Neonatal Hypoglycemia

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Education Gap

The differences between transitional and pathologic hypoglycemia of the newborn may be difficult to discern. In addition, clinicians are faced with 2 sets of recommendations from professional societies for the evaluation and treatment of these conditions. To make valid practice decisions, clinicians should understand the evidence and the limitations of the recommendations of the Pediatric Endocrine Society and the American Academy of Pediatrics in the evaluation and management of neonatal hypoglycemia.

Objectives After completing this article, readers should be able to:

1. Describe transitional hypoglycemia of the newborn.
2. Review the differential diagnosis, diagnostic evaluation, and management of neonatal hypoglycemia.
3. Provide a framework to understand the nuances of the recommendations from the Pediatric Endocrine Society and the American Academy of Pediatrics for the evaluation and management of neonatal hypoglycemia.

Abstract

Lower blood glucose values are common in the healthy neonate immediately after birth as compared to older infants, children, and adults. These transiently lower glucose values improve and reach normal ranges within hours after birth. Such transitional hypoglycemia is common in the healthy newborn. A minority of neonates experience a more prolonged and severe hypoglycemia, usually associated with specific risk factors and possibly a congenital hypoglycemia syndrome. Despite the lack of a specific blood glucose value that defines hypoglycemia, concern for substantial neurologic morbidity in the neonatal population has led to the generation of guidelines by both the American Academy of Pediatrics (AAP) and the Pediatric Endocrine Society (PES). Similarities between the 2 guidelines include recognition that the transitional form of neonatal hypoglycemia likely resolves within 48 hours after birth and that hypoglycemia that persists beyond that duration may be pathologic. One

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ABBREVIATIONS

AAP	American Academy of Pediatrics
IDM	infant of a diabetic mother
IUGR	intrauterine growth restriction
IV	intravenous
LGA	large for gestational age
PES	Pediatric Endocrine Society
SGA	small for gestational age

major difference between the 2 sets of guidelines is the goal blood glucose value in the neonate. This article reviews transitional and pathologic hypoglycemia in the neonate and presents a framework for understanding the nuances of the AAP and PES guidelines for neonatal hypoglycemia.

INTRODUCTION

Glucose provides metabolic fuel for the developing fetus. While in utero, the fetus receives a steady supply of glucose from its mother via facilitated diffusion across the placenta and produces its own insulin to permit euglycemia. Postnatally, the constant supply of glucose ceases and neonatal concentrations of insulin must be regulated. Lower blood glucose values are commonly seen in the healthy neonatal population in the first 24 to 48 postnatal hours as compared to values in the older child and adult populations. (1)(2)(3) These lower blood glucose values early after birth are observed in all mammals, leading to the conclusion that they may represent an evolutionary adaptation to early life outside the womb. (4) The lower values may be transitional and nonpathologic, occurring as the fetus acclimates to postnatal life while establishing a source of metabolic fuel. (4)(5)

The brain primarily uses glucose to meet its metabolic demands. The healthy newborn requires a higher glucose infusion rate (the rate at which glucose is made available to the body) that is up to 2 to 3 times more per kilogram of weight than that seen in adults because of the proportionally larger brain-to–body mass ratio of infants. (6) Accordingly, newborns need to maintain regular and more frequent feedings by the first few days after birth. Any inability to procure, take in, and metabolize feedings at a rate that supports the production and maintenance of standard blood glucose concentrations may lead to hypoglycemia that is severe and persistent in the newborn. Severe and prolonged hypoglycemia in the neonatal population may be associated with seizure activity and abnormal neurologic outcomes, although it is unclear at what specific values of blood glucose these metabolic aberrations occur and after how long a duration of hypoglycemia. (7)(8)(9)(10)

Despite the lack of clear evidence, the concern for severe neurologic sequelae has led to empirical screening recommendations to maximize detection and treatment of neonates with hypoglycemia. The algorithm selects those infants with particular risk factors for early hypoglycemia to be screened shortly after birth. The threshold for blood glucose that prompts concern, which is currently less than 47 mg/dL (2.61 mmol/L), is based on very limited observational evidence. Some infants with congenital disorders who may present with severe and persistent hypoglycemia may not have risk factors and, therefore, are not selected for initial screening. Hence, when they come to clinical attention, these infants may be in extremis. In addition, many of those screened are without symptoms even if they meet the current criteria for neonatal hypoglycemia and, thus, may be overtreated, adding to medical costs and separation from family, among other concerns.

This review is targeted to general pediatric clinicians and is designed to enhance their understanding of normal glucose homeostasis and the epidemiology and pathophysiology of neonatal hypoglycemia, with a focus on transitional hypoglycemia. We review screening criteria, the diagnostic assessment and management in the neonatal population, and the recognition and evaluation of persistent hypoglycemia. We also review the guidelines from the Pediatric Endocrine Society (PES) and the American Academy of Pediatrics (AAP) and compare and contrast the 2 sets of recommendations. (11)(12)

PHYSIOLOGY OF GLUCOSE HOMEOSTASIS

The brain does not have glucose or other metabolic fuel stores and, therefore, is dependent on a constant supply of glucose, usually achieved by the intake of enteral feedings. Hence, glucose is the primary metabolic fuel for the brain. However, in instances of prolonged starvation, the liver produces ketone bodies, which are partly able to produce fuel for the brain's metabolism; lactate may also be used for fuel. (13) Other tissues can use free fatty acids and ketone bodies as well as store glycogen. (14) Hence, when glucose supplies are low and ketone body production is negligible or inefficient, as with recently born infants and those with inborn errors of metabolism or other congenital reasons for hypoglycemia, severe and prolonged hypoglycemia may be associated with central nervous system symptoms.

Insulin and glucagon are the most important hormones in the immediate feedback control of glucose. When blood

glucose concentrations increase after a meal, insulin secretion increases, which stimulates the liver to store glucose as glycogen (Fig 1). As liver and muscle cells become saturated with glycogen, additional glucose is stored as fat. When blood glucose concentrations decrease, glucagon secretion causes an increase in blood glucose by stimulating the liver to undergo glycogenolysis to release glucose back into the bloodstream. In times of starvation, the liver maintains a normal glucose concentration via the process of gluconeogenesis, forming glucose from amino acids and the glycerol portion of fat. Muscle cells provide glycogen stores as well as protein to be broken down to amino acids, which are then used as substrates for gluconeogenesis in the liver. Fatty acids are catabolized to ketones, acetoacetate, and β-hydroxybutyrate and used as fuel by most tissues, including the brain. The hypothalamus stimulates the sympathetic nervous system, causing secretion of epinephrine by the adrenal glands. This permits additional release of glucose from the liver. With prolonged and sustained hypoglycemia, growth hormone and cortisol are secreted, thus decreasing the rate of glucose utilization by the body. (14)(15)

In the newborn, serum glucose values decline for 2 to 3 hours after birth, then spontaneously increase and are maintained with regular feedings. (3)(16) Liver glycogen stores are rapidly depleted within hours of birth in an attempt to maintain euglycemia, with gluconeogenesis accounting for approximately 10% of the source of glucose in the newborn by several hours of age. (5)(17) Newly born infants who have transitional hypoglycemia are generally inefficient at producing ketones, have lower amounts of free fatty acids to use as an alternate fuel source, are relatively hyperinsulinemic compared to older individuals due to incomplete suppression of insulin (immaturity in β-cell gene expression and regulation), and inappropriately retain their limited glycogen stores in the face of hypoglycemia. (5)(18)(19)(20)(21)

EPIDEMIOLOGY AND VARIATION IN THE DEFINITION OF NEONATAL HYPOGLYCEMIA

"Hypoglycemia" may occur in up to 10% of healthy term newborns, especially in the first 24 to 48 hours after birth. (1)(22) The definition of hypoglycemia varies because a single

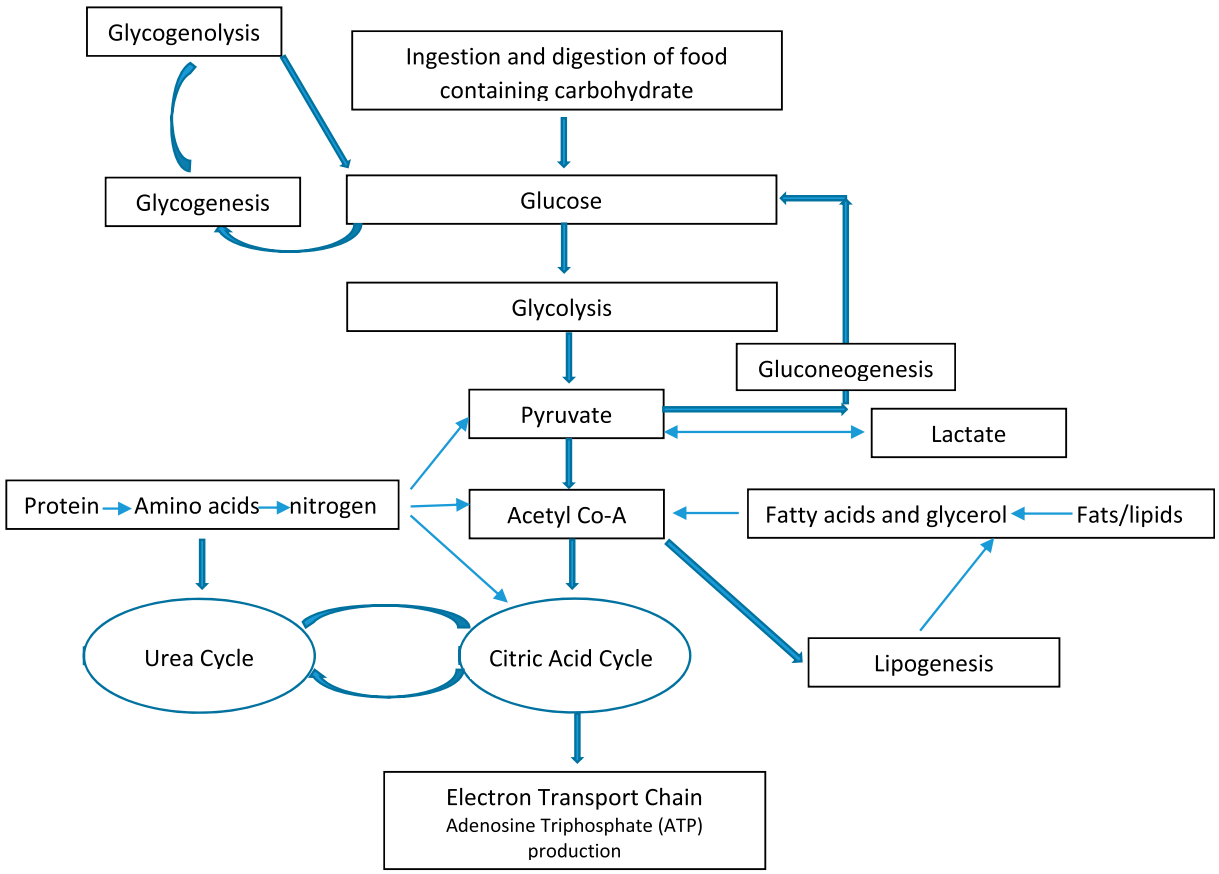

Figure 1. Glucose homeostasis. Co-A=coenzyme A.

specific glucose value does not inherently indicate symptomatology in the patient. (2)(3)(10) Blood glucose values may be as low as 30 mg/dL (1.67 mmol/L) in the first 1 to 2 hours after birth in healthy term neonates, rising to values similar to adults within 48 to 72 hours with established feeding cycles. (1) Many infants who have "low" blood glucose values are without risk factors and are clinically asymptomatic. Others exhibit poor feeding or have longer intervals without substantial feedings but are clinically asymptomatic or do not exhibit hypoglycemia. These findings point to an incomplete understanding of the mechanisms of blood glucose regulation in the newly born infant.

Currently there is ongoing discussion between the AAP and PES regarding the management of hypoglycemia, including the blood glucose values that should prompt concern, particularly after 48 hours of age (Fig 2). (11)(12) The AAP concedes that the current "definition" of neonatal hypoglycemia (blood glucose <47 mg/dL [2.61 mmol/L]) is based on an observational study of preterm infants weighing less than 1,850 g who had asymptomatic hypoglycemia occurring multiple times during their neonatal intensive care course. (23) These infants had impaired neurodevelopment at age 18 months. However, a follow-up study of the children at age 15 years did not document the initial neurodevelopmental outcome differences seen in the initial study. (24) Per recent PES recommendations, a blood glucose value of less than 50 mg/dL (2.77 mmol/L) in the first 48 hours after birth is being suggested as the threshold for neonatal hypoglycemia. (11) In addition, the PES endorses a threshold of 60 mg/dL (3.33 mmol/L) in the first 48 hours if there is concern for a congenital hypoglycemia disorder. Such thresholds are based on the thresholds for observation of symptoms in older children and adults and are not specific to neonates. However, transitional neonatal hypoglycemia likely reflects a state of peripartum adaptation, and affected infants are likely not at risk for a congenital hypoglycemia disorder. These higher thresholds of blood glucose values increase concerns for overtreatment, especially in asymptomatic neonates.

RISK FACTORS FOR NEONATAL HYPOGLYCEMIA

The underlying physiologic mechanisms leading to hypoglycemia in neonates include low hepatic glycogen stores, inadequate muscle stores as a source of amino acids to be used for gluconeogenesis, and inadequate lipid stores as a source of fatty acids. (5)(18) Other serious causes of persistent hypoglycemia include inappropriate secretion of insulin; hypopituitarism; cortisol deficiency; growth hormone deficiency; and inborn errors of metabolism affecting glucose, glycogen, and fatty acids (Table). (25)(26)(27)(28)

Of note, intrauterine growth restriction (IUGR) and small for gestational age (SGA) are common conditions that pose similar risks for neonatal hypoglycemia. The fetus that experiences IUGR fails to establish its growth potential due to in utero environmental or genetic causes. The SGA infant at birth measures below the statistical 10th or 3rd percentile for gestational age or more than 2 standard deviations below the mean for gestational age, depending on the definition used. Many fetuses that experience IUGR are not actually SGA at birth, and many SGA infants may not have a pathologic reason for their smallness. However, both of these sets of neonates may be predisposed to neonatal hypoglycemia due to inadequate glycogen and substrate sources for gluconeogenesis. They may also have genetic predispositions to hypoglycemia, such as hyperinsulinism, growth hormone or cortisol deficiency, and inborn errors of metabolism.

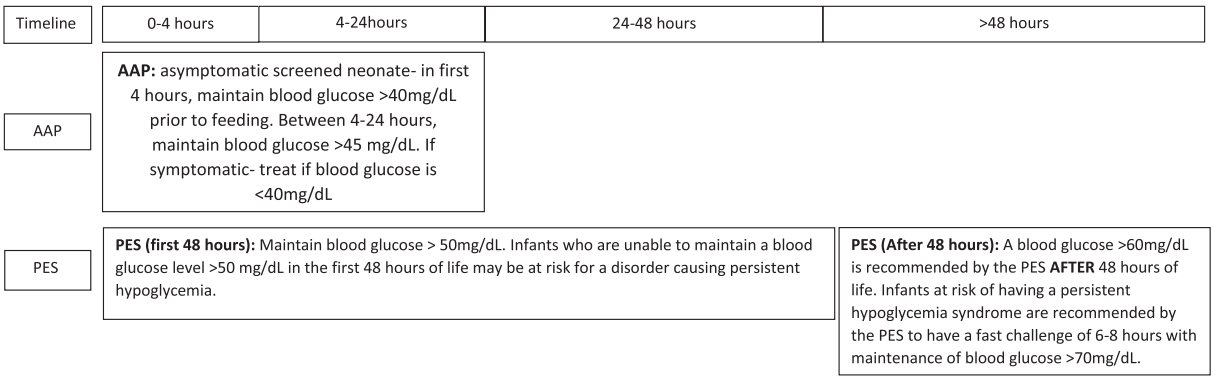

Figure 2. Pediatric Endocrine Society (PES) and American Academy of Pediatrics (AAP) neonatal hypoglycemia guidelines in the first 48 hours after birth and beyond.

TABLE. **Causes of Neonatal Hypoglycemia**

PHYSIOLOGIC MECHANISM	DISORDER
Inadequate glycogen stores and inadequate substrate source for gluconeogenesis	• Prematurity • Small for gestational age • Intrauterine growth restriction • Perinatal stress (sepsis, asphyxia) • Polycythemia
Hyperinsulinism	• Infant of diabetic mother • Beckwith-Wiedemann syndrome • Soto syndrome • Congenital hyperinsulinism
Growth hormone deficiency	• Turner mosaicism • Costello syndrome • Hypopituitarism
Cortisol deficiency	• Costello syndrome • Hypopituitarism • Congenital adrenal hyperplasia
Inborn errors of metabolism	
• Amino acid abnormalities	• Maple syrup urine disease
• Glycogen	• Hepatic glycogen storage diseases
• Glucose	• Hereditary fructose intolerance
• Fatty acids	• Galactosemia • Medium-chain acyl-coenzyme A dehydrogenase deficiency • Short-chain acyl-coenzyme A dehydrogenase deficiency • Carnitine palmitoyltransferase deficiency types I and II • Long-chain 3-hydroxy and very long-chain acyl-coenzyme A dehydrogenase deficiency

SIGNS AND SYMPTOMS OF HYPOGLYCEMIA IN NEONATES

Symptoms of hypoglycemia are categorized as neurogenic (adrenergic) or neuroglycopenic. Neurogenic signs and symptoms originate from activation of the sympathetic nervous system in response to hypoglycemia, and neuroglycopenic signs and symptoms derive from central nervous system deprivation of glucose. (11) Neurogenic/adrenergic signs and symptoms present earlier, at a higher value of blood glucose, compared to neuroglycopenic symptoms. These include sweating, pallor, temperature instability, irritability, hunger, tremulousness, tachycardia, and vomiting. Neuroglycopenic signs and symptoms include apnea, hypotonia, seizure, and coma that may progress to death if a source of glucose is not established. (29)

SCREENING

Screening is currently based on risk factors (Table) and/or the presence of symptoms concerning for hypoglycemia. Of note, the diagnosis and definition of maternal gestational diabetes has also been debated in recent years. Adjustment in maternal blood glucose cutoff values by just a few points in either direction changes the incidence of gestational diabetes, thereby changing the numbers of infants who are subsequently screened for hypoglycemia shortly after birth. Currently, between 6% and 7% of pregnancies are affected by gestational diabetes, using American College of Obstetricians and Gynecologists guidelines, (30) which reference the cutoffs generated by the National Diabetes Data Group and criteria by Coustan and Carpenter, recommending that practitioners choose 1 or the other set of guidelines for consistent use in their practice based on their patient population. In addition, the American Diabetes Association produced guidelines in which blood glucose values for detection of gestational diabetes are lower and, therefore, many more women would be diagnosed (approximately 18% of pregnant women) without an apparent improvement in clinical outcomes but with increased cost. (31)(32)

GUIDELINES

AAP

Per the most recent AAP guidelines, published in 2011, screening is recommended for 2 groups of infants: term and late preterm infants who are symptomatic and infants who are asymptomatic but have risk factors. The goal is to have blood glucose values of 45 mg/dL (2.5 mmol/L) or greater prior to a feeding. Infants of diabetic mothers (IDMs) and large-for-gestational age (LGA) infants are screened for 12 hours after birth; SGA and preterm infants are screened for the first 24 hours. (12)

PES

Within the first 48 hours of birth, the PES suggests that infants with an inability to maintain blood glucose values greater than 50 mg/dL (2.77 mmol/L) are at risk for persistent hypoglycemia, a value greater than that suggested by the AAP. The 50-mg/dL (2.77-mmol/L) value appears to be closely related to the 55- to 65-mg/dL (3.05- to 3.61-mmol/L) range of blood glucose, where experts believe that insulin suppression begins in neonates shortly after birth. In recommending which neonates to screen, the PES guidelines begin with identifying those at risk of persistent hypoglycemia at more than 48 hours after birth to exclude infants who simply are experiencing transitional hypoglycemia. After age 48 hours, the PES recommends maintaining blood glucose at greater than 60 mg/dL (3.33 mmol/L). Of note, for most stable infants of women who deliver vaginally, routine discharge may occur before age 48 hours. The recommendation to maintain a blood glucose of greater than 60 mg/dL (3.33 mmol/L) after age 48 hours in a patient who was identified as being at risk and was being monitored poses an issue. Strict adherence to this recommendation may increase lengths of stay and medical costs for the average patient with neonatal hypoglycemia without definitive evidence of benefit.

For neonates at higher risk for persistent hypoglycemia syndrome, the PES recommends maintaining a glucose value greater than 70 mg/dL (3.89 mmol/L) after a 6- to 8-hour fast. (11)(18) A newborn older than age 48 hours who fails to maintain a blood glucose value greater than 60 mg/dL (3.33 mmol/L) or a value greater than 70 mg/dL (3.89 mmol/L) after a 6- to 8-hour fast should be recognized as potentially at risk of having a syndrome causing persistent hypoglycemia, according to the PES.

Infants with hyperinsulinism may not initially be screened if they are without known risk factors and, therefore, may be recognized only after the emergence of symptomatology that may be severe. If this occurs after approximately age 48 hours, when the average patient born via vaginal delivery is discharged, the detection likely hinges on an astute caregiver or sufficiently severe symptoms to warrant medical attention. Because the current screening guidelines are for newborns still admitted to the hospital, infants with congenital hypoglycemia without the usual risk factors may be missed, at least early.

Despite screening guidelines, the challenge of managing asymptomatic neonates with "low" blood glucose values is fraught with concerns of possible over- and undertreatment. The AAP focuses on the transitional hypoglycemia occurring in the first 24 hours after birth and offers guidance for screening infants with symptoms or risk factors. The PES focuses on the period subsequent to age 48 hours, when hypoglycemia, as defined by a blood glucose value less than 60 mg/dL (3.33 mmol/L), portends a higher likelihood of a disorder causing persistent hypoglycemia and may require further testing.

TEST CHARACTERISTICS

Established differences exist in blood glucose values based on whether the sample is arterial, venous, or capillary, with the arterial sample measuring a higher glucose concentration. Plasma versus whole blood sampling also produces varying results, with plasma having a 10% to 12% higher glucose concentration. (33) Current point-of-care bedside devices provide a more rapid screening of whole blood glucose concentrations, with results confirmed via a plasma sample sent to a laboratory if concern exists. However, an accurate glucose measurement requires adequate tissue perfusion. Higher hematocrit produces a reduction in the blood glucose value measured. (34) In addition, there may be up to a 15% difference between results of the point-of-care device and laboratory analysis, usually an overestimation of blood glucose from a point-of-care device, possibly leading to lack of recognition of a hypoglycemic condition and resultant undertreatment. (35) At lower blood glucose values, point-of-care device measurements become less precise.

Variations in blood glucose results also can result from the amount of time between sample collection and analysis due to glycolysis from red blood cell metabolism. Delays in analysis or processing of the specimen should be avoided because they may lead to underestimation of the glucose value. (36) However, if the blood collection tube contains a glycolytic inhibitor, this artifactual low blood glucose result can be mitigated or prevented. (37) Hence, when clinicians are concerned for clinical or symptomatic hypoglycemia, an

abnormally low point-of-care blood glucose screening result should always be confirmed with a plasma sample, and the plasma specimen should always be requested to be processed as quickly as possible, without delaying treatment while awaiting results. With the sicker population in the ICU, the potential benefit of a more rapid assessment of blood glucose via a point-of-care device must be balanced with an understanding of the factors that affect interpretation of the results.

DIAGNOSIS

The diagnostic evaluation for neonatal hypoglycemia includes plasma confirmation of a low blood glucose value, especially if symptoms are present. Simultaneously, clinicians should measure insulin to assess for hyperinsulinism, cortisol for cortisol deficiency, and growth hormone for growth hormone deficiency. (38) C-peptide is a byproduct of the metabolism of insulin in the human body and is absent in cases where insulin is exogenously administered. It is not routinely measured in the hypoglycemic newborn in the first several days after birth. However, such assessment should be considered in any patient, newborn or otherwise, who is suspected to have inappropriate administration of exogenous insulin. An assessment of the mother's milk supply and infant's feeding ability and pattern is essential, as is recognition of LGA, SGA, IDM, and preterm status. A history of any peripartum stress should also be noted because it could potentially be a risk factor for hypoglycemia. Additional diagnostic evaluations may include assessment for polycythemia, infection, and perinatal asphyxia. An endocrine consultation is warranted if the hypoglycemia is severe, prolonged, or recurrent or lasts greater than 48 hours. (11) Further laboratory assessments that may be suggested by an endocrine consultation to evaluate for persistent or severe hypoglycemia include lactic acid, ammonia, urinary ketones, hydroxybutyrate, free fatty acids, acylcarnitine profile, plasma amino acids, and urine organic acids. (39) A consultation from a metabolic specialist may also be appropriate because inborn errors of metabolism should be considered if hypoglycemia persists despite standard treatment. In neonates at risk for a disorder causing persistent hypoglycemia in whom hypoglycemia remains at or beyond age 48 hours, the PES recommends a fasting challenge of 6 to 8 hours, with maintenance of blood glucose greater than 70 mg/dL (3.89 mmol/L), so as not to be confounded by the period of transitional hypoglycemia that is common in newborns.

TREATMENT

Treatment for the transitional form of neonatal hypoglycemia depends on the presence or absence of hypoglycemia symptoms, adequacy of human milk supply, and the infant's ability to nurse or feed via a bottle. Newborns with risk factors for hypoglycemia should be offered oral feedings within 1 hour of birth and before blood glucose is measured. (12) Breastfeeding support is crucial for those mothers who wish to exclusively breastfeed, coupled with an assessment of milk supply and the infant's ability to latch and nurse effectively. (40)(41)(42) A source of glucose must be established with regular feedings every 2 to 3 hours via breastfeeding or formula. If hypoglycemia continues, intravenous (IV) fluids containing dextrose should be administered.

Per the most recent AAP guidelines in 2011, any symptomatic newborn with a blood glucose measuring less than 40 mg/dL (2.22 mmol/L) should receive IV dextrose. If the at-risk newborn is asymptomatic and less than 4 hours old but blood glucose is less than 25 mg/dL (1.39 mmol/L) after a first feeding within 1 hour of birth, IV dextrose is administered. If the glucose measures more than 25 mg/dL (1.39 mmol/L) but less than 40 mg/dL (2.22 mmol/L), the infant can be fed again and blood glucose assessed 30 minutes after the feeding. If the at-risk but asymptomatic newborn is 4 to 24 hours old and the blood glucose screening result is less than 35 mg/dL (1.94 mmol/L), feedings should be administered every 2 to 3 hours, although IV glucose may be administered at this point as well. If the blood glucose measures 35 to 45 mg/dL (1.94-2.50 mmol/L), feedings may continue or IV glucose may be administered as needed. (12) Dextrose-containing fluids are usually administered in a special care nursery or ICU. The dextrose solution is gradually weaned until glucose values are maintained in a "normal" range with enteral feedings and symptoms are absent. Another treatment option is dextrose gel administered orally, which may allow the infant to remain with his or her mother rather than being admitted to a higher-level nursery. Such treatment has not been associated with adverse outcomes. (43)(44)

There are several additional treatment options for infants with more severe hypoglycemia. (45) The glucocorticoids dexamethasone and hydrocortisone enhance gluconeogenesis in the liver and reduce insulin sensitivity. (46) Glucagon acts on the liver to convert stores of glycogen to glucose and is useful for severe cases of neonatal hypoglycemia. (47) Diazoxide and octreotide decrease pancreatic insulin secretion and are usually reserved for more severe and refractory cases of neonatal hypoglycemia. (48)(49)(50) Nifedipine

reduces glucose tolerance and insulin secretion. (51)(52) Infants who have congenital neonatal hypoglycemia, depending on the cause, may require long-term treatment with cortisol, growth hormone, and special formulas or diets for those who have inborn errors of metabolism. Pancreatic resection is performed for infants with persistent hyperinsulinemic hypoglycemia of infancy who are resistant to medications. (53)(54)

OUTCOMES

The most concerning outcomes of neonatal hypoglycemia are seizures that may progress to coma and death or development of severe neurodevelopmental abnormalities. (7)(55)(56)(57) These outcomes can be seen with severe and persistent hypoglycemia but are usually infrequent with the transient form of neonatal hypoglycemia. (28)(58)(59)(60) However, the transient form of neonatal hypoglycemia may be difficult to differentiate at the onset of presentation. Overtreatment of neonatal patients with hypoglycemia may increase the risk of rebound hypoglycemia due to further activation of insulin from the dextrose provided during treatment. Other outcomes include NICU or special care nursery admission, both concerning for increased costs and the effect of the infant's separation from its family, particularly a mother who may be breastfeeding. (61)(62) In addition, results from the McKinlay follow-up trial in 2015 suggest that hypoglycemic infants who were treated and had later neurodevelopmental impairment had a steeper increase in their interstitial glucose measurements and higher glucose concentrations for 12 hours after birth compared to those without impairment. (7) This finding heightens concerns for overtreatment and a potential risk of adversely affecting development, albeit unintentionally.

Institutions may have varying policies and practices regarding where blood glucose screening physically occurs for well-appearing newborns. The screening may occur in the labor and delivery suite or in the newborn nursery. When possible, care should be taken to avoid separating mothers from infants, especially asymptomatic neonates who are simply being screened.

PREVENTION

Prevention of neonatal hypoglycemia includes prompt identification of at-risk neonates, initiation of early feeding, and provision of breastfeeding support. In addition, observation of symptoms attributable to hypoglycemia should prompt an urgent evaluation and the initiation of treatment to prevent the central nervous system effects of hypoglycemia.

FUTURE DIRECTIONS

Future research efforts should be aimed at clarifying the relationship between blood glucose concentrations and adverse neurologic outcomes. In the *Sugar Babies* follow-up study at 2 years, similar rates of neurodevelopment abnormalities were observed in hypoglycemic neonates receiving the treatment of dextrose gel and placebo groups (both groups allowed to feed). (63) In addition, although severe and prolonged hypoglycemia in the neonatal period clearly portends worse neurologic outcomes, the depth of the hypoglycemia as well as the duration and frequency of these events remain relatively unexplored in terms of their respective contributions to this serious morbidity. The McKinlay trial in 2015 attempted to answer this question by assessing the relationship between duration, frequency, and severity of neonatal hypoglycemia and neurosensory and processing impairment at 2 years. (7) They found that the risk of impairment was not increased in infants with hypoglycemia who were treated to maintain blood glucose of 47 mg/dL (2.61 mmol/L) or greater compared to infants without hypoglycemia. This finding of a lack of increased risk included children with multiple hypoglycemic episodes, hypoglycemic episodes on multiple days, and severe hypoglycemia. Further investigation is needed to identify protective features in those infants who do not exhibit symptoms despite having "low" blood glucose.

CONCLUSION

Transient neonatal hypoglycemia is a common phenomenon in the 48 hours after birth in healthy term infants and may be an evolutionary adaptation, as this is observed in all mammalian species. However, severe and prolonged hypoglycemia may lead to symptoms that include coma and death, although this is uncommon with the transient neonatal form. Symptoms of hypoglycemia, especially in the neonate, are associated with inconsistent blood glucose values, thus making a laboratory definition of "neonatal hypoglycemia" not possible. Currently, the AAP and the PES have slightly varying recommendations in their management and definition of neonatal hypoglycemia, particularly the blood glucose values that should be achieved after ages 24 to 48 hours and the need for a fasting challenge before hospital discharge. The AAP focuses on the screening and management of the at-risk or symptomatic infant in the first 24 hours, likely the transient form of hypoglycemia, while the PES addresses the period after 48 hours, when cases of congenital hypoglycemia are more likely.

Summary

- On the basis of well-designed studies with minor limitations (level of evidence B), newborn infants have lower blood glucose values in the first hours after birth compared to older children and adults. These lower values spontaneously increase in most infants after 2 to 3 hours. (3)
- On the basis of well-designed studies with minor limitations (level of evidence B), transitional hypoglycemia is common in up to 10% of newborns and may be an adaptation to postnatal life. This period of transitional glucose adaptation usually lasts approximately 24 hours. (1)(3)(5)
- On the basis of observational data (level of evidence C), currently there is a wide range of blood glucose values at which symptoms may be evident. (7)(8)(9)(10) However, because of concern for serious neurologic impairment, screening and management guidelines are generated for infants at risk and those with symptoms that may be attributable to hypoglycemia. (11)(12)
- On the basis of a lower level of evidence (C and D) and data from observational studies and expert opinion, the Pediatric Endocrine Society (PES) and the American Academy of Pediatrics (AAP) have guidelines to address neonatal hypoglycemia. Both endorse that hypoglycemia persisting beyond age 24 to 48 hours is not likely to be simply transitional. However, the guidelines differ in the values of blood glucose that trigger concern. Per the PES, in the first 48 hours after birth, a blood glucose value of 50 mg/dL (2.77 mmol/L) or less is suggested as abnormal. Per the AAP, a lower blood glucose value, ranging from 25 to 45 mg/dL (1.39-2.50 mmol/L) in the first 4 to 24 hours after birth, should prompt a treatment strategy that includes provision of enteral feedings and/or intravenous dextrose solution and continued blood glucose monitoring. (11)(12)
- On the basis of a lower level of evidence for the newborn population (level D) and expert opinion, the PES recommends a fasting challenge of 6 to 8 hours with maintenance of blood glucose greater than 70 mg/dL (3.89 mmol/L) if hypoglycemia persists beyond 48 hours in neonates at risk for a disorder causing persistent hypoglycemia. (11)
- On the basis of observational data and expert opinion (level of evidence C and D), the PES guidelines recommend blood glucose greater than 60 mg/dL (3.33 mmol/L) at more than 48 hours after birth for infants with the transitional form of hypoglycemia. (11) The AAP recommends maintenance of blood glucose at greater than 45 mg/dL (2.50 mmol/L) by age 24 hours. (12)

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References for this article are at http://pedsinreview.aappublications.org/content/38/4/147.

Additional Resources for Pediatricians

AAP Textbook of Pediatric Care, 2nd Edition

- Chapter 105: Transient Metabolic Disturbances in the Newborn: https://pediatriccare.solutions.aap.org/chapter.aspx?sectionid=106692104&bookid=1626

Point-of-Care Quick Reference

- Hypoglycemia: https://pediatriccare.solutions.aap.org/Content.aspx?gbosid=165598

Parent Resources from the AAP at HealthyChildren.org

- Causes of High Blood Glucose and Low Blood Glucose: https://www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Causes-of-High-Blood-Glucose-and-Low-Blood-Glucose.aspx

For a comprehensive library of AAP parent handouts, please go to the *Pediatric Patient Education* site at http://patiented.aap.org.

PIR Quiz

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1. Individual CME quizzes are available via a handy blue CME link under the article title in the Table of Contents of any issue.
2. To access all CME articles, click "Journal CME" from Gateway's orange main menu or go directly to: http://www.aappublications.org/content/journal-cme.

1. A 35-weeks pregnant woman comes to your office for a prenatal visit. She is a dietitian and has questions regarding fetal physiology in glucose metabolism. Which of the following is accurate regarding glucose use in the fetus?
    A. Because healthy newborn infants do not exhibit lower levels of glucose, if this occurs in the first 24 hours after birth, it is always pathologic.
    B. Insulin is transferred across the placenta via active transport due to its large molecular size.
    C. Lower levels of blood glucose may be considered normal in healthy newborns in the first 96 hours after birth.
    D. Newborn infants require an increased glucose infusion rate compared to adults due to their larger brain-to–body mass ratio.
    E. Placental transfer of glucose is via simple diffusion to ensure the fetus receives adequate supply during pregnancy.
2. During your preparation for a glucose homeostasis lecture for second-year medical students, you are approached by one of the students. He is attempting to understand glucose homeostasis in the newborn. He understands it is a complex interplay of regulatory and counterregulatory hormones and is confused by the interactions. Which of the following statements most accurately explains the factors that play a role in glucose homeostasis in the newborn?
    A. Amino acids are substrates used in hepatic gluconeogenesis to produce glucose in the fasting state.
    B. Glucagon is a hormone used to increase liver gluconeogenesis in an effort to increase blood glucose levels.
    C. Growth hormone and cortisol are hormones released acutely during a fasting episode and help to increase glucose utilization by the newborn.
    D. Insulin secretion is increased in a fasted state and, thus, helps to initiate glycogenolysis.
    E. Ketones are products of fatty acid metabolism and are used by all tissues for fuel except the brain.
3. You are called to the delivery room to assess a 38 weeks' gestation female born to a 32-year-old gravida 2 para 2 woman after an uncomplicated pregnancy. The parents have an older child with trisomy 21 and are worried about this infant's blood glucose. Physical examination reveals normal findings. The nurse informs you that a point-of-care blood glucose on this infant measures 35 mg/dL (1.94 mmol/L). Which of the following statements regarding glucose screening steps is more consistent with the American Academy of Pediatrics (AAP) screening guidelines?
    A. Infants of diabetic mothers and late preterm infants are encouraged to have glucose screenings for the first 24 hours after birth.
    B. Infants who should undergo routine glucose screening include only those infants who are symptomatic.
    C. Large-for-gestational age and small-for-gestational age infants should have glucose screenings for the first 12 hours after birth.
    D. Per the AAP guidelines, the goal is to have a preprandial blood glucose value of 47 mg/dL (2.61 mmol/L) or greater.
    E. The Pediatric Endocrine Society recommends a glucose value higher than the AAP recommendation in an attempt to exclude those with transitional hypoglycemia.
4. One of your colleagues at the local community hospital is the head of the Quality Improvement Committee that is reviewing and updating laboratory protocols and practices. She asks you to review the laboratory procedures for the newborn nursery and provide recommendations for improvement. As you analyze the methods used for

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newborn blood glucose determination, you identify discrepancies in the protocol. Which of the following may result in an overestimation of blood glucose in the newborn?

A. A blood collection tube that contains a glycolytic inhibitor.
B. A capillary glucose sample compared to a venous or arterial specimen because it is the most concentrated sample.
C. A laboratory delay in processing a glucose specimen.
D. Higher hematocrits due to red blood cell gluconeogenesis.
E. Point-of-care bedside devices may lead to overestimation, with up to a 15% difference from laboratory analysis.

5. In the middle of a particularly chaotic call night, a first-year pediatric resident pages you to discuss a newborn infant who was born appropriate for gestational age at 39 weeks' gestation. The infant is now 72 hours old and has had repeated preprandial glucose values of 41 mg/dL (2.28 mmol/L), 44 mg/dL (2.44 mmol/L), and 40 mg/dL (2.22 mmol/L). There is no history of maternal diabetes. The only maternal medication in pregnancy was prenatal vitamins. Assessment of which of the following is not necessary in the diagnostic evaluation of persistent neonatal hypoglycemia in the first 72 hours after birth?

A. C-peptide polypeptide.
B. Growth hormone.
C. History of neonatal asphyxia or other peripartum stress.
D. Insulin hormone.
E. Plasma laboratory confirmation of glucose.

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