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VIEWPOINT

Guidelines for Management of Neonatal Hypoglycemia
Are They Actually Applicable?

Carlo Dani, MD
Division of Neonatology, Careggi University Hospital of Florence, Florence, Italy; and Department of Neurosciences, Psychology, Drug Research and Child Health, Careggi University Hospital of Florence, Florence, Italy.

Iuri Corsini, MD
Division of Neonatology, Careggi University Hospital of Florence, Florence, Italy.

Corresponding Author: Carlo Dani, MD, Division of Neonatology, Careggi University Hospital, Largo Brambilla 3, 50134 Florence, Italy (cdani@unifi.it).

Hypoglycemia may occur in 10% of healthy term infants, mainly during the first 24 to 48 hours of life.[1] This fact is concerning because the high glucose consumption of the brain and the larger ratio of brain to body mass in newborns compared with children and adults increase newborns' need for glucose and can expose them to neurologic injuries and a risk of abnormal outcome.[2,3] Unfortunately, hypoglycemia can be asymptomatic or accompanied by nonspecific symptoms; therefore, screening programs have been developed to allow early detection and prompt treatment of hypoglycemia in high-risk infant populations (eg, infant of a diabetic mother, large for gestational age, or small for gestational age). Although this approach is accepted by neonatologists and widely diffused, it presents some evident limitations: infants with certain types of congenital disorders who are not included in the recognized high-risk categories are excluded from screening and can have a delayed diagnosis of severe and persistent hypoglycemia. On the other hand, asymptomatic euglycemic infants included in high-risk categories can experience excessive blood sampling, hospital admissions, and family separation.

The main challenge is to precisely define neonatal hypoglycemia by identifying specific normal blood glucose levels based on postnatal age. These values can be affected by individual patients' metabolic characteristics (ie, availability of alternative energy sources such as ketones), different thresholds for brain injury, effects of duration and degree of hypoglycemia, technical problems in measuring and interpreting blood (or plasma) glucose level,[2,3] and the lack of noninvasive methods for continuous blood glucose monitoring. Pediatric scientific societies such as the Pediatric Endocrine Society (PES)[2] and the American Academy of Pediatrics (AAP)[4] have recently published guidelines for management of neonatal hypoglycemia that are based on observational data and expert opinion (low level of evidence) and present some differences. The AAP recommends maintaining a blood glucose level greater than 40 mg/dL (to convert blood glucose levels to mmol/L, multiply by 0.0555) in the first 4 hours of life and greater than 45 mg/dL in hours 4 to 24 of life in high-risk neonates. These values are based on a single study in which preterm infants with birth weight less than 1850 g had asymptomatic hypoglycemia and showed neurodevelopmental impairment at 18 months of age[5] but not at the subsequent follow-up study at 15 years of age.[6] The PES suggests maintaining a plasma glucose concentration greater than 50 mg/dL or greater than 60 mg/dL in high-risk neonates without suspected congenital hypoglycemia disorders with postnatal age younger than 48 or 48 hours or older, respectively, and a plasma glucose concentration greater than 70 mg/dL in neonates with suspected congenital hypoglycemia.[2] These thresholds are not specific to neonates but are translated from children and adults who develop symptoms below these values.[3]

It is noteworthy that the PES refers to plasma glucose concentration,[2] whereas the AAP refers to blood glucose concentration[4] that is 10% to 12% lower than plasma level.[3] Thus, the PES and AAP recommend similar glucose levels (>45 mg/dL in blood vs >50 mg/dL in plasma) during the first 24 hours of life,[2,4] while only the PES suggests a normal plasma glucose level for infants within the first 24 to 47 hours of life (>50 mg/dL) or at 48 hours of life or after (>60 mg/dL).[2] Guidelines do not specify that glucose reference values are the same in infants who are or are not at high risk for hypoglycemia, but there are no reasons to think that this is not true.[2,4]

The AAP guidelines[2] are widely diffused, and many centers (such as ours) use the same blood glucose level (>45 mg/dL) as the cutoff for diagnosis of hypoglycemia also in infants after 24 hours of life. The PES recommendations are less widespread because application of their higher cutoff values for diagnosis of hypoglycemia would lead to a huge increase in admissions of both high-risk infants and infants in whom hypoglycemia is unexpectedly diagnosed (ie, infants with weight loss >10% or with jaundice in whom electrolytes or total bilirubin were measured with a blood gas analyzer that measures glycemia in the same sample). We found that, in our center, up to 10% of healthy term infants have glycemia of 45 to 49 mg/dL at 24 to 47 hours of life or 50 to 59 mg/dL at 48 hours of life or after during their stay in the hospital. This percentage represents the potential increase of diagnoses of hypoglycemia using the PES recommendations[2] compared with the present inappropriate application of AAP guidelines[4] after 24 hours of life. However, these infants are currently discharged without a diagnosis of hypoglycemia and, to our knowledge, they do not subsequently develop hypoglycemia or associated neurologic disorders, suggesting that this approach is not unsafe.

This situation, in our opinion, opens the way to questioning recommendations from scientific societies that are based on low levels of evidence and expert opinions and whose application may increase the number of admissions, lengths of stay, and medical costs without definitive evidence of benefit. In fact, although the text of the PES guideline is clear where it specifies that we are reading "weak suggestions" of "moderate" evidence and not "strong recommendations" of high evidence,[2] the endorsement of a prestigious scientific society might support the idea that it is better to apply these suggestions, perhaps to avoid legal issues, even if this application might not be in the infants' interest and might lead to an overtreatment unjustified by evidence.

In conclusion, we believe that guidelines for management of neonatal hypoglycemia from the AAP[4] and PES[2] are very important and their authors deserve our gratitude, but the lack of evidence from powerful studies limits their applicability, particularly in infants after 24 hours of life. We believe future guidelines should consider that the most diffused approach to hypoglycemia (ie, to maintain a glucose level >40 mg/dL in the first 4 hours of life and >45 mg/dL between 4 and 24 hours of life[4]) has not been associated with a burden of cases of undiagnosed hypoglycemia and subsequent neurological disorders. The suggestion of a higher cutoff level for diagnosis of hypoglycemia should be suitably accompanied by a preliminary evaluation of the increased number of diagnoses and admissions (with associated negative economic and familial effects); suggested cutoff levels need to be supported by strong, high-quality evidence before being implemented in clinical practice. Otherwise, it is likely that these guidelines will remain unapplied.

ARTICLE INFORMATION

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