Neonatal Hypoglycemia

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Disclosure

I have no actual or potential conflicts of interest in relation to this program/presentation to disclose

Objectives

• To understand normal glucose homeostasis in a newborn after birth
• To understand the origin and complexity behind the operational definition of hypoglycemia
• To understand updated screening recommendations of hypoglycemia
• To understand updated management recommendations for hypoglycemia
Fetal Glucose Metabolism

Uncomplicated Normal pregnancy:

- Glucose is primary fuel for fetus
- Fetal energy consumption =
  - 80% Glucose
  - 20% other means (i.e., FFAs, ketones, lactate, AAs)
- Fetal plasma BG concentration 70-80% of mothers
- Rapid response to fluctuations in maternal blood glucose
- Fetus does NOT produce glucose

Fetal Glucose metabolism

- Excess glucose stored as TG or glycogen
- Fetal liver contains all the enzymes necessary for synthesis and breakdown of glycogen
- Hepatic glycogen content:
  - Low in early gestation
  - Slow increase 15-20wks
  - Rapid increase late in gestation

Glucose homeostasis in newborn

- Cutting cord = abruptly cut off from mom's continuous glucose supply
- Healthy term newborn = instant surge of catecholamines and glucagon, fall in insulin → mobilization of hepatic glycogen and stimulation of gluconeogenesis
Glucose homeostasis in newborn

• Hepatic glucose output depends on
  1) Adequate glycogen stores
  2) Sufficient supply of endogenous gluconeogenic precursors
  3) Normally functioning hepatic gluconeogenetic and glycogenolytic system
  4) Normal endocrine system

Glucose requirement in newborn

• Brain has highest metabolic demand following birth, lower GA, lower weight
• Brain is capable of using alternative fuels such as ketone bodies and lactate for oxidative metabolism

Physiologic transient blood glucose “dip”

• After birth, plasma glucose concentrations fall in all infants,
• Nadir between 30-90 min after birth

Transient Neonatal Hypoglycemia

- Common condition that results from decreased glucose supply, increased utilization, or both
- Decreased supply: delay in initial feeding, preterm, SGA or IUGR infants
- Increased demand: sepsis, IDM, asphyxia

Approaches to define Hypoglycemia

- No consensus definition
- Approach based on clinical manifestations
- Approach based on epidemiological data
- Approach based on acute changes in physiologic responses
- Approach based on neurologic and developmental outcomes

Clinical Manifestation

- Altered level of consciousness
  - Lethargy
  - Irritability
  - Abnormal cry
  - Stupor
- Feeding difficulty
- Hypotonia, floppiness
- Tremors
- Convulsions
- Apnea/ cyanosis
- Hypothermia
- Coma
- Hypothermia
Tackling “clinical manifestation” approach

- Clinical manifestations NOT unique to neonatal hypoglycemia
- Must satisfy Whipple’s triad:
  - a reliable low BG measurement
  - Clinical ssx consistent with hypoglycemia
  - Resolution of ssx after restoring BG to normal values
- Misses several newborns with “asymptomatic” low blood glucose levels

Approach based on epidemiological data

- Based on “normal, healthy term newborns”
- Hypoglycemia = values more than 2 SD below the mean
- Limited by variations of “baseline normal” blood glucose concentrations
  - gestational age, birthweight, gender, type of measurement, feeding type
- No correlation between clinical outcomes and epidemiological definition

Approach based on physiologic response

- Hypoglycemia = blood glucose level below which newborns demonstrate counter-regulatory responses
  - changes in cerebral blood flow
  - inefficient hormonal responses
  - abnormal neurophysiological function
- Difficult to measure
- Limited data
- No data on correlation to outcome
Approach based on neurologic and developmental outcomes

- Landmark study: Lucas et al. 1988
- Observational data from a large multicenter feeding study
- 661 babies with BW < 1850g, 543 with neurodevelopmental assessment with Bayley at 18 months follow up
- Blood glucose level < 2.6mmol/l (47mg/dl) offered greatest predictive power for poor developmental outcome.
- Risk of reduced developmental scores associated independently with number of days level below cut-off value
  - For ≥ 3 days = 2x risk, for ≥ 5 days = 3.5x risk

Limitations of the Lucas Study

- 6800 BG levels obtained > weekly until discharge or 2kg (well baby nursery). Additional levels daily on NICU babies
- Authors stressed limitation of proving causation by observational study with failure to adjust for confounding factors

Subsequent developmental outcomes studies

- The Northern Neonatal Nursing Initiative Trial Group
- Blood glucose levels measured by glucose oxidase assay same time every am, 1st 10 days of life.
- 566 survived at 2 years of age and had Griffith Scales for Mental Development performed.
- 47 with BG level < 2.6mmol/l (47mg/dl) on 3 or more days, matched to those without low BG
- No differences in developmental progress or in physical disability detected at 2 years old CGA.
- 45/47 and all controls reassessed at 15 years of age: No difference in outcome studies
Conclusion from outcome studies

• There is no single numerical cut-off value of blood glucose, or the duration below this cut-off, that can be applied to all newborn infants to predict long-term neurological and developmental problems.

“Operational Thresholds”

• Proposed by a group of experts to provide margin of safety, while preventing unnecessary investigations and interventions.
• Concentrations at which clinicians should consider interventions:
  1) Single measurement of BG <1mmol/l (18mg/dl)
  2) BG level < 2mmol/l (36mg/dl) that remains below same value for next measurement.
  3) Single measurement of BG < 2.5mmol/l (45mg/dl) in a newborn with abnormal clinical signs.
• Higher therapeutic goal: > 2.5mmol/l (45mg/dl)

Cornblath et al. Pediatrics 2000

• Just as there is no consensus definition, there is lack of data to support one clear treatment strategy for neonatal hypoglycemia.
• Exception: infants with defects in certain metabolic pathways or in regulation of insulin secretion -> early identification, prevention and treatment of hypoglycemia critical for survival.
• Who is at risk? Who should be screened?
Risk Factors
The Sugar Babies Study, Harris et al. 2012 & AAP 2011 recommended management of asymptomatic hypoglycemia
- Identified 4 most commonly encountered newborns with asymptomatic hypoglycemia:
  - Late preterm (34-36 & 5/7 weeks)
  - Infant of diabetic mother
  - SGA
  - LGA
- AAP recommended treating duration of screening differently based on which risk factors present
- Harris et al: Recommended simplifying screening protocols to be unified for all at risk groups of infants

Variations in Measurements
- POC – bedside glucometers: reagent test strips
  + 10-20mg/dl variation
- Greatest variation at low glucose concentrations <50 mg/dl
- Must confirm with laboratory enzymatic methods (i.e. glucose oxidase, hexokinase, or dehydrogenase method)
- Laboratory variations to account for:
  - Plasma blood glucose 10-18% higher than whole blood values
  - Long delay to process: glucose levels can fall 14-18mg/dl/hr
  - Arterial samples > venous or capillary samples
- Current studies are looking at the use of Continuous glucose monitoring sensors in VLBW and IDM, late preterm, SGA/LGA

Management Strategy at VCU
- Based on extensive literature review and 2011 AAP recommendations, protocol review team led by Dr. Alison Chapman, updated protocol in 2013
- Operational Threshold: Hypoglycemia defined as blood glucose < 40mg/dl.
- At risk infants to have blood glucose monitoring using bedside glucose monitor for initial screening.
- All infants at risk infants to have initial blood glucose checked within one hour of admission
- Infants with new onset of signs of symptoms of hypoglycemia will have BG immediately checked at any time
At risk infants

- IDM
- SGA
- IUGR
- LGA
- Prematurity
- Perinatal asphyxia
- Sepsis
- Respiratory distress
- Discordant twins
- Polycythemia (HCT >65)
- Hypothermia
- Maternal tocolytic therapy
- Exchange transfusion
- Infants with congenital heart disease
- Post-operative patients
- Infants on high dose steroids
- Endocrine disorders
- Hyperinsulinism disorders (Beckwith-Weidman)
- Inborn errors of metabolism
- Respiration distress
- Discordan twins
- Polycythemia (HCT >65)
- Prematurity
- Perinatal asphyxia
- Sepsis
- Respiratory distress
- Discordant twins
- Polycythemia (HCT >65)
- Hypothermia
- Maternal tocolytic therapy

Essentially . . .

No need to screen any healthy term infant, born to healthy mom with normal pregnancy who is breastfeeding

***Remember: Feeding difficulties is a symptom, infants not eating well should be monitored***

Monitoring

- On admission: at risk infants BG within 1 hour, symptomatic BG ASAP
- For BG >40mg/dl

<table>
<thead>
<tr>
<th>If feeds planned</th>
<th>Daily feeds planned</th>
</tr>
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<tbody>
<tr>
<td>Check BG every 1 hour until IV access established and fluids started</td>
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<tr>
<td>Check BG every 1 hour until feeds initiated. Feeds should be attempted within first hour in at risk infant.</td>
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<tr>
<td>Monitor BG hourly until infant clinically stable and BG &gt;40 x 2</td>
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<tr>
<td>Monitor BG prior to each feed every 2-3 hours for first 12-24 hours of life until BG &gt;40 x 2</td>
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<td>Continue monitoring*</td>
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<td>Every 6 hours</td>
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</table>

* Unless otherwise instructed by physicians/NPN

Notify MD/NPN immediately for BG <40mg/dl or >200mg/dl
Monitoring

<table>
<thead>
<tr>
<th>Can discontinue</th>
<th>Must resume or increase freq of monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No longer require IV fluids as glucose source</td>
<td>• Changes in GIR</td>
</tr>
<tr>
<td>• Have been on full feeds for &gt;24 hours</td>
<td>• Feeding intolerance</td>
</tr>
<tr>
<td>• No glucose instability in &gt; 24 hours</td>
<td>• Feeds held</td>
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<tr>
<td></td>
<td>• Concern for IV infiltration or loss of central line</td>
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<td></td>
<td>• Maintenance glucose interrupted or reduced &gt;1hour for transfusion, medication administration, or loss of IV access</td>
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<tr>
<td></td>
<td>• Infant receiving medication known to affect BG: indomethacin, propranolol, steroids</td>
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<td></td>
<td>• Sepsis evaluation</td>
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<td></td>
<td>• Post operative</td>
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Interventions

- If admission or routine check BG <40mg/dl: send confirmatory STAT blood glucose in GREY top tube to lab (whole blood glucose with Na Flouride)
- Treatment should not be delayed waiting for confirmatory results, notify MD/NNP
- Infants who are symptomatic should always be treated immediately with D10W bolus 2ml/kg and have maintenance IVF started

<table>
<thead>
<tr>
<th>Blood glucose (mg/dl)</th>
<th>&lt;25 weeks / Unable to feed/IV access</th>
<th>&gt;25 weeks/ able to feed/ IV access</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 OR &lt; 40 &amp; Symptomatic</td>
<td>Place PIV, administer D10W bolus (2ml/kg), and start maintenance IVF to provide GIR: 4-6 mg/kg/min for term infants 5-8 mg/kg/min for preterm infants Recheck BG in 30 minutes</td>
<td>Start maintenance IVF as above, recheck in 30 min Feed infant, recheck in 30 min</td>
</tr>
<tr>
<td>&gt;25, &lt;40 Asymptomatic</td>
<td>If repeat BG same or less, Consider D10 bolus and increase GIR by 2</td>
<td>If repeat BG same or less, place IV and start maintenance IVF as above, recheck 30min If still BG same or less, consider D10 bolus and increase GIR x2</td>
</tr>
</tbody>
</table>

Recheck every 30-60min until BG >40 ±2 one hour apart, Then continue routine monitoring
Trial of feeds
- For asymptomatic infants, BG 25-40 mg/dl, ≥ 35 weeks and no contraindications to feed
- Direct breastfeeding is best option
- Breastmilk promotes ketogenesis
- Breastfed term infants may tolerate lower BG levels – higher concentrations of ketone bodies vs. formula fed
- Baby going to breast – stimulates/sustains milk supply
- If unable to nipple, give EBM via bottle or gavage feed EBM
- Formula feed only if mom/EBM unavailable or EBM contraindicated

Weaning IV dextrose infusion
- BG ≥ 60mg/dl for over 12-24 hours, and infant clinically stable, tolerating full feeds:
- Gradually decrease vs. abrupt discontinuation to avoid sudden reactive hypoglycemia due to hyperinsulinism
- Decrease GIR 1-2 mg/kg/min every 3-4 hours
- Check AC BG while weaning GIR

Special circumstances
- If BG <25mg/dl and IV access cannot be obtained:
- Asymptomatic and no contraindications: gavage feed
- If symptomatic, or contraindications:
  - Attempt low lying UVC
  - Give glucagon 0.1mg/kg/dose (max 1mg/dose) IM or SC every 30min
    - mobilizes liver glycogen stores and will buy time to secure IV access
    - may not be effective in SGA, premature, or stressed infants due to insufficient glycogen stores
Persistent hypoglycemia

- Increase glucose infusion rate stepwise in 2mg/kg/min increments up to 12-15mg/kg/min
- Avoid adjusting > than 2mg/kg/min in 2hr interval – may exacerbate insulin release
- Caution with increasing volume where volume overload concern
- Max via PIV < D12.5W → greater concentrations require CVC
- Avoid bolus:
  - if BG >25mg/dl or with >2ml/kg – increased risk of rebound
  - With >D10W – D25W or D50W = high osmolarity

Evaluate for pathologic cause

- Persistent hypoglycemia – GIR >12mg/kg/min, or > 72 hours
- Obtain Grey top glucose, plasma cortisol, growth hormone, and insulin concentrations when BG drops <40
- If not already performed, consider evaluation for sepsis, check liver function and pancreatic function
- If infant acidotic, or dysmorphic appearance, consider checking ketone levels (beta hydroxy butyrate) and free fatty acid levels, ammonia level, lactate level, urine ketones and reducing substances
- Consider endocrine consult

Persistent Hyperinsulinemic hypoglycemia of infancy (PHHI)

- Most common cause of persistent hypoglycemia in neonates and infants
- Genetic disorders (familial and sporadic forms): dysregulation of insulin secretion
Persistent Neonatal Hypoglycemia

- Endocrine disorders
  - Hyperinsulinism
  - Panhypopituitarism
  - Isolated GH deficiency
  - Cortisol deficiency
- Metabolic disorders:
  - Glucose metabolism disorder
  - Fatty acid oxidation disorder

Summary

- There still does not exist adequate data to provide a conclusive threshold to diagnose "neonatal hypoglycemia" which may cause long term impairment, nor management strategies to best prevent long term problems.
- Basic scientists need to continue studying impact of hypoglycemia on development
- Proper prospective studies are needed to compare management regimens
- Current best practices must utilize an "operational threshold" for hypoglycemia until further evidence is found to change current practice

Useful Formulas for calculating GIR

Infusion rate (mg/kg/min) =

1) \( \frac{\text{% of dextrose being infused} \times \text{rate (ml/hr)} \times \text{body wt. (kg)}}{6} \)

2) \( \frac{\text{IV rate (ml/kg/day)} \times \text{% of dextrose}}{144} \)

3) \( \frac{\text{Fluid rate (ml/kg/day)} \times 0.007 \times \text{% of dextrose}}{\text{kg}} \)
References


Thank you!
Questions?

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