



# Clinical Report—Postnatal Glucose Homeostasis in Late-Preterm and Term Infants

## Under Review

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David H. Adamkin, MD and COMMITTEE ON FETUS AND NEWBORN

### KEY WORDS

newborn, glucose, neonatal hypoglycemia, late-preterm infant

### ABBREVIATIONS

NH—neonatal hypoglycemia

D<sub>10</sub>W—dextrose 10% in water

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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## abstract

This report provides a practical guide and algorithm for the screening and subsequent management of neonatal hypoglycemia. Current evidence does not support a specific concentration of glucose that can discriminate normal from abnormal or can potentially result in acute or chronic irreversible neurologic damage. Early identification of the at-risk infant and institution of prophylactic measures to prevent neonatal hypoglycemia are recommended as a pragmatic approach despite the absence of a consistent definition of hypoglycemia in the literature. *Pediatrics* 2011;127:575–579

### INTRODUCTION

This clinical report provides a practical guide for the screening and subsequent management of neonatal hypoglycemia (NH) in at-risk late-preterm (34–36½ weeks' gestational age) and term infants. An expert panel convened by the National Institutes of Health in 2008 concluded that there has been no substantial evidence-based progress in defining what constitutes clinically important NH, particularly regarding how it relates to brain injury, and that monitoring for, preventing, and treating NH remain largely empirical.<sup>1</sup> In addition, the simultaneous occurrence of other medical conditions that are associated with brain injury, such as hypoxia-ischemia or infection, could alone, or in concert with NH, adversely affect the brain.<sup>2–5</sup> For these reasons, this report does not identify any specific value or range of plasma glucose concentrations that potentially could result in brain injury. Instead, it is a pragmatic approach to a controversial issue for which evidence is lacking but guidance is needed.

### BACKGROUND

Blood glucose concentrations as low as 30 mg/dL are common in healthy neonates by 1 to 2 hours after birth; these low concentrations, seen in all mammalian newborns, usually are transient, asymptomatic, and considered to be part of normal adaptation to postnatal life.<sup>6–8</sup> Most neonates compensate for “physiologic” hypoglycemia by producing alternative fuels including ketone bodies, which are released from fat.

Clinically significant NH reflects an imbalance between supply and use of glucose and alternative fuels and may result from a multitude of disturbed regulatory mechanisms. A rational definition of NH must account for the fact that acute symptoms and long-term neurologic sequelae occur within a continuum of low plasma glucose values of varied duration and severity.

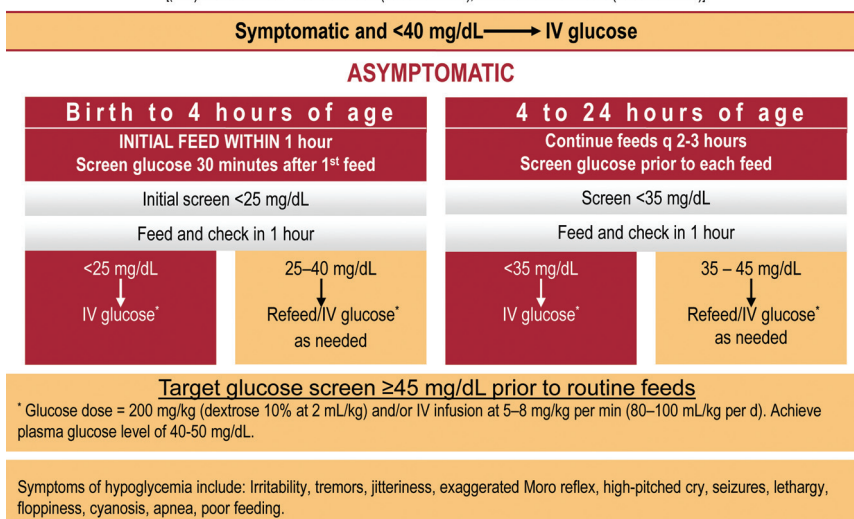
The authors of several literature reviews have concluded that there is not a specific plasma glucose concentration or duration of hypoglycemia that can predict permanent neurologic injury in high-risk infants.<sup>3,9,10</sup> Data that have linked plasma glucose concentration with adverse long-term neurologic outcomes are confounded by variable definitions of hypoglycemia and its duration (seldom reported), the omission of control groups, the possible inclusion of infants with confounding conditions, and the small number of asymptomatic infants who were followed.<sup>3,11,12</sup> In addition, there is no single concentration or range of plasma glucose concentrations that is associated with clinical signs. Therefore, there is no consensus regarding when screening should be performed and which concentration of glucose requires therapeutic intervention in the asymptomatic infant. The generally adopted plasma glucose concentration that defines NH for all infants (<47 mg/dL) is without rigorous scientific justification.<sup>1,3,4,9,12</sup>

### WHICH INFANTS TO SCREEN

Because plasma glucose homeostasis requires gluconeogenesis and ketogenesis to maintain normal rates of fuel use,<sup>13</sup> NH most commonly occurs in infants with impaired gluconeogenesis and/or ketogenesis,<sup>14,15</sup> which may occur with excessive insulin production, altered counterregulatory hormone production, an inadequate substrate supply,<sup>14–16</sup> or a disorder of fatty acid oxidation.<sup>15</sup> NH occurs most commonly in infants who are small for gestational age, infants born to mothers who have diabetes, and late-preterm infants. It remains controversial whether otherwise normal infants who are large for gestational age are at risk of NH, largely because it is difficult to exclude maternal diabetes or maternal hyperglycemia (prediabe-

## Screening and Management of Postnatal Glucose Homeostasis in Late Preterm and Term SGA, IDM/LGA Infants

[(LPT) Infants 34 – 36<sup>67</sup> weeks and SGA (screen 0-24 hrs); IDM and LGA ≥34 weeks (screen 0-12 hrs)]



**FIGURE 1**

Screening for and management of postnatal glucose homeostasis in late-preterm (LPT 34–36<sup>67</sup> weeks) and term small-for-gestational age (SGA) infants and infants who were born to mothers with diabetes (IDM)/large-for-gestational age (LGA) infants. LPT and SGA (screen 0–24 hours), IDM and LGA ≥34 weeks (screen 0–12 hours). IV indicates intravenous.

tes) with standard glucose-tolerance tests.

A large number of additional maternal and fetal conditions may also place infants at risk of NH. Clinical signs are common with these conditions, and it is likely that patients with such a condition are already being monitored and that plasma glucose analyses are being performed.<sup>13,17</sup> Therefore, for practicality, “at risk” in the management approach outlined in Fig 1 includes only infants who are small for gestational age, infants who are large for gestational age, infants who were born to mothers who have diabetes, and late-preterm infants. Routine screening and monitoring of blood glucose concentration is not needed in healthy term newborn infants after an entirely normal pregnancy and delivery. Blood glucose concentration should only be measured in term infants who have clinical manifestations or who are known to be at risk. Plasma or blood glucose concentration should be measured as soon as possible (min-

utes, not hours) in any infant who manifests clinical signs (see “Clinical Signs”) compatible with a low blood glucose concentration (ie, the symptomatic infant).

Breastfed term infants have lower concentrations of plasma glucose but higher concentrations of ketone bodies than do formula-fed infants.<sup>13,17</sup> It is postulated that breastfed infants tolerate lower plasma glucose concentrations without any clinical manifestations or sequelae of NH because of the increased ketone concentrations.<sup>8,12–14</sup>

### WHEN TO SCREEN

Neonatal glucose concentrations decrease after birth, to as low as 30 mg/dL during the first 1 to 2 hours after birth, and then increase to higher and relatively more stable concentrations, generally above 45 mg/dL by 12 hours after birth.<sup>6,7</sup> Data on the optimal timing and intervals for glucose screening are limited. It is controversial whether to screen the asymptomatic at-risk infant for NH during this

normal physiologic nadir. No studies have demonstrated harm from a few hours of asymptomatic hypoglycemia during this normal postnatal period of establishing “physiologic glucose homeostasis.”<sup>9</sup>

Infants born to mothers with diabetes may develop asymptomatic NH as early as 1 hour after birth<sup>18</sup> and usually by 12 hours of age.<sup>18</sup> In contrast, infants who are large for gestational age or small for gestational age may develop low plasma glucose concentrations at as early as 3 hours of age,<sup>19</sup> and these infants may be at risk of NH for up to 10 days after birth.<sup>20</sup> Therefore, at-risk infants should be screened for NH with a frequency and duration related to risk factors specific to the individual infant.<sup>5</sup> Screening the asymptomatic at-risk infant can be performed within the first hours of birth and continued through multiple feed-fast cycles. Late-preterm infants and infants who are small for gestational age should be fed every 2 to 3 hours and screened before each feeding for at least the first 24 hours. After 24 hours, repeated screening before feedings should be continued if plasma glucose concentrations remain lower than 45 mg/dL.

## LABORATORY DATA

When NH is suspected, the plasma or blood glucose concentration must be determined immediately by using one of the laboratory enzymatic methods (eg, glucose oxidase, hexokinase, or dehydrogenase method). Plasma blood glucose values tend to be approximately 10% to 18% higher than whole-blood values because of the higher water content of plasma.<sup>21,22</sup>

Although a laboratory determination is the most accurate method of measuring the glucose concentration, the results may not be available quickly enough for rapid diagnosis of NH, which thereby delays the initiation of treatment.<sup>23</sup> Bedside reagent test-strip

glucose analyzers can be used if the test is performed carefully and the clinician is aware of the limited accuracy of these devices. Rapid measurement methods available at the bedside include the handheld reflectance colorimeter and electrode methods. The blood sample is usually obtained from a warmed heel.

Test-strip results demonstrate a reasonable correlation with actual plasma glucose concentrations, but the variation from the actual level may be as much as 10 to 20 mg/dL.<sup>24–27</sup> Unfortunately, this variation is greatest at low glucose concentrations. There is no point-of-care method that is sufficiently reliable and accurate in the low range of blood glucose to allow it to be used as the sole method for screening for NH.

Because of limitations with “rapid” bedside methods, the blood or plasma glucose concentration must be confirmed by laboratory testing ordered stat. A long delay in processing the specimen can result in a falsely low concentration as erythrocytes in the sample metabolize the glucose in the plasma. This problem can be avoided by transporting the blood in tubes that contain a glycolytic inhibitor such as fluoride.

Screening of the at-risk infant for NH and institution of prophylactic measures to prevent prolonged or symptomatic NH is a reasonable goal. Treatment of suspected NH should not be postponed while waiting for laboratory confirmation. However, there is no evidence to show that such rapid treatment will mitigate neurologic sequelae.

## CLINICAL SIGNS

The clinical signs of NH are not specific and include a wide range of local or generalized manifestations that are common in sick neonates.<sup>12,13,17</sup> These signs include jitteriness, cyanosis, seizures, apneic episodes, tachypnea,

weak or high-pitched cry, floppiness or lethargy, poor feeding, and eye-rolling. It is important to screen for other possible underlying disorders (eg, infection) as well as hypoglycemia. Such signs usually subside quickly with normalization of glucose supply and plasma concentration.<sup>9,13</sup> Coma and seizures may occur with prolonged NH (plasma or blood glucose concentrations lower than 10 mg/dL range) and repetitive hypoglycemia. The more serious signs (eg, seizure activity) usually occur late in severe and protracted cases of hypoglycemia and are not easily or rapidly reversed with glucose replacement and normalization of plasma glucose concentrations.<sup>28–30</sup> Development of clinical signs may be ameliorated by the presence of alternative substrates.<sup>31</sup>

Because avoidance and treatment of cerebral energy deficiency is the principal concern, greatest attention should be paid to neurologic signs. To attribute signs and symptoms to NH, Cornblath et al<sup>12</sup> have suggested that the Whipple triad be fulfilled: (1) a low blood glucose concentration; (2) signs consistent with NH; and (3) resolution of signs and symptoms after restoring blood glucose concentrations to normal values.<sup>12</sup>

## MANAGEMENT

Any approach to management needs to account for the overall metabolic and physiologic status of the infant and should not unnecessarily disrupt the mother-infant relationship and breastfeeding. The definition of a plasma glucose concentration at which intervention is indicated needs to be tailored to the clinical situation and the particular characteristics of a given infant. For example, further investigation and immediate intravenous glucose treatment might be instituted for an infant with clinical signs and a plasma glucose concentration of less than 40 mg/

dL, whereas an at-risk but asymptomatic term formula-fed infant may only require an increased frequency of feeding and would receive intravenous glucose only if the glucose values decreased to less than 25 mg/dL (birth to 4 hours of age) or 35 mg/dL (4–24 hours of age).<sup>32</sup> Follow-up glucose concentrations and clinical evaluation must always be obtained to ensure that postnatal glucose homeostasis is achieved and maintained.

Because severe, prolonged, symptomatic hypoglycemia may result in neuronal injury,<sup>27,28,32</sup> prompt intervention is necessary for infants who manifest clinical signs and symptoms. A reasonable (although arbitrary) cutoff for treating symptomatic infants is 40 mg/dL. This value is higher than the physiologic nadir and higher than concentrations usually associated with clinical signs. A plasma sample for a laboratory glucose determination needs to be obtained just before giving an intravenous “minibolus” of glucose (200 mg of glucose per kg, 2 mL/kg dextrose 10% in water [D<sub>10</sub>W], intravenously) and/or starting a continuous infusion of glucose (D<sub>10</sub>W at 80–100 mL/kg per day). A reasonable goal is to maintain plasma glucose concentrations in symptomatic infants between 40 and 50 mg/dL.

Figure 1 is a guideline for the screening and management of NH in late-preterm infants and term infants who were born to mothers with diabetes, small for gestational age, or large for gestational age. In developing a pragmatic approach to the asymptomatic at-risk infant during the first 24 hours after birth, mode of feeding, risk factors, and hours of age were considered. This strategy is based on the following observations from Cornblath and Ichord<sup>13</sup>: (1) almost all infants with proven symptomatic NH during the first hours of life have plasma glucose concentrations lower than 20 to 25

mg/dL; (2) persistent or recurrent NH syndromes present with equally low plasma glucose concentrations; and (3) little or no evidence exists to indicate that asymptomatic NH at any concentration of plasma glucose in the first days of life results in any adverse sequelae in growth or neurologic development.<sup>13</sup>

Figure 1 is divided into 2 time periods (birth to 4 hours and 4–12 hours) and accounts for the changing values of glucose that occur over the first 12 hours after birth. The recommended values for intervention are intended to provide a margin of safety over concentrations of glucose associated with clinical signs. The intervention recommendations also provide a range of values over which the clinician can decide to refeed or provide intravenous glucose. The target glucose concentration is greater than 45 mg/dL before each feeding. At-risk infants should be fed by 1 hour of age and screened 30 minutes after the feeding. This recommendation is consistent with that of the World Health Organization. Gavage feeding may be considered in infants who are not nipping well. Glucose screening should continue until 12 hours of age for infants born to mothers with diabetes and those who are large for gestational age and maintain plasma glucose concentrations of greater than 40 mg/dL. Late-preterm infants and infants who are small for gestational age require glucose monitoring for at least 24 hours after birth, because they may be more vulnerable to low glucose concentrations, especially if regular feedings or intravenous fluids are not yet established.<sup>20</sup> If inadequate postnatal glucose homeostasis is documented, the clinician must be certain that the infant can maintain normal plasma glucose concentrations on a routine diet for a reasonably extended period (through at least 3 feed-fast periods) before dis-

charge. It is recommended that the at-risk asymptomatic infant who has glucose concentrations of less than 25 mg/dL (birth to 4 hours of age) or less than 35 mg/dL (4–24 hours of age) be refeed and that the glucose value be rechecked 1 hour after refeeding. Subsequent concentrations lower than 25 mg/dL, or lower than 35 mg/dL, respectively, after attempts to refeed, necessitate treatment with intravenous glucose. Persistent hypoglycemia can be treated with a minibolus (200 mg/kg [2 mL/kg] D<sub>10</sub>W) and/or intravenous infusion of D<sub>10</sub>W at 5 to 8 mg/kg per minute, 80 to 100 mL/kg per day; the goal is to achieve a plasma glucose concentration of 40 to 50 mg/dL (higher concentrations will only stimulate further insulin secretion). If it is not possible to maintain blood glucose concentrations of greater than 45 mg/dL after 24 hours of using this rate of glucose infusion, consideration should be given to the possibility of hyperinsulinemic hypoglycemia, which is the most common cause of severe persistent hypoglycemia in the newborn period. A blood sample should be sent for measurement of insulin along with a glucose concentration at the time when a bedside blood glucose concentration is less than 40 mg/dL, and an endocrinologist should be consulted.

## SUMMARY

Current evidence does not support a specific concentration of glucose that can discriminate euglycemia from hypoglycemia or can predict that acute or chronic irreversible neurologic damage will result. Therefore, similar to the Canadian Paediatric Society guidelines, a significantly low concentration of glucose in plasma should be reliably established and treated to restore glucose values to a normal physiologic range.<sup>5</sup> Recognizing infants at risk of disturbances in postnatal glucose homeostasis and providing a margin of safety by early measures to



prevent (feeding) and treat (feeding and intravenous glucose infusion) low concentrations are primary goals. Follow-up glucose measurements are always indicated to be sure an infant can maintain normal glucose concentrations over several feed-fast cycles. This will also permit recognition of infants with persistent hyperinsulinemic hypoglycemia and infants with fatty acid oxidation disorders.

#### LEAD AUTHOR

David H. Adamkin, MD

#### COMMITTEE ON FETUS AND NEWBORN, 2009–2010

Lu-Ann Papile, MD, Chairperson  
David H. Adamkin, MD  
Jill E. Baley, MD  
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Association of Neonatal Nurses*  
Tonse N. K. Raju, MD, DCH – *National Institutes  
of Health*

#### STAFF

Jim Couto, MA

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