

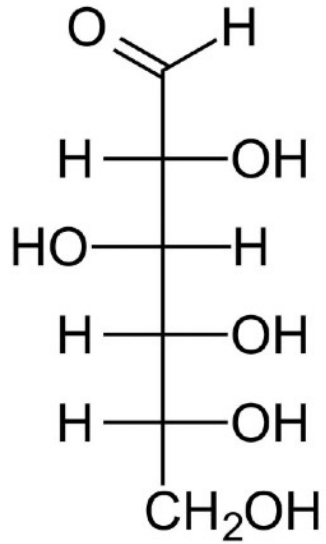
Guidelines for Detecting and Managing Neonatal Hypoglycemia: A Neonatologist's Perspective

Jeffrey R. Kaiser, MD, MA

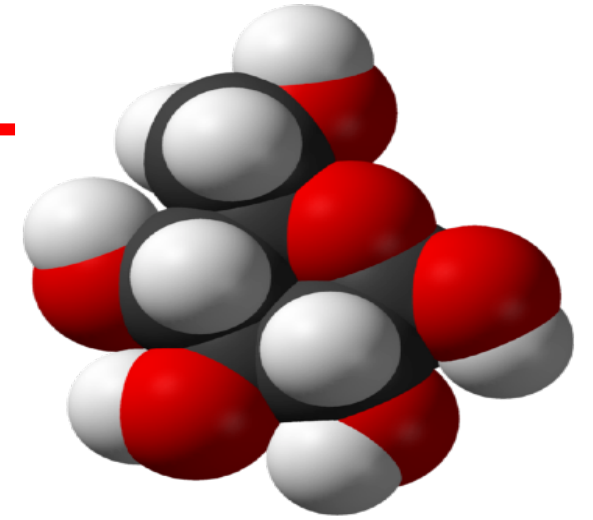
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Congenital Hyperinsulinism Family Conference
April 15, 2023

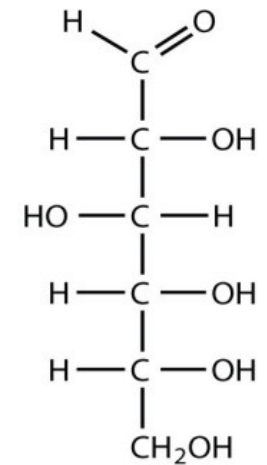
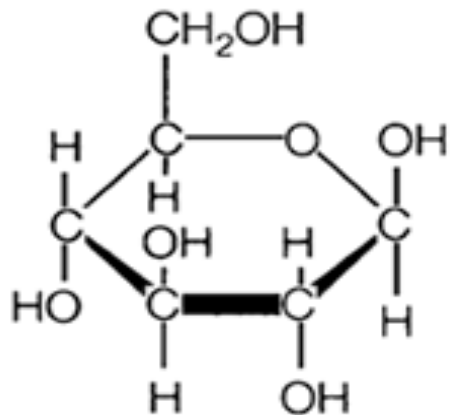
Disclosure Statement



I have nothing to disclose



Glucose



Other Than I Live in...



“The Sweetest Place on Earth”

Objectives

1. Discuss controversies about neonatal hypoglycemia
2. Screening algorithms
 1. American Academy of Pediatrics (AAP)
 2. Pediatric Endocrine Society (PES)
 3. Penn State
3. Characteristics of a good screening test
4. Are the AAP and PES guidelines good screening tests?
5. A suggestion (based on PES members)

Controversies about Clinically Significant Hypoglycemia

- “The definition of clinically significant newborn hypoglycemia remains one of the most confusing and contentious issues in contemporary neonatology...”
- *--Marvin Cornblath (2000)*
- This remains true 23 years later

Neonatal Hypoglycemia: Transient vs. Prolonged and Persistent

- Practical recommendations from international bodies (AAP and PES) are based on expert consensus rather than evidenced-based studies
- According to the AAP, Transient Neonatal Hypoglycemia
 - May be one of the most preventable causes of brain injury
 - Overtreatment, though, may lead to decreased breastfeeding and inflicting unnecessary repeated painful heel sticks
- Prolonged and persistent neonatal hypoglycemia (PES)
 - Permanent hypoglycemic brain injury still occurs in up to 50% of infants with congenital hyperinsulinism due to delays in diagnosis and treatment

Purpose of Newborn Hypoglycemia Screening

- To identify newborns with pathological forms of hypoglycemia (for ex., Congenital Hyperinsulinism) and provide timely treatment to prevent subsequent brain injury

Characteristics of a Good Newborn Screening Test

- Screening tests are used to determine if someone without signs of a disease, has a disease
- A **good** screening test will detect the disease early, when treatment is more effective than if diagnosed later (for ex., colon cancer screening, hypertension screening, gestational diabetes screening)
- Important considerations:
 - The disease
 - Causes significant morbidity and mortality
 - Treatment prevents poor outcomes if detected early
 - The screening test
 - Can detect a high proportion of the disease in its asymptomatic state
 - Safe, non-invasive, easy to administer
 - Leads to improved health outcomes
 - Be widely available, not just at Children's Hospitals

AAP Hypoglycemia Guidelines

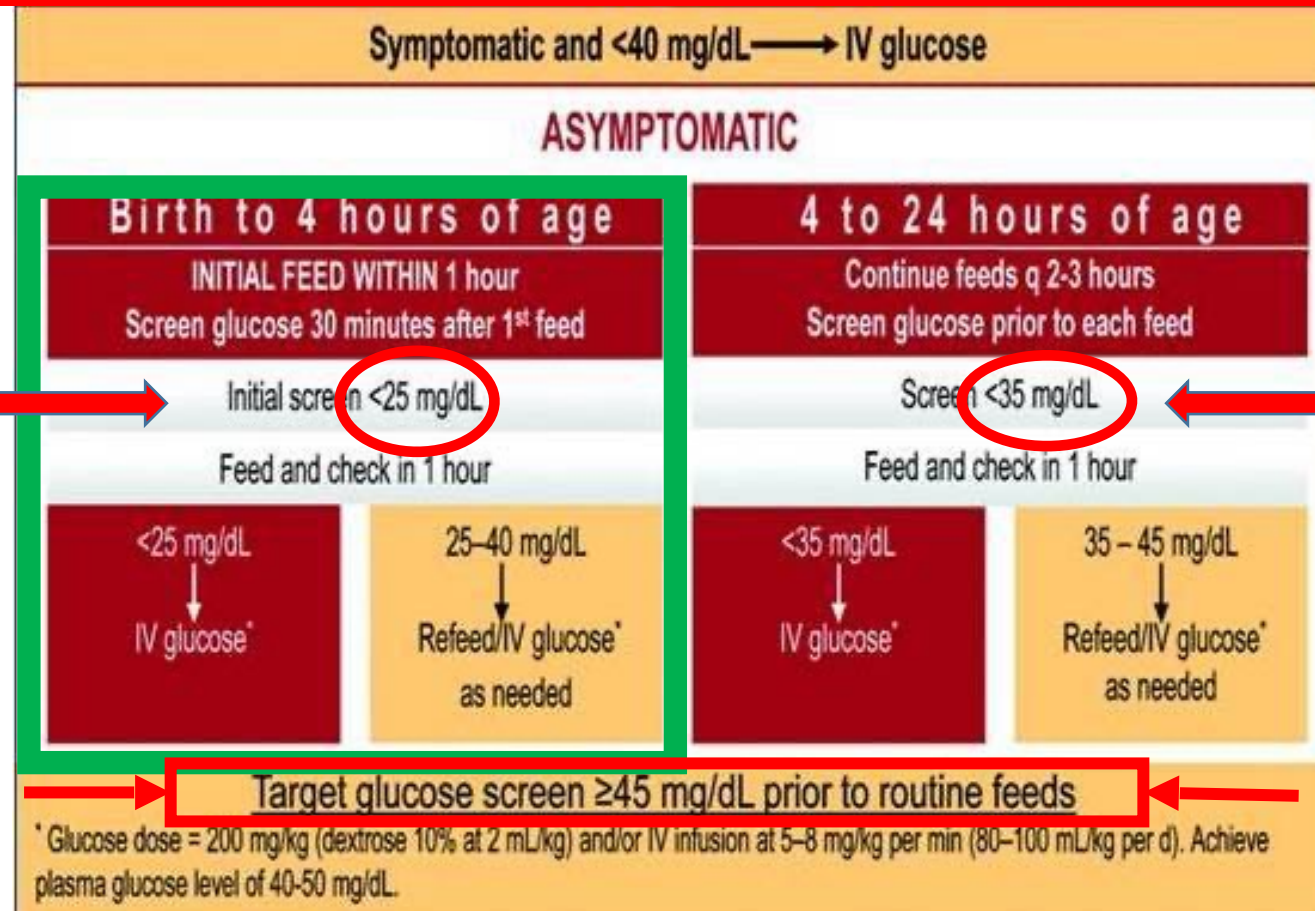
- In 2011, the AAP published a Clinical Report-Postnatal Glucose Homeostasis in Late-Preterm and Term Infants
- Because of a 2008 NIH Report that concluded there was a lack of evidence if transient hypoglycemia causes brain injury, and because "screening for, preventing, and treating neonatal hypoglycemia remains largely empirical"
- The AAP presented a pragmatic approach to screening and management of neonatal hypoglycemia in at-risk newborns with the implicit understanding that an evidenced-based definition does not exist, and guidance was needed

Algorithm Proposed in 2011 by the AAP

American Academy
of Pediatrics



DEDICATED TO THE HEALTH OF ALL CHILDREN®



Clinical Report—Postnatal Glucose Homeostasis in Late-Preterm and Term Infants

Primary goals: prevent and treat low glucose concentrations. Follow-up glucose measurements to permit recognition of CHI



Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children

2015

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• Neonatal Hypoglycemia

- During the first 48 hours after birth, focus on stabilizing glucose concentrations
- After 48 hours, persistently hypoglycemic infants should be worked-up to determine etiology

Condition	Age	Treatment Target
At-risk newborns <i>without</i> a suspected congenital hypoglycemia disorder	Birth to 48 Hours	≥50 mg/dL
	>48 Hours	≥60 mg/dL
At-risk newborns <i>with</i> a suspected congenital hypoglycemia disorder	Any Time	≥70 mg/dL

Many Hospitals have Developed Their Own Guidelines (Example: Penn State)

Age	Treatment Target
Birth-4 Hours	≥ 40 mg/dL
4-24 Hours	≥ 45 mg/dL
24-72 Hours	≥ 50 mg/dL
>72 Hours	≥ 60 mg/dL

Are the AAP and PES Screening Guidelines Good Screening Tests?

AAP Guideline

- In a word...*NO*
- Asymptomatic transient hypoglycemia has not been shown to cause brain damage
- Treatment has never been shown to improve outcomes

PES Guideline

- Not sure...
- In theory by having higher treatment targets, more infants are identified who cannot maintain those levels, and are worked up, diagnosed, and treated
- However, most neonatologists do not use the PES Guidelines, as they feel too many infants will be worked-up, have multiple needle sticks, and be removed from their mothers, when they do not have significant disease

Incidence of Congenital Disorders Identified Through Newborn Screening

Condition Abbreviation	Condition*	Incidence
Hemoglobinopathies	Sickle Cell Anemia, β -thalassemia, SC disease	1 / 2,000
CH	Congenital Hypothyroidism	1 / 3,000-4,000
SMA	Spinal Muscular Atrophy	1 / 10,000
PKU	Phenylketonuria	1 / 10,000-15,000
CAH	Congenital Adrenal Hyperplasia	1 / 15,000
X-ALD	X-linked Adrenoleukodystrophy	1 / 17,000
GAA	Pompe Disease	1 / 29,000
GALT	Galactosemia (Classical)	1 / 48,000
MPS I	Hurler Syndrome	1 / 91,000
MSUD	Maple Syrup Urine Disorder	1 / 185,000

*Conditions mandated for screening and follow-up by Pennsylvania Newborn Screening Program

Should Congenital Hyperinsulinism be Added to State Newborn Screening Tests?

- Incidence is 1 / 25,000-50,000 live births
- This incidence falls within the realm of disorders that are screened for in Pennsylvania, from 1 / 2,000 to 1 / 185,000 live births

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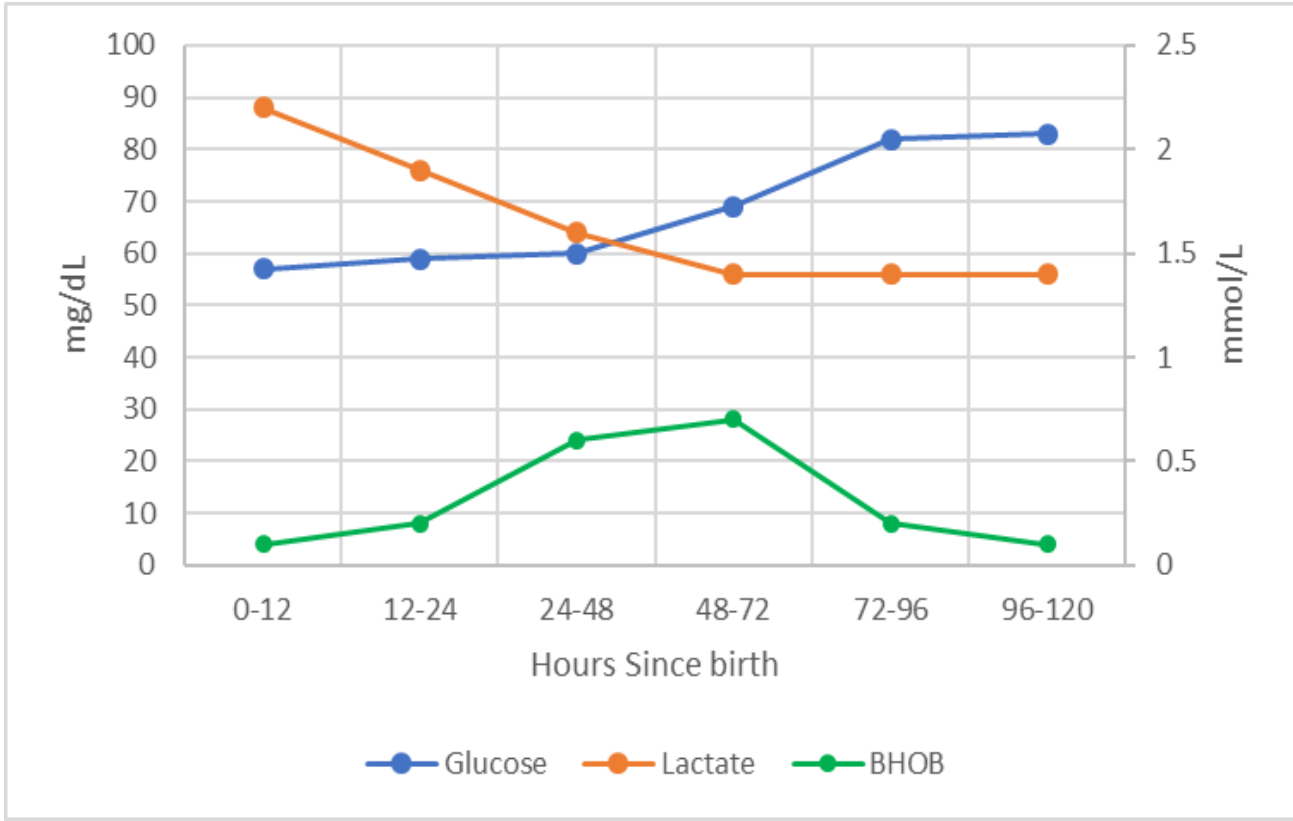
Should Congenital Hyperinsulinism be Added to State Newborn Screening Tests?

- Perhaps, a newborn screening test for Congenital Hyperinsulinism should be performed as well
 - It will also pick up other perinatal stress-induced hyperinsulinism, with an incidence of 1 / 1,200 live births, which causes prolonged hyperinsulinism
- Actually Not! State Newborn Screenings will be too late to prevent brain injury in newborns with congenital hyperinsulinism, as results are not available until day 7

Glucose, Alternative Fuels, and Brain Injury

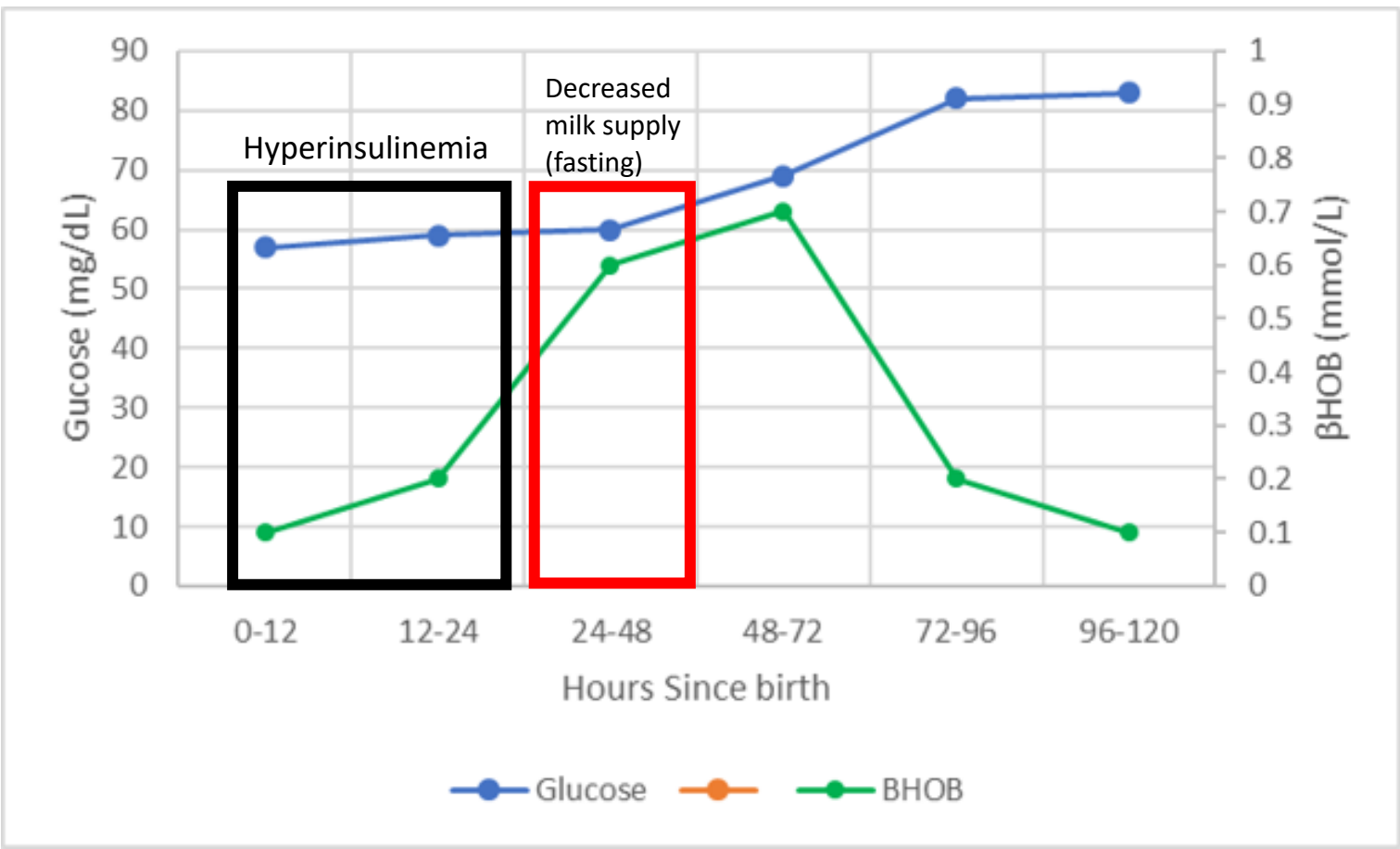
- Glucose is the primary energy source for the brain
- Newborns try to compensate for low fuel to the brain during hypoglycemia by using non-glucose brain fuels (alternative fuels) such as lactate and ketones
- Hypoglycemia is often due to hyperinsulinism, and insulin suppresses the making of ketones
- Unfortunately, alternative fuels cannot fully compensate for low glucose concentrations in the brain
- Thus, severe, prolonged, and persistent hypoglycemia leads to brain injury

Average Glucose, β -hydroxybutyrate (BOHB, ketones), and Lactate during the First 5 Days in Healthy, Term, Mostly Breastfed Neonates



- Determine average patterns of glucose concentrations and alternative fuels (BOHB and lactate) in healthy term newborns (mostly breastfed) during the first 5 days
 - 67 newborns
 - Interestingly, 39% of these healthy newborns had low glucose concentrations (most commonly during the first 12 hours after birth)

Glucose and β -hydroxybutyrate (BOHB, ketones) during the First 5 Days in Healthy, Term, Mostly Breastfed Neonates



In newborns, when insulin levels are high, ketone levels are low

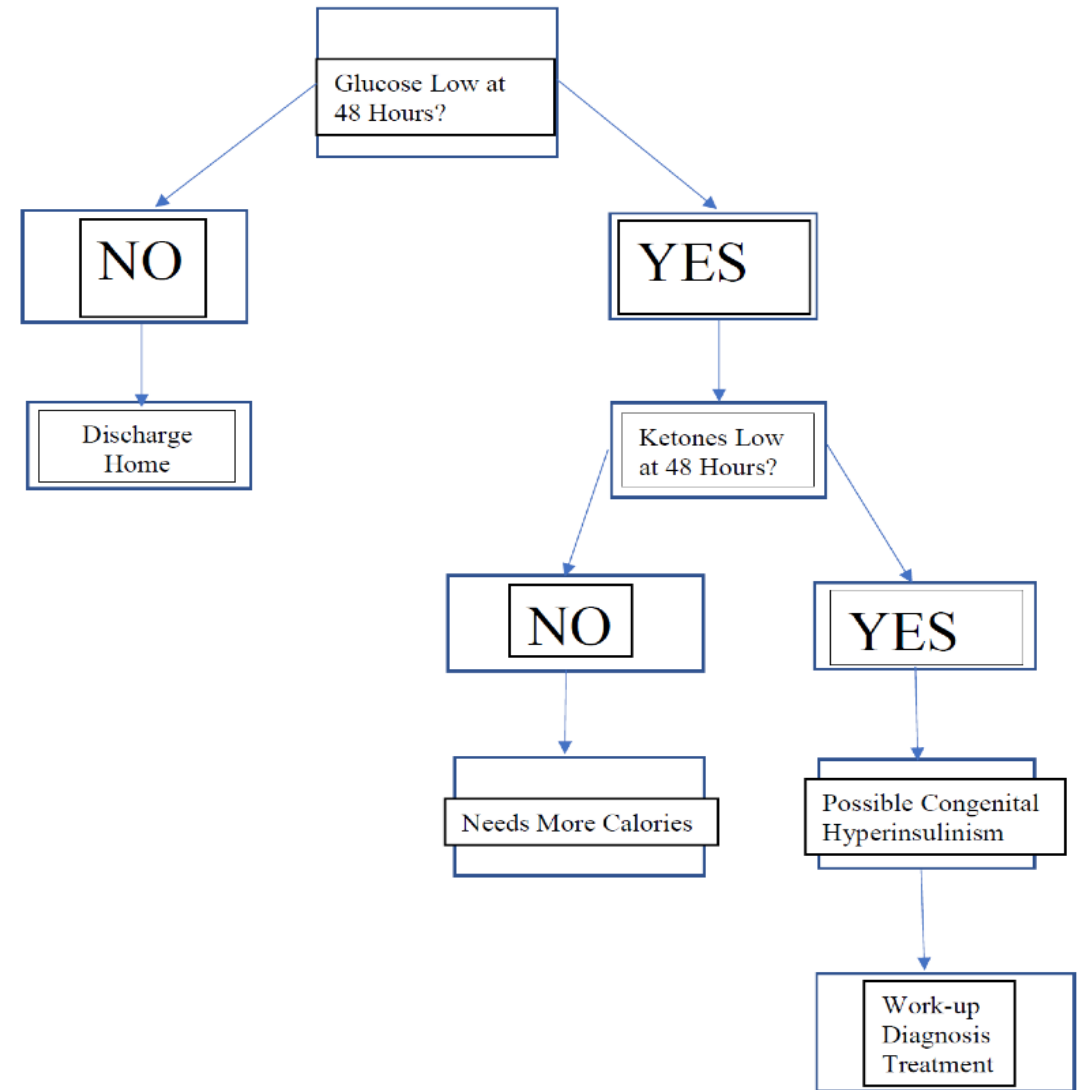
INSULIN ----> ketones

When insulin levels decrease, and there is not enough breast milk supply (or during fasting), ketone levels increase

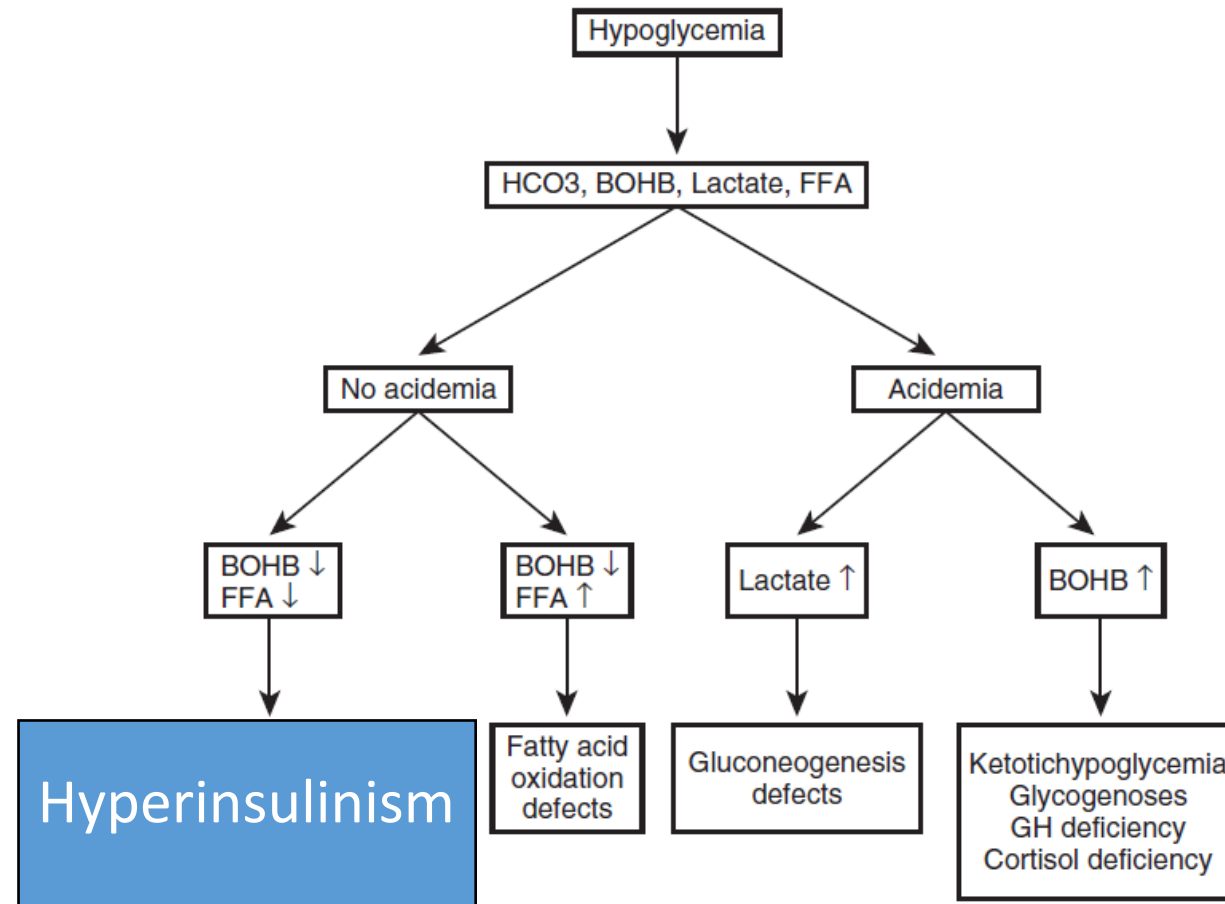
Insulin ----> **KETONES**

Suggestion for a Simple Screening Test*

- We can make use of what is known about Insulin physiology:
- At 48 hours after birth (or before discharge from the hospital) check Glucose and Ketones at the same time as the state Newborn Screen, **so only 1 needle stick is needed**



When there is a Low Glucose Concentration after 48 Hours, a Critical Sample is Taken



1. Critical sample
 - Plasma glucose
 - Electrolytes (or blood gas) to check acid/base status
 - B-hydroxybutyrate, to check ketones
 - Lactate
 - Free fatty acids (FFA)
 - Insulin level
 - Others
2. And then a glucagon challenge test

Guidelines for Detecting and Managing Neonatal Hypoglycemia: A Neonatologist's Perspective

- AAP guidelines are too lax
- PES guidelines are too conservative (for most neonatologists)
- Individual centers' guidelines are “just right”
- Do not add Congenital Hyperinsulinism to state Newborn Screening
- To screen for hyperinsulinism, at 48 hours after birth or at discharge, check glucose and ketones
 - This has been previously suggested by PES members
 - It is time for neonatologists to support this recommendation
- And follow-up studies should be performed to assess if this screening recommendation prevents more brain injury

This is Your Baby's Brain (When Glucose Concentrations are Adequate)



ANY
QUESTIONS
?

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