JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

# Neonatal Prolonged Persistent Hypoglycemia Clinical Pathway

JOHNS HOPKINS
All Children's Hospital

Johns Hopkins All Children's Hospital

# Neonatal Prolonged Persistent Hypoglycemia Clinical Pathway

## Table of Contents


1. Rationale
2. Background / Published Data and Levels of Evidence
3. Clinical Management
4. Summary
5. Pathway / Algorithm
6. Glossary
7. References
8. Outcome Measures
9. Appendix
10. Clinical Pathways Team Information



Updated: January, 2024

Owner & Primary author: Darah Yuhas, MD

Johns Hopkins All Children's Hospital

# Neonatal Prolonged Persistent Hypoglycemia Clinical Pathway

**Rationale**

This clinical pathway was proposed as a consensus amongst JHACH neonatologists and pediatric endocrinologists to standardize the clinical approach and management of infants with persistent hypoglycemia. It addresses the following clinical problems:

1. Defining persistent hypoglycemia
2. Timing of critical sample labs
3. Required critical sample labs
4. Diagnosing hyperinsulinism
5. Management of hyperinsulinism

**Background**

Hypoglycemia may be normal in the first 48-72 hours as neonates transition from intrauterine to extrauterine life. Clinical guidelines published by the American Academy of Pediatrics (AAP) have standardized the management of hypoglycemia during this transitional period (1,2). However, these guidelines do not address the diagnosis and management of disorders causing persistent hypoglycemia. Distinguishing physiologic glucose regulation in healthy newborns from pathologic hypoglycemia is important for effective treatment in order to avoid serious consequences.

Hyperinsulinism (HI) is the most common cause of persistent hypoglycemia. HI can be transient and related to perinatal stress, a part of an underlying syndrome or congenital. Common causes for transient HI in neonates are prematurity, IDM, IUGR, birth asphyxia, maternal preeclampsia, congenital heart disease and meconium aspiration syndrome. Beckwith-Wiedemann syndrome is the most common syndrome associated with HI. Turner, Soto and Kabuki syndrome are also known to be associated with HI (3,4).

Dysregulated insulin secretion results in suppression of the counterregulatory response to hypoglycemia and suppression of ketone bodies, which are crucial alternative fuels for the brain. The frequency of neurodevelopmental delays in HI is as high as 30-50%. Neurodevelopmental delays are seen not only infants with congenital forms of HI but also infants with transient causes of HI (5,6). Prompt recognition and appropriate management are critical to decrease the risk of these poor outcomes. It is also important to differentiate hyperinsulinism from less common causes of persistent hypoglycemia such as cortisol and/or growth hormone deficiency, glycogen storage diseases, gluconeogenesis defects and fatty acid oxidation defects. These conditions have different treatments and long-term follow-up which is out of the scope of this clinical pathway.

**Published Data and Levels of Evidence**

**I. Persistent hypoglycemia definition**

a. The GLOW study, a prospective, observational study was designed to determine postnatal changes in plasma glucose concentrations of healthy infants from birth to 120 hours of life. The mean glucose concentrations increased over the first 18 hours then remained stable to 48 hours (59 ± 11 mg/dL; 3.3 ± 0.6 mmol/L)] before increasing to a new plateau by the fourth day (89 ± 13 mg/dL; 4.6 ± 0.7 mmol/L). From the results, it was concluded that infants seem to complete their metabolic transition by day 4. (7)
b. It is difficult to distinguish suspected hypoglycemia disorders from transitional neonatal glucose concentrations during the first 48 hours of life. Diagnostic evaluation should be delayed until 2-3 days after birth. (2,8)
c. Per the AAP guidelines, if it is not possible to maintain a glucose concentration >45 mg/dL after 24 hours with using a GIR rate of 5-8 mg/kg/min, consideration should be given to the possibility of a disorder causing persistent hypoglycemia. (1)
d. Current evidence does not support a specific concentration of glucose that can lead to neurologic damage. In older children and adults neurologic symptoms can be perceived at a PG concentration of <55 mg/dL and cognitive function impairment at a PF concentration of < 50 mg/dL. A blood glucose > 60 mg/dL is recommended after 48 hours of life. (2)

## II. Investigation of persistent hypoglycemia

a. Glucose
    i. In a healthy infant, glucose homeostasis is tightly regulated. Insulin levels begin to decrease when plasma glucose is <85 mg/dL. If plasma levels continue to fall to <65 mg/dL, counterregulatory hormones begin to be secreted. Critical sample labs should be obtained when blood glucose <50mg/dL to allow for accurate interpretation. (9)
    ii. Whole blood glucose values may be ~15% lower than plasma glucose concentrations (2)
    iii. Delays in processing and assaying glucose can reduced glucose concentration by up to 6 mg/dL/hour because of red cell glycolysis (2)
b. Critical sample labs
    i. A retrospective study of critical samples in children with hyperinsulinism vs. children with other hypoglycemia disorders demonstrated (10)
        - Detectable insulin levels had an 82% sensitivity for diagnosing congenital hyperinsulinism. 23 of 28 subjects had detectable insulin (median, 6.7 μIU/mL).
        - Beta hydroxybutyrate of <1.8 mmol/L had a sensitivity of 100%
        - Suppressed fatty acids of <1.7 mmol/L had a sensitivity of 87%
c. Glucagon stimulation test
    i. Glucagon is a hormone that stimulates glycogenolysis to release glucose from the liver. It is inappropriate to have glycogen stores at the time of hypoglycemia. A positive glycemia response to glycogen suggests that insulin excess is the cause of hypoglycemia (2)

## III. Management of hyperinsulinism

### a. Continuous dextrose infusion

i. Per the Pediatric Endocrine Society (PES) consensus guidelines, neonates with a suspected congenital hypoglycemia disorder should maintain a plasma glucose concentration >70 mg/dL (2)

   i. From the adult literature, brain glucose utilization becomes limited at a plasma glucose concentration of approximately 55-65 mg/dL (11). In hypoketotic conditions such as hyperinsulinism or fatty acid oxidation disorders ketones and lactate are not available insufficiently high concentrations to substitute for glucose and the risk of energy failure is greater

   ii. Continuous glucose infusion is recommended as the first-line treatment for persistent hypoglycemia. The maximum rate of a glucose infusion is limited to the maximum dextrose concentration and volume of fluid that can be administered without causing hyponatremia and fluid overload. (2)

   iii. When euglycemia is not achieve by the maximum continuous glucose infusion or the glucose infusion cannot be withdrawn additional medications may be indicated (12)

### *b.* Diazoxide

*i.* Diazoxide is the only FDA-approved drug to treat hyperinsulinemic hypoglycemia. It is an activator of the ATP-sensitive potassium channels and suppresses insulin release from the pancreatic beta cells. It also decreases the excretion of sodium and water, resulting in fluid retention which may be clinically significant. (13)

ii. In 2015, the FDA released a safety announcement reporting 11 cases of pulmonary hypertension in infants treated with diazoxide. In all cases, pulmonary hypertension resolved or improved after diazoxide was discontinued. (14)

*iii.* In a retrospective study in 2018, of 295 patients with hyperinsulinism treated with diazoxide, 18% of patients were diagnosed with edema, 15.6% developed neutropenia (<1500/uL), 5% developed hyperuricemia and 2.4% developed pulmonary hypertension (PH). Infants diagnosed with PH were born at earlier gestation age and frequent had potential PH risk factors (15)

*iv.* In 2020, a working group of pediatrics endocrinologists proposed expert consensus practice guidelines for the appropriate use of diazoxide in infants and children with HI. (16) (Table 1)

| Practice Guidelines for Dosing and Monitoring for Adverse Events in Infants Treated with Diazoxide | |
|---|---|
| **Indication** | Diazoxide should be considered for the treatment of persistent neonatal hypoglycemia confirmed to be secondary to excess insulin secretion. (1\|++++) |
| **Diazoxide use for perinatal stress-induced hyperinsulinism** | Strong consideration should be given to avoid the use of diazoxide until after 7 to 10 days of life if euglycemia can be maintained by other means (especially in a patient with respiratory distress, prematurity, SGA, or IDM) (2\|+). |
| **Dosing** | Recommended dose range is 5 to 15 mg/kg/day in 2 to 3 divided doses (1\|+++). The starting dose should be selected according to the suspected cause and the risk profile of the neonate (2\|++). |
| **Consultation** | Diazoxide should be prescribed infants only after the consultation with a pediatric endocrinologist (1\|+) |
| **Fluid Management** | A thiazide diuretic be started concomitantly with the initiation of diazoxide (1\|+++) and limit the total fluid goal to less than 150 cc/kg/day (2\|+) |
| **Risk of PH** | Consideration of a baseline echocardiogram (2\|++). Recommend a pediatric cardiac consultation in infants with pulmonary hypoplasia, cardiomyopathy or significant structural heart disease prior to initiation. (1\|++). |
| **Monitoring for Adverse Events** | • Monitor for signs of fluid overload and/or PH (2\|+++).<br>• Consider ECHO one week after initiation (2\|+++).<br>• Baseline CBC and 5-7 days after initiation should be obtained (1\|+++).<br>• Baseline Uric acid and 5-7 days after initiation should be obtained (1\|++) |

Table 1. Evidence graded using the framework of the GRADE Working Group. The strength of the recommendation listed as GRADE 1 ("we recommend") or GRADE 2 ("we suggest"). Confidence of the evidence rates as high (++++), moderate (+++), low (++) and very low quality (+).

### c. Glucagon

i. Serum glucagon counterregulatory hormonal responses are blunted in congenital hyperinsulinism when compared to infants that have the same degree of hypoglycemia due to non-hyperinsulinemic causes (17)

ii. In a retrospective study of 40 infants with severe congenital hyperinsulinism, IV glucagon infusion was found to reduce the required GIR by 7.5 mg/kg/min within 24 hours of initiation, decreasing the risk associated with the administration of high fluid volumes or fluids with high-glucose concentrations (18)

iii. 40% of infants treated with glucagon infusion experienced adverse events such as respiratory distress (19%), vomiting (13%), and rash (2%) (18). Authors were unable to conclude if these were directly related to the glucagon infusion. Only one child in this study had thrombocytopenia, but this was present prior to the initiation of the glucagon infusion. There were no cases of hyponatremia.

***d.*** **Additional treatment options**

i. Octreotide
- Octreotide has been recommended as a possible second-line agent in children if a patient is unresponsive to diazoxide. However, treatment failure is common due to development of tachyphylaxis. (12,19).
- Multiple case series and reports have been published regarding the association with Octreotide use and NEC in young infants. (20-22)

ii. Glucocorticoids
- The PES discourages the use of glucocorticoids. Steroids are not effective therapy for HI and expose infants to unnecessary side effects such as iatrogenic adrenal insufficiency, hypertension and bone demineralization (2)

iii. Nifedipine
- calcium channel blockers have shown limited effectiveness in the infant population and should not be used for the treatment of HI (23)

*iv.* Sirolimus
- Sirolimus, a mammalian target of rapamycin inhibitor, was reported as a novel treatment but subsequent studies have failed to show efficacy (24, 25)

**Clinical Management**

I. Diagnosis of persistent hypoglycemia
   a. In late preterm and term infants when glucose is <60 mg/dL after 72 hours of life
   b. In preterm infants when glucose <60 mg/dL on 2+ tests while on full enteral feeds

II. History and physical assessment
   a. History should include the timing of hypoglycemia and its relationship to feeding, birth weight, gestational age and known risk factors for persistent hypoglycemia
   b. Physical examination should include any evidence of hypopituitarism (e.g., micropenis or cleft lip or palate, short stature), hepatomegaly, or Beckwith-Wiedemann syndrome (e.g., omphalocele, hemihypertrophy, macroglossia).

III. Timing of critical sample
   a. Obtain a critical sample lab when glucose is less than 50 mg/dL and
      i. There is a clinical concern for genetic syndrome, cortisol deficiency, growth hormone deficiency or metabolic disease
      ii. An infant is >72 hours old and requiring a GIR of > 10-12 mg/kg/min (even if there is a strong suspicion for transient hyperinsulinism)
      iii. Preterm infant on full enteral feeds with glucose <60 mg/dL x 2

IV. Critical sample labs
   a. Use the order set “Pediatric Hypoglycemia Critical Sample Focused” to obtain the following labs when glucose is <50 mg/dL
      i. Serum glucose, beta-hydroxybutyrate, insulin, cortisol, free fatty acid and growth hormone
      ii. Urine organic acids can be obtained from a bag urine specimen

iii. It is not standard to order a lactic acid or acylcarnitine profile unless suspicion for metabolic disorder

b. If blood is difficult to obtain and all the labs cannot be ordered, prioritize glucose, beta-hydroxybutyrate, insulin and cortisol

V. Interpreting Critical sample labs
   a. See Table 2 for expected values of critical sample labs during hypoglycemic state
   b. If cortisol level is low (<10 mcg/dL), it is recommended to perform an ACTH stimulation test before committing to a diagnosis of adrenal insufficiency
   c. It is important to know the normal laboratory reference ranges seen in EPIC for some of these tests may be inappropriate for interpreting values obtained during a hypoglycemic state.

VI. Glucagon Stimulation Test
   a. Indication
      i. Usually performed when there is a clinical suspicion for hyperinsulinism but the serum insulin level was low or if critical labs are unable to be obtained
   b. Protocol
      i. When glucose is <50mg/dL, give Glucagon 1mg IV/IM/SQ and follow bedside glucoses q10 min x 4
      ii. Positive response if glucose rises > 30 mg/dL during this time
      iii. Effect of glucagon lasts approximately 60 minutes. Rebound hypoglycemia may occur following glucagon administration

VII. Diagnostic criteria for hyperinsulinism
   a. When glucose is <50 mg/dL:
      i. Insulin concentration is inappropriately detectable (>2 uIU/mL)
      ii. Beta-hydroxybutyrate is inappropriately suppressed (<1.8 mmol/L)
      iii. Free fatty acids are inappropriately suppressed (<1.7 mmol/L)
      iv. Glycemic response of > 30 mg/dL in response to glucagon stimulation test

VIII. Management of hyperinsulinism
   a. Preterm Infants (see flowsheet)
      i. Adjustment to feeds
         1. If receiving enteral tube feeds, increase feeding time and calories
         2. Allow infant to continue PO attempts q3h per protocol
         3. If receiving all PO feeds, maintain q3h PO feeds and increase calories
      ii. If hypoglycemia is persistent despite feeding adjustments, initiate dextrose containing fluids to maintain plasma glucose concentration >70 mg/dL
      iii. Consult endocrinology if unable to wean off dextrose containing fluids and/or condense feeding times without hypoglycemia
   b. Late Preterm/Term Infants (see flowsheet)
      i. Initiate dextrose containing fluids and increase GIR as needed for goal glucose > 70 mg/dL

ii. Consider increasing feeding volume, fortifying and/or extending feeding times on an individual basis
iii. Consult endocrinology to discuss medical management with glucagon and/or diazoxide if GIR is close or at maximum amount (not a specific number, based on volume limitations and electrolyte disturbances)

c. Calculation of GIR from oral feeds (approximate value)
   i. [Sugar content of milk (g/dL) x rate (mL/kg/d)]/144
   ii. Amount of lactose/glucose in milk: Breast milk/term formula = 7.1 g/dL, preterm formula = 8.5 g/dL (based on 20kcal/oz)

d. Glucagon and diazoxide use
   i. Advisable to have on-site endocrinology when considering glucagon and/or diazoxide initiation
   ii. Continuous glucagon infusion
      1. Fixed dose of 1mg/day
      2. The only IV solution compatible with glucagon is dextrose. **Will crystalize with saline or heparin containing fluids.**
   iii. Diazoxide
      1. Obtain baseline ECHO. Do not initiate if evidence of cardiac disease, or pulmonary hypertension without consulting cardiology
      2. Initiate chlorothiazide/hydrochlorothiazide concurrently
      3. Starting dose of 5-15 mg/kg/day divided BID
      4. Typical response seen within 2-4 days of therapy. If no effect by ~7 days at maximum dosage discontinue medication
   iv. Weaning glucagon and/or diazoxide
      1. Discuss weaning strategy with endocrinologist

IX. Consultation
   a. Consult endocrinology when a maximum GIR has been reached prior to initiation of medications such as glucagon or diazoxide
   b. Consult metabolic/genetics if concern for hypoglycemia related to metabolic or genetic syndrome.

X. Discharge planning
   a. Perform a safety fast prior to discharge in infants with hyperinsulinism that required diazoxide/glucagon, infants being discharged with higher calories for hypoglycemia only (not growth) and/or required a prolonged continuous dextrose infusion
   b. Safety fast protocol
      i. At least 6 hours of fasting with all blood glucoses above 60 mg/dL
      ii. If patient passes safety fast, no home teaching or supplies needed
   c. If patient is going home on treatment such as diazoxide or hydrocortisone then patient will require home teaching and supplies provided by endocrinology team
      i. Glucose meter
      ii. Frequency of blood glucose checks
      iii. Normal glucose range

iv. Emergency medications such as glucagon (for hyperinsulinism) or solucortef (for adrenal insufficiency)

**Summary**

| **Definition of persistent hypoglycemia** |
|---|
| **Glucose <60 mg/dL**<br>after 72 hours of life |

| **Goal serum glucose** |
|---|
| **Glucose >70 mg/dL**<br>For infants with confirmed hyperinsulinism |

| **Critical Sample Labs** (Obtained when glucose < 50 mg/dL) | |
|---|---|
| **Test** | **Normal value in setting of hypoglycemia** |
| Serum Glucose | < 50 mg/dL |
| Beta-Hydroxybutyrate | > 2 mmol/L |
| Insulin | < 2 uIU/mL |
| Free Fatty Acids | > 2mmol/L |
| Cortisol | > 10mcg/dL |
| Growth Hormone | > 7 ng/mL |
| Lactic acid* | 0.6-2 mmol/L |
| Urine Organic Acids | Routine normals |
| Acylcarnitine Profile* | Routine normals |

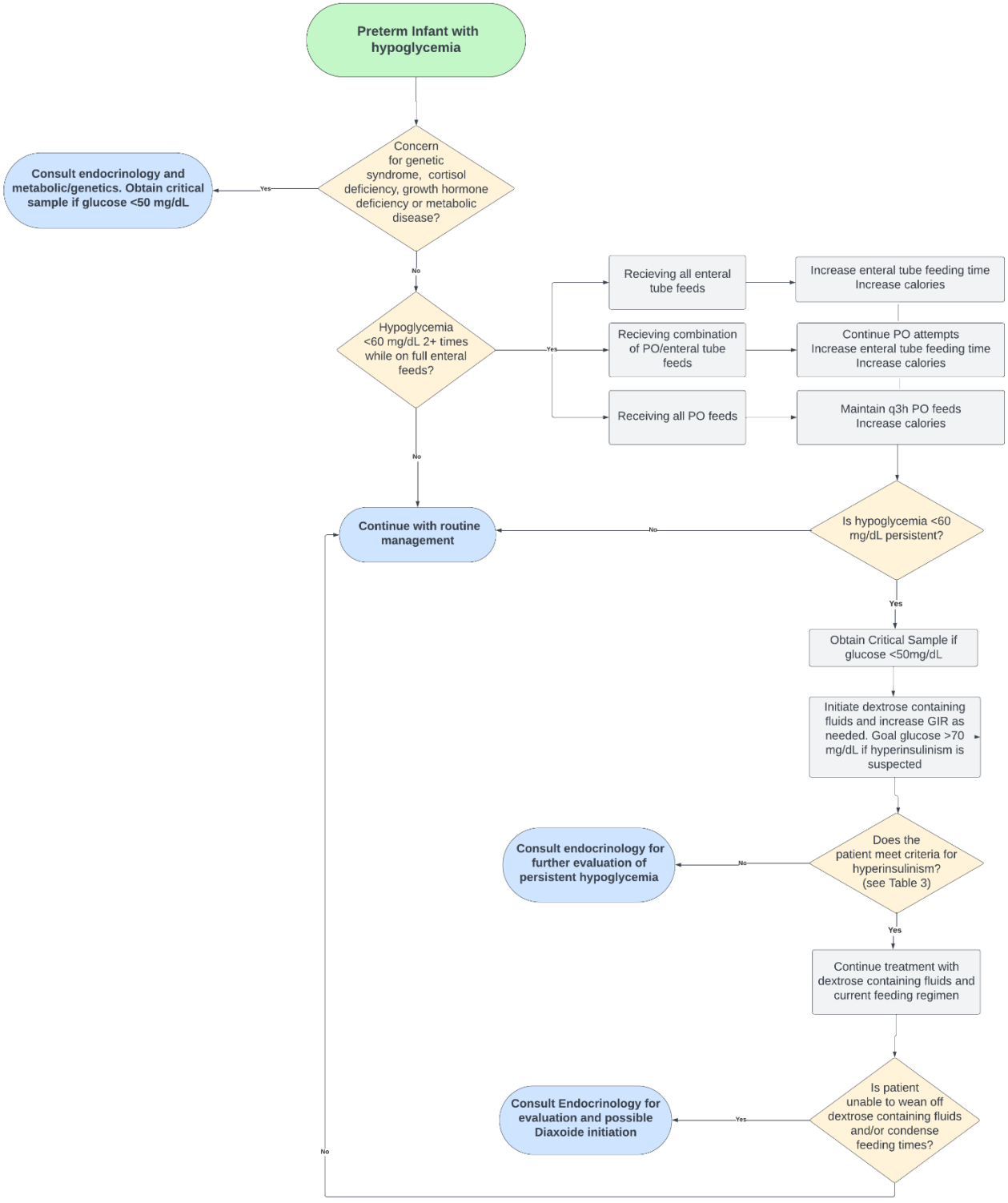
Table 2.
*Not routinely obtained

| **Diagnostic criteria for hyperinsulinism** |
|---|
| When glucose is <50 mg/dL:<br>• Beta-hydroxybutyrate <1.8 mmol/L<br>• Free fatty acids <1.7 mmol/L<br>• Insulin* >2 uIU/mL<br>• Glycemic response of > 30 mg/dL in response to glucagon stimulation test<br><br>***Insulin may have false-negative result; b-OH and FFA are the most sensitive tests** |

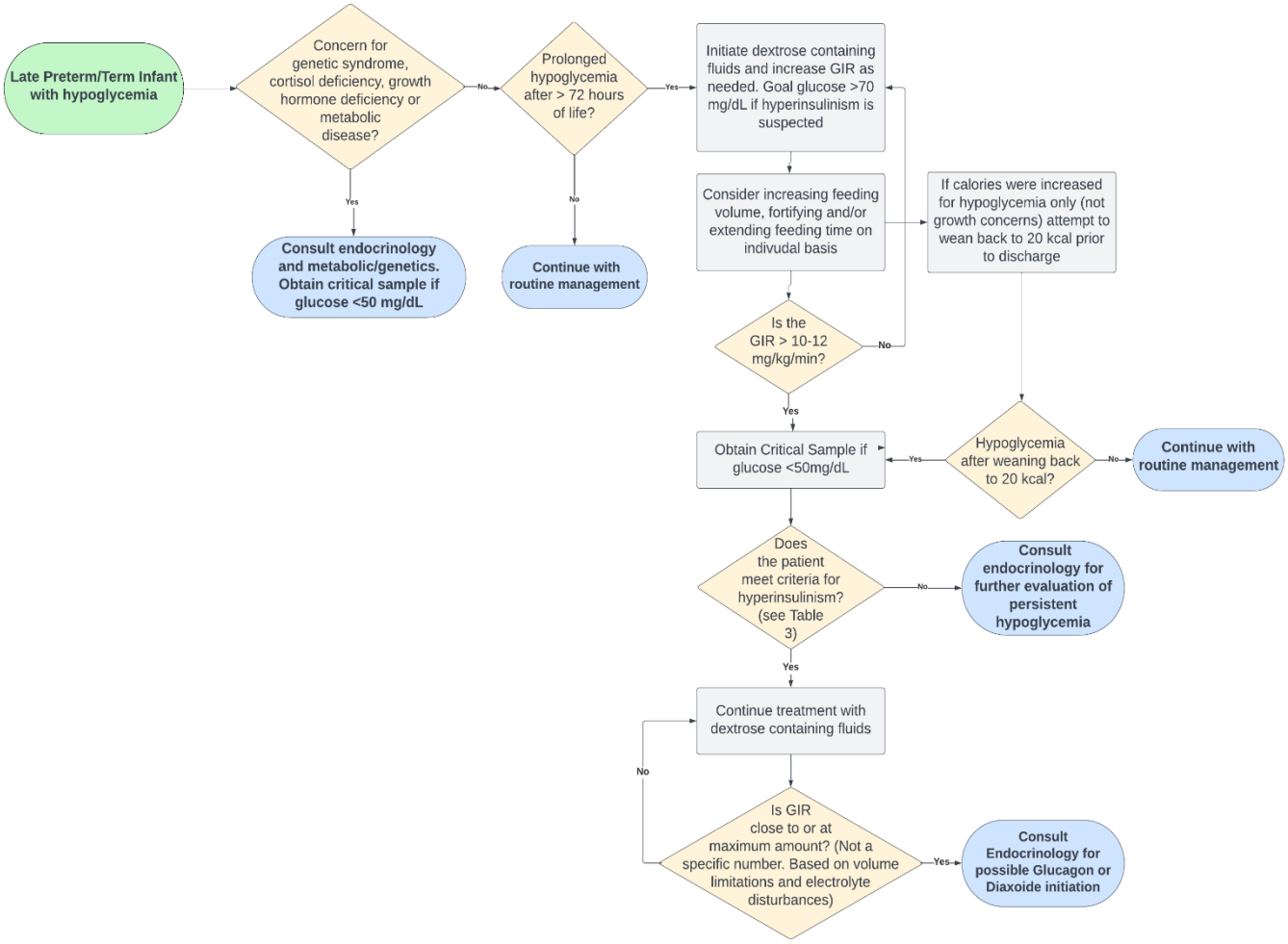
Table 3.

| **Risk factors for hyperinsulinism** |
|---|
| • Large for gestational age (LGA)<br>• Infant of diabetic mother (IDM)<br>• Premature or postmature delivery<br>• Perinatal stress (birth asphyxia, maternal preeclampsia, maternal hypertension, meconium aspiration)<br>• Family history or congenital syndromes |

**Management of Persistent Hypoglycemia in Preterm Infant Flowsheet Management of**



## Persistent Hypoglycemia in Late Preterm/Term Infant Flowsheet



**Glossary**
AAP – American Academy of Pediatrics
PES – Pediatric Endocrine Society
FDA – Food and Drug Administration
HI – Hyperinsulinism
SGA – Small for gestational age
IUGR – Intrauterine growth restriction
IDM – Infant of diabetic mother
NEC – Necrotizing enterocolitis
AE – Adverse events
GIR – Glucose infusion rates
PG – Plasma glucose

**References**


(1) Postnatal Glucose Homeostasis in Late-Preterm and Term Infants. (2011). *PEDIATRICS*, *127*(3), 575 579. https://doi.org/10.1542/peds.2010-3851
(2) Thornton, Paul S., et al. "Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children." *The Journal of Pediatrics*, vol. 167, no. 2, Aug. 2015, pp. 238–45, https://doi.org/10.1016/j.jpeds.2015.03.057.
(3) Lord, Katherine, and Diva D. De León. "Hyperinsulinism in the Neonate." *Clinics in Perinatology*, vol. 45, no. 1, Mar. 2018, pp. 61–74, https://doi.org/10.1016/j.clp.2017.10.007. Accessed 30 Sept. 2022.
(4) De Leon, Diva D., and Charles A. Stanley. "Congenital Hypoglycemia Disorders: New Aspects of Etiology, Diagnosis, Treatment and Outcomes." *Pediatric Diabetes*, vol. 18, no. 1, Oct. 2016, pp. 3–9, https://doi.org/10.1111/pedi.12453. Accessed 29 May 2020.
(5) Meissner, T., et al. "Long-Term Follow-up of 114 Patients with Congenital Hyperinsulinism." *European Journal of Endocrinology*, July 2003, pp. 43–51, https://doi.org/10.1530/eje.0.1490043. Accessed 15 June 2020.
(6) Hima Bindu Avatapalle, et al. "Abnormal Neurodevelopmental Outcomes Are Common in Children with Transient Congenital Hyperinsulinism." *Frontiers in Endocrinology*, vol. 4, Frontiers Media, Jan. 2013, https://doi.org/10.3389/fendo.2013.00060.
(7) Harris, Deborah L., et al. "Glucose Profiles in Healthy Term Infants in the First 5 Days: The Glucose in Well Babies (GLOW) Study." *The Journal of Pediatrics*, vol. 223, Aug. 2020, pp. 34-41.e4, https://doi.org/10.1016/j.jpeds.2020.02.079.
(8) Stanley, Charles A., et al. "Re-Evaluating 'Transitional Neonatal Hypoglycemia': Mechanism and Implications for Management." The Journal of Pediatrics, vol. 166, no. 6, June 2015, pp. 1520-1525.e1, https://doi.org/10.1016/j.jpeds.2015.02.045. Accessed 12 June 2021.
(9) Sprague, J. E., & Arbeláez, A. M. (2011). Glucose counterregulatory responses to hypoglycemia. *Pediatric endocrinology reviews: PER*, *9*(1), 463–475.
(10) Ferrara, Christine, et al. "Biomarkers of Insulin for the Diagnosis of Hyperinsulinemic Hypoglycemia in Infants and Children." *The Journal of Pediatrics*, vol. 168, Jan. 2016, pp. 212–19,

(11) Cryer, P. E., & Arbeláez, A. M. (2017). Hypoglycemia in diabetes. *Textbook of diabetes*, 513-533.
(12) Tohru Yorifuji, et al. “Clinical Practice Guidelines for Congenital Hyperinsulinism.” *Clinical Pediatric Endocrinology*, vol. 26, no. 3, Japanese Society for Pediatric Endocrinology, Jan. 2017, pp. 127–52
(13) *PROGLYCEM - Diazoxide*. Food and Drug Administration, Feb. 2008
(14) *FDA Warns about a Serious Lung Condition in Infants and Newborns Treated with Proglycem (Diazoxide)*. 15 July 2015, www.fda.gov/media/93285/download
(15) Herrera, Adriana, et al. “Prevalence of Adverse Events in Children with Congenital Hyperinsulinism Treated with Diazoxide.” *The Journal of Clinical Endocrinology & Metabolism*, vol. 103, no. 12, Sept. 2018, pp. 4365–72
(16) Brar, Preneet Cheema, et al. “Management and Appropriate Use of Diazoxide in Infants and Children with Hyperinsulinism.” *The Journal of Clinical Endocrinology & Metabolism*, vol. 105, no. 12, Aug. 2020, pp. 3750–61,
(17) Hussain, K., et al. “Serum Glucagon Counterregulatory Hormonal Response to Hypoglycemia Is Blunted in Congenital Hyperinsulinism.” *Diabetes*, vol. 54, no. 10, Sept. 2005, pp. 2946–51,
(18) Hawkes, Colin P., et al. “The Effect of Continuous Intravenous Glucagon on Glucose Requirements in Infants with Congenital Hyperinsulinism.” *Journal of Inherited Metabolic Disease*, vol. 45, Jan. 2018, pp. 45–50
(19) Lord, Katherine, and Diva D. De León. “Monogenic Hyperinsulinemic Hypoglycemia: Current Insights into the Pathogenesis and Management.” *International Journal of Pediatric Endocrinology*, vol. 2013, no. 1, Feb. 2013,
(20) McMahon, Ann W., et al. “Octreotide Use and Safety in Infants with Hyperinsulinism.” *Pharmacoepidemiology and Drug Safety*, vol. 26, no. 1, Dec. 2016, pp. 26–31, https://doi.org/10.1002/pds.4144.
(21) Laje, Pablo, et al. “Necrotizing Enterocolitis in Neonates Receiving Octreotide for the Management of Congenital Hyperinsulinism.” *Pediatric Diabetes*, vol. 11, no. 2, Wiley-Blackwell, Mar. 2010, pp. 142–47
(22) Hawkes, Colin P., et al. “Late Presentation of Fulminant Necrotizing Enterocolitis in a Child with Hyperinsulinism on Octreotide Therapy.” *Hormone Research in Paediatrics,* vol. 86, no. 2, Feb. 2016, pp. 131–36
(23) Guemes M, Shah P, Silvera S, et al. Assessment of nifedipine therapy in hyperinsulinemic hypoglycemia due to mutations in the ABCC8 gene. J Clin Endocrinol Metab 2017;102(3):822–30.
(24) Senniappan S, Alexandrescu S, Tatevian N, et al. Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia. N Engl J Med 2014;370(12):1131–7.
(25) Szymanowski M, Estebanez MS, Padidela R, et al. mTOR inhibitors for the treatment of severe congenital hyperinsulinism: perspectives on limited therapeutic success. J Clin Endocrinol Metab 2016;101(12):4719–29

**Outcome Measures**

- Compliance with guidelines on timing and correct orders for critical sample
- Frequency of hyperinsulinism requiring glucagon and/or diazoxide treatment

Clinical Pathway Team

Neonatal Prolonged Persistent Hypoglycemia

Clinical Pathway

*Johns Hopkins All Children's Hospital*

Owner & Primary author: Darah Yuhas, MD

Guideline Review Panel:

Sandra Brooks, MD, MPH Neonatologist, Chair NICU Clinical Pathway Council

Supamit Ukarapong, MD, Medical Director Pediatric Endocrinology

Clinical Pathway Management Team: Joseph Perno, MD; Courtney Titus, PA-C

Date Approved by JHACH MFNI Clinical Practice Council: January 23, 2024

Date Available on Webpage: February 13, 2024

**Disclaimer**

*Clinical Pathways are intended to assist physicians, physician assistants, nurse practitioners and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. The ultimate judgment regarding care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.*

*The information and guidelines are provided "AS IS" without warranty, express or implied, and Johns Hopkins All Children's Hospital, Inc. hereby excludes all implied warranties of merchantability and fitness for a particular use or purpose with respect to the information. Johns Hopkins All Children's Hospital, Inc. shall not be liable for direct, indirect, special, incidental or consequential damages related to the user's decision to use the information contained herein.*