Topic Expert Group: **Medical care and clinical practice**

Hypoglycaemia in at risk term infants

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Target group
Term newborn infants and parents

User group
Healthcare professionals, neonatal units, hospitals, and health services

Statement of standard
Measures are taken to identify, prevent, and manage hypoglycaemia in newborn infants who are at risk for impaired metabolic adaptation within the first 72 hours of life, including those with prolonged fetal distress, growth restriction, maternal diabetes, asphyxia, maternal beta-blocker medication.

Rationale
The goal is to prevent the adverse effect of hypoglycaemia while minimising unnecessary separation of mother and the newborn infant.

At birth, the discontinuation of nutrients from the mother results in a decline in plasma glucose level during the first two hours of postnatal life. Studies that have documented blood glucose concentration during the first 2-4 h of life reported values from as low as 1.1-1.4 mmol/L (20-25 mg/dL). (1) Although levels may be low early postnatally this stabilises within 48-72 hours post-delivery to levels more typical of later childhood.

Healthy newborn infants tolerate these initially low blood glucose levels even though glucose is the major oxidative fuel of the brain, because the neonatal brain also has the capacity to oxidise ketone bodies and lactate. During this period, endogenous production of glucose is promoted by glycogenolysis and gluconeogenesis. Enhancement of fat oxidative metabolism also contributes to the production of ketone bodies. Metabolic neonatal transition is integrated under the influence of a postnatal hormonal surge and timely production of key regulatory enzymes. (1)

However, the increased risk of hypoglycaemic exposure per se and impaired metabolic adaption resulting in inability to liberate alternative fuels such as ketones and lactate place some infants at increased risk from the adverse outcomes related to hypoglycaemia.

In addition to the risk categories listed above, perturbations of adaptive responses can occur in infants with sepsis, haemolytic disease and specific inborn errors of metabolism. They can also occur in term infants with congenital disorders that prevent infants from mounting an adequate counter-regulatory metabolic and endocrine response, such as hyperinsulinism. (2)

There are other well-known risk situations for hypoglycaemia such as preterm or late preterm birth, but these situations are not under the scope of this topic.

Benefits

Short-term benefits
- Reduced exposure to potentially harmful hypoglycaemia in at risk infants (3)
- Reduced unnecessary investigations and interventions (4)

- Minimised separation of mother and infant (consensus)
- Increased rate of diagnoses of infants with hypoglycaemic disorders before discharge (5)

Long-term benefits

- Improved neurologic outcome (consensus)

Components of the standard

Component	Grading of evidence	Indicator of meeting the standard
For parents and family		
1. Parents are informed by healthcare professionals about the importance of early energy provision and blood glucose monitoring. (6)	A (Low quality) B (High quality)	Patient information sheet
For healthcare professionals		
2. A unit guideline on identification, prevention, and management of hypoglycaemia is adhered to by all healthcare professionals.	B (High quality)	Guideline
3. Training on identification, prevention, and management of hypoglycaemia is attended by all responsible healthcare professionals.	B (High quality)	Training documentation
4. Risk factors for hypoglycaemia are identified at birth, and within the first days of life according to the clinical situation. (7)	A (Moderate quality)	Clinical records, guideline
5. An early feed, within one hour, is provided. (8,9)	A (High quality)	Clinical records, guideline
6. Thermal care, ideally given by skin-to-skin positioning, is provided. (10)	A (Moderate quality)	Clinical records, guideline
7. Blood glucose is measured at predetermined times. (3)	A (Moderate quality)	Clinical records, guideline
8. Observation of well-being and feeding documentation is conducted. (11)	B (High quality)	Clinical records, guideline
9. Interventions are administered according to operational thresholds approach. (12)	B (High quality)	Clinical records, guideline

For neonatal unit		
10. A unit guideline based on an operational threshold approach using values advocated by professional bodies is available and regularly updated in all maternity and neonatal units. (13)	A (Low quality) B (High quality)	Guideline
For hospital		
11. Training on identification, prevention, and management of hypoglycaemia is ensured.	A (High quality) B (High quality)	Training documentation
12. Equipment suitable for immediate and reliable blood glucose measurements is provided. (14)	A (High quality) B (High quality)	Audit report
13. Training in awareness of the limitations of the devices used for blood glucose monitoring is ensured. (14)	A (High quality) B (High quality)	Training documentation
For health service		
14. A national guideline based on an operational threshold approach using values advocated by professional bodies is available and regularly updated.	B (High quality)	Guideline

Where to go – further development of care

Further development	**Grading of evidence**
For parents and family	
N/A	
For healthcare professionals	
N/A	
For neonatal unit	
N/A	
For hospital	
N/A	
For health service	
• Prioritise scientific studies investigating impaired metabolic adaptation, and the long-term consequences of hypoglycaemia with or without clinical symptoms.	B (Moderate quality)

Getting started

Initial steps
For parents and family
• Parents are verbally informed by healthcare professionals about the importance of early energy provision and blood glucose monitoring.

For healthcare professionals

- Attend training on identification, prevention, and management of hypoglycaemia.
- Promote early skin-to-skin contact and breastfeeding as standard care.

For neonatal unit

- Develop and implement a unit guideline on identification, prevention, and management of hypoglycaemia, based on an operational threshold approach using values advocated by professional bodies.
- Develop information material about the importance of early energy provision and blood glucose monitoring for parents.

For hospital

- Support healthcare professionals to participate in training on identification, prevention, and management of hypoglycaemia.

For health service

- Develop and implement a national guideline on prevention, diagnosis and management of hypoglycaemia, based on an operational threshold approach using values advocated by professional bodies.

Description

Glucose levels and neurological outcomes

The association of neonatal hypoglycaemia with poor long-term neurodevelopment and neurocognition remains controversial. A systematic review showed that in early childhood (2-5 years), there was no neurodevelopmental impairment but an increased risk of visual impairment and executive dysfunction, and in mild childhood (6-11 years), an increased risk of neurodevelopmental impairment and low literacy and numeracy scores. However, there were important variations across the studies on blood glucose threshold (1.1 to < 2.6 mmol/L), as well as methods of glucose measurement, management strategies and treatments, outcome assessment methods, characteristics of the populations studied (low birth weight, preterm, infants of diabetic mothers), and other aspects of study designs that all raise the possibility of confounding. The authors concluded: "*Carefully designed randomized trials are required to determine the optimal management of neonates at risk of hypoglycaemia with long-term follow-up at least to school age.*" (15)

Also, the relationship between the severity, the frequency and the duration of low blood glucose level remains unclear. (15,16)

Recently, the HypoEXIT trial that randomised newborn at 35 weeks of gestation or later at risk for hypoglycaemia found that a 2.0 mmol/L threshold was not inferior to 2.6 mmol/L for psychomotor development at 18 months. None of the infants with hypoglycaemia had any clinical signs or symptoms of hypoglycaemia. (17) However, caution needs to be exercised in terms of extrapolation to all at risk neonates with hypoglycaemia. Firstly, the trial population of infants ‘at risk’ was formed with a third of infants whose risk was the classification of being large for gestational age (LGA). The level of risk for such infants is low and many centres would not consider this group would warrant screening as infants at risk for hypoglycaemia. (18) The study also excluded all neonates with severe hypoglycaemia before trial entry, and therefore may well have excluded neonates who could have a persistent hypoglycaemia-related disorder, such as congenital hyperinsulinism. Furthermore, the study reported on psychomotor development at 18 months, which is too young to investigate possible differences in neurocognitive function and is not a reliable marker of (potential) subtle influence of lower glucose concentrations on neurodevelopment. Studies that include follow-up to age 5 are required.

To date, there are strong arguments that symptomatic hypoglycaemia in newborn infants is associated with risk for brain damage and neurodevelopmental sequelae. (19) The potential for adverse outcome also exists if neonatal hypoglycaemia is over treated with a rapid rise in glucose concentrations after initial hypoglycaemia and in infants with less stable glucose concentrations, even within the normal range. (16)

Glucose thresholds for intervention

A recent study that determined postnatal changes in plasma glucose concentration in healthy infants receiving current recommended cares (breastfeeding and skin-to-skin as soon as possible after birth) reported that the 10th percentile for the first 48 hours approximated 2.6 mmol/L (47 mg/dL), although 39% showed at least one episode below this threshold of <2.6 mmol/L. There was a small increase in glucose concentration over the first 18 hours and a second increase after 48 hours, reaching values similar to adult's one after 96 hours. (20)

Data from the Sugar Babies Study which reported in a well-phenotyped group of infants (35–42 weeks gestational age) with risk factors for hypoglycaemia showed that blood glucose concentrations were <2.6mmol/L and < 2.0 mmol/L in 51% and 19%, respectively, but very few had abnormal clinical signs. 15% were too sleepy to feed when hypoglycaemic and 7% were noted to be jittery but 79% showed no clinical signs. (7)

- It is currently unknown at which glucose concentrations and after what duration neurologic injuries occur in newborn infants.
- Blood glucose levels below 1.0 mmol/L (18 mg/dL) that are associated with acute neurological dysfunction present the greatest risk of cerebral injury. (21–24)
- The tolerance to low glucose levels probably varies due to the newborn infant's ability to produce alternative substrates. (25)
- The concept of the "operational threshold" aims to provide clinicians with blood glucose values at which clinical interventions should be considered.

→ We need to implement practices that prevent harm which results from unrecognised or untreated hypoglycaemia whilst minimising unnecessary interventions and admission in neonatal unit.

- Measures to prevent and detect hypoglycaemia should be undertaken after birth in infants at risk, including: thermal care with skin-to-skin; support of breastfeeding; early energy provision and monitoring of blood glucose starting within the first hours of life.
- Feeding should be observed and abnormal feeding (not waking for feeds, not latching at the breast, not sucking effectively, appearing unsettled) should be recorded by the healthcare team.
- Glucose monitoring should be initiated before the second feed and no later than four hours after birth in asymptomatic infants, or at any time if there are abnormal clinical signs.
- Blood glucose concentration should be measured with validated devices. Local guidelines should be based on the operational threshold approach, using values advocated by professional bodies in their own country.

The lack of a clear evidence base for defining cerebral energy sufficiency is reflected in the contrast of recommendations between different organisations. (26)

1. Cornblath Operational Thresholds (2000) updated review of the literature subsequently (11), and used by the British Association of Perinatal Medicine (2017). (18) The suggested operational threshold concentrations at which clinicians should consider intervention are (12):
    - Blood glucose level <2 mmol/L (36 mg/dL) in an asymptomatic baby, that remains below the same value at next measurement.
    - A single measurement <2.5 mmol/L (45 mg/dL) in a newborn with abnormal clinical signs.
    - A very low concentration of blood glucose <1.0 mmol/L (<18 mg/dL) indicates the need for intravenous glucose infusion aimed at raising plasma glucose concentration above 2.5 mmol/L (45 mg/dL). The low value of 18 mg/dL is presumed to be near blood glucose concentrations that can cause brain damage.

    In symptomatic newborn infants with documented profound recurrent or persistent hyperinsulinic hypoglycaemia, therapeutic levels of 3.5 mmol/L (60 mg/dL) are recommended. (18) Infants with hypoxic ischemic encephalopathy have abnormal clinical signs by definition and the threshold of 2.5 mmol/L (45 mg/dL) should be used. (27)

2. The American Academy of Pediatrics (AAP) (2011)

    The American Academy of Pediatrics (AAP) proposed an algorithm with suggested thresholds for intervention in at risk newborn infants at ≥34 weeks' gestation depending upon postnatal age: 1.4-2.2 mmol/L (25-40 mg/dL) in the first 4 hours, 1.9-2.5 mmol/L (35-45mg/dL) from 4-24 hours and 2.5 mmol/L (45 mg/dL) after 24 hours. (8)

3. The Paediatric Endocrine Society (2015)
    The Paediatric Endocrine Society (PES) recommended higher plasma glucose levels to be considered safe in newborn infants: plasma glucose should be kept above 2.8 mmol/L (50 mg/dL) during the first 48 hours and above 3.3 mmol/L (60 mg/dL) for infants older than 48 hours. (5)

    Measurement of glucose levels

    - Accurate measurement of blood glucose level is essential for diagnosis and management of neonatal hypoglycaemia.
    - The ward-based blood gas biosensor should be considered the reference standard for measuring blood glucose based on accuracy and speed of result availability.
    - Blood gas analysers will produce glucose results as a calculated 'plasma glucose equivalent' concentration that should agree with laboratory plasma glucose results in the majority of cases.
    - Most handheld glucometers also report results as 'plasma glucose equivalents', some devices are available that measure true whole blood glucose by rupturing the blood cells and measuring combined plasma and cellular glucose.
    - This true whole blood glucose may be 10-15% lower than the corresponding plasma glucose. Practitioners should be aware that all current cot side technologies are prone to some inaccuracy, particularly in the range 0-2.0 mmol/l.
    - If handheld glucometers are being used to screen for low blood glucose, only those devices conforming to the ISO 15197:2013 standard should be used and their limitations should be understood: possible error of +/- 0.8 mmol/l (14.4 mg/dL) for values <5.5 mmol/l (<99 mg/dL).

- If a handheld glucometer is used, low values should be confirmed using an accurate method. (14)

Most common clinical symptoms in low blood glucose levels

Abnormal cry, pallor, hypothermia, lethargy, irritability, tremor/jitteriness, poor sucking, hypotonia, apnoea, bradycardia, respiratory distress, seizures, coma.

Clinical symptoms are not specific and not related to the severity of low blood glucose levels. All these clinical signs could be important signs of acute neurological dysfunction in the context of low blood glucose so need to be acted upon in the same way i.e. measurement of blood glucose.

Infants who initially had none of the risk factors for hypoglycaemia with abnormal feeding behaviour or with important loss of weight (>10%) become at risk and need clinical evaluation and may need glycaemia monitoring. Any healthy baby at birth who experiences adverse event during the neonatal period should also be monitored for hypoglycaemia.

Other considerations

- Neonates with congenital hyperinsulinism have to be identified at an early stage and receive appropriate treatment with a combination of high glucose intakes and sometimes, specific medication (glucagon, diazoxide…). Hyperinsulinism suppresses lipolysis and reduces ketones, which act as alternative fuels to maintain brain neuronal function; therefore, hypoglycaemia caused by congenital hyperinsulinism is detrimental to the brain, with adverse neurodevelopment in a third to half of children. (28,29)
- In term infants with hypoxic-ischaemic encephalopathy (HIE), glucose profiles vary widely during the first 72 hours of life. Early hypoglycaemia can occur, mainly in infants with severe HIE. (30)The optimal target blood glucose level for ensuring adequate energy provision to HIE remains unknown. However, data support guidance to maintain a blood glucose concentration of 2.5 mmol/L (45 mg/dL) or more in neonates with HIE. (27)
- Oral dextrose gel may be considered as an adjunct to a feeding plan in newborn infants at risk of hypoglycaemia. Prophylactic dextrose gel can reduce the incidence of neonatal hypoglycaemia, thus potentially reducing separation of mother and baby and supporting breastfeeding. (31,32)
- Newborn infants presenting with clinical signs of hypoglycaemia or with very low glucose levels should be treated with intravenous dextrose (an intravenous bolus of 2.5 ml/kg 10% glucose) as soon as possible, followed by constant rate infusion of glucose.
- Newborn infants with risk factors should not be discharged until at least two adequate-level consecutive pre-feed blood glucose measurements have been made, and effective feeding has been established over several fast-feed cycles.
- Hypoglycaemia that persists beyond 72 hours after birth might have a different aetiology than “transitional neonatal hypoglycaemia” and requires specific investigations. (5)

Source

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