Glucose Metabolism in The NICU

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Pediatrix Medical Group
Objectives

• To discuss the physiology of glucose metabolism
• To review the derivation of the definition of hypoglycemia
• To identify the most common causes for hypo- and hyper-glycemia
• To discuss management strategies to reduce the problems associated with both.
Physiology
Glucose Balance

• Blood glucose concentration is a balance between glucose input into the circulation from food intake and glucose extraction from blood for consumption by the tissues.

• Glucose input includes sugars and carbohydrates in the diet, glucose release from glycogen stores, and gluconeogenesis.

• Pathways of glucose extraction include glucose storage as glycogen in the liver and muscles, glucose conversion to lipid, and glucose oxidation.
Glucose Utilization

http://www.umanitoba.ca/dnalab/graduate/pancreas10.htm
### Glycogenolysis
- Breakdown of hepatic glycogen yielding glucose

### Gluconeogenesis
- Production of glucose from noncarbohydrate precursors

### Lipolysis
- Breakdown of fat

### Ketogenesis
- Creation of ketones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Glucose Oxidation</th>
<th>Glycogenolysis</th>
<th>Glucose Oxidation</th>
<th>Glycogenolysis</th>
<th>Glucose Oxidation</th>
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<tbody>
<tr>
<td>Insulin</td>
<td>↑</td>
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<td>Growth hormone</td>
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<td>Cortisol (ACTH)</td>
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<tr>
<td>Epinephrine</td>
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<tr>
<td>Glucagon</td>
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</tbody>
</table>
During periods of fasting, the source of energy shifts from the oxidation of glucose to the oxidation of fat.

Early in fasting, glucose is supplied by the breakdown of hepatic glycogen stimulated by epinephrine and glucagon.

After hepatic glycogen stores are depleted, the body depends on new glucose produced from precursors in muscle and adipose tissue.

Gluconeogenesis is stimulated by growth hormone and cortisol.

With prolonged fasting, adipose tissue is broken down into free fatty acids (FFA) and glycerol.

FFA can be used directly as a fuel by tissues and are oxidized in the liver to provide energy with resultant formation of ketone bodies (acetoacetate and β-hydroxy-butyrate).

Ketone bodies can be used as an alternate fuel as previously mentioned.
Definition of Hypoglycemia

We still do not know how to diagnose hypoglycemia.
The magnitude of concern about a medical disorder often is inversely related to the amount of accurate data defining it.

Dr. Cornblath describes how concern for neonatal hypoglycemia has grown exponentially over the past 50 years.

The characteristics of low glucose concentration that might cause irreversible neuronal injury remain relatively undocumented and poorly defined.
Two pediatric organizations, the Committee on the Fetus and Newborn from the American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society (PES), have provided expert opinion on the management of neonatal hypoglycemia.

*Using different approaches, the two organizations suggested different ranges of glucose levels to act on in the first 48 hours of life.*

The AAP relied on an analysis of the lower range of glucose that occurs during the establishment of postnatal glucose homeostasis and advised actionable ranges of 25-40 mg/dL for the first 4 hours of life and 35-45 mg/dL from 4 hours to 24 hours of age.

The PES used neuroendocrine and metabolic data to demonstrate that the first 48 hours can be characterized as a transitional hyperinsulinemia with low ketone levels, inappropriate preservation of glycogen, and mean glucose levels of 55-65 mg/dL.
• *The problem is that experts from both societies cannot agree on what these thresholds should be.*

• The higher the glucose threshold that is set for screening and the more often these tests are recommended, the more often asymptomatic patients with low blood glucose levels will be identified, which could result in a neonatal intensive care admission, separation from mother for an asymptomatic infant, and provide a hindrance to successful breastfeeding.

Pathogenesis, screening, and diagnosis of neonatal hypoglycemia – UpToDate. Paul J Rozance, MD


• With loss of the continuous transplacental supply of glucose, plasma glucose concentration in the healthy term newborn falls during the first two hours after delivery, reaching a nadir that usually is no lower than 40 mg/dL (2.2 mmol/L), and then stabilizes by four to six hours of age in the range of 45 to 80 mg/dL (2.5 to 4.4 mmol/L).

• Transient low blood glucose concentrations in neonates are normal, as the source of glucose at delivery changes from a continuous supply from the mother to an intermittent supply from milk feeds.
• Blood glucose concentrations as low as 30 mg/dL are common in healthy neonates by 1 to 2 hours after birth; these low concentrations, seen in all mammalian newborns, usually are transient, asymptomatic, and considered to be part of normal adaptation to postnatal life.

• Most neonates compensate for “physiologic” hypoglycemia by producing alternative fuels including ketone bodies, which are released from fat.

- There is not a specific plasma glucose concentration or duration of hypoglycemia that can predict permanent neurologic injury in high-risk infants.

- Data that have linked plasma glucose concentration with adverse long-term neurologic outcomes are confounded by variable definitions of hypoglycemia and its duration (seldom reported), the omission of control groups, the possible inclusion of infants with confounding conditions, and the small number of asymptomatic infants who were followed.

- In addition, there is no single concentration or range of plasma glucose concentrations that is associated with clinical signs. Therefore, there is no consensus regarding when screening should be performed and which concentration of glucose requires therapeutic intervention in the asymptomatic infant.
Glucose

Days Since Birth

Median Glucose (mg/dl)

23
36
90th
10th

• The authors sought to characterize the normal values of blood glucose levels in a large cohort of neonates admitted to the well-baby nursery.

• The blood glucose levels were measured with a point of care (POC) glucometer (Accu-Chek Performa) within 180 minutes after birth.

• The study population included 3,912 newborns with a mean birth weight of 3,322 +/- 439 g and a mean gestational age of 39.4 +/- 1.3 weeks.

• Sampling was performed at a median age of 73 minutes (interquartile range [IQR], 55-92 minutes).

• Median glucose concentration was 58 (IQR, 51-67) mg/dL, and first, third, and fifth percentiles were 34, 39, and 41 mg/dL, respectively.
Neonatal Hypoglycemia. Alecia Thompson-Branch, MD; Thomas Havranek, MD
Division of Neonatology, Children’s Hospital at Montefiore, Bronx, NY
Pediatrics in Review. Vol. 38 No. 4 APRIL 2017 147.

<table>
<thead>
<tr>
<th>Timeline</th>
<th>0-4 hours</th>
<th>4-24 hours</th>
<th>24-48 hours</th>
<th>&gt;48 hours</th>
</tr>
</thead>
</table>

**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 (first 48 hours)**: 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.

*Figure 2.* Pediatric Endocrine Society (PES) and American Academy of Pediatrics (AAP) neonatal hypoglycemia guidelines in the first 48 hours after birth and beyond.
Symptoms

• Jitteriness
• Cyanosis (blue coloring)
• Apnea (stopping breathing)
• Hypothermia (low body temperature)
• Poor body tone
• Poor feeding
• Lethargy
• Seizures
Causes of Hypoglycemia
Transient Hypoglycemia

- Infants of diabetic mothers
- Prematurity
- Hypothermia
- Intrauterine growth restriction (IUGR)
- Small for gestational age (SGA)
- Septicemia, asphyxia/birth depression
- Erythroblastosis fetalis
- Beckwith-Wiedemann syndrome
Diagnosis of Hyper and Hypoglycemia
Diagnosis of Hypoglycemia and Hyperglycemia

![Bar chart showing the percent with diagnosis of Hypoglycemia and Hyperglycemia for different percentiles.](chart.png)

- GT3rd
- GT10th
- GT25th
- GT50th
- GT75th
- GT90th
- GT97th

**Legend:**
- Hypoglycemia
- Hyperglycemia
Rare Causes of Hypoglycemia

The incidence of inborn errors of metabolism that lead to neonatal hypoglycemia are rare but can be screened in infancy:

- Carbohydrate metabolism disorders (>1:10,000)
- Fatty acid oxidation disorders (1:10,000)
- Hereditary fructose intolerance (1:20,000 to 1:50,000)
- Glycogen storage diseases (1:25,000)
- Galactosemia (1:40,000)
- Organic acidemias (1:50,000)
- Phosphoenolpyruvate carboxykinase deficiency (rare)
- Primary lactic acidosis (rare)
Persistent Hypoglycemia

• Hyperinsulinemia
  • PHHI
  • Beta-cell adenoma
  • Exogenous insulin administration
  • Sulfonylurea use

• Hormone deficiency
  • Growth hormone
  • Adrenal insufficiency
  • Glucagon
  • Hypothyroidism
  • *Panhypopituitarism*

• Errors of metabolism
  • Carbohydrate metabolism disorders
  • Fat metabolism disorders
  • Amino acid metabolism disorders
  • Ketotic hypoglycemia

• Liver Diseases
Congenital Hyperinsulinism
https://emedicine.medscape.com/article/923538-overview#a4

- The underlying genetic defects of b-cell regulation include a severe recessive disorder of the sulphonylurea receptor, a milder dominant form of hyperinsulinism, and a syndrome of hyperinsulinism plus hyperammonaemia.

- Estimates for the incidence of congenital hyperinsulinism vary from 1/40,000 live births in northern Europe to 1/2675 live births in Saudi Arabia where consanguineous marriages are common.

- This condition requires prompt medical and surgical therapy in order to prevent permanent brain damage.
CHI is a clinically, pathologically, and genetically heterogeneous disease. Most cases are sporadic. In approximately 50% of cases, no known genetic abnormality is found. Familial forms of CHI are rare but well documented. Currently, the following 9 genes are associated with CHI:

- ABCC8, also known as SUR1: Beta-cell high-affinity sulfonylurea receptor gene
- KCNJ11, also known as Kir6.2: Inwardly rectifying potassium channel gene
- GCK, also called GK: Glucokinase gene
- GLUD1, also called GUD1: Glutamate dehydrogenase gene - This gene is associated with hyperinsulinism with hyperammonemia
- HADH: 3-hydroxyacyl-coenzyme A dehydrogenase
- SLC16A1: Solute carrier family 16, member 1
- HNF4A: Hepatocyte nuclear factor 4-alpha
- HNF1A: Homeobox A
- UCP2: Uncoupling protein 2
Pancreatic specimen showing diffuse persistent hyperinsulinemic hypoglycemia of infancy (PHHI) viewed at low power. The paler-staining cells are the neuroendocrine (islet) cells, which should be arranged in discrete islands within the acinar lobules. Acinar cells are the exocrine cells that have denser-staining, dark eosinophilic cytoplasm. These acinar cells are arranged in acini-small glands. In PHHI, more of the neuroendocrine cells are present, and they are arranged more diffusely throughout the lobules. Image courtesy of Phil Collins, MD; eMedicine Specialties > Pediatrics: General Medicine > Endocrinology -- Persistent Hyperinsuliminic Hypoglycemia of Infancy Author: Robert S Gillespie, MD, MPH, Department of Pediatrics, Cook Children's Medical Center; Coauthor(s): Stephen Ponder, MD, CDE, Director, Division of Pediatric Endocrinology, Department of Pediatrics, Driscoll Children's Hospital; Professor, Texas A&M College of Medicine
Who needs to be screened?
High-risk groups who need screening

- Newborns who weigh more than 4 kg or less than 2 kg
- Large for gestational age (LGA) infants who are above the 90th percentile, small for gestational age (SGA) infants below the 10th percentile, and infants with intrauterine growth restriction
- Infants born to insulin-dependent mothers (1 in 1000 pregnant women) or mothers with gestational diabetes (occurs in 2% of pregnant women)
- Gestational age less than 37 weeks
- Newborns suspected of sepsis or born to a mother suspected of having chorioamnionitis
- Newborns with symptoms suggestive of hypoglycemia, including jitteriness, tachypnea, hypotonia, poor feeding, apnea, temperature instability, seizures, lethargy
- Significant hypoxia; perinatal distress; or 5-minute Apgar scores less than 5
- Mother on terbutaline, beta-blockers, or oral hypoglycemic agents;
- Possibility of an inborn error of metabolism or genetic disorder.
Diagnostic evaluation of persistent hypoglycemia

- Plasma confirmation of a low blood glucose value
- Simultaneously with the blood glucose measure
  - Insulin
  - Cortisol
  - Growth hormone
- Further laboratory assessments for severe or persistent hypoglycemia should include: lactic acid, ammonia, urinary ketones, hydroxybutyrate, free fatty acids, acylcarnitine profile, plasma amino acids, and urine organic acids.
HYPOGLYCEMIA

NO HEPATOMEGALY
Measure: Glucose
Insulin
Cortisol
Growth hormone
Lactate
β OH Butyrate*

HEPATOMEGALY

NORMAL
LACTATE †

LACTATE NL

HIGH INSULIN
β OH Butyrate

LOW HORMONE ↓
DEFECT IN GLUCONEOGENESIS
DEFECT IN GLYCOGEN METABOLISM

HYPERINSULINEMIA

DEFECT IN FATTY ACID OXIDATION
HORMONE DEFICIENCY

*β OH Butyrate is β-hydroxybutyrate (ketones)
Morbidity Associated with Hypoglycemia
Importance of Glucose to the Brain

- The brain and formed elements of blood have an obligatory glucose requirement.
- Brain cells are permeable to glucose and can utilize glucose without the intermediation of insulin.
- The brain is able to metabolize ketone bodies, acetoacetate, and beta-hydroxybutyrate for up to two-thirds of its energy requirements in the absence of glucose.
Fourth-grade achievement test scores in 1395 newborn-student pairs (71.8%). Transient neonatal hypoglycemia (glucose level <35, <40, and <45 mg/dL) was observed in 6.4% (89 of 1395), 10.3%(143 of 1395), and **19.3% (269 of 1395)** of newborns, respectively.

After controlling for gestational age group, race, sex, multifetal gestation, insurance status, maternal educational level and socioeconomic status, and gravidity, **transient hypoglycemia was associated with decreased probability of proficiency on literacy and mathematics fourth-grade achievement tests.**

Figure 1. Initial Newborn Glucose Concentrations From 1395 Matched Newborn-Student Pairs

<table>
<thead>
<tr>
<th>Glucose Concentration, mg/dL</th>
<th>No. of Newborn-Student Pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
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<tr>
<td>40</td>
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<td>60</td>
<td>30</td>
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<td>80</td>
<td>40</td>
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<td>100</td>
<td>50</td>
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<tr>
<td>120</td>
<td>60</td>
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<tr>
<td>140</td>
<td>70</td>
</tr>
<tr>
<td>160</td>
<td>80</td>
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</table>

To convert glucose concentration to millimoles per liter, multiply by 0.0555.

- Studied 35 term infants with early brain MRI scans after symptomatic neonatal hypoglycemia (median glucose level: 1 mmol/L) without evidence of HIE.
- Compared with equivalent data from 229 term, neurologically normal infants (control subjects), to identify risk factors for hypoglycemia.
- White matter abnormalities occurred in 94% of infants with hypoglycemia, being severe in 43%, with a predominantly posterior pattern in 29%
- Cortical abnormalities occurred in 51% of infants; 30% had white matter hemorrhage, 40% basal ganglia/thalamic lesions, and 11% an abnormal posterior limb of the internal capsule. Three infants had middle cerebral artery territory infarctions.
- Twenty-three infants (65%) demonstrated impairments at 18 months, which were related to the severity of white matter injury and involvement of the posterior limb of the internal capsule.
- Fourteen infants demonstrated growth restriction, 1 had macrosomia, and 2 had mothers with diabetes mellitus.
- Pregnancy-induced hypertension, a family history of seizures, emergency cesarean section, and the need for resuscitation were more common among case subjects than control subjects.
Patterns of injury associated with symptomatic neonatal hypoglycemia were more varied than described previously.

White matter injury was not confined to the posterior regions; hemorrhage, middle cerebral artery infarction, and basal ganglia/thalamic abnormalities were seen, and cortical involvement was common.

Early MRI findings were more instructive than the severity or duration of hypoglycemia for predicting neurodevelopmental outcomes.
The impact of isolated hypoglycemia on the developing brain has been well documented in animal experiments, including those on primates.

3 important principles

- First, prolonged and severe, rather than transient or minor, hypoglycemia was required for cerebral injury.
- Second, the pattern of injury involved neuronal injury to the upper cortical layers (2 and 3), particularly affecting the parieto-occipital regions, as well as injury to the hippocampus, caudate, and white matter.
- Finally, mild hypoglycemia combined with mild hypoxia-ischemia resulted in cerebral injury, whereas either of the 2 conditions in isolation did not.

• The level or duration of hypoglycemia that is harmful to an infant's developing brain is not known.

• Major long-term sequelae include neurologic damage resulting in mental retardation, recurrent seizure activity, developmental delay, and personality disorders.

• Some evidence suggests that severe hypoglycemia may impair cardiovascular function.

• Of the 985 infants enrolled in the Infant Health and Development Program, 745 infants had glucose levels recorded.

• Infants were stratified into 4 groups by glucose level. By using standardized cognitive, academic, and behavioral assessments performed at 3, 8, and 18 years of age, we compared groups after adjusting for intervention status, birth weight, gestational age, sex, severity of neonatal course, race, maternal education, and maternal preconception weight.

• No significant differences in intellectual or academic achievement were found between preterm infants with and without hypoglycemia.

• Using extended outcomes, our results are consistent with previous studies that found no significant neurodevelopmental outcomes associated with neonatal hypoglycemia in preterm-born children.

**TABLE 2**
Frequency of Patients in Each Glucose Category

<table>
<thead>
<tr>
<th>Glucose Group</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
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<tbody>
<tr>
<td>≤35 mg/dL</td>
<td>153</td>
<td>20.6</td>
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<tr>
<td>36–40 mg/dL</td>
<td>126</td>
<td>17.0</td>
</tr>
<tr>
<td>41–45 mg/dL</td>
<td>182</td>
<td>24.5</td>
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<tr>
<td>46–180 mg/dL</td>
<td>282</td>
<td>38.0</td>
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</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Normoglycemia</th>
<th>Hypoglycemia (≤45)</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean (SD)</td>
<td>n</td>
</tr>
<tr>
<td>3-y CBCL, total</td>
<td>67</td>
<td>47.4 (20.4)</td>
<td>128</td>
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<tr>
<td>PPVT-R</td>
<td>57</td>
<td>82.3 (17.0)</td>
<td>122</td>
</tr>
<tr>
<td>Stanford-Binet IQ, corrected age</td>
<td>68</td>
<td>81.3 (20.7)</td>
<td>137</td>
</tr>
<tr>
<td>8-y CBCL, total</td>
<td>57</td>
<td>35.3 (22.9)</td>
<td>123</td>
</tr>
<tr>
<td>PPVT-R, standard</td>
<td>57</td>
<td>83.1 (22.6)</td>
<td>124</td>
</tr>
<tr>
<td>WJ broad reading standard</td>
<td>58</td>
<td>90.5 (22.3)</td>
<td>120</td>
</tr>
<tr>
<td>WJ broad math standard</td>
<td>57</td>
<td>90.2 (23.1)</td>
<td>124</td>
</tr>
<tr>
<td>WISC-III verbal IQ</td>
<td>58</td>
<td>87.3 (16.3)</td>
<td>124</td>
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<tr>
<td>WISC-III performance IQ</td>
<td>58</td>
<td>85.7 (17.4)</td>
<td>124</td>
</tr>
<tr>
<td>WISC-III total IQ</td>
<td>58</td>
<td>85.3 (17.1)</td>
<td>124</td>
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</table>

*P* values are from 2-sample *t* test.
• Prospective cohort study involving 528 neonates with a gestational age of at least 35 weeks who were considered to be at risk for hypoglycemia; *all were treated to maintain a blood glucose concentration of at least 47 mg per deciliter (2.6 mmol per liter).*

• Continuously monitored interstitial glucose concentrations, which were masked to clinical staff.

• Of 614 children, 528 were eligible, and 404 (77% of eligible children) were assessed; 216 children (53%) had neonatal hypoglycemia (blood glucose concentration, <47 mg per deciliter).

• Hypoglycemia, when treated to maintain a blood glucose concentration of at least 47 mg per deciliter, was not associated with an increased risk of the primary outcomes of neurosensory impairment (risk ratio, 0.95; 95% confidence interval [CI], 0.75 to 1.20; P=0.67) and processing difficulty, defined as an executive-function score or motion coherence threshold that was more than 1.5 SD from the mean (risk ratio, 0.92; 95% CI, 0.56 to 1.51; P=0.74).

• The lowest blood glucose concentration, number of hypoglycemic episodes and events, and negative interstitial increment (area above the interstitial glucose concentration curve and below 47 mg per deciliter) also did not predict the outcome.

• CONCLUSIONS: In this cohort, neonatal hypoglycemia was not associated with an adverse neurologic outcome when treatment was provided to maintain a blood glucose concentration of at least 47 mg per deciliter.
Results of Interstitial Glucose Monitoring in Children with and Those without Neurosensory Disability at 2 Years.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants</th>
<th>Nonparticipants</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Neonatal Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Total no.)</td>
</tr>
<tr>
<td>Primary risk factor for neonatal hypoglycemia — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal diabetes</td>
<td>161 (40)</td>
<td>80 (37)</td>
</tr>
<tr>
<td>Late preterm: gestational age of 35 or 36 wk</td>
<td>129 (32)</td>
<td>71 (33)</td>
</tr>
<tr>
<td>Small: &lt;10th percentile or &lt;2.5 kg</td>
<td>60 (15)</td>
<td>39 (18)</td>
</tr>
<tr>
<td>Large: &gt;90th percentile or &gt;4.5 kg</td>
<td>42 (10)</td>
<td>17 (8)</td>
</tr>
<tr>
<td>Other**</td>
<td>12 (3)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Blood glucose monitoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age at first sample (IQR) — hr</td>
<td>1.5 (1.2–2.1)</td>
<td>1.5 (1.2–2.0)</td>
</tr>
<tr>
<td>Duration of monitoring — hr</td>
<td>52.8±27.2</td>
<td>58.9±27.4†</td>
</tr>
<tr>
<td>No. of samples in first week</td>
<td>14.7±5.7</td>
<td>16.3±6.0¶</td>
</tr>
<tr>
<td>Blood glucose (range) — mg/dl††</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12 hr</td>
<td>59.5±10.8</td>
<td>54.1±7.2</td>
</tr>
<tr>
<td></td>
<td>(9.0–137.0)</td>
<td>(9.0–127.9)¶</td>
</tr>
<tr>
<td>12 to &lt;24 hr</td>
<td>64.9±12.6</td>
<td>61.3±10.8</td>
</tr>
<tr>
<td></td>
<td>(32.4–154.9)</td>
<td>(32.4–127.9)¶</td>
</tr>
<tr>
<td>24 to &lt;48 hr</td>
<td>66.7±10.8</td>
<td>63.1±10.8</td>
</tr>
<tr>
<td></td>
<td>(16.2–155.0)</td>
<td>(16.2–155.0)¶</td>
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<tr>
<td>≥48 hr</td>
<td>75.7±14.4</td>
<td>72.1±12.6</td>
</tr>
<tr>
<td></td>
<td>(19.8–171.2)</td>
<td>(19.8–171.2)¶</td>
</tr>
</tbody>
</table>

Panel A shows the effect of hypoglycemia on the risk of the primary outcome. A hypoglycemic episode was defined as a blood glucose concentration of less than 47 mg per deciliter (2.6 mmol per liter) on a single measurement or consecutive measurements; severe hypoglycemia was defined as a blood glucose concentration of less than 36 mg per deciliter (2.0 mmol per liter). Results were adjusted for socioeconomic status, sex, and primary risk factor for neonatal hypoglycemia.

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Risk Ratio (95% CI) of Neurosensory Impairment</th>
<th>Adjusted Risk Ratio (95% CI) of Processing Difficulty</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Hypoglycemia (reference)</td>
<td>73/188 (39)</td>
<td>27/171 (16)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>79/216 (37)</td>
<td>27/198 (14)</td>
</tr>
<tr>
<td>Hypoglycemia ≥3 Episodes</td>
<td>9/34 (26)</td>
<td>2/31 (6)</td>
</tr>
<tr>
<td>Hypoglycemia ≥3 Days</td>
<td>1/12 (8)</td>
<td>0/11</td>
</tr>
<tr>
<td>Severe Hypoglycemia</td>
<td>28/64 (44)</td>
<td>10/53 (19)</td>
</tr>
</tbody>
</table>

Management
Glucose infusion

• Main treatment is to provide glucose
  • Feeding provide carbohydrates that can be used to produce glucose
  • IV infusion (normal glucose infusion rate 6-8 mg/kg/min)
  • If higher rates of glucose infusions are required a central line should be placed
• Initiate intravenous infusion of 10% dextrose at a rate of 80ml/kg/day (5.5mg glucose/kg/min). Check glucose 30 min after any change and adjust therapy (up to 100 ml/kg/day and/or 12.5% dextrose) in order to maintain glucose level ≥ 2.6mmol/l (approximately 45mg/dl).

• If rates in excess of 100 ml/kg/day of 12.5% dextrose are required investigation, consultation and/or pharmacological intervention are indicated.

• May start weaning IV 12 hours after stable blood glucose is established. Continued breastfeeding is encouraged.

- Babies aged 35-42 weeks' gestation, younger than 48-h-old, and at risk of hypoglycemia were randomly assigned to 40% dextrose gel 200 mg/kg or placebo gel.
- Randomization was stratified by maternal diabetes and birthweight.
- The primary outcome was treatment failure, defined as a blood glucose concentration of less than 2.6 mmol/L (48 mg/dl) after two treatment attempts.

• Of 514 enrolled babies, 242 (47%) became hypoglycaemic and were randomised.

• Dextrose gel reduced the frequency of treatment failure compared with placebo (16 [14%] vs 29 [24%]; relative risk 0.57, 95% CI 0.33-0.98; p=0.04).

• There were no serious adverse events. Three (3%) babies in the placebo group each had one blood glucose concentration of 0.9 mmol/L (16 mg/dl). No other adverse events took place.

• Treatment with dextrose gel is inexpensive and simple to administer.

• Dextrose gel should be considered for first-line treatment to manage hypoglycaemia in late preterm and term babies in the first 48 h after birth.

- Follow-up study of 184 children with hypoglycemia (<2.6 mM [47 mg/dL]) in the first 48 hours and randomized to either dextrose (90/118, 76%) or placebo gel (94/119, 79%).

- Co-primary outcomes were neurosensory impairment (cognitive, language or motor score below 1 SD or cerebral palsy or blind or deaf) and processing difficulty (executive function or global motion perception worse than 1.5 SD from the mean).

- Sixty-six children (36%) had neurosensory impairment (1 severe, 6 moderate, 59 mild) with similar rates in both groups (dextrose 38% vs placebo 34%, relative risk 1.11, 95% CI 0.75-1.63).

- Processing difficulty also was similar between groups (dextrose 10% vs placebo 18%, relative risk 0.52, 95% CI 0.23-1.15).

- Conclusions: Dextrose gel is safe for the treatment of neonatal hypoglycemia, **but neurosensory impairment is common among these children.**

• Two trials involving 312 infants.

• Dextrose gel compared with placebo gel or no gel did not alter the need for intravenous treatment for hypoglycaemia (typical RR 0.78, 95% CI 0.46 to 1.32; two trials, 312 infants; quality of evidence very low).

• Infants treated with dextrose gel were less likely to be separated from their mothers for treatment of hypoglycaemia (RR 0.54, 95% CI 0.31 to 0.93; one trial, 237 infants; quality of evidence moderate) and were more likely to be exclusively breast fed after discharge (RR 1.10, 95% CI 1.01 to 1.18; one trial, 237 infants; quality of evidence moderate).

• CONCLUSIONS: Treatment of infants with neonatal hypoglycaemia with 40% dextrose gel reduces the incidence of mother-infant separation for treatment and increases the likelihood of full breast feeding after discharge compared with placebo gel. No evidence suggests occurrence of adverse effects during the neonatal period or at two years' corrected age. Oral dextrose gel should be considered first-line treatment for infants with neonatal hypoglycaemia.

• NOT FDA APPROVED FOR THIS INDICATION

• This quasi-experimental study allocated asymptomatic at-risk newborn infants (late preterm, birth weight <2500 or >4000 g, and infants of mothers with diabetes) to receive prophylactic dextrose gel (Insta-Glucose; Valeant Pharmaceuticals North America LLC, Bridgewater, New Jersey); other at-risk infants formed the control group.

• After the initial feeding, the prophylactic group received dextrose gel (0.5 mL/kg) rubbed into the buccal mucosa. The blood glucose concentration was checked 30 minutes later. Initial glucose concentrations and rate of NICU admissions were compared between the prophylactic group and controls using bivariate analyses.

• There were 236 subjects (72 prophylactic, 164 controls). The first glucose concentration was not different between the prophylactic and control groups in bivariate analysis (52.1 +/- 17.1 vs 50.5 +/- 15.3 mg/dL, P = .69) and after adjusting for covariates (P = .18). Rates of NICU admission for treatment of transient neonatal hypoglycemia were 9.7% and 14.6%, respectively (P = .40).
Postnatal Glucose Homeostasis in Late Preterm and Term Infants
Committee on Fetus and Newborn
*Pediatrics* 2011;127:575-579; originally published online Feb 28, 2011;
DOI: 10.1542/peds.2010-3851

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

(LPT) Infants 34 – 36th weeks and SGA (screen 0-24 hrs); IDM and LGA ≥34 weeks (screen 0-12 hrs)

**Symptomatic and <40 mg/dl → IV glucose**

<table>
<thead>
<tr>
<th>ASYMPTOMATIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 4 hours of age</td>
</tr>
<tr>
<td><strong>INITIAL FEED WITHIN 1 hour</strong></td>
</tr>
<tr>
<td>Screen glucose 30 minutes after 1st feed</td>
</tr>
<tr>
<td>Initial screen &lt;25 mg/dL</td>
</tr>
<tr>
<td>Feed and check in 1 hour</td>
</tr>
<tr>
<td>&lt;25 mg/dL</td>
</tr>
<tr>
<td><strong>IV glucose</strong>*</td>
</tr>
<tr>
<td>25-40 mg/dL</td>
</tr>
<tr>
<td>Refeed/IV glucose* as needed</td>
</tr>
<tr>
<td>4 to 24 hours of age</td>
</tr>
<tr>
<td><strong>Continue feeds q 2-3 hours</strong></td>
</tr>
<tr>
<td>Screen glucose prior to each feed</td>
</tr>
<tr>
<td>Screen &lt;35 mg/dL</td>
</tr>
<tr>
<td>Feed and check in 1 hour</td>
</tr>
<tr>
<td>&lt;35 mg/dL</td>
</tr>
<tr>
<td><strong>IV glucose</strong>*</td>
</tr>
<tr>
<td>35 – 45 mg/dL</td>
</tr>
<tr>
<td>Refeed/IV glucose* as needed</td>
</tr>
</tbody>
</table>

**Target glucose screen ≥45 mg/dL prior to routine feeds**

* Glucose dose = 200 mg/kg (dextrose 10% at 2 mL/kg) and/or IV infusion at 5–8 mg/kg per min (80–100 mL/kg per d). Achieve plasma glucose level of 40-50 mg/dL.

Symptoms of hypoglycemia include: Irritability, tremors, jitteriness, exaggerated Moro reflex, high-pitched cry, seizures, lethargy, floppiness, cyanosis, apnea, poor feeding.
Drugs Used

• **Diazoxide** acts to inhibit insulin secretion. Can cause fluid retention

• **Octreotide** is a long-acting somatostatin analog that also acts to inhibit insulin secretion but it can suppress growth hormone, and increase abdominal distention

• **Nifedipine** is a calcium channel blocking agent and acts to decrease insulin secretion by closing the ATP potassium channels in the pancreatic beta cells.

• **Glucagon** is used as a temporizing agent and antagonizes insulin action by mobilizing hepatic glycogen stores

• **Glucocorticoids** have also been shown to be effective in managing hypoglycemia, but their use is minimal.
Thank You!

Questions?
Hyperglycemia
Definition

• Hyperglycemia is a serum glucose concentration > 125 mg/dL.
• The most common cause of neonatal hyperglycemia is iatrogenic
• Iatrogenic causes usually involve too-rapid IV infusions of dextrose during the first few days of life in very low-birth-weight infants (< 1.5 kg).
Causes of Hyperglycemia

• The other important cause of hyperglycemia is physiologic stress
  • Surgery,
  • Hypoxia,
  • Respiratory distress
  • Sepsis

• In premature infants, partially defective processing of proinsulin to insulin and relative insulin resistance may cause hyperglycemia.

• In addition, transient neonatal diabetes mellitus is a rare self-limited cause that usually occurs in small-for-gestational-age infants

• Corticosteroid therapy may also result in transient hyperglycemia.
Risks for Hyperglycemia

• Preterm birth
• Higher-than-needed rates of IV glucose infusion
• Intrauterine growth restriction (IUGR)
• Increased stress hormones
  • Increased catecholamine infusions and plasma concentrations
  • Increased glucocorticoid concentrations (from use of antenatal steroids, postnatal glucocorticoid administration, and stress)
  • Increased glucagon concentrations
• Early and high rates of intravenous (IV) lipid infusion
• Insufficient pancreatic insulin secretion
• Absence of enteral feedings, leading to diminished “incretin” secretion and action, limiting their potential to promote insulin secretion.
Diagnosis of Hyper and Hypoglycemia
Among preterm infants receiving continuous glucose infusions at 8 mg/kg per minute, 11 mg/kg per minute, or 14 mg/kg per minute, practically none of the infants in the lowest glucose infusion group developed hyperglycemia. In contrast, 50% or more of the infants in the middle infusion group and all of the infants in the highest infusion group developed increased blood glucose concentrations.

FIGURE 1. The plasma glucose concentration relative to the rate of IV glucose administered in a representative neonate in the 500-g birthweight category (a) and in one in the 900-g birthweight category (b). From Cowett AA, Farrag HM, Gelardi NL, Cowett RM. Hyperglycemia in the micropremie: evaluation of the metabolic disequilibrium during the neonatal period. Prenat Neonatal Med. 1997;2:360–365.

• Four eligible trials
• Two trials compared lower vs. higher rates of glucose infusion in the early postnatal period. These trials were too small to assess effects on mortality or major morbidities.
• Two trials, one a moderately large multicentre trial (NIRTURE, Beardsall 2008), compared insulin infusion with standard care.
• Insulin infusion reduced hyperglycemia but increased death before 28 days and hypoglycemia.
• Reduction in hyperglycemia was not accompanied by significant effects on major morbidities; effects on neurodevelopment are awaited.

• 194 to standard neonatal care on days 1 to 7. The efficacy of glucose control was assessed by continuous glucose monitoring.

• Compared with the control group, infants in the early-insulin group had lower mean glucose levels 112±25 vs. 121±40 mg/dl], P <0.01).

• Fewer infants in the early-insulin group had hyperglycemia for more than 10% of the first week of life (21% vs. 33%, P = 0.008).

• The early-insulin group had significantly more carbohydrate infused (51±13 vs. 43±10 kcal per kilogram per day, P<0.001) and less weight loss in the first week (standard-deviation score for change in weight, −0.55±0.52 vs. −0.70±0.47; P = 0.006).

• More infants in the early-insulin group had episodes of hypoglycemia (defined as a blood glucose level of <2.6 mmol per liter [47 mg per deciliter] for >1 hour) (29% in the early-insulin group vs. 17% in the control group, P = 0.005), and the increase in hypoglycemia was significant in infants with birth weights of more than 1 kg.

• **In the intention-to-treat analysis, mortality at 28 days was higher in the early insulin group than in the control group (P = 0.04).**
A Glucose Level

Mean Glucose (mmol/liter)

Study Day

Control
Early insulin
Complications

- Hypoglycemia
- Death

**Graph:**
- **Y-axis:** Percentage (%)
- **X-axis:** Complications (Hypoglycemia, Death)
- **Legend:**
  - Insulin
  - Control

- Hypoglycemia: Insulin 28%, Control 15%
- Death: Insulin 10%, Control 5%
Treatment

- Reduction of IV dextrose concentration, rate, or both
- Rarely insulin
- “Reasonable guidelines indicate that insulin treatment should be reserved until plasma glucose concentrations exceed 16.7 to 22.2 mmol/L (300 to 400 mg/dL) despite reducing the glucose infusion rate to less than 3 to 4 mg/kg per minute. The usual method of insulin administration involves a continuous infusion, beginning at 0.02 to 0.05 U/kg per hour. Although higher infusion rates have been used, they usually are not necessary and increase the risks of hypokalemia and subsequent hypoglycemia.”
- Hay -http://pedsinreview.aappublications.org/cgi/content/full/20/7/e16