Recommendations for Evaluation and Management of Hypoglycemia in Neonates, Infants, and Children

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Main Principles

1. Not over-investigate the normal infant

2. Not miss the infant who has a serious hypoglycemic disorder
• 3 Month old male
  • Started weaning overnight feeds
  • Staring and unresponsiveness and brought to ER
  • Diagnosed with Hypoglycemia and admitted
  • Diagnosed with Hyperinsulinism and transferred
• Cook Children’s Medical Center
  • Genetics: single paternally inherited mutation in ABCC8
  • Focal disease on 18F-DOPA PET scan
  • Surgery 10% pancreatectomy
• Outcome: Hypoglycemia cured
  • EXCEPT for his brain damage
• Story began at birth
  • Normal delivery, 3578g good condition
    • Hypoglycemia hour 1 POC <20mg/dL (1.1mmol/L)
    • Lab glucose 9 mg/dL (0.5mmol/L) and 18 mg/dL (1 mmol/L) on repeat.
    • IV glucose for 13 days with daily glucose < 50 mg/dL (< 2.7 mmol/L)
  • Day 7 they did some tests
    • Insulin 14 mIU/MI (normal fasting 0-17)
    • Glucose 45 mg/dL (2.5 mmol/L)
  • Glucagon given @ hypoglycemia and raised the glucose by >30mg/dl (>1.7 mmol/L)
• Weaned off IV glucose had glucose < 50 mg/dL (<2.7 mmol/L) on Q3H feeds
• Put on Q2H feeds with polycose and 3 glucose in a row of > 60 mg/dL (>3.3 mmol/L)
• Sent the baby home
• Told Mom to feed every 2 hours and baby will be fine
• Wrote a letter to family doctor and told her baby had neonatal hypoglycemia and it is settled
Study of late presenting babies with hypoglycemia

- 60% of patients with late presenting Hyperinsulinism had clues to diagnosis and should have been diagnosed prior to d/c from NICU

- 100% of hypopituitarism had clues to diagnosis and should have been diagnosed prior to d/c from NICU
Reasons Why Hypoglycemia Guidelines are Needed

• High risk of permanent brain injury in pediatric hypoglycemia disorders due to delays in diagnosis and adequate therapy
• Difficulties in distinguishing between neonates that have a persistent hypoglycemia disorder and those with self-limited transitional neonatal hypoglycemia
• Published guides do not exist for hypoglycemia in infants and children; guidelines exist for neonates
Transitional Hypoglycemia

- Normal glucose levels in transition period

<table>
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<th>&lt; 2 H</th>
<th>2-24 H</th>
<th>24-48 H</th>
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<tr>
<td>Mean</td>
<td>56</td>
<td>63</td>
<td>68</td>
<td>67</td>
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<td>(3.1)</td>
<td>(3.5)</td>
<td>(3.7)</td>
<td>(3.7)</td>
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<td>5%</td>
<td>&lt; 28</td>
<td>&lt; 40</td>
<td>&lt; 41</td>
<td>&lt; 48</td>
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Lubchenco and Bard: 1971. Incidence of glucose < 30 mg/dl (1.6 mmol/L) prior to first feeding in a normal newborn nursery.

Fig. 1. Incidence of hypoglycemia in newborn infants, classified by birth weight and gestational age. Glucose levels <30 mg/100 ml prior to first feeding.
Lubchenko and Bard
Conclusions

- 11% babies glucose <30 mg/dl (<1.6 mmol/L) within 12 hours prior to first feeding
- < 0.5% infants will develop glucose <50 mg/dl (2.7mmol/L) after 72 hours of life
- Greatest risk was SGA and hypoxemia
Outline of Recommendations

• **Section 1:** Which neonates, infants and children to evaluate for hypoglycemia

• **Section 2.** Workup / investigation of persistent hypoglycemia in neonates, infants, and children

• **Section 3.** Management of neonates, infants, and children with a documented persistent hypoglycemia disorder
Which infants and children to evaluate for hypoglycemia:

- For infants and younger children who are unable to reliably communicate symptoms, we recommend evaluation of those whose plasma glucose concentrations are documented by laboratory quality assays to be below the normal threshold for neurogenic responses:
  - 50-60 mg/dL (2.8 - 3.3 mmol/L)

- How common is hypoglycemia
  - 1:1400 children in the emergency department
Which neonates to evaluate for hypoglycemia

• For **newborn infants** who are **at increased risk** for the development of either acute or persistent hypoglycemia, glucose should be screened at birth and then pre feed for 24-48 hours until **stable**

• Stable
  • >50 mg/dL (2.7) at < 48 hours of age
  • >60 mg/dL (3.3) > 48 hours of age

• This is approximately 1/3 of all babies born.
Neonates at increased risk of hypoglycemia who require glucose monitoring

1. Neonates with symptomatic hypoglycemia
2. Neonates who had perinatal stress:
   - Birth asphyxia/ischemia; C-section for fetal distress
   - Maternal pre-eclampsia/eclampsia or hypertension
   - Intra-uterine growth restriction (small-for-gestational-age birth-weight)
   - Meconium aspiration syndrome, erythroblastosis fetalis, polycythemia, hypothermia
3. Congenital syndromes (such as Beckwith-Wiedemann), abnormal physical features (such as midline facial malformations, microphallus)
4. Family history of a genetic form of hypoglycemia
5. Large-for-gestational-age birth-weight
6. Premature or post-mature delivery
7. Infant of diabetic mother
Neonates in Whom to Exclude Persistent Hypoglycemia Prior to Discharge

- Neonates with severe hypoglycemia (e.g., an episode of symptomatic hypoglycemia or requiring iv dextrose to treat hypoglycemia)

- Neonates unable to consistently maintain pre-prandial plasma glucose concentrations > 50 mg/dL (2.7) at < 48 hours and > 60 mg/dL (3.3) after 48hrs of life

- Family history of a genetic form of hypoglycemia
Metabolic Clues to Hypoglycemia Diagnosis

Hypoglycemia

- HCO₃, BOHB, Lactate, FFA

No Acidemia

- BOHB↓
- FFA ↓
- Hyperinsulinism
  - Hypopituitarism in newborns
  - Transitional Neonatal Hypoglycemia
  - Perinatal Stress Hyperinsulinism
  - Factitious Hypoglycemia

- BOHB↓
- FFA ↑
- Fatty Acid Oxidation Defects

Acidemia

- Lactate ↑
- Gluconeogenesis Defects
  - Ethanol

- BOHB↑
- Ketotic Hypoglycemia
  - Glycogenoses
  - GH def
  - Cortisol def
Critical Sample

- Insulin, C-peptide, Cortisol, GH
- Free fatty acids
- Ketones bodies
  - $b$-hydroxybutyrate and acetoacetate
- Lactate, alanine
- Ammonia
- Carnitine & Acylcarnitine profile
- Urine organic acids and urine ketones
Diagnosis of HI

- Persistent hypoglycemia
  - Plasma glucose < 50 mg/dL
  - Short fasting duration
- Increased glucose utilisation
  - New-born - >4-6 mg/kg/min
  - Older child - >3-4 mg/kg/min
- Insulin > lower limit of detection
- Low plasma ketones < 1.8 mmol/L
- Low FFA <1.7 mmol/L
- Glycemic response to glucagon >30 mg/dL when hypoglycemic
• Elevated Ammonia
  • Specific to GLUD-1 HI
• Abnormal Urine organic acids
• IGF BP-1
• Genetic testing
• 18F DOPA Pet Scanning
Treatment targets
Neurogenic Responses:
- Glucagon & Epinephrine
- Cortisol & Growth Hormone

Neuroglycopenic Responses

Adapted from Cryer, et al. by Dr Stanley

Insulin suppressed

Target for Treatment

Target for terminating provocative tests

Good

Caution

Danger

30/1.6
50/2.7
70/3.8
100/5.5