Guideline

Hypoglycaemia – Newborn management

Key points

- Hypoglycaemia is defined as a true blood glucose (TBG) concentration < 2.6 mmol/L and should always be treated
- Newborns are screened for hypoglycaemia based on risk factors, starting at 1-2 hours after birth
- TBG should be used in preference to a blood sugar level (BSL) when available, and for ongoing screening in all infants who have had a BSL < 2.6mmol/L.
- 40% oral glucose gel rubbed into the buccal mucosa is the first-line treatment for hypoglycaemia in well newborns ≥ 34 weeks' gestation
- An episode of hypoglycaemia should last no longer than 2 hours without medical evaluation

1. Purpose

This guideline outlines the requirement for management of hypoglycaemia in newborn infants at the Women's.

Where processes differ between campuses, those that refer to the Sandringham campus are differentiated by pink text or have the heading **Sandringham campus.**

2. Definitions

Hypoglycaemia: TBG < 2.6 mmol/L[1]

Clinical signs which suggest clinically significant hypoglycaemia are non-specific and include jitteriness, irritability, high pitched cry, cyanotic episodes, apnoea, seizures, lethargy, hypothermia, hypotonia or altered or poor feeding. Most babies with hypoglycaemia will have no clinical signs[2].

True Blood Glucose (TBG): as measured by the glucose-oxidase method on a blood gas analyser in NICU, an iSTAT on the postnatal wards/ birth centre or SCN, or by laboratory measurement.

Blood Sugar Level (BSL): as measured using a non-glucose oxidase method with a blood glucose monitor and reagent strips in birth centre and postnatal wards. These measurements are less accurate at lower BSL. Therefore a TBG should be performed for any BSL < 2.6 mmol/L.

3. Responsibilities

All medical and nursing/midwifery staff caring for newborn infants.

4. Guideline

Neonatal hypoglycaemia is common, preventable and can both cause and potentiate neonatal brain injury. Although there is ongoing debate regarding the lowest threshold of blood glucose concentration that is considered safe, emerging evidence shows that even single episodes of hypoglycaemia in the neonatal period may be associated with adverse learning outcomes[3], with a dose-dependent relationship between severe hypoglycaemia and impaired executive function and visual-motor outcomes[4]. In well, term infants, the normal post-partum blood glucose nadir occurs at ~ 90 minutes, with mean minimum blood glucose concentrations of 3.3 mmol/L[5].

Currently, intermittent TBG monitoring is the only method to screen babies for hypoglycaemia, but may miss up to 25% of hypoglycaemic episodes in at risk infants[6]. The use of an enzymatic method to evaluate all blood glucose concentrations reduces the number of false-positive and false-negative results for hypoglycaemia, and decreases the number of repeat heel-prick tests required[7]. TBG should be used in preference to a BSL when available, and for ongoing screening in all infants who have had a BSL < 2.6mmol/L.

4.1 Identification of infants who require screening for hypoglycaemia

Do not measure blood glucose levels in well, term infants.
Infants who have one or more of the following risk factors require screening for hypoglycaemia:

- All low birthweight infants (< 2,500g), regardless of gestation
- All preterm infants (< 37 weeks' gestation)
- Small for gestational age infants (< 10th centile), as per table 1
- Macrosomic or large for gestational age infants (> 90th centile), as per table 1
- Infants of mothers with type 1, type 2 or gestational diabetes
- Infants of mothers treated with β-blockers
- Infants with clinical signs of hypoglycaemia
- Infants with poor feeding or limited/no enteral intake
- Unwell infants (including birth asphyxia, sepsis, polycythaemia)

Table 1: Birthweight thresholds for small and large for gestational age

Birth gestation (completed weeks)	10th centile (grams)	90th centile (grams)
36	2300	3300
37	2450	3600
38	2600	3800
39	2800	4000
40	2900	4200
41	3100	4400

4.2 Management of infants with risk factors for hypoglycaemia

All newborns with risk factors for hypoglycaemia should be offered a breastfeed within 1 hour of birth, then at least 3-hourly.

- Infants of mothers who choose to formula feed should be offered the equivalent of 60ml/kg/day
- Infants who are unable to feed enterally, for any reason, should have IV access obtained and intravenous glucose/nutrition commenced within 1 hour of birth

Infants with > 2 risk factors for hypoglycaemia are at increased risk of severe hypoglycaemia[2] and should be referred to the neonatal RMO/ paediatrician after birth and assessed for potential NICU/ SCN admission.

4.3 Screening newborns at risk for hypoglycaemia in birth centre and postnatal wards

- BSL should be measured no more than 2 hours after birth in infants with risk factors for hypoglycaemia
- If BSL < 2.6 mmol/L at any time, ongoing measurement should be by TBG (blood gas analyser, iSTAT,)[7].
- Measurement should continue prior to each feed (~Q3H) for 48 hours, **or** until 3 consecutive BSL/ TBGs ≥ 2.6 mmol/L **and** feeding is assessed as adequate[1].
- Neonatal RMO/ paediatrician to review infants daily until discharged from neonatal/ paediatric care.

- Infants managed for hypoglycaemia in the postnatal ward do not require routine neonatal outpatient follow-up.

4.4 Management of hypoglycaemia in birth centre and postnatal wards

Refer to **Appendix 1**.

Indications for NICU admission

- TBG < 1.5 mmol/L at any time
- TBG < 2.6 mmol/L 2 hours after initiation of treatment
- TBG < 2.6 mmol/L on ≥ 3 consecutive pre-feed samples
- Baby appears unwell

4.5 Management of infants with risk factors for, or diagnosis of hypoglycaemia, in NICU/ SCN

All preterm infants (< 37 weeks' gestation) are at risk of hypoglycaemia due to inadequate glycogen stores, inefficient or absent enteral feeding, blunted counter-regulatory responses to low blood glucose concentrations and transient hyperinsulinism resulting from perinatal stress (hypoxia, intrauterine growth restriction, etc).
The normal post-birth blood glucose nadir occurs earlier with decreasing gestational age[5]. For infants who are admitted to NICU/ SCN with multiple risk factors for hypoglycaemia, and those who are in NICU/ SCN due to other illnesses, hypoglycaemia may also be early and severe.

Prevention of hypoglycaemia

Provide an exogenous glucose source within **one** hour of birth

- Breastfeed/ EBM
- Formula (with maternal consent and if medically appropriate)
- IV glucose

Ensure normothermia

Small, early enteral feeds may aid glucose regulation in very preterm infants

Screening for hypoglycaemia

All blood glucose measurements are TBG.

Measure TBG one hour after birth.

Screening should continue pre-feeds, or twice daily if on IV fluids with stable blood glucose:

- Screening may be discontinued when infant is on full enteral feeds with 3 consecutive TBG readings ≥ 2.6mmol/L
- Screening should be recommenced if the feeding regimen changes (e.g. transition from full top ups to exclusive breast feeds) or if the infant's clinical condition changes

Note that infants born preterm are at increased risk of hypoglycaemia occurring beyond the usual 48 hour screening period[2].

Management of infants with risk factors for hypoglycaemia in NICU/ SCN

Refer to **Appendix 2**.

Calculate and document IV glucose delivery rate in mg/kg/min

Continue enteral feeds as tolerated and support breastfeeding (do not make nil orally unless enteral feeding contraindicated).

Increase feeds gradually, reducing IV glucose infusion accordingly when TBG readings are stable (at least 2 consecutive readings ≥ 2.6mmol/L).

Infants on 3 hourly sucking feeds may be discharged to postnatal ward as soon as TBG ≥ 2.6 mmol/L on 3 consecutive occasions. If hypoglycaemia has occurred, complementary feeds after breastfeeding may be necessary for a day or two until maternal breastmilk supply is established.

Infants admitted to NICU/ SCN for management of hypoglycaemia should remain under neonatal/ paediatric care in the postnatal ward for at least 72 hours.

Only infants admitted to NICU/ SCN for management of hypoglycaemia who receive IV glucose for more than 3 days, and/or glucagon infusion, and/or diazoxide will be reviewed in the general neonatal outpatient clinic.

4.6 Complicated hypoglycaemia

Persistent hypoglycaemia

Persistent hypoglycaemia occurs when hypoglycaemia persists beyond 4 hours despite treatment, or where episodes of hypoglycaemia occur ≥ 3 times in 24 hours.

Persistent hypoglycaemia may reflect hyperinsulinism, inadequate availability of substrate or increased metabolic demand.

Management options include:

- **Increase glucose supply**
    - Increase frequency of enteral feeds (Q2H)
    - Increase TFI up to 90ml/kg/day (IVF only) or 120ml/kg/day (enteral as tolerated) on day 1
    - Increase concentration of delivered dextrose
        - 12.5% dextrose may be given via a peripheral venous cannula
        - 15% dextrose **MUST** be given via central venous line
    - Calculate glucose infusion rates using a glucose calculator
- **Glucagon**:
    - May be used as an intramuscular injection for the acute management of hypoglycaemia, or as a continuous infusion where hypoglycaemia is treatment resistant
    - Allows mobilisation of hepatic glycogen stores
    - Less likely to be useful in infants < 34 weeks (due to minimal glycogen stores) or infants >24 hours postnatal age with inadequate feeding (stores deplete within 24 hours).
    - Glucagon I.M. injection may be repeated once if initial response was good (TBG ≥ 2.6 mmol/L).
    - See Neonatal Medicines Information

Any baby in whom hypoglycaemia persists beyond postnatal day 3 should be investigated for other causes of hypoglycaemia (see 4.7 Investigations for aetiology of severe or prolonged hypoglycaemia).

Hyperinsulinism

Hyperinsuinism is a common, transient phenomenon in infants of diabetic mothers, but may also be seen in relation to other conditions such as Beckwith-Weidemann syndrome. Any infant requiring a glucose infusion

rate of >10mg/kg/min should be investigated for hyperinsulinism.

Special considerations for infants with hyperinsulinism:

- Bolus enteral feeds may stimulate insulin release and cause paradoxical hypoglycaemia.
- Enteral feeds may need to be restricted to ~10% of total daily fluid allowance. Continue small enteral feeds where possible [8].
- Blood glucose concentrations should be maintained ≥ 3.3 mmol/L[9].
- Hyperinulinism prevents the normal counterregulatory responses to hypoglycaemia and impairs production of alternative cerebral fuels [9].
- **Diazoxide** is an anti-hypoglycaemic agent which blocks glucose-mediated pancreatic insulin secretion. It should only be used after consultation with an endocrinologist. Further information can be found in Neonatal Medicines Information.

4.7 Investigations for aetiology of severe or prolonged hypoglycaemia

Most cases of neonatal hypoglycaemia are transient, related to aberrant metabolic transition from fetal to neonatal life. In cases where hypoglycaemia is prolonged (beyond 48-72 hours), severe (glucose infusion rate > 10mmol/kg/min) or associated with a dysmorphic infant, further investigations should be undertaken.

Physical examination

Omphalocoele, ear notching, hemihypertrophy, macrosomia (Beckwith-Wiedemann syndrome)
Micropenis, ambiguous genitalia, midline facial deformity (hypopituitarism, septo-optic dysplasia)
Dysmorphic features, especially facial midline defects

Blood tests

A hypoglycaemia screen may be performed to investigate the hormonal response to low blood glucose concentrations. This should be performed when TBG < 2.6 mmol/L (preferably < 2mmol/L) and is most useful if done more than 48 hours after birth[9]. If there are concerns that hypoglycaemia may be the result of an inborn error of metabolism, ammonia, lactate and acyl-carnitine samples should be sent **urgently** regardless of TBG value. Discuss with neonatal consultant.

Tier 1 investigations - venous or arterial samples – to exclude hyperinsulinism and panhypopituitarism

- Paired insulin and glucose concentrations
- Cortisol
- Growth hormone
- Sodium, potassium (blood gas analyser)

If insulin secretion is not supressed and the diagnosis of hyperinsulinism is established, continue to treat, in severe cases with input from the paediatric endocrinologists at RCH. Genetic testing for hyperinsulinsim (ABCC8, KCNJ11 and other gene mutations) may be considered in severe and persistent cases with a suggestive family history and/or ethnic background.

If the insulin concentration is supressed, the diagnosis of hyperinsulinism is not established and tier 2 testing should be performed.

Any abnormal growth hormone or cortisol levels require tier 2 testing.

Tier 2 investigations - to exclude panhypopituitarism and congenital adrenal hyperplasia:

- 17-hydroxyprogesterone (17-OHP)
- Thyroid function (TSH and FT4)

- Urine osmolality and specific gravity
- Cranial ultrasound
- Eye examination by ophthalmologist
- Growth hormone and cortisol (if not already done with tier 1 testing)

Tier 3 investigations – to exclude inborn errors of metabolism
If hypoglycaemia persists despite normal 1st and 2nd line investigations, or where there are clinical features consistent with metabolic disease (encephalopathy, cardiomyopathy), the following tests should be performed without delay and advice sought from the RCH metabolic team:

- Ammonia level (free flowing sample)
- Lactate and pyruvate (arterial sample)
- Free fatty acids and acyl carnitine profile
- Triglyceride level
- Urine organic acids
- Urine metabolic screen, including reducing substances and ketones
- Plasma amino acids

Accelerated completion of the newborn screening test - call the VCGS screening laboratory and ask for the infant to be flagged as having a possible metabolic disorder. The metabolic screen will then be expedited.

5. Evaluation, monitoring and reporting of compliance to this guideline

Compliance to this guideline will be monitored via clinical incidents reported through VHIMS.

6. References

1. Harris DL, Weston PJ, Signal M, Chase G, Harding JE. Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial. Lancet 2013;382(9910):2077-83.
2. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycaemia in infants identified as at risk. J Pediatr 2012;161(5):7787-791.
3. Kaiser JR, Bai S, Gibson N, et al. Association between transient neonatal hypoglycaemia and fourth-grade achievement test proficiency: a population-based study. JAMA Pediatrics 2015;169(10):913-921
4. McKinlay CJD, Alsweiler JM, Anstice NS, et al. Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 years. JAMA Pediatrics 2107;171(10):972-983.
5. Kaiser JR, Bai S, Rozance PJ. Newborn plasma glucose concentration nadirs by gestational-age group. Neonatology 2018;113:353-359.
6. McKinlay CJD, Alsweiler JM, Anstice NS, et al. Neonatal glycaemia and neurodevelopmental outcomes at 2 years. New England Journal of Medicine 2015;373(16):1507-1518
7. Glasgow MJ, Harding JE, Edlin R for the CHYLD study team. Cost analysis of cot-side screening methods for neonatal hypoglycaemia. Neonatology 2018;114:155-162
8. Tottman AC, Bloomfield FH, Cormack BE, et al. Relationships between early nutrition and blood glucose concentrations in very preterm infants. Journal of Pediatric Gastroenterology and Nutrition. 2018;66(6):1
9. Thornton PS, Stanley CA, De Leon DD, et al. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycaemia in neonates, infants and children. J Pediatr.2015;167(2):238-245.

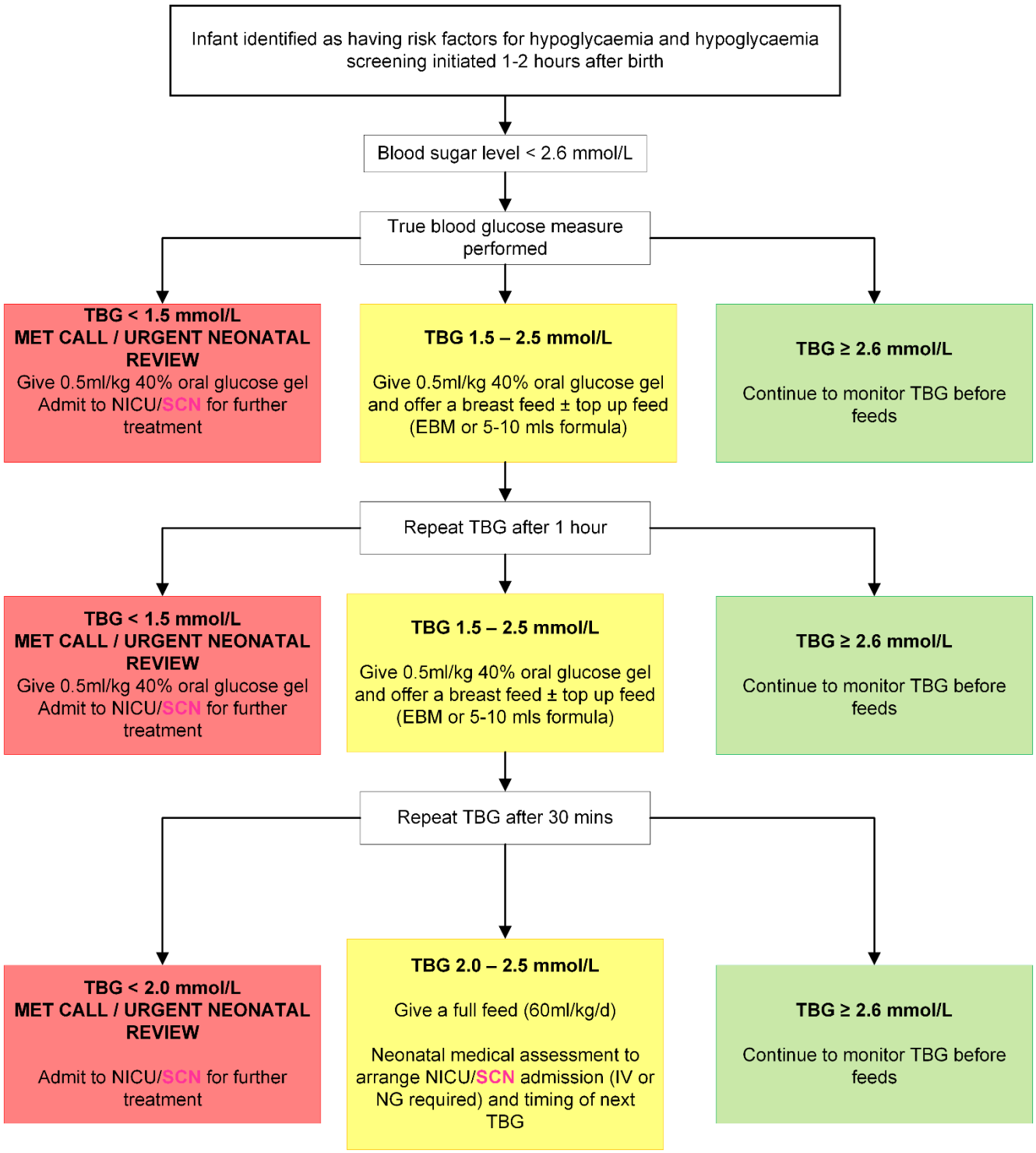
7. Legislation/Regulations related to this guideline

Not applicable.

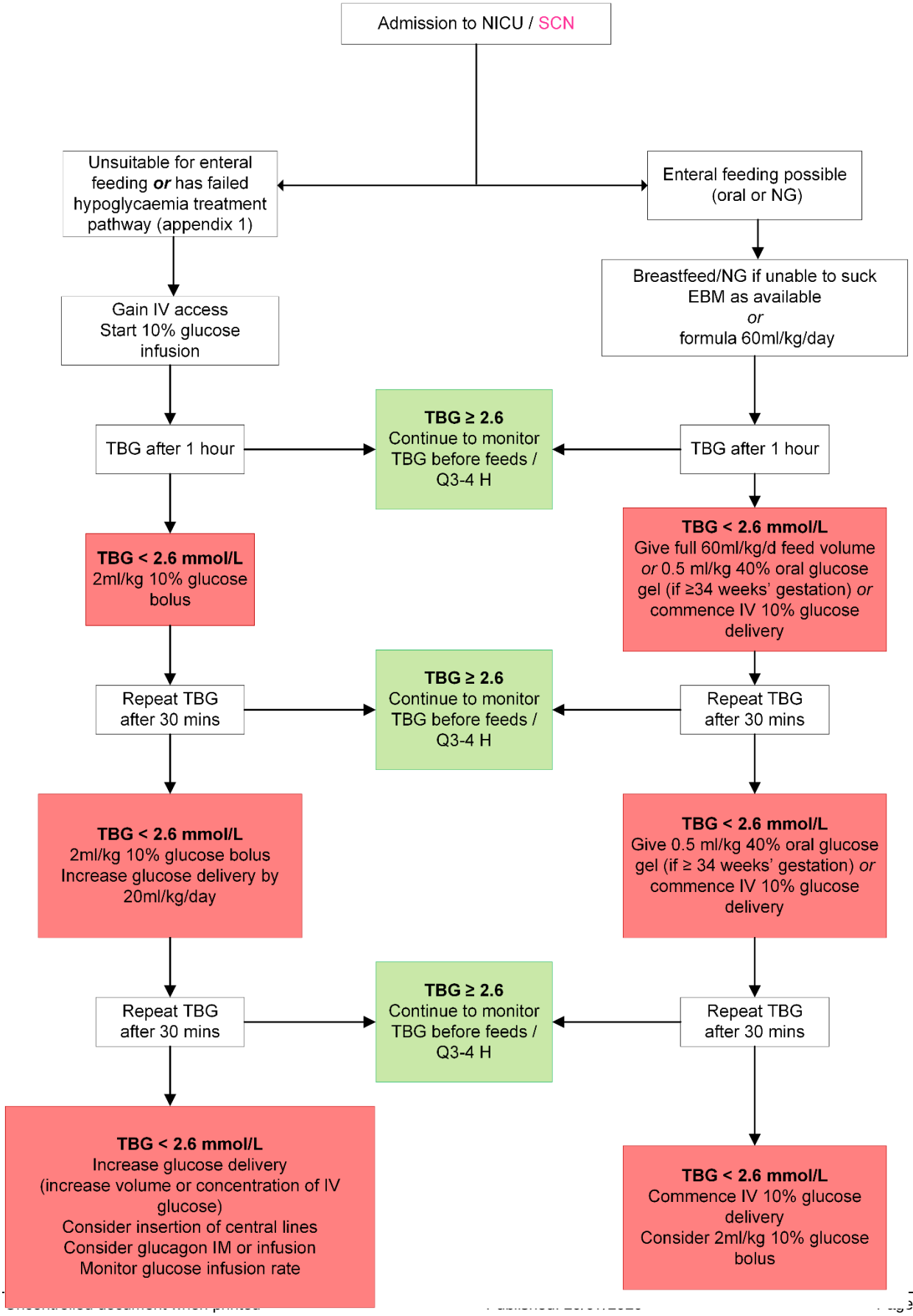
8. Appendices

Appendix 1: Management of hypoglycaemia in birth centre/ postnatal wards.
Appendix 2: Management of infants in NICU/ SCN with hypoglycaemia or risk factors for hypoglycaemia
Appendix 3: Investigation pathway for causes of prolonged or severe hypoglycaemia

Appendix 1. Management of infants with hypoglycaemia in birth centre and postnatal wards



Appendix 2. Management of infants in NICU/ SCN with hypoglycaemia or risk factors for hypoglycaemia



Appendix 3. Investigation pathway for causes of prolonged or severe hypoglycaemia