

Hypoglycemia in the Newborn

There is no universal definition for hypoglycemia.¹ Various investigators have empirically recommended different blood glucose levels (BGLs) that should be maintained in neonatal period to prevent injury to the developing brain.^{2,3} The “normal” range of blood glucose is variable and depends upon factors like birth-weight, gestational age, body stores, feeding status, availability of energy sources as well as the presence or absence of disease.^{4,5} Further, there is no concrete evidence to show the causation of adverse long-term outcomes by a particular level or duration of hypoglycemia.⁶ Hence, a consensus has been to evolve an “operational threshold” as definition.

Definition

The operational threshold for hypoglycemia is defined as *that concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on currently available evidence in literature.*⁷ Operational threshold has been defined as BGL of less than 40 mg/dL (plasma glucose level less than 45 mg/dL).⁸

WHO defines hypoglycemia as BGL of less than 45 mg/dL (2.2 mmol/L).

Screening for hypoglycemia

Screening for hypoglycemia is recommended in following high risk infants (Table 1).

Table 1: Indication for routine blood glucose screening ⁹	
1	Low birth weight infants (<2000 grams)
2	Preterm infants (≤35 weeks)
3	Small for gestational age infants (SGA) : birth weight <10 th percentile
4	Infant of diabetic mothers (IDM)
5	Large for gestational age (LGA) infants: birth weight >90 th percentile*
6	Infants with Rh-hemolytic disease
7	Infants born to mothers receiving therapy with terbutaline/propranolol/lebatolol/oral hypoglycemic agents
8	Infants with morphological IUGR. This group includes neonates with birth weight between 10 th to 25 th and possibly up to 50 th percentile, with features of fetal under-nutrition such as three or more loose skin folds in gluteal region, overall decreased subcutaneous fat, and head circumference to chest circumference difference > than 3 cm
9	Any sick neonate e.g. those with perinatal asphyxia, polycythemia, sepsis, shock etc, when they are in active phase of illness. The screening may be discontinued once their condition gets stabilized.
10	Infants on total parenteral nutrition

* LGA infants because of constitutional reasons such as infants of constitutionally large parents may be exempted from routine screening

Time schedule for screening

There is a paucity of the literature that looks into optimal timing and the intervals of glucose monitoring. Lowest blood sugar values are seen at 2 hours of life. IDMs frequently experience asymptomatic hypoglycemia very early viz. 1 to 2 hours and rarely beyond 12 hours (range 0.8 to 8.5 h), supporting need for early screening for this population.¹⁰ However, preterm and SGA may be at highest risk up to 36 h (range 0.8 to 34.2 h).¹¹

Some SGA and preterm infants may develop hypoglycemia when feeding is not established. Based on these assumptions and current knowledge, Table 2 elaborates the schedule and frequency of monitoring in different situations.

Table 2: Schedule of blood glucose monitoring		
	Category of infants	Time schedule
1	At risk neonates (SN 1-8 in Table 1)	2, 6, 12, 24, 48, and 72 hrs
2	Sick infants	Every 6-8 hrs (individualize as needed)
3	Stable VLBW infants on parenteral nutrition	Initial 72 h: every 6 to 8 hrs After 72 hr: once a day
<i>Infants exhibiting signs compatible with hypoglycemia at any time also need to be investigated.</i>		

Education and counseling of caregivers regarding the screening

Parents should be told that their infant is at-risk and therefore requires blood tests at regular intervals. This will ensure appropriate parental participation in monitoring and allay fears if further interventions are required.

Infants in whom screening is not required

Screening for hypoglycemia is not recommended in term healthy breast-fed appropriate-for-gestational age (AGA) infants. However, term infants with poor feeding, presence of inadequate lactation or presence of cold stress may be considered for screening.

Method of blood glucose level estimation

- *Point of care (POC) reagent strips (Glucose oxidase method):* Though widely used, glucose estimation by this method is unreliable especially at levels where therapeutic intervention is required such as BGL 40 to 50 mg/dL. They are useful for screening purpose but low values should be confirmed by proper laboratory analysis. However, treatment of hypoglycemia may be initiated based on the results of the reagent strips.

It is important to consider the variations between capillary and venous, blood and plasma, and immediate and stored samples (whole blood sugar value is 10% to 15% less than that of plasma value; the BGL can fall by 14 to 18 mg/dL per hour in samples that await analysis).¹² Arterial samples have slightly higher value compared to venous or capillary samples.

The first generation strips focused on change in color by enzymatic reaction on application of blood drop. The color can be read by naked eye or by reflectance meters. However, the results get affected by hematocrit values, acidosis, presence of bilirubin, etc.

- The newer generation glucose reagent strips generate a current on reaction of glucose with enzymes such glucose oxidase or glucose dehydrogenase. The amount of current is proportional to amount of sugar present in plasma. Though these second generation glucose readers are more accurate than the previous version but still are not reliable. Any abnormal BGLs by this technique must be confirmed by standard laboratory methods.
- *Laboratory diagnosis:* This is the most accurate method. In the laboratory, glucose can be measured by either the *glucose oxidase* (calorimetric) method or by the *glucose electrode method (as used in blood gas & electrolyte analyzer machine)*. Blood samples should be analyzed quickly to avoid erroneously low glucose levels.

Clinical signs associated with hypoglycemia

- **Asymptomatic:** It is well known that low BGL may not manifest clinically and be totally asymptomatic. There is considerable controversy in regard to the need for treatment the infants with low BGLs but without any symptoms.^{13,14}
- **Symptomatic:** A smaller proportion of infants with hypoglycemia can be symptomatic. Clinical signs of hypoglycemia are variable and may include stupor, jitteriness, tremors, apathy, episodes of cyanosis, convulsions, intermittent apneic spells or tachypnea, weak and high pitched cry, limpness and lethargy, difficulty in feeding, and eye rolling. Episodes of sweating, sudden pallor, hypothermia and cardiac arrest *have also* been reported.

Diagnosis

- **Asymptomatic hypoglycemia** is said to be present when BGL is less than 45 mg/dL (to be confirmed by laboratory estimation) and the infant does not manifest with any clinical features
- **Symptomatic hypoglycemia** should be diagnosed if hypoglycemia (BGL is less than 45 mg/dL) coexists with clinical symptoms. *Neonates* generally present with nonspecific signs that result from a variety of illnesses. Therefore, careful evaluation should be done to look for all possible causes especially those that can be attributed to hypoglycemia.

If clinical signs attributable to hypoglycemia persist despite intravenous glucose, then other causes of persistent / resistant hypoglycemia should be explored.

Management of asymptomatic hypoglycemia

Table 3 summarizes management of an infant with asymptomatic hypoglycemia

Table 3: Management plan of infants with asymptomatic hypoglycemia	
Blood sugar 20-45 mg/dL	• Trial of oral feeds (expressed breast milk or formula) and repeat blood test after 1 hour. 1. If repeat BGL is >45 mg/dL, two hourly feeds is ensured with 6 hourly monitoring of BGL for 48 hrs. the target blood glucose value is 50 to 120 mg/dL. 2. If repeat blood sugar is <45 mg/dL, IV Dextrose is started and further management is as for symptomatic hypoglycemia
Blood sugar levels <20 mg/dL	IV Dextrose is started at 6 mg/kg/min of glucose. Subsequent management is as for symptomatic hypoglycemia

Oral feeds – issues

Direct breast-feeding is the best option for trial of an oral feed. If the infant is unable to suck, expressed breast milk may be given. Breast milk promotes ketogenesis (ketones are important alternate sources for the brain along with other sources such as pyruvate, free fatty acids, glycerol, and amino acids). If breast milk is not available, then formula feeds may be given.

Some of the randomized clinical trials in SGA¹⁵ and appropriate-for-gestational age¹⁶ infants found that the sugar or sucrose fortified milk (5 g sugar per 100 mL milk) raises blood glucose and prevents hypoglycemia. Such supplementation may be tried in the asymptomatic neonates with blood sugar levels between 20 to 45 mg/dL. However, this practice carries a potential to compromise breast feeding rates, and therefore one should be prudent in exercising this option.

Management of symptomatic hypoglycemia

All symptomatic infants should be treated with IV fluids

For symptomatic hypoglycemia including seizures, a bolus of 2 mL/kg of 10% dextrose (200 mg/kg) should be given. This mini-bolus helps to rapidly correct BGL.¹⁴ The bolus should be followed by continuous glucose infusion at an initial rate of 6-8 mg/kg/min. BGL should be checked after 30 to 60 min, and then every 6 hours until blood sugar is >50 mg/dL.

If BGL stays below 45 mg/dL despite bolus and glucose infusion, glucose infusion rate (GIR) should be increased in steps of 2 mg/kg/min every 15 to 30 min until a maximum of 12 mg/kg/min.

After 24 hours of IV glucose therapy, once two or more consecutive BGLs are >50 mg/dL, the infusion can be tapered off at the rate of 2 mg/kg/min every 6 hours with BGL monitoring. Tapering has to be accompanied by concomitant increase in oral feeds. Once a rate of 4 mg/kg/min of glucose infusion is achieved and oral intake is adequate and the BGLs are consistently >50 mg/dL, the infusion can be stopped.

It is important to ensure continuous glucose infusion preferably using an infusion pump and without any interruption. Do not stop glucose infusion abruptly as severe rebound hypoglycemia may occur. Avoid using more than 12.5% dextrose infusion through a peripheral vein due to the risk of thrombophlebitis.

Practical tip: *If there is persistent hypoglycemia, check the intravenous line for functioning. Also recheck the intravenous fluid preparation and infusion rate.*

Recurrent / resistant hypoglycemia

This condition should be considered when infant fails to maintain normal BGL despite a GIR of 12 mg/kg/min or when stabilization is not achieved by 7 days of therapy. High levels of glucose infusion may be needed in the infants to achieve euglycemia.

Table 4 : Important causes of resistant hypoglycemia

Congenital hypopituitarism
Adrenal insufficiency
Hyperinsulinemic states
Galactosemia
Glycogen storage disorders
Maple syrup urine disease
Mitochondrial disorders
Fatty acid oxidation defect

Table 5 :Investigations to be done in resistant hypoglycemia

Serum insulin levels
Serum cortisol levels
Growth hormone levels
Blood ammonia
Blood lactate levels
Urine ketones and reducing substances
Urine and sugar aminoacidogram
Free fatty acid levels
Galactose 1 phosphate uridyl transferase levels

Besides increasing GIR for resistant hypoglycemia, certain drugs may be tried. Before administration of drugs, take the samples to investigate the cause (Table no 4). Drugs that are used include the following:

- Hydrocortisone 5 mg/kg/day IV or PO in two divided doses for 24 to 48 hrs
- Diazoxide can be given orally 10-25 mg/kg/day in three divided doses . Diazoxide acts by keeping the K_{ATP} channels of the β -cells of the pancreas open, thereby reducing the secretion of insulin. It is therefore useful in states of unregulated insulin secretion like in insulinomas.
- Glucagon 100 μ g/kg subcutaneous or intramuscular (max 300 μ g) – maximum of three doses. Glucagon acts by mobilizing hepatic glycogen stores, enhancing gluconeogenesis and promoting ketogenesis. These effects are not consistently seen in small-for-gestational age infants. Side effects of glucagon include vomiting, diarrhea and hypokalemia and at high doses it may stimulate insulin release.
- Octreotide (synthetic somatostatin in dose of 2-10 μ g/kg/day subcutaneously two to three times a day.

Do not use diazoxide and glucagon in small for gestational age infants.

Useful formulae

- (a) GIR (mg/kg/min) = $\frac{\% \text{ of dextrose being infused} \times \text{rate (mL/hr)}}{\text{body weight (in kg)} \times 6}$
- (b) Infusion rate (mg/kg/min) = $\frac{\text{IV rate (mL/kg/day)} \times \% \text{ of dextrose}}{144}$
- (c) Infusion rate (mg/kg/min) = Fluid rate (mL/kg/day) $\times 0.007 \times \% \text{ of dextrose infused}$

Follow-up and outcome

The outcome of hypoglycemia is determined by factors like, duration, degree of hypoglycemia, rate of cerebral blood flow, cerebral utilization of glucose, and also co-morbidities. Special attention should be paid to neuro-developmental outcome, overall IQ, reading ability, arithmetic proficiency and motor performance.

The infants can be assessed at one month corrected age for vision / eye evaluation. At 3, 6, 9, 12 and 18 months corrected age they can be followed up for growth, neurodevelopment, vision and hearing loss. Vision can be assessed with Teller acuity card and hearing should be assessed by Brainstem evoked auditory responses. Neurodevelopment will be assessed by the clinical psychologist using DASII 2. MRI at 4-6 weeks provides a good estimate of hypoglycemic injury and therefore should be considered in follow up of such infants subject to affordability.¹⁷

Hypoglycemia and Neurodevelopment outcome – what is the evidence

- Systemic review involving 18 studies concluded that there is no good correlation between the two and further well designed good quality studies are needed.¹⁸
- A recent study involving 35 neonates who had symptomatic hypoglycemia showed that 94% of them had some white abnormalities and on follow up at 18 months of age, 65% of them had demonstrated some impairment in development.¹⁹

Research needs

Table 7 provides list of some researchable issues in field of neonatal hypoglycemia.

Table 6 Achieving appropriate glucose infusion rate at different daily fluid intakes

Daily fluid volume (mL/kg/d)	Glucose infusion rate (GIR)					
	6 mg/kg/min		8 mg/kg/min		10 mg/kg/min	
	D10	D25	D10	D25	D10	D25
60	42	18	24	36	5	55
75	68	7	49	26	30	45
90	90	-	74	16	55	35
105	85*	-	99	6	80	25
120	100*	-	120	-	97	18

* Add 20mL/kg of normal saline to provide 32 mEq/kg of sodium.

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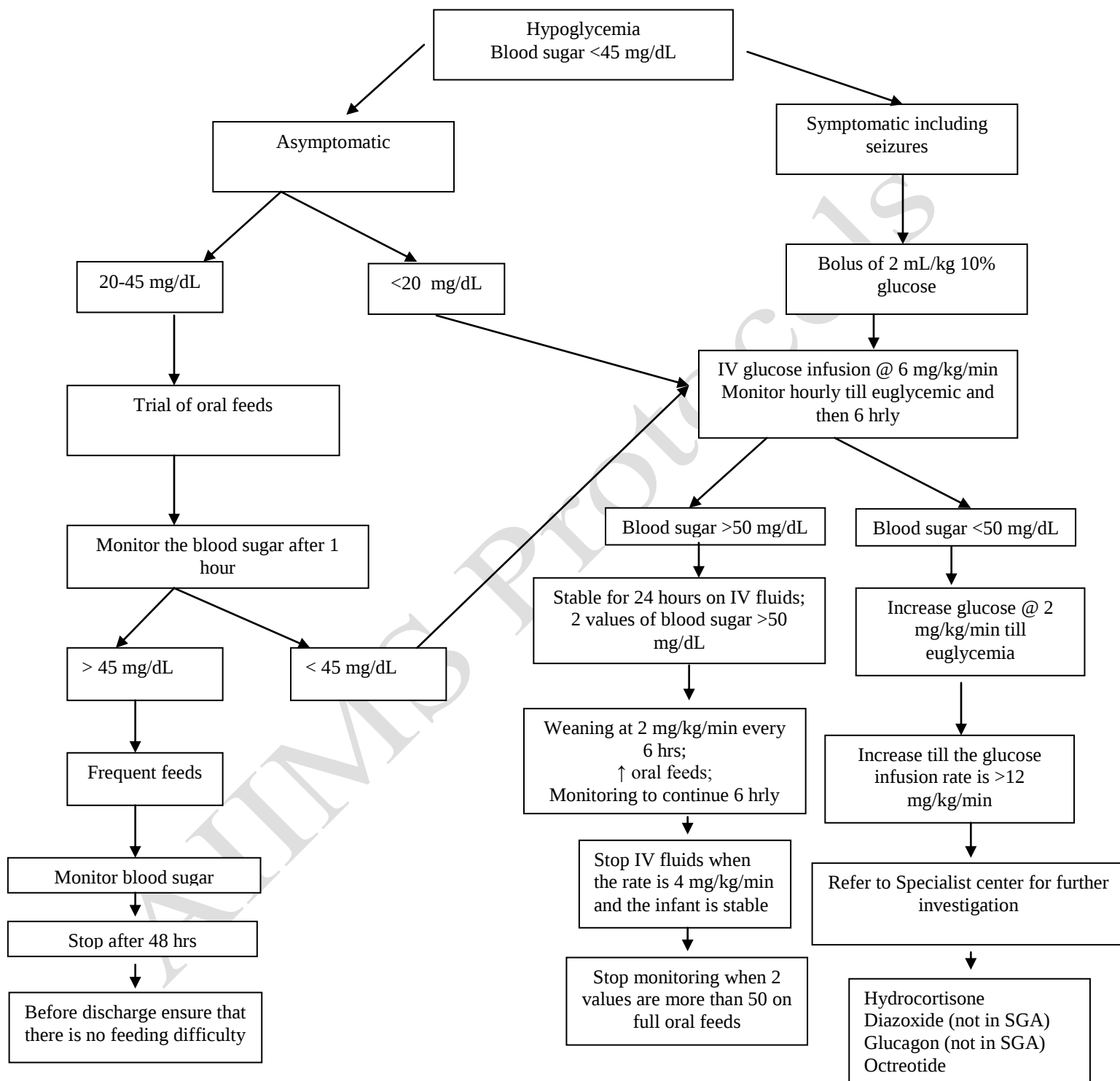
Figure 1. **Algorithm for management of neonatal hypoglycemia**

Table 7: List of researchable issues in neonatal hypoglycemia

S.NO	Research question	Type of study	Intervention	Outcome measures
1.	What is the incidence of neonatal hypoglycemia, age at onset, clinical manifestations and short term outcomes? (Epidemiology of hypoglycemia)	Cohort study by enrolling at risk infants (Table1)	Nil	Incidence, Age at which it is detected in hours, Rate of occurrence of different clinical manifestation, Neurological examination at discharge and MRI findings, Neurodevelopmental outcome at 18-24 months of age
2	Does asymptomatic hypoglycemia need treatment with intravenous glucose?	Randomized control trial	Group 1: Treat with IV fluids Group 2 : No IV fluids(unless symptoms appear)	Neurodevelopmental outcome at 18-24 months of age
3	Evaluation of accuracy of point of care with reagent strips when compared to lab values (gold standard) for detecting hypoglycemia.	Diagnostic evaluation study	Nil	Estimation of correlation and agreement between two methods.