Management of Neonatal Hypoglycemia

Summary of Recommendations

- Neonatal hypoglycemia is a common metabolic disorder and the operational threshold values of blood glucose < 40 mg/dL (plasma glucose < 45 mg/dL) should be used to guide management.
- All “at risk” neonates and sick infants should be monitored for blood glucose levels. Term healthy AGA infants without any risk factors need not be monitored routinely.
- Screening for hypoglycemia can be done by glucose reagent strips but confirmation requires laboratory estimation by either glucose oxidase or glucose electrode method. Treatment should not be delayed for confirmatory results.
- Asymptomatic hypoglycemia can be managed with a trial of measured oral feed if blood glucose is > 25 mg/dL and there is no contraindication to feeding.
- Symptomatic hypoglycemia should be treated with a mini-bolus of 2 ml/kg 10% dextrose and continuous infusion of 6 mg/kg/min of 10% dextrose.
- Refractory and prolonged hypoglycemia should be suspected and investigated if the glucose infusion requirement is > 12 mg/kg/min for more than 24 hours or the hypoglycemia persists > 5-7 days, respectively.
- Babies with hypoglycemia should be followed up for neurodevelopmental sequelae.

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Introduction

As the neonate adapts to a state of intermittent enteral supply of glucose from that of continuous transplacental glucose supply of intrauterine life, hypoglycemia, especially in the early neonatal period, is a common event. This tendency to develop hypoglycemia is accentuated by developmental immaturity of normal adaptive mechanisms like gluconeogenesis, hepatic glycogenolysis and ketogenesis. The effect of neonatal hypoglycemia on the developing brain, with the potential for long term damage is of great concern. Against this background, based on an extensive search of literature, an attempt has been made to address the following issues of practical relevance in the management of neonatal hypoglycemia:

- Operational threshold for management of neonatal hypoglycemia
- Screening for hypoglycemia
- Measurement of blood glucose
- Management of asymptomatic hypoglycemia
- Management of symptomatic hypoglycemia
- Diagnosis and evaluation of refractory and prolonged hypoglycemia
- Potentially best practices for prevention of hypoglycemia

Why should hypoglycemia in the newborn be managed aggressively?

Glucose is the predominant fuel for the newborn brain. Low blood glucose in the newborn period, in isolation as well as when associated with other morbidities, predisposes to long term neurological damage. The most common sequelae of hypoglycemia are disturbances of neurologic development and intellectual function, although minor deficits, especially spasticity and ataxia and seizure disorders can also occur. The occurrence of these may be related to etiology of hypoglycemia.

Evidence: A systematic review of literature reported inconclusive evidence on the effect of neonatal hypoglycemia on neurodevelopment. In one series of 151 infants with neonatal hypoglycemia followed for 1-4 years the occurrence of seizures as part of the neonatal neurological syndrome was associated with a clearly abnormal outcome in 50% and with transient neurological abnormalities an additional 12%. In contrast, infants with neurological features without seizures did only marginal worse than those with no neurological features. Findings from a large multicenter prospective study of preterm infants suggest that even moderate hypoglycemia (at least one daily value of plasma values <47 mg/dL) can have significant impact. There was a 30% incidence of neurodevelopmental sequelae if moderate hypoglycemia was present for 3 days or more and approximately 40% if present for 5 days or more. Stenninger et al reviewed the long-term, neurologic morbidity in 13 children with neonatal hypoglycemia, defined as blood glucose concentrations (< 27 mg/dL), compared with 15 children without neonatal hypoglycemia. Neurodevelopmental assessments were done at approximately 7.75 years of age. These investigators found that children with neonatal hypoglycemia had significantly more difficulties in a screening test for minimal brain dysfunction, and were more likely to be hyperactive, impulsive, and inattentive. These children also had lower developmental scores compared with controls. A recent Indian study by Udani and co-workers has concluded that neonatal hypoglycemia is the most common etiology of remote symptomatic infantile onset epilepsy.
**Recommendation:** Neonates with hypoglycemia should be followed up for long term neurodevelopmental sequelae.

**What should be the operational threshold for management for neonatal hypoglycemia?**

**Evidence:** Hypoglycemia in neonates has been defined as blood glucose concentrations less than 40 mg/dL (Level 4), but there are several issues related to using a single cutoff of blood glucose in all neonates. Confusion exists due to the fact that the “normal” range of blood glucose is different for each newborn and depends upon a number of factors including birth-weight, gestational age, body stores, feeding status, availability of energy sources as well as the presence or absence of disease. Cornblath et al suggested that ‘hypoglycemia’ is not readily defined for the individual neonate and that ‘operational threshold’ (concentration of blood glucose at which intervention should be considered) should be established. Operational thresholds are different from therapeutic goals, do not define normal or abnormal but provide a margin of safety. Importantly however, such operational definitions do not address whether the threshold level of blood glucose for intervention represents the threshold level for neuronal injury.

**Recommendation:** For practical purposes and uniformity of definition, a blood glucose value of < 40 mg/dL (plasma glucose < 45 mg/dL) should prompt intervention for hypoglycemia in all newborns. There is no rational basis for the historical practice of distinguishing between term and preterm infants when setting threshold criteria for intervention.

**Which neonates should be screened for hypoglycemia and what should be the screening schedule?**

**Evidence:** The high risk group of neonates warranting routine screening for blood glucose are listed in table 1. Healthy term, appropriate for gestational age (AGA) neonates without any risk factors for hypoglycemia need not be monitored for blood glucose levels except those with maternal fever during labor (Level 3/4). While adjusting to postnatal life, transient self-correcting hypoglycemia in the first few hours after birth is common in full-term well infants with the nadir being reported at 1-2 hours postnatally. Maternal oligohydramnios and a delay in initiation of breastfeeding beyond 2 hours have been reported as risk factors in one Indian study.

There is a paucity of literature that looks into optimal timing and the intervals of glucose monitoring. Most studies indicate that 97% to 98% of hypoglycemic episodes occur within the first 24 hours of birth in asymptomatic neonates at risk. In majority of studies, infants were screened at birth and thereafter 4 to 6 hourly till 24-48 hours of life. Holtrop et al found that the average times for finding low glucose levels in large for gestational age (LGA) and small for gestational age (SGA) infants were 2.9 h (range 0.8 h to 8.5 h) and 6.1 h (range 0.8 h to 34.2 h), respectively. If mother’s blood glucose is low which can happen if she has been starving, the baby can develop early hypoglycemia and in such situations, blood glucose should be tested even before 2 hours. One can infer that hypoglycemia usually occurs in LGA infants and IDMs within 12 h of birth, and screening beyond this period is not required provided blood glucose is maintained at > 45mg/dL and feeding has been established (Level 4). There is some suggestion that in the era of better glucose control in diabetic mothers, hypoglycemia is not detected beyond 2 hours (Level 3b). However it would not be appropriate to discontinue screening infants of diabetic mothers before 12 hours because diabetic control may not be optimum in Indian scenarios. Preterm and SGA infants may be vulnerable up to 36 h of age and perhaps later, particularly if regular feeds or intravenous infusions have not yet been established.

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**Recommendation:** All “at risk” neonates and sick infants should be monitored for blood glucose levels. Term healthy AGA infants without any risk factors need not be monitored routinely. All asymptomatic, at-risk neonates should be screened at two hours after birth and surveillance be continued 4-6 hourly thereafter, until feedings are well established and glucose values have normalized (generally till 48 hours of life). Monitoring before 2 hours may be required if mother has been starving or vomiting. The maximum risk for hypoglycemia is in first 24 hours but usually persists till 72 hours.

**How should blood glucose be tested in neonates and when should a sample be sent to the laboratory for confirmation?**

Glucose values are affected by screening method, operator technique, associated disease process, and sample site. Glucose reagent strips are commonly used in the newborn nurseries to screen for low blood glucose concentration.

**Evidence:** Glucose meters show large variations in values compared to laboratory methods, especially at low glucose concentrations, and are of unproven reliability to document hypoglycemia in newborns. Hence, this method should only be considered as a screen and should not be used as the basis of diagnosis.15-16 ‘Glucose oxidase’ (colorimetric method) or ‘glucose electrode method’ (as used in blood gas and electrolyte analyzer machine) are the two commonly used methods to assay blood glucose in the laboratory and are accurate and reliable. While testing the neonate’s glucose, it is important to remember that the level in whole blood is about 10-15% less than in a plasma sample. Further, samples not analyzed immediately can show a falsely low reading as glucose levels fall by 14 to 18 mg/dL per hour of storage27(Level 3b). Arterial glucose values are higher than capillary values, and capillary values are higher than venous values. Recently, subcutaneously inserted continuous glucose monitoring sensors have been used in very low birth weight infants to avoid repeated samplings.28

**Recommendation:** Glucose reagent strips are used to screen for hypoglycemia. If the values are low, a blood sample should be sent to the laboratory for confirmation by glucose oxidase or glucose electrode method. Treatment should be commenced on the basis of the screening test and should not be delayed till the laboratory results are available.

**How should a neonate with asymptomatic hypoglycemia managed?**

Babies with asymptomatic hypoglycemia are also at risk for developing long term neurodevelopmental sequelae and hence should be urgently treated.

**Recommendation:** In healthy asymptomatic hypoglycemic infants, initially a feed of measured breast milk can be given by spoon or gavage. If breast milk is not available, then formula milk may be used. Check blood glucose 30-60 min later before next feeding to ensure euglycemia. If repeat blood glucose is above 45 mg/dL, 2-3 hourly feed is ensured with 4-6 hourly monitoring for glucose up to 48 hrs.

IV glucose infusion should be started in babies with asymptomatic hypoglycemia if:

a) Blood glucose is < 25 mg/dL
b) Blood glucose remains below 40 mg/dL despite one attempt of feeding breast milk.
c) Enteral feeding is contraindicated.
d) Baby becomes symptomatic.
How should a neonate with symptomatic hypoglycemia managed?

Symptomatic hypoglycemia can result in a high incidence of neuronal injury. Hence, in neonates with any symptoms suggestive of hypoglycemia accompanied by a low blood glucose value less than 45 mg/dl, the measures listed below should be instituted as an emergency.

i) A bolus of 2 mL/kg of 10% dextrose is given intravenously (after sending a sample to the laboratory for confirmation of the diagnosis).  

ii) Following a bolus, an intravenous infusion of dextrose at a glucose infusion rate (GIR) of 6 mg/kg/min is started. This figure of the GIR is to strike a balance between the physiologic requirement of glucose and the risk of iatrogenic hyperglycemia followed by rebound hypoglycemia (Level2b).

iii) Blood glucose is re-checked after 15-30 min. If it remains well above 45 mg/dL, the frequency of checking can be gradually decreased from every hour to 4-6 hourly.

iv) If the blood glucose remains < 45 mg/dL, the GIR is increased in steps of 2 mg/kg/min every 15-30 min with repeat checks on blood glucose till the values are > 45 mg/dL.

v) Tapering of glucose infusion: Once the blood glucose values stabilize above 45mg/dL for about 24 hours, the infusion can be tapered off @ 2 mg/kg/min every 6 hours. Once a GIR of 4 mg/kg/min is reached, the infusion can be stopped if the neonate is euglycemic. In neonates who cannot be fed orally, the GIR is gradually brought down to the minimum at which euglycemia is maintained.

vi) If the neonate requires GIR of > 12 mg/kg/min, a diagnosis of resistant hypoglycemia should be entertained (after ensuring that there was no interruption in the glucose infusion) and investigations and management should be modified accordingly.

vii) Oral feeds: If there is no contraindication to feeding, oral feeds of breast or formula milk should be continued along with and their proportion increased as the intravenous infusion is tapered. Oral feeding ensures a more stable glycemic control.

Practice points

- Avoid using > 12.5% to 15% dextrose infusion through a peripheral vein due to the risk of thrombophlebitis.
- In addition to glucose infusion and monitoring, attention should be paid to reduce energy needs by correcting acidosis, maintaining a thermoneutral environment and treatment of other underlying conditions like sepsis.
- A continuous infusion of glucose should be ensured, preferably using a syringe infusion pump. Do not stop an IV infusion of glucose abruptly; severe rebound hypoglycemia may occur.
- Treatment of neonatal hypoglycemia with intermittent boluses alone is not logical; the need for such boluses is an indication for increasing the rate of continuous glucose infusion, and for considering other causes.

Recommendation: Symptomatic hypoglycemia should be treated intravenously by a mini-bolus of 2 ml/kg 10% dextrose followed by a continuous infusion of 6mg/kg/min. Oral feeding should be continued simultaneously unless contraindicated.
How should refractory and prolonged hypoglycemia be evaluated and managed?

Refractory and prolonged hypoglycemia should be suspected if GIR requirements are > 12 mg/kg/min for more than 24 hours or blood glucose levels remain unstable beyond 5 to 7 days, respectively. Refractory hypoglycemia in neonates is usually secondary to inappropriate and/or excessive insulin secretion or due to deficiency of one of the glucose regulatory enzymes of the liver. Some important causes of resistant hypoglycemia are hyperinsulinemia, hypopituitarism, adrenal insufficiency and metabolic disorders like galactosemia, glycogen storage disease, organic acidemias and mitochondrial disorders. A consultation with a pediatric endocrinologist is recommended for management of refractory hypoglycemia. Investigations like plasma insulin, cortisol, thyroid profile, ammonia, lactate and urine for ketones and reducing substances are done initially. If initial investigations are not helpful or a specific etiology is suspected, second line investigations include 17-OHP, GALT assay, TMS, growth hormone and glucagon levels. Persistent Hyperinsulinemia (PHHI) is diagnosed if there is hyperinsulinemia (plasma insulin > 2 μU/mL, depending on sensitivity of insulin assay) in presence of documented laboratory hypoglycemia (< 50 mg/dL). In consultation with the endocrinologist, drugs like hydrocortisone, diazoxide, octreotide, nifedipine or glucagon may be prescribed.

What are the potentially best practices for prevention of neonatal hypoglycemia?

Some of the practices that help prevent neonatal hypoglycemia include:

(a) Support and promote early exclusive breastfeeds (or oral feeds of expressed breast milk) within the first hour of life in all healthy newborns. Delayed initiation of breast feeds is an important risk factor for hypoglycemia. A controlled trial using sucrose fortified milk (5 g sucrose per 100 mL milk) fed orally has been shown to raise blood glucose levels and prevent hypoglycemia in small-for-gestational-age as well as appropriate-for-gestational-age neonates (Level 1b). However, this intervention is at the cost of compromising breastfeeding rates and potential risk of contamination.

(b) Maintenance of thermoneutral environment helps prevent hypoglycemia and skin to skin contact of neonate with mother should be encouraged as a strategy for temperature maintenance.

(c) Do not feed 5%, 10% or 25% dextrose as a substitute for breast milk. Plain dextrose feeding can induce vomiting and will cause increased insulin secretion, decreased glucagon, delayed gluconeogenesis and rebound hypoglycemia.

(d) Ensure that there is no interruption in the intravenous glucose infusion by maintaining a good intravenous access and using a syringe infusion pump to deliver at a steady rate.

References

Table 1: “At-risk” neonates for whom routine monitoring of blood glucose is recommended

- Preterm infants
- Small for gestation (SGA)
- Large for gestation (LGA)
- Infant of diabetic mother (IDM)
- Sick infants (e.g., sepsis, asphyxia, respiratory distress)
- Post exchange blood transfusion
- Infants on intravenous fluids and parenteral nutrition
- Infants whose mothers received beta blockers, oral hypoglycemic agents or intrapartum dextrose infusion
Fig 1: Management Algorithm for Hypoglycemia

1. **Hypoglycemia**
   - Full term AGA infant who is not at risk but incidentally detected to have hypoglycemia

2. **Blood glucose >25 mg/dL**
   - Give one full measured feed, preferably EBM. If EBM is not available, give formula milk.
   - Check blood glucose 1 hour after feeding
   - Normal blood glucose
     - Continue monitoring 6 hourly for 24 h
   - If BS found to be in hypoglycemic range anytime during monitoring, increase the glucose rate by 2 mg/kg/min. (Give a bolus of 10% dextrose only if symptomatic)
   - If glucose rate is >12 mg/kg/min/hypoglycemia persists for >7 days (Persistent or Refractory hypoglycemia)
     - Send first line investigations and start medications

3. **Blood glucose <25 mg/dL**
   - Take sample for laboratory estimation of plasma glucose
   - Ensure 2 IV lines in situ
   - Start glucose infusion at a rate of 6 mg/kg/min
     - Monitor BS every 15 min after starting infusion twice. If normal, monitor hourly for 4 h and every 6 h subsequently. If not, monitor q 15 min.
     - If BS rate remains in euglycemic range for 6 h or blood glucose remains >100 mg/dL for 2 h
     - Start tapering down glucose rate by 2 mg/kg/min every 6 hour. Don’t infuse >12.5% of dextrose through peripheral IV route
     - Send laboratory value if possible before increasing the glucose rate
   - If BS found to be in hypoglycemic range anytime during monitoring, increase the glucose rate by 2 mg/kg/min.
   - Don’t infuse >12.5% of dextrose through peripheral IV route
   - Arrange for glucagon if GR reaches 10 mg/kg/min

- Feeding helps in better glycemic control and should be initiated/continued along with IV therapy
Annexure

1. How to calculate the desired concentration of glucose in intravenous fluid and how to mix various solutions for creating a desired concentration of glucose in IV infusate?

The formula for preparing 100 mL of fluid with a desired concentration of glucose using 5% dextrose and 25% dextrose solutions is given by the formula $5X - 25 = Y$ where $X$ is the required percentage of dextrose and $Y$ is the amount of 25% dextrose (in mL) to be made up with 5% dextrose to make a total of 100 mL.

For example, to prepare 100 mL of 10% dextrose from 5% dextrose and 25% dextrose, add $5 \times 10 - 25 = 25$ mL of 25% dextrose to the remaining volume, i.e. $100 - 25 = 75$ mL of 5% dextrose.

To prepare 100 mL of 12.5% dextrose, add $5 \times 12.5 - 25 = 37.5$ mL of 25% dextrose to $62.5$ mL ($100 - 37.5$) of 5% dextrose.

2. How to calculate the glucose infusion rate (GIR) ?

Neonatal blood glucose concentrations correlate closely with glucose infusion rates. Glucose Infusion Rate (GIR) is expressed in terms of milligrams of glucose per kilogram body weight per minute (mg/kg/min). It can be calculated using one of the following formulae:

(a) $\text{GIR} = \frac{\% \text{ of dextrose being infused}}{(\text{mg/kg/min})} \times \frac{\text{rate of infusion (in ml/hr)}}{(\text{Body weight (in kg)}) \times 6}$

(b) $\text{GIR} = \frac{\text{Rate of IV fluids (in ml/kg/day)}}{(\text{mg/kg/min})} \times \frac{\% \text{ of dextrose infused}}{144}$

(c) $\text{GIR} = \frac{\text{Rate of IV fluids (in ml/kg/day)}}{(\text{mg/kg/min})} \times \frac{\% \text{ of dextrose infused}}{0.007}$

Method 1 for calculating GIR (same as (b) above)

(a) Decide desired fluid intake of the neonate in mL/kg/day (24 hrs)
(b) Convert this to mL/kg/min by dividing the figure by 1440

(Since 24 hours have 1440 minutes)
If 10% dextrose is being used, multiply the figure obtained in (b) above by 100 to find out the Glucose Infusion Rate (GIR) in mg/kg/min.

(Since 10% Dextrose has 100 mg/mL of dextrose. Similarly, 5% dextrose has 50 mg/mL; 7.5% dextrose has 75 mg/mL of dextrose and so on)

(c) Based on desired fluid intake and desired GIR, the concentration of dextrose in the IV infusate can be decided.

(d) Example

(i) Let the neonate’s fluid intake be 80 mL/kg/day
(ii) This is 80/1440 = 0.055 mL/kg/min
(iii) If 10% dextrose is given, then the GIR is :

\[0.055 \times 100 = 5.5 \text{ mg/kg/min}\]

Method 2 for fluid rate and GIR (Using 10% dextrose only)\(^{24}\)

*Step 1*

(a) 100 mL of 10% dextrose has 10 gm or 10,000 mg of glucose
(b) If this 100 ml is given over 24 hours then GIR is

\[10,000/1440 = 6.95 \text{ mg/min}; \text{ say } 7.0 \text{ mg/min}\]

(Since 24 hours have 1440 minutes)

(c) Therefore 1 mL/day of 10% dextrose will provide a GIR of 0.07 mg/min
(d) Based on the above, GIR for a neonate can be calculated as follows:

\[\text{GIR (mg/kg/min)} = \text{ IV fluid rate (mL/kg/day)} \times 0.07\]

*Step 2 – Increasing GIR by 1mg/kg/min*

(a) Add 2 mL/kg of 25% dextrose to the volume of fluid to be infused over 8 hrs – see explanation below:

[i] 25% Dextrose has 250 mg/mL of dextrose; 2 mL/kg has 500 mg/kg
[ii] The 8 hour period has 8 x 60 = 480 minutes
[iii] 2 mL/kg of 25% dextrose over 8 hrs will increase the GIR by

\[500/480 \text{ or roughly } 1 \text{ mg/kg/min}\]
(b) Example
1. Let the neonate’s fluid intake be 80 mL/kg/day.
2. With 10% dextrose the GIR is 80 x 0.07 = 5.6 mg/kg/min.
3. If GIR has to be increased by 1 mg/kg/min then add 2 ml/kg of 25% dextrose to the fluid to be infused over 8 hrs.

(c) Caveat: For this formula to work, the GIR has to be kept at or below a tenth of the total fluid intake in mL/kg/day – e.g. if the total fluid intake is 100 mL/kg/day, you cannot increase GIR beyond 10 mg/kg/min using this formula – to increase GIR beyond this limit, fluid intake has to be increased.

3. How to convert gm/dL to mmol/L & vice versa?

There are two main methods of describing concentrations: by weight, and by molecular count. Weights are in grams, molecular counts in moles.
To convert mmol/L of glucose to mg/dl, multiply by 18. To convert mg/dL of glucose to mmol/L, divide by 18 or multiply by 0.055.

4. How to calculate GIR in an infant on oral feeds along with simultaneous intravenous infusion of glucose? (also see Figures 2 and 3)

Glucose infusion needs to be calculated while giving feeding and can be done by the same formula:

Glucose infusion rate while on feeding (mg/kg/min) =

\[
[IV \ rate\ (ml/hr) \times \text{Dextrose conc (g/dl)} \times .0167 / wt\ (kg)] + [\text{Feed rate(ML/hr)} \times \text{Dextrose conc* (g/dl)} \times .0167 / wt\ (kg)]
\]

Amount of dextrose in milk : Breast milk = 7.1 gm/dL, Term formula = 7.1 gm/dL, Preterm formula = 8.5 gm/dL.
Figure 2: Calculating glucose concentration to be used based on amount of fluid and GIR

Figure 3 Calculation of GIR of baby on fluids and feeds (assuming breast milk or term formula)