the children's hospital at Westmead

BLOOD GLUCOSE MANAGEMENT IN THE GCNC - CHW

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- This document is for the blood glucose management of neonates cared for within the Grace Centre for Newborn Intensive Care. It covers the following components of care:
  - Hypoglycaemia and hyperglycaemia management
  - Critical bloods should be attended when the patient blood glucose level is <2.6mmol/L AND the neonate is greater than 24 hours of age

CHANGE SUMMARY

- N/A – New document
- **8 July 2022** – Minor change to Critical Bloods table on page 15 to blood tube required for Free Fatty Acids samples due to change in pathology processes

READ ACKNOWLEDGEMENT

- This practice guideline is to be read and acknowledged by all clinicians working in the Grace Centre for Newborn Intensive Care.

Approved by:	SCHN Policy, Procedure and Guideline Committee	
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NSW GOVERNMENT

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Background

Neonatal hypoglycaemia is common, occurring in 5-15% of all babies [1], and ~50% of at risk babies [2] but is often asymptomatic. Hypoglycaemia is a preventable cause of brain injury but the threshold at which management prevents irreversible adverse outcome is uncertain, and likely to be dependent on multiple factors in an individual infant.

Symptomatic, persistent and/or severe hypoglycaemia are considered significant and warranting management due to the higher risk of adverse neurological outcome, but there is no consensus about asymptomatic and transient hypoglycaemia. Foetal glucose is the primary metabolic fuel and is maintained by facilitated diffusion across the placenta, resulting in levels 70-80% of maternal glucose [3, 4]. The foetus can produce glucose in the setting of prolonged low supply from placental insufficiency or excess maternal insulin [3]. Insulin is secreted at lower glucose levels in the foetus to facilitate foetal growth. Maternal catecholamines and glucocorticoids released in labour increase blood glucose levels prior to birth [1, 4].

Clamping the umbilical cord interrupts glucose supply leading to a glucose nadir 1-2 hours after birth. Metabolic adaptation to this fall in glucose involves the baby reducing its insulin secretion, and increasing catecholamine and glucagon secretion to result in gluconeogenesis and glycogenolysis to gradually increase blood glucose to foetal levels by 2-4 hours and adult concentrations around 3-4 days of age [1, 4, 5].

Neonates have a proportionally large brain that consumes almost all available tissue glucose [1] with utilization rates of 4-6mg/kg/min in term neonates and up to 9mg/kg/min in preterm neonates [3]. Lactate can be used as a metabolic fuel in the first 48 hours [6], and free fatty acids and ketones after day 3-4 once the insulin level falls, but generally they provide a small proportion of metabolic fuel [1]. If neonatal glucose utilisation exceeds glycogenolysis and gluconeogenesis due to failure of metabolic adaptation then hypoglycaemia occurs [3]. In most babies this is transient, although some will persist for days to weeks due to persistent hyperinsulinism [4].

Critical illness disrupts glucose homeostatic mechanisms resulting in hypo- and hyperglycaemia, both of which are associated with poor outcomes in critically ill neonates [7].

Definition of normal BGL level (ranges) for neonate

Hypoglycaemia

BGL <2.6mmol/L require intervention

The definition of neonatal hypoglycaemia is contentious, with no sufficiently large randomized controlled trials and no consensus on levels that are clinically significant [3]. Ideally, we would recognise the threshold at which management of a neonatal glucose level is required to prevent brain injury. Unfortunately the threshold is likely variable in different babies depending on gestational age, postnatal age, concurrent metabolic demands, co-morbidities, duration of hypoglycaemia and availability of alternative fuels [1, 8].

The most widely used definition of neonatal hypoglycaemia as <2.6mmol/L arises from two studies, which included 661 preterm babies with birth weight <1,850g [9] and 5 newborns (as well as 12 children) [10] respectively. The first showed that infants with hypoglycaemia <2.6mmol/L on three or more days had an increased risk of developmental delay at 18 months, and in a subgroup at 8 years [9]. Koh, Aynsley-Green [10] showed neural dysfunction characterised by abnormal evoked potentials occurred only in babies with glucose concentrations <2.6mmol/L, but that the onset was variable with normal evoked potentials in one infant at 1.9mmol/L. In healthy, appropriately grown term babies a plasma glucose level of 2.6mmol/L approximates the 10th centile in the first 48 hours of life [5].

In systematic review of infants exposed to neonatal hypoglycaemia (definition ranging from <1.1mmol/L to <2.6mmol/L) without congenital malformations, metabolic disorders and congenital hyperinsulinism Shah, Harding [11] found an association with visual-motor impairment and executive dysfunction in early childhood, and neurodevelopmental impairment, low literacy and numeracy in mid-childhood. Initial blood glucose ≤2.2mmol/L has been shown to be independently associated with adverse neurological outcome and death in term infants with severe foetal acidaemia (pH <7.0) [12] but it is unclear if it is necessary to correct low levels in asymptomatic babies who have brief, early (<2hrs of age) hypoglycaemia [4].

Operational thresholds have been widely used with most intervening when the glucose level is below 2.6mmol/L [8]. This is particularly important for infants with risk factors for compromised metabolic adaptation, unwell infants with increased metabolic demand, infants on parenteral nutrition and symptomatic infants [7, 8]. Polycythaemia, hyperviscosity, hypotension and decreased cardiac output reduce cerebral plasma flow and therefore glucose delivery further exacerbating neuronal injury in the setting of hypoglycaemia [3]. Although some authors have reported no difference in developmental outcomes in infants managed with a threshold of 2.0mmol/L compared with 2.6mmol/L, this has been in healthy, asymptomatic, relatively mature infants [13].

Therefore, for babies admitted to Grace who are separated from their mother and/or unwell we intervene when the BGL is <2.6mmol/L. Occasional well babies admitted in the first 24 hours of life who can feed may warrant a lower threshold, particularly in the first few hours after birth and they are asymptomatic, but this should be based on neonatologist discretion.

Hyperglycaemia

A standard operational definition of hyperglycaemia in neonates has not been established, with considerable variability seen in the thresholds referred to in the current literature [24, 29 & 30]. These threshold definitions range from 7-13.3mmol/L, however contextual factors such as:

- Length of duration of hyperglycaemia
- The underlying cause of hyperglycaemia
- Severity of hyperglycaemia
- The presence of risk factors for hyperglycaemia

Are important when considering management of hyperglycaemia in the neonate as hyperglycaemia can be associated with increased morbidity and mortality), with the severity of the impact increasing with increased duration of hyperglycaemia [24, 29 & 30].

Potential consequences of prolonged and/or severe hyperglycaemia include [24, 29 & 30]:

- Dehydration secondary to osmotic diuresis
- Electrolyte imbalances
- Poor growth
- Impaired immunity and increased susceptibility to infection
- Diabetic ketoacidosis
- Increased risk of intracranial haemorrhage due to hyperosmolarity with osmotic shifts
- Hyperglycaemia-mediated brain injury
- Poorer neurodevelopmental outcomes

Risk factors

Below details the common causes of blood glucose instability:

Hypoglycaemia	Hyperglycaemia
Prematurity Intrauterine growth retardation (IUGR) Infants who have experienced perinatal stress due to: • Perinatal asphyxia • Maternal hypertension or preeclampsia/eclampsia • Meconium aspiration syndrome • Polycythaemia Sepsis Hypothermia Hyperinsulinism (transient/persistent) Infants of diabetic mothers Small for gestational age (SGA) infants Large for gestational age (LGA) infants Postmaturity (infants born at a gestational age >42 weeks) Maternal use of beta-adrenergic agents Maternal use of oral hypoglycaemic agents Congenital heart disease Infants with clinical signs of wasting Infants with respiratory distress syndrome Infants with haemolytic disease Inborn errors of metabolism Congenital syndromes associated with hypoglycaemia (e.g., Beckwith-Wiedemann and Kabuki syndromes)Erythroblastosis fetalis Exchange transfusion Islet cell dysplasia Family history of a genetic form of hypoglycaemia Infants with clinical signs of wasting Endocrinological disorders (e.g., hypopituitarism and congenital adrenal hyperplasia)	Prematurity Extremely low birth weight and very low birth weight infants Intrauterine growth restriction (IUGR) Critically unwell infants Post-operative stress Sepsis Neonatal diabetes mellitus Methyl xanthines (e.g. caffeine) Use of catecholamine infusions (e.g. noradrenaline and adrenaline) Corticosteroids use Absence of/delayed enteral feeding Administration of higher than required rates of intravenous glucose (i.e. inappropriately excessive glucose infusion rate)

Infants of diabetic mothers

Gestational diabetes mellitus (GDM) is characterised by diabetes which develops during pregnancy and affects approximately 16% of pregnancies in Australia every year [32]. It is diagnosed when elevated blood glucose levels are evident during oral glucose tolerance tests (OGTT) performed during the second trimester. The OGTT assesses the pancreas' ability to secrete insulin in response to the glucose (typically 75g glucose) and the body's response to the increase in insulin. GDM is typically diagnosed from 24 weeks gestation onwards but can be diagnosed sooner. Women with existing diabetes (Type I or II) are not classified as gestational diabetics.

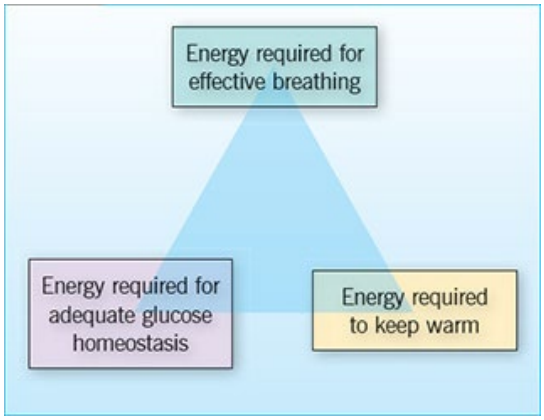
Of note, GDM is twice as common in Aboriginal and Torres Strait Islander women compared to non-indigenous women [32]. Mothers of Polynesian, Middle Eastern and Asian birth origin are 3 times as likely to have GDM compared to Australian born mothers [32]. Maternal GDM can lead to neonatal hypoglycaemia due to impaired metabolic adaptation and persistent hyperinsulinism.

Studies suggest that women with GDM have a decreased rate of breastfeeding and that the duration of breastfeeding is reduced compared with mothers who did not have a diagnosis of GDM [33]. This number was further reduced if the mother required insulin during their pregnancy or maternal obesity was present [33].

Neonatal energy triangle

At birth, the neonate's glucose level is 70% of the maternal blood glucose. After cord clamping, the neonate's blood glucose levels fall, reaching its lowest point at around two hours of life. At this point, hepatic glycogen stores are depleted & glycogenolysis is replaced by gluconeogenesis.

The thermoregulation energy triangle describes the way in which the neonate maintains homeostasis in temperature, blood glucose and oxygenation status. Therefore infants with respiratory distress and hypothermia are at higher risk of developing hypoglycaemia.



Neonatal energy triangle [22].

Physical Assessment

A comprehensive physical assessment should be conducted when blood glucose instability is suspected and/or has been identified.

Keeping in mind the neonatal energy triangle, neonatal glucose homeostasis and adaptation following birth, it is important to note that infants who present with the clinical signs of hypothermia and respiratory distress are at particular risk of developing hypoglycaemia and clinicians should closely monitor the blood glucose levels in these patients.

Neonates with hyperglycaemia or hypoglycaemia may be asymptomatic, and those who are symptomatic may present with clinical signs that are non-specific and may overlap or occur concurrently as a part of other newborn disorders/illnesses [23, 24]. Regular measurement of blood glucose levels in at-risk infants, thorough physical examination, and consideration of the clinical signs present may assist in prevention and early treatment of glycaemic disturbances.

Clinical signs and symptoms of hypoglycaemia [23]

	Clinical Signs & Symptoms
Neurological	Irritability Jitteriness Tremors Temperature instability Abnormal cry (weak and/or high-pitched cry) Hypotonia Lethargy Seizures Alterations in level of consciousness (e.g., coma, stupor) Poor feeding Breathing abnormalities
Respiratory	Tachypnoea Hypoventilation Apnoea
Cardiovascular	Bradycardia Tachycardia Diaphoresis Cyanosis Pallor

Clinical signs and symptoms of hyperglycaemia [24]:

Clinical signs and symptoms may be non-specific, and often relate to the underlying cause of the hyperglycaemia:

- Dehydration (due to osmotic diuresis)
- Polyuria
- Glucosuria (due to osmotic diuresis). A glucose value of 2+ or higher the in urine increases the risk on osmotic diuresis
- Weight loss and/or failure to thrive
- Feeding difficulties
- Fever

Investigations

Point of Care Testing Using a Glucometer

Please refer to the section below regarding the use of glucometers.

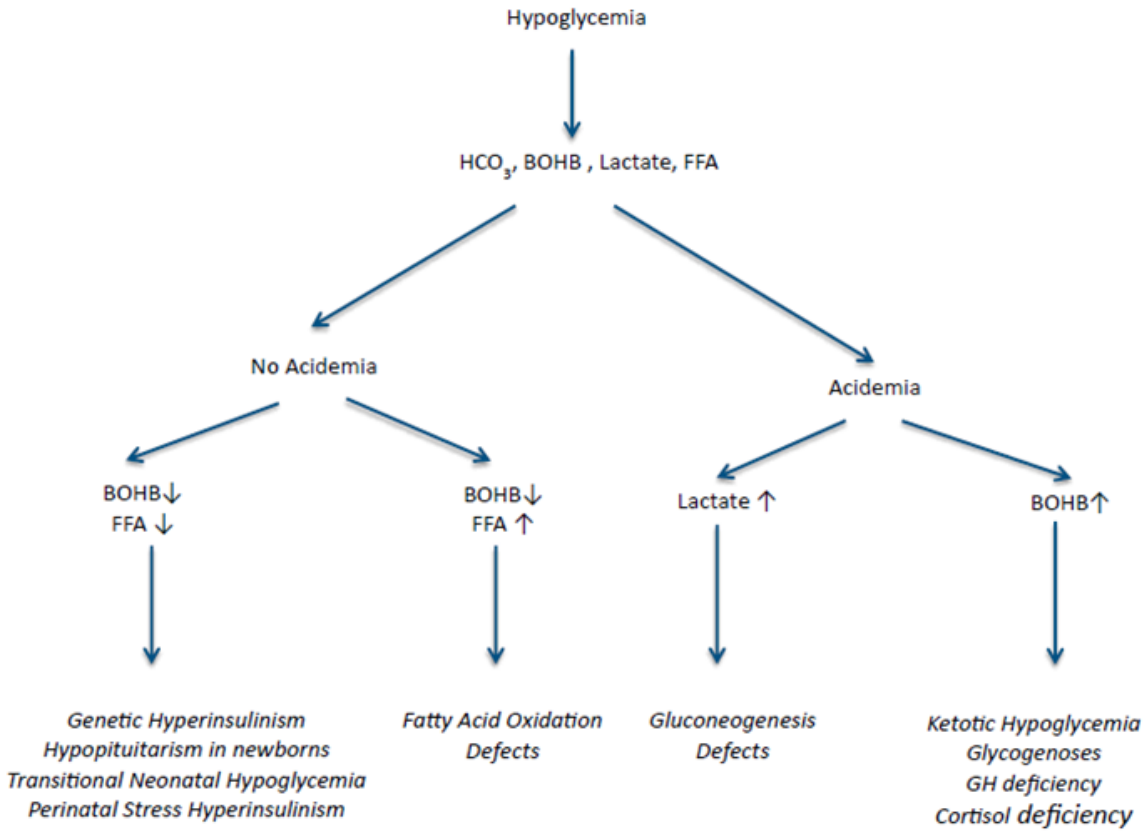
Point of Care Testing: Blood Gas

A blood gas is a useful point of care test that can provide valuable information including:

- Reliable blood glucose measurement
- Lactate (if sample is free flowing) and anion gap

Critical Bloods [25]

It is ideal to obtain critical bloods before treating the hypoglycaemia as some of these conditions (e.g., inborn errors of metabolism) can only be identified by abnormal results of tests taken while the patient is in a hypoglycaemic state.



*BOHB (beta-hydroxybutyrate), FFA (free fatty acids), GH (growth hormone), HCO3 (bicarbonate)

Algorithm showing how the major categories of hypoglycaemia can be determined from critical bloods results. [26]

Please refer to the section below on critical bloods for further information.

Other Investigations [26-28]

At the request of the neonatologist (often in consultation with the Endocrinology and/or Metabolic teams), additional investigations may be performed to help determine if an underlying metabolic or endocrinal condition is the cause of glycaemic disturbance in the neonate. These investigations include:

- *Urine Metabolic Screen (UMS):* collected as a random urine sample, a UMS can detect the presence of metabolic disorders (e.g. organic acidaemia, fatty acid oxidation defects, and glycolytic disorders). It consists of a simple dipstick test (which detects abnormal concentrations of protein, blood, glucose and reducing substances), measurement of amino acids, measurement of organic acids and acylglycines, and measurement of mucopolysaccharides. It is essential that the urine is collected at the time of hypoglycaemia, because markers of inborn errors of metabolism will not be able to be detected when the neonate is euglycaemic.
- *Reducing Substances (faecal):* this test detects the presence of reducing sugars (e.g. glucose, fructose, lactose and galactose) and which if positive, can indicate that disorders of impaired carbohydrate digestion may be present (e.g. galactosaemia, hereditary fructose intolerance).
- *Ammonia:* plasma ammonia is elevated in urea cycle disorders and hyperinsulin/hperammonaemia. Plasma ammonia may be elevated in several inhgerited metabolic disorders including fatty acid oxidation disorders and organic acidaemia.
- *Acylcarnitine Profile:* elevated acylcarnitines occur in fatty acid oxidation defects. The patterns of acylcarnitine species elevation can assist in determining which fatty acid oxidation disorder.
- *Liver Function Test:* abnormal liver function results can assist in identifying the presence of glycogen storage disorders (GSD) and other inborn errors of metabolism such as galactosaemia.
- *Uric Acid:* plasma uric acid or urate can identify hyperuricaemia which can be caused by inborn errors of purine metabolism including glycogen storage disorders.
- *Plasma Amino Acids:* this test can be vital in diagnosing inborn errors of metabolism
- *Creatine Kinase (CK):* extremely elevated CK levels can be present with certain inborn errors of metabolism (e.g. some of the glycogen storage diseases).
- *C-Peptide:* this test monitors endogenous insulin production by the beta cells in the pancreas and can help determine the cause of hypoglycaemia (i.e. can aid in diagnosis of neonatal diabetes).
- *Ophthalmology Review, Head Ultrasound & Brain MRI:* severe and persistent untreated hypoglycaemia in neonates has been associated with hypoglycaemic brain injury that predominantly affect the occipital and parietal regions of the brain. These investigations may assist in determining the presence and extent of neurological insult that has occurred.
- *Short Synacthen Test:* assess the response of the adrenal cortex to stimulation in suspected adrenocortical insufficiency (primary, secondary or tertiary) or in the

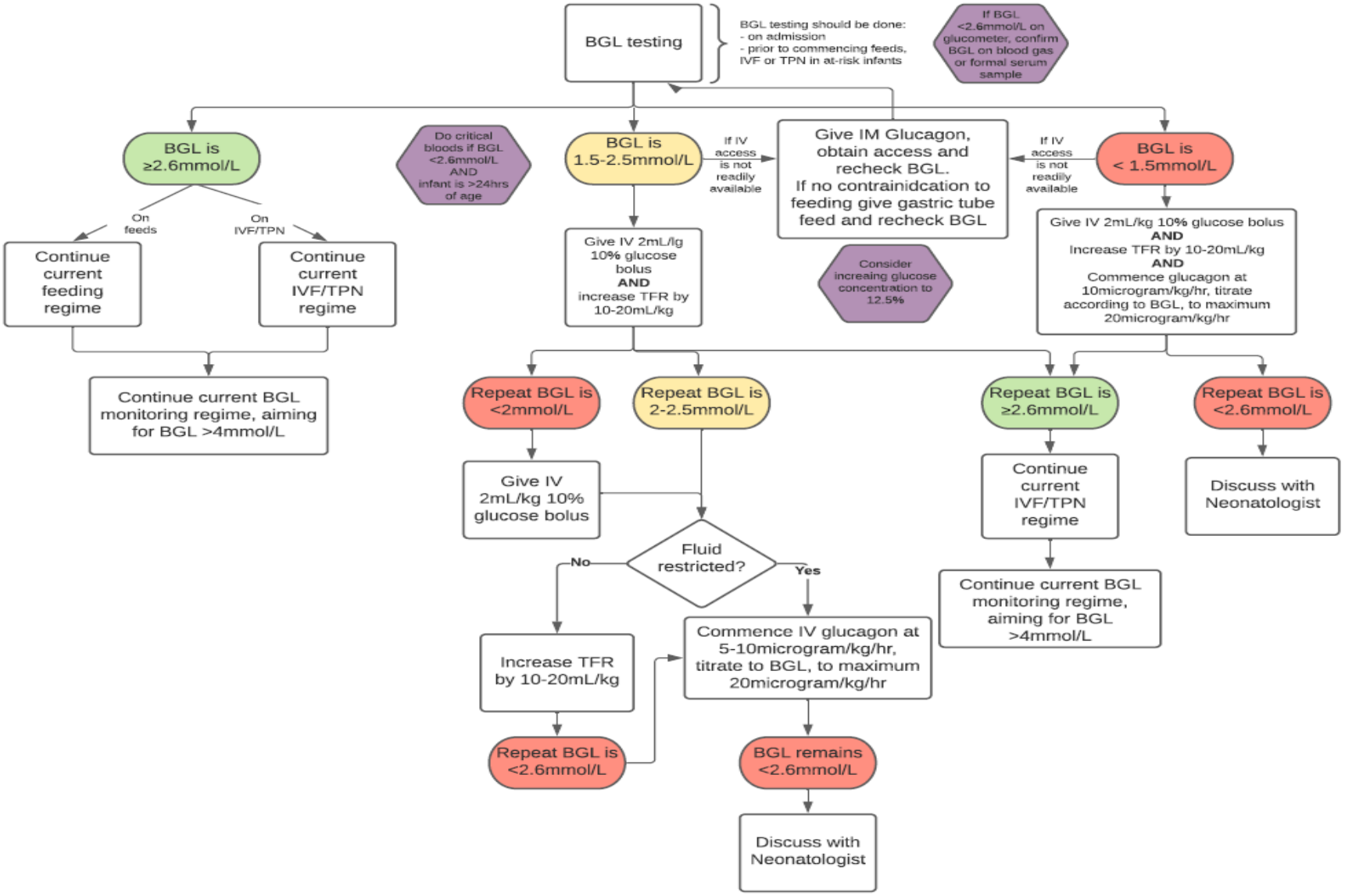
diagnosis of congenital adrenal hyperplasia. This test is typically requested when critical bloods sent during a period of hypoglycaemia show an inappropriately low cortisol level. For further information on this test, please refer to"4.23 Short ACTH (Synacthen) STANDARD DOSE Stimulation Test" in the Endocrinology and Metabolism Testing Protocols document

Hypoglycaemia management

The goal is to prevent and treat acute symptomatic hypoglycaemia to provide adequate cerebral fuel and decrease the risk of brain injury. Early feeding, skin to skin and keeping infants warm and dry are recommended prophylactic measures in well newborn babies [1]. Usual management for hypoglycaemia in non-surgical neonatal care settings may involve the use of glucogel and/or establishing feeds, with intravenous management reserved for severe or persistent hypoglycaemia to avoid unnecessary admission to NICU [1]. Grace babies are admitted for other indications where feeding can be contraindicated or not feasible initially with intravenous access being common place. As a result, glucogel is not currently a therapy that is used in GCNIC.

Prevention:
Maintain normothermia
Provide an exogenous source of glucose within 1 hour of birth
(IV glucose, breastmilk or formula)

Blood glucose should be measured on admission (not before 1 hour of age). Most admitted infants will be managed initially with IV fluids. If the BGL is ≥2.6 IV fluids should be continued with a therapeutic goal of 4mmol/L. If the BGL is <2.6mmol/L a 2mL/kg bolus of IV 10% dextrose should be given [36], followed by an increase in the glucose infusion rate, usually by increasing the rate of infusion rather than the percentage of dextrose. Excessive dextrose boluses and concentrations can lead to persistent hyperinsulinism with rebound hypoglycaemia and excessive glucose utilization [3] so consider initiating glucagon in infants with severe hypoglycaemia, high glucose infusion rates or repeated bolus. The recommended management of hypoglycaemia at Grace is shown in the following flowchart.


BGL testing
BGL testing should be done:
- on admission
- prior to commencing feeds, IVF or TPN in at-risk infants
If BGL <2.6mmol/L on glucometer, confirm BGL on blood gas or formal serum sample
BGL is ≥2.6mmol/L
On feeds
On IVF/TPN
Continue current feeding regime
Continue current IVF/TPN regime
Continue current BGL monitoring regime, aiming for BGL >4mmol/L
Do critical bloods if BGL <2.6mmol/L AND infant is >24hrs of age
BGL is 1.5-2.5mmol/L
If IV access is not readily available
Give IM Glucagon, obtain access and recheck BGL. If no contrainidcation to feeding give gastric tube feed and recheck BGL
Consider increaing glucose concentration to 12.5%
Give IV 2mL/kg 10% glucose bolus AND increase TFR by 10-20mL/kg
BGL is < 1.5mmol/L
If IV access is not readily available
Give IV 2mL/kg 10% glucose bolus AND Increase TFR by 10-20mL/kg AND Commence glucagon at 10microgram/kg/hr, titrate according to BGL, to maximum 20microgram/kg/hr
Repeat BGL is <2mmol/L
Repeat BGL is 2-2.5mmol/L
Repeat BGL is ≥2.6mmol/L
Repeat BGL is <2.6mmol/L
Give IV 2mL/kg 10% glucose bolus
Fluid restricted?
No
Yes
Increase TFR by 10-20mL/kg
Repeat BGL is <2.6mmol/L
Commence IV glucagon at 5-10microgram/kg/hr, titrate to BGL, to maximum 20microgram/kg/hr
BGL remains <2.6mmol/L
Discuss with Neonatologist
Continue current IVF/TPN regime
Continue current BGL monitoring regime, aiming for BGL >4mmol/L
Discuss with Neonatologist

All infants should be commenced on milk feeds, preferably via breastfeeding or expressed breastmilk, as soon as possible based on their underlying reason for admission. Breastfeeding stimulates release of regulatory factors from the gut as well as providing longer acting substrates such as fat in addition to glucose.

A 6-hour fasting challenge study should be considered prior to discharge if hypoglycaemia was persistent, required diazoxide (see medication information below) or there was an unexplained BGL <2.6mmol/L after 48hrs of age. This involves measuring the blood glucose every hour for 6 hours after a feed and recommencing feeds if the glucose falls below a pre-specified concentration [14].

Glucose Infusion Rate

The standard glucose infusion rate (GIR) for term infants generally ranges from 4-6mg/kg/min, whilst for premature infants, this is slightly higher and may be 6-8 mg/kg/min [30, 31].

The formula for GIR is as follows:

$$\textbf{GIR (mg/kg/min)} = \frac{\textbf{TFR} \times \textbf{Dextrose concentration}}{\textbf{144}}$$

Glucose mg/kg/minute					
mL/kg/day / %	60	80	90	100	120
5%	2.1	2.8	3.1	3.5	4.2
10%	4.2	5.6	6.3	6.9	8.3
12.5%	5.2	6.9	7.8	8.7	10.4
15%	6.3	8.3	9.4	10.4	12.5
20%	8.3	11	12.5	13.9	16.7

Critical bloods

In the majority of infants the likely cause of hypoglycaemia will be apparent from perinatal history and examination. Investigation for the underlying mechanism for hypoglycaemia is required in severe, persistent, recurrent, and atypical hypoglycaemia to assist in targeting management [1]. Critical bloods are diagnostic samples that are collected at the time of low blood glucose. In general they should be collected when hypoglycaemia occurs after the first 24-48 hours of life [15]. Note that insulin is released periodically, cleared rapidly by the liver and degrades in haemolysed samples so false negatives can occur, in which case hyperinsulinism is indicated by ketone and free fatty acid suppression [16]. Further investigations may be considered by the treating neonatologist or paediatric endocrinologist. The following table displays the critical samples that are recommended.

Critical bloods	Priority	Container, volume
Blood gas (with lactate & glucose)	1	Syringe or capillary tube
Insulin Cortisol	1	Heparin no gel (green), 1mL
Growth Hormone	2	Heparin no gel (green), 1mL
Beta-hydroxybutyrate # Free fatty acids #	3	Heparin no gel (green), 0.5mL EDTA (purple) , 1mL
Urine Ketones clinistix Metabolic screen Reducing substances		Yellow urine jar Dipstick 10mL 5mL (lab within 30 minutes)
Further investigations to consider		
Ammonia #		Heparin gel (lime green), 0.5mL
Acylcarnitine profile #		Heparin gel (lime green), 1mL
Carnitine #		Heparin gel (lime green), 1mL
LFT		Heparin gel (lime green), 1mL
Uric acid		Heparin gel (lime green), 0.5mL*
Plasma amino acids #		Heparin gel (lime green), 1mL
Creatine kinase		Heparin gel (lime green), 0.5mL*
Ophthalmology review		
Head ultrasound +/- MRI Brain		

#needs to go on ice *0.2mL sufficient if other biochemical tests sent

Glucagon

Glucagon infusion volumes should not be included in TFR calculation

Glucagon is known to reduce hypoglycaemia and glucose infusion rates in congenital hyperinsulinism [17] as well as other causes of resistant neonatal hypoglycaemia [18]. Carman, Loughran-Fowlds [15] reviewed 137 infants treated with IV glucagon at Grace between 2000 and 2016 and found that glucagon achieved euglycaemia rapidly (mean 1.5hrs, SD +/- 0.8hrs) and was efficacious in similar doses across all causes of hypoglycaemia, including prematurity and IUGR infants. Approximately $^{1}/_{3}^{rd}$ of these infants had an antenatally diagnosed congenital anomaly and 54% had 3 or more risk factors for hypoglycaemia. Most infants had mild or moderate hypoglycaemia, with 20% having severe hypoglycaemia with a BGL <1.1mmol/L. This reflects commencement of glucagon prior to escalating glucose infusion rates due to the need for fluid restriction in cardiac and surgical neonates. Infants with hyperinsulinism also benefit from early initiation of glucagon as high glucose infusion rates can increase and prolong insulin secretion. Of the infants who had insulin measured in the study [15], 97% had inappropriately elevated insulin levels, and the remaining infants had risk factors for high insulin levels, suggesting Grace infants are very commonly hyperinsulinaemic.

Carman, Loughran-Fowlds [15] also assessed glucagon dose initiation, escalation and weaning. Doses of glucagon were used up to 200microg/kg/hr, however all but 6 infants were able to be managed with a dose up to 20microg/kg/hr. They have recommended commencing glucagon early at 5-10microg/kg/hr and found weaning by 0.5-1 microg /kg/hr with regular BGL monitoring was safe, particularly when the glucose level was ≥5mmol/L

Glucagon can also be administered IM for infants without IV access with good efficacy, and in some cases may avoid the need for IV access in infants who are being fed [19].

To view the Glucagon monograph on Australasian Neonatal Medicines Formulary (ANMF), click here

Diazoxide

Diazoxide is a K_{ATP} channel agonist that impedes ß cell depolarisation and insulin release and is effective in most cases of hyperinsulinism. The advantage of diazoxide is that it is orally or IV administered in a dose of 5-15mg/kg/day in divided doses [15, 37]. Traditionally it has been used for persistent hyperinsulinism but it is also effective in transient hyperinsulinism so is an option for infants where IV access is difficult. Side effects include sodium and fluid retention, hypertrichosis [16] and there may be an increased risk of necrotising enterocolitis (NEC) [20]. Hydrochlorothiazide is often administered with diazoxide to counteract the fluid retention.

Some genetic causes of hyperinsulinism do not respond to diazoxide due to mutations affecting the K_{ATP} channel. In these infants octreotide, a long acting somatostatin analogue

that inhibits insulin release by hyperpolarising the pancreatic ß cells [16] distal to the K_{ATP} channel, can be used.

To view the Diazoxide monograph on Australasian Neonatal Medicines Formulary (ANMF), click here

Glucocorticoids

There are case reports of using dexamethasone and hydrocortisone for management of hypoglycaemia in the literature [21, 23]. Glucocorticoids reduce insulin secretion and increase insulin resistance as well as enhancing gluconeogenesis and glucogenolysis [21, 23]. It is reasonable to consider using hydrocortisone as a therapy for hypoglycaemia in the difficult to control infant, however glucocorticoid side effects are significant (e.g. hypertension, feeding intolerance, and growth suppression) and must be considered for each individual patient [38].

To view the Hydrocortisone monograph on Australasian Neonatal Medicines Formulary (ANMF), click here

Blood glucose testing and sampling methods

Blood glucose can be measured using a Glucometer, the onsite laboratory blood gas analysis machine or via Pathology in a lithium heparin green top collection tube.

If blood glucose testing frequency is >12hrly, sampling can be attended via heel prick using a pink coloured lancet if capturing a BGL via dextrostix. Purple lancet may be required if trying to obtain a complete capillary blood gas sample size.

Please refer to GCNC blood collection policy for guidelines on attending a heel prick. If other blood tests are being attended via venepuncture or a PIVC is inserted blood glucose should be collected at the same time to reduce the number of painful skin breaking procedures for the neonate. More frequent blood glucose sampling requires insertion of an arterial line, for example neonates on glucagon or insulin infusions.

For prolonged blood glucose sampling, the FastClix – Accu-Chek™ lancing device can be used for heel pricks. These can be obtained from the Nurse Practitioners.

Glucometers

Glucometer measurements can be inaccurate, particularly in the hypoglycaemic range, and must be confirmed with a glucose oxidase method, eg iSTAT, blood gas machine or laboratory analysis. Alterations in pH, oxygenation and haematocrit can all impact glucometer measurements in critically ill patients [7]. Plasma levels are approximately 15% higher than whole blood measurements.

Unit-based monthly checks are to be attended by the Assistant in Nursing (AIN) for each glucometer with both the Hi and Low calibrating solution provided.

Note: Every pack of Glucometer strips comes with a **Hi** and **Low** calibrating solution, and the recommendation is whenever a new pack of glucometer strips is opened the glucometer requires calibrating and gets documented in the booklet provided. The AINs attend to this procedure.

Quality check solutions are sent monthly from the biochemistry department to calibrate glucometers. Each glucometer gets individual packs of **Hi** and **Low** quality check solution.

The AIN performs the calibration for each glucometers and writes the **Hi and Low** results on the respective packs and sends it to the Biochemistry department.

The nominated person receives glucose meter external quality assurance report/ survey on a monthly basis from the Biochemistry department to follow up any amber, red or non-submitted results. The monthly biochemistry results indicate the levels and ranges in Green, Orange, and Red for each of the meters. A copy of a document prepared by the RCPAQAP is attached to assist in trouble-shooting outliers. If in orange/red, the nominated per son takes the glucometer to Biomed to trouble-shooting outliers and, if needed, gets a replacement device.

If a glucometer is lost, with discussion with the NUM, a new glucometer can be obtained from the biomedical engineering department with its identification number. This has to be communicated to the nominated person within the unit, and to the Biochemistry department.

For detailed instructions on how to calibrate a glucometer, please see this document.

Hyperglycaemia Management

Goals for management of hyperglycaemia are the prevention of hyperglycaemia and the early detection with appropriate treatment of hyperglycaemia when it occurs.

This involves early initiation of enteral feeds where possible as establishing enteral feeding can promote the release of incretin hormones which facilitates insulin secretion by the pancreas may help to correct hyperglycaemia [30]

Additionally, targeting the optimal glucose infusion rate (GIR) for each neonate by calculating the GIR whenever changes in total fluid requirement are made so that excessively high dextrose concentrations can be avoided is also important for preventing hyperglycaemia and also limiting iatrogenic hyperglycaemia that is due to excessive intravenous dextrose administration [24].

Optimising (and if required, supplementing) protein intake via parenteral nutrition when full enteral feeding is yet to be established, or via enteral feeding may increase protein synthesis and anabolism, thereby increasing endogenous insulin secretion which may prevent hyperglycaemia [24, 30].

As hyperglycaemia is typically multifactorial, addressing the underlying causes of hyperglycaemia is vital in the initial phases of hyperglycaemia management [30]. For example, by addressing the situations that contribute to physiological stress in neonates (e.g. surgery, pain, hypoxia, respiratory distress, poor perfusion and sepsis) through effective management of these conditions, hyperglycaemia may be avoided or corrected [24, 30]. Furthermore, modifiable risk factors for hyperglycaemia (e.g. corticosteroid use, catecholamine use, administration of lipid infusions) should be minimised if and where possible [24, 30].

If hyperglycaemia persists in spite of all the aforementioned management strategies, insulin therapy may be required.

Insulin [24, 28 & 30]

Insulin is a polypeptide hormone that stimulates the cellular uptake, utilisation and storage of glucose, resulting in the lowering of blood glucose concentration. Insulin does this by:

- Stimulating the liver to store glucose in the form of glycogen
- Facilitating the entry of glucose into muscle and adipose tissue
- Inhibiting lipolysis, proteolysis and gluconeogenesis
- Enhancing protein synthesis Converting excess glucose into fat

To view the Insulin monograph on Australasian Neonatal Medicines Formulary (ANMF), click here

Indications for Use

The exact indications for insulin therapy are not very well defined and as a result, commencing therapy is typically at the discretion of the Consultant Neonatologist.

Insulin therapy is usually commenced in infants with persistent hyperglycaemia despite employment of the first-line management strategies discussed in the section above, or in the case of severe hyperglycaemia with associated clinical signs

Things to Consider

- Close monitoring of blood glucose concentration is required to ensure that hypoglycaemia is avoided
- Monitor electrolytes as insulin can cause hypokalaemia due to activation of cellular sodium ATPase causing potassium shift into the intracellular space
- Bolusing insulin therapy has a high risk of causing hypoglycaemia and should therefore be avoided
- Insulin non-specifically binds to the plastic of giving sets. Flushing the plastic tubing with prepared insulin solution prior to connecting to the infant may assist in saturating this binding and optimising availability of insulin to the patient
- Take care not to adjust the rate of other infusions (including maintenance fluids or TPN) when insulin is commenced or when the insulin rate has been altered, as this can increase the risk of hypoglycaemia occurring
- Administer via separate IV access (if possible) to avoid inadvertent insulin bolus when administering other IV bolus medications
- Different brands of insulin are not bioequivalent, and as such, it is imperative that substitutions between brands do not occur.

Nursing care and management of blood glucose instability

Nursing care of the neonate with blood glucose instability should be considered a priority of care. Maintaining basic neonatal principles as stated above in the neonatal energy triangle is imperative to optimise patient condition – remember: pink, warm and sweet. For example, nursing considerations may be to transfer the hypoglycaemic patient to an open care bed to provide external heating.

Nursing assessment

Each shift the nurse should assess for signs and symptoms of blood glucose instability in the at risk neonate. Observing for jittering, lethargy and alterations in level of consciousness as well as performing a urinalysis daily to observe for glucose excretion. Glycosuria reflects the kidney's ability to manage glucose and is typically observed in the patient with hyperglycaemia. Glycosuria can cause osmotic diuresis and dehydration as a result. Attending a daily urinalysis should be a component overall nursing care. Further guidance on normal ranges of a urinalysis can be found in the Urinary Care guideline.

Feeding

Calculate individual total fluid requirements for the neonate. Consider enteral feeding more frequently, such as second hourly, or on a continuous feed in the event of hypoglycaemia. The hypoglycaemic patient may display signs of lethargy putting them at risk of aspiration of oral feeds.

Monitor blood glucose levels as per flowchart guidelines.

Fasting and preoperative considerations

A blood glucose level should be checked pre-operatively when the neonate is fasting. This also provides a valuable baseline blood glucose level as a comparative post operatively.

Attend a BGL on admission if the neonate has been NBM for transfer.

Fluid restriction considerations

Optimising IV infusions to 5% dextrose as the diluting solution where compatibility allows can assist in hypoglycaemia management on a fluid restricted neonate. It is important to note that neither glucagon nor insulin infusions are to be included in TFR calculations.

Post-operative stress

The neonate who has undergone a surgical procedure is likely to have an elevated blood glucose level due to a stress hormone response. This is typically a result of tissue and organ damage and nociceptive stimulation resulting in an endocrine and metabolic responses, specifically the adrenocorticotropic hormonal (ACTH) via the hypothalamic-pituitary axis [34, 35]. This elevated blood glucose level should return to the baby's baseline within 24 hours of the surgical procedure, and post-operative blood glucose levels should be monitored accordingly [34, 35].

Sucrose

Sucrose administration does not alter blood glucose levels and should be used for painful procedures only, as per the Network guideline which can be found here

Endocrine team referral criteria

At the request of the Consultant Neonatologist, referral to the Endocrinology team should be made if there is:

- Severe hypoglycaemia, especially if there is alteration in consciousness and/or seizures
- Persistent and/or prolonged hypoglycaemia that is unresponsive to first line treatments (e.g. increase of glucose infusion rate and glucagon)
- Hyperglycaemia that requires insulin therapy

Additionally, referral to the Endocrinology team should be considered if there is:

- Severe acute hyperglycaemia
- Persistent hyperglycaemia despite the use of management strategies
- Hyperglycaemia that persists despite commencing insulin therapy
- Persistent glycaemic disturbance requiring multiple management strategies

Metabolic Team Referral Criteria

It is important to note that hypoglycaemia is often a late presentation for many of the inherited metabolic disorders.

Following discussion with the Consultant Neonatologist, a referral to the Genetic Metabolic Disorder Service should be made when there is hypoglycaemia that is associated with:

- Encephalopathy
- Elevated ammonia levels
- Metabolic acidosis with high anion gap
- Recurrent hypoglycaemia episodes which are not explained by endocrine critical hypoglycaemia investigations (i.e. appropriate counter-regulatory hormones).

Additionally, the metabolic team can be consulted if:

- There is a history of inborn errors of metabolism in the infant's parent or sibling and suspicion of same in the patient
- There is glycaemic disturbance in the presence of elevated lactates, dysmorphic features, and/or hepatomegaly

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