

# Neonatal Hypoglycemia

#### When should you treat?

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#### No financial disclosure



### **Objectives:**

•By the end of this presentation, the participant will:

- Gain an understanding of hypoglycemia in the newborn.
- Identify neonates at risk for hypoglycemia during the immediate newborn period.
- Describe the signs and symptoms of hypoglycemia in the neonate.
- Identify the treatment for asymptomatic and symptomatic hypoglycemia in the neonate.



# Trivia



- Hypoglycemia has been documented as far back as 150 AD by a Greek physician known as Arateus
- •Diabetic symptoms were described in 1552 in Egypt
- •Officially named "Diabetes Mellitus" in 1675
- •Chemical test created in 1800's to identify the existence of sugar in urine
- •1916: Elliott Joslin wrote *The Treatment of Diabetes Mellitus* which is still used today to teach patients the basics of diabetes and lifestyle changes.

McCoy, 2009



- •1<sup>st</sup> incubator used in 1857 by Jean Louis Paul Denucé.
- Infant Welfare Movement (IWM) began in 1870 in Europe to decrease infant mortality.
- •IWM moved to United States in 1896.
- •Early 1900's saw the introduction of artificial feeding when breastfeeding was unavailable -Artificial feeding included milk, cream, and sugar
- •1922: 1<sup>st</sup> unit for premature infants at Sarah Morris Hospital in Chicago

•Neonatal hypoglycemia first reported in 1937

Lussky, 1999



## General Information



#### History

•Early 1900's: signs of hypoglycemia were first reported

•1920's low blood sugar was felt to be physiologic

 1930's: adopted clinical definition based on neonatal symptoms



### History

•1960's: began to define hypoglycemia based on normal values in the general population

 2000's: Returned to definition of hypoglycemia based on physiological signs and symptoms with an interventional threshold used to guide decision making



### Definition

- Hypoglycemia occurs when plasma glucose levels decrease leading to signs and symptoms of impaired brain function.
  - -Numerical definitions for hypoglycemia still remain controversial depending on context
  - "Operational threshold" is defined as the concentration of plasma or whole blood glucose at which clinicians should consider intervention. (Chandran, Rajadurai, Alim, & Hussain, 2014)



### Definition

#### Categories of hypoglycemia

- -Mild: 35 45 mg/dl
- -Moderate: 25 35 mg/dl
- -Profound: < 25 mg/dl



### Definition

#### Newborn period:

- Transient neonatal hypoglycemia
  - •1<sup>st</sup> 24 hours of life: plasma level < 30 mg/dl
  - •24 hours of life or greater: plasma level < 48 mg/dl
- -Persistent hypoglycemia
  - Persisting beyond 48 hours of life

#### Glucose level <36 mg/dl in 1<sup>st</sup> 4 hours of life

- There is no specific "cut off" level which would prevent brain injury
- Symptoms can and do occur across a range of plasma levels
- Altered brain responses can be impacted by alternative fuels such as ketones



#### **General Information**

Overall incidence of symptomatic hypoglycemia is 1 - 3 per 1000 live births.

Most common metabolic problem in neonates.

Most infants with hypoglycemia are either asymptomatic or only exhibit non-specific signs and symptoms.

Cranmer, 2018; Su & Wang, 2012



#### **General Information**

Persistent and recurrent hypoglycemia can severely impair brain growth and function

While both term and preterm infants can have neurological effects at glucose levels of 45, preterm infants are more likely to have adverse, irreversible neurological injury compared to term infants.

Cranmer, 2018; Su & Wang, 2012



### At Risk

- •Birth weight < 2 kg or > 4 kg
- •Large for gestational age (LGA)
- •Small for gestational age (SGA)
- Intrauterine growth restriction (IURG)
- •Neonates of insulin-dependent mother (1:1000 pregnant women)
- Mothers with gestational diabetes (~2% of pregnant women)
- •Preterm or Late Preterm neonates
- •Suspected of sepsis or chorioamnionitis



### At Risk

- Significant hypoxia
- Perinatal distress
- •5 minute Apgar 5 or less
- •Hypothermia
- Isolated hepatomegaly
- Microcephaly
- Multiple congenital anomalies
- Suspected inborn error of metabolism
- Maternal history of terbutaline, beta blockers, or oral hypoglycemic medications





#### Glucose

# Fetal storage of glucose occurs primarily in the 3<sup>rd</sup> trimester in the form of glycogen

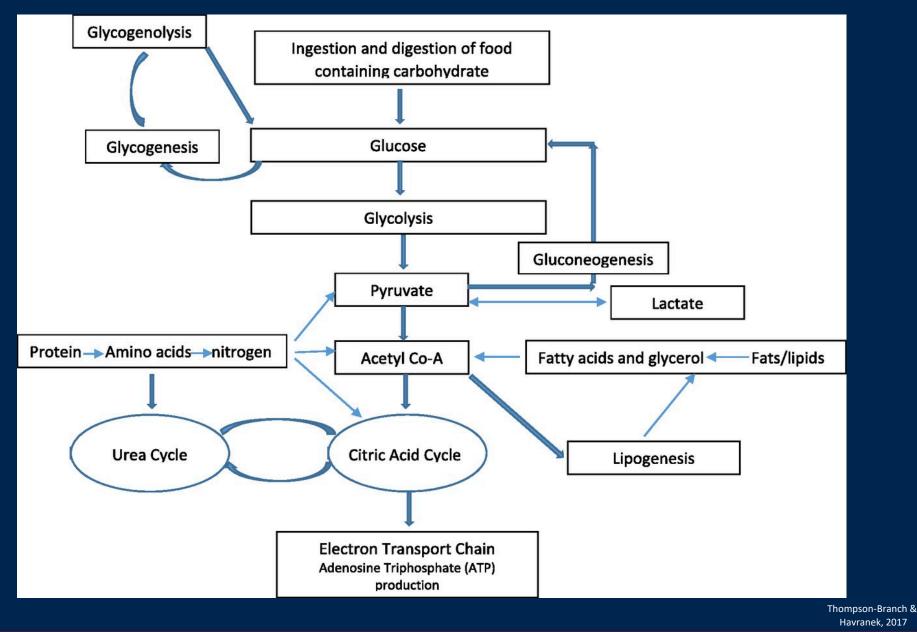
- ~ 70 – 80% of maternal glucose levels can be seen in fetus during pregnancy

#### After birth

- Glycogen is broken down into glucose molecules which are released back into the blood stream to be used as energy

Karlson, 2013







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### **Causes of Hypoglycemia**

Inappropriate changes in hormone secretion

•Inadequate substrate reserve -Hepatic glycogen

•Inadequate muscle stores -Source of amino acids for gluconeogenesis

•Inadequate lipid stores -Release of fatty acids



#### •Hormones which regulate glucose levels

-Insulin

-Glucagon

#### •How does it work?

- Insulin is secreted after food intake to increase insulin levels
- Insulin stimulates liver to store glucose as glycogen
- -When muscle/liver cells are saturated with glycogen extra glucose is stored as fat
- -When glucose levels fall
  - Glycogen is secreted to increase glucose levels through glycogenolysis
  - •Glycogenolysis releases glucose back into the blood



#### •After birth

- -Serum glucose levels decline during the 1<sup>st</sup> 3 hours after birth then begin to stabilize
- -Should reach nadir level ~ 1 hour after birth
- -Glycogen stores in the liver rapidly deplete within 1<sup>st</sup> 12 hours of life.
- -Glucose starts to increase spontaneously after 3 hours of life.
- -Gluconeogenesis accounts for ~10% of glucose usage by the neonate by several hours of age.

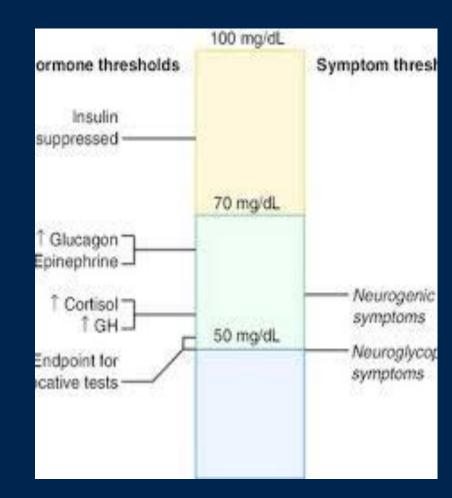


Gluconeogenesis is defined as "the formation of glucose from amino acids and the glycerol portion of fat. Muscle provides a store of glycogen and muscle protein breaks down to amino acids, which are substrates utilized in gluconeogenesis in the liver."



Glucose is the major fuel for brain functions/ metabolism

Response to hypoglycemia is hormonal (insulin suppression) and metabolic (gluconeogenesis)



Cranmer, 2018; Hawkes & Stanley, 2016



•Hypoglycemia can lead to changes such as "brain cell softening, swelling, necrosis, gyrus atrophy or white matter demyelination" (Tam et al., 2012)



#### Difference of Opinions AAP vs. PES

Timeline	0-4 hours	4-24hours	24-48 hours	>48 hours
ААР	AAP: asymptomatic screened neonate- in first 4 hours, maintain blood glucose >40mg/dL prior to feeding. Between 4-24 hours, maintain blood glucose >45 mg/dL. If symptomatic- treat if blood glucose is <40mg/dL			
PES	<b>PES (first 48 hours):</b> Maintain blood glucose > 50mg/dL. Infants who are unable to maintain a blood glucose level >50 mg/dL in the first 48 hours of life may be at risk for a disorder causing persistent hypoglycemia.			PES (After 48 hours): A blood glucose >60mg/dL is recommended by the PES AFTER 48 hours of life. Infants at risk of having a persistent hypoglycemia syndrome are recommended by the PES to have a fast challenge of 6-8 hours with maintenance of blood glucose >70mg/dL.

Thompson-Branch & Havranek, 2017





Signs, Symptoms, & Causes of Hypoglycemia

#### Who to screen?

#### Neonates at risk for asymptomatic hypoglycemia

- -Preterm
- -Late preterm
- -LGA
- -SGA
- -IUGR
- -GDM/IDM

-Neonates requiring resuscitation at birth



### **Signs and Symptoms**

Fall into two categories

Neurogenic symptoms
Affect activity along the sympathetic nervous system
Are both adrenergic and cholinergic
Neuroglycopenic symptoms
Due to brain dysfunction from a deficient glucose supply

#### Infant's may be asymptomatic or symptomatic

- -Symptomatic includes
  - CNS symptoms
  - Cardiopulmonary symptoms



#### Symptomatic Signs and Symptoms

Hypotonia Lethargy, apathy Tachypnea, apnea Poor feeding Jitteriness, seizures **Congestive heart failure** Cyanosis Apnea Hypothermia, temperature instability



### **Signs and Symptoms**

#### Autonomic nervous system

- -Adrenergic symptoms
  - •Anxiety, tremulousness
  - •Tachycardia
  - Palpitations
- -Cholinergic symptoms
  - •Diaphoresis
  - •Pallor
  - •Hunger, nausea, and vomiting



### **Causes of Hypoglycemia**

Limited glycogen stores

-Prematurity -SGA -IUGR



#### How does it work?

#### Inadequate storage

- Who is at risk?
  - Preterm and Late preterm
  - •SGA/IUGR

-What happened? Limited to no glucose storage

- •Premature birth prior to timing of glucose storage during end of 3<sup>rd</sup> trimester
- •Glucose utilization secondary to hostile uterine environment

-What does that mean?

Rapid depletion of limited storage of glucose



### **Causes of Hypoglycemia**

Hyperinsulinemia or Persistent hyperinsulinemia hypoglycemia of infancy (PHHI)

-IDM

-Congenital Hyperinsulinemia

-Congenital Hypopituitarism



#### How does it work?

#### •Hyperinsulinemia

- Who is at risk?
  - •IDM/GDM
  - •LGA
  - Congenital diabetes
- -What happened? Increased fetal insulin production
  - •Elevated glucose levels cross placenta to which fetus responds by increasing insulin production
  - Insulin levels remain high after delivery
- -What does that mean?
  - Hypoglycemia secondary to increased insulin production
  - Neonate will readjust insulin level production over next several days after delivery



### **Causes of Hypoglycemia**

#### Increased glucose use

- -Hyperthermia
- -Polycythemia
- -Sepsis
- -Growth hormone deficiency

#### Depleted glycogen stores

- -Stress
- Prolonged resuscitation
- -Asphyxia
- -HIE



## How does it work?

#### Increased utilization

- Who is at risk?
  - Hypoxia/Perinatal Asphyxia
  - Shock/Sepsis
  - Respiratory distress
  - Cardiac disease
  - •Hypothermia
- -What happened?
  - Increased utilization of glucose secondary to increased metabolic rate
- -What does that mean?
  - •Rapid depletion of adequate glucose stores



## **Causes of Hypoglycemia**

 Decreased glycogenolysis, gluconeogenesis, or use of alternate fuels

 Inborn errors of metabolism
 Adrenal insufficiency



## How does it work?

•Decreased glycogenolysis, gluconeogenesis, or use of alternate fuels

- Who is at risk?

Chromosomal anomaly – inborn error of metabolism

Galactosemia

- •MSUD
- •PKU

-What happened?

 Inability to turn glucose into energy secondary to lacking specific protein enzymes

-What does that mean?

Damage to liver, kidneys, brain, and eyes if not recognized



# Treatment for hypoglycemia



#### Treatment

#### Identified infants at risk for hypoglycemia

- -Breast or bottle feed within 1<sup>st</sup> hour of life
- -Check glucose level 30 minutes after initial feeding
- -Continue to follow glucose levels for next 12 hours prior to feedings for IDM/LGA and next 24 hours for SGA/late preterm neonates

Rozance & Hay, 2016



#### When to Treat

#### •Borderline hypoglycemia – asymptomatic

- EBM or formula
- Buccal glucose gel

#### •Moderate hypoglycemia (20 – 25 mg/dl) - IV glucose 2 ml/kg/dose



#### When to Treat

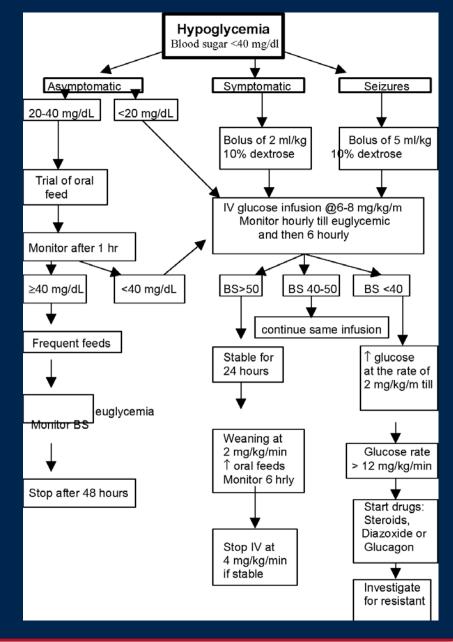
Profound hypoglycemia (< 20 mg/dl)</li>
 - IV glucose - D10w 2 ml/kg/dose

- IV fluids - D10w at 80 ml/kg/day

•Symptomatic hypoglycemia - IV glucose - D10w 2 ml/kg/dose - IV fluids – D10w at 80 ml/kg/day



## Hypoglycemic Algorithm





## Treatment

#### Asymptomatic

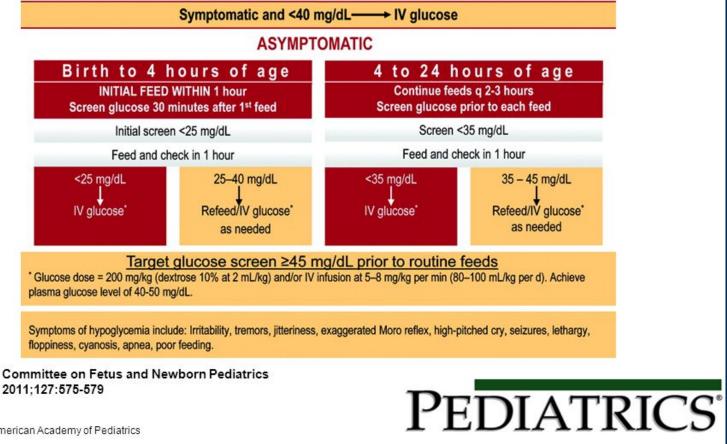
- Offer breastfeed or formula per parental preference
- Glucose Gel 40%
  - Dry cheek mucosa
  - Apply dose to mucosa and massage into cheek
  - •Dose: 0.5 ml/kg/dose
  - •For glucose levels >35 during 1<sup>st</sup> 48 hours of life
- Follow up glucose level after feed or per algorithm



Screening for and management of postnatal glucose homeostasis in late-preterm (LPT 34-3667 weeks) and term small-for-gestational age (SGA) infants and infants who were born to mothers with diabetes (IDM)/large-for-gestational age (LGA) infants.

#### Screening and Management of Postnatal Glucose Homeostasis in Late Preterm and Term SGA, IDM/LGA Infants

(LPT) Infants 34 – 3667 weeks and SGA (screen 0-24 hrs); IDM and LGA ≥34 weeks (screen 0-12 hrs)]





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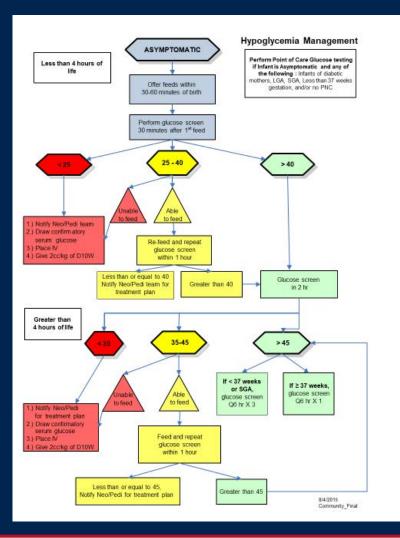
## Treatment

#### •Symptomatic

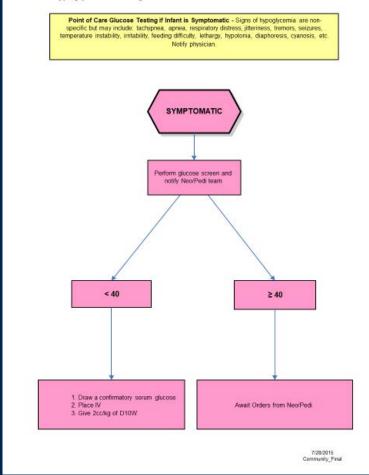
- D10w bolus 2 ml/kg/dose
- IV maintenance fluids start at 80 ml/kg/day to give GIR 5.5 mg/kg/min
- Recheck glucose level 30 minutes after treatment given
  - Goal of 50 110 mg/dl x 2
- If low, repeat bolus and/or increase IV fluids
  - "Stair step" subsequent increase in treatments
    - •D10 to 100 ml/kg/day
    - •If need to increase change to D12.5 w
- If need to increase to D15 or higher, UCV or PICC line must be placed



## **TCH Hypoglycemia Algorithm**

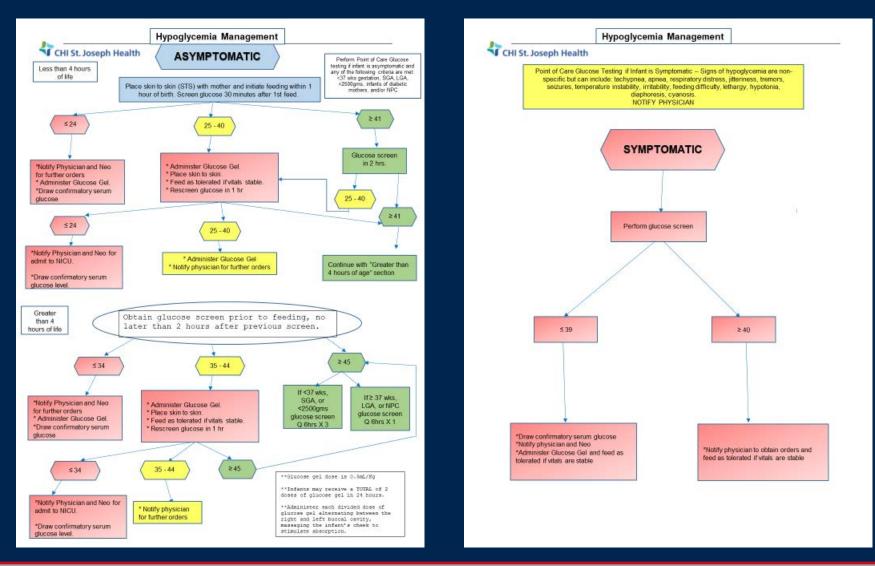


#### Hypoglycemia Management





#### **SJHRH Hypoglycemia Algorithm**





# Outcomes Short and Long Term



## Prognosis

 It is not known at exactly what level or for how long hypoglycemia must occur in order to affect the neonate's developing brain.

- -However, risk of adverse neurologic damage increases with severity and duration of hypoglycemia
- Infants are 2 3 times more likely to have issues with planning, memory, attention, problem-solving, and visualmotor coordination by 4 – 5 years of age
- -Raising glucose levels too fast, too high has an even greater risk of brain damage



## Prognosis

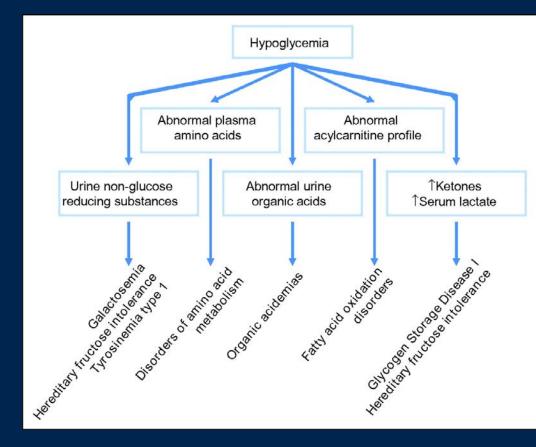
#### •Major long-term sequelae include

- -Neurologic damage
  - Mental retardation
  - Recurrent seizure activity, epilespy
  - Cerebral palsy
  - Developmental delay
  - Personality disorders
- -Cardiovascular impairment
  - Myocardial ischemia
  - Prolonged QT interval



## **Inborn Errors of Metabolism**

Prognosis and long term outcomes are related to the timing of diagnosis and interventions to correct hypoglycemia





#### **Brain Damage**

 Irreversible brain damage with seizures noted with hypoglycemia of 20 mg/dl
 Also known as Hypoglycemic Encephalopathy

•Seizures are located in the occipital and parietal lobes with similar patterns noted -Occipital lobe epilepsy

•Specific injury can be seen on MRI with injury to the posterior white matter and pulvinar edema

(Wong et al., 2013)



## Conclusion

#### •Further research is needed

- To determine treatment of asymptomatic hypoglycemia
- Identify specific definitions for neonatal hypoglycemia
  - How low is too low

#### •Treatment

- Algorithm further definition with consistent compliance in both NBN and NICU
- Avoid swings from too low to too high



## **Questions?**





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