Neonatal Hypoglycemia

Presented by
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Learning Objectives
At the conclusion of this module, participants should be better able to:

• Treat asymptomatic neonatal hypoglycemia with buccal dextrose gel

• Develop patient-specific approaches to intravenous dextrose therapy for neonatal hypoglycemia
Fetal Glucose Concentrations Normally Persist for Up to 48 Hours After Birth and Then Transition to Adult Concentrations

Marconi, 1996
Srinivasan, 1986
Common Complications of Pregnancy May Exaggerate and Prolong This Transitional Physiology

• The main at risk groups:
  – Placental insufficiency (IUGR/SGA)
  – Diabetes during pregnancy and other causes of fetal over nutrition (IDM, LGA)
  – Prenatal and perinatal stress
  – Late preterm delivery

• All of these complications impact fetal glucose metabolism and the transition to postnatal glucose metabolism.

• They all impact neonatal glucose concentrations.
Why Do We Care About Asymptomatic Hypoglycemia?

• Early diagnosis and treatment of severe genetic and/or congenital hypoglycemia disorders
  – Persistent Congenital Hyperinsulinism - (1:40,000)
  – Fatty Acid Oxidation Disorders (and other metabolic defects) - (1:10,000-15,000)
  – Hypopituitarism - (1:20,000)

• Progression to symptomatic hypoglycemia
  – Associative data

• Persistent asymptomatic hypoglycemia
  – Associative and Controversial !!!!!!
Outcome Data in the Main At-Risk Groups

• There are studies in most of the main at-risk groups which show worse outcomes than healthy term newborns.

• In some of these studies an association exists between low glucose concentrations and worse neurodevelopmental outcomes.

• No studies have robustly tested whether treating asymptomatic hypoglycemia improves neurodevelopmental outcomes.
AAP Guidelines 2011

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

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

Symptomatic and <40 mg/dL → IV glucose

### ASYMPTOMATIC

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

Gaps and Controversies in the AAP Statement

• Symptomatic infants without risk factors
• Other high risk groups
• How to manage beyond the first 24 hours
  – When and how to consider a hypoglycemic disorder
  – Other biochemical studies
  – How to determine safety for discharge
• Why are there gaps and controversies in the AAP Statement?
  – Any protocol that is specific enough to be useful will create controversy
Pediatric Endocrine Society Recommendations 2015

Medical Progress

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

Paul S. Thornton, MB, BCh\textsuperscript{1}, Charles A. Stanley, MD\textsuperscript{2}, Diva D. De Leon, MD, MSCE\textsuperscript{2}, Deborah Harris, PhD\textsuperscript{3}, Morey W. Haymond, MD\textsuperscript{4}, Khalid Hussain, MD, MPH\textsuperscript{5}, Lynne L. Levitsky, MD\textsuperscript{6}, Mohammad H. Murad, MD, MPH\textsuperscript{7}, Paul J. Rozance, MB\textsuperscript{8}, Rebecca A. Simmons, MD\textsuperscript{9}, Mark A. Sperling, MBBS\textsuperscript{10}, David A. Weinstein, MD, MMSc\textsuperscript{11}, Neil H. White, MD\textsuperscript{12}, and Joseph I. Wolfsdorf, MB, BCh\textsuperscript{13}
AAP vs PES
Key Differences

• What glucose concentrations to use for treatment targets.
• Who and how to investigate for a hypoglycemia disorder.
• When to obtain critical labs and what critical labs should be obtained.
• Is the patient ready for discharge.
AAP vs PES
When to use which guideline?

• AAP – “Screening and management...”
  — Screening at-risk asymptomatic newborns
  — Management in the first 24-48 hours
• PES – “…evaluation and management...”
  — Management
    • Other groups of patients
    • Especially after 48 hours
    • Discharge
  — Diagnosis
So What Is One to Do?
One Person’s Practical Approach

- For the first 24 hours of life use the AAP guidelines.
  - If the baby requires IV dextrose, use the PES guidelines for treatment goals.
- For hours 24-48 use either AAP or PES guidelines mg/dL as treatment targets (>40-50 mg/dL vs >50 mg/dL)
- For >48 hours of age use PES guidelines.
  - Once the patient has transitioned to a “dextrose weaning phase” accept glucose concentrations >50 mg/dL.
- For symptomatic patients, especially without risk factors, use the PES guidelines.
- For discharge use PES guidelines.*
Approach to Discharge

• Patient specific
• **Safety fasting test skip one feed**
  – Hypoglycemia with:
    • Neurological signs
    • No known risk factors, but needed intravenous dextrose
    • Family history of sudden infant death of unknown cause in a sibling
    • Physical exam consistent with a congenital disorder associated with hypoglycemia (Beckwith-Wiedemann, hypopituitarism)
    • Inability to consistently maintain plasma glucose above 60 mg/dL.
  – Family history of a chronic hypoglycemia disorder (in consultation with an endocrinologist)
The “Minimum” or “Safety” Fasting Study

• 3-4 hours after the last feed begin checking glucooses
• Use a rapid “blood gas analyzer” if available or a highly accurate bedside glucometer
  – If it is not available consider using 40 mg/dL as a cut-off
• When glucose is <50mg/dL (consider 40 mg/dL if using a glucometer) immediately draw:
  – Glucose, insulin, beta-hydroxybutyrate, cortisol, growth hormone
• Feed after labs are drawn
• If patient is >60-65 mg/dL after 6 hours it is probably OK to stop and feed the patient
• If 50-60 mg/dL consider extending to 9 hours and if patient is >50 mg/dL it is probably OK to stop and feed the patient
Neonatal Glycemia and Neurodevelopmental Outcomes at 2 Years

- At-risk groups for asymptomatic hypoglycemia
  - SGA, LGA, IDM, Late preterm (>35 weeks)
- Definition of hypoglycemia and treatment goal
  - 47 mg/dL
- Screening frequency
  - Before each feed for up to 48 hours
- Hypoglycemic babies had similar outcomes as normoglycemic babies at 2 years.
Three Associations

1. Those who did not have glucose lower than 54 mg/dL did worse than those who did.
   - By CGMS those with worse outcomes had a glucose concentration that was 2.9 mg/dL higher on average.

2. Of hypoglycemic infants, those with worse outcomes had a steeper rise in their glucose concentrations after treatment with dextrose.

3. Infants who had more time with glucoses outside the range of 54-72 mg/dL did worse.
   - Glycemic variability

A More Rapid Rise After Treatment Was Associated With Worse Outcomes

Intravenous Treatment of Hypoglycemia:
Skip the 2 ml/kg D10W bolus for asymptomatic SGA, LGA, IDM, and late preterm newborns


Neonatal Glycemia and Neurodevelopmental Outcomes at 4.5 Years

- Hypoglycemic (<47 mg/dL) babies had worse executive function and worse visual motor function compared to normoglycemic babies at 2 years.

- There were not significant differences in parental assessment of their children.

- However, the poor executive function and visual motor performance may impact learning and school achievement.

- The other associations reported at 2 years of age were not reported at 4.5 years of age.
What Do These Studies Show?

• Using a screening and treatment strategy to actively increase glucose concentrations to >47 mg/dL, those with a glucose concentration <47 mg/dL:
  – Had equivalent outcomes at 2 years of age, but
  – Had worse outcomes at 4.5 years of age compared to patients that did not have a glucose concentration < 47 mg/dL

• They do not define one management strategy as better than another.

• Importance of longer term follow-up.
How Aggressively Do You Diagnose and Treat Hypoglycemia?

Benefits
- Early treatment of severe hypoglycemia disorders
- Potential to prevent symptoms
- Potential to prevent neurological injury
- Correct an abnormality
- Less legal risk

Risks
- Separation from mother
- NICU admission
- Hospital stay and cost
- Decreased breast feeding
- Intravenous catheters
- Medication side effects
- Hyperglycemia
The Sugar Babies Study (Dextrose Gel)

- At risk groups - SGA, IDM, LGA, Late Preterm (>35 weeks)
- Plasma glucose measured before each feed for 48 hours
- Hypoglycemia defined as a plasma glucose ≤ 47 mg/dL
- Treated with dextrose gel or placebo gel (blinded) and feeds
  - When a low glucose concentrations was identified placebo gel or dextrose gel (200 mg/kg) was massaged into the buccal mucosa and the baby was encouraged to feed
  - The blood glucose concentrations was rechecked 30 minutes after gel administration
  - Primary endpoint: Treatment failure defined as a blood glucose concentration ≤ 47 mg/dL after the second of 2 doses of study gel
  - After 2 study gel doses the clinicians could use open label dextrose gel
  - Up to 6 total doses of gel (study + open label) could be give over a 48 hour period
  - Rebound hypoglycemia = low glucose concentration within 6 hr of successful treatment
  - Recurrent hypoglycemia = low glucose after successful treatment, within 48 hr after birth
  - Continuous glucose monitoring sensor (blinded) used in 74% of subjects and this captured about 23% of the episodes of low glucose

1002 mothers identified and contacted

588 provided consent

514 enrolled

74 babies not enrolled
34 not eligible at birth
18 treated
9 withdrew consent
7 not notified
5 born elsewhere
1 intrauterine death

272 did not become hypoglycaemic

242 became hypoglycaemic and were randomised

5 randomised in error

119 assigned to placebo gel

118 assigned to dextrose gel

Dextrose Gel Decreases NICU Admissions for Hypoglycemia

<table>
<thead>
<tr>
<th>Volume of study gel (mL/kg)</th>
<th>Dextrose gel (n=118)</th>
<th>Placebo gel (n=119)</th>
<th>Relative risk or median difference p value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure</td>
<td>0·84 (0·43–2·44)</td>
<td>0·97 (0·47–2·49)</td>
<td>0·005 (–0·01 to 0·02) 0·45</td>
</tr>
<tr>
<td>Admitted to NICU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies (n)</td>
<td>16 (14%)</td>
<td>29 (24%)</td>
<td>0·57 (0·33 to 0·98) 0·04</td>
</tr>
<tr>
<td>For hypoglycaemia (n)</td>
<td>45 (38%)</td>
<td>55 (46%)</td>
<td>0·83 (0·61 to 1·11) 0·24</td>
</tr>
<tr>
<td></td>
<td>16 (14%)</td>
<td>30 (25%)</td>
<td>0·54 (0·31 to 0·93) 0·03</td>
</tr>
</tbody>
</table>

NNT=9

Dextrose Gel Facilitates Breastfeeding

<table>
<thead>
<tr>
<th>Any Formula Feeding at 2 Weeks of Age</th>
<th>Dextrose Gel</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4%</td>
<td>13%*</td>
</tr>
</tbody>
</table>

### Blood glucose

<table>
<thead>
<tr>
<th></th>
<th>Dextrose gel (n=118)</th>
<th>Placebo gel (n=119)</th>
<th>Rate ratio or median difference</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rebound episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes per baby</td>
<td>0</td>
<td></td>
<td></td>
<td>1.46</td>
<td>0.67 to 3.26</td>
</tr>
<tr>
<td></td>
<td>104 (88%)</td>
<td>109 (92%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>12 (10%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2 (2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recurrent episodes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes per baby</td>
<td>0</td>
<td></td>
<td></td>
<td>0.89</td>
<td>0.55 to 1.44</td>
</tr>
<tr>
<td></td>
<td>90 (76%)</td>
<td>91 (76%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>23 (20%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5 (4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥3</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Interstitial glucose

|                    | Babies (n) |                     |                                |             |         |
|--------------------|------------|---------------------|                                |             |         |
| **Rebound episodes** |            |                     |                                |             |         |
| Episodes per baby  | 25 (21%)   | 30 (25%)           |                                |             |         |
|                    | 0          | 20 (80%)           |                                |             |         |
|                    | 1          | 3 (12%)            |                                |             |         |
|                    | 2          | 2 (2%)             |                                |             |         |
| **Recurrent episodes** |            |                     |                                |             |         |
| Episodes per baby  | 16 (64%)   | 18 (60%)           |                                |             |         |
|                    | 8 (32%)    | 4 (13%)            |                                |             |         |
|                    | 0          | 3 (10%)            |                                |             |         |
|                    | 1          | 5 (17%)            |                                |             |         |

Dextrose Gel Does Not Correct Hypoglycemia More Rapidly Than Feeding Alone

<table>
<thead>
<tr>
<th></th>
<th>Dextrose Gel</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time taken for interstitial glucose concentration to be restored</td>
<td>Minutes (Median, 95% CI)</td>
<td>20.3 (0.2-215.4)</td>
</tr>
</tbody>
</table>

## Two Year Outcomes Are Equivalent Between Dextrose Gel and Placebo

<table>
<thead>
<tr>
<th></th>
<th>Randomized to dextrose gel</th>
<th>Randomized to placebo gel</th>
<th>RR or mean difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at assessment, mo</td>
<td>90</td>
<td>94</td>
<td>24.2 ± 1.2</td>
<td>24.5 ± 1.9</td>
</tr>
<tr>
<td>Neurosensory impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>56 (62%)</td>
<td>62 (66%)</td>
<td>32 (34%)</td>
<td>31 (33%)</td>
</tr>
<tr>
<td>Mild</td>
<td>28 (31%)</td>
<td>31 (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (6%)</td>
<td>1 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing difficulty</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental delay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>59 (66%)</td>
<td>63 (68%)</td>
<td>30 (32%)</td>
<td>31 (34%)</td>
</tr>
<tr>
<td>Mild</td>
<td>25 (28%)</td>
<td>29 (31%)</td>
<td>29 (31%)</td>
<td>30 (32%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (6%)</td>
<td>1 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>2 (2%)</td>
<td>0 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bayley-III Composite scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive</td>
<td>90</td>
<td>93</td>
<td>93 ± 11</td>
<td>94 ± 9</td>
</tr>
<tr>
<td>Language</td>
<td>89</td>
<td>93</td>
<td>96 ± 14</td>
<td>99 ± 9</td>
</tr>
<tr>
<td>Motor</td>
<td>90</td>
<td>93</td>
<td>99 ± 10</td>
<td>99 ± 13</td>
</tr>
<tr>
<td>Social emotional</td>
<td>88</td>
<td>90</td>
<td>105 ± 15</td>
<td>104 ± 16</td>
</tr>
<tr>
<td>General adaptive</td>
<td>89</td>
<td>91</td>
<td>101 ± 13</td>
<td>99 ± 14</td>
</tr>
<tr>
<td>Executive function</td>
<td>87</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite score</td>
<td>10.9 ± 4.1</td>
<td>10.0 ± 4.0</td>
<td>0.93 (−0.24 to 2.11)</td>
<td></td>
</tr>
<tr>
<td>Children with z score &lt; −1.5</td>
<td>5 (6%)</td>
<td>8 (9%)</td>
<td>0.66 (0.22 to 1.94)</td>
<td>.45</td>
</tr>
<tr>
<td>BRIEF-P Index scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibitory self control</td>
<td>55 ± 11</td>
<td>54 ± 10</td>
<td>1.09 (−1.88 to 4.06)</td>
<td>.47</td>
</tr>
<tr>
<td>Flexibility</td>
<td>52 ± 10</td>
<td>52 ± 10</td>
<td>0.24 (−2.67 to 3.15)</td>
<td>.87</td>
</tr>
<tr>
<td>Emergent Metacognition</td>
<td>60 ± 12</td>
<td>58 ± 12</td>
<td>2.17 (−1.26 to 5.60)</td>
<td>.21</td>
</tr>
<tr>
<td>Global Executive Composite</td>
<td>58 ± 11</td>
<td>56 ± 11</td>
<td>1.71 (−1.48 to 4.89)</td>
<td>.29</td>
</tr>
<tr>
<td>Vision</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motion coherence threshold</td>
<td>40.2 ± 12.8</td>
<td>41.5 ± 15.7</td>
<td>−1.31 (−5.55 to 2.93)</td>
<td>.55</td>
</tr>
<tr>
<td>Children with z score &gt; 1.5</td>
<td>4 (5%)</td>
<td>8 (9%)</td>
<td>0.52 (0.16 to 1.66)</td>
<td>.27</td>
</tr>
<tr>
<td>Vision problem</td>
<td>90</td>
<td>93</td>
<td>26 (29%)</td>
<td>23 (25%)</td>
</tr>
<tr>
<td>Refractive error</td>
<td>51</td>
<td>49</td>
<td>3 (6%)</td>
<td>5 (10%)</td>
</tr>
</tbody>
</table>

Harris, 2015
University of Colorado Hospital Well Baby Nursery and NICU

Mary Kohn
Jim Barry
Bill Hay
Paul Rozance

Started January 2017

Dramatically reduced NICU admissions for “low glucose not responsive to early feeding.”
Dextrose Gel - CAUTION!!

Beware of the:

- Term baby with symptomatic hypoglycemia who has no risk factors
  - Strongly consider investigating these babies for a persistent hypoglycemia disorder

- Mothers with the following characteristics:
  - Young, inexperienced, first time mother
  - Trying to breastfeed for the first time
  - Uncertain in anyway
  - Any sign of illness
  - Difficulties breastfeeding in the nursery
  - Limited home support
  - Keep these women and their infants in the nursery until everything is normal, and stays that way.
Other Strategies to Safely Manage Hypoglycemia
Breastfeeding Is Best!

Table II. The impact of treatment choices and infant characteristics on the change in blood glucose concentration (mg/dL)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Factor present</th>
<th>Factor absent</th>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (hours)</td>
<td>n (%)</td>
<td>Change (SE)</td>
<td>Change (SE)</td>
<td>Marginal change (95% CI)</td>
</tr>
<tr>
<td>295 (100)</td>
<td>—</td>
<td>—</td>
<td>0.05 (—0.5 to 1.5)</td>
<td>.32</td>
</tr>
<tr>
<td>Initial glucose concentration</td>
<td>295 (100)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dextrose gel</td>
<td>147 (50)</td>
<td>13.3 (1.0)</td>
<td>10.0 (0.7)</td>
<td>3.3 (0.9 to 5.7)</td>
</tr>
<tr>
<td>Male sex</td>
<td>143 (48)</td>
<td>11.0 (0.9)</td>
<td>12.3 (0.8)</td>
<td>—1.7 (—4.1 to 0.8)</td>
</tr>
<tr>
<td>Milk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expressed breast milk</td>
<td>117 (40)</td>
<td>10.3 (0.9)</td>
<td>12.6 (0.8)</td>
<td>—1.9 (—4.3 to 0.4)</td>
</tr>
<tr>
<td>Breast</td>
<td>168 (57)</td>
<td>12.5 (0.7)</td>
<td>10.5 (1.0)</td>
<td>1.7 (—0.6 to 4.0)</td>
</tr>
<tr>
<td>Formula</td>
<td>55 (19)</td>
<td>15.5 (1.8)</td>
<td>10.8 (0.6)</td>
<td>4.2 (1.3 to 7.2)</td>
</tr>
</tbody>
</table>

However, breastfeeding was associated with a reduced odds of a second treatment of hypoglycemia!
(OR 0.52, 95% CI 0.28-0.944; P<0.05)

Other Strategies to Safely Manage Hypoglycemia—Are All Risk Factors the Same?

- **Normal Glucose Utilization Rate is 4-6 mg/kg/min**
- **IDM/LGA**
  - Increased adiposity
  - Less glucose utilization per kg
  - Hyper-responsive insulin secretion

- **IUGR/SGA**
  - Decreased adiposity
  - Increased brain to body weight ratio
  - More glucose utilization per kg
  - Hyper- or Hypo responsive insulin secretion

- **Late Preterm or Otherwise NPO**

GIR = 3-5 mg/kg/min
GIR = 4-7 mg/kg/min
GIR = 6-8 mg/kg/min

Other Strategies to Safely Manage Hypoglycemia
On The Horizon:

• Accurate devices to measure glucose concentrations
  – Typical bedside glucometers are less accurate than blood gas biosensors.
    • 2017 British Association of Perinatal Medicine:
      “The ward-based blood gas biosensor should be considered the reference standard for measuring blood glucose based on accuracy and speed of result availability.”
  – Role of newer generation bedside glucometers.
  – Continuous interstitial glucose monitoring sensors
• Rapid and accurate measurement of alternative fuels
• Non-glucose based methods to screen for persistent severe hypoglycemia disorders
• Clinical and translational research to better stratify patients based on risk for prolonged hypoglycemia and to better screen for persistent hypoglycemia disorders
Low Glucose Concentrations Are Common in the First 48 Hours of Life

- At risk groups - SGA, IDM, LGA, Late Preterm
- Plasma glucose measured before each feed for 48 hours
- Hypoglycemia defined as a plasma glucose ≤ 47 mg/dL
- 50% had a low glucose concentration
  - More common if using continuous interstitial glucose monitoring
- These at risk groups represent over 25% of all newborns
- At least 12.5% of all newborns have a low glucose concentration
  - >500,000/year in the United States
- 10% of these needed intravenous dextrose
  - >50,000/year in the United States

**What Targets to Use for Treatment?**

**AAP**

- Target glucoses >40-50 mg/dL in the first 24 hours

**PES**

- Target >50 mg/dL in the first 48 hours
- Target >60 mg/dL if on IV Dextrose or age >48 hours
## Who to Investigate for a Hypoglycemic Disorder?

<table>
<thead>
<tr>
<th>AAP</th>
<th>PES</th>
</tr>
</thead>
</table>
| If it is not possible to maintain blood glucose concentrations of greater than 45 mg/dL after 24 hours of using 5-8 mg/kg/min of glucose infusion | Neonates with severe hypoglycemia  
• Symptomatic hypoglycemia, especially neurologic symptoms, in an otherwise healthy infant  
• Required prolonged and/or high rates of dextrose infusion to treat hypoglycemia  
Neonates unable to consistently maintain pre-prandial glucose concentrations >60 mg/dL after 48 hours of age  
Family history of a genetic hypoglycemia disorder  
Abnormal physical exam features suggestive of a syndromic hypoglycemia disorder (midline facial malformation, microphallus, Beckwith-Wiedemann) |
## How to Investigate for a Hypoglycemic Disorder?

<table>
<thead>
<tr>
<th>AAP</th>
<th>PES</th>
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</thead>
<tbody>
<tr>
<td>Insulin should be measured when the glucose is &lt;40 mg/dL</td>
<td>While glucose is &lt;50mg/dL*</td>
</tr>
<tr>
<td>An endocrinologist should be consulted</td>
<td>• Insulin</td>
</tr>
</tbody>
</table>

* assumes an accurate device

- Beta-hydroxybutyrate
- Cortisol
- Growth hormone
- Lactate
- ± Subcutaneous glucagon
  - Be prepared to treat rebound hypoglycemia
When to Obtain Critical Labs?

PES

While glucose is <50 mg/dL (* caveat for bedside glucometers)

- At presentation if >48 hours of age
  - Extremely difficult in the first 4 days of life
- While weaning IV dextrose
- Pre-feed
- Provoked by a fast

Done before treatment
**Is the Patient Ready for Discharge?**

<table>
<thead>
<tr>
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</table>
| Be certain that the infant can maintain normal plasma glucose concentrations on a routine diet for a reasonably extended period before discharge  
  • through at least 3 feed-fast periods | Maintain glucose concentrations through regular feed-fast cycles:  
  • >50 mg/dL if <48 hours of age  
  • >60 mg/dL if >48 hours of age  
  “Safety” fasting challenge  
  • 6-8 hour fast (one skipped feed)  
  – Maintain glucose >60 mg/dL, for most patients  
  – Special considerations for patients with a known risk of a genetic hypoglycemia disorder |

“Discharge from the nursery should not occur until these infants maintain glucose levels >70 mg/dL through several normal fast-feed cycles.”