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Neonatal Glucose Monitoring

Making Education Easy 2019

Independent expert commentary provided by Rachel Smith

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Abbreviations used in this review:

BGL = blood glucose level; **CI** = confidence interval; **CNS** = central nervous system; **CP** = cerebral palsy; **DW-MRI** = diffusion weighted magnetic resonance imaging; **GDH** = glucose dehydrogenase; **GLUT1** = glucose transporter 1; **GLUT2** = glucose transporter **2**; **GO** = glucose oxidase; **hGH** = human growth hormone; **HH** = hyperinsulinaemic hypoglycaemia; **HX** = hexokinase; **IDM** = infants of diabetic mothers; **IUGR** = intra-uterine growth restriction; **IVT** = intravenous treatment; **MRI** = magnetic resonance imaging; **NE** = neonatal encephalopathy; **NHBI** = neonatal hypoglycaemic brain injury; **POC** = point-of-care; **RR** = relative risk; **SCHAG** = short chain acyl-CoA dehydrogenase; **SGA** = small for gestational age.

This publication is intended as an educational resource for healthcare professionals, particularly those who may deal with neonatal hypoglycaemia in a clinical setting such as midwives, nurses and obstetricians in birthing suites, neonatal intensive care units, special care nurseries, special care baby units and maternity wards. It aims to clarify diagnosis of neonatal hypoglycaemia and reviews definition, etiology, risk factors, prognosis and management strategies. Particular emphasis is given to providing clear information about the correct point-of-care technology to use when quantifying biochemical blood glucose levels in infants. In this setting, Abbott's *iSTAT*® or *iSTAT Alinity*® system, portable handheld blood gas glucose analysers are an invaluable tool capable of accurately and reliably providing real-time blood glucose measurements and allowing timely therapeutic care.

Introduction

At birth a baby undergoes a sudden transition from a wholly dependent fetus provided with a continuous flow of energy through the umbilical cord to an independent neonate capable of extra uterine life. This transition requires a series of hormonal and metabolic adaptations to produce adequate levels of glucose to maintain normal blood glucose levels. Endocrine changes after birth assist the infant to switch on endogenous production of glucose until an exogenous nutritional supply is established. This process can fail to an extent in any infant but at-risk infants such as preterm and small for gestational age are especially susceptible due to low glycogen stores and lack of enzyme maturation. Up to 70% of at-risk infants are affected by a hypoglycaemic episode in the first 36-hrs of life. In the US, the overall incidence of symptomatic hypoglycaemia in infants varies from 1.3-3 per 1000 live births. The single most common metabolic problem in infants is hypoglycaemia[1] with a single episode capable of causing intellectual impairment. Recurrent or prolonged hypoglycaemic episodes can have major long –term sequelae include neurologic damage resulting in intellectual impairment, recurrent seizure activity, developmental delay and personality disorder. There is some evidence to suggest that neonatal hypoglycaemia may also result in impaired cardiovascular function. Whilst a definitive definition of neonatal hypoglycaemia which is predictive of adverse outcomes is not available, the operational thresholds at which a clinician should consider treatment has been set at < 2.5 - 2.6 mmol/L (depending on the evidence sited, facilities set either <2.5 or <2.6 as the operational threshold for intervention. Clinicians should check their local guidelines/policies for the level used in their facility. This review will use <2.6 mmol/L as the limit). In a clinical setting, enzymatic-based laboratory analysers are the gold standard for quantification of blood glucose levels, however, portable blood gas analysers such as Abbott's *iSTAT*® or *iSTAT Alinity*® portable Clinical Analyser system with either a glucose or Chem8 cartridge can also provide an accurate, reliable and fast result using a small blood sample. Point-of-care devices based on strip glucose technology are not suitable for use in a neonatal population. The *iSTAT*® system (or laboratory analysis in the absence of an *iSTAT*® analyser) should be used to confirm a screening glucose level of < 2.6 mmol/L to enable rapid medical intervention. Aggressive treatment even in asymptomatic infants should be undertaken immediately to prevent adverse outcomes. Since neonatal hypoglycaemic episode are common, may have no overt clinical signs, have severe consequences but can be easily treated it is of the utmost importance for clinicians to have access to reliable, fast and appropriate blood glucose testing technology.

Expert Comment

Glucose provides fuel for the brain and in the majority of newborns, normal extra-uterine transition physiology supports adequate blood glucose levels. Hypoglycaemia is the most common metabolic disorder in neonates and as such it is of utmost importance that clinicians support newborn transition to ensure the protective physiological changes occur. The *'warm, sweet and pink'* rule should be followed at every birth and in the early neonatal period. Supporting immediate and sustained skin-to-skin contact at birth provides temperature stability (warm), glucose production and consumption (sweet) and oxygen consumption (pink).
Neonatal hypoglycaemia is recognised as a contributor to neurodevelopmental impairment in childhood and beyond and is linked to cognitive impairment, emotional-behavioural difficulty, lower literacy levels and conditions such as epilepsy. Given the potential long-term neurological sequelae, neonatal hypoglycaemia needs to be accurately diagnosed and promptly treated.

Neonatal hypoglycaemia

Definition

Infants have a lower blood glucose reference range than adults with 2.6 – 5.0 mmol/L considered normo-glycaemic (euglycemic). This corresponds to 60%-80% of maternal levels.[2,3] A numerical definition for neonatal hypoglycaemia remains controversial because of a lack of significant correlation among plasma glucose concentration, clinical signs, and long-term sequelae. In addition, blood glucose test results vary with the source of the blood sample, the assay method, and whether whole blood, plasma, or serum glucose concentration is determined. The incidence of neonatal hypoglycaemia varies depending on the definition. Proposed numeric

definitions of neonatal hypoglycaemia range from < 1.67 - ≤ 3.33 mmol/L (< 30 to ≤ 60 mg/dL)[4] and usually vary according to age of the infant. Studies in term infants, breast-fed and formula-fed, of 2500 – 4000g show a nadir blood glucose level of 1.6 mmol/L[5] occurs between 1-2 hrs after birth[3] after which it rises to an equilibrium at approximately 72-hrs post birth[6]. Statistical ranges of low thresholds for plasma glucose level based on hours after birth in healthy term infants are presented in **Table 1**.[4]

Table 1. **Population low thresholds for neonatal blood glucose concentrations**

	Age of infant (hrs after birth)		
	< 3	3-24	< 24
≤ 5th percentile plasma glucose level	< 1.6 mmol/L	< 2.2mmol/L	< 2.6 mmol/L

Notes: Adapted from Alkalay, AL et al. Population meta-analysis of low plasma glucose thresholds in full-term normal newborns. Am J Perinatol 2006;23:115–19.[4]

This information has been used to formulate operational threshold guidelines (**Table 2**) which provide glucose concentrations at which clinicians should consider intervention.[35]

Table 2. **Operational BGL thresholds for infants**

Infant	BGL	Treatment
Asymptomatic infant[a]	If < 2.6 mmol/L	Clinical intervention to increase BGL
Infant with clinical signs	If < 2.6 mmol/L[57,58,59]	Clinical intervention to increase BGL
At-risk infant[b]	Initiate glucose monitoring within 2-3-hrs post-birth If BGL < 2.6 mmol/L	Clinical interventions to increase BGL

Notes: BGL = blood glucose level.[a] Srinivasan et al.[8] suggest a threshold of < 2.0mmol/L at 2 consecutive readings or a single reading < 1.0 mmol/L for asymptomatic infants.[b] See **Table 4**.

The World Health Organisation, the American Academy of Pediatrics, the U.S. National Institutes of Health and the National Childbirth Trust of the United Kingdom do not recommend routine monitoring of blood glucose in healthy, normal weight, term infants.[16]

Etiology

New babies in the first 36-hrs of life are very susceptible to hypoglycaemia for a range of reasons. Maintenance of normal blood glucose levels is dependent on the availability of substrates (glycogen, amino acids, lactate and glycerol), integrity of the glycogenolytic, gluconeogenic and lipolytic pathways and glucose-regulating hormones such as insulin, glucagon, adrenaline, growth hormone and cortisol[6] and deficiencies in any of these areas can lead to persistent or transient low blood sugar (hypoglycaemia). Healthy full-term infants have liver glycogen stores of up to 3 times greater than that found in an adult liver[7], however, these stores only last for 10-12-hrs post-birth[8] after which blood glucose maintenance is dependent on milk feeds.[9] These stores can be rapidly depleted by environmental stressors at birth that cause increased energy demands such as low temperatures[10,11], asphyxia (results in the infant switching to anaerobic metabolism) or infection.[12] Infants of diabetic mothers may also experience hypoglycaemia due to hyperinsulinism.[13] Transient neonatal hypoglycaemia usually resolves in a few days.[14] Newborns do have some mechanisms for neuroprotection during times of hypoglycaemia including glycogen stores in astrocytes[15] and the use of alternate cerebral energy substrates such as lactate and ketone bodies[15,16], although ketone bodies are low in all infants until milk feeds are established.[17,10] Breast-fed infants have greater levels of ketones than formula-fed infants.[16,18,19] These neuroprotection mechanisms provide limited defence and permanent brain damage can occur if hypoglycaemic episodes are frequent, severe or persistent. Low birthweight and preterm infants are particularly vulnerable to episodes of hypoglycaemia due to particularly poor counter-regulatory ketogenic responses[15,20], reduced ability to digest and extract glucose from the disaccharide lactose in milk (activity of the lactase enzyme has a direct correlation to gestational age[21]) and inadequacy of gluconeogenesis.[22,23] Persistent or recurrent neonatal hypoglycaemia is most commonly caused by hyperinsulinaemic hypoglycaemia (HH)[24], either congenital or secondary to certain risk factors. Congenital hyperinsulinism results in unregulated insulin secretion due to mutations in a range of genes (e.g. *ABCC8* and *KCNJ11*) or defects in the enzymes glucokinase, glutamate dehydrogenase and short chain acyl-CoA dehydrogenase (*SCHAD*).[25] Most infants with HH respond well to therapy with oral diazoxide and episodes can be resolved in a few months.[26, 28,27] **Table 3** lists some common causes of neonatal hypoglycaemia and risk factors are summarised in **Table 4**. Asymptomatic neonatal hypoglycaemia has been noted in up to 70% of extremely low birthweight babies (≤ 1000g) in the first week of life.[28,29]

Table 3. **Etiology of hypoglycaemia**

Etiology		Pathology	Effect
Lack of availability of energy substrates		Prematurity SGA IUGR Perinatal events such as low temperature, lack of oxygen, infection	Transient
Lack of control of glucose-regulating hormones	Insulin excess	Infant of diabetic mother Congenital hyperinsulism (HH) Beckwith-Wiedemann syndrome Sotos syndrome	Transient/ persistent
	hGH deficiency	Growth hormone deficiency Costello syndrome	Transient/ persistent
	Cortisol deficiency	Addison's disease Congenital adrenal hyperplasia Congenital hypopituitarism	Transient/ persistent
Syndromes		Turner syndrome Down's syndrome	Persistent
Iatrogenic		Tocolytic administration in mother (β-adrenergic)	Transient
Metabolic disorders		Organic acidemias such as Maple Syrup Urine Disease Glycogen storage disorders Hereditary fructose intolerance Galactosemia Fatty acid oxidation disorders	Persistent
Defects of glucose transporters		GLUT 1 and GLUT 2 deficiency	Persistent

hGH = human growth hormone; **HH** = hyperinsulinaemic hypoglycaemia; **IUGR** = intra-uterine growth restriction; **SGA** = small for gestational age.

Table 4. **Risk factors for neonatal hypoglycaemia**

	Risk factor	Incidence (%)
Maternal risk factors	Maternal diabetes mellitus[60, 61, 62, 63, 64]	Up to 50
	Intrapartum administration of glucose[65]	
	Maternal drug therapy including:[66]	
	β- blockers	
	Oral hypoglycaemia agents	
	Valproate[67]	
	Family history of metabolic disorders (e.g. medium-chain acyl-CoA dehydrogenase deficiency)[68]	
Infant risk factors	Preterm (<37 weeks)[69]	16 -67
	Late Term	16 -67
	Small for gestational age (<10th percentile)[70] or intrauterine growth-restricted	18- 72
	Large for gestational age (>90th percentile)	4 -38
	Low birthweight (< 2500g)	Up to 70
	Other:	
	hypothermia	
	macrosomia[71]	
	Perinatal hypoxic-ischaemic insult	
	Respiratory distress	
	Sepsis or suspected infections	
	Polycythaemia	
	Congenital cardiac abnormalities	
	Endocrine disorders	
	Inadequate feeding	
	Syndromes – Beckwith-Wiedemann, Timothy, Laron, Sotos	

Adapted from Woo et al. Glucose monitoring in neonates: need for accurate and non-invasive methods. Arch Dis Child Neonatal Ed 2014; 99:F153-76.[70]

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Babies at risk of hypoglycaemia

Maternal and neonatal risk factors

Risks for neonatal hypoglycaemia may be due to a range of maternal or infant factors. A list of risk factors can be seen in **Table 4**.

Prognosis

The level or duration of hypoglycaemia that is harmful to an infant's developing brain is not known, however it is known that there are many adverse impacts of a symptomatic hypoglycaemic incident in a neonate including neurologic damage[30,31,32,33], development delay[34,35,36] and personality disorders. A critical value below which the risk of neurodevelopmental impairment occurs can vary depending on the infant's energy demands and alternative energy fuels. Prolonged duration of hypoglycaemia, rather than its severity, has a greater risk for permanent brain damage.[37,51,52] The most common cause of remote symptomatic epilepsy with onset in the first 3 years of life is neonatal hypoglycaemia.[38] Pathologic changes in the brain caused by neonatal hypoglycaemia can be visualised using diffusion weighted magnetic resonance imaging (DW-MRI)[39] and include swelling of the neuronal and glial cells, necrosis, gyrus atrophy and white matter demyelination.[54,40] Damage is most commonly observed in the occipital and parietal lobes[54] with the cerebellum and brainstem generally unaffected. **Table 5** summarises studies investigating the neurodevelopmental outcomes of infants with hypoglycaemia.[56]

Prevention

The following strategies can assist in preventing neonatal hypoglycaemia:

1. Keep the baby warm (36.5-37.2˚ C)[15]
2. Initiate early, and encourage on-going, skin to skin contact[39]
3. Initiate early feeds within 30-60 minutes of birth
4. For at risk babies – continue oral feeding at least three hourly[13] or more frequently in response to feeding cues

Table 5. **Risk factors and neurodevelopmental outcome of infants with hypoglycaemia**

No	Authors	Study and subjects	Threshold values for NHBI	Findings	Risk factors
1	Lucas et al.[20]	Preterm 30.5±2.7-wks Birth weight <1850g (n=661)	< 2.6 mmol/L	At 18-months mental developmental scores lower by 14 points Motor developmental score < 13 pts Increased risk of CP or developmental delay RR 3.5 (95% CI: 1.3-9.4)	Recurrent hypoglycaemia for 5 or more days
2	Koh et al.[47]	Full term Asymptomatic	< 2.2 mmol/L	Abnormal evoked potentials Reversible CNS injury	Asymptomatic
3	Stenninger et al.[48]	IDM Term 38.2±1.4-wks Asymptomatic (n=28)	< 1.5 mmol/L	At 8-years – increased minimal brain dysfunction and deficits in attention, motor control and perception.	Asymptomatic
4	Duvanel et al.[52]	Preterm/SGA 31.9-week (27-34 weeks), 1160g (585 -1680g) (n=85)	< 2.6 mmol/L	At 3.5 and 5-years of age - Lower psychomotor scores - Reduced head circumference	Recurrent hypoglycaemia
5	Filan et al.[49]	Transient HH, IUGR, sepsis, IDM 36-40-weeks (n=4)	0.7 – 1.5 mmol/L	MRI (day 4-7) Occipital cerebral injury Motor delay, microcephaly, visual impairment	Hyperinsulinism
6	Alkalay et al.[4,50]	Symptomatic hypoglycaemia (n=89)	< 1.4 mmol/L	CNS injury in 21% (95% CI: 14-27)	Symptomatic hypoglycaemia
7	Tam et al.[53]	Term infants at risk for NE (n=94)	< 2.6 mmol/L	At 1-year, increased corticospinal tract injury by 3.7-fold. 15-point lower cognitive and language scores	At risk for NE

CI = confidence interval; **CNS** = central nervous system; **CP** = cerebral palsy; **HH** = hyperinsulinemic hypoglycaemia; **IDM** = infants of diabetic mothers; **IUGR** = intra-uterine growth restriction; **MRI** = magnetic resonance imaging; **NE** = neonatal encephalopathy; **NHBI** = neonatal hypoglycaemic brain injury; **RR** = relative risk; **SGA** = small for gestational age.
Reproduced from Chandran et al. Research and Reports in Neonatology 2015;5:17-30[72]
Note: Asymptomatic and symptomatic hypoglycaemias have been reported to be associated with varying grades of brain injury in both pre-term and full-term infants.

Expert comment

Despite the routine practice of screening of newborn babies deemed to be 'at risk' of hypoglycaemia much debate continues around the definition of hypoglycaemia in the newborn and the threshold at which intervention is recommended. A recent systematic review and meta-analysis on neonatal glycaemia and neurodevelopmental outcomes included studies where the definitions of hypoglycaemia ranged from 1.11 mmol/L to 2.6 mmol/L.[41] There continues to be a lack of consensus and as such, definitions and thresholds for intervention differ in clinical practice across Australia. A quick review of State-based policies and tertiary health service guidelines demonstrates ranges between 2.0 mmol/L for well neonates and 2.5-2.6 mmol/L for symptomatic and/or at-risk neonates. This lack of consensus is not surprising given the lack of high-quality evidence. Multiple authors in the field recommend carefully designed trials to better determine thresholds for treatment. Maternal and newborn risk factors for hypoglycaemia are well recognised and guide screening programs. It is important to remember that prevention of neonatal hypoglycaemia should not only begin at birth through supporting transition but start pre- and during pregnancy through the provision of information and support so women can reduce their risk factors for conditions such as diabetes, hypertension and improved clinican recognition and prevention of preterm labour and fetal growth problems.

Diagnosis - quantification of glucose in a clinical setting

Clinical manifestations of hypoglycaemia in neonates

Neonatal hypoglycaemia is often present without any clinical symptoms. Symptomatic neonatal hypoglycaemia can present with a range of manifestations and the presence of clinical symptoms are associated with an increased chance of permanent neuronal injury[18] although asymptomatic hypoglycaemia has been associated with abnormal evoked potentials[47], minimal brain dysfunction and deficits in attention, motor control and perception at 8-years of age in infants of diabetic mothers.[48] Common symptoms of hypoglycaemia include cyanosis, tremors, apnoea and convulsions (see **Table 6**). These symptoms are not unique to hypoglycaemia and are seen in a variety of conditions.[42] There is no single clinical symptom that defines hypoglycaemia as a pathological condition.

Table 6. **Clinical symptoms of neonatal hypoglycaemia**

Clinical signs of neonatal hypoglycaemia			
Symptoms associated with activation of the autonomic system due to rapid decline in blood glucose level		**More severe symptoms associated with decreased cerebral oxygen utilisation due to severe prolonged hypoglycaemia**	
Tremors/ jitteriness[45,18]	Eye rolling	Lethargy	Respiratory distress
Nausea, vomiting	Pallor[82]	Irritability	Apnoeic episodes
Poor feeding[38]	Hypothermia[83]	Restlessness	
Tachypnoea	Sweating	Seizure/ Convulsion	
Weak or high pitched cry	Tachycardia	Coma	
Temperature instability		Cyanotic episodes	

Current glucose monitoring methods

The gold standard for the determination of blood glucose concentration in a clinical setting is laboratory analysis[43,44] utilising the enzymatic reactions glucose oxidase, hexokinase or glucose dehydrogenase.[45] Central laboratory analysis is minimally impacted by varying metabolites in blood or hematocrit.[35] The primary drawback to laboratory testing is the delay in results. For this reason, a range of point-of-care (POC) devices based on a chemically- treated strip (dry reagent test strips) have been developed that provide on the spot results from a very small blood sample (≤ 0.3 µL)[35] and enable timely therapeutic decisions to be made. These devices were developed for use in adults and are not sensitive enough at low glucose concentrations such as that found in infants to be reliable in this setting[46,27,47] with deviations from laboratory results as great as 0.55 – 1.1 mmol/L.[48,49,64] Dry-reagent test strip POC devices are also subject to errors in glucose quantification readings due to analytical interference from oxygen, haematocrit levels, lipids, maltose, xylose and reducing substances such as paracetamol, uric acid and Vitamin C. Environmental factors such as temperature, humidity and altitude also affect dry-reagent test strip POC devices. Research into the use of continuous interstitial subcutaneous glucose monitoring has found it to be a reliable method[50] of monitoring glucose levels, however, it is not currently recommended for use in neonatal intensive care units because of the increased risk of infection and problems associated with interstitial glucose measurements in infants with oedema.[33] There are several glucose monitoring systems based on blood gas analysis, such as Abbott's *iSTAT*® or *iSTAT Alinity*® portable Clinical Analyser system with either a glucose or Chem8+ cartridge, that are reliable at low glucose concentrations[51] such as those in neonatal medicine, do not suffer interference from oxygen levels, haematocrit or environmental variables and can be reliably used in infants. Current methodologies for glucose monitoring are summarised in **Table 7**.

Factors affecting glucose results

Quantification of glucose is a complex process and accurate readings can be impacted by a variety of factors including the type of blood sample (whole blood, plasma, venous, capillary or arterial), the oxygen content of blood, individual hematocrit and patient factors such as hypotension, shock, dehydration and diabetic ketosis. A list of factors that impact accurate glucose quantification can be seen in **Table 8**. The use of dry-reagent test strip POC devices is not recommended in patients in critical care or in infants. In these situations, blood glucose concentration should be determined by blood gas analysis (such as the *iSTAT*® or *iSTAT Alinity*® portable Clinical Analyser) or central laboratory analysis.

Table 8. **Factors affecting the accuracy of blood glucose measurements in POC devices and result interpretation**

Factor		Impact
Type of blood sample	Whole blood or plasma	Plasma glucose values are 10-18% higher than whole blood glucose values because of plasma's high water content[73]
		Arterial or capillary samples overestimate the plasma glucose concentration by 10% in non-fasting patients
Interference from other blood factors	Haemoglobin concentrations Packed cell volumes[61, 64] Metabolic acidosis[74] High bilirubin levels[75] Oedema[76]	Results in inaccurate POC glucose measurement
Haematocrit	Percentage of red blood cells	Increase in hematocrit percentages result in decreased glucose concentration reading[77,78]
Blood oxygen concentrations		Oxygen interference in GO systems range from minimal to significant[79,80] Oxygen levels < 20 mmHg (2.66 kPa) at 37°C may decrease glucose results[81]
Patient factors	Hypotension Shock Dehydration Diabetic ketosis Newborns	Glucose meter readings inaccurate or significantly lower than lab glucose results**

** Dry-reagent test strip POC devices cannot be used in these conditions and blood gas or central lab analysis should be used[84] **GO** = glucose oxidase; **POC** = point-of-care

Table 7. **Current methodologies for glucose monitoring**

Glucose monitoring modality	Type of analyser	e.g.	Method of analysis		Source of sample	Assay range (mmol/L)	Sample volume (µl)	Neonatal	Advantages	Disadvantages
			Enzyme	Analysis						
Laboratory analysers		Radiometer ABL 725 blood gas analyser	GO HX or GHD	Electrochemical	Plasma/ serum	0 - 50	25	YES	Gold standard	Invasive, requires blood sampling Long lag time to obtain results
Point-of-care devices*	Dry-reagent test strip Glucose meters	HemoCue 201	Enzyme (GO or HX)	Electrochemical or colourometry	Whole blood	~ 1.1 – 33.3		NO	Fast results Minimal blood sample required	Inaccurate at low glucose concentrations Prone to inaccuracies from O_2, hematocrit and in critically unwell patients. **NOT SUITABLE FOR USE IN NEONATES**
	Blood Gas Analysers	iSTAT®(Abbott) or iSTAT Alinity	GO-based	Amperometry	Whole Blood	1.1 – 38.8	65	YES	Fast results Accurate at low GC No interference from variations in O_2 or hematocrit levels Small blood sample required Comparable accuracy to laboratory analysis	
Continuous glucose monitors	Subcutaneous	MiniMed Guardian REAL-Time	GO	Catheter	Interstitial fluid			NO	Real time rather than intermittent sampling	Invasive May be inaccurate and levels not detected in infants with oedema Foreign body response and biofouling-induced sensor degradation
	Microdialysis	Menarini GlucoDay S	GO		Interstitial fluid			NO	Sensor is outside the body	Open wound with tissue inflammation Long lag times for interstitial fluid to reach the sensor Discomfort from protruding probes

*The standard set by Clinical and Laboratory Standards Institute for meter accuracy: glucose meter must be ± 0.67 mmol/L of the lab result at glucose concentrations < 5.55 mmol/L and within ± 12.5% at glucose concentrations ≥ 5.55 mmol/L.

Recommended for clinical diagnosis and monitoring of hypoglycaemia in infants.

Enzyme-based reactions, **GO** = glucose oxidase; **HX**= hexokinase; **GDH** = glucose dehydrogenase; **GC** = glucose concentration.

Blood gas glucose analysis devices – Abbott Point of Care *iSTAT*® and *iSTAT Alinity*® Portable Analysers

A B

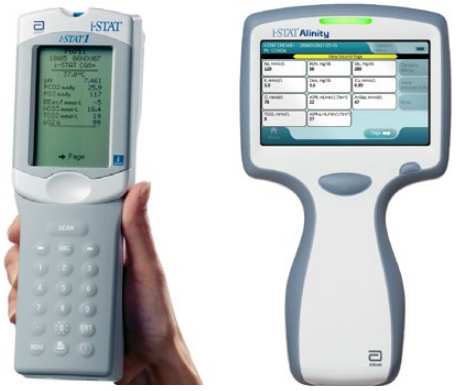

Figure 1: The Abbott Point of Care (A) *iSTAT*® portable analyser system and (B) *iSTAT Alinity*® portable analyser system. To be used in conjunction with either a Glucose or Chem8 cartridge for blood glucose concentration determination.

The *iSTAT*® and *iSTAT Alinity*® portable Clinical Analyser systems are composed of a hand-held analyser and single-use disposable bio-cartridges (Glucose or Chem8 cartridges are suitable for blood glucose quantification) with in-built calibrator and electrochemical multi-sensor array. Blood glucose levels are quantified by gas analysis using glucose oxidase-based amperometric peroxide detection. Glucose oxidase catalyses the oxidation of glucose to hydrogen peroxide. An amperometric sensor detects the stoichiometrically produced hydrogen peroxide on an electrode. The reduction current is proportional to the concentration of glucose in the test fluid. The chemical reaction is summarised in **Figure 2**. The *iSTAT*® and *iSTAT Alinity*® analyser provide medical professionals a fast, easy and convenient way to monitor blood glucose levels, even in infant populations where very low concentrations are found, and improves patient care by allowing rapid, in-time diagnostic and medical decisions to be made. The technical specification of the *iSTAT*® and *iSTAT Alinity*® for clinical blood glucose quantification can be seen in **Table 9**.

$$\text{D – glucose} + O_2 + H_2O \xrightarrow{\text{glucose oxidase}} \text{D – gluconic acid} + H_2O_2$$
$$H_2O_2 \longrightarrow 2H^+ + O_2 + 2e^-$$

Figure 2 Oxidation of glucose is catalysed by the glucose oxidase enzyme to gluconic acid and hydrogen peroxide. Measurement of hydrogen peroxide levels allow accurate determination of glucose concentrations.

Advantages of the *iSTAT*® and *iSTAT Alinity*® blood gas analyser for neonatal blood glucose quantification:

- Small, portable and easy to use
- Convenient method to screen, monitor and diagnose hypoglycaemia in a neonatal population
- Fast results
- Low cost
- Accurate glucose measurement at low concentrations in precise agreement with laboratory analysis
- A lower detection limit of 1.1 mmol/L (20 mg/dL)
- High analytical specificity (little interference from oxygen as long as the oxygen level is sufficient to run the reaction)[63]
- Not affected by haematocrit variations[84,85,86,87]
- No interference from environmental factors such as temperature, altitude or humidity.

Table 9. **Technical specifications of the *iSTAT*® and *iSTAT Alinity*® blood gas portable analysers for blood glucose quantification**

				Methodology			
	Manufacturer	**Assay range (mmol/L)**	**Sample type**	**Enzyme**	**Analysis**	**Sample volume (µl)**	**Time for results (s)**
iSTAT® and *iSTAT Alinity*®	Abbott	1.1 - 3.8 (20-700 mg/dl)	Whole Blood	Glucose oxidase	Amperometic	65	120

Expert comment

Unfortunately, in clinical practice, the most common method for detecting neonatal hypoglycaemia is also the least accurate. Point of Care (POC) testing using a glucometer and dry-reagent strips is subject to error when used in neonates as they were designed for use in adults and are not sensitive at low glucose concentration, and they do not use the current 'gold standard' of enzymatic analysis. However, they continue to be used as clinicians are familiar with the technology, they are inexpensive, and they provide immediate results from a very small amount of blood. Although many of the POC test dry-reagent strip glucometers used meet International Organization for Standardization (ISO) standards for medical devices, the compliance testing is undertaken on adults and does not take into consideration the unique differences in newborn blood factors such as haemoglobin concentrations, percentage of red blood cells and high bilirubin levels. Despite evidence that these devices can be inaccurate they continue to be used on neonates thus exposing newborns to increased risk for long term neurodevelopmental sequelae.
In the clinical setting, if the initial POC testing (using a glucometer that may be inaccurate) is normal, no further analysis takes place. Many argue that this is not an effective screening program and poses unacceptable risk to the newborn and advocate for more reliable forms of POC testing that utilise the 'gold standard' analysis such as the Abbott *iSTAT*®, *iSTAT Alinity*® or other similar analysis devices.

Management

Screening recommendations

Infants, asymptomatic or otherwise, with any of the risk factors should be screened for hypoglycaemia from ≥ 2hr of life to 36 hours (level 5 evidence; expert opinion).[36, 37,52] Asymptomatic, term babies without risk factors do not need to undergo routine BGL screening.[67] Any screening result of < 2.6 mmol/L should be confirmed using an *iSTAT*® or *iSTAT Alinity*® gas analyser or by central laboratory test and treatment immediately commenced.[53]

Treatment

Babies who are hypoglycaemic, with or without clinical symptoms, should be treated immediately to raise BGL to ≥ 2.6 mmol/L. Standard treatments include increased feeding, 0.5 mL/kg of Glucose Gel 40%[54] and regular BGL monitoring using the *iSTAT*® or *iSTAT Alinity*® analyser and appropriate cartridge. BGL levels < 1.5 mmol/L in any baby, even asymptomatic[40], require urgent intravenous treatment starting at 10% Glucose 4.2 mg/kg/min and potentially a 2 mL/kg bolus of 10% Glucose.[55] If the BGL remains low the Glucose 10% infusion can be incrementally increased up to 100ml/kg/day.[39] If hypoglycaemia is severe (glucose >10 mg/kg/min fails to control BGL), persistent or recurrent an endocrinology assessment needs to be done and pharmacological interventions started in this order:

1. Glucagon: 10-20 µg/kg/hr IV infusion[55]
2. Hydrocortisone: 1-2 mg/kg 6 hourly IV infusion
3. Diazoxide: initial dose 5 mg/kg/dose twice a day orally[56] and
4. Octreotide: 1-2 µg/kg 6-8 hourly subcutaneously.

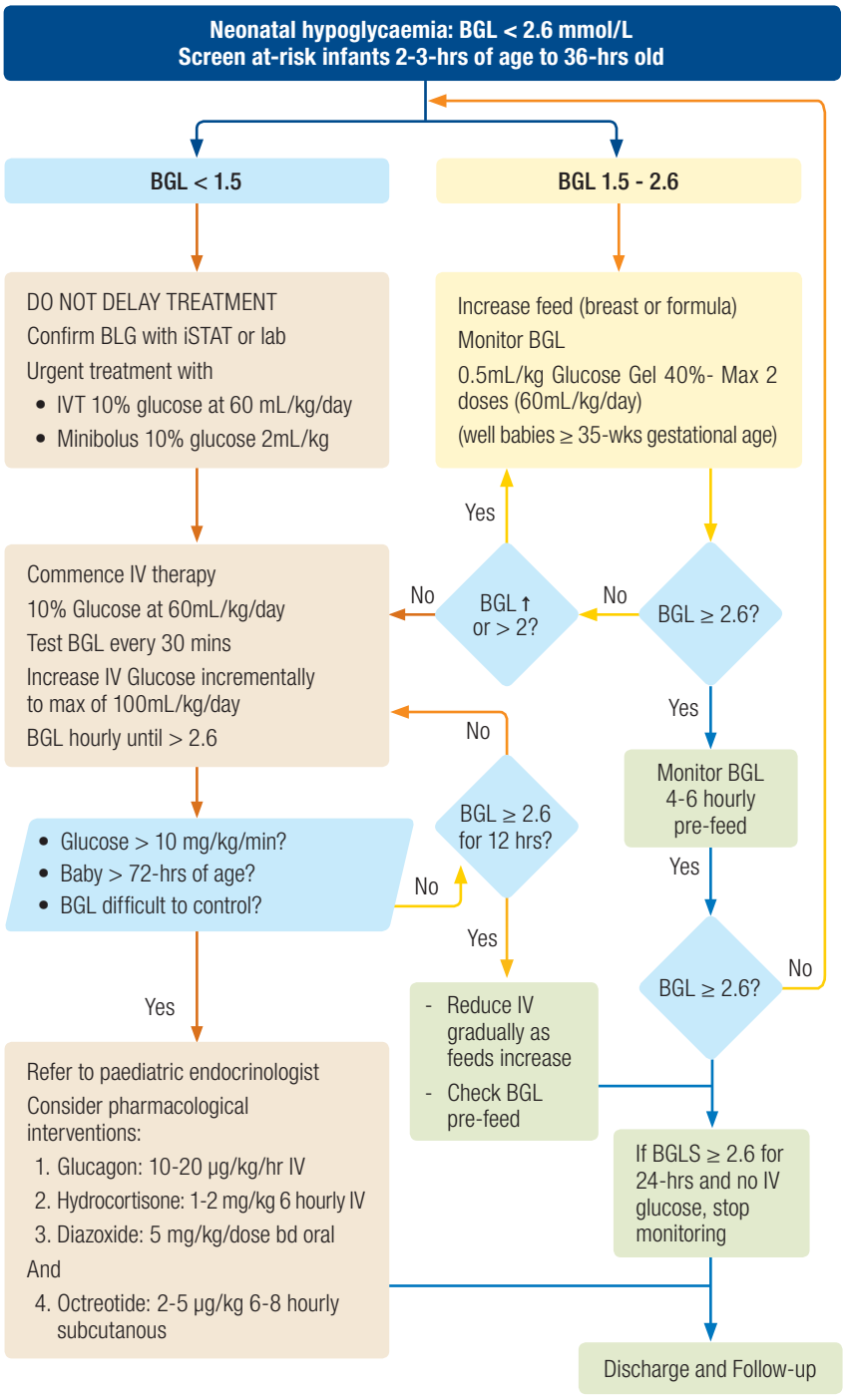

Figure 3: Flowchart: management of neonatal hypoglycaemia. Adapted from QLD Clinical guidelines.[88]
Notes: All blood glucose measurements are in mmol/L. All BGL measurements should be done using an iSTAT® handheld blood gas glucose analyser with a glucose or Chem8 cartridge or, if that is not available, by central laboratory analysis.
BGL = blood glucose level; **IVT** = intravenous treatment.

A full flowchart of clinical management procedures for neonatal hypoglycaemia can be found in **Figure 3**.

Conclusions

Glucose is the primary fuel source of infants and essential for brain function. Neonatal hypoglycaemia is a common emergency that can be easily treated but can have serious ramifications including encephalopathy which may result in permanent brain damage, especially if hypoglycaemic episodes are prolonged or recurrent. Clinical diagnosis of neonatal hypoglycaemia requires an assessment of physical symptoms (although asymptomatic hypoglycaemia is also possible) in conjunction with biochemical confirmation of blood glucose levels. The operational threshold value of blood glucose concentration < 2.6 mmol/L has been set to guide clinicians as to an appropriate level when intervention is necessary. All infants at-risk, such as pre-term or small for gestational age infants, for neonatal hypoglycaemia should be regularly screened between 2-hrs of life to at least 36-hours. Where a screening glucose measurement < 2.6 mmol/L is obtained, a follow up confirmation should be obtained using either an *iSTAT*® or *iSTAT Alinity*® portable handheld blood gas glucose analyser with a glucose or Chem8 cartridge or by central laboratory analysis. It is critical to establish neonatal blood glucose levels at the point of care setting quickly and accurately to enable medical intervention in a timely manner. Only blood gas POC glucose analysers such as the *iSTAT*® or *iSTAT Alinity*® are suitable for use in infants where glucose concentrations are very low (reference range 2.2 – 5.0 mmol/L) and critical clinical decisions need to be made regarding treatment around the 2.6 mmol/L threshold. The *iSTAT*® and *iSTAT Alinity*® generate real time results, allowing immediate treatment. Dry-reagent test strip glucose meters have shown variance of up to 0.83 mmol/L at levels below 5.5 mmol/L when compared with reference analysers and do not allow certainty in decision making, leading to delays in treatment, incorrect treatment or costly mistakes. Aggressive treatment, even in asymptomatic infants, should be undertaken immediately to prevent adverse outcomes.

Expert conclusions

- Prevention of neonatal hypoglycaemia is paramount and includes pre-pregnancy advice and support regarding reducing maternal risk factors; close monitoring and support during pregnancy to reduce risk factors; supporting transition at birth and in the early neonatal period by initiating and maintaining skin-to-skin contact, early initiation of chosen feeding method and frequent feeding intervals alongside monitoring of at-risk neonates
- Clinicians should be aware of the diagnostic and threshold levels in use at the institution they practice at and work within guidelines and policies in place.
- Accurate diagnosis and timely treatment of hypoglycaemia is required to prevent long-term neurodevelopmental sequelae and as such access to most accurate testing should be available in all areas providing newborn care
- Treatment options should be based on evidence where available, and include prioritising breastfeeding/breastmilk where this is the woman's preferred method of feeding; when appropriate, oral dextrose gel should be offered as evidence supports its efficacy in increasing blood glucose levels, supporting continuation of exclusive breastfeeding and decreasing the need for admission to a neonatal unit thus keeping mother and baby together
- Clinicians should also provide evidence-based information to women to enable them to make decisions in regard to monitoring and treatment options for their baby

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