




Neonatal hypoglycemia: a review of the current diagnostic and management guidelines

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ABSTRACT

Neonatal hypoglycemia is the most common metabolic disorder during the neonatal period. Despite its frequency of occurrence, there is no specific glucose concentration that defines it. Various symptoms and clinical manifestations characterize it, and its complications are related to its severity and duration. This review aims at comparing the recommendations of the American Academy of Pediatrics, the Pediatric Endocrine Society, and the Academy of Breastfeeding Medicine regarding the risk factors, the diagnosis, and the management of hypoglycemia. The complexity of hypoglycemia management and the research questions that need to be answered are highlighted by comparing the three guidelines. Preventing neonatal hypoglycemia by monitoring the maternal glucose concentrations, exploring and defining the optimal glycaemic targets, investigating the long-term benefits after following these guidelines, and searching for less invasive diagnostic and therapeutic tools may help healthcare professionals make informed decisions to achieve better outcomes for these neonates.

KEYWORDS

neonatal hypoglycemia, blood glucose levels, definition, guidelines, management

How to cite this article: Zervoglou K., Harizopoulou V., Bouroutzoglou M., Kallia T., Antonakou A.: Neonatal hypoglycemia: a review of the current diagnostic and management guidelines. *Rev. Clin. Pharmacol. Pharmacokinet. Int. Ed.* 38(3): 259-271 (2024).
DOI: [10.61873/UCHB6154](https://doi.org/10.61873/UCHB6154)

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1. INTRODUCTION

Hypoglycemia is the most common metabolic disorder in the early neonatal period. It affects 5%-15% of all neonates, while its incidence reaches 50% in high-risk neonates [1-3]. Internationally, a precise definition of neonatal hypoglycemia is lacking, but the most widely used definition defines it as a glucose concentration below 47 mg/dL [3-5].

Neonatal hypoglycemia is divided into transient and persistent, mainly based on duration. Transient usually affects the first 48 h of life and occurs most frequently in neonates of diabetic mothers, neonates with hypothermia, premature neonates, neonates small for gestational age, neonates who have suffered perinatal asphyxia, intracranial haemorrhage, and neonates with congenital anomalies [6]. Transient hypoglycemia in normal neonates resolves in two to three days [7].

The high-risk groups and causes of persistent hypoglycemia are mainly similar to those of transient hypoglycemia, with the differences being in duration and severity. Persistent is characterised by consistently low blood glucose concentrations over time, persisting beyond the first three days of life. It also requires further investigation as it may be due to several other underlying mechanisms, including congenital disorders such as hyperinsulinism, glycogen storage diseases, fatty acid oxidation disorders or other metabolic conditions that affect glucose regulation and homeostasis [3,7].

It has been observed that healthy neonates experience transient hypoglycemia as part of their normal adaptation to extrauterine life, so as to maintain homeostasis after birth [8]. Defining normal blood glucose concentrations is challenging because these levels are not routinely checked in healthy newborns who lack any hypoglycemia risk factors [9]. After cord ligation, the neonate uses its glucose storage until carbohydrate is administered exogenously. Blood glucose concentrations can be as high as 20-25 mg/dL in the first 2-3 h of life. This drop in glucose concentration is thought to be necessary for activating an offset mechanism [10]. During this fall, plasma insulin concentrations decrease and those of glucagon, growth hormone, catecholamines, and cortisol increase. These hormones act antagonistically and promote the release of stored glucose as an alternative energy source [11].

On the other hand, in neonates of diabetic mothers, hypoglycemia occurs due to fetal hyperinsulinemia in response to maternal hyperglycemia. Additional risk of hypoglycemia appears to be faced by neonates of mothers treated with insulin during pregnancy, neonates of mothers with hyperglycemia at delivery, and male neonates [10]. Glucose crosses the placenta, which maternal insulin cannot do. Consequently, fetal pancreatic beta-cell hyperplasia and hyperinsulinemia are induced to enable the fetus to cope with the elevated glucose concentrations. However, after birth, this hyper-glucose delivery ceases, resulting in neonatal hypoglycemia [12,13].

The clinical manifestations of hypoglycemia are non-specific. Some neonates with hypoglycemia may be asymptomatic or with such mild symptoms, almost undetectable. Clinical manifestations of hypoglycemia include irritability, tremor, apnea, cyanosis, feeding difficulties, coma, sweating, hypothermia, hypothermia, high-pitched crying, lethargy, nervousness, and increased release of the Moro reflex [10,14]. Thus, since many neonates do not show symptoms, and when they do, they are non-specific, it is recommended that all neonates with risk factors should undergo a monitoring of

glucose concentrations [3]. Most guidelines recommend glucose testing within 1-4 h after delivery and re-testing every 3 or 4 h until euglycemia is achieved and maintained on two or three consecutive measurements [3].

The complications of hypoglycemia are proportional to its severity and duration. Severe, prolonged hypoglycemia in the neonatal period can have adverse effects such as cerebral palsy, mental retardation, epilepsy, neurological damage, behavioural and personality disorders, and death [15].

The present descriptive review provides an overview and a synthesis of the most widely used guidelines for managing neonatal hypoglycemia. It examines their differences, the populations they target, and the potential for early diagnosis of hypoglycemia. It also discusses the place of breastfeeding within the guidelines for preventing, managing, and treating neonatal hypoglycemia.

2. HYPOGLYCEMIA MANAGEMENT GUIDELINES

Management of low blood glucose concentrations in the first 48 h of life is one of the most common problems encountered in newborns of diabetic mothers. The glucose concentrations that inform decision-making are derived more from expert opinion than research evidence and results. For this reason, differences between management protocols are observed depending on the organisation [16].

Two US pediatric organisations, the American Academy of Pediatrics (AAP) in 2011 and the Pediatric Endocrine Society (PES) in 2015, used different approaches and proposed different thresholds of hypoglycemia that deserve management. The AAP's guidelines cover the first 24 h of a newborn's life, while the PES focuses on newborns with persistent or severe hypoglycemia beyond 48 h. Finally, the Academy of Breastfeeding Medicine (ABM) takes a less intrusive approach, emphasising the role of breastfeeding. Table 1 presents a summary and a side-to-side comparison of the three guidelines (AAP, PES, and ABM) on the risk factors, clinical signs, screening, diagnosis, and management of neonatal hypoglycemia. The content of these three guidelines is summarised and synthesised below.

2.1. The AAP guidelines

The AAP guidelines [17] focus on the management of hypoglycemia in term and late preterm neonates. According to them, neonates who are both

small and large for gestational age, neonates of diabetic mothers, and late preterm neonates are high-risk groups for hypoglycemia. The reported clinical manifestations of hypoglycemia are jitteriness, cyanosis, seizures, apneic episodes, tachypnea, weak or high-pitched cry, floppiness or lethargy, poor feeding, and eye-rolling. In contrast, coma and seizures are signs of prolonged and repetitive hypoglycemia [18,19]. The AAP recommends monitoring plasma glucose concentrations in symptomatic neonates and those in high-risk groups. The optimal period for postpartum glucose measurement and duration of follow-up is not stated, but it is suggested that the results be individualised according to the risk factors. Moreover, AAP highlights that any approach to the management of hypoglycemia should consider the metabolic and physiological status of the newborn, without unnecessarily disrupting the mother-newborn dyad and maternal breastfeeding [17].

The glucose concentration defining neonatal hypoglycemia for all neonates' first day of life is <47 mg/dL, but insufficient scientific evidence supports this claim [1,18,20,21]. The lower limits of glucose concentrations for which the AAP suggests intervention vary depending on the time after birth and the preceding steps. Laboratory enzymatic analysis methods (glucose oxidase, hexokinase or dehydrogenase) are reported as reliable methods for diagnosing hypoglycemia, but obtaining results may be delayed. For this reason, the AAP is not negative, and glucose strips and a glucose meter are used. However, it points out that the healthcare professional should perform the test with caution, thereby recognising the limited accuracy of the method.

The AAP proposes an algorithm for monitoring and managing glucose homeostasis, with feeding and intravenous (IV) administration of a 10% dextrose solution as treatment options. Newborns carrying risk factors are recommended to be fed within the first hour of life and checked half an hour later. If the glucose concentration is <25 mg/dL (<4 h of life) or <35 mg/dL (4-24 h of life), then feeding is resumed and the glucose is rechecked 1 h after feeding. An IV glucose administration is deemed necessary if the glucose concentrations at the second measurement are <25 mg/dL or <35 mg/dL, respectively.

In symptomatic neonates, the threshold glucose concentration that indicates the need for treatment is <40 mg/dL, as a result of laboratory testing. Therapeutically, a single IV administration of a 10% dextrose solution (200 mg glucose/kg) and the initiation of a continuous infusion of a 10% dextrose solution (5-8 mg glucose/kg/day) is recommended. The therapeutic glycemic target for

this group of neonates is 40-50 mg/dL.

According to the AAP guidelines, the target glucose concentration for all neonates is ≥ 45 mg/dL before each feeding. Before discharge, the neonate should be confirmed to maintain normal plasma glucose concentrations through at least three feed-fast periods while being fed normally.

2.2. The PES guidelines

The PES guidelines [7] address assessing and managing persistent hypoglycemia in neonates, infants, and children.

According to the PES, neonates at increased risk for developing persistent hypoglycemia include those who are large or small for gestational age, those with perinatal stress, asphyxia, or ischemia, those born by mothers with diabetes, preeclampsia, eclampsia, hypertension, premature or postmature delivery, neonates with a history of meconium aspiration, erythroblastosis, polycythemia, or hypothermia, neonates with a family history of genetic hypoglycemia, neonates with congenital syndromes, and those with abnormal physical features (e.g. midline facial malformation, microphallus) [22]. Newborns with these risk factors or who are symptomatic should have their glucose concentrations monitored. The reported clinical manifestations include palpitations, tremors, anxiety, sweating, hunger, paresthesia, confusion, coma, and seizures.

According to PES, the normal blood glucose concentration limits for neonates in the first 24-48 h of life are 55-65 mg/dL, and for neonates older than 48 h of life are 70-100 mg/dL. Regarding the method of diagnosis, PES recommends laboratory analysis as the primary tool. PES refers to standard strip glucose meters as an easy but limited-accuracy method; therefore, laboratory testing confirmation is always recommended for a final diagnosis.

The management of symptomatic neonates with hypoglycemia mainly involves the immediate IV administration of dextrose. The initial dose is 200 mg/kg, followed by an infusion of 10% dextrose at a maintenance rate according to the day of life. Additionally, glucagon may be used in cases of hyperinsulinism, such as in neonates with genetic hypoglycemia disorders [7]. Glucagon is administered at a dose of 0.5-1.0 mg, regardless of the neonate's weight, IV, intramuscularly, or subcutaneously. This dose can raise plasma glucose concentrations within 10-15 min and maintain them elevated for at least 1 h. Lower doses of glucagon (0.03 mg/kg) may have milder side effects, such as a lower risk of transient nausea and vomiting, but may be ineffective if not administered IV.

No guidance on the management of non-symptomatic neonates is provided in this protocol.

The therapeutic goal in neonates with a suspected congenital hypoglycemic disorder, older infants, and children with a confirmed hypoglycemic disorder is plasma glucose concentrations >70 mg/dL. In high-risk neonates without a suspected congenital disorder in glucose metabolism, the goal is to achieve plasma glucose concentrations >50 mg/dL in the first 48 h, and >60 mg/dL after

the first 48 h of life.

The PES recommends distinguishing between neonates with transient hypoglycemia and those at increased risk of persistent hypoglycemia with a genetic background before discharge. For neonates with a known risk of genetic or other persistent hypoglycemia (e.g. congenital hyperinsulinism), specific counselling and diagnostic tests are recommended to exclude certain disorders.

Table 1. A summary and a side-to-side comparison of the three guidelines (American Academy of Pediatrics or AAP, Pediatric Endocrine Society or PES, and Academy of Breastfeeding Medicine or ABM) on the risk factors, clinical signs, screening, diagnosis and management of neonatal hypoglycemia. Other abbreviations used: IV, intravenous; NICU, neonatal intensive care unit.

	AAP guidelines	PES guidelines	ABM guidelines
Date issued	March 2011	August 2015	May 2021
Title	Clinical Report - Postnatal Glucose Homeostasis in Late-Preterm and Term Infants	Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children	ABM Clinical Protocol #1: Guidelines for Glucose Monitoring and Treatment of Hypoglycemia in Term and Late Preterm Neonates, Revised 2021
Risk factors	Neonates small or large for gestational age, neonates of diabetic mothers, late preterm neonates	Neonates who are large or small for gestational age, neonates with perinatal stress / asphyxia / ischemia, neonates of mothers with diabetes / pre-eclampsia / eclampsia / hypertension, premature or postmature delivery, neonates with a history of meconium aspiration / erythroblastosis / polycythemia or hypothermia, neonates with a family history of genetic hypoglycemia, neonates with congenital syndromes and abnormal physical features (e.g. midline facial malformation, microphallus)	Maternal-related: diabetes, pre-eclampsia, hypertension, history of delivering macrosomic neonates, substance use, treatment with tocolytic β -agonists during pregnancy, treatment with oral hypoglycemic agents and late antepartum or intrapartum IV glucose administration Related to the neonate: intrauterine growth restriction, small for gestational age or low birth weight (<2,500 g) neonates, neonates with clinically evident wasting of fat and muscle bulk and those who are large for gestational age or have macrosomic appearance, discordant twin development, prematurity, perinatal stress, severe acidosis or hypoxia-ischemia, cold stress, polycythemia / hyperviscosity, fetal erythroblastosis, Beckwith-Wiedemann syndrome, microphallus or midline defects that indicate an underlying endocrine disorder, suspected infection, respiratory distress, suspected endocrine disorders, admission to the NICU

Clinical signs	Jitteriness, cyanosis, seizures, apneic episodes, tachypnea, weak or high-pitched cry, floppiness or lethargy, poor feeding, eye-rolling Prolonged and repetitive hypoglycemia: coma and seizures	Palpitations, tremors, anxiety, sweating, hunger, paresthesia, confusion, coma and seizures	Irritability, tremors, jitteriness, tachypnea, sweating, pallor, vasomotor instability, hypothermia or temperature instability, tachycardia, increased release of the Moro reflex, high-pitched crying, excessive signs of hunger, vomiting, weak sucking or refusal to feed, lethargy, listlessness, limpness, hypotonia, seizures or myoclonic jerks, coma, apnea or irregular breathing, cyanosis
Prevention	Feeding	-	Breastfeeding, ideally in the first 30-60 min of life and skin-to-skin contact
Diagnosis-operational thresholds	For all neonates: <47 mg/dL 25-40 mg/dL in the first 4 h, 35-45 mg/dL from 4-24 h and 45 mg/dL after 24 h of life	-	<47 mg/dL
Diagnostic methods	Laboratory enzymatic analysis methods (glucose oxidase, hexokinase, or dehydrogenase); clinicians should be aware of the limited accuracy of bedside reagent test-strip glucose analysers	Clinical laboratory method; the point-of-care meters have limited accuracy; therefore, confirmation by laboratory testing is recommended	Glucose meters and confirmation by laboratory analysis
Hypoglycemia screening (when?)	When there are risk factors or symptoms Personalised; newborns with risk factors should be fed within the first hour of life and checked 30 min later	When there are risk factors or symptoms	When there are risk factors or symptoms Personalised; for neonates with suspected severe hyperinsulinemia, monitoring should start within 60 min of birth, while for other neonates with risk factors, monitoring should start before the second feeding or 2-4 h after birth
Management of symptomatic neonates	Plasma must be obtained, and laboratory analysis should be performed before starting IV glucose minibus (200 mg glucose/kg, 2 mL/kg dextrose 10% in water IV) or continuous glucose infusion (dextrose 10%, 80-100 mL/kg/day)	Administration of IV dextrose at an initial dose of 200 mg/kg followed by an infusion of dextrose 10% at an age-appropriate maintenance rate	In neonates with symptoms or blood glucose concentrations <20-25 mg/dL, treat initially with bolus IV dextrose 10% solution (1-2 mL/kg) followed by continuous IV infusion at a rate of 5-8 mg/kg per min
Management of asymptomatic neonates	Asymptomatic neonates should be fed within the first hour of life and screened 30 min later; if glucose <25 mg/dL (<4 h of life) or <35 mg/dL (4-24 h of life), repeat feeding and recheck in 1 h; if the second glucose measurement values are <25 mg/dL or <35 mg/dL, respectively, treatment with IV glucose is necessary	-	In high-risk neonates without clinical signs and with glucose >20-25 mg/dL but <35-45 mg/dL, treatment with glucose gel 40% 0.5 mL/kg (200 mg/kg) up to two times and intensify breastfeeding. If glucose is still low, start treatment with IV glucose

Target glucose concentration	≥ 45 mg/dL before feeds	>70 mg/dL for neonates with a suspected hypoglycemic congenital disorder, as well as older infants and children; for high-risk neonates without a congenital hypoglycemic disorder, the target is >50 mg/dL for those up to 48 h of age and >60 mg/dL for those older than 48 h	Any neonate with persistent hypoglycaemia (>4 days) or who requires IV glucose therapy should not be discharged until blood glucose concentrations >70 mg/dL are achieved and maintained
Discharge plan	Neonates should be capable of maintaining normal glucose concentration throughout at least three feed-fast periods	For neonates with a known risk of genetic or other persistent form of hypoglycaemia: provide counselling and diagnostic tests, fasting test to ensure that plasma glucose concentration can be maintained above 70 mg/dL A fasting test should be performed for high-risk neonates without a suspected persistent hypoglycemia disorder to determine whether postprandial plasma glucose concentration >60 mg/dL can be maintained or if additional management or investigation is required	Any neonate with persistent hypoglycaemia (>4 days) or who requires IV glucose therapy should not be discharged until blood glucose concentrations >70 mg/dL are achieved and maintained

A fasting test is recommended in these neonates to ensure the plasma glucose concentration can be maintained above 70 mg/dL if feeding is omitted for at least 6-8 h. For high-risk neonates without suspected persistent hypoglycemia and in whom hypoglycemia is likely to resolve soon, it is recommended that a fasting test be performed before discharge to determine whether the plasma glucose concentration can be maintained at >60 mg/dL or whether additional management or investigation is required [7]. Therefore, it is safe to discharge when transient hypoglycemia has resolved, and the possibility of persistent hypoglycemia has been ruled out with the help of the fasting test and other specific diagnostic tests.

Long-term treatment of glucose metabolism disorders is based on the diagnosis of the cause and the etiological management and treatment by a specialized team of healthcare professionals. In some disorders, such as hyperinsulinism, cortisol deficiency, and growth hormone deficiency, medication is available and may be given. Depending on the disorder, a special diet or surgery may be required, while in milder forms, avoiding prolonged fasting may be the only necessary treatment [7].

2.3. The ABM guidelines

The ABM guidelines [11] address the control of glucose concentrations and treatment of hypoglycemia in term and late preterm infants. Risk factors for neonatal hypoglycemia may be related to the mother or the neonate itself [23-25]. Maternal-related risk factors include diabetes, pre-eclampsia, hypertension, history of delivering macrosomic neonates, substance use, treatment with tocolytic beta-agonists during pregnancy, treatment with oral hypoglycemic agents, and late antepartum or intrapartum IV glucose administration [23-25]. Neonatal risk factors include intrauterine growth restriction, small for gestational age or low birth weight (<2,500 g) neonates, neonates with clinically-evident wasting of fat and muscle bulk, and those who are large for gestational age or have macrosomic appearance. Additional risk factors include asymmetric twin development, prematurity, perinatal stress, severe acidosis or hypoxia-ischemia, cold stress, polycythemia or hyperemia, fetal erythroblastosis, Beckwith-Wiedemann syndrome, microphallus or midline defects that indicate an underlying endocrine disorder, suspected infection, respiratory distress, and suspected endocrine dis-

orders. In addition, neonates admitted to the neonatal intensive care unit (NICU) and neonates with clinical manifestations that may be associated with hypoglycemia carry an increased likelihood of hypoglycemia [23-25].

According to the ABM, the following are clinical manifestations of hypoglycemia: irritability, tremor, nervousness, tachypnea, sweating, pallor, vasomotor instability, hypothermia or temperature instability, tachycardia, increased release of the Moro reflex, high-pitched crying, excessive signs of hunger, vomiting, weak sucking or refusal to feed, lethargy, listlessness, limpness, hypotonia, seizures or myoclonic jerks, coma, apnea or irregular breathing, and cyanosis.

The ABM recommends that all newborns carrying the above risk factors or exhibiting symptoms of hypoglycemia should be screened for hypoglycemia [1,17,23,26,27]. The frequency and duration of the follow-up should be individualised. For neonates with suspected severe hyperinsulinemia, monitoring is recommended to start within the first hour after birth [17,28]. In contrast, for other neonates with risk factors, monitoring is recommended to start before the second feeding or 2-4 h after birth [27-29].

Regarding the diagnosis, the ABM acknowledges the usefulness and convenience of standard glucose meters, but stresses the need for confirmation by laboratory analysis [30,31]. In symptomatic neonates, these guidelines suggest starting treatment (based on glucose values from a glucose meter or blood gas analyzer) without delay [32].

In contrast to the other guidelines included in this review, the ABM refers more extensively to the critical role of breastfeeding in the prevention and treatment of hypoglycemia. The ABM recommends initiating breastfeeding as soon as possible, ideally within 30-60 min after delivery, alongside skin-to-skin contact between mother and newborn [33,34]. This helps maintain the newborn's body temperature, reduce energy expenditure, and stimulate milk production [35-37].

According to ABM, breastfed infants have higher ketone body concentrations than formula-fed infants, even when their blood glucose concentrations are similar. This indicates that breastfed infants can tolerate lower plasma glucose concentrations without significant clinical manifestations or adverse events [21,38,39]. Breastfeeding promotes the production of ketone bodies in the neonate, especially during the initial postnatal period when glucose concentrations are lower. Ketone bodies are produced when the body breaks down fat without sufficient glucose. Therefore, in contrast to breastfed infants, formula-fed infants tend

to have slightly higher glucose concentrations and lower ketone body concentrations [38,39]. This difference may affect neonatal metabolism and how nutrients are handled and utilised. Based on the above, the ABM protocol encourages uninterrupted skin-to-skin contact and breastfeeding in high-risk neonates without clinical signs and with blood glucose between 20-25 mg/dL, but less than 35-45 mg/dL [36,37].

Another specificity of the ABM guidelines is the extensive reference and recommendation for using glucose gel to manage and treat neonatal hypoglycemia. Glucose gel, also known as dextrose gel, has become an important tool in recent years. It is a non-invasive and inexpensive therapeutic option that can be administered orally to increase glucose concentrations in neonates with hypoglycemia or at risk of hypoglycemia.

The first recommendation for the use of dextrose gel in neonatal hypoglycemia appeared in the literature in 1992. Since 2000, randomised controlled trials have confirmed the safety and efficacy of a standard dose of 200 mg/kg (=0.5 mL/kg of a 40% dextrose gel) [40-42]. Since then, several studies have confirmed the multiple benefits of glucose gel. Its use has been shown to improve blood glucose concentrations, reduce the likelihood of neonatal separation from the mother, reduce the possibility of neonatal admission to the NICU for hypoglycemia, increase rates of exclusive breastfeeding at discharge and weeks after discharge, increase parental satisfaction, and it is a well-tolerated and cost-effective treatment option [28,43]. A recent study that aimed to evaluate the effects of introducing glucose gel in the care of late preterm and full-term neonates reported that the use of glucose gel was associated with a reduction in the number of medical interventions, formula milk use, and the frequency of IV glucose administration [44]. A systematic review stated that glucose gel "should be considered first-line treatment for infants with neonatal hypoglycemia" [45]. In the updated version of the systematic review, it is reported that glucose gel may reduce the risk of significant neurological disability at two years of age and older. However, more evidence is needed on its effect on later neurological disorders [46].

Glucose oral gel 40% is administered at 0.5 mL/kg (200 mg/kg) along with a feeding schedule (preferably breastfeeding) when glucose concentrations are low or borderline. An additional dose can be given if needed, as it is considered safe. Glucose concentrations are rechecked 30 min after administration of the glucose gel and before subsequent breastfeeding until they are within acceptable limits and stable (usually ≥ 45 mg/dL). If glucose remains low despite feeding, it is neces-

sary to initiate IV glucose administration, adjusting the rate based on blood glucose concentration [17]. If the neonate is unable to suck or feeding is not tolerated, force-feeding is contraindicated, and IV glucose therapy is administered. In those cases, careful examination, assessment, and evaluation of the infant for other underlying diseases is required, mainly if the infant had been feeding well earlier.

During IV glucose therapy, breastfeeding or oral feeding shall be encouraged and continued when the newborn is able and willing. More specifically, ABM reports that feeding during IV glucose therapy reduces the required treatment duration and is associated with a lower glucose infusion rate [47]. Once the serum glucose concentration is within normal values, IV glucose administration is gradually discontinued, and feeding with milk (breast milk or formula) is increased. Neonates who have developed persistent hypoglycemia for more than four days or have been given IV glucose therapy should have several glucose measurements. The neonate is discharged when glucose concentrations are consistently above 70 mg/dL.

The management modality varies in symptomatic neonates with blood glucose concentrations <20-25 mg/dL. Treatment begins with a single dose of 1-2 mL/kg of a 10% dextrose solution and continues with a continuous IV infusion of 5-8 mg/kg per min. Glucose gel is not recommended in symptomatic neonates unless there is a delay or difficulty in accessing an IV route.

Finally, neonates who have had severe hypoglycemia accompanied by symptoms such as seizures, impaired consciousness, or circulatory collapse are recommended to undergo magnetic resonance imaging and should receive long-term follow-up [48-50].

3. DISCUSSION

Multiple guidelines and recommendations have been developed in order to address the challenges of neonatal hypoglycemia. These guidelines emphasise the importance of integrated care, multidisciplinary collaboration, and an individualised approach. Additionally, they highlight the need for optimal glycemic control, regular monitoring, early recognition, and management of potential complications [51]. The available guidelines present similarities, but also significant differences. The similarities concern agreement on symptomatology, risk factors, and diagnostic tools. On the other hand, the differences also justify adopting many different local policies for managing neonatal hypoglycemia.

More specifically, the most widely used guide-

lines for managing neonatal hypoglycemia included in the present review address the prevention, definition, management, and therapeutic targets of neonatal hypoglycemia differently.

3.1. Prevention of neonatal hypoglycemia

The ABM and AAP guidelines recommend early breastfeeding initiation or early feeding shortly after birth to prevent neonatal hypoglycemia. The ABM also emphasises the importance of skin-to-skin contact, as it contributes to the newborn's thermoregulation and reduces its energy expenditure. In contrast, PES focuses on preventing recurrent episodes of hypoglycemia, which may increase the risk of subsequent hypoglycemic episodes [51].

Monitoring and regulating maternal glucose concentrations peripartum is important to prevent neonatal hypoglycemia. Currently, recommendations for maternal glucose concentrations to prevent neonatal hypoglycemia vary, suggesting a minimum maternal concentration of 70-72 mg/dL and a maximum of 117-144 mg/dL [52-54]. Therefore, it would be valuable to investigate optimal maternal glucose concentrations further and include them in future protocols for managing neonatal hypoglycemia. This would lead to a more causal management of neonatal hypoglycemia.

3.2. Definition of hypoglycemia

There is a discrepancy in guidelines regarding the glucose concentrations that define hypoglycemia and the view of the role of hypoglycemia as part of neonatal physiology. The AAP accepts hypoglycemia as part of the expected transition to extrauterine life, with relatively low glucose cutoff values (<40 mg/dL in the first 4 h of life and <45 mg/dL in 4-24 h of life). While this helps to reduce the proportion of neonates diagnosed with hypoglycemia and NICU admissions, it may lead to underdiagnosis. Therefore, it has been argued that AAP thresholds may miss a proportion of hypoglycemic neonates, which could develop neurological damage in the long term [55]. Similarly, guidelines that define hypoglycemia at higher glucose concentrations may lead to overtreatment, a practice that has documented adverse effects. Excessive intervention can cause such problems as mother-newborn separation, interruption of breastfeeding, unnecessary invasive interventions, and a waste of medical resources [43,56].

Overtreatment may also cause hyperglycemia, which should not be underestimated, especially in premature or acutely ill neonates who are treated with IV glucose because intestinal feeding is

insufficient or delayed [57]. For this reason, more studies are needed to clarify optimal glycemic targets and to investigate the long-term effects of introducing these guidelines into clinical practice.

Even though most guidelines use glucose as the main biochemical marker for the diagnosis and management of neonatal hypoglycemia, recent evidence suggests that blood glucose values are not the only marker for monitoring, and that other markers (e.g. ketone bodies, lactate) associated with the metabolism of glucose should be considered for a proper assessment [58].

Regarding diagnostic methods, the three organisations place more trust in the results of laboratory analyses. However, it would be reasonable to guide clinicians and incorporate recommendations in the guidelines to increase the reliability of the point-of-care testing (POCT) glucose meters, as they give faster results, which is significant in emergencies. Recommendations such as making regular comparisons between measurements to ensure that clinicians are aware of any existing discrepancies and considering the possibility of adjusting treatment algorithms to take account of identified discrepancies in POCT glucose meters, could be beneficial [59].

3.3. Management of asymptomatic neonates

When managing asymptomatic neonates, the AAP adopts an algorithm divided into two periods: feeding the neonate during the first hour of life and monitoring glucose half an hour later. This method emphasises the importance of early feeding and glucose monitoring, with the following steps, including IV glucose administration if necessary. Adequate and early feeding has been shown to prevent the progression of hypoglycemia in high-risk neonates [42]. However, the potential for overtreatment remains a matter of concern, as strict monitoring and intervention guidelines could lead to unnecessary NICU admissions and increased parental distress.

On the other hand, the ABM guidelines recommend a less invasive approach, advocating the use of glucose gel and increased breastfeeding efforts in neonates with glucose levels between 20-25 mg/dL and 35-45 mg/dL. This strategy reduces the disruption of the breastfeeding process, supports the mother-infant bond, and effectively stabilises blood glucose concentrations without needing immediate IV intervention, as demonstrated in a randomised controlled trial [41,60].

In contrast, the PES guidelines do not support routine management of asymptomatic newborns, thereby reflecting a rather conservative attitude that aligns with existing research showing that

transient low blood glucose levels are often benign and self-limiting [14]. This approach minimises the risk of overtreatment, but raises concerns about the potential missed cases that may require intervention.

3.4. Management of symptomatic neonates

For symptomatic neonates with glucose concentrations lower than 40 mg/dL, the AAP recommends administering a single dose of glucose IV followed by a continuous infusion of 10% dextrose solution. This approach ensures rapid control of hypoglycemia, which is crucial for the prevention of potential neurological damage [21].

The ABM guidelines also prioritize immediate glucose administration and recommend using glucose gel only in cases where IV access is delayed. In addition, they encourage continued breastfeeding, as it may reduce the duration of IV therapy.

The PES guidelines align with the AAP and ABM in recommending IV glucose administration for symptomatic neonates. However, they do not specify a preferred procedure for initial management, which may also indicate the need for individualized care.

3.5. Therapeutic targets in neonatal hypoglycemia

The therapeutic targets for infant glucose concentrations differ between guidelines, which indicates differences of opinion on what might represent a safe and effective range.

The AAP recommends that the glucose concentration be greater than 45 mg/dL pre-prandial, and that normal glucose concentrations be maintained for at least three consecutive measurements while the neonate is fed. Studies indicate that lower limits increase the risk for neurodevelopmental disorders [49].

According to the PES guidelines, different therapeutic targets should depend on the neonate's age and clinical context. The therapeutic goal for older infants and children with a confirmed disorder is a glucose concentration above 70 mg/dL. In high-risk neonates without suspected impaired glucose metabolism, the goal is to achieve a plasma glucose concentration greater than 50 mg/dL in the first 48 h and more than 60 mg/dL after the first 48 h. This graduated approach recognises the physiological changes in the postnatal period and that neonates need higher glucose concentrations during the transition to extrauterine life.

Finally, the therapeutic goal, according to the ABM, is 45-54 mg/dL. This range is supported by

research suggesting that moderate hypoglycemia is often well-tolerated, and that interventions need to be balanced against the potential harms of disrupting breastfeeding [11].

4. CONCLUSION

In conclusion, the ABM guidelines deviate significantly from the earlier AAP and PES guidelines on managing neonatal hypoglycemia, focusing on early and frequent breastfeeding and the use of glucose gel, resulting in a reduction in NICU admissions and an increase in breastfeeding rates. Recent guidelines and some encouraging research results support glucose gel. Such comparison highlights the complexity of management and, therefore, how the knowledge and skills of clinicians need to be continually updated. Further research is needed to establish guidelines and evidence-based practices for neonatal hypoglycemia prevention, diagnosis, and treatment.

ACKNOWLEDGMENTS

The authors would like to thank the anonymous reviewers for their insightful comments and suggestions. This review is not funded by any agency and is being conducted independently by the authors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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