Owner: Pediatric Department	Protocol Code: PR-PED-004
Title of the Protocol: Management of Acute Hypoglycemia in Neonate & Children	

Definition:

- The definition of hypoglycemia is difficult, however Hypoglycemia should be strongly considered if plasma glucose less than 50 mg/dl (< 2.8 mmol/l), while, children and adults maintain their glucose more than 60 mg/dl.
- **Important notices:**

  Electrophysiological changes indicate significant neuroglycopenia evident at a glucose level below 2.8 mmol/l. Basal glucose requirements (mg/kg/min) vary with age: neonates 5- 6, infants and children 3 - 5, adults 2 - 3 mg/kg/min.

Causes of Hypoglycemia:

Neonate < 48-72 hrs.	Preterm, IUGR, perinatal asphyxia, hypothermia, sepsis, respiratory distress, diabetic mother, macrosomia, syndrome (e.g. Beckwith-Wiedemann), pancreatic dysfunction.
Neonate – 2yrs.	Congenital hyperinsulinism (most common cause of persistent hypoglycemia <2yrs), inborn errors of metabolism, congenital hormone deficiencies (e.g. growth hormone / cortisol deficiency).
Child	Accelerated starvation (previously known as "ketotic hypoglycemia"), hypopituitarism, growth hormone / cortisol deficiency.
Adolescent	Insulinoma, adrenal insufficiency, anorexia nervosa.

Clinical Features:

Symptoms arise from neurogenic or neuroglycopenic mechanisms.

- **Neurogenic**: tremors, sweating, pallor, tachycardia, anxiety, weakness and hunger.
- **Neuroglycopenic:** apnea, cyanosis, hypotonia, coma, seizures, poor feeding, headache, lethargy, irritability, confusion, visual disturbance…. etc.

Congenital Hyperinsulinism (CHI):

- Is the most common cause of persistent hypoglycemia in infants and children.
- Dysregulated insulin secretion by the beta cells of the pancreas causes severe and recurrent hypoglycemia and can be monogenic (resulting from genetic defects affecting important factors in the regulation of insulin secretion), transient (resulting from perinatal stress), or syndromic.
- Given the severe hypoglycemia, and lack of alternative fuels (ketones).
- CHI carries a high risk of neurologic damage and developmental delays, with up to 50 % of children developing neurocognitive abnormalities.

Clues to Diagnosis of Hyperinsulinism:

Large for gestational age, severe & persistent hypoglycemic requiring high GIR (> 8 mg/kg/min).

"Critical" Blood Sampling:

Because tests performed when the blood glucose levels are normal are not helpful in determining the underlying cause of hypoglycemia, critical blood test samples" for the diagnostic evaluation should be obtained when plasma glucose levels are < 50 mg/dL (2.8 mmol/L) when measured in a laboratory, or < 40 mg/dL (2.2 mmol/L) when measured with a bedside glucometer.

The tests to obtained are: Insulin, beta-hydroxybutyrate, venous pH, bicarbonate, lactate, ammonia, free fatty acids, C-peptide, growth hormone, cortisol, serum amino acids, urine organic acids and urine for ketones.

Diagnosis of Congenital Hyperinsulinism:

During hypoglycemia (RBS < 50 mg/dL) with the following: Inappropriately low beta-hydroxybutyrate (< 0.6 mmol/L), inappropriately low free fatty acids (< 0.5 mmol/L) with +/- inappropriately elevated insulin.

Glucagon Stimulation test:

When glucose < 50 mg/dL, give glucagon 1 mg IV/IM, then monitor blood glucose every 10 minutes for 40 minutes. A positive response is If the plasma glucose increases by ≥30 mg/dL (1.7 mmol/L) within 40 minutes after glucagon administration. Failure to response is seen in the possibility of a glycogen storage disorder, defect in glycogen synthesis or fatty acid oxidation disorder.

Important Notices:

- Low cortisol and/or growth hormone at time of hypoglycemia not diagnostic of cortisol or GH deficiency ► other stimulation testing needed to prove cortisol or GH deficiency.

- Insulin levels are not always elevated at the time of hypoglycemia in children with hyperinsulinism, but normal measurable insulin level, absent urine ketone, low free fatty acids and a positive response to glucagon are enough to make the diagnosis.

- Children who have undergone a Nissen fundoplication or other gastric surgeries are at risk of postprandial hypoglycemia ("late dumping syndrome") which is due to excessive insulin response to feeding and therefore could look like hyperinsulinism. Establishing the timing of the hypoglycemia in relationship with feedings is helpful to distinguishing these cases.

- Do not use glucocorticoids to treat hyperinsulinism or unspecified hypoglycemia unless diagnosis of adrenal insufficiency is confirmed.

- Hypertrophic cardiomyopathy is common in infants with CHI, to consider ECHO +/- Cardiology consult.

Management:

Parenteral dextrose infusion:

- An intravenous (IV) bolus of dextrose, is given *over 5 to 15 minutes (2 – 4 mL/kg of 10 % dextrose), followed by continuous administration of dextrose infusion at a rate of 5 to 8 mg/kg of dextrose per minute.* Plasma glucose concentration should be measured 30 to 45 minutes after the initiation of parenteral therapy, and the infusion rate or dextrose concentration adjusted as needed to maintain plasma glucose concentration >50 mg/dL (2.8 mmol/L) in the first 48 hours of life & > 60 mg/dL (3.3 mmol/L) after 48 hours of age with an upper limit of 90 - 100 mg/dL (5 to 5.5 mmol/L). Repeat measurements are obtained 30 to 45 minutes after any change in the IV dextrose infusion rate.
- The maximum dextrose concentrations for fluid administered through a peripheral IV catheter or a low lying umbilical venous catheter is 12.5 %, while, through a central venous catheter (including a centrally positioned umbilical venous catheter) is 25 %.

Glucagon:

- Neonates & infants on maximal rates of parenteral dextrose, a continuous IV infusion of 1 mg glucagon total for 24 hours (approximately 10 to 20 mcg/kg per hour) can be used until reaching the cause of hypoglycemia.

Diazoxide:

Is the first line therapy 15 mg/kg/day (dosed 5-15 mg/kg/day divided into 3 doses). Start with 5 mg/kg/ day, then increase gradually if still hypoglycemia episodes till maximum dose. Occasionally dose could be raised up to 20 mg/kg/day.

Adverse effects:

- The most common side effects include hypertrichosis, which may be severe, and sodium and water retention.

- Other side effects include mild hyperuricemia, decreased immunoglobulin G concentration, decreased neutrophil counts, and thrombocytopenia.
- Water retention can be reduced by a thiazide diuretic, which may further reduce insulin secretion. Life-threatening complications such as heart failure is rare.
- If diazoxide failure, stop diazoxide and start second line therapy.

Octreotide:

Has been used in the treatment of newborns, infants, and children with congenital hyperinsulinism (CHI), since the 1980s and is currently broadly used around the world for the management of children with diazoxide-unresponsive CHI. However, one of the first reports in the literature of Octreotide-related NEC was in 2010. Octreotide is a long-acting analog of somatostatin that suppresses insulin secretion for the short-term management of hypoglycemia. Dose of 5-25 μg/kg/day divided into 2-3 doses. No clear maximum dose has been established for these children with hyperinsulinism.

Surgical therapy:

Is warranted in children older than several weeks of age in whom hyperinsulinism is proven and pharmacologic therapy fails to control hypoglycemia.

Referencies:

Lord K, De León DD. Monogenic hyper insulinemic hypoglycemia: current insights into the pathogenesis and management. Int J Pediatr Endocrinol. 2013 Feb 6; 2013(1):3.

Palladino, AA, Stanley, CA. A specialized team approach to diagnosis and medical versus surgical treatment of infants with congenital hyperinsulinism. Semin Pediatr Surg. 20(1):32-7, 2011 Feb.

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