown which lead to the building blocks for gluconeogenesis. Also increase release of hepatic glucose and decrease insulin secretion

Fowden AL. Effects of adrenaline and amino acids on the release of insulin in the fetal sheep fetus. J Endocrinol. 1980;87:113-121
IV lipid infusions

-leads to increase in free fatty acids (FFA), which limit glucose oxidation competitively by providing additional carbon substrates for oxidative metabolism.

-FFA also increase glucose levels by enhancing the enzymes in the gluconeogenesis pathway.

Sunehag AL. The role of parenteral lipids in supporting gluconeogenesis in very premature infants. Pediatr Res. 2003;54:480-486
Insulin Dependent Diabetes Mellitus

- Uncommon but important to diagnose
- Transient and permanent forms
- Usually occurs in first weeks of life
- In addition to hyperglycemia, will present with severe dehydration from polyuria (glycosuria).
- Caused by lack of insulin secretion from pancreatic beta cells
Should we even care . . .

What are the concerns relating to hyperglycemia?
- Glucosuria leading to dehydration
- Hyperosmolar coma with cerebral and neuronal edema, seizures and intracranial hemorrhage
- Increased morbidity and mortality
- Impaired immunity, increased infection
- Poor wound healing
- Loss of skeletal muscle and cardiac mass
Hyperosmolality from hyperglycemia

- Typically seen with very rapid increase of plasma glucose concentration to excessively high values, 
  > 500 mg/dl.

- Each 18 mg/dl of plasma glucose concentration produces 1 mOsm/L, therefore glucose of 500 mg/dl provide an additional 25 mOsm/L.

- If present for lengthy periods of time can lead to brain cell dehydration, capillary dilation and cerebral bleeding.

Remains no widely accepted method of how to treat, when to treat . . . or should we treat.

Very little data (term/preterm newborns) on possible harm and if treatment makes any difference at all.

Best treatment is to figure out the etiology and “treat that”, ie dec stress, treat infection, dec pressors, dec lipid infusion . . . dec GIR.
To use insulin or not to use insulin . . .

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
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<tbody>
<tr>
<td>Rapid lowering of plasma glucose</td>
<td>Often causes hypoglycemia</td>
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<tr>
<td>Decrease osmolality from hyperglycemia</td>
<td>No study shows the use of insulin improves outcomes</td>
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<tr>
<td>Decreases hyperkalemia (if present)</td>
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**Insulin does NOT promote uptake or utilization by the brain**

Insulin

- Would consider using if plasma glucose >400-500 mg/dL and GIR less than 4 mg/kg/min.
- Continuous administration 0.02 to 0.05 U/kg/hr
- May give “one time” doses
- Obvious risk of hypoglycemia but also hypokalemia
- Need to check glucose levels frequently (q1-2 hrs)
Improving nutrition

- Is there an association with amino acid intake and glucose metabolism?

- Providing a positive protein balance, especially the ELBW infants, will promote insulin secretion thus avoiding hyperglycemia\(^1\).

- Enteral feedings also promote pancreatic function and the secretion of insulin. (Neoreviews 1999)

Questions
Hypoglycemia Summary

- No consensus definition of hypoglycemia but for your purposes 40 mg/dl in first 24 hours and >45-50 mg/dl after 24 hours of life
- Think of symptomatic neonatal hypoglycemia as a medical emergency
- You should follow your nursery’s protocol but just know that there is little or no evidence existing that asymptomatic neonatal hypoglycemia at any concentration in the first days of life results in any adverse sequelae in growth or neurologic development
Hyerglycemia Summary

- Common entity in ELBW infants (>1kg)

- Best treatment is addressing the inciting cause, ie dec GIR, dec stress, etc.

- Use of insulin is controversial and there is no evidence in newborns that it even changes outcomes.