

Hypoglycemia in the Newborn

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Abstract

Since a universal definition for hypoglycemia is lacking, an operational threshold for initiating therapy has been defined. Hypoglycemia is encountered in a variety of neonatal conditions including prematurity, growth retardation and maternal diabetes. Since hypoglycemia may be asymptomatic, routine screening for this condition in certain high-risk situations is recommended. Supervised breast-feeding may be a 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/m should be investigated for refractory causes of hypoglycemia. Hypoglycemia has been linked to poor neuro-developmental outcome and hence aggressive screening and treatment is recommended.

Hypoglycemia in the newborn

1. Introduction

Although hypoglycemia is a common disorder^{1,2}, there is still no universally accepted definition for this disorder³. 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 as well as the presence or absence of disease^{4,5}. There is no concrete evidence to show the causation of adverse long-term outcomes by a particular level or duration of hypoglycemia^{3,6}. A recent consensus has been to evolve an “operational threshold”.

2. 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*”^{3,6}. This threshold is currently believed to be a blood glucose value of less than 40 mg/dL (plasma glucose less than 45 mg/dL).

1. Screening for hypoglycemia

Screening for hypoglycemia is recommended in (a) Very low birth weight infants (<1500 grams) (b) Preterm infants (≤ 35 weeks) (c) Small for gestational age infants (SGA) with birth weight <10th percentile (d) Infant of diabetic mother (insulin dependent and gestational diabetes) (e) Large for gestational age (LGA) infants with birth weight >90th percentile. (f) Infants with Rh-hemolytic disease (g) Infants born to mothers receiving therapy with terbutaline/propranolol/oral hypoglycemic agents (h) Neonates with

perinatal asphyxia, polycythemia, sepsis, shock, respiratory distress, hypothermia (i) Infants with morphological growth retardation. This group includes neonates with birth weight between 10th – 90th percentile with features of fetal under-nutrition in the form of skin peeling, loose skin folds and deficient buccal pad of fat. (j) Infants on intravenous fluids and total parenteral nutrition

4. Infants in whom screening is not required⁴

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 should be screened for hypoglycemia.

5. Method of Glucose estimation:

Reagent strips (Glucose oxidase): Though popular and widely used, they are not accurate especially at blood glucose levels less than 40-50mg/dL^{4,5}. They are useful for screening purposes but low values should be always confirmed by accurate laboratory estimation before a diagnosis of hypoglycemia is made.

Laboratory diagnosis: This is the most accurate method. In the laboratory (lab) glucose can be measured by either the *glucose oxidase* (calorimetric) method or by the *glucose electrode method*. The method used in our lab is the glucose oxidase method. Blood samples should be analyzed quickly to avoid erroneously low glucose levels.

6. Clinical signs associated with hypoglycemia:

Asymptomatic: It is also well known that low blood glucose may not manifest with any sign and may be totally asymptomatic.

Symptomatic: Clinical signs of hypoglycemia are non-specific and can be seen in a wide variety of neonatal illnesses. These include apathy, lethargy, stupor, coma, irritability, jitteriness, tremors, apnea, cyanosis, poor feeding, vomiting, hypotonia, weak or high pitched cry and seizures^{2,3}.

7. Diagnosis:

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.

Symptomatic hypoglycemia: This diagnosis should be made if the criteria according to Whipple's Triad⁷ are satisfied: (i) Presence of signs attributable to hypoglycemia; (ii) Low blood glucose documented by accurate, sensitive and precise methods and (iii) Resolution of clinical signs within minutes to hours once the blood glucose level is normalized.

If the signs are not alleviated by IV glucose, then other diagnostic possibilities should be considered.

8. Time schedule for screening:

In high-risk infants, screening for hypoglycemia should be done at 2, 6, 12, 24, 48 and 72 hours of age, prior to feeding. Asymptomatic hypoglycemia on a feed trial should have a test after one hour of feed. In infants with hypoglycemia on glucose infusion, blood

glucose should be checked at hourly intervals till euglycemia is achieved and then 6 hourly. Hypoglycemia stable on glucose infusion (blood glucose values $>50\text{mg/dL}$) should have a test every 6 hours. Tests should be repeated 6 hourly during weaning from infusion therapy.

9. Screening is stopped when:

- At the end of 72 hours, a high risk infant has not had hypoglycemia;
- An infant on total oral feeds has two consecutive values $>50\text{ mg/dL}$.

10. Management of asymptomatic hypoglycemia

This condition applies to high-risk infants detected to have hypoglycemia on routine screening. Recommended protocol for these patients is

Blood sugar 20-40 mg/dL

Trial of oral feed and repeat test after 1 hour

If repeat blood sugar $\leq 40\text{ mg/dL}$, start glucose infusion.

If repeat blood sugar $> 40\text{ mg/dl}$, 2 hourly feeding and 6 hourly monitoring

Blood sugar $<20\text{ mg/dL}$

Start glucose infusion

No glucose bolus is required in asymptomatic infants.

11. 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. If breast

milk is not available, then formula feed may be given in at-risk neonates. If oral feeds are contraindicated, start glucose infusion.

Oral feeds should not be tried in symptomatic hypoglycemia.

12. Parenteral therapy

A glucose infusion is indicated if there is⁴ :

- Failure of oral feed trial in asymptomatic hypoglycemia
- Severe asymptomatic hypoglycemia (blood sugar values <20 mg/dL)
- Symptomatic hypoglycemia
- Hypoglycemic convulsions
- Infant unable to feed enterally.

For hypoglycemic convulsions, a bolus of 5-10 ml/kg of 10% dextrose should be given.

For otherwise symptomatic infants, a bolus of 2 ml/kg of 10% dextrose should be given.

Immediately after the bolus, a glucose infusion at an initial rate of 6-8 mg/kg/min IV should be started. Check a blood sugar after 1 hr and then 6 hourly if blood sugar >50 mg/dL. Repeat hypoglycemic episodes may be treated by increasing the glucose infusion rate by 2 mg/kg/min till a maximum of 12 mg/kg/min. (see Section 12). 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 then the infusion can be stopped without further tapering.

Do not stop an IV infusion of glucose abruptly; severe rebound hypoglycemia may occur.

Avoid using > 12.5% dextrose infusion through a peripheral vein due to the risk of thrombophlebitis

13. 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 5 to 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. 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 μ g/kg subcutaneous or intramuscular (max 300 μ g). 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 release⁴.

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

Causes of resistant hypoglycemia include multiple endocrine deficiency, congenital hypopituitarism, adrenal insufficiency, hyperinsulinemic states and inborn errors of metabolism like galactosemia, glycogen storage disorders, maple syrup urine disease and

mitochondrial disorders. These patients should be investigated during an episode of hypoglycemia. Investigations to be considered include (a) Serum Insulin levels, (b) Serum cortisol levels (c) Growth hormone levels (d) Blood ammonia (e) Blood lactate levels, (f) Urine ketones and reducing substances (g) Ketone bodies in blood and (h) Urine and serum aminoacidogram.

14. Useful formulae

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

$$(b) \text{ Infusion rate (mg/kg/min)} = \frac{\text{IV rate (ml/kg/day)} \times \% \text{ of dextrose}}{144}$$

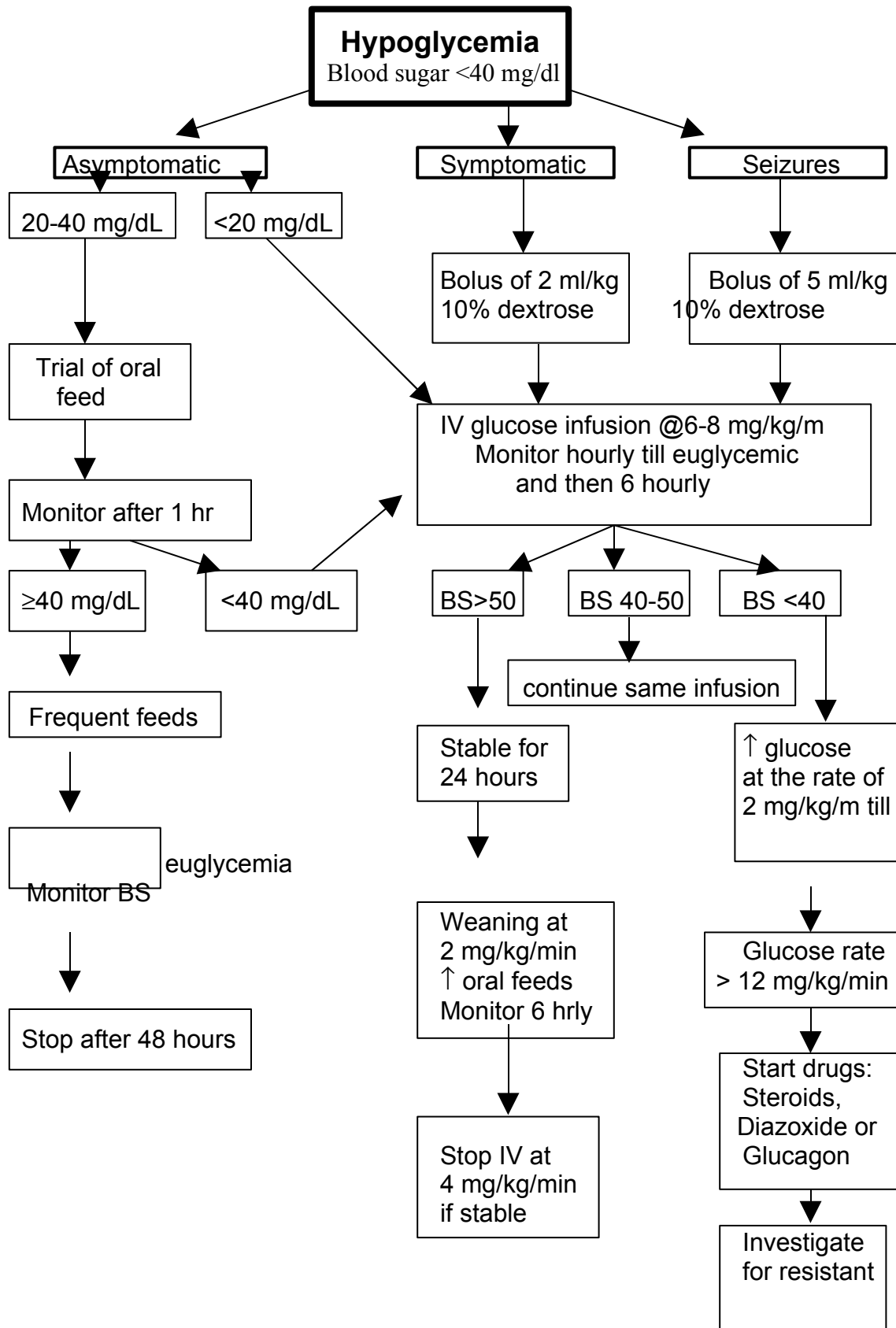
15. Follow up and outcomes

Lucas in 1988, linked hypoglycemia to long term adverse outcomes in a retrospective multicentric study⁸. Though this study has major limitations; in the absence of any subsequent and better study, it would seem prudent to follow up all infants who had confirmed hypoglycemia in the high-risk category. Special attention should be paid to neuro-developmental outcome, overall IQ, reading ability, arithmetic proficiency and motor performance over long term⁹.

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

hypoglycemia