PART I: Background

Risk factors for neonatal hypoglycemia
  o Inadequate glycogen stores
    ▪ Small for gestational age (SGA)
    ▪ Intrauterine growth restriction (IUGR)
    ▪ Prematurity (<37 weeks gestational age)
    ▪ Post-term gestation (≥42 weeks gestational age)
  o Increased glucose utilization
    ▪ Large for gestational age (LGA)
    ▪ Infant of a diabetic mother (IDM)
      • Includes mothers with pre-existing diabetes (DM1 or 2) or gestational diabetes (GDMA1 = diet-controlled or GDMA2 = medication-controlled)
    ▪ Conditions which increase metabolic demand: sepsis, encephalopathy, HIE, perinatal stroke, seizures, hypothermia, prematurity, polycythemia, hemolytic disease, metabolic disease, respiratory distress, endocrine abnormalities, congenital heart disease, maternal substance use
  o Hyperinsulinemia
    ▪ LGA
    ▪ IUGR
    ▪ IDM
    ▪ Certain genetic/metabolic conditions (e.g. Beckwith-Weidemann Syndrome)

Sequelae of neonatal hypoglycemia
  o Neurodevelopmental Sequelae
    ▪ Association with worse cognitive and motor performance on developmental testing at 18 months, 3 years, 5 years; lower school achievement in children at 4th grade
    ▪ NOTE: recurrent episodes of hypoglycemia are more predictive of long-term sequelae
    ▪ CAVEAT: causality has not been determined for these associations, nor effectiveness / safety of screening and intervention to raise glucose levels

PART II: Definition of hypoglycemia

Definition of hypoglycemia
  o “Plasma glucose concentration below which normal brain function cannot occur”
  o Published thresholds for diagnosing hypoglycemia:
    ▪ NOTE: difficult to define a single blood glucose concentration that warrants intervention in every neonate. Published literature and guidelines primarily rely on normative values since defining hypoglycemia based on presence/absence of sequelae or performing prospective clinical trials is impossible.
    ▪ NOTE: units for all glucose values are in mg/dL
- Alkalay, et al. (2006) - estimate of 5th percentile (breast and formula fed infants):
  - 1-2hrs: 27
  - 3-23hrs: 40
  - 24-47hrs: 41
  - 48-72hrs: 48
- Cornblath & Ichord (2000) - formula fed infants:
  - All infants <20-25
  - First 24hrs <30-35 (sick <45-50)
  - >24hrs <40-50
- Canadian Pediatric Society (2004):
  - <32 hrs post-feed
  - <36 post-subsequent feed
  - Birth-4hrs <25 (target >40)
  - 4-24hrs <35 (target >45)
- Academy of Breastfeeding Medicine (ABM) (2014):
  - <20-25 requires intervention (goal >40)

• UCSF NCNC consensus thresholds for hypoglycemia:
  o NOTE: values based primarily on 2011 AAP Clinical Report
  o Target/goal neonatal glucose:
    - ≥ 45 prior to routine feeds @ 0-24 hours after birth
    - ≥ 50 prior to routine feeds @ >24 hours after birth

PART III: Screening of asymptomatic, at risk infants
- Screening criteria for asymptomatic, well-appearing, at risk infants
  o IDM (pre-existing maternal diabetes, GDMA1, GDMA2)
  o Growth Restricted or Macrosomic (defined by average of male & female weights on Fenton 2013 intrauterine growth curves):
    - Growth Restricted (<5th%)
    - Macrosomic (>97.5th%)
    - NOTE: use of a strict birthweight criteria for all term infants is no longer recommended (e.g. <2500, >4000)

<table>
<thead>
<tr>
<th></th>
<th>37-37*6/7 weeks</th>
<th>38-38*6/7 weeks</th>
<th>39-39*6/7 weeks</th>
<th>40-40*6/7 weeks</th>
<th>&gt;41 weeks</th>
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<tbody>
<tr>
<td>Growth restricted (5th%)</td>
<td>2280 g</td>
<td>2470 g</td>
<td>2650 g</td>
<td>2820 g</td>
<td>3000 g</td>
</tr>
<tr>
<td>Macrosomic (97.5th%)</td>
<td>3950 g</td>
<td>4180 g</td>
<td>4400 g</td>
<td>4630 g</td>
<td>4880 g</td>
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</table>
  - Late preterm (34-37 weeks)
  - Post term (≥42 weeks)
  - Additional consideration: neonates with conditions known to be associated with secondary hypoglycemia (i.e. polycythemia, sepsis) should also be considered for hypoglycemia screening
- Method of screening
  o Glucometer
    - NOTE: accuracy in low range depends on make/model of glucometer; newer meters are more accurate in low range

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2
• **NOTE**: sample should be drawn from warmed heel stick
  o Confirm low values with iSTAT if available or stat blood sample sent to laboratory
  o **NOTE**: Consider initiating treatment for hypoglycemia prior to confirmatory testing if waiting for laboratory result will delay treatment excessively

**Timing of screening**
- General principles:
  - Initial screen after first (breast)feeding (by ~1 hour after birth)
  - More frequent screening in first 2-4 hours of life, then [pre-prandial](#) screening that is roughly linked to feeding schedule
  - Stop screening at 12 hours for macrosomic, IDM infants (very low risk of late hypoglycemia)
  - Continue screening until 24 hours for growth restricted, late preterm infants (greater risk of late hypoglycemia)
  - Consider 36 hour screening for growth restricted, late preterm infants if glucose consistently <45 in first 24 hours after birth
- Time points for Glucose Screening: ~1, 2, 4, 6, 9, 12, 24 hours unless intervention is required
- “Early exit”: consider discontinuing glucose screening prior to completion of all time points in asymptomatic infants with “stable”, “normal” glucose values in the first 24 hours after birth:
  - Glucoses >45 on 3 occasions
  - Repeat one pre-prandial glucose measurement at 24 hours after birth for growth restricted, late pre-term infants
  - **NOTE**: these recommendations are consensus-based; no specific evidence is currently available to support these recommendations

**PART IV: Management of asymptomatic infants**
- See APPENDIX 2 for summary clinical pathway / decision tree (ASYMPTOMATIC)
- Intervention thresholds (see PART II above for details):
  - **NOTE**: treatment thresholds vary at 0-4 hours and 4-24 hours after birth to reflect changing physiology / normal values during transition to postnatal life
- **Treatment**:
  - See algorithm for full work flow and indications for treatment
  - Oral feeding (breast or formula):
    - **Method**:
      - **Breastfeeding**
        - Re-check glucose 1 hour after *initiation* of feeding
        - Repeat breastfeeding if glucose remains below threshold; if glucose remains below threshold after >2 breastfeeding attempts, then consider oral formula supplementation
        - Oral administration of expressed maternal breastmilk (MBM) is also an acceptable form of treatment
      - **Formula**
        - Use protein hydrolysate formula (i.e. Alimentum, Nutramigen, Pregestimil) preferentially if available to reduce exposure to cow milk protein
- 1-4 hours $\rightarrow$ 10-20 mL
- 4-24 hours $\rightarrow$ 15-30 mL
  - Re-check glucose 1 hour after initiation of feeding
  - If glucose remains below threshold after >2 oral feedings, then consider IV treatment

- Oral glucose gel
  - Method:
    - Glucose (Dextrose) 40% gel
    - Administer 0.5ml/kg with max of 2.5 mL
    - Dry newborn’s mouth with 2x2 gauze
    - Massage the ordered amount of glucose gel using gloved fingertips into the buccal mucosa, instilling no more than 0.5ml into each cheek at a time
  - Important considerations
    - MAXIMUM of THREE doses per 24 hours of oral glucose gel before proceeding to IV treatment.
    - Consider IV treatment prior to 3rd dose of oral glucose if infant is not having sequentially rising gluoses in response to oral therapy.

- IV treatment:
  - Indications:
    - Glucoses not responding appropriately to oral glucose and feeding therapy
    - Persistent hypoglycemia after 3 doses of oral glucose gel
    - Any glucose <35 after 5 HOL
  - Method:
    - D10W 2-3 ml/kg IV bolus, followed by:
    - D10W @ 80 ml/kg/day (3.5 ml/kg/hr)
      - Glucose infusion rate (GIR) 5.5 mg/kg/min
      - Increase D10W in increments of 20 ml/kg/day (0.8 ml/kg/hr) if needed for persistent hypoglycemia
      - NOTE: If total fluid administration exceeds 150 ml/kg/day (6.25 ml/kg/hr), consider increasing dextrose concentration to D12.5 rather than IV rate to avoid fluid overload
    - Continue IV treatment until glucose levels are stable >50, then wean IV gradually
  - NOTE: For any infant with persistent hypoglycemia, consider further evaluation for underlying etiology in parallel with treatment

PART V: Management of symptomatic infants
- See APPENDIX 3 for summary clinical pathway / decision tree (SYMPTOMATIC)
- Symptoms of hypoglycemia may include:
  - General symptoms:
    - Abnormal cry, poor feeding, hypothermia, diaphoresis
  - Neurologic symptoms:
    - Tremors, jitteriness, hypotonia, irritability, high-pitched cry, lethargy, seizures
- Cardiorespiratory disturbances:
  - Cyanosis, pallor, tachypnea, apnea, cardiac arrest

- Differentiation of “concerning” (“definite”) versus “possible” symptoms of hypoglycemia:
  - “CONCERNING”: seizure, lethargy/poorly responsive, hypotonia, apnea, cyanosis
  - “POSSIBLE”: jitteriness, tremors, irritability, exaggerated Moro reflex, high-pitched cry, poor feeding, excessive sleepiness/drowsiness

- Thresholds for intervention & treatment:
  - “CONCERNING” (regardless of age)
    - <45 → IV treatment
    - Use IV treatment method from PART IV above
    - If symptoms do not resolve after glucose >50, pursue work-up of other potential causes of symptoms
    - Reasonable to give small aliquots of oral glucose gel (0.5 mL at a time) while obtaining IV access
  - “POSSIBLE” (regardless of age)
    - 35-45 → oral treatment (breastfeeding or formula) + oral glucose gel
    - <35 → IV treatment after one attempt at oral feeding
    - Use IV or oral treatment method from PART IV above
    - If symptoms do not resolve after glucose >50, pursue work-up of other potential causes of symptoms

- NOTE: For any infant with persistent hypoglycemia, consider further evaluation for underlying etiology in parallel with treatment. Strongly consider Neonatologist involvement and Endocrine consultation prior to considering glucagon, octreotide, or other therapies.

PART VI: NICU and Special Care / Transitional Care Nursery
- Treatment thresholds and treatment methods are different for infants in these higher level care settings; consult neonatology for recommendations
References


Fetal-infant Growth Chart for preterm infants - girls
(Curves equal the female WHO Growth Standard at 50 weeks)

Length

Head Circumference

Weight

Curves equal the girl's WHO Growth Standard at 50 weeks.

Source: Intrauterine section - Germany (Weight 2010), United States (Ghori 2010), Australia (Roberts 1999), Canada (Brunner 2001), Scotland (Bovill 2004), and Italy (Berti 2005). Post term section - the World Health Organization Growth Standard, 2006.

http://www.members.shaw.ca/growthchart/
APPENDIX 2: Screening & Management of Neonatal Hypoglycemia in ASYMPTOMATIC infants ≥ 34wks GA

Screening and Management of Neonatal Hypoglycemia in Asymptomatic infants >= 34 Weeks Gestational Age

1st HOL

Initial Feed within 1 hour --> Screen glucose 30 mins after initiation of 1st feed

<25

-Oral glucose gel
-Feed

 >=25

Routine Care

2nd HOL

Screen glucose at 2 HOL (before feed)

<39

-Oral glucose gel
-Feed
-Re-check glucose in 1 hour

 >=40

Routine Care

3rd HOL

Glucose Re-check at 3 HOL (before feed)

<25

IV treatment

25-39

-Oral glucose gel
-Feed
-Re-check glucose in 1 hour

 >=40

Routine Care

4th HOL

Glucose Re-check at 4 HOL (before feed)

<45

-Oral glucose gel (MAX 3 doses in 24 hours)
-Feed
*Consider IV Treatment*
-Re-check glucose in 1 hour

 >=45

Routine Care

5-24 HOL

Glucose Check (before feed)

<35

IV treatment

35-44

Routine Care

>=45

Continue glucose screening (before feeds at 6, 9, 12 HOL, +/- 24 HOL, if SGA or pre-term), if glucose is >=45 x 3, stop screening (and recheck at 24 HOL if growth restricted or pre-term)

MAXIMUM of THREE doses of oral glucose before proceeding to IV treatment.

Consider IV treatment prior to third dose of oral glucose gel if infant is not having sequentially rising glucose in response to oral therapy.
APPENDIX 3: Screening & Management of Neonatal Hypoglycemia in SYMPTOMATIC infants ≥ 34wks GA

Screening and Management of Neonatal Hypoglycemia in SYMPTOMATIC infants ≥ 34 Weeks Gestational Age

"CONCERNING" symptoms:  
- Seizure  
- Lethargy/decreased responsiveness  
- Hypotonia  
- Apnea  
- Cyanosis

Target glucose >= 45 prior to routine feeds

"Possible" Symptoms: check glucose

- Oral glucose gel
- Feed
- Recheck glucose in 1 hour

Glucose <45

- Oral glucose gel
- Feed
- Recheck glucose in 1 hour

Glucose >=45

- Oral glucose gel
- Feed
- Recheck glucose in 1 hour

Glucose <35

- Oral glucose gel
- Feed
- Recheck glucose in 1 hour

Glucose 35-44

- Oral glucose gel
- Feed
- Recheck glucose in 1 hour

Glucose >=45

IV Treatment

Evaluate for other causes of symptoms

Recheck glucose 15 mins after IV glucose complete.

<45

>=45

It is reasonable to trial oral glucose gel (in small aliquots, 0.5mL at a time) in babies with concerning symptoms while attempting to obtain IV access.

For infants not at risk for hypoglycemia but who develop symptomatic hypoglycemia, evaluate for underlying etiology. Repeat glucose per "at risk" category time intervals.