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Swedish national guideline for prevention and treatment of neonatal hypoglycaemia in newborn infants with gestational age ≥ 35 weeks

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Short title: Swedish guideline for neonatal hypoglycaemia.

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Abstract

Aim: Postnatal hypoglycaemia in newborn infants remains an important clinical problem where prolonged periods of hypoglycaemia are associated with poor neurodevelopmental outcome. The aim was to develop an evidence based national guideline with the purpose to optimise prevention, diagnosis and treatment of hypoglycaemia in newborn infants with a gestational age $\geq 35+0$ weeks.

Methods: A PubMed search based literature review was used to find actual and applicable evidence for all incorporated recommendations. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach was used for grading the evidence of the recommendations.

Results: Recommendations for prevention of neonatal hypoglycaemia were extended and updated, focusing on promotion of breastfeeding as one prevention strategy. Oral dextrose gel as a novel supplemental therapy was incorporated in the treatment protocol. A new threshold based screening and treatment protocol presented as a flowchart was developed.

Conclusion: An updated and evidence based national guideline for screening and treatment of neonatal hypoglycaemia will support standardised regimes, which may prevent hypoglycaemia and the risk for hypoglycaemia related long-term sequelae.

Key notes:

- Hypoglycaemia is a frequent complication in the early neonatal period among newborn infants and there is need for evidence based guidelines for prevention and treatment.
- In the new guideline, dextrose gel was introduced as a novel supplementary therapy and a treatment flowchart protocol was incorporated.
- This national guideline will support standardised regimes, which may reduce the risk of neonatal hypoglycaemia and hypoglycaemia related long-term sequelae.

Key words:

Breastfeeding, dextrose gel, guideline, hypoglycaemia, newborn infant

INTRODUCTION

Hypoglycaemia is one of the most common complications during the neonatal period. Based on unpublished data from the Swedish National Perinatal Quality register approximately one out of five infants are admitted to a neonatal care unit due to hypoglycaemia and hypoglycaemia is also commonly observed and treated at labour and maternity wards. Since prolonged periods of low plasma glucose is associated with increased risk of neurodevelopmental impairment, it is an important priority to prevent hypoglycaemia in newborn infants. Certain risk groups, including small for gestational age infants, preterm infants and infants of diabetic mothers, are at high risk of hypoglycaemia (1). Prevention, early diagnosis and prompt treatment is important for high-risk infants who develop hypoglycaemia, to minimise the severity and duration of hypoglycaemic episodes, which are associated with adverse outcomes. The duration and number of hypoglycaemic episodes are known to be associated with poor neurological outcomes (2).

Since the seminal study by Harris in 2013 (3), several studies have confirmed that orally applied dextrose gel, in addition to standard treatment of hypoglycaemia, reduces the risk of admission to the neonatal ward, reduces separation of infants from parents, and increases the chances that the infant is breastfed at discharge (3–6).

The evidence of long-term effects of postnatal hypoglycaemia is still conflicting (7) but in a follow-up study of infants at risk of hypoglycaemia, infants who were exposed to postnatal hypoglycaemia had worse visual, motor and executive function at 4.5 years of age (8). Furthermore, moderate postnatal hypoglycaemia could be associated with adverse neurocognitive outcome at 2-6 years of age (9).

The aim of these guidelines was to facilitate a safe, evidence-based and more uniform care of infants at risk of hypoglycaemia and of infants who develop hypoglycaemia after birth.

METHODS

On behalf of the Swedish Neonatal Society the group of experts developed and authored the flowchart and the new guideline as an update of the 2010 version of the national Swedish guideline. The expert group consists of midwives, neonatologists and paediatric endocrinologists. One aim was to enhance the prevention chapter to promote early breast feeding and non-separation of the mother and the infant. The Swedish guideline is intended as a ready-to-use guidance, coping with all management aspects in this specific patient group. The flowchart and screening and treatment recommendations were developed in consensus discussions based on clinical practice and best evidence. Literature review was performed using PubMed to find actual and applicable evidence for all recommendations. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach was used as a standardised evidence judgment tool. GRADE is the most used system for evidence grading. It consists of an evaluation of the scientific basis and a part that describes the level of certainty one can recommend using a method. Evidence grading must be objective and an important basis for the recommendation. In the recommendation, subjective factors can also be weighed in, such as preferences and financial aspects (Table1) (10,11). Two experts graded the quality of evidence of the references used for recommendations independently. In case of dissents the grading was discussed between the authors. Recommendations based on insufficient or lacking evidence were discussed within the expert group until a consensus was reached and were defined as “consensus recommendation”. The screening and treatment protocol is based on clinical practice and consensus discussion within the expert group, why grading of evidence has not been applied in this section.

GUIDELINES

Glucose homeostasis at birth

Glucose is the most important substrate for energy production in the body, both during foetal life and after birth, being used not only for energy production but also for building glycogen stores in muscle and liver, where the glycogen stores increase the most during the last trimester (12).

Foetal glucose consumption is higher (5-7 mg/kg/min) than that of the newborn infant (4-6 mg/kg/min) and the adult (2-3 mg/kg/min). Under normal conditions, the foetus has no endogenous glucose production, instead it is dependent on the glucose flux via the placenta (12).

The newborn's brain accounts for around 50% of the total glucose consumption. Glucose uptake to the brain is not insulin dependent, but is determined by a glucose concentration gradient with the help of specific glucose transport proteins. The levels of these proteins are low in the first week of life, but increase thereafter (13).

In the first days of life, around 70% of the brain's energy supply is estimated to be derived from glucose (14). Besides glucose, the brain of the newborn infant can to some extent also use ketone bodies and lactate as alternative energy sources. However, newborn infants have an initially lower degree of ketogenesis, which results in lower levels of ketone bodies and lactate can therefore be a more important cerebral fuel in the first two days after birth (15,16).

At birth, a comprehensive metabolic adaption takes place, and the newborn infant needs to produce its own glucose until the feeding starts. The infant will also have to adapt to bolus feeds, after being used to a continuous supply of nutrients through the umbilical cord.

The stress that arises in connection with birth and the simultaneous reduction of the glucose level facilitates the metabolic transformation. Several hormones are involved in this transformation process, where the initiation of breakdown of glycogen, fat and protein (glycogenolysis, lipolysis, proteolysis), generates substrate for endogenous production of glucose (gluconeogenesis) (Figure 1) (12). Newer data indicates that gluconeogenesis probably not only is present in the liver, but also

in other organs, like the kidneys (17). Glycogenolysis and gluconeogenesis are the most important sources for the energy metabolism in the first few hours after birth. Thereafter, lipolysis and subsequent beta-oxidation becomes more important. Despite presence of a well-controlled metabolic adaptation after birth, the newborn infant is at greater risk of developing hypoglycaemia than older children or adults.

There are several reasons for the increase of risk including the abrupt termination of the continuous maternal glucose supply at birth.

- Limited glycogen depots especially in preterm or growth-restricted infants.
- The lower activity of liver enzymes for gluconeogenesis and glycogenolysis during the first 1-3 days of age among full-term and even during a prolonged period among preterm infants (18).
- A high basal glucose consumption related to a proportionally large brain in relation to body weight (19).
- Inappropriately high insulin concentrations during the transitional period after birth suggesting a transient altered set-point for insulin release (12,20).

Definition of neonatal hypoglycaemia

The definition of neonatal hypoglycaemia remains controversial both in the literature and in clinical practice (12,21). Nor is it possible to define a definite cut-off value for hypoglycaemia using epidemiological data, physiological or electrophysiological examinations or through neurological outcomes (21).

However, clinical thresholds for treatment have been established and the most commonly used threshold is plasma-glucose (p-glucose) below 2.6 mmol/L, which is based on the publication by Lucas et al from 1988 (22). In the last decennium, there is a general agreement that blood glucose has to be regarded as a continuum during the postnatal adaptation that takes place from birth until approximately 72 hours of age when the adaptation should be finished.

A healthy appropriate-for-gestational-age infant will have an instantaneous postnatal drop in blood

glucose concentrations during the first 2–4 hours of life, which is essential for the postnatal adaptation (Figure 1). It is of importance that the glucose value is related to other existent or non-existent alternative energy fuels and counter-regulating hormones (12). Although there is currently a lack of evidence for a defined cut-off value, randomised studies provide support for aiming for a plasma glucose level above 2.6 mmol/L after the initial adaptation phase, i.e. after three hours postnatal age (Figure 2) (23,24). After completed adaptation process at about 72 hours after birth, plasma glucose should remain steady above 3 mmol/L (12).

Infants at risk

There are both maternal and neonatal factors increasing the risk of neonatal hypoglycaemia (Table 2). With increasing numbers of risk factors, the risk for hypoglycaemia amplifies for the infant (1).

Infants at risk have less capacity for counter-regulation of low blood glucose and often develop hypoglycaemia during the first day of life. Delayed or prolonged hypoglycaemia often has a different underlying cause, e.g. infection or metabolic disorders.

Maternal diabetes entails an elevated risk of hypoglycaemia, especially in infants with macrosomia. Elevated maternal glucose levels expose the foetus to elevated glucose levels, which increases foetal insulin production. Hyperinsulinism persists until the insulin production is down regulated to the infant's individual glucose levels. In addition, these infants often have a degraded hormonal counter-regulation after birth, which results in lower catecholamine and glucagon levels (25).

Metformin is increasingly used in the treatment of mothers with glucose disorders during pregnancy. Metformin crosses the placenta, in contrast to insulin. The risk of postnatal hypoglycaemia in the infants is comparable to that in infants of insulin treated mothers during pregnancy (26).

Treatment with antidepressants during pregnancy are relatively commonly occurring and both tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors have been associated with an increased risk of neonatal hypoglycaemia. The frequency of hypoglycaemic events has been described to be between 11 and 34% depending on the used drug (27,28).

Infants born premature have a higher glucose demand (6-8 mg/kg/min in week 28 of gestation) compared to full-term infants (4-6 mg/kg/min) and their glucose levels therefore drop faster after birth as compared to full-term infants. Furthermore premature infants have smaller glycogen depots (29,30).

Growth-restricted infants have an elevated risk of hypoglycaemia due to smaller fat, amino acid and glycogen depots and an impaired postnatal adaptation ability (31).

Infants who are born large for gestational age (LGA) have an elevated risk of hypoglycaemia (1). An epidemiologic review of LGA infants shows that anthropometric proportion -proportional versus disproportional- is of lesser significance with regard to the risk of hypoglycaemia. The most important risk factor for these infants is the occurrence of maternal diabetes or gestational diabetes (32).

Among infants subjected to perinatal asphyxia, postnatal hypoglycaemia increases the risk of neurological sequelae. This is probably due to a higher peripheral energy demand, which results in faster consumption of the infant's glycogen depots. In addition, the brain cells have an increased sensitivity to energy deficiencies (33–35).

Symptoms

Clinical symptoms (Table 3) may initially be subtle (especially in premature infants), but become clearer when the hypoglycaemia progresses as follows (36):

- Hypoglycaemia with adequate metabolic adaptation: No symptoms are seen in infants with hypoglycaemia as long as there is access to alternative energy sources.
- Hypoglycaemia with impaired metabolic adaptation: If alternative energy substrates run out, unspecific symptoms like poor feeding, hypotonia, tremors or jitteriness can be observed. It is unlikely that hypoglycaemia will lead to long-term impairment at this stage.
- Hypoglycaemia with failed metabolic adaptation: Without treatment and ongoing hypoglycaemia infants will present distinct clinical signs like seizures and impaired consciousness. Treatment must be initiated immediately to avoid harm. If treatment is not provided immediately after symptom onset, hypoglycaemia at this stage can lead to long-term impairment and in severe cases circulatory arrest.

No studies could be identified that evaluated the reliability of specific symptoms and hypoglycaemia. The symptoms poor feeding and jitteriness have been associated with hypoglycaemia in the study by Harris and co-workers (1). Based on clinical experience it is rational to use the described symptoms as clinical signs for hypoglycaemia. *Level of evidence: very low.*

Consensus recommendation

Prevention

To prevent hypoglycaemia, the following interventions have been suggested for all infants:

- To be given the opportunity to breastfeed as soon as possible after the delivery (37,38). If the mother cannot give breast milk or does not aim to breastfeed, infant formula is suggested to be given instead. *Level of evidence: moderate*
- To be cared for with safe skin-to-skin with the parents (39–41). *Level of evidence: moderate*
- To be kept warm. Prevent hypothermia (42,43). *Level of evidence: low*

To facilitate breastfeeding, the following interventions have been suggested for infants:

- Be breastfed on demand and not be given a pacifier in the first few days. Pacifier use during this period may lead to fewer breastfeeding sessions, less breast milk intake and less stimulation of the mother's milk supply (44,45). *Level of evidence: low*
- If there is a need for supplementary feeding, primarily use cup feeding or when necessary tube feeding instead of bottle feeding if the mother aims to breastfeed (46–49). Although evidence derives mostly from studies including preterm infants, cup feeding seems a reasonable feeding approach also in the term and near-term population. *Level of evidence: low - moderate*

Mothers who are separated from their infants or have infants who do not suck strong or not often enough, shall be given the opportunity for early breast stimulation/breast milk expression preferably during the first hour after delivery. This early breast stimulation will allow the infant to be fed with the mother's own milk earlier, and the mother achieves a richer milk production (50,51). *Level of evidence: high*

Thereafter, breast stimulation/breast milk expression can continue at least 8 times a day. Breast stimulation/expression does not need to take place at regular intervals (52,53). *Level of evidence: low*

As complement to breastfeeding, asymptomatic infants at risk for hypoglycaemia (Figure 3: Infants at risk) are recommended to receive supplementary feeding beginning no later than at an age of one hour (37,54,55). *Level of evidence: low*

Thereafter, frequent breastfeeding is strived for as soon as the infants signals that it wants to breastfeed and at least every two to three hours. If possible, when feeding, one should try to simulate the normal eating pattern, which means frequent feedings (56,57). *Level of evidence: low*

Supplementary feeding is recommended to be given following breast feeding. *Consensus recommendation*

During breastfeeding, breastfeeding assessment is important to assess whether the infant is alert, sucking strongly and with a rhythmic suction pattern (58–60).

In a Swedish study (32) the incidence of hypoglycaemia was as low as 1.7% in LGA infants, which means that the number needed to treat with formula supplementation to prevent one case of hypoglycaemia is high. Breastfeeding has also been demonstrated to be superior to both expressed breast milk as well as formula for stabilization of blood glucose (61). Further, to minimize cow-milk based formula exposure the following exceptions to routine supplementation with formula are recommended for infants breastfeeding actively:

Upon satisfactory breastfeeding in the delivery room, one can wait with supplementary feeding but still monitor blood glucose in infants:

- born LGA where the mother did not have diabetes (32).

Consensus recommendation

- born AGA and the mother had a diet-treated gestational diabetes (37,38,62).

Level of evidence: low. Consensus recommendation

- born between 36+0 and 36+6 weeks of gestation having no other risk factors for hypoglycaemia (1,63,64). *Consensus recommendation*

If the infant is not assessed to being alert and sucking strongly with a rhythmic suction pattern, early supplementary feeding should be given also to these groups of infants.

Sick infants who are cared for at a neonatal ward are suggested to receive supplementary feeding, beginning at 30-60 minutes of age and then every two to three hours.

Prevention with Dextrose gel has been proposed as an alternative to early supplementary feeding with infant formula to infants at risk of hypoglycaemia. Since actual evidence is conflicting this cannot be generally recommended (65,66).

Milk amount and selection

In the first day, 5-7 ml/kg per supplementary feed is given (for hypoglycaemia, one can give up to 7-12 ml/kg per feed). Thereafter, the volumes are gradually increased during the following days. If the mother aims to breastfeed, supplemental feed volumes should be diminished or terminated as soon as clinical feasible. Although evidence for feeding volumes are lacking, 5-7 ml/kg given every second/every third hour is the common practice at Swedish neonatal units.

Consensus recommendation

The mother's own breast milk is preferred, and is always given as a first choice (67,68). In the use of donated breast milk or formula, the parents' opinions and approval must be obtained before it is given. *Consensus recommendation*

To protect and promote breastfeeding, the parents have to be provided with information that formula is usually only needed during a transitional period of a couple of days and a feeding care plan is recommended to be prepared. If supplementary feeding with infant formula is ongoing at hospital discharge, in combination with breastfeeding, information needs to be provided about how supplementary feeding has to be given and how it can be phased out (69,70).

Level of evidence: very low

There is no evidence that hydrolysed formula reduces later allergy risks in infants with or without heredity for cow milk protein allergy (71,72). *Level of evidence: high*

Measurement methods and sampling techniques

For screening and management of hypoglycaemia in the newborn infant fast and reliable blood tests are needed. Most of the measurement methods today report plasma glucose even when sampling is done on whole blood. Built-in algorithms are used to convert whole blood glucose to plasma glucose. With normal haematocrit, p-glucose is around 11% higher in comparison to whole blood glucose. This is based on the red blood cells' lower glucose content. At higher haematocrit, the difference increases (73). At present, there is conflicting evidence regarding differences between glucose values from arterial, venous or capillary samples (74,75).

In the choice of blood glucose meters, it is important that the instrument is validated for newborn or premature infants (76).

Based on reliability, glucose meters are divided into two categories:

The first is glucose meters, used at clinical chemical laboratories or accredited blood gas analysers, with very high reliability, using for example the glucose oxidase method.

The second category is glucose meters used bedside also called Point-of-Care meters (POC). These instruments have lower reliability especially at low glucose values and are used primarily as screening tool. Due to measurement inaccuracy, unexpected results measured by POC instruments have to be re-confirmed by the laboratory or blood gas analyser (77).

Large haematocrit variations in newborn entail most POC meters to overestimate p-glucose at low haematocrit values and underestimate p-glucose at high haematocrit levels. Despite POC instruments have built-in correction algorithms, they rarely improve the certainty in this respect among newborns or premature infants (77–79).

In special cases, it may be of value to use subcutaneous continuous glucose monitoring systems (CGMS) that displays glucose readings every five minutes. CGMS has been validated in newborn and premature infants. The method needs to be regularly calibrated against blood samples and is primarily seen as a screening method, where deviating or unexpected readings have to be

confirmed with blood samples that are analysed with a validated method (80–82). Its feasibility as a screening tool in newborn infants of diabetic mothers has recently been studied (83).

Sampling method

Both capillary and venous sampling are painful procedures and the use of adequate pain relief is strongly advised. Venepuncture by experienced personnel is recommended as the first line procedure for blood glucose testing in newborn infants (84–86). *Level of evidence: high*

Pain relief with breastfeeding/breast milk or with up to 1 ml concentrated glucose solution (300 mg/ml) given orally immediately before sampling is strongly recommended (87,88). *Level of evidence: high*

No evidence could be identified whether oral sucrose, breastfeeding or breast milk interferes with the results of a glucose blood sampling. In clinical practice pain relief with sucrose, breastfeeding or breast milk seems not to significantly alter blood glucose sampling results.

Sampling from central catheters such as umbilical arterial or venous catheter or central venous catheter with ongoing or recent glucose infusion may provide inaccurate and often falsely high p-glucose readings and cannot be used for measuring p-glucose levels.

Clinical screening and treatment protocol (Flowchart, Figure 3)

Immediate postnatal care for all newborn infants

Early and continuous safe skin-to-skin care is advised for all infants immediately after birth. This promotes an early start of breastfeeding, the parents' bonding and stabilises the infant's body temperature. Ensuring and maintaining a normal temperature in the newborn is furthermore recommended by the Swedish and European Resuscitation Councils and has been positively associated with improved neurological outcome (89–91).

All mothers to newborn infants are suggested to be encouraged and given the opportunity to start breastfeeding alternatively start breast milk expression (breast stimulation) as early as possible. Upon a need for supplementary feeding, the mother's own breast milk is given as a first choice. If the mother cannot provide breast milk or does not aim to breastfeed, infant formula has to be chosen instead (see Prevention).

Healthy newborns without risk factors and symptoms of hypoglycaemia should not be routinely monitored for hypoglycaemia.

Newborn infants at risk for hypoglycaemia

Newborns at risk for developing hypoglycaemia require special consideration in terms of breastfeeding or supplementary feeding and glucose control (1,92).

Because of currently conflicting evidence regarding prophylactic use of dextrose gel, this strategy cannot be generally recommended (65,66).

To avoid hypoglycaemia, it is important to promote/enable an early breastfeeding start. In addition supplemental feeding with the mother's own breast milk, alternatively with infant formula during the first hour of life, is strongly recommended for all infants at risk for hypoglycaemia (see Prevention).

To promote breastfeeding and diminish early cow milk-based infants formula exposure, one can consider to withhold supplementary feeding upon adequate breastfeeding and normal glucose values in the following cases:

- Large for gestational age infants to mothers NOT having any form of diabetes (type 1 or 2 diabetes or gestational diabetes)
- Appropriate for gestation age infants to mothers with SOLELY diet-controlled gestational diabetes.
- prematurely born infants born between 36+0 and 36+6 weeks of gestation with no other additional risk factors for hypoglycaemia.

P-glucose has to be checked before the second meal, but not later than three hours after birth.

Infants presenting hypoglycaemia-related symptoms:

Blood glucose has to be checked immediately in newborns showing symptoms of hypoglycaemia, such as tremor, jitteriness, hypotonus, lethargy, poor feeding or hypothermia.

Newborn infants presenting with serious symptoms, such as cyanosis, pallor, apnea, tachypnea, irritability, seizures, bradycardia or circulatory collapse require immediate admission to a neonatal or paediatric ward, to avoid prolonged hypoglycaemic periods and the risk of neurological sequelae (Table 3) (1,21,92).

Infants with p-glucose < 1.5 mmol/L

In infants with p-glucose level below 1.5 mmol/L or/and presenting with serious hypoglycaemia-related symptoms, treatment must be initiated immediately.

If possible, the infant receives a dose of dextrose gel (400 mg/ml) adjusted to body weight (0.5 ml/kg) massaged into the buccal mucosa. Simultaneously a peripheral or central venous access has to be established and an intravenous bolus of glucose has to be administered. It is advised to start glucose infusion immediately after the glucose bolus. Start with step I and increase gradually upon

continued low blood glucose levels (see Intravenous glucose treatment). At the same time and possibly with the help of a nasogastric tube, enteral feeding is given.

P-glucose has to be rechecked within 30 minutes.

Infants with p-glucose 1.5-1.9 mmol/L

A body-weight adjusted dose of dextrose gel (400 mg/ml) massaged into the infants buccal mucosa is advised. Breastfeeding and supplementary feeding shall be intensified by increasing the volume or shortening the interval between the feeds.

If hypoglycaemia persists (1.5-1.9 mmol/L) after one (to two) meals of supplementary feeds/dextrose gel, consider to start intravenous glucose treatment. Start with step I and increase gradually upon continued low blood glucose levels (see Intravenous glucose treatment).

P-glucose has to be rechecked within 30-60 minutes.

Infants with p-glucose of 2.0-2.5 mmol/L (without symptoms)

In infants not presenting hypoglycaemia related symptoms and with p-glucose between 2.0-2.5 mmol/L, a dose (0.5 ml/kg) of dextrose gel (400mg/ml) massaged into the buccal mucosa is recommended. Concomitantly breastfeeding and supplementary feeding shall be intensified by increasing the volume or shortening the time between feeding intervals. If there is persisting hypoglycaemia (2.0-2.5 mmol/L) after two to three meals and max two doses of dextrose gel, consider intravenous glucose infusion. Start with step I and increase gradually upon continued low blood glucose levels (see Intravenous glucose treatment).

P-glucose has to be rechecked within 1-2 hours.

Infants with p-glucose 2.6-3.0 mmol/L

Breastfeeding and supplementary feeding has to be continued with the same intensity. If ongoing intravenous glucose treatment continue with unchanged infusion rate.

P-glucose is suggested to be rechecked before the next feeding.

Infants with p-glucose > 3.0 mmol/L

Consider to increase the interval for p-glucose checks. Consider reducing the infusion rate in case of ongoing glucose infusion.

Dextrose gel

Two randomised control studies have been published comparing buccal administered dextrose gel to placebo in infants at risk of hypoglycaemia (3,5). Both studies have been included in a meta-analysis, demonstrating a reduced risk of hypoglycaemia, reduced number of admissions to the neonatal ward and thereby separation of infant and parents and increased breastfeeding frequency at discharge (4,6,61). In subsequent studies the effect was reproducible, when using dextrose gel in various maternity/neonatal wards (93–96).

Administration of dextrose gel (400 mg/ml):

Dosage: 200 mg/kg = 0.5 ml/kg.

The gel is drawn up into a syringe for enteral use in the recommended dose and is massaged into the buccal mucosa for a rapid uptake. If p-glucose level remains below 2.6 mmol/L a physician has to be informed and intravenous glucose treatment alternatively further doses of dextrose gel have to be considered. In the “Sugar Babies Study” protocol up to six doses of dextrose gel could be applied during 48 hours after birth (3). *Level of evidence: moderate - high*

Intravenous glucose treatment

Glucose bolus (“Minibolus”)

Dosage: 2 ml/kg of glucose 100 mg/ml

An intravenous glucose bolus is recommended at very low glucose levels ($<1.5\text{mmol/L}$) to normalise blood glucose levels more quickly. As an administration of a glucose bolus inhibits the production of endogenous glucagon the glucose bolus administration has to be followed immediately by a glucose infusion (97). *Level of evidence: low*

Glucose infusion

Intravenous glucose treatment has to be increased gradually to meet the infant’s current glucose needs (Figure 3).

If a high glucose volumes are needed to maintain euglycemia, the use of more concentrated glucose solutions is suggested (150, 200 or 250 mg/ml). Glucose 150 mg/ml and 200 mg/ml can be administered via a peripheral venous catheter in full-term infants with stringent observance of the venous catheter, but more hypertonic glucose solutions must always be administered via a central venous catheter (98). Monitoring of fluid and electrolyte balance is required in case high amounts of intravenous fluids have to be administered. Today no evidence is available regarding infusion rates and glucose concentration for treating newborn infant for hypoglycaemia. Recommendations are based on consensus and clinical practice. *Consensus recommendation*

Investigation of severe and/or prolonged hypoglycaemia

Newborn infants requiring high glucose supplementation $> 12\text{--}15\text{ mg/kg/min}$ and neonates with hypoglycaemic seizures should have an extended evaluation for a more severe underlying condition. Furthermore, consider early investigation in newborn infants with symptomatic hypoglycaemia who do not belong to any of the risk groups (Figure 3) and also in those without any other risk factor (Table 2). Investigation is suggested also be done upon persistent need of intravenous glucose $>10\text{ mg/kg/min}$ after 48 hours (99). *Level of evidence: very low*

The suggested primary investigation below consists of first line samples, the secondary investigation is more extensive. If possible collect one serum, one plasma and one urine sample for later laboratory analyses. To get a complete assessment picture, -if possible- sampling has to be coordinated at the same time and preferably take place during a hypoglycaemic period ($< 2.6\text{ mmol/L}$). Never let the sampling delay the infant's treatment. Always note the glucose level when collecting samples. The occurrence of ketone bodies in the urine or blood and lactate in blood may be a guide to determine the cause of hypoglycaemia (Figure 4); Urinary ketone bodies can most often provide enough information whether the condition is related to ketotic or non-ketotic hypoglycaemia. Blood ketone bodies can also be tested, but newborn infants ability is limited to produce ketone bodies as alternative energy sources upon low blood sugar. Moderate lactate levels are probably a more important energy substrate during the first days of life (15).

Investigation of severe and/or prolonged hypoglycaemia has to be discussed with paediatric specialists in metabolic and endocrine disorders.

The most common cause of *non-ketotic hypoglycaemia* is hyperinsulinism, which has to be primarily be suspected upon high glucose consumption. Transitory forms are seen in diabetes fetopathy, sepsis, asphyxia and growth restriction or other stressful events. These conditions may entail a delayed down regulation of insulin release at low blood glucose levels possibly caused by a defective regulation of the enzyme glucokinase in the pancreatic β -cells (16).

More prolonged hyperinsulinism is seen in diffuse or focal β -cell hyperplasia and in certain syndromes, e.g. Beckwith-Wiedemann syndrome, Sotos syndrome, CDG syndrome (congenital disorders of glycosylation) (100).

In persisting hyperinsulinism, the underlying genetic defect is known in at least 50% of the cases and target genetic diagnostics can sometimes provide guidance if the infant has a focal or diffuse form of hyperinsulinism (101). Both recessive and dominant heredity is described, as well as sporadic forms. Some of these mutations (above all recessive or focal forms) can cause foetal hyperinsulinism, which is associated with macrosomia at birth. Hyperinsulinism entails hypoglycaemia and at the same time reduces lipolysis (low level of free fatty acids) and ketone body formation (low/immeasurable levels of ketones). Non-ketotic hypoglycaemia is also seen in disorders of fatty acid oxidation when ketone bodies cannot be produced.

Ketotic hypoglycaemia is seen in newborn infants with a shortage of counter-regulating hormones, such as growth hormone and cortisol. In combination with low levels of thyroid hormones suspicion of pituitary insufficiency is strengthened. Disruption of gluconeogenesis and glycogenolysis also results in ketotic hypoglycaemia (99,102). Simultaneous lactate increase and acidosis can be seen in organic acidurias (Figure 4).

Clinical examination

The physical examination of the infant is important since the underlying cause may be suspected in conjunction with some clinical findings. In a LGA newborn infant macroglossia, omphalocele, or transverse ear crease are findings consistent with Beckwith-Wiedemann syndrome. LGA is also seen in neonates with diabetes foetopathy. In Sotos syndrome macrocephaly is present. Micropenis or midline facial defects is observed in infants with pituitary insufficiency, which also is associated with impaired liver function and jaundice in the neonatal period. Hepatomegaly rises suspicion of disorders of glycogen metabolism.

Pharmacological treatment

In persisting severe hypoglycaemia, pharmacological treatment may be necessary (103,104), especially if euglycemia cannot be achieved with intravenous glucose infusion (Figure 3). Treatment should, if possible, targeting on the most likely diagnosis and the drugs are not given in priority order. Before the start of a pharmaceutical treatment, an endocrinological and metabolic investigation should be done in consultation with specialists in endocrine and metabolic disorders (Table 4).

Follow up

Infants who have had severe hypoglycaemia accompanied by cerebral symptoms such as seizures, impaired consciousness or circulatory collapse or in infants where cerebral magnetic resonance imaging show hypoglycaemia related changes (101), are suggested to receive a long term follow-up. According to the national Swedish follow-up programme these infants are recommended to receive a follow-up until 5.5 years of age using a standardised schedule (105).

Level of evidence: low. Consensus recommendation

Infants with endocrine or metabolic disorders as a cause of hypoglycaemia or who have been under pharmacological treatment shall also be followed by the paediatric endocrinologist.

DISCUSSION

This guideline update and flowchart where breastfeeding friendly and family centred care approaches have been incorporated is intended to give health care providers a precise and evidence based screening and treatment strategy for infants at risk or with established postnatal hypoglycaemia. The metabolic evaluation section provides information of how to diagnose and investigate prolonged hypoglycaemia. The intention with the multidisciplinary authoring team was to achieve a broad acceptance among all categories of health care providers such as nurses, midwives and doctors to facilitate the harmonization of the guideline strategies.

One limitation is that the evidence for recommendations given in this guideline was gathered by a literature review which was not a comprehensive systematic literature research. As this guideline covers a wide range of aspects and recommendations a literature review seemed more applicable than a systematic literature research. Furthermore, the recommendations in this guideline are to a part based on consensus from clinical expert opinions, which implies risk of bias. To increase transparency of the evidence used for the given recommendations we introduced the GRADE approach in this guideline update. The GRADE approach offers a standardised assessment tools for evidence grading. Standardised evidence grading is advised for clinical guideline development (10,11).

CONCLUSION

An updated and evidence based national guideline for screening and treatment of neonatal hypoglycaemia will support standardised regimes, which may prevent hypoglycaemia and the risk for hypoglycaemia related long-term sequelae.

CONFLICT OF INTEREST

None of the authors have any conflict of interest to declare.

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Abbreviations

AGA - Appropriate for gestational age

CGMS - Continuous glucose monitoring system

DM - Diabetes mellitus

GDM - Gestational diabetes mellitus

GA - Gestational age

IUGR - Intrauterine growth retardation

LGA - Large for gestational age (birthweight $> +2SD$)

p-glucose – Plasma glucose

POC - Point of care (Bedside analysis)

SDS - Standard deviation score (Standard deviation from the mean value)

SGA - Small for gestational age (birthweight $< -2SD$)

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Table 1. Criteria for quality assessment under GRADE based on study design. Factors that reduce the grade of evidence can be low study quality, poor agreement between different studies, poor relevance, imprecise or inadequate data, and bias. Factors that raise the grade of evidence can be a large effect, high agreement between studies, high relevance to the care situation, dose-response correlation, no or good control of confounding factors (10).

Grade of evidence / Level of recommendation	Study design	Interpretation
High	Randomised studies	Further research is unlikely to change our confidence in the estimate of effect.
Moderate		Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Observational studies	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low		Any estimate of effect is very uncertain.

Table 2. Maternal and neonatal risk factors for neonatal hypoglycaemia (92).

Maternal risk factors	Neonatal risk factors
<ul style="list-style-type: none"> - Maternal diabetes or deviations in glucose tolerance tests during pregnancy - Preeclampsia and maternal hypertension - Earlier pregnancy with a large infant - Treatment with antidepressants - Treatment with tocolytics - Treatment with beta blockers - Drug abuse 	<ul style="list-style-type: none"> - Premature birth (<37 weeks) - Intrauterine growth restriction (IUGR) or small for gestational age (SGA) - Large for gestational age (LGA) - Perinatal asphyxia, hypothermia, breathing disorders, sepsis, congenital heart defects - Delayed start of breastfeeding - Diabetic fetopathy - Congenital metabolic or endocrine disorder

Table 3. Symptoms associated with neonatal hypoglycaemia (21,92)

Neurological	Circulatory and respiratory	General
<p>Hypotonia</p> <p>Irritability</p> <p>Lethargy</p> <p>Seizures</p>	<p>Cyanosis, Pallor</p> <p>Apnoea</p> <p>Tachypnoea</p> <p>Bradycardia</p> <p>Circulatory collapse</p>	<p>Poor feeding</p> <p>Hypothermia</p> <p>Sweating</p> <p>Tremors and jitteriness</p>

Table 4. Investigation of severe or persistent neonatal hypoglycaemia. Adapted from Zschocke J, Hoffmann GF. Vademecum Metabolicum (99)

<i>Primary testing</i>	<i>Secondary testing / investigation</i>
<ul style="list-style-type: none"> - Blood gas bedside test; pH, sodium, potassium, lactate, haemoglobin - U-ketones* - B-ketones (bed-side)* - P/S-cortisol* - S-insulin* - S-acylcarnitines, fractioned - U-organic acids 	<ul style="list-style-type: none"> - S-17-OH-progesterone, consider early sample for neonatal screening laboratory if available - B-lactate - P-β-hydroxybutyric acid* - P-C-peptide* - S-growth hormone (GH)* - P/S-TSH, -free thyroxine (fT4) - P/S-ACTH - P/S-ASAT, -ALAT, -ALP, -GT - P-free fatty acids* - P-ammonium-ion - P-amino acids - S-carbohydrate deficient transferrin (CDT) - Ultrasound abdomen (adrenal cortex bleeding?) - Ultrasound/MRI of the brain (cerebral haemorrhage, midline abnormalities?) - Ultrasound heart (myocardial hypertrophy?) - DNA-extraction (white blood cells, fibroblasts)

P=plasma; S=serum; B=whole blood; U=urine

*Preferably coordinate the tests with a hypoglycaemic episode (P-glucose <2.6 mmol/L) or with a hypoglycaemic episode with clinical symptoms.

Figure 1. Postnatal adaptation of glucose homeostasis. Adapted from Güemes et al. (12)

Figure 2. Postnatal plasma glucose values among 344 infants. Adapted from Srinivasan et al. (24)

Figure 3. Flowchart – Screening, prevention and treatment of neonatal hypoglycaemia issued by the

DM, Diabetes mellitus; GDM, gestational diabetes mellitus; LGA, large for gestational age; SGA, small for gestational age; AGA, appropriate for gestational age; GA, gestational age; BW, birth weight; SDS, standard deviation score; suppl., supplementary; conc., concentration; NICU, neonatal intensive care unit.

Figure 4. Flow chart for investigation of severe or persistent neonatal hypoglycaemia. Adapted from Stanley et al. (16)