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ABM Clinical Protocol #1: Guidelines for Glucose Monitoring and Treatment of Hypoglycemia in Term and Late Preterm Neonates, Revised 2021

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Abstract

A central goal of The Academy of Breastfeeding Medicine is the development of clinical protocols for managing common medical conditions that may impact breastfeeding success. These protocols serve only as guidelines for the care of breastfeeding mothers and infants and do not delineate an exclusive course of treatment or serve as standards of medical care. Variations in treatment may be appropriate according to the needs of an individual patient.

Purpose

To provide guidance in the first hours/days of life to:

- Differentiate transitional neonatal hypoglycemia from persistent pathologic hypoglycemia
- Prevent clinically significant hypoglycemia in newborn infants
- Appropriately monitor blood/plasma glucose levels in at-risk term and late preterm neonates
- Manage clinically significant hypoglycemia in newborn infants to prevent neurologic injury
- Maximize breast milk provision to babies
- Establish and preserve maternal milk supply during medically necessary supplementation for hypoglycemia or during separation of mother and baby.

About the 2020 Revised Protocol

Key research articles before 2014 were retained and more recent information was added from primary studies and compilations. Specific studies were assigned a level of evidence, and Strength of Recommendation Taxonomy (SORT: A, B, C)[1] was used for recommendations. The SORT rating system addresses the three key elements (quality, quantity, and consistency) recommended by the Agency for Healthcare Research and Quality. Levels of evidence are applied after each specific recommendation in brackets, e.g., [A], [B], [C].

Recommendations are updated based on the last 6 years of new information and critical older studies. This clinical protocol is intended to provide practitioners with pragmatic evidence-based guidance to keep infants safe while minimizing unjustified interventions and adverse effects, such as heightened parental anxiety, excessive painful procedures, unnecessary supplementation with artificial milk, decrease in breastfeeding, and avoidable neonatal intensive care unit (NICU) admission.

Background

The term *hypoglycemia* refers to a low blood or plasma glucose concentration and reflects a relative imbalance between the supply and utilization of glucose, but does not consider the supply and utilization of alternative fuels to glucose covered under the broader concept of metabolic adaptation. Transient low blood glucose levels in the first 1–2 hours after birth are common, occurring in almost all mammalian newborns. In healthy term human infants, even if early enteral feeding is withheld, transitional neonatal low glucose is usually self-limited, asymptomatic, and considered to be part of adaptation to postnatal life.[2,3] However, profound, persistent, or recurrent neonatal hypoglycemia, especially in a term previously healthy newborn with no risk factors, invariably presents with abnormal clinical signs and may reflect genetic, metabolic, or endocrine dysregulation or defects and require more aggressive evaluation and care.[4,5]

Despite >60 years recognition that low blood glucose can cause neurologic compromise, we still do not know how low, for how long, and in which specific infants. New evidence has come to light, but so have new varying recommendations, based on differing perspectives. Also, peripartum care of the mother and newborn has changed dramatically in the past six decades with infants staying with their mothers and encouraged to feed sooner.

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Perinatal glucose homeostasis

Before birth the fetus is entirely dependent on the mother for a continuous transplacental transfer of glucose.[4,6–8] As maternal insulin does not cross the placenta, fetal glucose levels are dependent on maternal glucose levels and fetal insulin secretion.[4] Although a major action of fetal insulin is as a growth factor for the fetus, metabolic actions of insulin include an increase in cellular glucose uptake, deposition of glucose as glycogen, lipogenesis, and inhibition of breakdown of triglycerides and fatty acids to prepare for newborn transitional energy needs.[4,6,7]

At birth, the neonate's blood glucose concentration falls rapidly, reaching a nadir as low as 20–25 mg/dL (1.11–1.39 mmol/L)[9,10] at 1–1.5 hours after birth, and then rising to stabilize by 3 hours of life even in the absence of exogenous nutritional intake.[9] During this period, plasma insulin levels fall (but are not completely suppressed[7]) and plasma glucagon levels increase, possibly due to the stress of the birth process mediated through a catecholamine surge.[6] Glucagon, growth hormone, catecholamines, and cortisol are counterregulatory hormones that help mobilize stored glucose and provide alternative fuel sources for energy.[4] The blood glucose concentrations continue to rise slowly and stabilize between 43 and 90 mg/dL (2.4 and 5 mmol/L) by 12–24 hours of age, and reach levels found in older children and adults by 2 to 4 days after birth.[9,11,12] The decrease in glucose concentrations soon after birth may be necessary to stimulate physiologic processes that are required for postnatal survival.[10]

The compensatory provision of alternative fuels constitutes a normal adaptive response to transiently low nutrient intake during the establishment of breastfeeding,[11,13] resulting in breastfed infants tolerating lower plasma glucose levels without any significant clinical manifestations or sequelae.[13] Indeed, breastfed babies have higher ketone body levels than formula-fed babies, even at equivalent blood glucose levels.[11] Lactate concentrations are high in the first 2–3 hours of life.[6] Although ketone levels appear low in the first 24 hours after birth, they increase on days 2–3 in breastfed babies,[4,11] and seem to be more bioavailable for the neonatal brain than for older children or adults.[6,11]

As oral intake is not the main energy source for healthy term neonates in the first days after birth, small physiologic volumes of colostrum are sufficient to meet metabolic demands. In some studies, feeding at breast or with artificial milk in the first 1–3 hours of life did not have a significant effect on the blood glucose level over fasting.[14,15] In another study of low birth weight infants (1.6–2.49 kg), delayed breastfeeding (>1 hour postbirth) was the most commonly noted risk factor for hypoglycemia.[16]

Definitions of Hypoglycemia

The definition of hypoglycemia in the newborn infant remains controversial because of a lack of significant correlation between plasma glucose concentration, clinical signs, and long-term sequelae.[3,13,17] There have been four main approaches to defining hypoglycemia: (1) epidemiologic/statistical analysis of measured glucose values, (2) clinical manifestations fulfilling Whipple's Triad, (3) acute changes in metabolic/endocrine responses and measures of neurologic function, and (4) long-term neurologic outcomes. An expert panel convened by the U.S. National Institutes of Health (NIH) in 2008 concluded that there has been no substantial evidence-based progress in defining what constitutes clinically important neonatal hypoglycemia, particularly regarding how it relates to brain injury.[18] As of 2020, there is still significant dispute over the definition and ''the number.''[3–5]

Epidemiologic approach

Breastfed, formula-fed, and mixed-fed infants follow the same pattern of glucose values with an initial fall in glucose over the first 2 hours of life, followed by a gradual rise in glucose over the next 96 hours, whether fed or not.[9,19] As expected, preterm infants drop their blood glucose more rapidly than late preterm or term infants.[20,21] Artificially fed infants tend to have slightly higher glucose and lower ketone bodies than breastfed infants.[11,12,22] Studies of blood or plasma glucose levels over time in *exclusively* breastfed infants are infrequent.[16,23,24]

Clinical manifestations of hypoglycemia approach

The clinical manifestations of hypoglycemia are *nonspecific*, occurring with a variety of other neonatal problems.[13] Even in the presence of an arbitrary low glucose level, the physician must assess the general status of the infant to rule out other disease entities and processes that may need additional laboratory evaluation and treatment. Signs of hypoglycemia are categorized as neurogenic (adrenergic) or neuroglycopenic.[5] Neurogenic/adrenergic signs present earlier, at a higher value of blood glucose and represent activation of the sympathetic nervous system. Neuroglycopenic signs and symptoms include apnea, hypotonia, seizure, and coma that may progress to brain injury or death if a source of glucose is not established. Some common clinical signs are listed in Table 1.

Hoops et al.[25] found that of the 23 maternal/infant risk factors and infant signs studied, only ''jitteriness'' and tachypnea were statistically predictive of low blood glucose.

Table 1. Clinical Manifestations of Possible Hypoglycemia

Neurogenic/adrenergic (sympathetic nervous system activation)
Irritability
Tremors, jitteriness
Tachypnea
Sweating
Pallor, vasomotor instability
Hypothermia; temperature instability
Tachycardia
Exaggerated Moro reflex
High-pitched cry
Excessive hunger signs
Vomiting
Poor suck or refusal to feed
Neuroglycopenic (brain dysfunction due to inadequate glucose)
Lethargy, listlessness, limpness, hypotonia
Seizures or myoclonic jerks
Coma
Apnea or irregular breathing
Cyanosis

However, jitteriness is a very nonspecific sign and likely to result in many false positives. A diagnosis of hypoglycemia also requires that signs abate after normoglycemia is restored,[26,27] unless brain injury has already been sustained.[28]

Acute physiologic changes approach

This approach was used in an attempt to define neonatal hypoglycemia as the blood glucose level below which newborns demonstrate counter-regulatory responses such as changes in cerebral blood flow and hormonal responses,[29] or abnormalities in neurophysiologic function.[17,30] Neurophysiologic monitoring, including electroencephalography, visual evoked potentials, and brainstem auditory evoked responses failed to define a threshold for neurologic damage.

Neurologic and developmental outcomes approach

This approach is obviously the most important, and most difficult to define. Animal studies suggest that the immature brain is very resistant (through several mechanisms) to damage from even profound hypoglycemia.[31]

Evidence from tissue culture and animal models indicates that the neural damage attributed to hypoglycemia is not simply a matter of inadequate energy stores, but rather a result of accumulation of toxic substances, such as aspartic acid and glutamate.[32] Because this process requires time (hours to days), transient single brief periods of hypoglycemia are unlikely to cause permanent neurologic damage.[33,34]

A 2019 systematic review of neonatal hypoglycemia and neurodevelopmental outcomes[35] evaluated 12 studies from 1971 to 2017.[36–40] All were either retrospective or prospective cohort studies with the newborns varying in gestational age and risk. The authors concluded that neonatal hypoglycemia may have important long-lasting adverse effects on neurodevelopment that may become apparent at later ages, but that randomized controlled trials are still required, with follow-up at least to school age. The CHYLD study, which used 47 mg/dL (2.6 mmol/L) as threshold for treatment with clinicians blinded to subcutaneous continuous glucose monitoring, suggested that higher interstitial, more unstable, and a steep rise in glucose values may be associated with neurosensory impairment at 2-year follow-up.[37] At 4.5-year follow-up, neonatal hypoglycemia was not associated with major neurologic deficits, but was associated with a two- to threefold increased risk of poor executive and visual motor performance.[38] They demonstrated the potential for adverse outcomes with both undertreatment and overtreatment of neonatal hypoglycemia.[38]

A subsequent multicenter randomized noninferiority trial involving 689 otherwise healthy at-risk newborns ≥35 weeks gestation compared two threshold values for treatment of *asymptomatic* moderate hypoglycemia (36 mg/dL versus 47 mg/dL [2.0 mmol/L versus 2.6 mmol/L]).[41] Bailey-III-NL scores and psychomotor development at 18 months, maternal and infant hospital stays, and health care costs were similar in both groups. There were fewer and less severe hypoglycemic episodes in the 47 mg/dL group, but that group had more invasive diagnostic and treatment interventions. The authors concluded that, in otherwise healthy newborns with moderate hypoglycemia, a lower glucose treatment threshold (36 mg/dL) was noninferior to the ''traditional'' threshold (47 mg/dL).[41]

Hypoglycemia-mediated cerebral injury in the newborn (1) requires severe and prolonged hypoglycemia, (2) affects the upper cortical layers, especially the parieto-occipital regions, as well as injury to the hippocampus, caudate, and white matter, (3) has a different neuropathology from ischemic cerebral injury, and (4) results in cerebral injury when mild hypoxia–ischemia is combined with mild hypoglycemia, but neither alone.[31,42]

Establishing cause and effect in neonatal hypoglycemia and neurologic impairment involves both demonstrating the ''significant'' hypoglycemia occurred, and that the nature of the neurologic impairment is characteristic of hypoglycemic brain injury. As hypoglycemia often occurs alongside other confounding factors (e.g., perinatal hypoxia–ischemia, sepsis, and prematurity), this is often difficult to prove.[28]

In a review of legal claims made relating to hypoglycemia in the National Health Service in the United Kingdom from 1995 to 2010, Hawdon et al.[43] noted that cases of neonatal hypoglycemia sufficiently severe to cause brain injury were rare, but had enormous human and financial costs. Despite standard guidelines, several avoidable deficits in care were reported. The most common risk factors were low, or borderline low birth weight, and the most common presenting sign was abnormal feeding behavior. In many cases mothers' concerns were not heeded by staff.

Multiple experts have concluded that no specific plasma or blood glucose concentration or duration can be linked to either clinical signs or permanent neurologic injury.[2,18,35,44] No studies to date have shown that treating transiently low blood glucose levels results in better short-term or long-term outcomes compared with no treatment, and there is no evidence that ''asymptomatic'' hypoglycemic infants benefit from treatment.[2,18,45] The risks of overtreatment in babies who are undergoing normal neonatal transition must be balanced against the benefits gained by aggressive treatment of patients with potentially dangerous hypoglycemia.[46]

Risk Factors for Hypoglycemia

Neonates at increased risk for developing neonatal hypoglycemia should be routinely monitored for blood glucose levels irrespective of the mode of feeding. At-risk neonates fall into two main categories: (1) excess utilization of glucose, which includes the hyperinsulinemic states, and (2) inadequate production or substrate delivery.[27] Maternal and infant categories at increased risk for hypoglycemia are listed in Table 2.[47–49] Large for gestational age infants born to *screened* nondiabetic mothers appear not at risk of hypoglycemia[50] nor at increased risk of poor psychomotor development at 4 years of age.[51]

Umbilical cord blood glucose does not seem to predict early hypoglycemia.[52] Infants who are appropriate for gestational age by weight, but with low body fat percentage, are at risk for hypoglycemia.[53] Conversely, constitutionally small babies with adequate fat stores are not at risk of hypoglycemia. Early feeding improves breastfeeding, but results are contradictory as to whether it improves blood glucose.[14–16] Confounding may be the answer, as a baby with borderline low blood glucose may not feed well.

A recent study, screening only at *at-risk infants* (12% of all infants) and using the American Academy of Pediatrics (AAP) 2011 protocol (reaffirmed in 2015),[2] found low

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Table 2. At-Risk Infants for Whom Routine Monitoring of Blood Glucose is Indicated

Maternal conditions
Pre-existing or gestational diabetes, or abnormal result of glucose tolerance test, especially if poorly controlled
Pre-eclampsia and pregnancy induced, or essential hypertension
Previous macrocosmic infants (as a proxy for undiagnosed diabetes in pregnancy)
Substance abuse
Treatment with beta-agonist tocolytics
Treatment with oral hypoglycemic agents
Late antepartum or intrapartum administration of IV glucose
Neonatal conditions
Intrauterine growth restriction or marked wasting
Low birth weight (<2,500 g)
Small for gestational age; <10th percentile for weight[a]
Babies with clinically evident wasting of fat and muscle bulk
LGA; >90th percentile for weight & macrosomic appearance[b]
Discordant twin; weight 10% < larger twin
Infants of poorly controlled diabetic mothers
Prematurity (<35 weeks or late preterm infants with clinical signs or extremely poor feeding)
Perinatal stress; severe acidosis or hypoxia–ischemia
Cold stress
Polycythemia (venous hematocrit >70%)/hyperviscosity
Erythroblastosis fetalis
Beckwith–Wiedemann syndrome
Microphallus or midline defect (indicating an underlying endocrine condition)
Suspected infection
Respiratory distress
Known or suspected inborn errors of metabolism or endocrine disorders
Any infant admitted to the neonatal intensive care unit
Infants displaying signs associated with hypoglycemia (Table 1)

[a]In the United States and WHO definition is <10th percentile and British <2nd percentile.

[b]In unscreened populations, LGA may represent undiagnosed/untreated maternal diabetes.

IV, intravenous; LGA, large for gestational age.

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blood glucose in 27% of the at-risk cohort. Although infants received an average of seven blood samples, the number of samples needed to detect one episode of hypoglycemia was 20.[54]

Assessment of Glucose Levels

Blood glucose measurements vary enormously with the source and timing of the blood sample, the assay method, and whether whole blood, plasma, serum, or interstitial fluid is used. Plasma or serum glucose concentrations may be 10–18% higher than in whole blood.[55]

Bedside point of care (POC) nonenzymatic glucometers are convenient, inexpensive, give rapid results, and require a small sample of blood, but are much less accurate in the low glucose ranges of normal newborns, with deviations from actual levels as much as 10–20 mg/dL (0.55–1.11 mmol/L).[55–57] POC nonenzymatic glucose assessments may be utilized for screening, but laboratory levels sent for immediate determination (e.g., glucose oxidase, hexokinase, or dehydrogenase method) must confirm results before a diagnosis of hypoglycemia can be made, especially in asymptomatic infants. More accurate POC glucometers (e.g., blood gas analyzers) are now available that use an enzymatic reaction, not requiring laboratory confirmation. Although more expensive initially, they have been shown to be very cost-effective.[57]

Continuous (subcutaneous) glucose monitoring (CGM), as used in the management of adults and children with glucose dysregulation, has been used experimentally in NICUs, and has great potential. Current limitations include the size of the inserted sensor, the need for frequent calibration with laboratory glucose samples, the tendency to ''drift'' as the sensor ages, the need to replace the sensor approximately every 7 days, and the risk of infection.[58] Interestingly procedural pain during insertion of a CGM device in preterm infants was associated with less pain than a heelstick.[59] Newer less invasive more reliable models are in development, but at present CGM should be limited to research studies,[58,60,61] such as the Glucose in Well Babies (GLOW) study,[62] which found, using CGM, that healthy infants complete their metabolic transition by day 4 of life, and that many had glucose concentrations <47 mg/dL (2.6 mmol/L).

Dextrose Gel Treatment

Diabetes experts have long recommended ingestion of 15 g of carbohydrate to treat hypoglycemic episodes in conscious adults. The first use of dextrose gel for neonatal hypoglycemia appeared in the literature in 1992.[63] Since 2000, randomized controlled trials have confirmed the safety and efficacy of a standard dose of 200 mg/kg (=0.5 mL/kg 40% dextrose gel).[64–66]

The Sugar Babies Study,[66] a randomized controlled trial with at-risk infants 35 to 42 weeks gestation randomized to 40% dextrose gel versus placebo gel generated valuable insights.[64–67] Dextrose gel reduced the risk of treatment failure (RR 0.57, 95% CI 0.33–0.98, $p=0.04$) for hypoglycemia defined as <2.6 mmol/L (<47 mg/dL) and was inexpensive, safe, and simple to administer,[66] with an overall mean increase in blood glucose concentration after treatment of 11.7 mg/dL (0.65 mmol/L), 95% CI 10.4–12.8).[65] A 2-year follow-up study[64] revealed no difference in long-term outcome, but there was an unusually high incidence of neurosensory impairment in both groups. Treating hypoglycemic babies with dextrose gel 200 mg/kg did not suppress subsequent feeding.[67] Either glucose gel or formula increased blood glucose, but not breastfeeding or human milk alone. However, dextrose gel in combination with breastfeeding was sufficient to increase blood glucose and was optimal for *maintaining* blood glucose levels, thereby avoiding repeat glucose gel administration. The volume of expressed breast milk (and assumed intake at the breast) was significantly less than the intake of formula (0.5 mL/kg versus 4.5 mL/kg). *The authors concluded that dextrose gel plus breastfeeding should be considered the first line oral treatment of infants with hypoglycemia.*[65]

Other quality improvement pre–post studies[68–72] have confirmed the benefits of glucose gel: improving blood glucose levels, preserving skin-to-skin care, decreasing mother–infant separation, reducing NICU admissions for

hypoglycemia, increasing exclusive breastfeeding at discharge and weeks postdischarge, improving parent satisfaction, well tolerated by the infants, and reducing cost.[72,73] Use of prophylactic dextrose gel had mixed results.[74,75] A 2017 review article[73] and a 2016 Cochrane Library review agree that dextrose gel at 200 mg/kg ''should be considered first-line treatment for infants with neonatal hypoglycemia.''[76]

Operational Thresholds

As the ''normal'' range of blood glucose is different for each newborn and depends upon a number of factors[13] including birth weight, gestational age, availability of energy stores, feeding status, and presence or absence of disease, any hypoglycemia management must account for the overall metabolic and physiologic status of the infant, and should not unnecessarily disrupt the mother–infant relationship and breastfeeding. Several authors have suggested algorithms for screening and treatment,[2,47,48,77–79] and the United Nations Children's Fund (UNICEF UK) published a monograph on how to develop a policy on the prevention and management of newborn hypoglycemia.[80] Of the multiple guidelines, algorithms, and practice frameworks available, there are few that are as clear as those from the AAP,[2] the Canadian Paediatric Society,[47] the Swedish National Guideline,[78] and the British Association of Perinatal Medicine[79] as summarized by Dr. Jane Hawdon in 2019[81] (Fig. 1).

The AAP and Pediatric Endocrine Society

Two U.S. pediatric organizations, the Committee on the Fetus and Newborn of the AAP[2] in 2011 (reaffirmed in 2015) and the Pediatric Endocrine Society (PES)[5,7] in 2015 provided expert opinion on the management of neonatal hypoglycemia.[10] Using different approaches, the two organizations suggested different glucose levels as operational thresholds. The AAP guidance covered the first 24 hours of life, and the PES focused on infants beyond 48 hours of life with persistent and/or severe hypoglycemia. Although the PES relied on neuroendocrine and metabolic data, and child and adult normal mean glucose levels, the AAP relied on an analysis of the lower range of glucose that occurs during the establishment of postnatal glucose homeostasis. Newer studies added additional concerns, such as rapid rises in glucose, higher glucose levels, and previously unrecognized glucose instability with continuous glucose monitoring.[17,36–38,41] The dangers of overdiagnosis and overtreatment of asymptomatic transitional newborns and the dangers of missing a persistent hypoglycemia are well recognized by both the AAP and PES.

General Management Recommendations

A. Early and exclusive breastfeeding meets the nutritional and metabolic needs of healthy term newborn infants.[2,47,79]
   1. All stable infants should initiate breastfeeding as soon as possible after birth, hopefully by 30–60 minutes of life.[82–84] [A] Late preterm infants may need additional assistance with breastfeeding. Early breastfeeding is not precluded because the infant meets the criteria for glucose monitoring.
   2. Infants should continue breastfeeding on cue [B].[85,86] Crying is a very late sign of hunger.[82,83] After the initial awake period of ~2 hours, some infants have a sleep/rest period of 6 to 8 hours with very brief periods of semiwakefulness.[87] Infants at risk for hypoglycemia should be offered breastfeeding opportunities during these 6–8 hours as well.
   3. Initiation and establishment of breastfeeding is facilitated by skin-to-skin contact between mother and infant. [A] This maintains normal infant body temperature and reduces energy expenditure (enabling maintenance of normal blood glucose) while stimulating suckling and milk production.[22,77,88,89]
   4. Routine supplementation of healthy term infants with water, glucose water, or formula is unnecessary and may interfere with normal metabolic compensatory mechanisms[3] and establishing normal breastfeeding.[82–84,90] [A]

GLUCOSE OPERATIONAL THRESHOLDS				
	0-4 Hours	4-24 Hours	24-48 Hours	>48 Hours
AAP, 2011/2015[2]	*< 25-40 mg/dL (1.39-2.22 mmol/L)	*< 35-45 mg/dL (1.94-2.5 mmol/L)	< 45mg/dL (2.5 mmol/L)	< 60 mg/dL (3.3 mmol/L)
PES, 2015[5,7]	< 50mg/dL (2.8 mmol/L)			< 60mg/dL (3.3 mmol/L)
BAPM, 2017[79]	< 18 mg/dL (1.0 mmol/L) at any time < 45 mg/dL (2.5 mmol/L) with abnormal clinical signs < 36 mg/dL (2.0 mmol/L) X 2 with risk factor(s) but no clinical signs			
CPS, 2019[47]	Unwell or abnormal clinical signs at any time < 47 mg/dL (< 2.6 mmol/L) with risk factor(s)			
SN, 2020[78]	< 27 mg/dL (1.5 mmol/L) < 47 mg/dL (2.6 mmol/L) with abnormal clinical signs < 27-45 mg/dL (1.5-2.5 mmol/L) X 2			
Notes	* any symptomatic infant with glucose <40mg/dL (2.22mmol/L will require IV glucose			

FIG. 1. Comparison of AAP, PES, BAPM, SN, CPS. AAP, American Academy of Pediatrics, Committee on the Fetus and Newborn; PES, Pediatric Endocrine Society; BAPM, British Association of Perinatal Medicine; SN, Svenska Neonatalföreningen; CPS, Canadian Paediatric Society. Adopted from figure by Dr. Alberto Heart. Color images are available online.

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5. Clinicians must identify and document risk factors, coexisting conditions, clinical signs/normality, and make assessments and decisions to avoid harm from hypoglycemia, but also to avoid iatrogenic harm, such as the effects of separation of mother and infant.[82] [C] Clinicians need skills to distinguish between abnormal feeding behaviors, suggesting illness and mere reluctance to feed.[8]

B. Glucose screening should be performed *only* on at-risk infants and those with clinical signs compatible with hypoglycemia.[2,18,24,47,79,82] [B] No study has evaluated optimal timing and intervals for glucose screening.[47]
   1. At-risk infants should be screened for hypoglycemia with a frequency and duration related to the specific risk factors of the individual infant.[2,47] [C]
      a. Monitoring should begin within 60 minutes after birth for infants with suspected significant hyperinsulinemia (e.g., poorly controlled maternal diabetes or known genetic hyperinsulinemia).[2,73] [C]
      b. Monitoring should commence before the second feeding, or 2–4 hours after birth, in other at-risk groups. (i.e., not so soon after birth that the physiologic fall in blood glucose level causes confusion and overtreatment).[73,79,91] [B]
   2. Monitoring should continue until acceptable preprandial levels are consistently obtained (until the infant has had at least three satisfactory measurements). A reasonable (although arbitrary) goal is to maintain plasma glucose concentrations ≥45 mg/dL (2.5 mmol/L).[2] If energy intake falls, glucose monitoring should be recommenced. [C]
   3. For hypoglycemia persisting beyond 48 hours, or for severe hypoglycemia at any time, urgent investigation is recommended.[2,5,81] [A]
   4. For severe persistent hypoglycemia, the PES recommends a ''safety'' fast of 6–8 hours before discharge, maintaining preprandial glucose >60 mg/dL (3.3mmol/L).[5] [C]
   5. Late preterm and small for gestational age infants and babies who have clinical features of intrauterine growth restriction should be monitored (with decreasing frequency) for 24 hours.[2] [C]
   6. Bedside nonenzymatic glucose screening tests must be confirmed by formal laboratory testing, although treatment should begin immediately in symptomatic infants. POC enzymatic glucometers (e.g., blood gas analyzers) do not need confirmation.[92] [A]

Management of Documented Hypoglycemia

(See also Appendix A2)

A. At-risk infant with no clinical signs and blood glucose >20–25 mg/dL (1.1–1.4 mmol/L) but <35–45 mg/dL (2.0–2.5 mmol/L):
   1. Continue skin-to-skin care.[88,89] [A]
   2. Continue breastfeeding as frequently as possible, or feed any available amount of colostrum, or 2–10 mL per feed (first 24 hours), and 5–15 mL per feed (24–48 hours of life), of substitute nutrition (pasteurized donor human milk,[93,94] artificial milk).[95] [B] Glucose water (5% or 10%) is not suitable because of insufficient energy and lack of protein.
   3. Buccal 40% dextrose gel is recommended at 0.5 mL/kg (200 mg/kg) in conjunction with a feeding plan (preferably breastfeeding) when the glucose is low or borderline, and the blood glucose is checked before the next feeding.[65–67] [A] A single repeat dose of buccal dextrose appears safe. [B]
   4. Recheck blood glucose concentration before subsequent feedings until the value is acceptable and stable (usually >45 mg/dL or ≥2.5 mmol/L). [C] If staff is unavailable to check blood glucose, and an infant has no clinical signs, breastfeeding should not be delayed while waiting for the preprandial blood glucose to be checked.
   5. If glucose remains low despite feedings, begin intravenous (IV) glucose therapy, and adjust IV rate by blood glucose concentration.[2] [A]
   6. If the neonate is unable to suck or feedings are not tolerated, avoid forced feedings and begin IV therapy.[2] [C] Such an infant requires a careful examination and evaluation for other underlying illness, especially if the infant had been feeding well earlier.[5] [C]
   7. Breastfeeding or oral feeding should continue during IV glucose therapy when the infant is interested and will suckle. Gradually wean the IV glucose as serum glucose normalizes and feedings increase. [B] Feeding during IV therapy for hypoglycemia reduces the duration of IV therapy needed and is associated with lower maximum glucose infusion rates.[96]
   8. Carefully document physical examination, screening values, laboratory confirmation, treatment, and changes in clinical condition (i.e., response to treatment). [A]
   9. Any infant with persistent hypoglycemia (>4 days) or requiring IV glucose therapy for symptomatic or asymptomatic low glucose levels should not be discharged until reasonable levels of blood glucose (>70 mg/dL; 3.9mmol/L) are maintained through several fast-feed cycles.[3,37,38,97] [A]

B. Infants with abnormal clinical signs, or infants with blood glucose levels <20–25 mg/dL (<1.1–1.4 mmol/L)[2] or <1.0 mmol/L (18 mg/dL):[79]
   1. Initiate IV 10% glucose solution with a bolus of 1–2 mL/kg and continuous IV at 5–8 mg/(kg·min).[2] [B]
   2. If the neonate is unable to suck or feedings are not tolerated, avoid forced feedings and begin IV therapy.[2] [C] Such an infant requires a careful examination and evaluation for other underlying illness, especially if the infant had been feeding well earlier.[5] [C]
   3. The glucose concentration in symptomatic infants should be maintained >45 mg/dL (>2.5 mmol/L).[2] [C]
   4. Encourage frequent breastfeeding after initiation of IV therapy. [C]
   5. Monitor glucose concentrations before feedings as the IV is gradually weaned, until values are stabilized off IV fluids. [B]
   6. Document physical examination, screening values, laboratory confirmation, treatment, and changes in clinical condition (i.e., response to treatment). [A]
   7. Do not use glucose gel on infants with clinical signs unless there is a delay in establishing IV access. [C]

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8. Infants who have had severe hypoglycemia accompanied by cerebral symptoms such as seizures, impaired consciousness, or circulatory collapse should receive magnetic resonance imaging and long-term follow-up.[37,38,78] [C]

Supporting the Mother and Family

Giving birth to an infant thought to be normal and healthy, but who develops hypoglycemia, is of concern to the mother and family and may jeopardize the establishment of breastfeeding. Mothers should be explicitly reassured that there is nothing wrong with their milk, and that supplementation is usually temporary. Having the mother hand express or pump colostrum that is then fed to her infant can overcome feelings of maternal inadequacy and help establish a full milk supply.[98]

Women with pre-existing or gestational diabetes may wish to prevent formula supplementation of their at-risk infants by antenatal milk expression and storage. The Diabetes and Antenatal Milk Expressing study[99] found there was no harm in expressing milk from 36 weeks gestation, but also no difference in the proportion of infants admitted to the NICU between the standard care and expressing groups. In another effort to facilitate breastfeeding while maintaining glucose stability in infants of diabetic mothers, a hospital established a new hypoglycemia algorithm (lower threshold, first blood glucose at 90 minutes of life), encouraged continuous skin-to-skin care, delayed the bath for 12 hours, and instituted early breastfeeding and feeding with drops of colostrum obtained from maternal *peripartum* hand expression.[100] Despite receiving less volume of colostrum than formula as supplementation, there was more stability in glucose values, decreased formula supplementation (increased exclusive breastfeeding), and less transfers to the NICU for IV glucose.[100]

Quality improvement projects often use bundles of changes that make it difficult to ascertain what individual change is making the most difference. In a U.S. study of infants born ≥35 weeks gestation with at least one risk factor for hypoglycemia, early skin-to-skin care, early breastfeeding, and obtaining a blood glucose in asymptomatic infants at 90 minutes of life decreased the NICU transfer rate from 17% to 3% and saved ~$100,000 per year.[77]

Recommendations for Supporting the Mother and Family

1. Provide parents with verbal and written information that explains why their baby is receiving extra support and blood glucose monitoring.[79] [C] (See Appendix A3: Parent Information)
2. Teach mothers to hand express and give the resulting colostrum to the infant. [C]
3. Consider antenatal/perinatal milk expression in mothers with gestational diabetes, as well as delayed baths to further support maintenance of normal glucose homeostasis among high-risk newborns.[99,100] [B]
4. Provide manual and/or mechanical breast expression with appropriate frequency (ideally eight times in 24 hours) until the baby is latching and suckling well to protect mothers' milk supply. [A]
5. Keep the infant at breast or return the infant to the breast as soon as possible to maintain breastfeeding, as well as breast milk supply. [C]
6. Encourage continuous skin-to-skin care. [A] Skin-to-skin care may lessen the trauma of intervention, while providing physiologic thermoregulation and metabolic homeostasis. Delaying or omitting the bath (unless medically indicated) may also reduce stress and maintain thermoregulation.
7. Provide expert, consistent, and sustained breastfeeding support by trained experienced members of the health care team. [A]

Recommendations for Future Research

1. Well-controlled studies are needed that look at plasma glucose, alternative brain fuel concentrations, clinical symptoms, and long-term sequelae to determine what ranges of blood glucose are the minimum safe levels for term healthy and various groups of at-risk infants.
2. Blood glucose over time in exclusively breastfed babies in hospitals with baby-friendly policies (i.e., current perinatal best practices) should be compared with nonbaby-friendly designated hospitals.
3. Development of more reliable bedside testing methods would increase the efficiency of diagnosis and treatment of clinically relevant glucose abnormalities. Noninvasive glucose monitoring is needed.
4. The role of other glucose-sparing fuels and the methods to measure them in a clinically meaningful way deserve further study.
5. Research into how much enteral glucose, and in what form, is necessary to raise blood glucose is important for clinical management, considering it may vary by weight, gestational age, time after birth, and comorbidities.
6. Measures of brain function in relation to a comprehensive portfolio of neural fuels (glucose, ketone bodies, and lactate), adaptive changes in cerebral microcirculation, and local factors are needed.
7. The mechanism of the ability of breast milk to enhance ketogenesis needs elucidation.

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ABM protocols expire 5 years from the date of publication. Content of this protocol is up to date at the time of publication. Evidence-based revisions are made within 5 years or sooner if there are significant changes in the evidence.

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Appendix

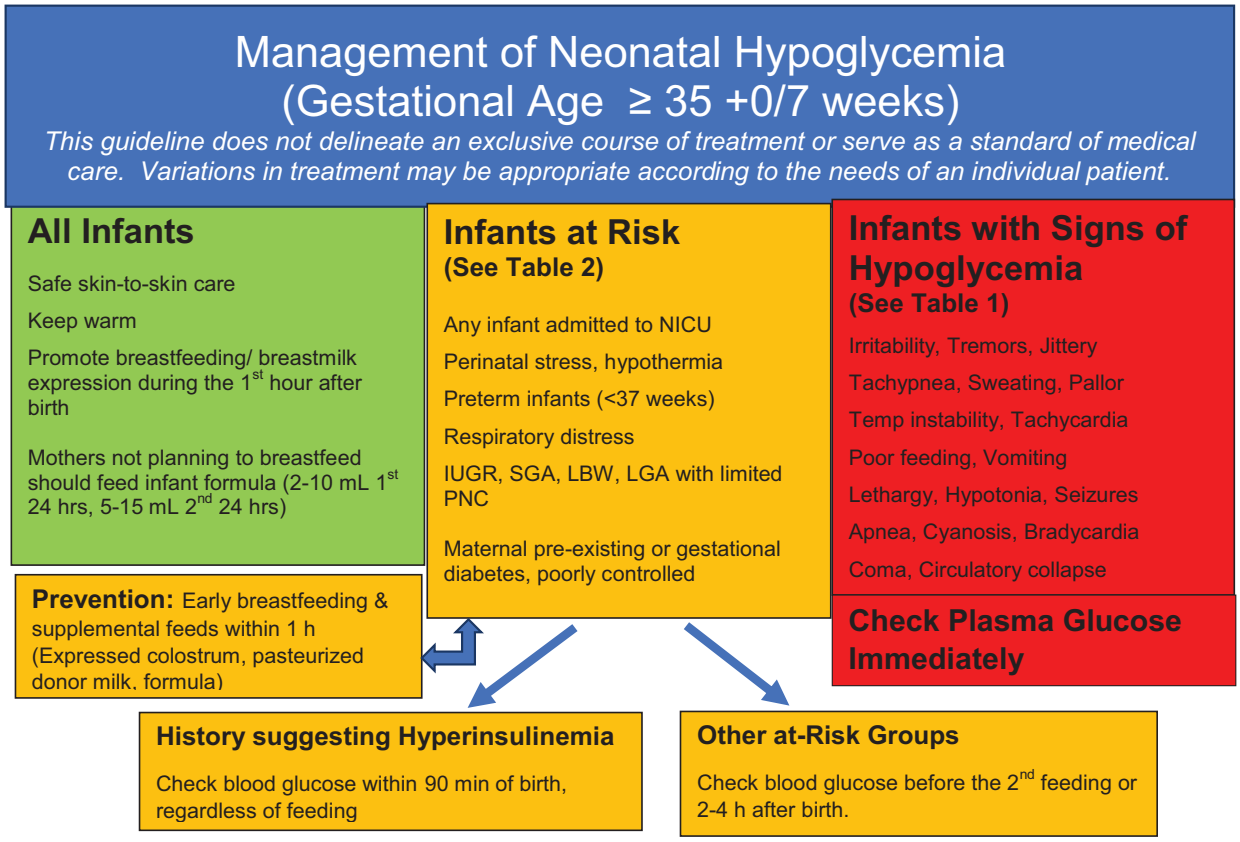
Appendix A1. Conversion Table and Calculations

Conversion	
mg/dL	*mmol/L*
20	1.1
30	1.7
40	2.2
50	2.8
60	3.3
70	3.9
80	4.4
90	5.0
100	5.5
180	10

To convert mg/dL to mmol/L, divide by 18 or multiply by 0.055. To convert mmol/L to mg/dL, multiply by 18.

(*Appendix continues* →)

Appendix A2. Algorithm



Blood Glucose mg/dL (& mmol/L)

< 20-25 mg/dL (<1.1-1.4 mmol/L) OR glucose < 45 & serious signs e.g. apnea, seizures, impaired consciousness	25-34 mg/dL (1.4-1.9 mmol/L)	35-45 mg/dL (2.0-2.5 mmol/L) without signs	>45 mg/dL (2.5 mmol/L)
IV Treatment Apply glucose gel if delay in establishing IV	**Breastfeeding Supplementary Feeding**	**Breastfeeding Supplementary Feeding**	**Breastfeeding Supplementary Feeding**
-Insert IV -IV bolus (1-2 mL/kg D10W) -Continuous drip D10W 5-8 mg/kg/min -Target Glu 45-54 (2.5-3.0) -Breastfeed or supplemental feed as tolerated	-Apply glucose gel -Intensify breastfeeding or supplemental feeding -If < 25 (1.4) at next check, may repeat glucose gel X 1 -consider IV glucose -If ongoing IV glucose, increase rate	-Apply glucose gel -Intensify breastfeeding or supplemental feeding -If < 35 (2.0) at next check, may repeat glucose gel X 1 -Consider IV glucose -If 35-45 (2.0-2.5) at next check, refeed	-Continue breast or supplementary feeding -Recheck until 3 normal AC glucoses -Target > 54 (3.0) -Consider glucose check at 24 hours of age for SGA or LBW infants
Recheck plasma glucose within 30 min.	**Recheck plasma glucose in ½ to 1 h**	**Recheck plasma glucose in 1-2 h**	**Increase intervals for glucose recheck**
If persistent (>72 h) or severe (>10-12 mg/kg/min) glucose requirement, further investigation required.	**Glucose Gel:** Concentration: 400 mg/mL Dose: 0.5 ml/kg Application: Dry infant's mouth. Massage gel into buccal mucosa.		Adapted from Swedish National Guideline, 2020, Reference # 78

(*Appendix continues* →)

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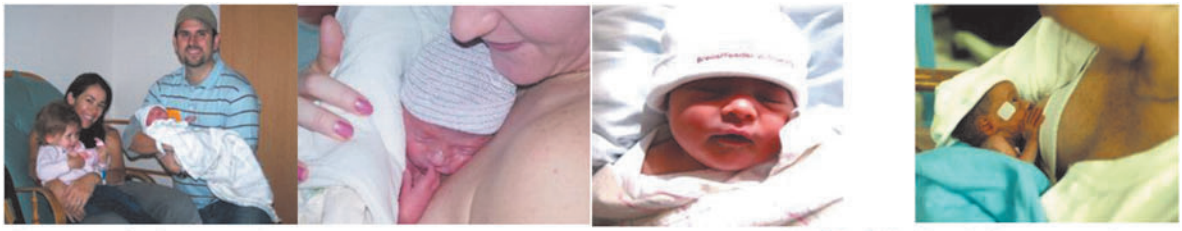
Appendix A3



Parent Information **ABM Clinical Protocols**

Newborn Hypoglycemia

What is newborn hypoglycemia?

Hypoglycemia is a condition that results from a low blood glucose (sugar) level. It is often self-limited and commonly seen during the first 2-3 hours in healthy infants after birth.

Is hypoglycemia harmful to your baby?

Normal blood glucose levels are required for healthy brain, muscle and other organ function. Severe or persistent low blood glucose levels can damage your baby's brain. Babies who are known to be at risk of developing low blood glucose will receive prompt testing. Appropriate treatment and close monitoring will reduce the chance of any harm to your baby.

Are some babies more likely to get hypoglycemia than others?

Approximately two out of 1,000 babies have hypoglycemia. Babies are more likely to become hypoglycemic if their:

- birth weight is less than 2,500 grams (5.5 lbs)
- birth weight is greater than 4,500 grams (10 lbs) in mothers not tested for diabetes
- mother has diabetes (Type 1, 2 or gestational)
- mother suffers from obesity
- body is under stress, such as requiring resuscitation at birth or being cold (low body temperature); stress causes a baby's body to use more glucose

Or they are:

- not feeding well
- born premature (before 37 weeks)
- too small for their gestational age
- sick or unwell (e.g. babies with an infection)
- born with a health problem known to cause low blood glucose (e.g. liver disease, birth defects, congenital metabolic diseases)

This information sheet aims to answer some commonly asked questions about newborn hypoglycemia.

IMPORTANT: This is general information only. Ask your health care provider about what care is right for you and your baby.

How do you know if your baby has hypoglycemia?

Your baby may show some visible signs of hypoglycemia. However, this varies with every baby and some babies *may have no signs*. A baby with low blood glucose may show any of the following:

- not feeding well
- a weak or high-pitched cry
- jitteriness or tremors
- skin that is cool to the touch
- sweating
- pale or bluish skin color
- breathing very fast
- being weak with limp arms and legs
- irritability or seizures (fits)

How is hypoglycemia in the newborn diagnosed?

If your baby has any of the above signs, or is at risk of having low blood glucose, a simple blood test can diagnose hypoglycemia. A drop of blood may be drawn from a heel stick, or with a needle from the baby's arm.

What is the treatment for hypoglycemia?

Specific treatment for hypoglycemia will be determined by your baby's health care provider based on:

- detailed medical history
- complete physical examination
- initial lab testing

Treatment for hypoglycemia depends on how low your baby's blood glucose is and how well your baby is feeding. In some cases, frequent feeding is enough to improve your baby's blood glucose level. In other cases, your baby may be given:

- extra expressed breastmilk, pasteurized donor human milk, or infant formula (with your permission)
- glucose gel rubbed into your baby's mouth
- intravenous glucose

(*Appendix continues* →)

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If the blood glucose level is extremely low, your baby is unwell or the blood glucose does not improve after feeding, glucose may need to be given directly through a drip into a baby's vein. In some situations, your baby may require specialist care in a special care nursery and/or neonatal intensive care unit. If your hospital cannot provide this specialist care, your baby may be transferred to another hospital.

Testing and monitoring of your baby's blood glucose levels will continue until your baby is feeding well and the blood glucose results are within a healthy range.

What can be done to prevent hypoglycemia?

During the pregnancy, the fetus gets a steady stream of glucose through the umbilical cord from the mother. After birth newborn babies need to adjust to life outside the uterus. Maintaining a healthy blood glucose level with intermittent feeding is part of this change. To reduce the risk of your baby becoming hypoglycemic it is important to:

- maintain the blood glucose of mothers with diabetes in tight control, to lower fetal insulin secretion
- keep your baby warm, particularly immediately after birth
- hold your baby skin-to-skin as soon as possible after birth as your and your baby's conditions permit
- feed your baby shortly after birth (within 30-60 minutes)
- keep you and your baby together as much as possible, to encourage frequent feeding
- offer feeds at least every 3 hours or more frequently to babies who are at increased risk of hypoglycemia

Can you still breastfeed if your baby has hypoglycemia?

Yes. When your baby has low glucose levels it does not mean there is anything wrong with your breastmilk. Breastfeeding early and often helps your baby maintain healthy blood glucose levels. If your baby is not feeding well or is unwell, it is particularly important to express your breastmilk frequently by hand, breast pump or both. This milk can be given to your baby until your baby is ready to breastfeed.

What causes ongoing hypoglycemia?

Hypoglycemia with treatment usually only lasts from a few hours to a few days. However, hypoglycemia that continues beyond 3 days may be caused by conditions that:

- Lower the amount of glucose in the blood stream (as in too much insulin production by the baby's pancreas)
- Prevent or reduce the storage of glucose
- Use up glucose stored in the liver (glycogen stores)
- Stop or delay the use of glucose by the body

These conditions are rare. If hypoglycemia continues and continued treatment is needed, your health care provider will discuss further investigations and treatment options with you.

Your baby may need specialist consultation and more extensive testing to figure out the exact cause of the hypoglycemia.

This parent information handout was adapted from Queensland Health, Australia, 2018 Clinical Guidelines and the British Association of Perinatal Medicine's Framework for Practice, 2017.

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