

Hypoglycemia in the Newborn

Ashish Jain, Rajiv Aggarwal¹, M. Jeevasanker, Ramesh Agarwal, Ashok K. Deorari and Vinod K. Paul

WHO Collaborating Center for Training & Research in Newborn Care, Division of Neonatology, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, ¹Narayana Hridalaya, Bangalore, India

ABSTRACT

Hypoglycemia in a neonate has been defined as blood sugar value below 40mg/dL. Hypoglycemia is encountered in a variety of neonatal conditions including prematurity, growth retardation and maternal diabetes. Screening for hypoglycemia in certain high-risk situations is recommended. Supervised breast-feeding may be an initial treatment option in asymptomatic hypoglycemia. However, symptomatic hypoglycemia should always be treated with a continuous infusion of parenteral dextrose. Neonates needing dextrose infusion rates above 12 mg/Kg/min should be investigated for the cause of hypoglycemia. Hypoglycemia has been linked to poor neuro-developmental outcome, and hence aggressive screening and treatment is recommended. [Indian J Pediatr 2008; 75 (1) : 63-67] E-mail: aranag@rediffmail.com

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Hypoglycemia is a common disorder.^{1,2} There is still no universal definition for this disorder.³ Koh *et al* did a detailed survey and found that the definitions ranged from 18 mg/dL to 72 mg/dL.⁴ 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.^{5,6} Thus the definition of hypoglycemia should be flexible and encompass all these aspects. Further, there is no concrete evidence to show the causation of adverse long-term outcomes by a particular level or duration of hypoglycemia.⁷ A recent consensus has been to evolve an “operational threshold”.

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 the evidence currently available in literature.⁷ This threshold is currently believed to be a blood glucose value of less than 40 mg/dL (plasma glucose less than 45 mg/dL).

Screening for hypoglycemia

Normal blood glucose levels are maintained by gluconeogenesis.⁸ Neonatal hypoglycemia most

commonly occurs in infants with impaired gluconeogenesis, brought about by increased insulin production, altered counter-regulatory hormone production or an inadequate substrate supply. Screening for hypoglycemia is recommended in the following high risk infants.

Infants in whom screening is not required

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

Method of Glucose estimation

a. Reagent strips (Glucose oxidase): Though widely used and are important ‘point of care’ method, they are unreliable especially, at blood glucose levels less than 40-50mg/dL. They are useful for screening purpose but low values should be always confirmed by formal laboratory analysis, before a diagnosis of hypoglycemia is made (however, treatment must be instituted based on results of reagent strips). It is important to also consider the variations between capillary and venous, blood and plasma, and immediate and stored samples (whole blood sugar is 10-15% less than the plasma sugar, the glucose levels can fall by 14-18 mg/dL per hour in blood samples that await the analysis.⁹)

b. Laboratory diagnosis: This is the most accurate method. In the laboratory (lab), glucose can be measured

Correspondence and Reprint requests : Dr. Ramesh Agarwal, Assistant Professor, Department of Pediatrics, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110029, India

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by either the *glucose oxidase* (calorimetric) method or by the *glucose electrode method* (as used in *blood gas and electrolyte analyser machine*). Blood samples should be analyzed quickly to avoid erroneously low glucose levels.

Clinical signs associated with hypoglycemia

a. Asymptomatic: It is also well known that low blood glucose may not manifest with any sign and may be totally asymptomatic. These babies should also be treated in view of possible adverse long term effects.^{10,11}

b Symptomatic: Clinical signs of hypoglycemia in approximate order of frequency are stupor, jitteriness, tremors, apathy, episodes of cyanosis, convulsions, intermitant 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

a. Asymptomatic hypoglycemia: This diagnosis is made when the blood glucose level is below the operational threshold (to be confirmed by laboratory estimation) in the absence of clinical signs.

b. Symptomatic hypoglycemia: This diagnosis should be made if hypoglycemia coexists with clinical symptomatology. 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, other diagnostic possibilities should be strongly considered.

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 h. 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 early screening for this population. However, preterm and SGA may be at risk up to 36 h (range 0.8 to 34.2 h).¹² Few SGA and preterms 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

Education and counseling of caregivers regarding the screening

Parents should be made aware that their baby is symptomatic or 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.

Screening is stopped

- At the end of 72 hours in at risk babies (Table no 1)
- An infant after stopping of the IV fluids and has two consecutive values >50 mg/dL on total oral feeds

MANAGEMENT OF ASYMPTOMATIC HYPOGLYCEMIA

Oral feeds – issues

Direct breast-feeding is the best option for a trial of an oral feed. If the baby is unable to suck, expressed breast milk may be used. Breast milk promotes ketogenesis (ketoacids are important alternate sources for the brain along with less important pyruvate, free fatty acids, glycerol, amino acids). If breast milk is not available, then formula feed may be given in at-risk neonates. If oral feeds are contraindicated, start glucose infusion.

Some of the randomized clinical trials in SGA¹³ and appropriate-for-gestational age¹⁴ infants found that the sugar or sucrose fortified milk (5g sugar per 100 mL milk) raises blood glucose and prevents hypoglycemia. Such a

TABLE 1. High Risk Situations Where Screening is Recommended

1	Low birth weight infants (<1800 g)
2	Preterm infants (≤35 wk)
3	Small for gestational age infants (SGA) : birth weight <10 th percentile
4	Infant of diabetic mothers (IDM) -insulin dependent and gestational diabetes
5	Large for gestational age (LGA) infants with birth weight >90 th percentile. Some doubt has been raised as to whether LGA infants who are not IDMs are truly at risk ⁸
6	Infants with Rh-hemolytic disease
7	Infants born to mothers receiving therapy with terbutaline/propranolol/oral hypoglycemic agents
8	Infants with morphological growth retardation. This group includes neonates with birth weight between 10 th – 25 th percentile with features of fetal under-nutrition such as three or more loose skin folds in gluteal region, decreased overall subcutaneous fat, and head circumference to chest circumference difference more than 3 cm
9	Any sick neonate such as 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

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supplementation may be tried in the asymptomatic neonates with blood sugar levels between 20 to 40 mg/dL. However, this practice carries a potential to compromise breast feeding rates. Symptomatic babies should be treated with IV fluids

rebound hypoglycemia may occur. Avoid using > 12.5% dextrose infusion through a peripheral vein due to the risk of thrombophlebitis

MANAGEMENT OF SYMPTOMATIC HYPOGLYCEMIA

For symptomatic hypoglycemia including seizures, a bolus of 2 mL/Kg of 10% dextrose should be given. This mini-bolus helps to rapidly achieve the steady state levels of blood glucose.¹⁵ Immediately after the bolus, a glucose infusion at an initial rate of 6 mg/Kg/min should be started. Check blood sugar after 1 h and then 6 hourly, if blood sugar is >50 mg/dL.

Repeat subsequent hypoglycemic episodes may be treated by increasing the glucose infusion rate by 2 mg/Kg/min till a maximum of 12 mg/Kg/min. If two or more consecutive values are > 50 mg/dl after 24 hours of parenteral therapy, the infusion can be tapered off at the rate of 2 mg/Kg/min every 6 hours, with glucose monitoring. Tapering has to be accompanied by concomitant increase in oral feeds. Once a rate of 4 mg/Kg/min of glucose infusion is reached and oral intake is adequate and the blood sugar values are consistently > 50 mg/dL the infusion can be stopped without further tapering. Ensure continuous glucose infusion without any interruption preferably using infusion pump.

Do not stop an IV infusion of glucose abruptly; severe

RECURRENT/RESISTANT HYPOGLYCEMIA

This condition should be considered when there is a failure to maintain normal blood sugar levels despite a glucose infusion of 12 mg/Kg/min or when stabilization is not achieved by 7 days of life. High levels of glucose infusion may be needed in the infants to achieve euglycemia.

Besides increasing the rate of glucose infusion, drugs may also be tried in the treatment of resistant hypoglycemia. Before administration of the drugs, take the samples to investigate the cause (Table 3). Drugs that are used include the following:

(1) Hydrocortisone 5mg/Kg/day IV or PO in two divided doses (2) Diazoxide 10-25mg/Kg/day in three divided doses PO. 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. (3) Glucagon 100 mg/Kg subcutaneous or intramuscular (max 300 mg) – 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

TABLE 2. Schedule of Blood Glucose Monitoring

Symptomatology of babies	Time schedule for screening
At risk neonates (S.no 1-8 in Table no 1)	2, 6, 12, 24, 48, 72 h
Sick babies	
Sepsis, asphyxia, shock in the active phase of illness	6-8 h (individualize as needed)
Stable VLBW babies on parenteral nutrition	Once/day, after initial 72 h (in initial 3 days frequency as for at risk babies)
Growing VLBW babies	Once a week, as a part of weekly work-up
Asymptomatic babies with blood sugar levels between 20-40 mg/dL on screening	After 1 hour of oral /fortified feed, Later every 6 hrs till 48 h if blood sugar levels > 50mg/dL.
Asymptomatic babies with blood sugar levels below 20mg/dL	After 1 hour of starting IV fluids and then every hour (after every stepwise augmentation of GIR by 2 mg/kg/min till blood sugars remain below 50 mg/dL)
Asymptomatic with blood sugar levels below 40mg/dL even after 1 hour of fortified/oral feeds	Once the blood sugar levels are above 50 mg/dL they are monitored every 6 h for 48 h
Symptomatic babies	
Babies exhibiting signs compatible with hypoglycemia at any time also need to be screened.	

TABLE 3. Management Plan of Babies with Asymptomatic Hypoglycemia on Screening

Blood sugar 20-40 mg/dL	Trial of oral feeds/fortified feeds (prepared by adding 5g sugar in 100ml or by constituting formula in 5% dextrose instead of water) and repeat test after 1 h. If repeat blood sugars are above 40 mg/dL, 2 nd hourly feed is ensured with 6 hrly monitoring for 48 h If repeat blood sugars are < 40mg/dL then IV fluids are started and the management is as for symptomatic hypoglycemia
Blood sugar levels < 20 mg/dL	IV fluid are started at 6 mg/Kg/min of glucose, the further management is as for symptomatic hypoglycemia

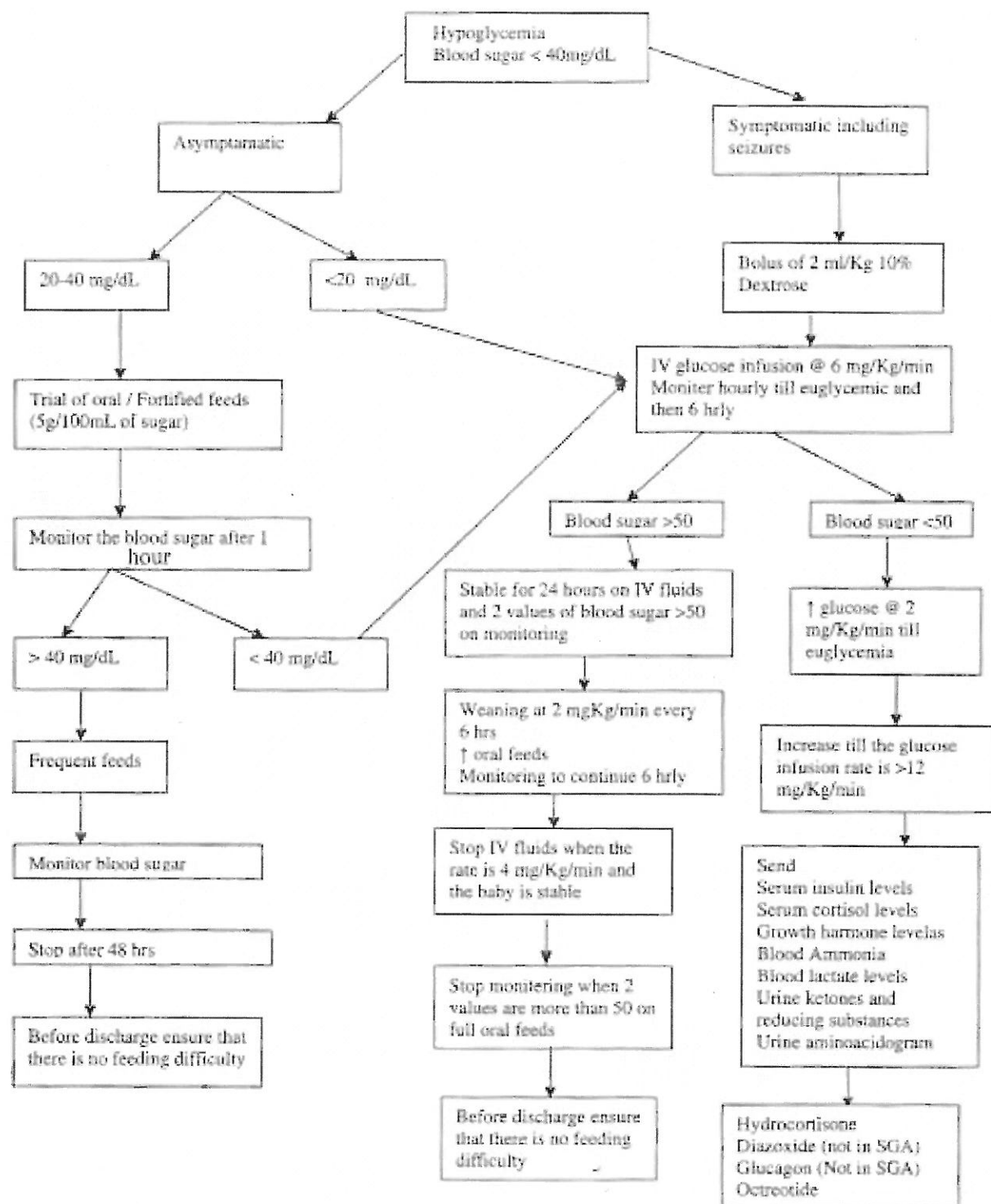


Fig. 1. Algorithm for management of neonatal hypoglycemia

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TABLE 4. Important Causes of Resistant Hypoglycemia and Investigations

Important causes of resistant hypoglycemia	Investigations to be considered
Congenital hypopituitarism	Serum insulin levels
Adrenal insufficiency	Serum cortisol levels
Hyperinsulinemic states	Growth hormone levels
Galactosemia	Blood ammonia
Glycogen storage disorders	Blood lactate levels
Maple syrup urine disease	Urine ketones and reducing substances
Mitochondrial disorders aminoacidogram	Urine and sugar

stimulate insulin release. (4) Octreotide (synthetic somatostatin in dose of 2-10 µg/Kg/day subcutaneously two to three times a day.

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

Useful formulae

- (a) Infusion rate (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 = $\frac{\text{Fluid rate (mL/Kg/day)}}{x 0.007} \times \% \text{ of dextrose infused}$

Follow-up and outcome

Lucas in 1988, linked hypoglycemia to long term adverse outcomes in a retrospective multicentric study. Later a similar relationship of lower head circumference and developmental scores was highlighted by Duvanel *et al.*¹⁶ Further, a systematic review of 18 studies on neurodevelopment after hypoglycemia, showed poor methodological quality of all but 2 studies. None of the studies provided a valid estimate of the effect of neonatal hypoglycemia on neurodevelopment.¹⁷ Though these studies have major limitations, it would seem prudent to follow up all infants who had confirmed hypoglycemia in the high-risk category, till a future optimal study is performed.¹⁷ The outcome of hypoglycemia is determined by factors like, duration, degree of hypoglycemia, rate of cerebral blood flow and cerebral utilization of glucose. Special attention should be paid to neuro-developmental outcome, overall IQ, reading ability, arithmetic proficiency and motor performance.

The babies 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.

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