Identification and Management of Neonatal Hypoglycaemia in the Full Term Infant

Framework for Practice

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Organisations and representatives involved in the consultation process

British Association of Perinatal Medicine membership
Bliss
Royal College of Nursing
Royal College of Midwives
Neonatal Nurses Association
NHS Improvement
Unicef Baby Friendly Initiative
National Infant Feeding Network
Neonatal Nurses Association
NHS England Highly Specialised Services Team: Congenital Hyperinsulinism (CHI) service

Executive Summary of Recommendations

1. Term infants at risk of impaired metabolic adaptation and hypoglycaemia include infants of diabetic mothers, infants whose mothers have taken beta-blockers, and infants with intrauterine growth restriction (IUGR). IUGR should be defined using gestational age and sex specific 2nd centile values, and / or clinical wasting.

2. Infants at risk of impaired metabolic adaptation and hypoglycaemia should be identified at birth and placed on a care pathway that includes early provision of energy, regular assessment of feeding and clinical condition, and blood glucose (BG) monitoring.

3. Breast milk is the ideal source of energy during postnatal metabolic adaptation; women should be supported to establish effective breastfeeding.

4. Parents are partners in the care of infants at risk of impaired metabolic adaptation and hypoglycaemia. Parents should be given verbal and written information that describes why their baby is receiving extra support and blood glucose monitoring; how to reduce the likelihood of hypoglycaemia; the signs that indicate when a baby is becoming unwell; and how to raise concerns about their baby's well-being or feeding pattern. A parent information sheet is provided (Appendix 1).

5. Ward based blood gas analysers provide accurate and rapid measurement of neonatal blood glucose concentration, which supports real-time clinical decision making. Most handheld glucometers are not sufficiently accurate in the range of 0-2.0mmol/l so should not be used to guide the management of neonatal hypoglycaemia.

6. An operational threshold approach should be used to guide interventions intended to raise blood glucose:

    - A value <1.0mmol/l at any time
    - A single value <2.5mmol/l in a neonate with abnormal clinical signs
    - A value <2.0mmol/l and remaining <2.0mmol/l at next measurement in a baby with a risk factor for impaired metabolic adaptation and hypoglycaemia but without abnormal clinical signs.

7. Buccal dextrose gel may be used in conjunction with a feeding plan when the blood glucose is 1.0-1.9mmol/l.

8. Severe (BG <1.0mmol/l) or persistent hypoglycaemia (3 or more measurements < 2.0mmol/l in the first 48 hours after birth) requires urgent medical review and investigation.

9. Practitioners need skills to distinguish between infants with abnormal feeding behaviours that can occur with other signs to suggest illness, and infants who are well but reluctant to feed. A plan for supporting reluctant feeders and their mothers is provided (Appendix 2, Flowchart D).

1. Introduction

1.1 Background and purpose of the framework

The NHS has prioritized the reduction of admission of full term infants (> 37 weeks' gestation) to neonatal units because admission to neonatal care can indicate that harm has taken place somewhere in the maternity or neonatal pathway, and it results in separation of mother and baby.

Hypoglycaemia is a leading cause of term admission to neonatal units: anonymised patient-level data from neonatal admissions in England between 2011-2013 showed that hypoglycaemia accounted for around 10% of term admissions, and yet the first recorded blood glucose concentration was >2.0mmol/l in 52% of cases and >2.6mmol/l in 28% of cases. One third of cases were admitted within four hours of birth[1]. These observations suggest that compliance with recommended BAPM / Baby Friendly Initiative guidance for management of the metabolic transition to postnatal nutrition is variable. Indeed, a recent survey of practice in 135 Neonatal Units found wide variations in the definition of hypoglycaemia, risk factors for impaired metabolic adaptation, and thresholds for intervention[2].

In rare circumstances neonatal hypoglycaemia is sufficiently severe to cause brain injury and long-term neurodevelopmental impairment, with considerable costs to individuals, families and the NHS[3]. Therefore, it is incumbent upon clinicians to implement practices that prevent harm that can result from unrecognised or untreated hypoglycaemia, whilst minimising unnecessary interventions and admissions to neonatal units.

In 2016 NHS Improvement and British Association of Perinatal Medicine (BAPM) convened a working group to develop a Framework for Practice (FfP) to: address variation in practices in the identification, management and admission thresholds of babies admitted to neonatal units for hypoglycaemia; and to promote safer practices that avoid unnecessary separation of mother and baby.

1.2. Target users

All healthcare professionals involved in the care of infants born at term during the first 48 hours after birth. The framework should be delivered in partnership with parents.

2. Process

The Framework for Practice includes recommendations based on:

- literature review including existing guidelines
- data analysis of litigation themes
- data analysis of admissions for hypoglycaemia
- national audit of practice including admission and thresholds for intervention
- clinical experience

Members of the group met to identify key areas of practice concerning the identification and management of term neonates with hypoglycaemia. Members were then tasked with undertaking a literature search around specified topic areas. This included searches of Medline and PubMed 1976-2016. Further telephone conferences were held to discuss each area and agree practice points based either on published evidence or, when evidence was

lacking, professional consensus. The group met by telephone conference to respond to comments raised during consultation and to agree the final version of the Framework.

3. Framework for Practice

SECTION A: Practice points

A synopsis of supporting evidence is given for each practice point in section B.

Identification of infants at risk of impaired metabolic adaptation and recognition of clinical signs

1. The following groups are at risk of neurological sequelae of neonatal hypoglycaemia, and measures should be in place to identify them at birth for early milk / energy provision and monitoring of blood glucose concentration*:

    - Intrauterine growth restriction (birth weight 2nd centile, Table 1), or clinically wasted
    - Infants of diabetic mothers
    - Infants of mothers taking beta-blockers in the third trimester and / or at time of delivery

Birth weight on 2nd centile / kg		
Gestational age / weeks	Boys	Girls
37	2.10	2.00
38	2.30	2.20
39	2.50	2.45
40	2.65	2.60
41	2.80	2.75
42	2.90	2.85

Table 1. Second centile birth weights for boys and girls by week of gestation (from BAPM Newborn Early Warning Trigger and Track Framework for Practice[4])

*Moderate to late preterm infants are at risk of hypoglycaemia. Energy provision and blood glucose monitoring should be planned as part of the care pathway for this group of infants. Care of the moderate to late preterm infant in the postnatal ward setting is beyond the scope of this FfP.

2. Measurement of blood glucose concentration should be performed for any infant who has one or more of the following diagnoses or clinical signs:

    - Perinatal acidosis (cord arterial or infant pH <7.1 and base deficit ≥ -12mmol/l)
    - Hypothermia (<36.5°C) not attributed to environmental factors
    - Suspected / confirmed early onset sepsis
    - Cyanosis
    - Apnoea
    - Altered level of consciousness
    - Seizures
    - Hypotonia
    - Lethargy
    - High pitched cry

Abnormal feeding behaviour (not waking for feeds, not sucking effectively, appearing unsettled and demanding very frequent feeds), especially *after a period of feeding well* may

be indicative of hypoglycaemia. It should prompt a full clinical assessment and consideration of blood glucose measurement.

Jitteriness, defined as excessive repetitive movements of one or more limbs, which are unprovoked and not in response to a stimulus, is common and is not by itself an indication to measure blood glucose.

Devices for accurate measurement of blood glucose in the newborn

3. Accurate measurement of blood glucose level is essential for diagnosis and management of neonatal hypoglycaemia. The ward-based blood gas biosensor should be considered the reference standard for measuring blood glucose based on accuracy and speed of result availability. Blood gas analysers will produce glucose results as a calculated 'plasma glucose equivalent' concentration that should agree with laboratory plasma glucose results in the majority of cases.

4. Most handheld glucometers also report results as 'plasma glucose equivalents', although some devices are available that measure true whole blood glucose by rupturing the blood cells and measuring combined plasma and cellular glucose. This true whole blood glucose may be 10-15% lower than the corresponding plasma glucose. However, all current cot side technologies are prone to some inaccuracy, particularly in the range 0-2.0mmol/l. If handheld glucometers are being used to screen for low blood glucose, only those devices conforming to the ISO15197:2013 standard should be used and their limitations should be understood: possible error of +/-0.8mmol/l for values < 5.5mmol/l. If a handheld glucometer is used, low values should be confirmed using an accurate method so that assignment to the correct clinical pathway can be made. All operators of glucometers must be made aware of their specific limitations during training.

5. Be aware that the neonatal packed cell volume (PCV) is a potential source of error in hand-held glucometers that do not auto-correct for this variable. Samples with high PCV can produce erroneously low glucose results and vice versa.

6. Samples should be taken from a warm well-perfused heel by heel-prick, or from a free flowing venous / arterial sample, using local guidelines for skin asepsis and patient comfort. Air bubbles in capillary tubes should be avoided. Abnormal lipid or protein content in samples may reduce the accuracy of all glucose results. Do not aspirate the sample from a catheter that has had a dextrose infusion running through it.

Management of infants identified to be at risk of impaired metabolic adaptation: general care, feeding support, energy provision and blood glucose monitoring

7. Provide parents with verbal and written information that explains: why their baby is receiving extra support and blood glucose monitoring; how the likelihood of hypoglycaemia can be minimized; the signs that could indicate that baby is becoming unwell; and how to raise concerns about their baby's well-being or feeding pattern to staff. An example parent information sheet is provided in **Appendix 1**. This information may be communicated during the antenatal period or during labour if the risk factors listed in **Practice Point 1** are known.

8. Immediately after birth the baby should be dried and a hat put on. He / she should be placed in skin-to-skin contact with the mother to provide warmth and to facilitate the initiation of feeding. Ensure that ambient temperature is warm, the room is free from draughts, show mother safe positioning of the baby, and commence observations using

the BAPM Newborn Early Warning Trigger and Track Framework. ***Begin care pathway in Flowchart A***.

9. Ensure that baby is offered the breast within the first 60 minutes and assess the need for helping the mother with: 1. breastfeeding support; 2. recognition of early feeding cues (rapid eye movements under the eye lids, mouth and tongue movements, body movements and sounds, sucking on a fist); and 3. signs of effective attachment.

10. Assess and document feeding cues and feeding effectiveness at each feed.

11. Offer the breast in response to feeding cues as often as possible. Do not allow more than three hours to pass between feeds, until blood glucose measurements have been above 2.0mmol/l on two consecutive occasions. Continue feeding support until mother and midwife are satisfied that effective feeding is established.

12. If the baby is not showing signs of effective feeding encourage continuous skin-to-skin contact and teach the mother to hand express. Any colostrum expressed should be fed immediately to the baby, using a method that is best suited to the infant's capabilities and parent's preferences and consistent with local policy. Continue to express at least 8-10 times per 24-hour period until baby is feeding effectively, and provide active feeding support until breastfeeding is established. If no colostrum is available and after discussion with the mother, consider supplementing with formula milk (10-15ml/kg per feed) until colostrum is available. Support to resume breast milk feeds as soon as possible.

13. For women who choose to formula feed offer 10-15ml/kg within the first hour and plan to feed 3 hourly. Feed responsively when blood glucose measurements have been above 2.0mmol/l on two consecutive occasions. If the baby does not show feeding cues, i.e. is a reluctant feeder and has no signs of illness, refer to **Practice Points 25 and 26**.

14. Measure the blood glucose level before the second feed (2-4 hours after birth). Measure blood glucose immediately if there are clinical signs suggestive of hypoglycaemia (**Practice Point 2**).

15. Based on the result of the first blood glucose (BG) measurement, place the baby on one of the following care pathways:

    Flowchart B: First pre-feed BG 1.0-1.9mmol/l, and no abnormal signs
    Flowchart C: First pre-feed BG <1.0mmol/l, and / or clinical signs consistent with hypoglycaemia at higher BG concentration

16. Do not transfer babies with risk factors for impaired metabolic adaptation and hypoglycaemia to community care until you are satisfied that the baby is maintaining blood glucose levels >2.0mmol/l on at least two consecutive occasions and is feeding well. Infants at risk of hypoglycaemia should not be transferred to the community until they are at least 24 hours old.

Consideration of special treatments

17. Infants being managed using the pathway in **Flowchart A** are fed within the first 60 minutes and must have a blood glucose level measured prior to the 2nd feed. If the first BG is 1.0-1.9mmol/l or there is a subsequent blood glucose measurement <2.0mmol/l, 40% buccal dextrose gel (200mg/kg) may be given alongside feeding support (**Flowchart B, Appendix 3**).

18. If BG <1.0mmol/l arrange for urgent medical review which will include siting an intravenous cannula for treatment with IV glucose. If there is a delay in obtaining intravenous access, consider either IM glucagon (200micrograms/kg, maximum 1mg as a single dose) or 40% buccal dextrose gel (200mg/kg).

19. If BG is <1.0mmol/l 40% buccal dextrose gel should only be used as an interim measure while arranging for treatment with IV glucose.

Investigations for hypoglycaemia

20. A newborn with persistent (more than 2 measurements <2.0mmol/l within the first 48 hours after birth) or severe hypoglycaemia (<1.0mmol/l at any time), and infants with signs of acute neurological dysfunction and blood glucose <2.5mmol/l should be referred urgently to a paediatrician for the following investigations *during* the period of hypoglycaemia:

    - Blood glucose, insulin, cortisol, growth hormone, fatty acids, ketone bodies, carnitine, acylcarnitine profile, amino acids, ammonia, lactate.
    - Urine ketones and organic acids
    - Consider evaluation for early onset sepsis

    Further investigations should be based on the results of the initial screen and taken following specialist advice.

    Infants with abnormal neurological signs should be admitted to the Neonatal Intensive Care Unit for neurocritical care investigations and monitoring.

21. Transient hypoglycaemia defined as one measurement of 1.0-1.9mmol/l within the first 48 hours after birth in an infant with no abnormal signs who is feeding effectively does not require the investigations listed in **Practice Point 20**.

Persistent low blood glucose measurement

22. Persistent hypoglycaemia (more than 2 measurements <2.0mmol/l within the first 48 hours after birth) can be the first sign of hyperinsulinism or another metabolic disorder characterized by neonatal hypoglycaemia. It is important to refer to a paediatrician and screen such infants (see **Practice Point 20** for list) to identify hyperinsulinism or another disorder that requires specific therapy.

23. Hyperinsulinism should be considered if blood glucose concentration remains low (<2.0mmol/l on three or more occasions in first 48 hours despite adequate energy provision and a feeding plan), or if a glucose dose greater than 8mg/kg/min is required.

24. In cases of suspected or confirmed hyperinsulinism, aim to maintain blood glucose concentration >3.0mmol/l.

Management of the reluctant feeder with no risk factors for impaired adaptation

25. A thorough clinical assessment should be made and documented within 6 hours after birth, at which time practitioners should differentiate between a well baby who is reluctant to feed versus a baby whose feeding pattern suggests an abnormal clinical state due to illness. Signs of reluctant feeding include not waking for feeds, not latching at the breast, not sucking effectively, and appearing unsettled. Skin-to-skin contact and

laid-back nursing will stimulate the baby to use innate abilities and help his / her mother recognize feeding cues. Feeding support should be provided to reluctant feeders using **Flowchart D** and **Appendix 2,** and medical review should be prompt if there are concerns that feeding behaviours may reflect an abnormal clinical state.

26. Blood glucose should be measured if reluctant / non-effective feeding follows a period of effective feeding or if there are any abnormal clinical signs in addition to reluctant feeding.

SECTION B: Synopsis of supporting evidence

Identification of infants at risk of impaired metabolic transition and recognition of clinical signs clinical signs: Practice Points 1 and 2.

Infants with intrauterine growth restriction (IUGR) are at risk of hypoglycaemia due to low glycogen stores, increased peripheral insulin sensitivity, impaired gluconeogenesis due to a poorly coordinated response to hypoglycaemia by counter-regulatory hormones, and increased insulin secretion[5-12].

IUGR should be defined as ≤2nd centile using the gestation and sex specific values listed in the BAPM NEWTT chart (reproduced in Table 1)[4]. Use of an arbitrary weight threshold (e.g. 2.5kg) fails to detect growth restriction in infants > 40 weeks' gestation, and this practice was identified as a contributory factor in litigation[3]. Be aware that IUGR can manifest as low subcutaneous fat stores (so called 'wasted' or 'scrawny' appearance) despite birth weight above 2nd centile. At present there is insufficient evidence to recommend the use of customised growth charts for detection of infants at risk of hypoglycaemia[13,14], and clinical assessment of IUGR at birth remains the gold standard.

Diabetes is the most common medical disorder of pregnancy in the UK, affecting 2-5% of pregnancies[15]. Infants of diabetic mothers are at increased risk of hypoglycaemia due to transient hyperinsulinism[16]; the risk is reduced but not completely ameliorated by good glycaemic control[17,18]. Therefore all infants of diabetic mothers, irrespective of the type of diabetes, should be monitored for hypoglycaemia[15].

Exposure to beta-blockers used to treat maternal disease is associated with hypoglycaemia due to transplacental transfer of drug and interruption of glycogenolysis in the offspring[9,19].

The clinical signs associated with hypoglycaemia are non-specific so blood glucose measurement should be undertaken in any infant who presents with one or more of the abnormal signs listed in **Practice Point 2**[20,21].

Blood glucose should be monitored in infants with diseases associated with: 1) low energy availability (e.g. moderate to severe perinatal hypoxia-ischaemia); 2) impaired hormone / enzyme responses (e.g. moderate to severe perinatal hypoxia-ischaemia, suspected or confirmed early onset sepsis, pituitary / adrenal insufficiency, inborn errors of metabolism); or 3) hyperinsulinism (e.g. congenital hyperinsulinaemic hypoglycaemia, Beckwith-Wiedemann syndrome, islet cell adenoma).

It is controversial whether infants who are large-for-gestational age (LGA, >90th centile) are at risk of hypoglycaemia: data from a registry and a case series have been interpreted by some to suggest that LGA is a risk factor for hypoglycaemia[22,23], but features of study design including retrospective data collection, inconsistent measurement devices, variations in timing of sampling, and limited clinical phenotyping of study groups, leave doubt about causation. The working group considers that if there is no evidence of maternal diabetes and the baby does not have dysmorphic features suggestive of Beckwith-Wiedemann syndrome, then routine screening of LGA infants for hypoglycaemia is not indicated.

Occasionally, it will be appropriate to screen infants based on history of first degree relative with a heritable disorder associated with neonatal hypoglycaemia. Where possible, this should be planned in advance of the birth so that parents and staff are prepared.

Devices for accurate measurement of blood glucose in the newborn: Practice Points 3-6

The ward-based blood gas biosensor should be considered the reference standard for measuring blood glucose based on accuracy and speed of result availability. Blood gas analysers produce glucose results as a calculated 'plasma glucose equivalent' concentration that should agree with laboratory plasma glucose results in the majority of cases[24], and they have the advantage of accessibility and speed in most maternity and newborn facilities. Blood gas machines may be configured to give a 'glucose only' reading on a small sample.

Central laboratory measurement of glucose from samples sent in fluoride oxalate tubes is inconsistent due to variable inhibition of glycolysis in the first 30-90 minutes, and variability in time taken to reach the laboratory for processing. Processing time may lead to impractical delays in obtaining results and guiding clinical management.

Hand-held glucometers. Current cot side technology for measuring blood glucose is still prone to significant limitations especially in the range of 0-2.0mmol/l[25-27]. The new International Organisation for Standardisation (ISO) standard 15197:2013 was implemented on 1st June 2016. Although the ISO standard is not intended to apply to blood glucose meters for professional use, it is the only standard available and is therefore used as a benchmark for performance by glucometer manufacturers and their products are awarded CE marks based upon compliance with the standard. The new standard specifies that 95% of the measured glucose values shall fall within either 0.83mmol/l of the average measured values of the reference measurement procedure at glucose concentrations <5.55mmol/l. Although handheld glucometers are available that meet the ISO standard the limits of their accuracy must be understood by the user.

In centres where handheld devices are used to screen for low blood glucose, health care providers must be aware of the lack of reliability of these devices and low values should be confirmed by accurate measurement to ensure infants are assigned to the appropriate care pathway.

Glucose biosensors, which might permit non-invasive and accurate continuous measurement of transdermal glucose, are currently under development with the potential for enormous impact[28].

It is essential that blood samples are collected in an optimal manner that includes skin asepsis measures for patient comfort according to local policy, and that samples are taken from a warm well-perfused heel (or venous / arterial blood). Avoid air bubbles if collecting in a capillary tube.

In summary, analysis of plasma glucose equivalent using a blood gas machine provides a rapid and accurate measurement of neonatal blood glucose to support real-time clinical decisions. Consideration should be given to providing access to this ward based technology in all clinical settings where newborn infants are looked after.

Management of infants identified to be at risk: general care, feeding support, energy provision and blood glucose monitoring: Practice Points 7-16

The principles of management are: antenatal or immediate postpartum identification of infants at risk for impaired metabolic adaptation; thermal care; early energy provision and feeding support; monitor blood glucose concentration with an accurate device that provides

results in real time; and listen and respond to parents views about infant feeding and well-being[3,21,29,30].

Be aware that maternal obesity is associated with lower breastfeeding rates, which may be mediated in part by impaired lactogenesis[31-33]. Obese women may require additional support to establish breastfeeding successfully.

Cold stress is associated with hypoglycaemia, and should be avoided by looking after mother and baby in a warm environment free from drafts with skin-to-skin contact, and placement of a hat[30].

There should be regular assessment of the baby when awake, including colour, tone, respiratory rate, heart rate, temperature, level of consciousness, and signs associated with hypoglycaemia (listed in **Practice Point 2**). This should include assessment of feeding behaviours, which may be a presenting sign of significant hypoglycaemia[3]. Thorough clinical assessment cannot be made effectively during sleep. The BAPM NEWTT chart is recommended for documenting clinical information.

If a baby has abnormal clinical signs suggestive of hypoglycaemia, blood glucose should be measured immediately and urgent review by a paediatrician or advanced neonatal nurse practitioner should be sought.

The aim should be to ensure that needs are met as far as possible by breastfeeding, or by the use of expressed colostrum / breast milk (EBM) because: exclusive breastfeeding optimises health outcomes for mother and infant (http://www.unicef.org.uk/BabyFriendly/What-is-Baby-Friendly/benefits-of-breastfeeding/); breast milk feeds may optimise the metabolic adaptation by improving availability of alternative cerebral fuels[34,35]; and type of milk feed has modifying effects on the pioneering microbiota[36,37], which may have implications for life long immune and metabolic health[38-40]. If the baby is unable to breastfeed effectively, the mother should be encouraged to express her milk in order to feed colostrum to her baby and to maximise future lactation. For mothers who intend to formula feed, the aim should be to ensure frequent, effective feeding. Because exclusive formula feed has been associated with lower availability of alternative cerebral fuels, we recommend that 80-100ml/kg/day is offered.

The optimal time to measure BG concentration is just prior to the second feed[9,21]. In practice, for the infant who is well, this will be within 4 hours of delivery. If the infant is not showing any feeding cues within 4 hours, then this should be considered a sign of possible hypoglycaemia and should prompt BG measurement.

There is no evidence to support routine supplementation of feeds with energy supplements.

There is increasing interest in antenatal breast milk harvesting in some centres[41], but at present there is insufficient evidence to support or refute antenatal expression of milk in preparation for the birth of an infant at risk of hypoglycaemia[42]. The results of the Diabetes and Antenatal Milk Expression (DAME) trial (Safety and efficacy of antenatal milk expressing for women with diabetes in pregnancy) are awaited[43].

Infants of diabetic mothers should not be transferred to the community before 24 hours[15] and other infants with risk factors should not be transferred until two consecutive blood glucose measurements are >2.0mmol/l and mother and staff are satisfied that effective feeding has been established and maintained over several fast-feed cycles.

Thresholds for intervention

The level of blood glucose (BG) concentration that leads to cerebral injury in newborns and adverse neurodevelopmental outcome is unknown[44]. Although attempts have been made to identify a single 'safe' BG value[45-47], studies have been confounded by inclusion of infants with independent risk factors for adverse neurodevelopmental outcome such as perinatal asphyxia, have not taken account of different risk profiles for impaired metabolic transition, have seldom documented duration of hypoglycaemia, have been uncontrolled, and follow-up has not been sufficiently long and complete. There is some consensus based on the literature that BG levels below 1.0mmol/l that are persistent beyond 1–2 hours (or are recurrent) *and* are associated with acute neurological dysfunction present the greatest risk for cerebral injury, and that brief episodes of hypoglycaemia in the absence of acute neurological dysfunction or an associated disorder are less likely to lead to cerebral injury and poor outcome[48].

A detailed description of the metabolic transition from fetal to neonatal life is beyond the scope of this FfP and is reviewed elsewhere[10,49]. In summary, the fetal brain is exposed to glucose concentrations that are around 0.5mmol/l lower than those of maternal plasma[50], so the lower limit of fetal glucose concentration is around 3.0mmol/l[51]. Following separation from the placental circulation there is a physiological decline in blood glucose concentration to a nadir at 1-2 hours, and in healthy neonates levels begin to increase 2 to 3 hours after birth, largely driven by endogenous glucose production rather than by feeding. Levels that are typical of infants, children and adults (3.5-5.5mmol/l) are not reached until 3 to 4 days after birth[52-54]. It is not unusual for healthy, breast fed newborn infants to have blood glucose values of less than 2mmol/l in the first 24 hours after birth[34,55,56] without apparent adverse consequence, and in a well-phenotyped group of infants (35–42 weeks gestational age) with risk factors for hypoglycaemia, concentrations <2.6mmol/l and <2.0mmol/l occurred in 51% and 19% respectively, but very few had abnormal clinical signs[57].

Given the uncertainties of defining a 'safe' lower limit of BG and the need to take account of differences in availability and mobilisation of alternative cerebral fuels between patient groups, an 'operational threshold' approach to the management of neonates with hypoglycaemia was developed by expert consensus in 2000[29]. This defines 'the concentration of plasma or whole BG at which clinicians should intervene based on evidence currently available in the literature.' In this model infants at risk of impaired metabolic adaptation and neurological sequelae from hypoglycaemia are identified, and interventions to raise the BG are recommended at specified thresholds. There are two caveats: first, acute neurological dysfunction in association with low BG at any level should prompt urgent investigation and treatment; and second, there are special circumstances such as hyperinsulinism and perinatal asphyxia when the threshold should be raised.

The operational threshold model has been adopted widely, but controversy remains about threshold values for diagnosis and intervention. For example, the 2011 American Academy of Pediatrics guidance recommends screening high risk infants (defined as late preterm [34-36^{+6}], SGA, IDM and LGA) 30 minutes after the first feed, and intervening with feed or IV glucose for values 25-40mg/dl (1.4-2.2mmol/l). The threshold range for intervention increases to 35-45mg/dl (1.9-2.5mmol/l) between 4 and 24 hours after birth. Once hypoglycaemia has been diagnosed the guideline recommends targeting glucose concentrations > 45mg/dl (2.5mmol/l)[58]. The 2015 Pediatric Endocrine Society guideline recommends that in the first 48 hours after birth the target blood glucose concentration should be 50mg/dl (2.8mmol/l), stating that "neurogenic and neuroglycopenic symptoms usually occur when the plasma glucose concentration decreases to 50-70mg/dl (2.8-3.9 mmol/l)"[59]. We did not find evidence to support this statement for healthy neonates born at term.

The variation in recommended thresholds in published guidance is reflected in practice in English Neonatal Units, which define hypoglycaemia between 2.0 and 4.0mmol/l[2].

The Children with Hypoglycaemia and Their Later Development (CHYLD) study group reported 2 year outcomes of infants born at 35 weeks or more with risk factors for hypoglycaemia defined as maternal diabetes, birth at <37 weeks, and birth weight that was low (<10th percentile or <2500 g) or high (>90th percentile or >4500 g). Hypoglycaemia was defined as <2.6mmol/l, and according to this definition over half of participants experienced hypoglycaemia. A treatment strategy was in place to maintain blood glucose >2.6mmol/l. The study reports the following important observations about at-risk infants who receive treatment aimed at targeting blood glucose of at least 2.6mmol/l. The first is that hypoglycaemia was not associated with an increased risk of neurosensory impairment (RR 0.95, 95% CI 0.75-1.20, p=0.67) or processing difficulty, defined as an executive-function score or motion coherence threshold that was more than 1.5 SD from the mean (RR 0.92, 95% CI 0.56-1.51, p=0.74). The second is that the mean difference in blood glucose concentration between those who did and those who did not have a poor outcome was only 0.16mmol/l. These observations raise the possibility that adverse outcomes that were prevalent in this study group may be a function of the underlying risk profile rather than blood glucose concentration *per se*.

In summary, no study has shown that treatment of asymptomatic hypoglycaemia in 'at risk' groups improves neurodevelopmental outcome, and no randomised trial comparing different treatment thresholds with sufficiently long and complete follow-up has been carried out. In the absence of these forms of evidence the group considered that there is no new argument to support a change in the operational threshold approach proposed by Cornblath et al in 2000[29], reviewed on several occasions since[44,47,48]:

1. A value <1.0mmol/l at anytime
2. Baby with abnormal clinical signs: single value <2.5mmol/l
3. Baby at risk of impaired metabolic adaptation but without abnormal clinical signs: <2.0mmol/l and remaining <2.0mmol/l at next measurement

The recommended operational threshold should be 3.0mmol/l in neonates with suspected hyperinsulinism in the first 48 hours after birth[60] . Although beyond the scope of this Framework, the operational threshold should be increased to at least 2.5mmol/l in infants with moderate-severe hypoxic-ischaemic encephalopathy (for review see[61]), and it is possible that higher BG concentration may confer benefit in this patient group[62].

Consideration of special treatments: Practice Points 17-19

Treatment with buccal dextrose gel is a simple and safe treatment for initial care of infants with low blood glucose[63]. Buccal dextrose gel can be used as first-line treatment to manage hypoglycaemia in late preterm and term babies in the first 48 hours after birth, enabling babies to remain with their mothers, avoid NICU admission and increase likelihood of breastfeeding after discharge. It is important to use dextrose gel in conjunction with an infant feeding plan to enable establishment of oral feeds. Buccal dextrose can be a useful adjunct to Baby Friendly approaches for managing low blood glucose soon after birth glucose[64].

The use of dextrose gel in neonates is not new, it was recommended over 20 years ago[65], but a previous randomised trial that was designed to assess intermittent blood glucose concentrations did not show differences between gel and placebo[66]. More recently the 'Sugar Babies' trial assessed whether treatment with dextrose gel was more effective than feeding alone for reversal of neonatal hypoglycaemia in at-risk babies[67]. This study showed

that infants randomised to dextrose gel (40% dextrose gel) had significantly less treatment failure, defined as glucose <2.6mmol/l after 2 treatment attempts with dextrose gel versus placebo (relative risk 0.57, 95% CI 0.33 – 0.98). Treatment with dextrose gel also lowered rates of neonatal intensive care unit (NICU) admission for hypoglycaemia compared with placebo (16 [14%] *vs* 30 [25%]), with a number needed to treat of 8. In addition, fewer infants were formula feeding at 2 weeks of age in the dextrose gel group compared with placebo group (5 [4%] *vs* 15 [13%]). Despite treatment with dextrose gel 12% of infants treated had at least 1 rebound episode of hypoglycaemia (within 6 hours), and 24% had at least 1 recurrent episode of hypoglycaemia (within 48 hours of birth). So although the gel decreased the need, it did not completely eliminate the use of intravenous dextrose.

Finally, a 2-year follow-up study of the "Sugar Babies" trial reported that rates of neurosensory impairment, processing difficulties, and multiple secondary growth and developmental outcomes were equivalent between the dextrose gel and placebo groups[68].

Although rebound hypoglycaemia and recurrent hypoglycaemia were similar between groups in the original study and there was reassuring continuous glucose monitoring sensor data, a theoretical concern remained that the dextrose gel treatment might have delayed definitive treatment with intravenous dextrose and adversely impacted long-term neurodevelopmental outcomes. The 2-year follow-up data is reassuring that the early benefits seen with dextrose gel do not come at a cost of worse neurodevelopmental outcomes at 2 years of age. However, dextrose gel treatment was targeted to infants at-risk for hypoglycaemia who were otherwise asymptomatic, therefore the results do not apply to infants with symptomatic, severe, prolonged, or recurrent hypoglycaemia (i.e. the infant with severe hyperinsulinism.), and should not be used in these circumstances except as an emergency measure if there is a delay in gaining IV access and IM glucagon is unavailable.

In a dose finding study dextrose gel given at 1 hour after birth to neonates with risk factors for hypoglycaemia reduced the number of infants with BG less than 2.6mmol/l during the following 48 hours with a NNT of 10, but 95% confidence intervals were wide (5 - 115) and the study was not designed to evaluate the effect of prophylaxis on clinical outcomes[69]. Results from the randomised trial of neonatal hypoglycaemia prevention with oral dextrose gel (hPOD) study are awaited[70]. The FfP group does not recommend use of prophylactic dextrose gel until more information about its effect on important clinical outcomes is available.

Investigations for hypoglycaemia: Practice Points 20-21

Transient hypoglycaemia (BG 1.0-1.9mmol/l observed on one or two occasions over the first 48 hours after birth) in the absence of abnormal clinical signs does not require additional investigations[20].

A newborn with persistent (BG 1.0-1.9mmol/l on >2 occasions) or severe hypoglycaemia (<1.0mmol/l on one occasion) should have investigations listed in **Practice Point 20** to look for the cause *during the period of hypoglycaemia*[21,71]. The results of these investigations and the possible need for additional tests should be discussed with a specialist in paediatric metabolic medicine and / or paediatric endocrinology.

Infants with abnormal neurological signs and hypoglycaemia should have neurocritical care monitoring in NNU[72], and brain MRI with long-term follow-up is recommended because of the risk of brain tissue injury and neurodevelopmental impairment in this group[73].

Persistent or recurrent low blood glucose measurement: Practice Points 22-24

Persistent or recurrent hypoglycaemia (>2 measurements 1.0-1.9mmol/l during the first 48 hours after birth) can be the first presentation of an underlying disorder of glucose metabolism[71,74]. Early detection of this group of infants is important because specific interventions designed to reduce the risk of brain injury may be required[60].

Detailed clinical assessment and screening investigations should be performed urgently.

Hyperinsulinaemic hypoglycaemia (HH) is one of the most frequent causes of persistent or recurrent low BG. It is a heterogeneous condition caused by dysregulation of insulin secretion from pancreatic beta cells. If HH is suspected, diagnosis should be made promptly by confirming high plasma insulin levels and BG levels should be maintained >3.0mmol/l during the first 48 hours; increasing to an operational threshold of 3.5mmol/l from day 3[60]. Treatment should be initiated before results from other components of the screening tests (**Practice Point 20**) have been processed.

Although most infants with HH have no other abnormal clinical signs, the condition is associated with several recognisable syndromes so careful clinical assessment can be informative for guiding subsequent tests[75-79]:

- Beckwith Wiedemann syndrome
- Turners syndrome
- Costello syndrome
- Prader-Willi syndrome
- Sotos syndrome

Non-syndromic genetic disorders of congenital HH[60] and other rare disorders cause persistent hypoglycaemia and may require specific long-term treatment and management; these include metabolic disorders of glycogen storage, fatty acid oxidation and gluconeogenesis, hypopituitarism and adrenal insufficiency leading to deficiencies in growth hormone and cortisol[9]. Sometimes there may be diagnostic clues such as hyperpigmentation of the skin suggesting the diagnosis of familial glucocorticoid deficiency (FGD)[80], or ambiguous genitalia, but typically no other signs are present and extensive laboratory evaluation is required, guided by specialist advice.

In summary, the approach to babies with persistent or recurrent low BG is: early detection by ensuring relevant appropriate screening investigations are collected; admit to NNU to ensure that management with adequate energy provision is provided; keep BG > 3.0mmol/l until insulin levels are known; and seek early specialist advice about additional investigations and management.

Parent information: why baby is being monitored, how to tell if your baby may be unwell, and how to escalate concern (Practice Point 25, appendix 1)

To empower parents of babies at risk of hypoglycaemia to serve as informed partners in their baby's care, they should be provided with information that explains why their baby is being monitored, how to assess their baby's general condition, and how to assess feeding cues and effective feeding. Mothers should be provided with a clear method for escalating concerns to the healthcare team[81]. A recurrent theme in litigation cases concerning neonatal hypoglycaemia is failure of the healthcare team to record and take heed of maternal concerns about infant well-being[3]. The working group endorses the recommendation from the paper that "maternal concerns should not be discounted and should be followed by a

detailed and documented history and assessment of the baby's condition." See **Appendix 1** for suggested parent information sheet**.**

Management of the reluctant feeder with no risk factors for impaired transition: Practice Points 25-26

We recommend pro-active support of feeding in the immediate post-partum period for all term infants[30]. This should be followed by an assessment within 6-8 hours to identify whether initiation of feeding has been effective, or whether the infant is a reluctant feeder (does not show feeding cues). Practitioners need to be skilled in the clinical assessment of *effective* feeding and *reluctant* feeding, and be able interpret feeding behaviour in the context of a general assessment of well-being. Infants with no risk factors (**Practice Point 2**) and no abnormal clinical signs, but are reluctant to feed should be given an active feeding plan (**Appendix 2**).

Infants who are not feeding effectively, especially after a period of effective feeding, or have one or more abnormal clinical signs should have blood glucose measured.

Appendix 1. Parent Information Sheet.

PROTECTING YOUR BABY FROM LOW BLOOD GLUCOSE

What is low blood glucose?

You have been given this leaflet because your baby is at increased risk of having low blood glucose (also called low blood sugar or hypoglycemia).

Babies who are small, premature, unwell at birth, or whose mothers are diabetic or have taken certain medication (beta-blockers), may have low blood glucose in the first few hours and days after birth, and it is especially important for these babies to keep warm and feed as often as possible in order to maintain normal blood glucose levels.

If your baby is in one of these "at risk" groups, it is recommended that they have some blood tests to check their blood glucose level. Extremely low blood glucose, if not treated, can cause brain injury resulting in developmental problems. If low blood glucose is identified quickly, it can be treated to avoid harm to your baby.

Blood glucose testing

Your baby's blood glucose is tested by a heel-prick blood test. A very small amount of blood is needed and it can be done while you are holding your baby in skin-to-skin contact. The first blood test should be done before the second feed (2-4 hours after birth), and repeated until the blood glucose levels are stable.

You and your baby will need to stay in hospital for the blood tests.

You will know the result of the test straight away.

How to avoid low blood glucose

- **Skin-to-skin contact**
  Skin-to-skin contact with your baby on your chest helps keep your baby calm and warm and helps establish breastfeeding. During skin-to-skin contact your baby should wear a hat and be kept warm with a blanket or towel.

- **Keep your baby warm**
  Put a hat on your baby for the first few days while he / she is in hospital. Keep your baby in skin contact on your chest covered with a blanket and look into you babies eyes to check his / her well-being in this position, or keep warm with blankets if left in a cot.

- **Feed as soon as possible after birth**
  Ask a member of staff to support you with feeding until you are confident, and make sure you know how to tell if breastfeeding is going well, or how much formula to give your baby.

- **Feed as often as possible in the first few days**
  Whenever you notice "feeding cues" which include rapid eye movements under the eyelids, mouth and tongue movements, body movements and sounds, sucking on a fist, offer your baby a feed. Don't wait for your baby to cry – this can be a late sign of hunger.

- **Feed for as long, or as much, as your baby wants**.
  To ensure your baby gets as much milk as possible.

- **Feed as often as baby wants, but do not leave your baby more than 3 hours between feeds.**
  If your baby is not showing any feeding cues yet, hold him/her skin-to-skin and start to offer a feed about 3 hours after the start of the previous feed.

- **Express your milk (colostrum).**
  If you are breastfeeding and your baby struggles to feed, try to give some expressed breast milk. A member of staff will show you how to hand express your milk, or watch the UNICEF hand expression video (search "UNICEF hand expression"). If possible, it is good to have a small amount of expressed milk saved in case you need it later, so try to express a little extra breast milk in between feeds. Ask your midwife how to store your expressed milk.

Don't hesitate to tell staff if you are worried about your baby

If your baby appears to be unwell, this could be a sign that they have low blood glucose. As well as doing blood tests, staff will observe your baby to check he / she is well, but your observations are also important, as you are with your baby all the time so know your baby best. **It is important that you tell staff if you are worried** that there is something wrong with your baby, as parents' instincts are often correct.

The following are signs that your baby is well:

- **Is your baby feeding well?**
  In the first few days your baby should feed effectively at least every 3 hours, until blood glucose is stable, and then at least 8 times in 24 hours. Ask a member of staff how to tell if your baby is attached and feeding effectively at the breast, or how much formula he / she needs. If your baby becomes less interested in feeding than before, this may be a sign they are unwell and you should raise this with a member of staff.

- **Is your baby warm enough?**
  Your baby should feel slightly warm to touch, although hands and feet can sometimes feel a little cooler. If you use a thermometer the temperature should be between 36.5^0C and 37.5^0C inclusive.

- **Is your baby alert and responding to you?**
  When your baby is awake, he/she will look at you and pay attention to your voice and gestures. If you try to wake your baby, they should respond to you in some way.

- **Is your baby's muscle tone normal?**
  A sleeping baby is very relaxed, but should still have some muscle tone in their body, arms and legs and should respond to your touch. If your baby feels completely floppy, with no muscle tone when you lift their arms or legs, or if your baby is making strong repeated jerky movements, this is a sign they may be unwell. It can be normal to make brief, light, jerky movements. Ask a member of the team if you are not sure about your baby's movements.

- **Is your baby's colour normal?**
  Look at the colour of the lips and tongue – they should be pink.

- **Is your baby breathing easily?**

Babies' breathing can be quite irregular, sometimes pausing for a few seconds and then breathing very fast for a few seconds. If you notice your baby is breathing very fast for a continuous period (more than 60 breaths per minute), or seems to be struggling to breathe with very deep chest movements, nostrils flaring or making noises with each breath out – this is not normal.

Who to call if you are worried

- In hospital, inform any member of the clinical staff.
- At home, call your community midwife and ask for an urgent visit or advice.
- Out of hours, call NHS 111 or [local number for urgent assessment]
- If you are really worried, take your baby to your nearest Paediatric A&E or dial 999. [Insert local information]

What happens if your baby's blood glucose is low?

If the blood glucose test result is low, your baby should feed as soon as possible and provide skin-to-skin contact. If the level is very low the neonatal team may advise urgent treatment to raise the blood glucose and this could require immediate transfer to the Neonatal Unit.

Another blood glucose test will be done before the next feed or within 2-4 hours.

If you are breastfeeding and your baby does not breastfeed straight away, a member of staff will review your baby to work out why. If he / she is happy that your baby is well, s/he will support you to hand express your milk and give it by oral syringe / finger / cup / spoon.
If your baby has not breastfed, and you have been unable to express any of your milk, you will be advised to offer infant formula.

In some hospitals the team may prescribe a dose of dextrose (sugar) gel as part of the feeding plan because this can be an effective way to bring your baby's glucose level up.

If you are breastfeeding and advised to give some infant formula, this is most likely to be for one or a few feeds only. You should continue to offer breastfeeds and try to express milk as often as possible to ensure your milk supply is stimulated.

Very occasionally, if babies are too sleepy or unwell to feed, or if the blood glucose is still low after feeding, he / she may need to go to the Neonatal Unit / Special Care Baby Unit. Staff will explain any treatment that might be needed. In most cases, low blood glucose quickly improves within 24-48 hours and your baby will have no further problems.

Going home with baby

It is recommended that your baby stays in hospital for 24 hours after birth. After that, if your baby's blood glucose is stable and he / she is feeding well, you will be able to go home.

Before you go home, make sure you know how to tell if your baby is getting enough milk. A member of staff will explain the normal pattern of changes in the colour of dirty nappies and number of wet/dirty nappies. For further information, if you are breastfeeding, see 'How you and your midwife can recognise that your baby is feeding well' (Search 'UNICEF Baby Friendly assessment tool').

It is important to make sure that your baby feeds well **at least 8 times every 24 hours** and most babies feed more often than this.

There is no need to continue waking your baby to feed every 2–3 hours as long as he / she has had at least 8 feeds over 24 hours, unless this has been recommended for a particular reason. You can now start to feed your baby responsively. Your midwife will explain this.

If you are bottle feeding, make sure you are not overfeeding your baby. Offer the bottle when he / she shows feeding cues and observe for signs that he / she wants a break. Don't necessarily expect your baby to finish a bottle – let him / her take as much milk as he/she wants.

Once you are home, no special care is needed. As with all newborn babies, you should continue to look for signs that your baby is well, and seek medical advice if you are worried at all about your baby.

Appendix 2. Management of reluctant feeding in healthy infants ≥37 weeks.

See Flowchart D.

Managing breastfed healthy term infants

Healthy term babies may feed enthusiastically at birth and then sleep for many hours. In order to prevent a potential negative effect on a baby's wellbeing, establishment of feeding and the stimulation of lactation follow the flow chart overleaf from birth for all well, term babies.

Feeding Cues

Feeding cues indicate the beginning of feeding readiness when babies are more likely to latch on and suck and can occur during periods of light sleep as well as when a baby is awake. Cues include rapid eye movements under the eyelids, mouth and tongue movements, body movements and sounds, sucking on a fist. Crying can be a way of indicating that the feeding cues have been missed. If this doesn't occur, support should be provided and documented until effective feeding is established.

Assisted feeding (cup, spoon, oral syringe)

Occasionally it may be helpful to give a baby small amounts of colostrum using a cup, spoon or oral syringe.

To give a cup feed safely, hold baby in an upright position, ensuring that baby's neck and shoulders are well supported. Make sure baby is fully awake, calm and alert. Half-fill the cup and hold it so that it just touches baby's mouth. It should reach the corners of her/his mouth and rest lightly on her/his bottom lip. Allow her/him just a tiny sip, to encourage drinking – do not pour the milk into her/his mouth; tip the cup just enough so that baby can lap up. Keep the cup in this tilted position and allow her/him to start again when she/he is ready.

To give a syringe feed safely, the calm and alert baby should be held in the mother's arms slightly upright, not flat. The oral syringe is gently placed in between the gum and cheek and a little colostrum gently instilled, no more than 0.2ml at a time. Allow the baby time to taste and enjoy the milk. Stop if the baby starts sucking, allow time to swallow, then give a little more. Move onto cup feeding once you have more than 5ml to give. If there is a clinical indication to provide formula or a mother makes an informed choice to provide formula this can also be given in a cup. A nasogastric tube may be required if the baby shows no cues in response to assisted feeding methods.

Boosting confidence

You can help and support the mother and boost her confidence by teaching her to hand express. Give her a supply of oral feeding syringes and feeding cups, encourage skin contact, especially in the laid-back position and help her to recognize her baby's feeding cues. Encourage the mother to offer her breast to her baby when he/she is ready, and to feed her baby expressed breast milk until he/she is breastfeeding actively and effectively. Mother-led feeding will empower the mother as well as saving you time.

If the mother does not want to hand express

The length of labour and the type of birth may influence the mother's feelings about hand expressing and giving colostrum intensively for the first few hours. The mother may ask to give formula instead (see below).

If the mother chooses not to express colostrum

If the mother cannot or chooses not to express her colostrum it is the responsibility of the midwife to ensure this is an informed decision based on awareness of the benefits of breastfeeding and the risks of formula. This will be documented by the midwife in the

woman's notes. The milk should be given by cup in volumes appropriate to the baby's age i.e. first day 10-15ml/kg per feed. Formula should not exceed 20mls per feed once lactation is established.

Recognising effective feeding - ensuring mothers and staff are able to identify
The baby should be alert, actively sucking but settled at the breast; s/he should end breastfeeding spontaneously and remain settled for a short period until the next feed. The feed should be pain free and the baby should demonstrate adequate wet and dirty nappies appropriate to age. For further information see the Baby Friendly Breastfeeding assessment tool.

Appendix 3. Use of dextrose gel

Indications

- Blood glucose 1.0-1.9mmol/l in infant with no abnormal clinical signs
- Infants ≥ 35 weeks' gestational age and younger than 48 hours after birth

Notes

- Must be used in conjunction with a feeding plan
- For babies with severe hypoglycaemia (BG <1.0mmol/l) use oral dextrose gel only as an interim measure while arranging for urgent medical review and treatment with IV glucose

Dose

- Use 40% dextrose gel 200mg/kg, up to two doses given 30 minutes apart per episode of hypoglycaemia and a maximum of six doses of buccal dextrose gel in 48 hours.
- If a weight per weight preparation of 40% dextrose gel is used, practitioners should be aware of the weight of 1ml of the preparation and calculate the ml/kg volume required to deliver 200mg/kg of dextrose. Advice from the local pharmacist is recommended. Practitioners may decide that variations in dextrose content per 1ml dextrose gel are unlikely to be clinically significant.

Method of administration

- Draw up correct volume of 40% dextrose gel using a 2.5 or 5ml oral / enteral syringe
- Dry oral mucosa with gauze, gently squirt gel with syringe (no needle) onto the inner cheek and massage gel into the mucosa using latex-free gloves
- Offer a feed preferably breast milk, immediately after administering dextrose gel
- Repeat blood sugar measurement as requested
- Repeat oral dextrose gel if baby remains hypoglycaemic according to flow chart

Up to 6 doses can be given over a 48-hour period but any more than one dose should be discussed with the neonatal team and it is advisable for the baby to be examined before the 3rd dose is administered.

Appendix 4. Intravenous dextrose concentration.

Flow rate of 10% dextrose (ml/kg/day)	Infusion rate (mg/kg/min)
40	2.77
60	4.16
80	5.55
100	6.94
120	8.33
130	9.03
140	9.72
150	10.42

How to calculate mg/kg/min from ml/kg/day for any concentration of glucose:

Formula: Rate (ml/kg/day) / 144 x glucose% = mg/kg/min

How to make up any concentration of glucose in any volume:

Desired volume = V ml

Desired concentration of glucose = D%

Lower concentration of glucose = L%

Volume of lower concentration of glucose to add = LV ml

Higher concentration of glucose = H%

Volume of higher concentration of glucose to add = HV ml

Formula: HV = V (D-L) / (H-L)
LV = V – HV
Add HV ml and LV ml to get V ml of D%

References

1. Deshpande SU, M; Hawdon, J.M. Admissions of term newborn infants for hypoglycaemia: their characteristics and preventability. The Neonatal Society; 2016; Cambridge.
2. Dixon KC, Ferris RL, Marikar D, et al. Definition and monitoring of neonatal hypoglycaemia: a nationwide survey of NHS England Neonatal Units. *Archives of disease in childhood Fetal and neonatal edition.* 2016.
3. Hawdon JM, Beer J, Sharp D, Upton M. Neonatal hypoglycaemia: learning from claims. *Archives of disease in childhood Fetal and neonatal edition.* 2016.
4. Medicine BAoP. *Newborn Early warning Trigger and track (NEWTT) - a Framework for Practice.* 2015.
5. Hawdon JM, Weddell A, Aynsley-Green A, Ward Platt MP. Hormonal and metabolic response to hypoglycaemia in small for gestational age infants. *Archives of disease in childhood.* 1993;68(3 Spec No):269-273.
6. Pallotto EK, Kilbride HW. Perinatal outcome and later implications of intrauterine growth restriction. *Clinical obstetrics and gynecology.* 2006;49(2):257-269.
7. Limesand SW, Rozance PJ, Smith D, Hay WW, Jr. Increased insulin sensitivity and maintenance of glucose utilization rates in fetal sheep with placental insufficiency and intrauterine growth restriction. *American journal of physiology Endocrinology and metabolism.* 2007;293(6):E1716-1725.
8. Leos RA, Anderson MJ, Chen X, Pugmire J, Anderson KA, Limesand SW. Chronic exposure to elevated norepinephrine suppresses insulin secretion in fetal sheep with placental insufficiency and intrauterine growth restriction. *American journal of physiology Endocrinology and metabolism.* 2010;298(4):E770-778.
9. Hawdon JM. Disorders of blood glucose homeostasis in the neonate. In: Rennie JM, ed. *Rennie and Roberton's Textbook of Neonatology.* Vol 5th: Elsevier Churchill Linvingstone; 2012:851-868.
10. Stanley CA, Rozance PJ, Thornton PS, et al. Re-evaluating "transitional neonatal hypoglycemia": mechanism and implications for management. *J Pediatr.* 2015;166(6):1520-1525.e1521.
11. Barry JS, Rozance PJ, Brown LD, Anthony RV, Thornburg KL, Hay WW, Jr. Increased fetal myocardial sensitivity to insulin-stimulated glucose metabolism during ovine fetal growth restriction. *Experimental biology and medicine (Maywood, NJ).* 2016;241(8):839-847.
12. Rozance PJ, Hay WW, Jr. New approaches to management of neonatal hypoglycemia. *Maternal health, neonatology and perinatology.* 2016;2:3.
13. Carberry AE, Gordon A, Bond DM, Hyett J, Raynes-Greenow CH, Jeffery HE. Customised versus population-based growth charts as a screening tool for detecting small for gestational age infants in low-risk pregnant women. *The Cochrane database of systematic reviews.* 2011(12):Cd008549.
14. Stock SJ, Myers J. Defining Abnormal Fetal Growth and Perinatal Risk: Population or Customized Standards? *PLoS Med.* 2017;14(1):e1002229.
15. National Institute for Health and Clinical Excellence. *Diabetes in pregnancy: management from preconception to the postnatal period.* 25/02/2015 2015.
16. Cordero L, Treuer SH, Landon MB, Gabbe SG. Management of infants of diabetic mothers. *Archives of pediatrics & adolescent medicine.* 1998;152(3):249-254.

17. Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. *The New England journal of medicine.* 2008;358(19):1991-2002.
18. Metzger BE, Persson B, Lowe LP, et al. Hyperglycemia and adverse pregnancy outcome study: neonatal glycemia. *Pediatrics.* 2010;126(6):e1545-1552.
19. Bateman BT, Patorno E, Desai RJ, et al. Late Pregnancy beta Blocker Exposure and Risks of Neonatal Hypoglycemia and Bradycardia. *Pediatrics.* 2016;138(3).
20. Williams AF. Hypoglycaemia of the newborn: a review. *Bulletin of the World Health Organization.* 1997;75(3):261-290.
21. Deshpande S, Ward Platt M. The investigation and management of neonatal hypoglycaemia. *Seminars in fetal & neonatal medicine.* 2005;10(4):351-361.
22. Schaefer-Graf UM, Rossi R, Buhrer C, et al. Rate and risk factors of hypoglycemia in large-for-gestational-age newborn infants of nondiabetic mothers. *Am J Obstet Gynecol.* 2002;187(4):913-917.
23. Groenendaal F, Elferink-Stinkens PM, Netherlands Perinatal R. Hypoglycaemia and seizures in large-for-gestational-age (LGA) full-term neonates. *Acta paediatrica (Oslo, Norway : 1992).* 2006;95(7):874-876.
24. Inoue S, Egi M, Kotani J, Morita K. Accuracy of blood-glucose measurements using glucose meters and arterial blood gas analyzers in critically ill adult patients: systematic review. *Critical Care.* 2013;17(2):R48-R48.
25. Beardsall K. Measurement of glucose levels in the newborn. *Early HumDev.* 2010;86(5):263-267.
26. Woo HC, Tolosa L, El-Metwally D, Viscardi RM. Glucose monitoring in neonates: need for accurate and non-invasive methods. *Archives of disease in childhood Fetal and neonatal edition.* 2014;99(2):F153-157.
27. Villar J, Giuliani F, Fenton TR, Ohuma EO, Ismail LC, Kennedy SH. INTERGROWTH-21st very preterm size at birth reference charts. *Lancet.* 2016;387(10021):844-845.
28. Ge X, Lam H, Modi SJ, LaCourse WR, Rao G, Tolosa L. Comparing the performance of the optical glucose assay based on glucose binding protein with high-performance anion-exchange chromatography with pulsed electrochemical detection: efforts to design a low-cost point-of-care glucose sensor. *Journal of diabetes science and technology.* 2007;1(6):864-872.
29. Cornblath M, Hawdon JM, Williams AF, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. *Pediatrics.* 2000;105(5):1141-1145.
30. The Baby Friendly Initiative UU. *Guidance on the development of policies and guidelines for the prevention and management of hypoglycaemia in the newborn.* 2013.
31. Nommsen-Rivers LA, Chantry CJ, Peerson JM, Cohen RJ, Dewey KG. Delayed onset of lactogenesis among first-time mothers is related to maternal obesity and factors associated with ineffective breastfeeding. *The American journal of clinical nutrition.* 2010;92(3):574-584.
32. Matias SL, Dewey KG, Quesenberry CP, Jr., Gunderson EP. Maternal prepregnancy obesity and insulin treatment during pregnancy are independently associated with delayed lactogenesis in women with recent gestational diabetes mellitus. *The American journal of clinical nutrition.* 2014;99(1):115-121.

33. Ma RC, Schmidt MI, Tam WH, McIntyre HD, Catalano PM. Clinical management of pregnancy in the obese mother: before conception, during pregnancy, and post partum. *The lancet Diabetes & endocrinology.* 2016.
34. Hawdon JM, Ward Platt MP, ynsley-Green A. Patterns of metabolic adaptation for preterm and term infants in the first neonatal week. *ArchDisChild.* 1992;67(4 Spec No):357-365.
35. de Rooy L, Hawdon J. Nutritional factors that affect the postnatal metabolic adaptation of full-term small- and large-for-gestational-age infants. *Pediatrics.* 2002;109(3):E42.
36. Jost T, Lacroix C, Braegger CP, Chassard C. New insights in gut microbiota establishment in healthy breast fed neonates. *PloS one.* 2012;7(8):e44595.
37. Biesbroek G, Tsivtsivadze E, Sanders EA, et al. Early respiratory microbiota composition determines bacterial succession patterns and respiratory health in children. *American journal of respiratory and critical care medicine.* 2014;190(11):1283-1292.
38. Sonnenburg JL, Backhed F. Diet-microbiota interactions as moderators of human metabolism. *Nature.* 2016;535(7610):56-64.
39. Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. *Nature.* 2016;535(7610):65-74.
40. Honda K, Littman DR. The microbiota in adaptive immune homeostasis and disease. *Nature.* 2016;535(7610):75-84.
41. Cox SG. Expressing and storing colostrum antenatally for use in the newborn period. *Breastfeeding review : professional publication of the Nursing Mothers' Association of Australia.* 2006;14(3):11-16.
42. East CE, Dolan WJ, Forster DA. Antenatal breast milk expression by women with diabetes for improving infant outcomes. *The Cochrane database of systematic reviews.* 2014(7):Cd010408.
43. Forster DA, Jacobs S, Amir LH, et al. Safety and efficacy of antenatal milk expressing for women with diabetes in pregnancy: protocol for a randomised controlled trial. *BMJ open.* 2014;4(10):e006571.
44. Hay WW, Jr., Raju TN, Higgins RD, Kalhan SC, Devaskar SU. Knowledge gaps and research needs for understanding and treating neonatal hypoglycemia: workshop report from Eunice Kennedy Shriver National Institute of Child Health and Human Development. *J Pediatr.* 2009;155(5):612-617.
45. Koh TH, Aynsley-Green A, Tarbit M, Eyre JA. Neural dysfunction during hypoglycaemia. *Archives of disease in childhood.* 1988;63(11):1353-1358.
46. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *Bmj.* 1988;297(6659):1304-1308.
47. Boluyt N, van KA, Offringa M. Neurodevelopment after neonatal hypoglycemia: a systematic review and design of an optimal future study. *Pediatrics.* 2006;117(6):2231-2243.
48. Rozance PJ, Hay WW. Hypoglycemia in newborn infants: Features associated with adverse outcomes. *BiolNeonate.* 2006;90(2):74-86.
49. Guemes M, Rahman SA, Hussain K. What is a normal blood glucose? *Archives of disease in childhood.* 2016;101(6):569-574.

50. Marconi AM, Paolini C, Buscaglia M, Zerbe G, Battaglia FC, Pardi G. The impact of gestational age and fetal growth on the maternal-fetal glucose concentration difference. *Obstetrics and gynecology.* 1996;87(6):937-942.
51. Kalhan SC, D'Angelo LJ, Savin SM, Adam PA. Glucose production in pregnant women at term gestation. Sources of glucose for human fetus. *The Journal of Clinical Investigation.* 1979;63(3):388-394.
52. Heck LJ, Erenberg A. Serum glucose levels in term neonates during the first 48 hours of life. *J Pediatr.* 1987;110(1):119-122.
53. Srinivasan G, Pildes RS, Cattamanchi G, Voora S, Lilien LD. Plasma glucose values in normal neonates: a new look. *J Pediatr.* 1986;109(1):114-117.
54. Hoseth E, Joergensen A, Ebbesen F, Moeller M. Blood glucose levels in a population of healthy, breast fed, term infants of appropriate size for gestational age. *Archives of disease in childhood Fetal and neonatal edition.* 2000;83(2):F117-119.
55. Swenne I, Ewald U, Gustafsson J, Sandberg E, Ostenson CG. Inter-relationship between serum concentrations of glucose, glucagon and insulin during the first two days of life in healthy newborns. *Acta paediatrica (Oslo, Norway : 1992).* 1994;83(9):915-919.
56. Diwakar KK, Sasidhar MV. Plasma glucose levels in term infants who are appropriate size for gestation and exclusively breast fed. *Archives of disease in childhood Fetal and neonatal edition.* 2002;87(1):F46-48.
57. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. *J Pediatr.* 2012;161(5):787-791.
58. Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics.* 2011;127(3):575-579.
59. Thornton PS, Stanley CA, De Leon DD, et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. *J Pediatr.* 2015;167(2):238-245.
60. Rozenkova K, Guemes M, Shah P, Hussain K. The Diagnosis and Management of Hyperinsulinaemic Hypoglycaemia. *Journal of clinical research in pediatric endocrinology.* 2015;7(2):86-97.
61. Boardman JP, Hawdon JM. Hypoglycaemia and hypoxic-ischaemic encephalopathy. *Developmental medicine and child neurology.* 2015;57 Suppl 3:29-33.
62. Basu SK, Kaiser JR, Guffey D, Minard CG, Guillet R, Gunn AJ. Hypoglycaemia and hyperglycaemia are associated with unfavourable outcome in infants with hypoxic ischaemic encephalopathy: a post hoc analysis of the CoolCap Study. *Archives of disease in childhood Fetal and neonatal edition.* 2016;101(2):F149-155.
63. Weston PJ, Harris DL, Battin M, Brown J, Hegarty JE, Harding JE. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. *The Cochrane database of systematic reviews.* 2016(5):Cd011027.
64. Stewart CE, Sage EL, Reynolds P. Supporting 'Baby Friendly': a quality improvement initiative for the management of transitional neonatal hypoglycaemia. *Archives of disease in childhood Fetal and neonatal edition.* 2016;101(4):F344-347.
65. Bourchier D, Weston P, Heron P. Hypostop for neonatal hypoglycaemia. *The New Zealand medical journal.* 1992;105(926):22.
66. Troughton KEVC, N.P. ;Tait, R.M.E. Hypostop gel in the treatment of neonatal hypoglycemia: a randomised controled trial. *Arch Dis Child.* 2000;82 (suppl 1): A30.

67. Harris DL, Weston PJ, Signal M, Chase JG, Harding JE. Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2013;382(9910):2077-2083.
68. Harris DL, Alsweiler JM, Ansell JM, et al. Outcome at 2 Years after Dextrose Gel Treatment for Neonatal Hypoglycemia: Follow-Up of a Randomized Trial. *J Pediatr.* 2016;170:54-59.e51-52.
69. Hegarty JE, Harding JE, Gamble GD, Crowther CA, Edlin R, Alsweiler JM. Prophylactic Oral Dextrose Gel for Newborn Babies at Risk of Neonatal Hypoglycaemia: A Randomised Controlled Dose-Finding Trial (the Pre-hPOD Study). *PLoS medicine.* 2016;13(10):e1002155.
70. Harding JE, Hegarty JE, Crowther CA, Edlin R, Gamble G, Alsweiler JM. Randomised trial of neonatal hypoglycaemia prevention with oral dextrose gel (hPOD): study protocol. *BMC pediatrics.* 2015;15:120.
71. Hussain K. Investigations for neonatal hypoglycaemia. *Clinical biochemistry.* 2011;44(7):465-466.
72. Boardman JP, Wusthoff CJ, Cowan FM. Hypoglycaemia and neonatal brain injury. *ArchDisChild EducPractEd.* 2012.
73. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. *Pediatrics.* 2008;122(1):65-74.
74. Menni F, de Lonlay P, Sevin C, et al. Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinemic hypoglycemia. *Pediatrics.* 2001;107(3):476-479.
75. DeBaun MR, King AA, White N. Hypoglycemia in Beckwith-Wiedemann syndrome. *Seminars in perinatology.* 2000;24(2):164-171.
76. Alexander S, Ramadan D, Alkhayyat H, et al. Costello syndrome and hyperinsulinemic hypoglycemia. *American journal of medical genetics Part A.* 2005;139(3):227-230.
77. Kapoor RR, Flanagan SE, Arya VB, Shield JP, Ellard S, Hussain K. Clinical and molecular characterisation of 300 patients with congenital hyperinsulinism. *European journal of endocrinology / European Federation of Endocrine Societies.* 2013;168(4):557-564.
78. Harrington RA, Weinstein DA, Miller JL. Hypoglycemia in Prader-Willi syndrome. *American journal of medical genetics Part A.* 2014;164a(5):1127-1129.
79. Pietzner V, Weigel JF, Wand D, Merkenschlager A, Bernhard MK. Low-level hyperinsulinism with hypoglycemic spells in an infant with mosaic Turner syndrome and mild Kabuki-like phenotype: a case report and review of the literature. *Journal of pediatric endocrinology & metabolism : JPEM.* 2014;27(1-2):165-170.
80. Francescato G, Salvatoni A, Persani L, Agosti M. A rare genetic disorder causing persistent severe neonatal hypoglycaemia the diagnostic workup. *BMJ case reports.* 2012;2012.
81. National Institute for Health and Clinical Excellence. *Postnatal care up to 8 weeks after birth.* 2006, updated 2015.

Flowchart A. Management of term infants (≥37 weeks) at risk of hypoglycaemia (Box 1)

Dry and place baby skin-to-skin care in a warm, draught free room.

Put hat on baby, and cover with a warm blanket.

Encourage and support early breast feeding within the first hour after birth.

For women who chose to formula feed give 10-15ml/kg within the first hour after birth.

Provide verbal and written information to parents that explains how to prevent hypoglycaemia, why their baby needs blood glucose monitoring, lists signs that may indicate hypoglycaemia (see Box 2), and advises parents to inform a member of the healthcare team if they are concerned about their baby's well-being (**Appendix 1**).

↓

Check pre-feed blood glucose level prior to second feed (2-4 hours after birth):
Is the blood glucose level ≥2.0mmol/l?

YES ↓

NO → **See Flowchart B**

Encourage frequent feeding and ensure no longer than 3 hours between feeds.

Assess the need for helping the mother with: ongoing help with feeding; hand expression; recognition of early feeding cues; and signs of effective attachment and feeding.

For women who chose to formula feed, give 10-15ml/kg per feed 3 hourly over the first 24 hours after birth.

Check blood glucose level prior to third feed (no longer than 8 hours after birth):
Is the blood glucose level ≥2.0mmol/l?

NO → **See Flowchart B**

YES ↓

Continue to support responsive breast feeding and ensure that mother understands how to assess effective feeding and knows how to escalate concerns.

If formula fed give 10-15ml/kg per feed 3 hourly over the first 24 hours after birth.

No further blood glucose monitoring required unless there are clinical signs of hypoglycaemia (**Box 2**).

Observe feeding for 24 hours.

Complete at least one recorded breastfeeding assessment using local / BFI tool prior to transfer home.

Box 1. Infants who require routine blood glucose monitoring

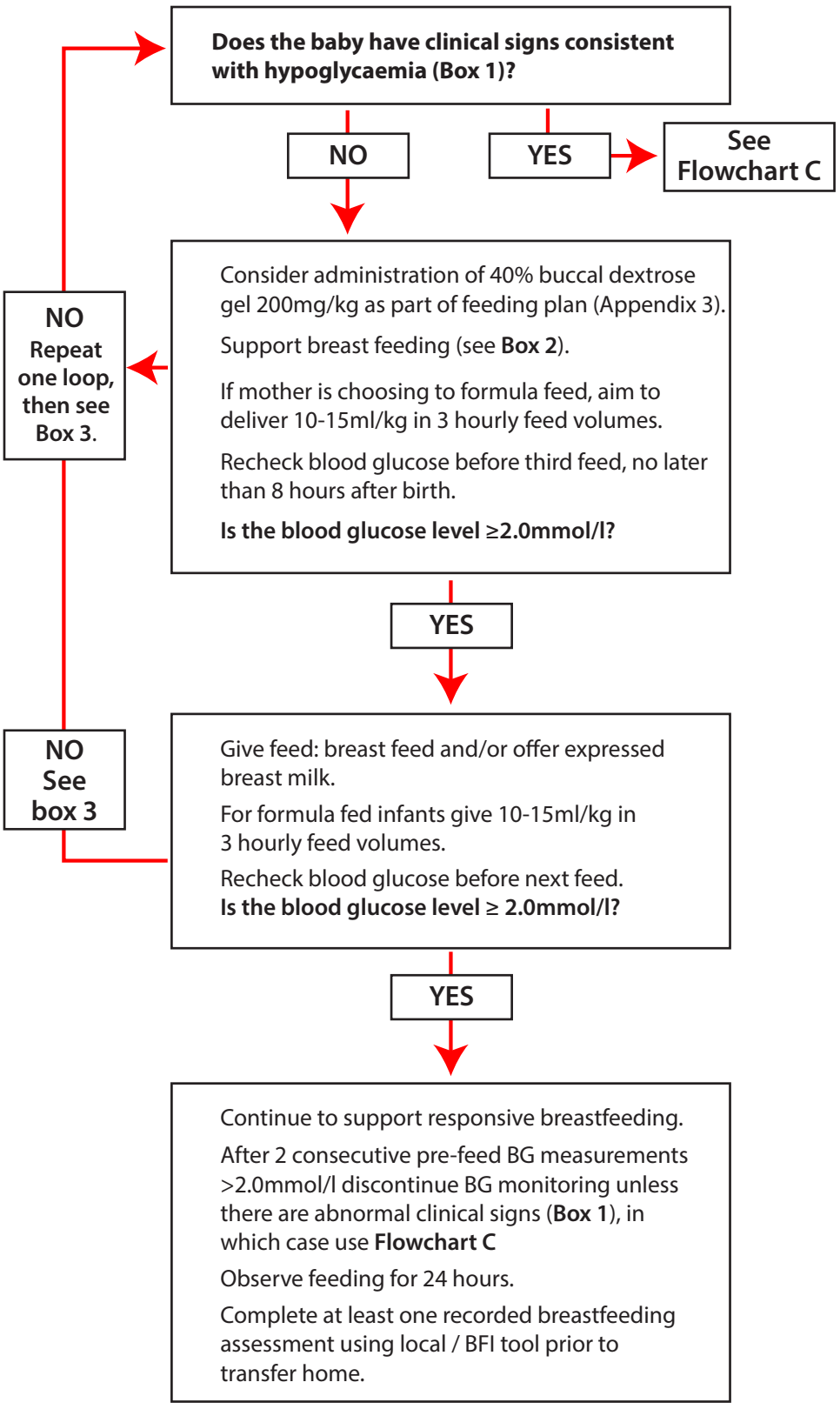
- Intrauterine growth restriction (≤2rd centile for gestation age and sex, refer to BAPM NEWTT thresholds) or clinically wasted
- Infants of diabetic mothers.
- Maternal beta blocker use.

Box 2. Signs that may indicate hypoglycaemia

- Lethargy
- Abnormal feeding behaviour especially after a period of feeding well
- High pitched cry
- Altered level of consciousness
- Hypotonia
- Seizures
- Hypothermia (<36.5°C)
- Cyanosis
- Apnoea

Identification and Management of Neonatal Hypoglycaemia in the Full Term Infant: A Framework for Practice. British Association of Perinatal Medicine, 2017.

Flowchart B. Pre-feed BG 1.0 – 1.9mmol/l and no abnormal clinical signs



Box 1. Signs that may indicate hypoglycaemia

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- High pitched cry
- Altered level of consciousness
- Hypotonia
- Seizures
- Hypothermia (<36.5°C)
- Cyanosis
- Apnoea

Box 2. Supporting breast feeding

- Encourage skin-to-skin contact.
- Offer breast feed and if not feeding effectively teach mother to hand express.
- Give colostrum obtained to baby by the method suitable to parents.
- Continue to encourage hand expression at least 8-10 times in 24 hours and support feeding on the breast until infant is feeding effectively.

Box 3. If more than 2 measurements 1.0-1.9mmol/l, inform neonatal team.

- Investigate for causes of hyopglycaemia, consider sepsis.
- Consider increased feed frequency, nasogastric tube insertion or IV infusion of 10% glucose.

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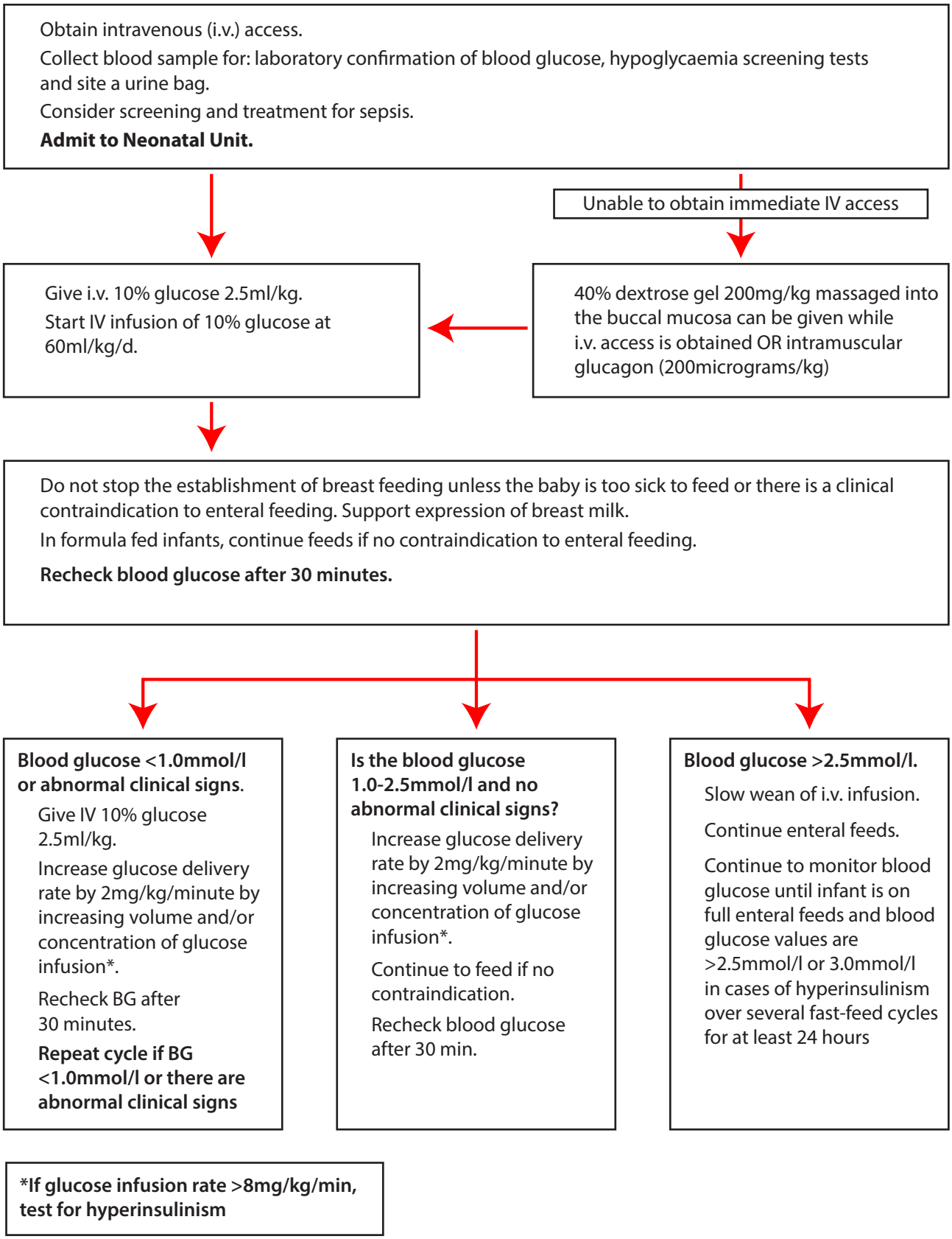
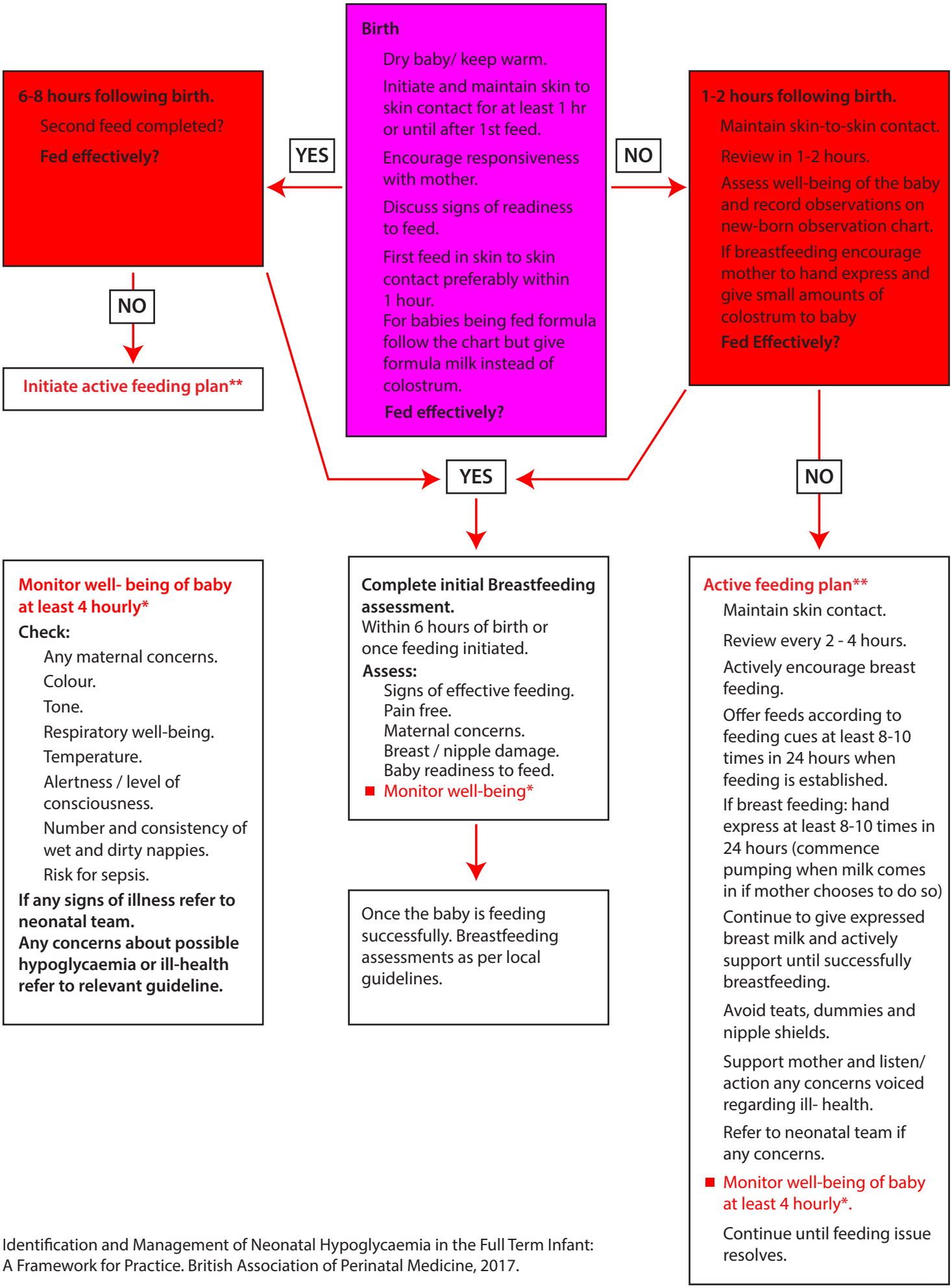
Flowchart C. Blood glucose < 1.0mmol/l and / or clinical signs consistent with hypoglycaemia



***If glucose infusion rate >8mg/kg/min, test for hyperinsulinism**

Identification and Management of Neonatal Hypoglycaemia in the Full Term Infant: A Framework for Practice. British Association of Perinatal Medicine, 2017.

Flowchart D. Management of reluctant feeding in healthy term infants ≥ 37 weeks



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