Neonatal Hypoglycemia

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Disclosure:

"Please note that this Power Point presentation is an educational tool that is general in nature. It is not intended to be an exhaustive review of the subject matter or the opinion of Palmetto Health. Materials presented in this presentation should not be considered a substitute for actual statutory or regulatory language. Always refer to your legal counsel and the current edition of a referenced statute, code and/or regulation for precise language."

Objectives

- Define three factors affecting glucose levels
- List signs and symptoms of neonatal hypoglycemia
- Recall treatment methods for neonatal hypoglycemia

Neonatal Hypoglycemia

- Most common metabolic problem in neonates
- Major long-term sequelae
  - Neurologic damage
  - Recurrent seizure activity
  - Developmental delay
- When is it harmful to an infant's brain?
  - Still really unknown

Challenge of Defining Neonatal Hypoglycemia

- Clinically significant hypoglycemia requiring intervention cannot be defined by a precise numerical blood glucose concentration because:
- Neonatal blood glucose levels:
  - Most newborns remain asymptomatic despite very low glucoses
  - Some will become symptomatic at the same or even higher glucose levels
  - Many variables with clinical response to low glucose levels
    - Gestational age
    - Presence of other sources of energy (lactate and ketone bodies)
    - Circumstances that affect glucose metabolism and cerebral glucose uptake and utilization

Challenge of Defining Neonatal Hypoglycemia

- Clinically significant hypoglycemia requiring intervention cannot be defined by a precise numerical blood glucose concentration because:
- Lack of outcome data:
  - Defining a blood glucose concentration needing intervention
  - Uncertainty over level and duration of hypoglycemia that cause damage
  - Little evidence of susceptibility of infants brain at different gestational ages

Why is Hypoglycemia a Problem?

- Glucose is the primary fuel for the brain
- Brain needs a steady supply to function
- Glucose is the infant only source of carbohydrate
- Glucose levels drop in first few hours after birth
- In healthy newborn, usually drops no lower than 40mg/dl and stabilizes within 4-6 hours to levels of 45-80mg/dl

What is Normal?

- Defining a normal glucose level remains controversial
  - 50-110 mg/dl (Karlsen, 2006)
  - ≥ 40 mg/dl (Verklan & Walden, 2004)
  - ≥ 30 term, ≥ 20 preterm (Kenner & Lott, 2004)
  - ≥ 45 mg/dl (Cowett, R. as cited by Barnes-Powell, 2007)
  - ≥ 50 mg/dl (Sick infants at PHR)
  - ≥ 45 mg/dl (SCN/Couplet infants at PHR w/risk factors)

Preparation for Extrauterine Life

- In utero, fetus relies primarily on placental transfer of glucose and nutrients from mother to meet energy demands
- The fetus stores glucose in the form of glycogen
- Fetus stores glucose in form of glycogen in the last trimester
- Glycogen is stored in the liver, heart, lung and skeletal muscle
- Fetus has limited ability to convert glycogen to glucose

Extrauterine Adaptation

- At birth
  - Glucose levels are 60-80% of the maternal values
  - When the cord is cut, infant no longer receives glucose from the mother
  - The infant will adapt to meet energy demands by mobilizing of glucose and fatty acids from glycogen

Extrauterine Adaptation

- Birth
  - Glucose levels maintained by glycogenolysis
    - Glycogen in the liver is transformed into glucose and released into the blood
  - Glycogen stores depleted during first 8-12 hours of life
  - Glucose levels maintained by gluconeogenesis
    - Glucose is formed from non-carbohydrate sources (amino acids and glycerol portion of fats)
  - Feeds established with adequate carbohydrates, glucose levels no longer dependent on gluconeogenesis
  - Feeds delayed 3-6 hours after birth, approximately 10% of normal term infants cannot maintain glucose levels above 30mg/dl

http://www.uptodate.com/contents/pathogenesis-screening-and-diagnosis-of-neonatal-hypoglycemia

Extrauterine Adaptation

- At birth
  - During first 2 hours of life
    - Decline in glucose levels
    - Followed by a rise reaching a steady-state by 2-3 hours of life
  - Hepatic release of glucose
    - Normal glucose utilization rate in fasting healthy term infant is 4-6 mg/kg/min

Factors Influencing Glucose Levels

- Three main factors that impact blood glucose levels after birth:
  - Inadequate glycogen stores
  - Hyperinsulinemia
  - Increased glucose utilization



Factors Influencing Glucose Levels

- Inadequate glycogen stores
- High Risk Infants
  - Premature
    - Glycogen stored in liver, heart, lung and skeletal muscle
    - Increase slowly in first and second trimester
    - Majority stored in third trimester
    - At term, glycogen accounts for 5 to 8% of the liver and muscle weight and 4% of the cardiac muscle weight
    - Premature infants have inadequate amounts and they rapidly deplete the glycogen

Factors Influencing Glucose Levels

- Inadequate glycogen stores
- High Risk Infants
  - Small for Gestational Age
    - Birth weight below 10% for gestational age
    - Chronically stressed
    - Higher metabolic demands
  - Term Small for Gestational Age
    - 25% at risk for hypoglycemia
  - Premature Small for Gestational Age
    - Higher risk due to chronic stress to placenta and decreased glycogen stores

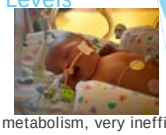
Factors Influencing Glucose Levels

- Hyperinsulinemia
- High Risk Groups
- Infant of a Diabetic Mother
  - Insulin does not cross placenta
  - Increase insulin production
  - Umbilical cord is cut, insulin level remains elevated
  - Glucose levels fall quickly
  - Insulin levels may remain elevated for days

Factors Influencing Glucose Levels

- Hyperinsulinemia
- High Risk Groups
- Large for Gestational Age
  - Birth weight greater than 90% for their gestational age
  - Insulin major growth hormone
  - Insulin is surfactant production suppressant
  - Unrecognized maternal diabetes

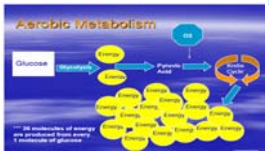
Factors Influencing Glucose Levels



- Increased glucose utilization
- High Risk Groups
  - All sick infants
  - High energy needs
  - Hypoxic infants may rely on anaerobic metabolism, very inefficient
  - Large amounts of glucose are consumed
  - Rapidly deplete glycogen stores
- Causes of Sick, Stressed Infants
  - Birth stress
  - Infection
  - Shock
  - Respiratory distress
  - Cardiac disease

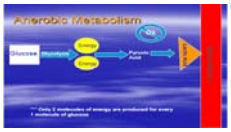
Aerobic Metabolism

- Aerobic Conditions
  - Oxygen content sufficient inside cells
  - Glucose is metabolized into energy
  - Yields 38 ATP per molecule of glucose
  - ATP is produced for energy



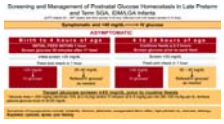
Anaerobic Metabolism

- Anaerobic Metabolism
  - Hypoxic infants may rely on anaerobic metabolism for energy
  - Oxygen level is low in the cells
  - Anaerobic metabolism yields 2 ATP per molecule of glucose
  - Very inefficient, infant consumes large amounts of glucose but gains very little energy



Which Infant's to Screen?

- 2011 AAP Guideline
  - Which infants to screen
  - When to screen
  - Laboratory data
  - Clinical signs
  - Management
- Algorithm Goal
  - Guidelines to screen and manage infants to prevent symptoms
  - Symptomatic infants will be treated promptly



Which Infants to Screen ?

- Infants at risk for hypoglycemia include:
  - Late Preterm
    - 34-36 6/7 weeks
  - Small for Gestational Age
    - Preterm
    - Term
  - Infant of Diabetic Mother
  - Large for Gestational Age
  - Stressed, sick infants

Signs and Symptoms of Hypoglycemia

- Screen At Risk and Sick Infants
- Some infants may not show any signs

General	Neurologic	Cardio respiratory
• Abnormal cry • Poor feeding • Hypothermia	• Tremors/jitteriness • Irritability • Hypotonia • Seizures	• Apnea • Tachypnea • Cyanosis

STABLE 6th Edition

Maternal Medications and Effect on the Neonates Glucose Metabolism

Medication*	Used for treatment of:	Effect on neonate's glucose metabolism
Beta-sympathomimetics[43,44,45] Terbutaline	Preterm labor	Maternal hyperglycemia leads to fetal pancreatic beta cell stimulation and increased fetal insulin secretion. Drug crosses the placenta and breaks down glycogen in the fetus.
Sulfonylureas[46,47] Chlorpropamide † Glyburide † Glipizide	Type 2 diabetes	Maternal hyperglycemia leads to fetal pancreatic beta cell stimulation and increased insulin secretion. Drug crosses the placenta and promotes insulin secretion directly.
Beta blockers[48,49] Labetalol Propranolol Metoprolol Pindolol Atenolol	Hypertension Migraine headaches Propranolol is also used for thyrotoxicosis	**Blocks** fetal β_2 adrenergic receptors (adrenoceptors) preventing their stimulation of hepatic glycogen breakdown (glycogenolysis) and pancreatic release of glucagon. Drug persists in the neonate after birth and prevents glycogenolysis.
Thiazide diuretics[50] Chlorothiazide Hydrochlorothiazide Chlorthalidone	Hypertension Edema	Maternal hyperglycemia leads to fetal pancreatic beta cell stimulation and increased insulin secretion.
Tricyclic antidepressants[51,52] Amitriptyline Nortriptyline Imipramine Desipramine	Depression	Maternal hyperglycemia leads to fetal pancreatic beta cell stimulation and increased insulin secretion.
Maternal IV dextrose † administration during labor[53]	Labor hydration	Glucose crosses the placenta and causes increased fetal insulin secretion.

STABLE 6th Edition

Blood Glucose Monitoring

- Gold standard for monitoring blood sugar level is plasma glucose value
  - Requires sample of whole blood to obtained and processed by the lab
- Most common test performed is whole blood glucose screening at bedside
  - Estimates plasma sugar level
  - May be 10-18% lower than plasma value
  - If low, obtain plasma glucose level STAT
    - Notify lab that serum glucose being sent STAT
      - RBC's will continue to consume glucose in the tube
    - DO NOT DELAY TREATING INFANT

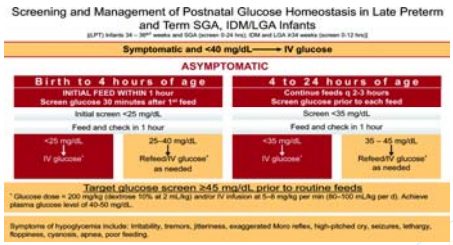
Bedside Monitoring of Blood Glucose

- Currently no point-of-care screening method reliable for sole method for screening neonatal hypoglycemia
- Evaluate blood sugar by method most rapidly available at your hospital
- Common bedside methods are:
  - OneTouch
  - ACCU-Chek
  - StatStrip
- i-STAT
  - Handheld portable blood analyzer
  - Provides access to real-time, lab quality results within minutes, rather than hours

Big Question: When to Treat?

- What we know:
  - Neonatal hypoglycemia remains one of the most controversial issues in neonatology
  - Blood glucose levels have become the grounds for litigation and for alleged malpractice
  - Managing blood glucose levels in nurseries, SCN and NICU is common
  - 2011 AAP provided guidelines for treatment

When Do We Treat?



Screening At Risk Infants

- Screening Schedule varies slightly for Late Preterm and SGA infants:
  - Feed every 2-3 hours and check blood glucose before each feeding
  - For first 24 hours after birth
- IDM and LGA infants 34 weeks gestation and greater
  - Blood glucoses screened for the first 12 hours after birth
- At risk infants should maintain normal plasma glucose for at 3 feedings before discharge

How Much Do They Need?

- Glucose requirement for healthy near term/term infant is 4-6 mg/kg/min
- IVF's with D10W at 80cc/kg/day
  - Gives GIR of 5.5mg/kg/min
- How do we calculate
  - GIR (mg/kg/min)= $\frac{\text{IV rate} \times \%\ \text{Dextrose} \times .167}{\text{wt in kg}}$

Example: Infant weight 4000 grams, IV rate is at 80cc/kg/day. How much glucose per kg is infant requiring?

IV rate calculation: $\frac{80 \times 4}{24} =$

GIR: $\frac{13.33 \times 10 \times .167}{4.0} =$

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GIR: $\frac{13.33 \times 10 \times .167}{4.0} =$ 5.5 mg/kg/min of glucose

Treatment

- Asymptomatic Infant
  - Feeding within 1 hour of age with breast milk or formula
  - Blood glucose 30 minutes after feeding
  - AAP Guidelines determine treatment by blood glucose
    - Initial screen <25mg/dl, feed and check glucose in 1 hr
    - 1 hour screen <25mg/dl, IV glucose
      - Treat with a mini-bolus of D10W at 2ml/kg give over 10 minutes
      - Treat with D10W at 80-100cc/kg/day
  - Goal is to give 5-8mg/kg/min of glucose infusion rate

Treatment

- Symptomatic At Risk Infants
- Glucose level less than 40mg/dl
- Treat with a mini-bolus of D10W at 2ml/kg give over 10 minutes
  - Glucose dose=200mg/kg
  - Recheck glucose 30 minutes after bolus complete
- Treat with D10W at 80-100cc/kg/day
  - Goal is to give 5-8mg/kg/min of glucose infusion rate

Glucose Screening of Newborns #6105

Profiled by: | 24 Hr. Check by:
Order # 6105 | Page 1 of 2

Use this guideline for the screening and management of glucose in **late preterm** infants (34 to 36 6/7 weeks gestation), **term** small for gestational age **(SGA)** infants (≥ 37 weeks gestation), infants of diabetic mothers **(IDM)** (≥ 34 weeks gestation) and large for gestational age **(LGA)** infants (≥ 34 weeks gestation) or **any infant** displaying **symptoms** of hypoglycemia.

Symptoms of hypoglycemia include: irritability, tremors, jitteriness, exaggerated Moro reflex, weak or high-pitched cry, seizures, lethargy, floppiness, cyanosis, tachypnea, apnea, poor feeding, eye-rolling.

All point of care test (POCT) glucoses that read in the low range (< 20 mg/dL) require a STAT serum confirmation glucose sent to the lab per policy.

[For Symptomatic Infants]

1. Obtain POCT glucose.
2. Notify physician immediately.
3. If POCT glucose reads (< 40 mg/dL), give 2 ml/kg dextrose (D10W) IV over 10 minutes. Recheck POCT glucose 30 minutes after D10W "mini-bolus".

[For Asymptomatic Infants (At Risk)]: **Late Preterm** infants, **Term SGA** infants, **IDM** and **LGA** infants (see above).

(Birth to 4 hours of age)

1. Give initial feed (breast feed or formula) within first hour of life and obtain POCT glucose immediately 30 minutes after this feed. If POCT glucose reads (< 25 mg/dL), feed again and recheck POCT glucose immediately 1 hour after feed. If POCT glucose < 25 mg/dL then check POCT glucose before next feed (AC) *[see # 4 below]*.
2. If POCT glucose 1 hour after second feed is required *[see above]* and reads (< 25 mg/dL) give 2 ml/kg dextrose (D10W) IV over 10 minutes and notify physician. Recheck POCT glucose 30 minutes after D10W "mini-bolus" and await further orders from physician. If POCT glucose reads 25 to 40 mg/dL await orders from physician regarding refeeding or IV glucose.
3. If infant unable to feed adequately, notify physician.

(4 to 24 hours of age)

4. Continue feeds q 2 to 3 hours. Check POCT glucose before each feed (AC). Continue AC glucoses until 12 hours of age in **IDM and LGA** infants and until 24 hours of age in **late-preterm and term SGA** infants.
5. If a POCT glucose AC reads (< 35 mg/dL) feed again and recheck POCT glucose immediately 1 hour after feed. If POCT glucose 1 hour after feed reads (< 35 mg/dL) give 2 ml/kg dextrose (D10W) IV over 10 minutes and notify physician. Recheck POCT glucose 30 minutes after D10W "mini-bolus" and await further orders from physician. If POCT glucose reads 35 to 45 mg/dL await orders from physician regarding refeeding or IV glucose.

When to Treat?

- Sick, Stressed Infants
  - Respiratory Distress
  - Birth stress (HIE)
  - Infection
  - Shock
  - Cardiac disease
- Target Glucose for Sick Infants
  - Screen on admission
  - Treat if blood glucose is Less than 50 mg/dL

Treatment of Sick Infants with Blood Glucose < 50 mg/dL

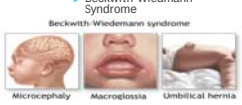
- NPO
- Give bolus of D10W 2cc/kg IV at a rate of 1.0cc/min (this dose equals 200mg/kg)
- Begin IV infusion of D10W at 80cc/kg/day
  - Provides glucose infusion rate of 5.5mg/kg/min
- Screen blood glucose every 15-30 minutes after bolus
- Document response to treatment

Treatment If Glucose Continues to be <50 mg/dL

- Repeat IV bolus of 2cc/kg/minute with D10W
- Other Options of treatment
  - Increase IV rate to 100-120cc/kg/day
  - Increase dextrose concentration to D12.5W or D15W
    - Note: Highest concentration of glucose that can be infused through a peripheral line is D12.5
  - Continue to follow glucose levels per policy
    - Every 30-60 minutes until blood glucose greater than 50mg/dl on at least two consecutive test

Persistent Hypoglycemia

- Hypoglycemia persisting or recurring over a period >7 days
- Causes:
  - **Hormone Excess Hyperinsulinism**
    - Beckwith-Wiedmann Syndrome



  - **Hormone Deficiencies**
    - Growth hormone deficiency
    - Thyroid deficiency
    - Glucagon deficiency
    - Cortisol deficiency
  - **Hereditary Defects in Carbohydrate Metabolism**
    - Glycogen storage disease type I
    - Fructose Intolerance
    - Galactosemia
  - **Hereditary Defects in Amino Acid Metabolism**
    - Maple syrup urine disease
  - **Hereditary Defects in Fatty Acid Metabolism**
    - Medium Long Chain

Management for Persistent Hypoglycemia

- Endocrine Consult
- Workup is driven by Endocrine consult
  - Laboratory studies
    - Glucose, ketones, free fatty acids, lactate, uric acid, growth hormone, cortisol, glucagon
    - Urine amino acids, organic acids
- Treatment
  - Trial of corticosteroids
  - Human growth hormone
- Note: All workups should be done at Level III center

New on the Horizon

- Sugar Babies Study published September 2013
  - Randomized, double blind, placebo controlled
  - New Zealand between December 1, 2008 and November 31, 2010
  - Large enrollment group (514), 242 became hypoglycemic and were randomized
  - 40% Dextrose Gel (200mg/kg) or placebo gel
  - Focus on at risk infants
    - 35 weeks or older
    - 48 hours of age or less
    - IDM
    - SGA
    - LGA
- Findings
  - Dextrose gel reduced the frequency of treatment compared with placebo
- Interpretation
  - Dextrose gel should be considered for first-line treatment in late preterm and term infant in the first 48 hours after birth

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)61645-1/abstract

Sugar Babies Study

- Sugar Babies Study using 40% Dextrose Gel 200mg/kg
  - More effective than feeding alone
  - Treatment is simple
  - Inexpensive
    - $2/infant
  - Well tolerated and effective
  - Supports breast feeding
    - Less need to supplement with formula
    - Supports use of colostrum
    - Supports exclusive breastfeeding
    - Supports infants staying with mothers
  - No rebound hypoglycemia
  - Less admission to the NICU
  - No adverse effects

http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)61645-1/abstract

Procedure

- Dry infants mouth with gauze
- Squirt a small amount of dextrose gel into a small cup
- Using syringe, draw up 0.5ml/kg (200mg/kg) of gel
- Using gloved finger, dispense ½ the dose onto buccal mucosa of one cheek and massage thoroughly
- Repeat with the other ½ dose on the other cheek
- Encourage infant to feed

Nutrition Facts
Serving size 1.3 oz (1 tube)
Servings per container 1
Calories 60

Amount/Serving	% Daily Value*
Total Fat 0g	0%
Sodium 80mg	3%
Potassium 98mg	3%
Total Carbohydrates 15g	5%
Sugars 15g	
Protein 0g	

Not a significant source of other nutrients.
*Percent Daily Values based on a 2,000 calorie diet.

Ingredients: purified water, dextrose (d-glucose) USP 40%, glycerin, grape flavoring and preservatives in an oral gel base.

In Closing

- Neonatal hypoglycemia is the most common metabolic condition treated in the infants
- No uniform consensus on a definition
- 2011 AAP guidelines have provided some type of standardization for testing
- Remember SICK infants do not fall under the 2011 AAP guidelines
- Know your units policy on screening "At risk and High Risk" infants

Thank you!

- Questions?
- **You will receive an email following the webinar with an evaluation, please complete the evaluation and your CE certificate will be sent electronically.**
- Please contact me for any further questions.
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  - Cathy.White@palmettohealth.org