

Quality Improvement Initiative Protocol

Title: Baby Friendly Hypoglycaemia Care Quality Improvement Initiative (BFHQI)

Version: draft 0.3

Clinical condition: Severe and/or recurrent transitional neonatal hypoglycaemia

Patient group: Near-term and term newborn infants (≥ 36 weeks' gestation and ≥ 2.5 kg) admitted to Kidz First Neonatal Care with severe and/or recurrent transitional hypoglycaemia

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Funding: Currently unfunded

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Introduction

Key documents

This quality improvement initiative uses the methodology of the Evidenced-based Practice for Improving Quality (EPIC),¹ developed by the Canadian Neonatal Network and adopted by the Australian and New Zealand Neonatal Network. This protocol is based on the Standards for Quality Improvement Reporting Excellence, 2.0 (SQUIRE).²

Before this quality improvement initiative, members of the quality team have conducted extensive research on neonatal hypoglycaemia, including intervention trials,³⁻⁶ clinical taxonomy,^{7,8} long-term outcome studies,⁹⁻¹⁷ neurological imaging,^{18,19} parental care priorities,²⁰ glucose monitoring,²¹⁻²³ systematic reviews^{14,24-26} and expert reviews.²⁷⁻³⁰ This quality improvement initiative seeks to translate the best available evidence to address complex, multifactorial clinical problems.

Problem description

Transitional hypoglycaemia refers to low blood glucose concentrations (BGC) with onset in the first 48 h after birth, in late preterm and term newborn babies (≥ 35 weeks' gestation) who are otherwise well and do not have any underlying metabolic, endocrine, or genetic disorders affecting glucose metabolism.⁸ In New Zealand, the definition of hypoglycaemia used in these babies is a whole blood or plasma glucose concentration on a gas analyser or chemical analyser, respectively, of < 2.6 mmol/L (gas analysers are calibrated to give plasma equivalent values); this threshold is entirely operational, and neither defines normal physiology nor optimal glycaemia in at-risk babies.²⁷ Transitional hypoglycaemia may be further classified as severe (< 2.0 mmol/L), recurrent (≥ 3 episodes) or prolonged (episodes ≥ 72).^{7,9} The term transitional hypoglycaemia is usually not applied to babies born at < 35 weeks' gestation, as these babies are managed almost exclusively in neonatal care units, where they receive either dextrose (D glucose isomer) containing intravenous fluids or milk supplementation (artificial or human donor) on admission. It should also not be used to describe first onset of neonatal hypoglycaemia ≥ 48 h after birth, which typically occurs in maternal-infant dyads where there is inadequate breastfeeding and delayed onset of lactogenesis II (breastfeeding hypoglycaemia may be a better term). These infants often do not have any risk factors for transitional hypoglycaemia.

Using a risk-based approach, approximately 30% of newborn babies born at ≥ 35 weeks' gestation warrant screening for transitional hypoglycaemia,³¹ of whom nearly 50% will develop hypoglycaemia in the first 48 h after birth (60% if preterm; 72% if exposed to pre-gestational diabetes mellitus, 52% if small for gestational age [SGA] or large for gestational age [LGA] and exposed to gestational diabetes mellitus).³² From 65% to 80% have mild episodes (2.0 to 2.5 mmol/L), and 20% to 35% have severe episodes (< 2.0 mmol/L).³³⁻³⁶ Of babies with mild transitional hypoglycaemia, 70% have their first episode within 6 h of birth, 15% from 6 to 12 h and 15% from 12 to 48 h.³⁷ Severe transitional hypoglycaemia almost always presents within the first 6 h after birth.⁷

Overall, approximately 20% of newborn babies screened for transitional hypoglycaemia are admitted to Kidz First Neonatal Care (KFNC) for further management of severe or recurrent hypoglycaemia (~225 per annum).³ Half of these babies are Pacific and 20% are Māori, with a male to female ratio of 2:1, and 70% are born by caesarean.³ The average inflation-adjusted

cost for each admission is \$15,217,³⁸ bringing the total annual estimated hospital costs for managing babies admitted to KFNC with transitional hypoglycaemia to \$3,423,934.

This quality improvement initiative seeks to address three key problems in the care of newborn babies who are admitted to KFNC with severe and/or recurrent transitional hypoglycaemia. These quality issues were identified and prioritised by the quality group through discussion, after reviewing local data, the wider literature, and parental survey results.

1. High burden of ongoing hypoglycaemia with current treatment, increasing the risk of neurological sequelae.
 - Over half of babies who are admitted to KFNC with transitional hypoglycaemia and are treated with IV dextrose have further episodes of hypoglycaemia, and 20% have severe or recurrent (≥ 3) episodes after initial stabilisation.³
 - On discharge from KFNC to the postnatal ward, most babies (93%) treated with IV dextrose continue to have silent and untreated hypoglycaemic events¹⁰ on continuous glucose monitoring (CGM).³
 - Some babies are being discharged home before completing normal metabolic transition.
2. Prolonged duration of KFNC admission, increasing separation of mother and baby.
 - Babies who are commenced on IV dextrose for transitional hypoglycaemia have a median stay in KFNC of 4 days and median duration of hospitalisation of 8 days.³
3. Poor establishment of breastfeeding.
 - Of babies admitted to KFNC with transitional hypoglycaemia whose mothers plan to breastfeed, >90% receive formula in hospital and <50% are fully breastfeeding at discharge home.³

These problems align with parental priorities at Counties Manukau. Among parents whose babies were admitted to KFNC with transitional hypoglycaemia (N=47; 19% Māori, 53% Pacific, 15% Indian, 13% European), 98%, 91%, 83% and 74% rated preventing damage to baby's brain, avoiding separation of mum and baby, reducing time in the neonatal unit and establishing breastfeeding at discharge as important or very important, respectively.²⁰

Available knowledge

Physiology of newborn metabolic transition

The fetus has negligible synthesis of glucose; thus, along with other key physiological transitions – lung aeration, pulmonary vascular perfusion, regular breathing – survival after birth depends on activation of hepatic glucose output, especially until enteral feeds are well established.³⁹ In the early newborn period, glucose is the main energy substrate, followed by lactate; fatty acids and ketones soon become important additional energy sources, although ketogenesis is minimal in the first 6 to 12 h after birth, even in healthy babies.^{40,41}

During fetal life, a low pancreatic β cell glucose set-point for insulin secretion and a continuous transplacental glucose supply maintain a high insulin-to-glucagon molar ratio (up to 10 to 15), which inhibits gluconeogenesis and promotes glycogenesis, lipogenesis and fetal growth.^{42,43} In late gestation, fetal adrenal activation and the resulting increase in fetal cortisol secretion prime hepatocytes for glucose production by inducing key enzymes responsible for gluconeogenesis (phospho-phenolpyruvate carboxykinase, glucose-6-phosphate) and glycogenolysis (glucose-6-phosphate).⁴⁴ After birth, the primary trigger for initiation of hepatic

glucose output is a rapid fall in the insulin-to-glucagon ratio, resulting from both a surge in glucagon secretion from pancreatic α cells and falling insulin secretion from β cells,^{43,45} responses that are facilitated by fetal release of catecholamines during labour.⁴⁶ Lipolysis increases postnatally, releasing glycerol for gluconeogenesis⁴⁷ and fatty acids for tissue oxidation and ketogenesis, and is stimulated by increases in cortisol and thyroxine around the time of birth.^{48,49} In newborn babies, adipose tissue appears to be relatively insulin resistant; thus, even babies with severe hypoglycaemia and elevated insulin concentrations have detectable plasma free fatty acids.⁷ As hepatic oxidation of fatty acids increases on the first day, more cofactors and adenosine triphosphate (ATP) are generated within the liver to support gluconeogenesis, whereas fatty acid oxidation in peripheral tissues produces gluconeogenic precursors, such as lactate, pyruvate and alanine, and may have a glucose-sparing effect.^{50,51} Although adipose is relatively insulin resistant, hepatic insulin sensitivity remains high in newborn babies, such that ketoacidosis is rare.

A critical process in newborn metabolic transition is the shift of the β cell from a relatively continuous pattern of insulin secretion in fetal life to intermittent postnatal secretion.⁵² Babies with transitional hypoglycaemia rarely have high insulin concentrations;^{3,53} nevertheless, babies presenting with severe or recurrent episodes have a high glucose-to-insulin ratio (median ~ 4.5 IU/mol),^{3,7} indicating that impaired suppression of insulin secretion at low BGC is a key pathophysiological feature of transitional hypoglycaemia. In contrast, in newborn babies who have successfully undergone metabolic transition, plasma insulin is usually undetectable after a short fast.

Insulin secretion is primarily regulated by β -cell membrane ATP-sensitive potassium channels (K_{ATP}) that contribute to cell membrane polarisation via potassium efflux and cause depolarisation when inactivated (closed) by increasing intracellular glucose-generated ATP, thereby triggering insulin vesicle release. In immature β cells, the low glucose set-point for insulin secretion is related to a relatively low cell membrane K_{ATP} density,⁵⁴ and postnatal β cell adaptation likely involves increased trafficking of K_{ATP} to the cell membrane. Dynamic changes to the nutrient sensor Target of Rapamycin Complex 1 (mTORC1), which acts as an intrinsic negative feedback regulator of insulin exocytosis,⁵⁵ may also facilitate postnatal adaptation by reducing the stimulatory effect of amino acids on β -cell insulin content, which is an important mechanism supporting growth in fetal life.^{30,56}

Postnatal β -cell adaptation appears to occur in two phases, as reflected by pre-feed BGC profiles of healthy breastfed babies. In the first 48 h, mean neonatal BGC stabilise to values only slightly lower than that of the fetus in late gestation (~ 3.5 mmol/L).^{57,58} During normal labour, mean fetal glucose concentrations increase to ~ 4.6 mmol/L, with slightly higher concentrations reported after instrumental birth (~ 5.8 mmol/L) and lower concentrations after elective caesarean birth (~ 3.9 mmol/L).⁵⁹⁻⁶¹ After birth, mean neonatal BGC falls to ~ 2.9 mmol/L by 30 minutes of age,^{62,63} increasing to ~ 3.1 mmol/L by 60 to 90 minutes of age,^{64,65} and ~ 3.3 mmol/L at 12 to 48 h of age (3rd centile ~ 2.1 , 10th ~ 2.6 , 25th ~ 2.8 mmol/L).^{40,66} At 48 to 72 h, there is an inflection point, leading to the second phase, in which normal neonatal mean concentrations of ~ 4.5 mmol/L are achieved by 96 h (3rd centile ~ 3.5 , 10th ~ 3.7 , 25th 4.0 mmol/L).^{40,66,67} During the first phase, there is considerable variation in individual BGC, with up to 39% of healthy breastfed babies experiencing ≥ 1 episode of hypoglycaemia.⁶⁶ However, the majority of these episodes are mild, resolve by 72 h, and ketogenesis is usually evident from 12 h of age.^{40,68,69} Thus, normal metabolic transition commences shortly after birth and is completed around day four.

Given that healthy babies without risk factors may experience low BGC, transitional hypoglycaemia cannot itself be considered a disorder; rather, it should be considered a marker for impaired metabolic transition. The latter is characterised as transitional hypoglycaemia that does not resolve with first-line measures (feeding ± dextrose gel) or is severe, and is associated with delayed onset of ketogenesis (>12 h).⁸ While all babies are at risk of transitional hypoglycaemia, those with risk factors – preterm birth, exposure to maternal diabetes mellitus, fetal growth restriction and fetal overgrowth (macrosomia) – are at highest risk of severe hypoglycaemia and impaired metabolic transition.

Pathophysiology of neuroglycopaenia

Transitional hypoglycaemia is of concern because it may lead to neuroglycopaenia, i.e., a critical decrease in brain glucose supply leading to cell injury. The neonatal brain is dependent on a continuous supply of glucose to generate energy as ATP, as developing neurons have reduced capacity to use alternative substrates (lactate and ketones may be oxidised but not fatty acids) and limited high-energy phosphate reserves.⁷⁰ Furthermore, glucose transporter proteins (GLUT1 and GLUT3) at the blood-brain barrier, which enable glucose uptake into the brain by facilitated diffusion, are not fully expressed for several days to weeks after birth.⁷⁰

The cell injury that occurs in neuroglycopaenia is primarily due to excitotoxicity, rather than energy deficiency *per se*.²⁷ Low glycolytic flux decreases pyruvate production, which in turn reduces generation of oxaloacetate via the citric acid cycle. Low intracellular concentrations of oxaloacetate result in excess generation of glutamate, an excitatory neurotransmitter, which spills out into the extracellular fluid. Activation of glutamate receptors causes a sustained influx of calcium and activates several enzymes, including phospholipases, endonucleases, and proteases, which damage cell structures. The influx of calcium also increases intracellular zinc, which activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, leading to superoxide production in mitochondria. Increased calcium and superoxide hyperactivate poly-ADP-ribose-polymerase 1 (PARP- 1), which causes additional damage to mitochondria and cytosolic depletion of nicotinamide adenine dinucleotide (NAD⁺), an essential cofactor in glycolysis.

As neuroglycopaenia progresses, cell injury becomes irreversible, leading to necrosis. In neonates, the occipital and parietal cortex, associated subcortical white matter and corpus callosum have selective vulnerability to neuroglycopaenia,⁷¹⁻⁷³ possibly related to a higher cerebral metabolic rate for glucose,⁷⁴ regional reductions in GLUT expression,⁷⁵ and active synaptogenesis with increased expression of postsynaptic excitatory amino acid receptors.⁷⁶ In extensive neuroglycopaenic insult, the internal capsule, thalamus and basal ganglia may be involved.^{71,77} Neuroglycopaenia can affect glial cells and immature oligodendrocytes, but this occurs to a much lesser degree.^{78,79} Thus, neuroglycopaenia is largely associated with regional selective neuronal necrosis.

An important consequence of cytosolic NAD⁺ depletion and its impact on glycolysis is that reperfused glucose is shunted through the hexose monophosphate pathway, generating more NADPH and superoxide, thereby worsening neuronal injury.^{27,80} Notably, superoxide production is proportional to BGC during the reperfusion period.⁸⁰ This phenomenon, termed glucose reperfusion injury, has been observed clinically; in a cohort of children exposed to transitional hypoglycaemia, the likelihood of neurosensory impairment up to mid-childhood was increased in those with higher or more rapid increases in BGC after neonatal hypoglycaemia, especially with dextrose treatment.^{9,11} Contrary to common practice, the optimal timeframe for correction

of hypoglycaemia was several h, potentially reflecting reperfusion injury with more rapid correction with exogenous dextrose.¹¹ The potential for harm with dextrose treatment has been emphasised by several animal studies in which hypoglycaemic-induced neuronal injury was only reversed with substrates that can be metabolised without NAD⁺, such as ketones, lactate and pyruvate.⁸¹⁻⁸³

Clinical manifestations of neuroglycopenia

The clinical signs of neuroglycopenia include lethargy, apnoea, poor feeding and seizures;⁷¹ however, the extent to which subclinical neuroglycopenia occurs is unknown, as it currently cannot be detected with cot-side monitoring.^{84,85} Similarly, restricted diffusion and T1 and T2 signal abnormalities are common on brain magnetic resonance imaging within 7 days of symptomatic neonatal hypoglycaemia,⁷¹ but the effect of asymptomatic hypoglycaemia has not been investigated. New Zealand data suggest that subclinical neuroglycopenia can occur, as 9-to-10-year-old children who were exposed to transitional hypoglycaemia, most of whom were asymptomatic, had a thinner occipital cortex and smaller caudate lobes, compared to those born at-risk but without neonatal hypoglycaemia (there was no effect on white matter volumes or microstructure).¹⁹ However, interpretation of these findings is not straightforward, as there was no apparent relationship between brain volumetric findings and the severity of hypoglycaemia. Moreover, despite these volumetric brain differences, cognitive, visual-motor and educational outcomes did not differ between children who were and were not exposed to hypoglycaemia, regardless of severity, although this apparent lack of association may have been due to the poor outcomes in the cohort overall.¹⁴

In other cohort studies, severe and/or recurrent transitional hypoglycaemia has been more consistently associated with altered neurodevelopment,^{16,33,34,86,87} especially visual-motor and emotional-behavioural function, consistent with the neuroimaging findings^{16,18} and visual processing theory.⁸⁸ Nevertheless, the exposure effects are generally modest and not universal. Taken together, these studies suggest that asymptomatic severe and/or recurrent transitional hypoglycaemia is a necessary but not sufficient cause of neuroglycopenia and that other factors, including effects of treatment, influence the risk of neuronal death, subsequent dysmaturation and later functional impairment.

Dextrose gel and feeding

Primary treatment for transitional hypoglycaemia with buccal dextrose gel (40% 0.2 g/kg, repeated after 30 min, if required) was adopted worldwide following a New Zealand placebo-controlled trial of 237 babies, which showed that dextrose gel had a modest beneficial effect on correction of hypoglycaemia compared to feeding alone (86% vs. 76%). However, the effect of dextrose gel on BGC was small (0.2 to 0.5 mmol/L)³⁷ and the overall risk of admission was similar between trial groups.³

In the trial, formula was used in 37% of trial episodes and in 60% of babies overall. Among breastfed babies, 41% developed rebound hypoglycaemia after dextrose gel. Moreover, in severe hypoglycaemia, only 11% of breastfed babies responded to dextrose gel, but 70% were subsequently corrected with formula. Consistent with these findings, in another randomised trial of babies with severe transitional hypoglycaemia, formula supplementation was superior to dextrose gel and breastfeeding in preventing persistent or recurrent hypoglycaemia (90% vs. 71%).³⁶ Thus, for women who have elected to formula feed, increasingly formula intake is likely to be sufficient for most infants with transitional hypoglycaemia, including those with severe

episodes. However, for women who want to avoid formula feeding, alternative strategies are needed to manage severe and/or recurrent transitional hypoglycaemia.

One option is human donor milk supplementation, which appears to have similar efficacy to formula in correcting hypoglycaemia.^{89,90} In a quality programme at one site, introduction of dextrose gel for treatment of transitional hypoglycaemia did not reduce neonatal unit admissions nor increase exclusive breastfeeding at discharge. However, nurse-led use of donor milk for transitional hypoglycaemia increased the proportion of at-risk infants who were exclusively breastfed from 33% to 55% (monthly average 43%).⁹¹ Similarly, in another quality programme, 53% of babies who received donor milk for initial treatment of hypoglycaemia were exclusively breastfed during their hospital admission, whereas virtually all such babies had previously received formula milk.⁹² Use of donor milk, compared with formula, for term and near-term babies with medical indications for supplementation, such as hypoglycaemia, was also associated with increased exclusive breastfeeding to 6 months of age.⁹³ Thus, provision of donor milk may be an important intervention to increase breastfeeding in babies with transitional hypoglycaemia.

Despite its short-term benefit on the correction of hypoglycaemia, dextrose gel has not been associated with improvements in neurodevelopment.^{94,95} On the contrary, at 9 to 10 years of age, children randomised to dextrose gel for initial treatment of transitional hypoglycaemia, compared to placebo (feeding alone), were twice as likely to have impaired visual perception.⁴ While the authors attributed this to type 1 error, given the vulnerability of the occipital cortex to neuroglycopenia, this is of some concern. An alternative explanation is that infants treated with dextrose may have increased rebound hypoglycaemia, as the adverse effect of treatment on visual perception was seen primarily in babies with recurrent hypoglycaemia, although this remains speculation.

A more recent trial evaluated dextrose gel in 291 breastfed babies with transitional hypoglycaemia and a mean BGC of 1.2 mmol/L;⁹⁶ only 11% of babies allocated to dextrose gel required IV dextrose for ongoing hypoglycaemia compared to 40% with standard care. However, this study was at high risk of bias as there was no blinding and the attending clinicians performed the allocation, administered the dextrose gel and determined subsequent care.

Intravenous dextrose

Until recently, the effectiveness and safety of using IV dextrose to treat transitional hypoglycaemia had not been critically evaluated. Small case series in the 1970s and 1980s suggested that IV dextrose infusions of 8 mg/kg/min corrected BGC within 60 min in most babies, or within 20 min when combined with an IV dextrose bolus of 0.2 g/kg.^{97,98} However, the ongoing effectiveness of IV dextrose as a treatment for transitional hypoglycaemia was not assessed. In a recent evaluation of babies admitted to KFNC with transitional hypoglycaemia who were treated with IV dextrose, over half had further hypoglycaemia after stabilisation, and 20% had severe or recurrent episodes.³ The median (IQR) duration of neonatal unit admission was 4 (2, 7) days,³ which is consistent with another report of a median NICU stay of 6 (4, 9) days.⁹⁹ Of further concern, most babies (93%) had silent and untreated hypoglycaemic events, detected on continuous glucose monitoring (CGM), when discharged back to the postnatal ward; the median (IQR) number of hypoglycaemic events was ~9 (4, 12), with some being prolonged.³ On average, metabolic transition was not completed in these babies for 4 to 5 days after stopping IV dextrose, with some being discharged home before metabolic transition was confirmed.³ Thus, while IV dextrose may initially correct BGC, it appears to only have a

temporising effect but does not promote metabolic transition, increases the risk of delayed hypoglycaemia and prolongs hospital admission.

Babies who are treated with IV dextrose are also exposed to frequent invasive procedures. In KFNC, babies had a median (IQR) of 21 (16, 28) heel pricks, increasing to 49 (43, 56) in prolonged transitional hypoglycaemia.^{3,7} Another study reported that babies with transitional hypoglycaemia who were treated with IV dextrose had a median (IQR) of 29 (19, 40) heel pricks, with 25% of babies having ≥ 40 heel pricks.⁹⁹ Furthermore, given that the mean functional period for peripheral cannulae in neonates is only 24 to 58 h,¹⁰⁰⁻¹⁰² most babies on IV dextrose will require two intravenous cannulae, with some receiving three or more. In general, 60% of peripheral cannulae in neonates are replaced for extravasation.¹⁰³

There are few studies comparing IV dextrose to alternative treatments for transitional hypoglycaemia. In a randomised trial, glucose fortified breastmilk had similar efficacy to IV dextrose for correction of hypoglycaemia.¹⁰⁴ Comparisons with physiological treatment approaches are discussed below.

Physiologically targeted treatment

Effective treatment for transitional hypoglycaemia requires correction of the underlying pathophysiology and promotion of metabolic transition. For babies at highest risk of neuroglycopenia, especially those with symptomatic hypoglycaemia, provision of energy substrates that can generate ATP without NAD⁺ may be directly neuroprotective.^{80,81,83} β -hydroxybutyrate is the most likely candidate for clinical intervention as it can be provided enterally from commercially available ketone esters and salts.^{105,106} Acute ketone therapy is an area of active research in type 1 diabetes mellitus¹⁰⁶ and adult traumatic brain and spinal injury,¹⁰⁷ but it has not yet been evaluated in babies. Until sufficient evidence emerges to support neonatal ketone treatment, promotion of hepatic glucose output and ketogenesis through other physiologically based treatments remains the best clinical strategy. This requires a decrease in the insulin-to-glucagon ratio, which can be achieved by administering glucagon, followed by manipulation of β -cell glucose sensing using a K_{ATP} agonist, such as diazoxide. Ultimately, for metabolic transition to occur babies must acquire the ability to suppress insulin secretion at low BGC.

In a systematic review of neonates with hypoglycaemia, glucagon was shown to increase BGC on average by 2.3 mmol/L (95% CI 2.1, 2.5) at 1 to 2 h, and $\geq 80\%$ achieved normoglycaemia within 4 h of administration.²⁶ Similar responses were seen with intramuscular injection (IMI), IV bolus and continuous IV infusion. In one large centre, glucagon was used successfully in babies born at ≥ 36 weeks' gestation as primary treatment for severe neonatal hypoglycaemia (1.1 to 2.2 mmol/L) unresponsive to formula, and for initial therapy in babies with profound hypoglycaemia (< 1.1 mmol/L) while awaiting IV cannulation (universal dose 1 mg by IMI).¹⁰⁸ All but one of the 158 babies in the study responded to IMI glucagon, with mean increases in BGC of 1.4, 2.2 and 2.3 mmol/L at 30, 60 and 120 min, respectively.

The main limitation of glucagon is that rebound hypoglycaemia is common, occurring in up to 55% of babies on stopping an infusion or after correction by bolus treatment.¹⁰⁸ Thus, it is important to pair glucagon with other interventions that promote euglycaemia. While there are no formal reports on the safety of glucagon in neonates, studies of neonatal glucagon use have not reported any adverse effects,²⁶ and there are no case reports of neonatal side effects

currently in Medline. Glucagon has also been administered safely as an infusion for prolonged periods in young children with refractory congenital hyperinsulinism.¹⁰⁹

Diazoxide is a reversible K_{ATP} agonist, acting on the K_{ATP} sulfonylurea receptor to maintain the channel in an active or open state. In the β cell, this increases K^+ efflux and membrane polarization, resulting in a dose-dependent attenuation of glucose-stimulated insulin secretion.⁹ This improves the ability of the β cell to suppress insulin secretion and to do so at a higher glucose set-point (more glucose-generated ATP is required for K_{ATP} inactivation/closure), but it does not prevent insulin secretion (there is no risk of ketoacidosis).³ Because the neonatal liver is highly sensitive to insulin, BGC can be titrated by adjusting the diazoxide dose in relation to glucose load.³ However, in profound neonatal hypoglycaemia, simultaneous increases in glucagon may be needed to restore hepatic glucose output.⁴⁵ Although less well studied, diazoxide also increases hepatic ketogenesis – with potential for neuroprotective effects – by lowering insulin plasma concentrations in the fasting state.

Diazoxide has been used for many decades in babies with congenital hyperinsulinism, although high doses (10 to 15 mg/kg/day) are generally required due to the associated inactivating mutations of K_{ATP} subunits, and indeed several subtypes are largely resistant to the agonist effect of diazoxide (e.g., ABCC8 and KCNJ11 mutations).¹¹⁰ Diazoxide has also been used to good effect in babies with prolonged transitional hypoglycaemia, which primarily occurs in males with fetal growth restriction.^{7,111}

More recently, diazoxide has been investigated for the early treatment of transitional hypoglycaemia.²⁴ In a randomised trial of 30 babies who were born SGA and had transitional hypoglycaemia, diazoxide at 9 to 12 mg/kg/day, compared to placebo, reduced the time to euglycaemia by 1 day and the duration of IV dextrose and time to full enteral feeds by 2 days.⁵³ There were no adverse effects of starting diazoxide within the first 5 days after birth. Another trial of early diazoxide treatment for babies of diabetic mothers with asymptomatic mild hypoglycaemia (2.0 to 2.5 mmol/L) was commenced in Canada (NCT00994149) but could not be completed due to loss of clinical equipoise in favour of diazoxide.²⁴

The Neonatal Glucose Care Optimisation (NeoGluCO) Study was a randomised trial of early low dose diazoxide (3 mg/kg/day), compared to placebo, in babies admitted to the neonatal care unit with severe or recurrent transitional hypoglycaemia (N=74).³ Most babies were recruited on the first day and 65% were receiving IV dextrose at the time of randomisation. The primary outcome, defined as time to resolution of hypoglycaemia (enteral bolus feeding without IV dextrose and stable BGC 2.6 to 5.4 mmol/L for ≥ 24 h), did not differ between groups, as diazoxide was more effective than expected, with many babies in the active intervention group having elevated BGC above the trial BGC target range. However, babies in the diazoxide group had a ~30% reduction in the time to establish enteral bolus feeding, time on IV dextrose, time in the neonatal unit and number of heel pricks. The *post hoc* outcome (invited by JAMA) of stable BGC ≥ 2.6 mmol/L on enteral bolus feeding was reached 2 days earlier in the diazoxide group.³

Importantly, diazoxide rapidly improved glycaemic stability. Following the loading dose, only 6% of babies in the active intervention group had further hypoglycaemia (single episode only), which resolved with a small increase in diazoxide dose, compared to over half of babies in the placebo group who experienced further hypoglycaemia. On CGM, diazoxide effect was evident from 1.5 h and peak effect occurred at ~6 h, after which mean interstitial glucose concentrations were maintained ~4.5 mmol/L, the normal neonatal concentration at completion of metabolic transition. This was achieved with a mean (SD) diazoxide plasma

concentration of 20 (5) $\mu\text{g/mL}$, which resulted in a 50% decrease in pre-feed plasma insulin concentrations and a 70% decrease in the insulin-to-glucose ratio. The median duration of diazoxide therapy was 2.5 days, with most babies completing treatment on the postnatal ward. After stopping diazoxide, babies maintained mean interstitial BGC ~ 4.5 mmol/L for up to 4 days of continuous monitoring, with only 9% having a subsequent hypoglycaemic event (compared to 93% in the placebo group on CGM), suggesting that diazoxide directly facilitated a change in the β cell glucose set-point for insulin secretion.

Diazoxide is generally well tolerated in neonates but has been rarely associated with pulmonary hypertension. The most detailed study of this association comes from the Children's Hospital of Philadelphia, a large specialist referral centre for congenital hyperinsulinism.¹¹² Among 295 babies with hyperinsulinism (39% non-genetic) and treated with diazoxide, 14 (5%) had pulmonary hypertension as defined by independent cardiology review of echocardiograms. However, half of these babies had evidence of pulmonary hypertension before starting diazoxide, and of the seven remaining cases, five were very preterm, one had respiratory failure, and one had congenital heart disease. In a similar study from another large hyperinsulinism centre in Texas, among 165 babies with hyperinsulinism (40% non-genetic) and treated with diazoxide, eight (5%) had echocardiographic defined pulmonary hypertension. However, in keeping with the Philadelphia study, five had anatomical cardiac abnormalities, one had genetic hyperinsulinism, one was on high-dose diazoxide (15 mg/kg/day), and one was retrialled on diazoxide without adverse effect. A retrospective neonatal network report of 1066 babies exposed to diazoxide found that 24 (2%) developed pulmonary hypertension after a median (IQR) duration of treatment of 8 (4, 18) days.¹¹³ No details were provided about how the diagnosis of pulmonary hypertension was made, nor its severity. The indication for diazoxide use was also not provided, although the cohort of exposed babies was not typical for transitional hypoglycaemia (47% born at <36 weeks' gestation; 33% outborn; 43% <2.5 kg; median hospital stay 19 days). In the NeoGluCO Study, babies were monitored closely for respiratory effort, oxygen use, blood pressure, patent ductus arteriosus, cardiac function, pulmonary blood flow, pulmonary hypertension, feed intolerance and gastrointestinal bleeding, and no adverse effects of diazoxide were detected.³ In fact, fewer babies in the diazoxide group, compared with placebo, were commenced on respiratory support or oxygen therapy after randomisation (8% vs. 11%).³ Of the two published placebo-controlled trials of early diazoxide therapy, no babies had diazoxide stopped for suspected side effects.^{3,53} Taken together, these studies show that the risk of pulmonary hypertension with brief, low-dose diazoxide treatment in well babies born at ≥ 36 weeks and birthweight ≥ 2.5 kg with no underlying cardiac disease is very low and is not of material clinical concern. Moreover, when pulmonary hypertension has occurred in association with diazoxide, it has fully resolved on stopping treatment.^{114,115}

Diazoxide has also been associated with necrotising enterocolitis. A neonatal network report found that of 1066 babies treated with diaoxide, 10 ($<1\%$) developed necrotising enterocolitis.¹¹³ Nine of these babies were preterm, and no further information was provided about the cases. The two hyperinsulinism centres reported one case each of necrotising enterocolitis among babies receiving diazoxide ($<1\%$). One infant had multiple medical problems and malformations, which likely caused the necrotising enterocolitis;¹¹⁶ no details were provided about the second infant.¹¹² In preparing for the NeoGluCO Study, the Auckland City Hospital neonatal database was interrogated over a 10-year period and no cases of necrotising enterocolitis were identified in association with diazoxide (personal communication Dr David Knight). In the NeoGluCO Study, no babies had feed intolerance or gastrointestinal bleeding.³ Similarly, in the other early diaoxide trial that used higher dose therapy (9 to 12

mg/kg/day) in babies with fetal growth restriction – a major risk factor for necrotising enterocolitis – no gastrointestinal complications occurred.⁵³ Thus, there is no evidence to suggest an association between diazoxide and necrotising enterocolitis in well near-term and term babies.

Parent perspectives

In addition to the previously mentioned parental priorities, 70% of parents in KFNC regarded a nasogastric tube as important or very important to avoid, and 82% reported that reducing heel pricks was important or very important. Two-thirds of parents in KFNC agreed or strongly agreed that oral medications, such as diazoxide, should be used before formula or IV dextrose.²⁰ If IV dextrose was commenced, 58% agreed or strongly agreed to withholding formula to allow establishment of breastfeeding.

Other recent qualitative studies among parents of children who experienced neonatal hypoglycaemia have emphasised the importance of providing clear information to both parents, including before birth; involving whanau in decision making; recognising the complex pregnancy journey often experienced before hypoglycaemia occurs (e.g., fetal growth concerns, maternal diabetes mellitus); the confronting nature of heel prick testing and the distress this causes to babies and parents; providing a clear rationale for tests and interventions; preparing the infant and parent for heel prick testing (e.g., skin-to-skin care, breastfeeding during testing, karakia); support and reassurance from health professionals; culturally safe care; and post-discharge information and support.¹¹⁷⁻¹¹⁹

Summary of evidence

- Key priorities for parents in severe and/or recurrent transitional hypoglycaemia are preventing further hypoglycaemia, avoiding separation of mum and baby, reducing time in the neonatal unit, establishing breastfeeding at discharge, reducing heel pricks, and avoiding a nasogastric tube; current management of neonatal hypoglycaemia in Counties Manukau is not effectively addressing these parental priorities.
- Dextrose gel has limited efficacy in severe hypoglycaemia.
- IV dextrose is a temporising strategy, but it fails to eliminate hypoglycaemia, does not promote metabolic transition, is associated with prolonged neonatal and hospital admission, contributes to a high burden of painful procedures, and may increase brain injury after hypoglycaemia in some babies.
- A physiologically based approach to treatment is needed in breastfeeding babies to promote metabolic transition, enable safe discharge from KFNC, and support exclusive/full breastfeeding; increasing the glucagon-to-insulin ratio and promoting suppression of insulin secretion between feeds is key.
- IMI glucagon corrects hypoglycaemia within 30 to 60 min in the majority of babies with severe transitional hypoglycaemia, but must be accompanied by other treatments to avoid rebound hypoglycaemia.
- In severe and/or recurrent transitional hypoglycaemia, 48 to 72 h of low-dose oral diazoxide largely eliminates further hypoglycaemia, reduces admission time and painful procedures, and appears to directly promote metabolic transition without rebound on stopping.
- Glucagon and diazoxide are well tolerated in neonates, and side effects are rare in otherwise well near-term and term babies.

Rationale

The Baby Friendly Hypoglycaemia Care Quality Improvement Initiative (BFHQI) focuses on near-term and term newborn babies admitted to KFNC with transitional hypoglycaemia. These babies have evidence of impaired metabolic transition, i.e., failure to correct with first-line management or severe hypoglycaemia, and are at greatest risk of neuroglycopenia and subsequent brain dysmaturation with potential for neurocognitive sequelae. Initially, BFHQI will be restricted to babies born at ≥ 36 weeks' gestation and with a birthweight of ≥ 2.5 kg as these babies are expected to be able to exclusively breastfeed. However, all babies with transitional hypoglycaemia are likely to benefit from BFHQI initiatives. Future iterations of BFHQI may focus on earlier preterm groups.

Three key compounding quality issues have been identified: 1) current management in KFNC, which relies primarily on IV dextrose, lacks efficacy, creates a high burden of care and is associated with safety concerns, including ongoing hypoglycaemia and potential for exacerbation of neuroglycopenia; 2) long duration of admission; and 3) poor establishment of breastfeeding.

Underpinning BFHQI is the recognition that exclusive breastfeeding is recommended for all babies by the World Health Organisation, and clinicians have an obligation under the Baby Friendly Aotearoa Programme to support women and babies to breastfeed whenever possible, regardless of medical complications. While women who make an informed choice to formula feed should be supported in this decision, for those who are aiming to breastfeed, clinicians have a duty to actively promote and enable exclusive breastfeeding. Current management approaches to hypoglycaemia in KFNC do not provide effective or safe options for women and babies who want to exclusively breastfeed.

Aim

To improve the care of near-term and term newborn babies who are admitted to KFNC with transitional hypoglycaemia (impaired metabolic transition).

Objectives

For near-term and term newborn babies who are admitted to KFNC with transitional hypoglycaemia (impaired metabolic transition), to develop a care model that:

1. Reduces exposure to hypoglycaemia (improves metabolic transition)
2. Decreases the duration of admission to KFNC (reduces separation of mother and baby)
3. Increases the proportion of babies who are fully breastfed at discharge to home (exclusive breastfeeding where possible).

Methods

Context

Middlemore Hospital

Each year, Middlemore Hospital has approximately 7,500 births, and approximately 8,000 women domiciled in the Counties Manukau district give birth. The proportion of babies with risk factors for transitional hypoglycaemia is steadily increasing, especially exposure to diabetes

mellitus in pregnancy. Over the past decade, the proportion of women with diabetes mellitus in pregnancy has doubled to 13%, and this risk would be >20% if the international WHO diagnostic criteria for gestational diabetes mellitus were applied.

Babies are eligible for postnatal ward care if they are born at ≥ 35 weeks' gestation and have a birthweight of >2 kg. A limited number of medical procedures may be provided by postnatal ward staff, including blood glucose monitoring, nasogastric tube feeding, phototherapy, oral medications and intravenous antibiotics. The majority of postnatal ward staff caring for babies with hypoglycaemia are nurses with a medical background. Babies who require intravenous fluids, respiratory support or intensive monitoring are admitted to KFNC.

Physical layout

The architecture of Middlemore Hospital is poorly designed for mothers and babies with a distance of over 200 m between the postnatal wards and KFNC. Moreover, to reach KFNC, mothers must navigate two lifts and multiple doors. There are currently no dedicated supports to enable women to be with their babies in KFNC, especially for those who are breastfeeding, such as KFNC orderlies or liaison midwives. Women are often not able to feed their baby because they are required to be present on the postnatal ward for ward rounds, observations and medications. Although it would be feasible for much of this maternal care to be provided in KFNC, this is currently not supported.

Hypoglycaemia guidelines

The current guideline for screening and management of babies at risk of transitional hypoglycaemia in the Maternity Care was published in 2019 and the guideline for management of babies admitted to KFNC with transitional hypoglycaemia was published in 2020. Because of the limited treatment options available at the time, women whose babies were deemed to be at high risk of hypoglycaemia (type 1 diabetes mellitus, type 2 diabetes mellitus with poor control, or ≥ 3 risk factors) were encouraged to formula feed their infants, and babies who failed dextrose gel treatment were required to have a trial of formula feeding before admission to KFNC. The admission criteria were BGC <1.2 mmol/L despite two doses of dextrose gel; BGC 1.2 mmol/L to <2.6 mmol/L despite two doses of dextrose and formula feed 5 ml/kg; three episodes of hypoglycaemia within 48 h; or suspected seizures. For admitted infants, treatment options were either to increase formula volume (100 ml/kg/day on day one or 120 ml/kg on day two) or commence IV dextrose, starting at 4.2 mg/kg/min (60 ml/kg/day of 10% dextrose).

As highlighted above, recent evidence has raised many concerns about current management in KFNC, including suboptimal glycaemic control, risk of reperfusion injury, incomplete metabolic transition, high burden of care, prolonged neonatal admission, and limited parental choice, especially for those wanting to breastfeed their infants. Given the new treatment options available, it is timely that the guidelines are reviewed.

Diazoxide use

Since the completion of the NeoGluCO Study, the use of diazoxide in KFNC has slowly increased. Diazoxide is now compounded by Optimus, a local pharmaceutical provider, at a concentration of 10 mg/mL, as per the methods established for the NeoGluCO Study.¹²⁰ Not only does this reduce costs, but it enables safer dosing of diazoxide for babies with transitional hypoglycaemia. The commercial solutions of diazoxide (e.g. Proglycem 50 mg/mL) are too concentrated to titrate accurately, especially in growth-restricted babies (e.g., a 3 kg baby

receiving 1.5 mg/kg would only require 0.09 mL). The Starship Hospital Endocrine Service is now recommending early use of low-dose diazoxide in prolonged transitional hypoglycaemia, using the algorithms developed below.

Donor breastmilk

Unlike many neonatal units in New Zealand, KFNC does not have a breastmilk bank. A limited supply of pasteurised donor breastmilk is gifted from Wellington Hospital periodically, but this is reserved for extremely preterm babies. Acceptance of donor milk by parents in KFNC is also variable.

Analysis of quality issues

Using the EPIC framework, the quality group undertook the following analysis of problems and probable causes.

| Objectives | Description of problems | Probable causes |
|--|--|--|
| 1. Reduce exposure to hypoglycaemia | <ul style="list-style-type: none"> High burden of ongoing hypoglycaemia in babies managed with IV dextrose (>50%) including severe hypoglycaemia (>20%) Hypoglycaemia on postnatal ward after discharge from KFNC (may be silent) Discharge to home without completion of normal metabolic transition | <ul style="list-style-type: none"> No treatment margin (using the same BGC threshold for diagnosis and treatment) Too much focus on BGC rather than establishing normal metabolic transition No physiologically targeted treatment Failure of IV dextrose to promote metabolic transition Separation of mother and baby impairs normal establishment of breastfeeding and lactation |
| 2. Decrease the duration of admission to KFNC | <ul style="list-style-type: none"> Median duration of admission to KFNC of 4 days in babies managed with IV dextrose | <ul style="list-style-type: none"> IV dextrose does not promote metabolic transition Separation of mother and baby impairs normal establishment of breastfeeding Rebound hypoglycaemia during weaning of IV dextrose Unclear guidance about how to transition infants to enteral feeding Maternal discharge when baby is admitted to KFNC |
| 3. Increase the proportion of babies who are fully breastfed at discharge home | <ul style="list-style-type: none"> Less than half of women who plan to breastfeed are fully breastfeeding at discharge home | <ul style="list-style-type: none"> Separation of mother and baby impairs normal establishment of breastfeeding Current guidance favours use of formula due to the lack of alternative treatments Prolonged admission and delayed metabolic transition increase pressure to start formula Once formula is started, it is continued because of concern about rebound hypoglycaemia |

Interventions

The following interventions were identified by the quality group as being most likely to address the quality problems.

| Objectives | Priority interventions | Future interventions for consideration |
|---|---|--|
| 1. Reduce exposure to hypoglycaemia | <ul style="list-style-type: none"> • Reduce the threshold for admission to KFNC^a • Increase feed volumes to 10-12 ml/kg in the first 48 h for infants who are formula fed and develop hypoglycaemia^b • Increase the BGC treatment target range in KFNC (i.e., once the baby is admitted to KFNC) to 2.8 mmol/L (25th centile <48 h) to 6.0 mmol/L (97th centile ≥96 h)^c • Define metabolic transition as maintaining BGC ≥3.3 mmol/L (50th centile <48 h) for ≥48 h on normal enteral feeding of the parent's choice^c • Introduce physiologically targeted medical therapy (glucagon and low dose diazoxide), either as primary treatment or as rescue from IV dextrose^d • Provide clear and simple treatment guidance for staff, supported by visual algorithms for each pathway^e • Have a single coordinated guideline for the hospital^e • Staff education and feedback^f • Provide consumer-focused information so that parents make informed antenatal decisions about feeding to ensure that infants who develop hypoglycaemia are quickly commenced on the appropriate pathway^g | <ul style="list-style-type: none"> • Donor breastmilk bank • Concentrated formula or formula additives for formula-fed infants • Intranasal glucagon analogues • Consumer videos |
| 2. Decrease the duration of admission to KFNC | <ul style="list-style-type: none"> • Promote collaboration of Neonatal and Maternity Services to ensure that breastfeeding women can maximise the time they spend with their infant in KFNC^h • Actively promote metabolic transition by introducing physiologically targeted medical therapy (glucagon and low-dose diazoxide)^d • Complete medical therapy on the postnatal ward | <ul style="list-style-type: none"> • Dedicated ordelies • Liaison midwife in KFNC • Develop neonatal care models that do not require admission to KFNC for management of hypoglycaemia |

| Objectives | Priority interventions | Future interventions for consideration |
|---|---|--|
| | <ul style="list-style-type: none"> • Provide clear and simple guidance to staff on when and how to discharge infants with hypoglycaemia^e • Staff education and feedback^f | |
| 3. Increase the proportion of babies who are fully breastfed at discharge to home | <ul style="list-style-type: none"> • Provide treatment pathways that do not rely on use of formula^d • Decrease the duration of admission to KFNC, as above • Staff education and feedback^f | <ul style="list-style-type: none"> • Develop neonatal care models that do not require admission to KFNC for management of hypoglycaemia |

Intervention details:

- a. The quality group reviewed the admission criteria to KFNC and simplified the criteria as follows:
- Profound hypoglycaemia at any stage (<1.2 mmol/L)
 - Ongoing hypoglycaemia (<2.6 mmol/L) after 2 doses of dextrose gel and feeding of the parents' choice in a single episode
 - Third episode of hypoglycaemia
 - Suspected seizures

The new criteria emphasise active support of the parents' intended feeding method, including removal of the requirement for formula to be trialled in breastfed infants before admission to KFNC. The criteria also emphasise earlier intervention for infants with impaired metabolic transition, i.e., those who present with severe hypoglycaemia and those who do not respond well to first-line management (including recurrent hypoglycaemia), to ensure that exposure to ongoing hypoglycaemia is reduced.

- b. Formula volumes of 10 to 12 ml/kg/feed (80 to 96 ml/kg/day) are tolerated by most infants, even on day one. This provides the equivalent of 4.3 to 5.2 mg/kg/min of glucose and 55 to 66 kcal/kg/day of energy.
- c. Having a treatment target for babies admitted to KFNC that is higher than the diagnostic threshold provides a margin of safety for infants who have been identified as having impaired metabolic transition. Defining the treatment target after admission as ≥ 2.8 mmol/L and metabolic transition as achieving stable BGC ≥ 3.3 mmol/L is consistent not only with normative data from healthy breastfed infants^{40,66} but also international expert consensus.¹²¹
- d. Physiologically targeted medical therapy provides an opportunity for breastfed infants to continue exclusive breastfeeding, while directly addressing the underlying pathophysiology that causes impaired metabolic transition. Current evidence indicates that glucagon and early low-dose diazoxide are the most effective treatments for severe and/or recurrent transitional hypoglycaemia.
- e. For the bundle of interventions to work successfully, clinical guidance documents must be succinct, clear, unambiguous and easy for staff to follow. The quality group prioritised the presentation of treatment algorithms as decision-based flow charts, created using Lucid

software. Three flow charts have been developed using FRESCO methodology;¹²² one for screening of at-risk infants and first-line management of hypoglycaemia in Maternity Care; one for primary medical therapy of transitional hypoglycaemia in breastfeeding infants admitted to KFNC; and one for rescue medical therapy of transitional hypoglycaemia in breastfeeding infants admitted to KFNC on IV dextrose (Appendix). The flowcharts have been designed to be used as standalone guides within each treatment pathway. Laminated flowcharts will be provided for clinical areas. The treatment algorithms may undergo revision with quality audit and feedback cycles, including changes to doses and frequency of medications, BGC monitoring, and transfer and discharge processes.

Initially, primary medical therapy will only be offered to infants who are expected to successfully breastfeed, including being born at ≥ 36 weeks and ≥ 2.5 kg, who demonstrate feeding cues and are taking EBM or who achieve D-F breastfeeds, and whose mother can attend KFNC or send EBM and attend within an hour of admission. These criteria may be widened during future stages of the quality improvement initiative.

- f. Staff will be supported by an education package, including videos to explain the key physiological principles and proposed treatment approaches for transitional hypoglycaemia. As part of the quality cycles, staff will be provided with feedback about the performance of clinical care. Where issues are identified, a deeper analysis of barriers and enablers of the quality interventions will be undertaken.
- g. Consumer Information will be developed to enable parents to make an informed choice about their preferred treatment pathway, especially when breastfeeding is planned. If funding can be secured, this will be presented as an online video. Parent information will be provided via antenatal clinics (e.g., Diabetes in Pregnancy service), antenatal wards, postnatal wards, neonatal staff and lead maternity carers.
- h. Collaboration between services will be increased by the introduction of single perinatal electronic medical record (March 2025) with task management and clinical care workflows; a hospital-wide approach to staff education, training, feedback and case review sessions; a single set of coordinated algorithms; audit of care across both clinical environments; promotion of patient choice, beginning in the antenatal period; and combined staff surveys to identify barriers and enablers of the quality objectives.

Study of the interventions

Following three weeks of focused staff training (23 March to 12 April), interventions will be phased in from 13 April to 24 May 2026, with ongoing staff education and support. Three six-month quality cycles will be run, each involving a 6-week period of audit, a staff survey, review of interventions by the quality group, modification of the intervention bundle, if required, and staff feedback and education. The staff survey will assess perceived barriers and potential solutions to delivering the quality interventions (Appendices). The quality cycles will be supported by periodic case review sessions to discuss selected cases that highlight successes and challenges in implementing the quality interventions. The case review sessions will be part of the wider KFNC quality and audit meeting programme. Formal review of audit data will be presented at KFNC grand rounds. Maternity and neonatal staff will be invited to attend all

quality presentations. At all stages of the quality improvement initiative, staff will be able to give verbal or written feedback to the quality group about the quality interventions.

Timeline

| Phase | Baseline | | Implementation | Cycle 1 | Cycle 2 | Cycle 3 | Close |
|-------------------------|--|--|--|--------------------------------|---------------------------|---------------------------|----------------------------|
| Dates | 1/9/25 to 12/4/26 | | 23/3/26 24/5/26 | 25/5/26 to 22/11/26 | 23/11/26 to 23/5/27 | 24/5/27 to 24/10/27 | 25/10/27 to 22/12/27 |
| Audit data collection | 1/9/25 to 13/10/25 (retrospective) | 2/3/26 to 12/4/26 (prospective) | | 25/5/26 to 5/7/26 | 23/11/26 to 3/1/27 | 24/5/27 to 4/7/27 | 25/10/27 to 5/12/27 |
| Staff survey | | 16/3/26 to 27/3/26 | | 2/6/26 to 12/6/26 | 1/12/26 to 11/12/26 | 31/5/27 to 11/6/27 | |
| Review of interventions | | | Commence interventions 13/4/26 | 6/7/26 to 17/7/26 | 5/1/27 to 16/1/27 | 5/7/27 to 16/7/27 | |
| Education and feedback | | Commence training 23/3/26 to 12/4/26 | Focused education 23/3/26 to 12/4/26 Followed by ongoing training and support | 20/7/26 to 31/7/26 | | 19/7/27 to 30/7/27 | Write up quality report |
| Case review sessions | | | | 15/6/26 10/8/26 19/10/26 | 8/2/27 3/5/27 | 9/8/27 | |

Measures

Audit data will be collected in six-week epochs and include all infants in the quality improvement initiative target population, i.e., admitted to KFNC for management of severe and/or recurrent transitional hypoglycaemia within 48 h of birth, born at ≥ 36 weeks' gestation and with a birthweight of ≥ 2.5 kg. The audit data items are summarised below.

Background data

- Sex
- Birthweight (to nearest 100 g)
- Customised birthweight centile
- Gestation in completed weeks
- Plurality
- Prioritised baby ethnicity: Māori, Pacific, Indian, Asian, Other, European
- Maternal diabetes and type: type 1, type 2, MODY/other, GDM (OGTT fasting ≥ 5.3 , 1 h ≥ 10.6 , 2 h ≥ 9.0 mmol/L), early GDM (diagnosed < 20 weeks), suspected type 2 at booking (HbA1c ≥ 48 mmol/mol < 20 weeks), suspected prediabetes at booking (HbA1c 42 to 47 mmol/mol < 20 weeks)
- Antenatal diagnosis of FGR (as per national guideline)
- Mother intends to breastfeed
- Received formula before KFNC admission
- Evidence of establishing breastfeeding before KFNC admission (if intends to breastfeed): taking EBM or D-F breastfeed

Outcome measures

- Prioritised admission criterion (baseline phase): seizure > profound hypoglycaemia <1.2 mmol/L despite 2 doses of dextrose gel > hypoglycaemia 1.2 to 2.5 mmol/L despite two doses of dextrose buccal gel and trial of supplementary feed 5 ml/kg > third episode of hypoglycaemia
- Prioritised admission criterion (intervention phase): seizure > profound hypoglycaemia (<1.2 mmol/L), ongoing hypoglycaemia <2.6 mmol/L after two doses of dextrose gel and feeding of the parents' choice in a single episode > third episode of hypoglycaemia
- Initial management pathway in KFNC (formula, IV dextrose, IV dextrose and formula, primary medical therapy)
- If the initial management pathway is primary medical therapy:
 - Glucagon given within 20 min of admission to KFNC
 - Diazoxide given within 20 min of admission to KFNC
 - Breastfed or given EBM within 1 h of admission to KFNC
- Rescue diazoxide therapy
- If diazoxide is used, diazoxide dose is titrated up
- If diazoxide is used, diazoxide duration
- Time to first BGC ≥ 2.8 mmol/L in KFNC
- Hypoglycaemia ≥ 90 min after admission to KFNC: no (all BGC from 90 min ≥ 2.8 mmol/L), borderline hypoglycaemia (any BGC 2.6 to 2.7 mmol/L), 1 or 2 episodes of hypoglycaemia (<2.6 mmol/L), recurrent hypoglycaemia (≥ 3 episodes <2.6 mmol/L)
- Severe hypoglycaemia (<2.0 mmol/L) ≥ 90 min after admission to KFNC
- Hyperglycaemia >7 mmol/L after admission to KFNC
- Hypoglycaemia <2.6 mmol/L after discharge from KFNC
- Hyperglycaemia >7 mmol/L after discharge from KFNC
- Time from admission to KFNC to metabolic transition (BGC maintained ≥ 3.3 mmol/L for ≥ 24 h on normal enteral feeding)
- Seizure after admission to KFNC
- Commencement of oxygen therapy or respiratory support after admission to KFNC
 - If yes, maximal FiO₂
 - If yes, maximal support level: low flow oxygen, high flow, CPAP, mechanical ventilation, other
 - If yes, primary diagnosis: TTN, pneumonia, air leak, PPHN, congenital malformation, other
- Formula given in KFNC
- Feed type at discharge from KFNC (last 6 h): breastfeeding/EBM, formula, mixed
- Formula given after discharge from KFNC
- Feeding status at discharge to home: exclusive breastfeeding (only mother's milk since birth or medications), full breastfeeding (only mother's milk for 48 h before discharge or medications), formula or mixed feeding (any formula in the 48 h before discharge)
- Total duration of admission in KFNC for hypoglycaemia

Data management

The above audit data will be collected in REDCap. To ensure confidentiality, data will be de-identified by using the random BadgerNet number as the record identifier. Only approved hospital staff with BadgerNet access will be able to re-identify the baby. Additional

confidentialisation will be achieved by only recording gestation in completed weeks and birthweight to the nearest 100 g, and no dates will be recorded. Time-based measures will be calculated in a temporary spreadsheet, which will be deleted once the outcomes are entered into REDCap.

An online staff survey will be delivered via a REDCap project, accessed by a QR code that will be made available in staff areas. The survey will be anonymous but staff will be given the option to give their name and contacts, if they wish to talk to a member of the quality group.

Access to REDCap projects will be limited to the quality group lead and quality team members collecting and analysing data. After the quality project, the REDCap projects will be deleted, and the deidentified and confidentialised data files will be securely archived by the quality group lead. No data files will be shared outside of the quality group. Quality group reports will present only summary data.

Analysis

Audit data and staff survey results will be summarised with appropriate descriptive statistics during each quality cycle.

The primary quality measures are:

- Hypoglycaemia from 90 min after admission to KFNC until discharge to home, defined as <2.8 mmol/L while in KFNC and <2.6 mmol/L after discharge from KFNC (denominator: all babies eligible for audit)
- Total duration of admission in KFNC during the primary hospital stay (denominator: all babies eligible for audit)
- Full breastfeeding at discharge to home (denominator 1: all babies eligible for audit; denominator 2: all babies eligible for audit and mother intending to breastfeed)

The overall effectiveness of the quality interventions will be evaluated against the primary quality measures using a single interrupted time series with segmented regression analysis.¹²³ Analyses will be undertaken with SAS software (v9.4).

Secondary analysis will explore interactions between the effect of quality interventions on the primary quality measures by ethnicity and primary risk factor for hypoglycaemia.

Other audit data will be used to explain changes (or lack of) in the primary quality measures and to identify areas for improvement in the quality interventions.

Ethical considerations

Health care systems have a duty to improve the quality of clinical care provided, especially when elements of practice have been shown to have limited effectiveness and contribute to patient harm, as is the case with neonatal hypoglycaemia (e.g., ongoing hypoglycaemia, high burden of painful procedures, prolonged admission, low exclusive breastfeeding).^{124,125}

This quality improvement initiative is not clinical research because it is seeking to translate the best available knowledge into every day practice; is not aiming to produce generalisable new knowledge but is addressing a complex, context-specific clinical problem; is focusing on quality issues identified by patients; is promoting patient autonomy by providing a better range of treatment options; is seeking to prevent harm caused by current practice; has a high

likelihood of offering direct benefit to all patients; and will introduce a multifaceted bundle of care with regular quality cycles based on audit, feedback and other quality methodologies.¹²⁵

New Zealand does not have a mature pathway for oversight of quality improvement activities, although general ethical considerations are provided (National Ethical Standards 18.1-18.8), all of which have been met by this quality improvement initiative.¹²⁵ The Hastings Centre has developed an ethical framework of seven fundamental obligations that constitute a necessary condition of adequate ethics in health improvement.¹²⁴ These obligations have also been met by this quality improvement initiative, as outlined below.

| Obligations | Explanation | How the quality improvement initiative will meet the obligation |
|---|---|--|
| Respect patients | A central patient right is to have one's autonomy respected. Respect is also shown by protecting confidentiality, evaluating the effectiveness of health care in terms of outcomes that matter to patients, and helping patients understand what is happening to them. | The objectives of the quality improvement initiative are based on parental priorities. The quality interventions will increase patient autonomy through better information sharing and by providing a better range of treatment options. Privacy will be protected in the collection of audit data by deidentification and confidentialisation of data fields and values. Audit data will not be shared outside of the quality group. |
| Respect clinician judgement | The exercise of clinical judgment can further the health interests of patients in achieving the best clinical outcome and can advance the autonomy interests of patients. However, clinician judgment may also fail to achieve the best health outcomes for patients, especially when there is an absence of good empirical evidence, or when that evidence does not factor in the forming of the judgment. | The evidence for and understanding of transitional hypoglycaemia has changed substantially since the current hospital guidelines were written. There is now evidence that aspects of current practice have limited effectiveness and contribute to patient harm. The quality interventions will improve clinician understanding of the pathophysiology of transitional hypoglycaemia and ensure that practice is physiologically based. They will also reduce non-clinical variation in care. Clinician judgment will still be important in responding to atypical metabolic responses to treatment and in recognising the need to consider alternative diagnoses. |
| Provide optimal care to each patient | Advance the welfare interests of each patient by providing optimal care aimed at securing the best possible clinical outcome. The expected net clinical benefit for the patients affected by a learning activity should be compared to the net benefit they likely would have experienced if their care had not been affected by that activity. | The quality interventions are very likely to achieve net benefit for all babies, compared to current practice. For formula-fed infants, increasing feed volumes after hypoglycaemia will decrease the risk of ongoing hypoglycaemia, and need for and duration of admission to KFNC. For breastfeeding infants, the quality improvement initiative will offer a pathway that will support safe exclusive breastfeeding, in addition to promoting metabolic transition and shorter hospital stay. |
| Avoid imposing non-clinical risks and burdens | These include risks to privacy of health information, employment, reputation, or additional tests or visits. | The privacy of health information will be fully protected as above. The quality interventions are likely to reduce the overall burden of care. |
| Address unjust inequalities | Learning activities should not disproportionately benefit patients who are already socially and economically advantaged, and potential negative effects should not fall disproportionately on socially and economically disadvantaged groups. | All eligible patient groups will be equally involved in this quality improvement initiative. Ethnicity will be collected to allow a comparison of the primary quality measures by ethnic group. Potential inequity will be addressed by the quality group. |

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| Conduct continuous learning activities that improve the quality of clinical care and health care systems | Learning activities must be individually assessed for the extent to which they hold the prospect of contributing to the improvement of health care services and systems. | The quality interventions are very likely to achieve net benefit for each baby compared to current practice. All the quality interventions are low or minimal risk. |
| Patient contribution to the common purpose of improving the quality and value of clinical care and the health care system | Patients have a common interest in supporting just institutions and an obligation to participate in and facilitate health system learning. This requires near-universal participation in learning activities that are integrated, on an ongoing basis, with the clinical care that patients receive. | Parents will be informed of the quality improvement initiative and the collection of audit data. Patient autonomy will be respected by providing a better range of treatment options. |

National Ethical Standards 18.9-18.10 provide guidance about patient consent for quality improvement initiatives.¹²⁵ If change is made at a system level to improve outcomes, is supported by evidence of benefit in similar populations, and is not being made solely to improve efficiency or for the benefit of the healthcare provider, only routine patient consent is required, i.e., verbal assent after a discussion of the treatment options by a clinical provider. These discussions should be documented as part of routine clinical practice.

Clinical and ethical oversight for this quality improvement initiative is provided by the quality group, the executive sponsor, and the KFNC quality programme, which reports to the senior leadership.

Responsiveness to Māori

Currently, there are no clinical staff working in KFNC who identify as Māori. Ms Jenny Rogers, Ngāi Tahu, will assist the quality group by providing a Māori perspective on quality initiatives and information given to whānau, and will guide analysis of audit data relating to Māori babies. Ms Rogers is a Māori paediatric researcher with over 15 years of experience in studying transitional hypoglycaemia, including intervention trials and long-term follow-up studies. She is an investigator of the NeoGluCO Study.³ Ms Rogers has a wealth of expertise relating to the experience of Māori mothers, babies and whānau with neonatal hypoglycaemia.¹¹⁹

This quality initiative seeks to improve outcomes for all patient groups, including Māori babies. Māori women have a higher risk of preterm birth and are more likely to have diabetes mellitus and low birthweight babies, compared to European women,^{126,127} all of which are risk factors for transitional hypoglycaemia. However, the proportion of Māori infants admitted to KFNC with severe or recurrent hypoglycaemia is similar to that of the background pregnancy population (~20%), suggesting that the screening and diagnosis of transitional hypoglycaemia among Māori infants may be inadequate. There may also be differences by ethnic group in the type or intensity of treatment offered or clinical outcomes, although this is currently unknown. BFHQI will track audit data by ethnicity and will highlight any potential inequities of care in KFNC for Māori compared with non-Māori babies. Should this occur, additional steps will be taken to adjust quality interventions and ensure that they remain cultural safe and relevant for Māori.

This quality initiative is aligned with other key priority areas for Māori in neonatal care, including promotion of breastfeeding¹²⁸⁻¹³⁰ and maintaining contact between babies and their whānau. For Māori, being close to a newborn baby and being able to hold them is critical to bonding and

emplacing them in whakapapa networks, processes that are severely disrupted by admission to KFNC.¹³¹ BFHQI will dramatically reduce the time babies spend in KFNC (and in hospital), thereby reducing separation of mother and baby, and promoting an environment more conducive to successful breastfeeding. Kaupapa Māori studies have emphasised the importance of involving whānau in breastfeeding education and discussions and provision of timely, culturally relevant and comprehensive information,^{128,129} and this will be a focus of BFHQI.

Other studies

As a quality initiative, this project is not undertaking any primary research on transitional hypoglycaemia. However, the audit of quality measures may raise new questions for further inquiry. The quality group is well placed to initiate parallel clinical research studies, both quantitative and qualitative, if required. Such research studies will have a separate protocol, and require ethical and locality research approval.

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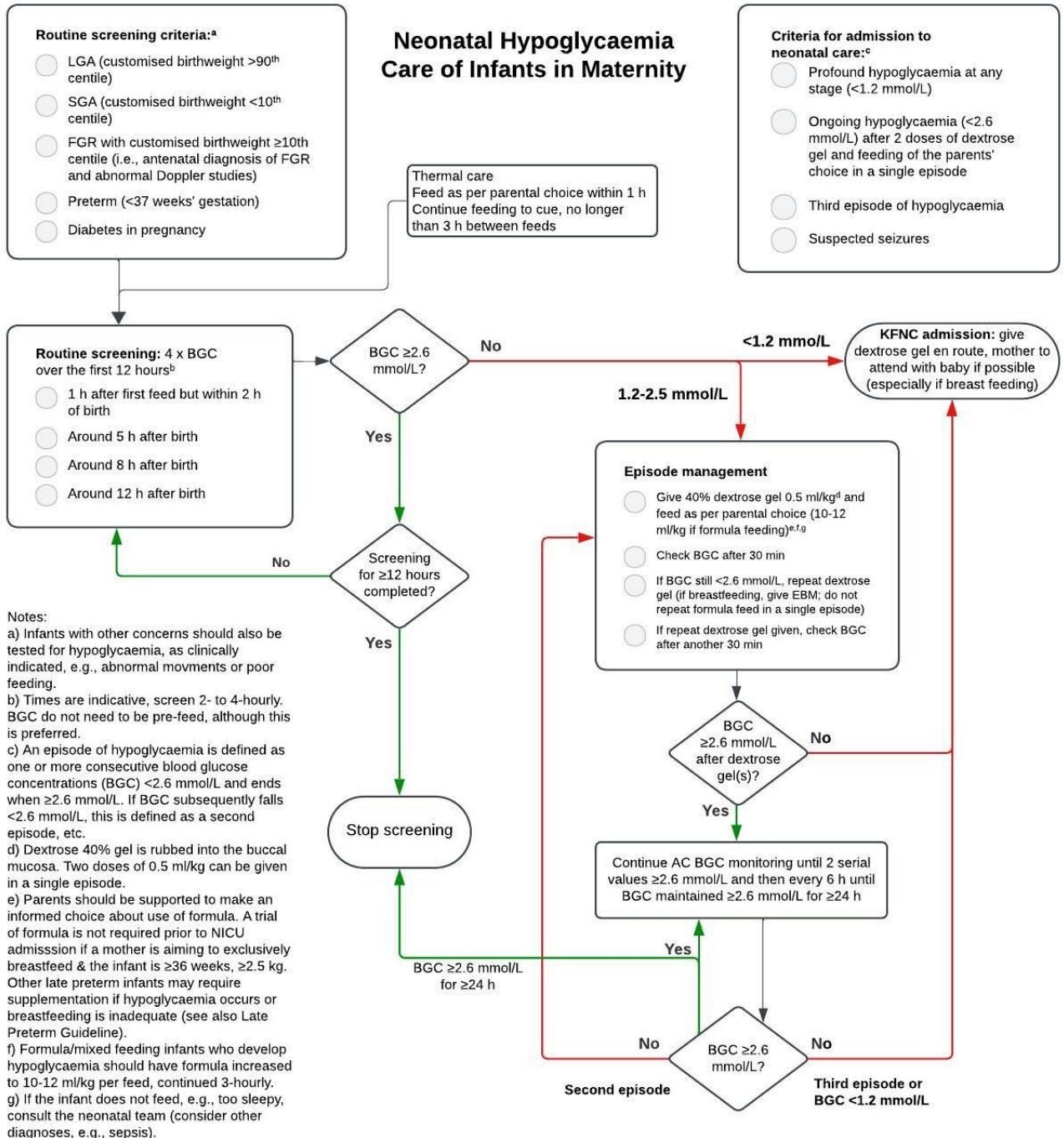
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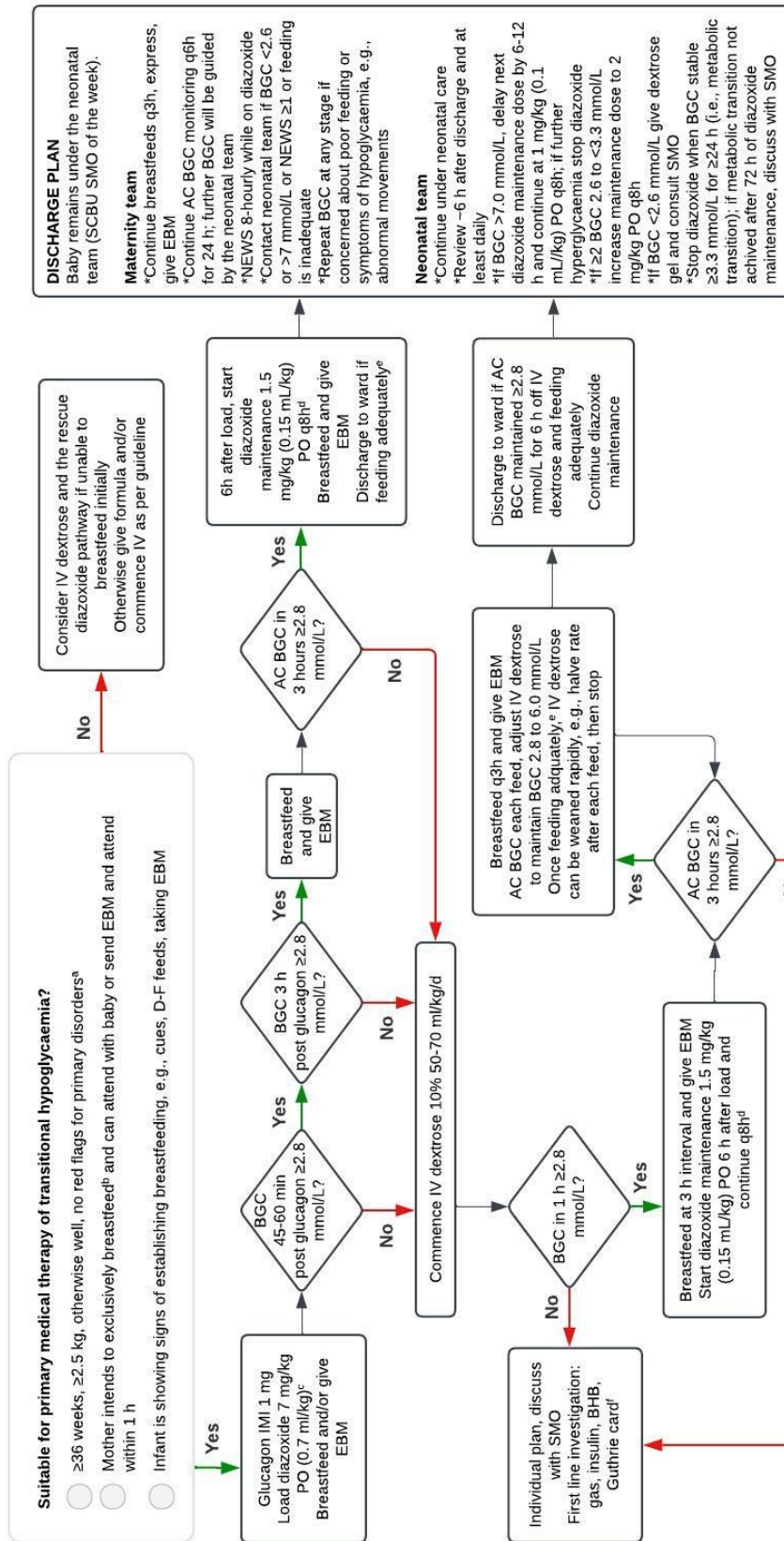
Appendices

Appendix 1: Screening and management of infants at risk of hypoglycaemia in Maternity Care



Appendix 2: Primary medical therapy for breastfeeding infants with transitional hypoglycaemia

Primary Medical Therapy for Transitional Hypoglycaemia



Notes:

a) Red flags include: absence of perinatal risk factors for transitional hypoglycaemia; family history of genetic disorder affecting glucose metabolism or hypopituitarism; known central or major brain malformation or cleft palate (hypopituitarism); ambiguous genitalia or micropenis (hypoadrenalism, hypopituitarism); bradycardia or arrhythmia (fatty acid oxidation defect); clinical signs of Beckwith-Wiedemann, Kabuki or Turner syndrome (hyperinsulinism).

b) Exclusive breastfeeding is defined as receiving only mothers milk from birth, except for prescribed medicines: full breastfeeding at discharge is defined as receiving only mothers milk in the previous 48 hours, except for prescribed medicines.

c) There are two diazoxide concentrations, 50 mg/mL and 10 mg/mL. Only 10 mg/mL is stocked in neonatal areas. Diazoxide should only be given to well infants. Avoid diazoxide in hypoxia, pulmonary hypertension, severe anaemia and cardiac disease: **Diazoxide dose should be charged in mL with the dose in mg and mg/kg recorded on the drug chart, along with the suspension concentration.** Ensure that the correct suspension is used, which should be 10 mg/mL (1 mg/kg = 0.1 mL/kg).

d) If BGC > 7 mmol/L after load, delay commencement of maintenance by -6h, and discuss with SMO.

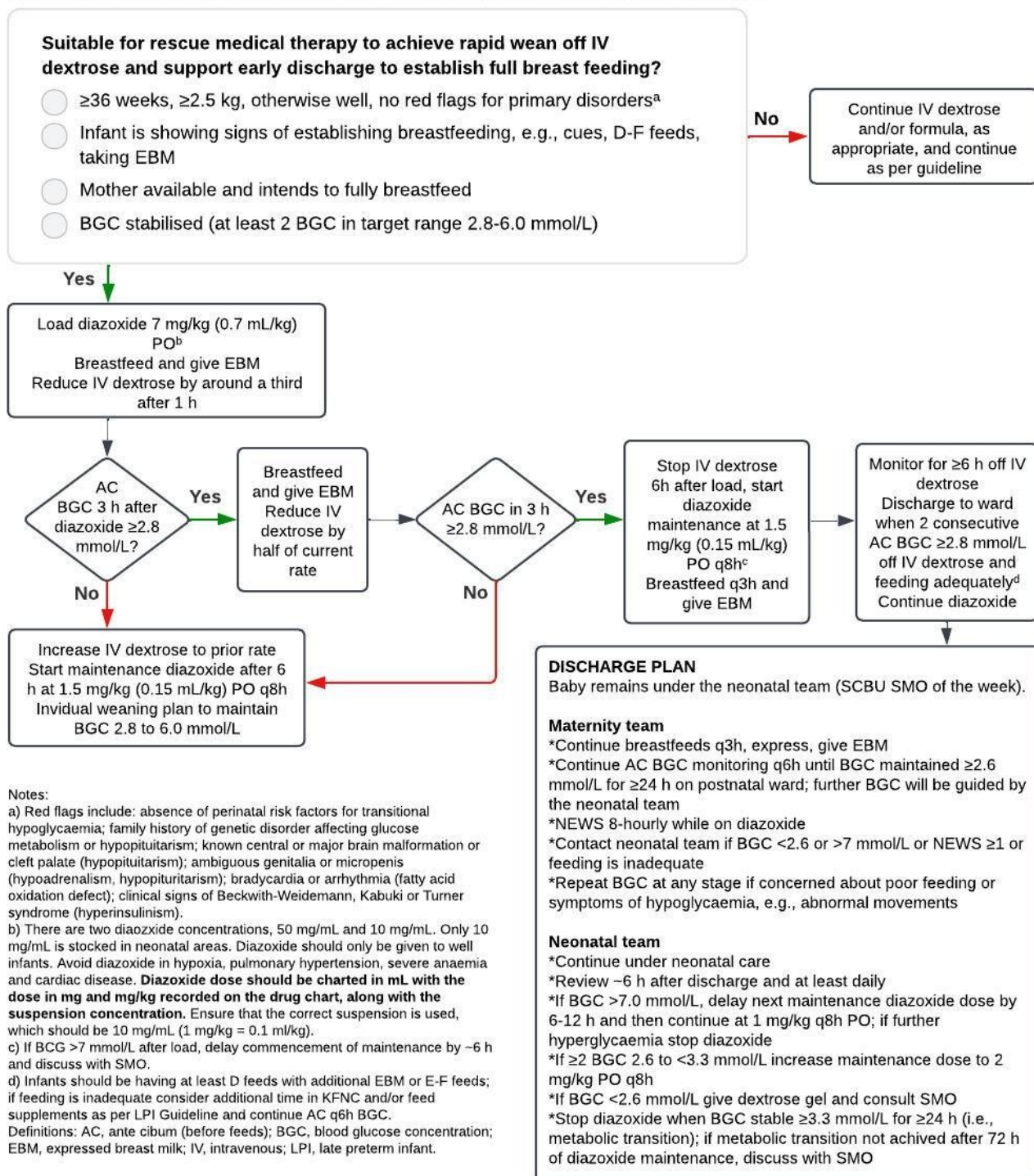
e) Infants should be having at least D feeds with additional EBM or E-F feeds; if feeding is inadequate consider additional time in KFNC and/or feed supplements as per LPI Guideline, and continue q6h AC BGC.

f) With adequate response to diazoxide, AC plasma insulin is typically decreased by 50% and BHB concentrations will be increased.

Definitions: AC, ante cibum (before feeds); BGC, blood glucose concentration; BHB, β hydroxy butyrate; EBM, expressed breast milk; IMI, intramuscular injection; IV, intravenous; LPI, late preterm infant.

Appendix 3: Rescue medical therapy for breastfeeding infants with transitional hypoglycaemia

Rescue Medical Therapy for Transitional Hypoglycaemia



Appendix 4: Protocol ammendements

| Version | Description of ammendment | Date approved by quality group |
|---------|---------------------------|--------------------------------|
| | | |
| | | |
| | | |

Appendix 5: Staff training approach

TBC

Appendix 6: Staff survey

TBC