Guideline objective

The purpose of this document is to provide guidance for all healthcare professionals in the Simpson Neonatal Unit and St John's SCBU who provide care for term babies with hypoglycaemia which persists **beyond 72h**. This includes guidance on the suspicion and management of hyperinsulinism (HI).

Who are these babies?

Most babies who have ongoing hypoglycaemia have been admitted to neonatal services after hypoglycaemia was detected by the at-risk screening programme and did not resolve with postnatal ward management. Others are admitted with symptomatic hypoglycaemia requiring rapid escalation in intravenous treatment.

How to measure blood glucose?

Blood glucose (BG) should be measured using the ward-based ABL90 FLEX PLUS blood gas analyser – this is the most accurate device, particularly in the range 0 – 2.5mmol/L. At **72h**, our BG thresholds change (see Table 1), such that we now expect most healthy term babies to be able to maintain a pre-feed glucose of **≥3mmol/L**. A small number of healthy term babies may take another day or two to achieve metabolic transition and until then, may continue to have BG values in the range 2.6 – 2.9mmol/L.

These babies should be discussed with a consultant before fluid management is escalated solely to raise the BG level. Consultants may consider a BG value in the range 2.6-2.9mmol/L to be acceptable in well babies who are establishing breast-feeding and who are able to utilise other cerebral energy fuels.

Table 1: Blood glucose operational thresholds

	< 72h	**≥ 72h**	**≥ 120h**
Term baby	≥ 2mmol/L	≥ 3mmol/L	≥ 3mmol/L
Term + signs of hypoglycaemia or Term + HIE	≥ 2.5mmol/L	≥ 3mmol/L	≥ 3mmol/L
Preterm	≥ 2.5mmol/L	≥ 3mmol/L	≥ 3mmol/L
Any gestation with suspected *or* proven **hyperinsulinism***	≥ 3mmol/L	≥ 3mmol/L*	≥ 3.5mmol/L

The glucose levels associated with a risk of hypoglycaemic brain injury are not accurately known. These thresholds above are consensus-based guides to target levels for glucose considered likely to provide a margin of safety and do not represent thresholds below which injury is expected to occur.

See page 4 for more detail

How to manage hypoglycaemia and when to measure BG

Most term babies ≥72h will be managed quite simply by supporting enteral feeding (breast / bottle / NG as required) and offering top-ups with more milk volume (MEBM or formula) or reducing the feed interval (i.e., going from 3hrly to 2hrly bolus feeds) until glucose normalises. Standard BG testing in these circumstances would be for pre-feed BGs, with a maximum of 4 hours between feeds. If BG is below the operational threshold, intervene (e.g. increase milk volume) and recheck BG in 15-30mins and then again, pre-feed. **Stop measuring BG when two pre-feed values above the appropriate operational threshold have been achieved.**

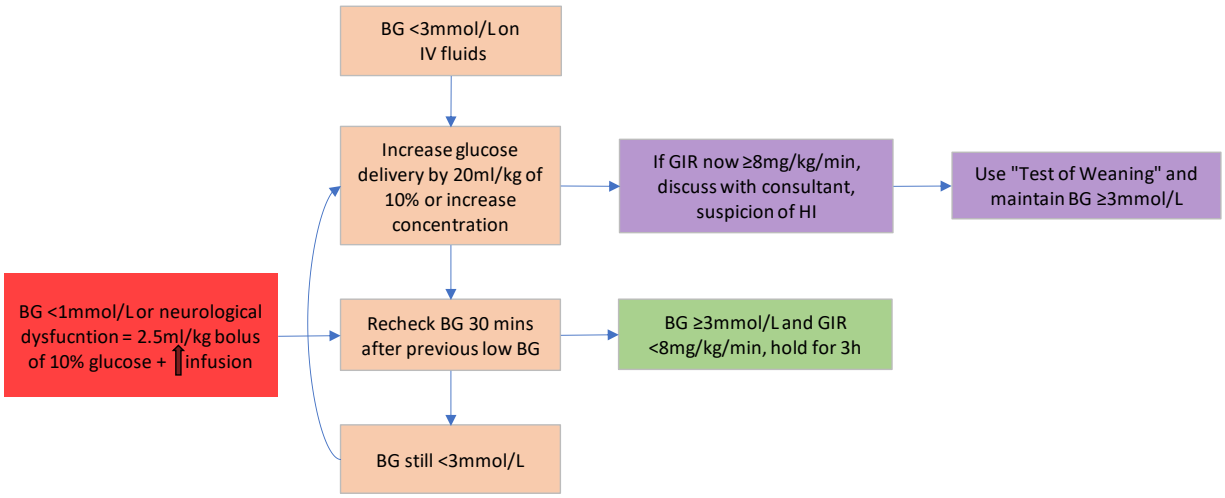
If babies continue to require large volumes of IV glucose to maintain normoglycaemia, calculate the **intravenous glucose infusion rate** (GIR).

Intravenous glucose infusion rate (GIR) in mg/kg/min =

[Total daily volume of IV glucose (ml/kg/d) x concentration of glucose (%)] / 144

If babies have hypoglycaemia while receiving IV glucose (check the cannula), increase the glucose load by increasing the 10% glucose fluid volume by 20ml/kg (watch the sodium) or glucose concentration (see figure 1). **Reserve a 2.5ml/kg bolus only for babies who have neurological dysfunction or a BG <1mmol/L**. Recheck the BG 15-30 minutes after the previous low blood glucose. 15% glucose can be delivered peripherally for a short time while central access is planned and secured.

Figure 1: Managing hypoglycaemia ≥72h with IV fluids before HI is suspected



How to wean off IV glucose – hypoglycaemia (not HI)

A standard way to reduce IV fluids is to wean off over two steps - halve the intravenous volume (recheck a BG in 1hr) and then stop (recheck a BG in 1hr). If this weaning pattern results in hypoglycaemia, try smaller volume weans at consultant discretion.

When should I perform a hypoglycaemia screen?

In the first 72h of life this should be considered for babies who have two or more BGs <2mmol/L, or any episode of severe hypoglycaemia <1mmol/L, or in those who had neurological dysfunction with BG <2.5mmol/L. This screen includes:

Must be collected during hypoglycaemia	**Can be collected later if sampling difficult**
Glucose, lactate	Acylcarnitine
Insulin, C-peptide (should be undetectable)	Amino acids
Ketone bodies (B-hydroxybutyrate), Fatty acids	Ammonia (on ice) (>150µmol/L abnormal)
Cortisol (<100µmol/L potentially abnormal)	Urine ketones and organic acids
Growth hormone (10 – 50 ug/ml is usual range)	

Consider sepsis investigations...

For term babies now ≥72h, a hypoglycaemia screen can be considered if baby is **hypoglycaemic <3mmol/L.** This screening test could be most informative if carried out beyond when metabolic transition is expected to be complete i.e., **after day 5**, if hypoglycaemia is an ongoing problem. Insulin samples are processed at the Western General Hospital biochemistry lab on a Friday. (The lab will not analyse insulin, cortisol, B-hydroxybutyrate or growth hormone if the absence of hypoglycaemia).
It can also be helpful to perform a hypoglycaemia screen if a baby becomes hypoglycaemic when they are having a controlled fast as part of HI home planning (see details in later section).

<u>Hyperinsulinism – Identifying babies at risk</u>
The current **hypoglycaemia at-risk screening proforma** carried out after birth by the midwifery team includes babies who may have a transient form of hyperinsulinism (HI). These are:

- babies born to diabetic mothers
- babies with intrauterine growth restriction (<2nd centile)
- babies with intrauterine asphyxia

If affected, these babies are likely to experience a course of variable duration, but one which will ultimately resolve and be transient. HI may or may not have resolved prior to discharge from the neonatal unit.
Babies can also have genetic or syndromic forms of HI (e.g., Beckwith Wiedemann, Turner or Kabuki syndromes) which may be identifiable through features or clinical signs.

Hyperinsulinism – Diagnosis, ruling in and ruling out

HI can be suspected when there is:

Intravenous GIR of ≥8mg/kg/min required to maintain normoglycaemia*

*See glucose threshold table on page 1

HI may also be suspected if babies are recurrently severely hypoglycaemic when IV glucose is disrupted. The GIR may not be high enough to meet the definition above. The diagnosis of HI is confirmed biochemically when inappropriately detectable levels of insulin / c-peptide occur during hypoglycaemia. It is important that the diagnosis is proven wherever possible. Note that HI may have resolved between the blood test being obtained and the result becoming available.

It is just as important to rule out HI if it is not present, since the ongoing delivery of excess glucose can lead to delayed metabolic transition, prolonged hospital admission, family separation and reduced breast-feeding rates.

Hyperinsulinism – **Test of weaning**

In view of these important potential risks to baby and family wellbeing, in babies in whom we **suspect** a transient form of HI, we recommend continuing with a threshold of 3mmol/L to test weaning from the high intravenous GIR.

To help with metabolic transition, 30ml/kg/d of enteral milk administered as 3 hourly bolus feeds should be commenced as extra to current requirements. Measure pre-feed BGs using the gas machine. For this period, the IV glucose can be reduced without a specific weaning pathway, aiming to maintain BG ≥3mmol/L.

One example could be, reduce intravenous GIR by 1mg/kg/min when 1 x BG ≥3mmol/L. Weaning can occur 3 or 6hrly.

A test of weaning failure occurs if there is any BG <3mmol/L. If this occurs, promptly perform a hypo screen, treat hypoglycaemia with buccal glucogel and give the feed which is due. Repeat a BG within 30minutes*. A test of weaning failure should invoke a consultant discussion to determine if he/she is content to hold at the current GIR, wait and recheck, or if they would wish to escalate treatment. The many clinical variables involved mean that management is likely to vary. In most cases a test of weaning failure will lead to raising the operational BG threshold to 3.5mmol/L.

*If on repeat the BG is still <3mmol/L, give a second glucogel and increase the GIR by 1mg/kg/min. Recheck within 30mins. If a third BG is still <3mmol/L, give a 2.5ml/kg bolus of 10% glucose, increase the GIR by 2mg/kg/min and recheck within 30mins.

If there is not a test of weaning failure and the intravenous GIR is <8mg/kg/min before 120h of life, then we can have some confidence that there has been a quick resolution in the transient HI. We should continue to use 3mmol/L as the ongoing glucose threshold.

If there is an ongoing need for GIR ≥8mg/kg/min beyond 120h we have agreed we should then consider involving the endocrine team for ongoing advice and routinely elevating the operational threshold to 3.5mmol/L.

Hyperinsulinism - Clinical course

This condition, which usually presents at birth (but can present later), can vary in duration.

- **'Short transient'** – babies can require a high GIR for a small number of days but wean successfully onto standard milk (MEBM/term formula) by day 7 and maintain a BG of ≥3mmol/L. These babies are managed by the neonatal team. No follow-up occurs.

- **'Long transient'** – babies continue to require a high GIR beyond day 7 as attempts to wean to standard milk lead to hypoglycaemia. HI will resolve over time. Treatment (diazoxide or high calorie formula) may be necessary to progress care towards discharge. These babies are typically managed in the neonatal unit with advice from the endocrine team and a small number will be discharged home on high calorie formula or medication, with ongoing follow-up.

- **'Permanent'** – babies have a persistent, structural, or genetic condition which causes an inappropriately increased production of insulin and are likely to need treatment with medication. These babies are managed initially in the neonatal unit with endocrinology advice but may require to be transferred to RHCYP if the clinical course is prolonged.

Hyperinsulinism - BG testing and operational thresholds

If the "Test of Weaning" results in BGs <3mmol/L this provides further suspicion that HI is actively ongoing. Maintaining BG in babies with HI is important as alternative brain energy fuels (lactate, ketones) are less accessible. It is recommended that the BG in babies with confirmed HI should therefore be maintained slightly higher than other term babies and after a "test of weaning" failure, the operational threshold should change to ≥3.5mmol/L.

We continue to use the ward-based blood gas analyser for BG measurement until at least day 5. When we have confirmed the biochemical diagnosis of HI, or baby is 7 days old, we can thereafter measure BG on a point of care testing monitor (e.g., Accu-Chek®) using a soft-touch lancet, to allow smaller size blood sampling. The BG operational threshold remains ≥3.5mmol/L. It is helpful to engage parents in performing BG measurements as this may be required at home.

Hyperinsulinism - Management

The sections below now focus on the management of babies who have suspected or confirmed HI, who have 'failed' a test of weaning and in whom our management aims to keep the glucose ≥3.5mmol/L.

General points

- Even when the GIR is high, continue/start enteral milk (start at 30ml/kg/d as **3-hourly bolus feeds**) to support metabolic transition and counter-regulatory hormone secretion, which is enhanced by gut stimulation.
- If increases in total daily fluids occur, aim to add this extra volume to the milk volume rather than IV volume.
- Consider the need for central access early.
- Prescribe glucogel (see monograph) in the PRN section of the drug kardex for all HI term babies.
- The attending consultant should make a "Consultant Plan" on Badger.

Hyperinsulinism - weaning of IV glucose and management of hypoglycaemia

Too rapid weaning of IV glucose in HI can result in hypoglycaemia and inappropriate escalation of treatment. Therefore, do not reduce the GIR more frequently than 3-hourly.

When **BG is ≥3.5mmol/L**, wean IV glucose by 1mg/kg/min and add the equivalent volume of milk to the ongoing 3-hourly feeds (hourly volume x 3). Weaning occurs as below in **table 2**.
As a general principle, consider how many hypos (if any) there have been in the preceding 24h. If there have been 3 or more, consider a pause in weaning for 24h.
All BG values count towards the weaning schedule, even those measured post-wean. Please also always refer to the blood glucose maps for babies with suspected or proven HI with a high intravenous GIR, or full milk feeds, (Appendices 1 and 2) to help guide management, as these present similar information in a stepwise, pictorial manner.

Contemplation of choice of IV glucose preparation when >10% glucose is needed for a prolonged duration (e.g., one week):

- High glucose infusion rates can result in hypokalaemia; therefore, serum potassium should be monitored as supplementation may be required.
- Parenteral nutrition can be considered for babies still receiving a substantial proportion of their daily fluid volume via IV glucose from day 7; however, the preferred approach is to concentrate the IV glucose preparation further and allow the additional fluid volume to be given as milk.

To achieve this, for example:

- Calculate the current GIR e.g., 150ml/kg/d of 15% glucose = 15.6mg/kg/min
- Plan to give approximately the same GIR using **20% glucose via a central line** and give MEBM/formula as 3hrly feeds to make up the remaining volume - this will be additional glucose, and is fine
  - 15.6mg/kg/min delivered as 20% glucose = (15.6 x 144) / 20] {NB calculation on page 2} = 112ml/kg/day of 20% glucose
  - Give the remaining volume (38ml/kg/d) as 3hourly milk feeds
- Use the glucose calculator to reduce the **intravenous** glucose requirement by 1mg/kg/min when a BG is ≥3.5mmol/L

Table 2: Weaning from a high intravenous GIR

BG Measurement	Change to IV fluids	Comments
1 x BG ≥3.5mmol/L	Reduce rate of IV glucose infusion by 1 mg/kg/min and increase 3-hrly milk feed by corresponding volume (usually most simple to wean glucose concentration first – **use the glucose calculator**). Measure BG pre-feed.	Take care if baby is receiving diazoxide treatment – if so, maintain total fluid volume (IV + enteral) at 130ml/kg/d
<3.5mmol/L AND ≥3mmol/L	This can be tolerated for <u>one feed cycle</u> as we expect the BG to rise as baby adapts. Recheck BG pre-feed in 3h. If a **second consecutive BG is between 3mmol/L and 3.5mmol/L,** then give glucogel and the feed which is due. Recheck BG in 15-30 mins. If a **third consecutive BG is between 3mmol/L and 3.5mmol/L** then give glucogel and increase the GIR by 1mg/kg/minute. Recheck BG in 15-30mins.	*First line treatment with oral glucogel. Move to IV glucose only if 2 previous glucogel have failed to increase BG
<3mmol/L AND ≥1mmol/L	Give glucogel to treat hypoglycaemia and any feed which is due. Recheck BG in 15-30 mins. If a **second consecutive BG is between 1mmol/L and 3mmol/L,** then give glucogel and increase the GIR by 1mg/kg/minute. Recheck BG in 15-30 mins. If a **third consecutive BG is between 1mmol/L and 3mmol/L** then give 2.5ml/kg IV 10% glucose bolus and increase the GIR by 2mg/kg/min. Recheck BG in 15-30mins.	*First line treatment with oral glucogel. Move to IV glucose only if 2 previous glucogel have failed to increase BG
<1mmol/L **OR** any neurological concerns	Give 2.5ml/kg IV 10% glucose bolus and increase the GIR by 2mg/kg/min. Recheck BG in 15-30mins.	

Babies who progress steadily with this weaning schedule may be able to satisfactorily reach standard milk (MEBM / term formula) within days. The ideal feed for babies is maternal breast milk. All mothers should be supported and encouraged to express milk with the hope that partial or full breastfeeding may be possible at a later stage. If breast milk is not available, then standard term formula is the next best option. Some babies will maintain the recommended feeding volume orally, but some may require partial or total nasogastric tube feeding. In our pilot studies, most term babies tolerate the wean from IV glucose to 3-hourly milk feeds very well. If BG values are not satisfactorily maintained on 3 hourly feeds, 2 hourly feeds can be trialled. A degree of pragmatism is needed.

Resolution of HI can be defined as:

- The **maintenance of BG ≥3mmol/L after a reduction in IV GIR to <8mg/kg/min in a term baby <120h**
- The **maintenance of BG ≥3.5mmol/L for 24h on 3 hourly feeds of standard milk in a term baby who had a persistent need for IV GIR ≥8mg/kg/min and is now older than 120h**

If resolution occurs before day 7, this has been a 'short transient' HI course and no further BG testing or discharge planning need occur, even if the insulin level was inappropriately high.

If resolution occurs **after day 7 and before discharge**, BG testing continues, babies are progressed to 4 hourly feeding and undergo a 6-hour fast (see section below).

No further dietetic follow-up or home BG checking is required thereafter unless specifically stipulated by the neonatal dietician or endocrine team.

<u>Hyperinsulinism - When to discuss suspected or confirmed HI with the Endocrinology team</u>

Babies that fulfil the diagnostic criteria and are demonstrating ongoing HI with high GIR on day 5 - 10 of life should be discussed with the paediatric endocrinology consultant of the week or registrar (bleep 9187). The generic email RHCYP.Endocrine@nhslothian.scot.nhs.uk can be used.

Consider an early discussion (day 5) if HI syndromes are suspected. Consider discussing those likely 'long transient' babies at day 7-10 in whom the intravenous glucose infusion rate has not been able to be weaned. This discussion should include available laboratory results, the need for additional specialist investigations and the planning of ongoing management, which may be conservative, or focused on optimising substrate provision and/or pharmacological treatment. Please see the referral form in Appendix 5. Early discussion can lead to earlier introduction of diazoxide treatment when indicated and can facilitate a timelier discharge. Please keep Endocrinology informed with a weekly progress update. The Endocrinology team will record their involvement on Trak.

Hyperinsulinism – Management of HI with feeds and/or medication

Some babies with ongoing HI cannot satisfactorily wean from IV glucose and may require more carbohydrate than breast milk or standard term formula can provide. Consideration should be given to specialist products such as high calorie formula (e.g., Infatrini peptisorb first line in the Simpson) and glucose polymers (e.g., Maxijul), which will provide a higher carbohydrate load. Both high energy formula and glucose polymers are usually only used with endocrine or dietetic input. Please note that using these products will provide a high energy intake which will require close monitoring, as it can result in rapid weight gain for some babies, which may not be appropriate. BG measurement continues and management advice is offered in the BG map "HI and full milk feeds".

Specialist feeds can be ordered from the Special Feeds Unit under dietetic supervision. Contact Hester Blair, specialist neonatal dietitian by email Hester.Blair@nhslothian.scot.nhs.uk. If a special feed request is made at the weekend or a bank holiday, an email can be sent before 11am to the special feeds unit to order this: Specialfeedunit.RHSC@nhslothian.scot.nhs.uk . Please ensure the attending neonatal consultant is copied in.

Points to note about using specialist nutritional products:

- The protein-energy ratio is disrupted with the addition of glucose polymer and care should be taken to ensure it is maintained between 7.5 – 12% for term feeds
- Adding additional glucose polymer increases osmolality which may affect feed tolerance (and potentially increase the risk of NEC, but this is uncommon in term babies)
- Infatrini peptisorb is a very nutrient dense formula and, although it offers a seemingly easy way to increase carbohydrate concentration with more volume, there is a risk of excessive nutrition being given which could be potentially harmful. It is recommended not to give more than 150ml/kg/d of Infatrini peptisorb unless there is a need for very high nutritional requirements.

Important feeding points to note with Diazoxide:

- Diazoxide is known to suppress appetite and may result in poor feeding in a baby who has previously fed well. If a baby requires treatment with Diazoxide, total fluid intake must be limited to 130 ml/kg/day. This may be liberalised to 150 ml/kg/day **once established** on Diazoxide if fluid overload has not been problematic. If a baby requires additional calories to gain weight, this should therefore be provided with higher calorie milk, rather than an increase in feed volume.

Table 3, below, highlights the nutritional content of commonly used milks and products in NHS Lothian at the time of writing, for reference.

Table 3

Feed	Carbohydrate g/100ml	Protein g/100ml	Energy content Kcal/100ml	Protein: energy ratio %
Mums expressed breast milk (MEBM)	7.2	1.3	69	7.5
MEBM + SMA Gold Prem BMF	8.5	2.74	86.2	12.7
Term formula	7.1 – 7.4	1.3	65 - 67	7.8 - 8.0
Infatrini peptisorb	10.2	2.6	100	10.4
Infatrini peptisorb +1% Maxijul	11.2	2.6	104	10
Infatrini peptisorb + 2% Maxijul	12.2	2.6	108	9.6

Vomiting is common in babies but can lead to particular staff and parental worry in babies with HI. For a small vomit or posset, check a pre-feed BG at the next feed and take appropriate action if indicated on the BG map. After a large vomit, try offering baby a half feed volume as extra and check the BG in 1h. Take action for BG as required. Recheck BG pre-feed. If vomiting is recurrent and problematic, aim to understand the cause e.g., reflux and consider treatment.

Several medications can be used under specialist endocrinology guidance for treatment of congenital HI. These include:

Diazoxide (always prescribed concurrently with chlorothiazide and requires echocardiography to confirm a structurally normal heart and absence of pulmonary hypertension prior to commencement)
Octreotide
Nifedipine
Glucagon

<u>Hyperinsulinism - Genetic testing</u>

The endocrinology team may recommend genetic testing for the cause of HI if:

- Examination suggests a possible syndromic diagnosis (e.g., Beckwith-Wiedemann, Kabuki, Turner)
- There is a family history of congenital HI
- The baby does not respond to diazoxide treatment alone
- The baby has no risk factors for the development of transient hyperinsulinism

After discussion and consent, blood samples (1 x Lihep and 1 x EDTA) should be obtained from the baby and both parents. The samples should be sent to the Genetics Lab at the Western General Hospital (who will forward the samples to the specialist lab in Dundee) and a request made for microarray and hyperinsulinism panel. Please include details of current hyperinsulinism management. Include the email address of the lead Endocrinology Consultant, so results can be communicated rapidly. The parental samples will only be processed if the baby is found to have one of the known genetic mutations.

Hyperinsulinism - Preparing for home

Resolution of HI can be defined as:

- The **maintenance of BG ≥3mmol/L after a reduction in IV GIR to <8mg/kg/min in a term baby <120h**
- The **maintenance of BG ≥3.5mmol/L for 24h on 3 hourly feeds of standard milk in a term baby who had a persistent need for IV GIR ≥8mg/kg/min beyond 120h**

If resolution occurs before day 7, this has been a 'short transient' HI course and no further BG testing or discharge planning need occur, even if the insulin level was inappropriately high.
If resolution occurs **after day 7 and before discharge**, BG testing continues, babies are progressed to 4 hourly feeding and undergo a 6-hour fast (see section below).
No further dietetic follow-up or home BG checking is required thereafter unless specifically stipulated by the neonatal dietician or endocrine team.

Discharge criteria for babies with ongoing HI (i.e., there is a requirement for high calorie milk or medication to maintain normoglycaemia and resolution has not occurred before discharge)

- Blood glucose is maintained ≥3.5mmol/L on current feed and/or medication regimen for **≥48hours**
- A controlled 6 hour fast has been passed (see below)
- Parents have been trained in BG testing
- Parents have been provided with a feed and blood glucose diary (Appendix 3)
- A written hypoglycaemia management plan has been agreed with the parents (Appendix 4) and **demonstration given of glucogel administration**
- Ongoing supplies of BG test strips, lancets, and glucose 40% gel have been requested from the GP (see below)
- **A Trak alert has been added** (see text below). Add a Trak alert by selecting tab "Allergies / Alerts" and creating a "New alert". This text should also be added to the baby's neonatal discharge letter which will be uploaded to SCI store.

Trak alert to guide RHCYP ED management:
Diagnosis: Hyperinsulinaemic hypoglycaemia
At risk of severe and profound hypoglycaemia, particularly with poor feeding or gastrointestinal illness. If presents acutely due to hypoglycaemia:

- Admit and monitor blood glucose (BG) hourly.
- Maintain BG ≥3.5mmol/L.
- Follow the patient held hypoglycaemia plan.
- If hypoglycaemia fails to respond to two oral treatments, or if they are unable to tolerate feeds, an IV cannula should be sited, and a 1ml/kg IV 10% glucose bolus given to treat hypoglycaemia. **Repeat this every 10 minutes until BG is ≥3.5 mmol/L**. Then immediately commence a maintenance IV fluid infusion containing 10% glucose.
- Diazoxide treatment can precipitate fluid overload and therefore an accurate fluid balance and regular reassessment is essential.

Please contact the endocrine team for early review. Bleep 9187.

Hyperinsulinism - Controlled fast prior to discharge:

All babies with 'long transient' or 'permanent' HI should have a controlled fast prior to discharge to ensure they are not at high risk of hypoglycaemia if there is an unexpected delay to a feed. These babies must pass a 6 hour fast whilst being able to tolerate 4 hourly feeds. **Before the test begins we must first check that the fatty acid result is normal to exclude a fatty acid oxidation defect.**

The baby should receive their usual feed volume at the feed preceding the fast. When the next feed is due, BG should be measured, and the feed omitted. BG should then be measured hourly until the end of the fast period. If BG is **<3mmol/L at any time**, the fast should be ended* and hypoglycaemia treated with glucogel and a feed. If the BG is 3.0-3.4mmol/L, repeat BG again to see if there is a spontaneous increase. If the BG remains <3.5mmol/L, end the fast and treat the hypoglycaemia with glucogel and a feed.

*If a baby becomes hypoglycaemic <3mmol/L during a fast, please quickly **perform a hypoglycaemia screen**. This is very informative in babies who are not on drug treatment for HI, to confirm whether ongoing hypoglycaemia is secondary to HI or something else. If a baby develops hypoglycaemia during a controlled fast, their HI treatment (i.e., diazoxide dose or feeding regimen) needs to be adjusted prior to the controlled fast being repeated, at least 48 hours later.

Discharge prescription:

The following items should be requested for discharge, and the GP emailed to request a repeat prescription:

- Accu-Chek® Performa Nano Test strips (4 boxes)
- Accu-Chek® fastclix lancets (204)
- Glucose 40% gel (e.g., Glucogel®) 3x25gms triple pack
- Medication as relevant (for diazoxide specify Proglycem® preparation)
- Specialist formula prescription if applicable (this is ordered via the dietician)

The hospital discharge prescription is usually sufficient for < 1 week of BG testing and therefore the family must be aware to collect the GP prescription within 24h of discharge. Please ensure babies have been registered with their GP prior to discharge.

Hyperinsulinism - After discharge

Babies treated with Diazoxide will be followed up by the endocrine team where the following will apply:

- The baby should continue to be fed with the same frequency and volume as pre-discharge (e.g., 130 mL/kg/day of MEBM, 4 hourly, over a 24h period)
- BG testing should be carried out prior to every feed
- See appendix 3 for glucose and feed diary to be given to the family
- The written hypoglycaemia plan should be followed if BG is <3.5mmol/L
- The initial contact point should be the neonatal unit until the first appointment at Endocrine out-patient clinic
- Contact should be made 1 week after discharge to review BG readings and feeding (ideally at the endocrine clinic, or by telephone if a clinic appointment is not possible). Frequency of BG testing may then be reduced to alternate feeds if there have been no episodes of hypoglycaemia.

Babies managed with high calorie formula will be followed up by the neonatal team where the following will apply:

- The baby should continue to be fed with the same frequency and volume as pre-discharge
- BG testing should be carried out prior to every second feed if stable
- See appendix 3 for glucose and feed diary to be given to the family
- The written hypoglycaemia plan should be followed if BG is <3.5mmol/L
- The initial contact point should be the neonatal unit or the RHCYP dietetic department
- Dietetic contact should be made 1 week after discharge to review BG readings and feeding via phone or Near-me video consultation. A plan will be discussed to start weaning high calorie formula if blood sugars have been stable.
- Developmental follow-up plans are not yet determined.

Associated materials

Appendix 1. Blood glucose (BG) map for babies with suspected or proven hyperinsulinism who at 120h still had an intravenous GIR ≥8mg/kg/min and have a BG threshold of 3.5mmol/L

Appendix 2. Blood glucose (BG) map for babies with suspected or proven hyperinsulinism on full milk feeds

Appendix 3. Glucose and feed diary

Appendix 4. Hypoglycaemia home management plan

Appendix 5. HI Endocrine referral form

Evidence base

Harris D.L, Weston P.J, Gamble G.D, Harding J.E. Glucose profiles in Healthy Term Infants in the first 5 days: The Glucose in Well Babies (GLOW) Study. *J Pediatr.* 2020;223:34-41

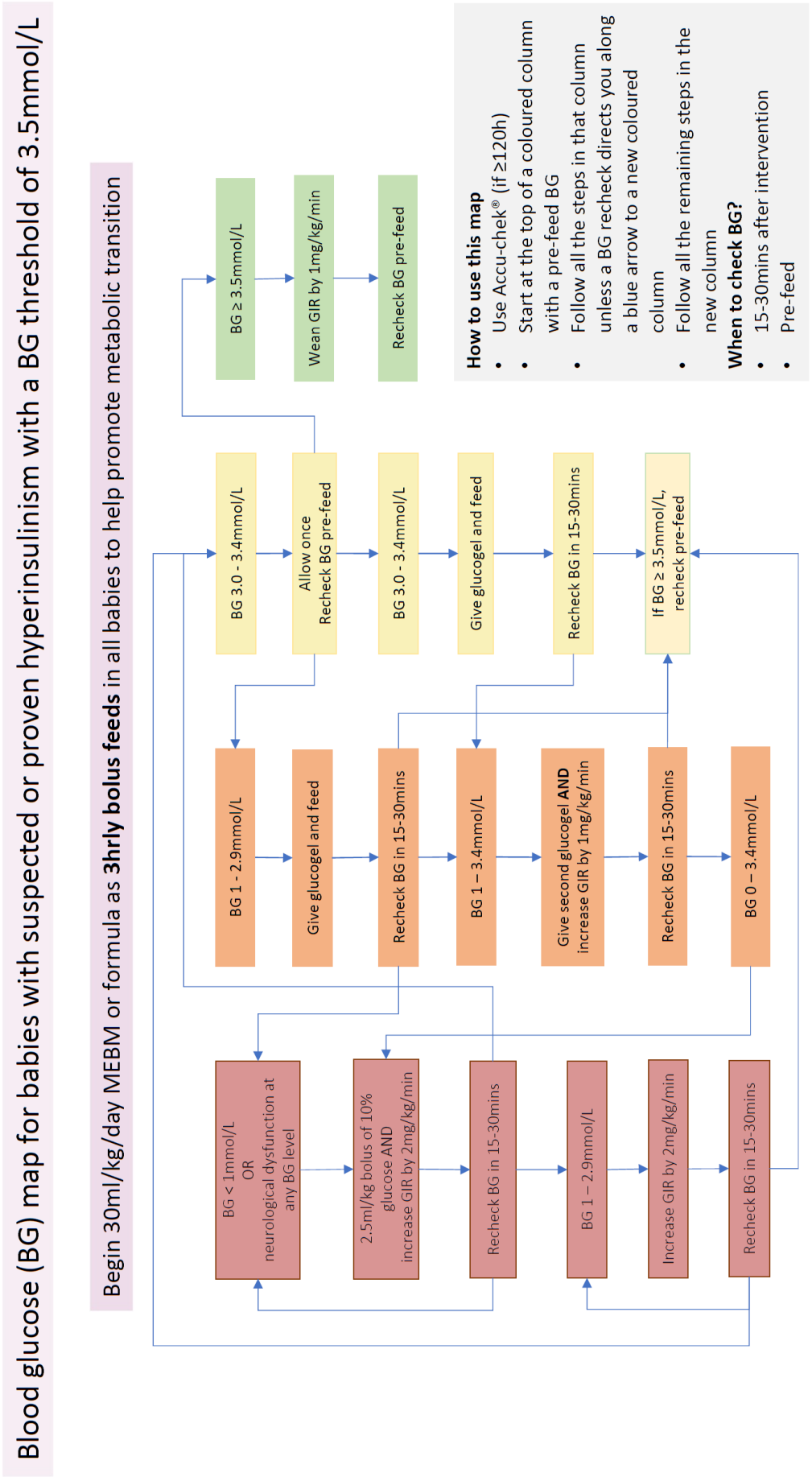
Banerjee I, Salomon-Estebanez M, Shah P, Nicholson J, Cosgrove KE, Sunne MJ. Therapies and outcomes of congenital hyperinsulinism-induced hypoglycaemia. *Diabet. Med. 2019;* 36: 9– 21

Roženková K, Güemes M, Shah P, Hussain K. The Diagnosis and Management of Hyperinsulinaemic Hypoglycaemia. *J Clin Res Pediatr Endocrinol*. 2015;7(2):86-97

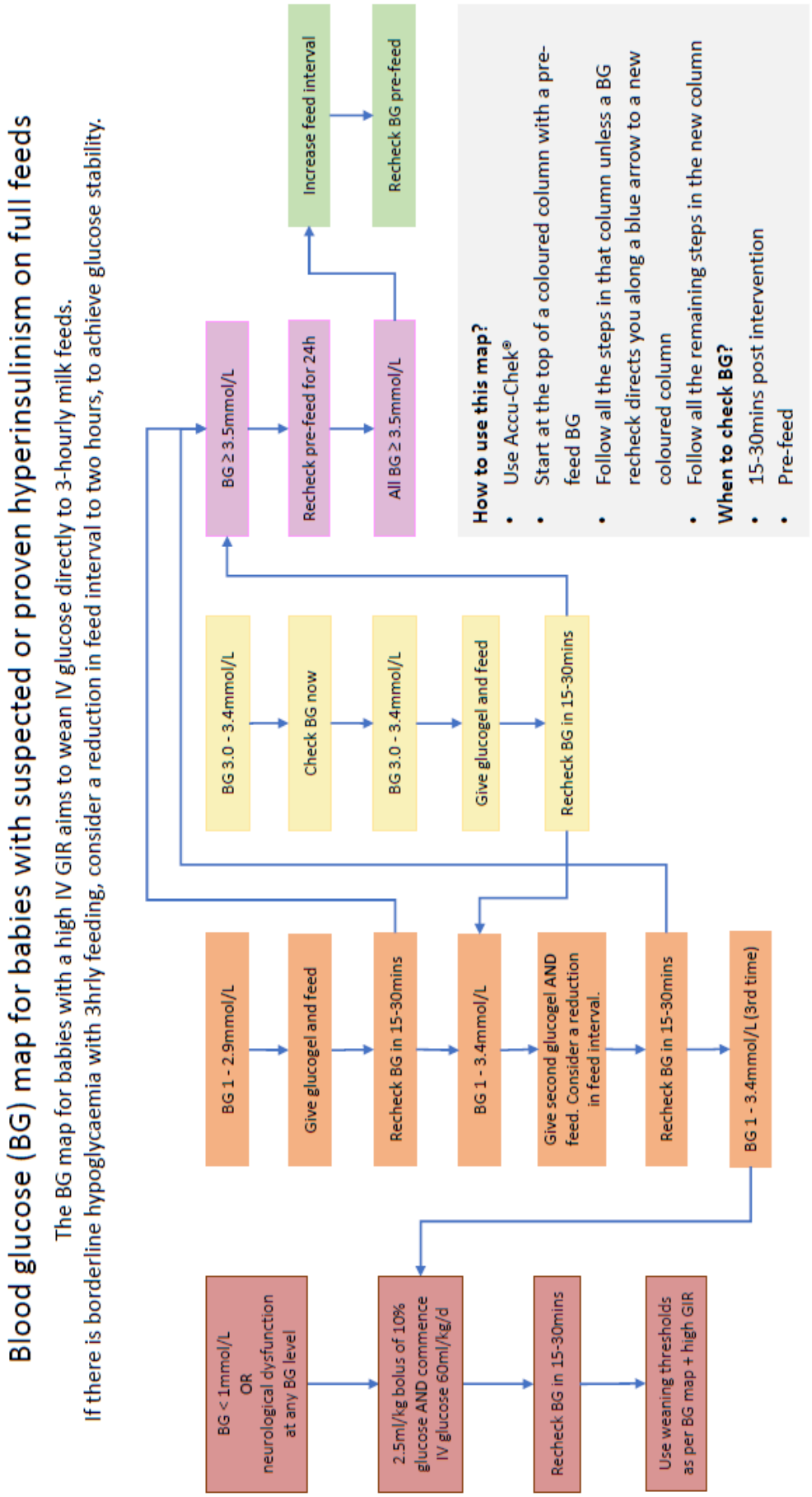
Fafoula O, Alkhayyat H, Hussain K. Prolonged hyperinsulinaemic hypoglycaemia in newborns with intrauterine growth retardation. Arch Dis Child Fetal Neonatal Ed. 2006 Nov; 91(6): F467

Munns C.F.J, Batch J.A. Hyperinsulinism and Beckwith-Wiedemann syndrome. Arch Dis Child Fetal Neonatal Ed 2001;84:F67–F69

Appendix 1


Blood glucose (BG) map for babies with suspected or proven hyperinsulinism with a BG threshold of 3.5mmol/L
Begin 30ml/kg/day MEBM or formula as **3hrly bolus feeds** in all babies to help promote metabolic transition
How to use this map
Use Accu-chek® (if ≥120h)
Start at the top of a coloured column with a pre-feed BG
Follow all the steps in that column unless a BG recheck directs you along a blue arrow to a new coloured column
Follow all the remaining steps in the new column
When to check BG?
15-30mins after intervention
Pre-feed
BG ≥ 3.5mmol/L
Wean GIR by 1mg/kg/min
Recheck BG pre-feed
BG 3.0 - 3.4mmol/L
Allow once
Recheck BG pre-feed
BG 3.0 - 3.4mmol/L
Give glucogel and feed
Recheck BG in 15-30mins
If BG ≥ 3.5mmol/L, recheck pre-feed
BG 1 - 2.9mmol/L
Give glucogel and feed
Recheck BG in 15-30mins
BG 1 – 3.4mmol/L
Give second glucogel **AND** increase GIR by 1mg/kg/min
Recheck BG in 15-30mins
BG 0 – 3.4mmol/L
BG < 1mmol/L OR neurological dysfunction at any BG level
2.5ml/kg bolus of 10% glucose AND increase GIR by 2mg/kg/min
Recheck BG in 15-30mins
BG 1 – 2.9mmol/L
Increase GIR by 2mg/kg/min
Recheck BG in 15-30mins

Appendix 2


Blood glucose (BG) map for babies with suspected or proven hyperinsulinism on full feeds
The BG map for babies with a high IV GIR aims to wean IV glucose directly to 3-hourly milk feeds.
If there is borderline hypoglycaemia with 3hrly feeding, consider a reduction in feed interval to two hours, to achieve glucose stability.
BG < 1mmol/L OR neurological dysfunction at any BG level
2.5ml/kg bolus of 10% glucose AND commence IV glucose 60ml/kg/d
Recheck BG in 15-30mins
Use weaning thresholds as per BG map + high GIR
BG 1 - 2.9mmol/L
Give glucogel and feed
Recheck BG in 15-30mins
BG 1 - 3.4mmol/L
Give second glucogel AND feed. Consider a reduction in feed interval.
Recheck BG in 15-30mins
BG 1 - 3.4mmol/L (3rd time)
BG 3.0 - 3.4mmol/L
Check BG now
BG 3.0 - 3.4mmol/L
Give glucogel and feed
Recheck BG in 15-30mins
BG ≥ 3.5mmol/L
Recheck pre-feed for 24h
All BG ≥ 3.5mmol/L
Increase feed interval
Recheck BG pre-feed
How to use this map?
Use Accu-Chek®
Start at the top of a coloured column with a pre-feed BG
Follow all the steps in that column unless a BG recheck directs you along a blue arrow to a new coloured column
Follow all the remaining steps in the new column
When to check BG?
15-30mins post intervention
Pre-feed

Appendix 3 Glucose and feed diary

Name: ..... Weight:.....kg Feed volume (ml/kg/day)..... = ...ml feed every .....hours

	Time	Glucose	Milk volume	Time	Glucose	Milk volume	Time	Glucose	Milk volume	Time	Glucose	Milk volume	Time	Glucose	Milk volume	Time	Glucose	Milk volume
MONDAY ...../...../.....																		
TUESDAY ...../...../.....																		
WEDNESDAY ...../...../.....																		
THURSDAY ...../...../.....																		
FRIDAY ...../...../.....																		
SATURDAY ...../...../.....																		
SUNDAY ...../...../.....																		

Appendix 4 **Hypoglycaemia home management plan**

Name:

CHI:

If blood glucose is 3.5 mmol/l or higher:

1. No action is needed. Continue to follow the feed plan given at hospital discharge.

If pre- feed blood glucose is less than 3.5 mmol/l:

1. Re-check after 10 minutes
2. If the blood glucose level is still below 3.5 mmol/l, give one-third of a Glucogel® tube and the feed
3. Re-check the blood glucose level 10 minutes later to ensure it has risen
4. If they continue to be hypoglycaemic and do not respond to Glucogel®, please repeat step 2 (with a second small feed) and call an ambulance to take them to the nearest hospital

If random blood glucose is less than 3.5 mmol/l:

1. Re-check after 10 minutes
2. If the blood glucose level is still below 3.5 mmol/l, give one-third of a Glucogel® tube and a small feed
3. Re-check the blood glucose level 10 minutes later to ensure it has risen
4. If they continue to be hypoglycaemic and do not respond to Glucogel®, please repeat step 2 and call an ambulance to take them to the nearest hospital

If hospital attendance is required due to low blood glucose:

1. Admission should be arranged to have blood glucose levels monitored
2. If they are unwell and unable to tolerate feeds, or hypoglycaemia has not responded to two oral treatments with glucose, an intravenous cannula should be inserted and 10% glucose given to stabilise blood glucose levels

Urgent contact details: Attend nearest Emergency Department

Non-urgent contact details:

Endocrine Nurse Specialists, Royal Hospital for Sick Children
0131 536 0807

Endocrine Secretary, Royal Hospital for Sick Children
0131 536 0611

Other:
Neonatal Unit 0131 242 2601/2602 if before first Endocrine review

Appendix 5

Endocrine referral document

Background	
Name	
CHI	
Gestation	
Birth weight	
Pregnancy history (maternal diabetes, hypertension, medication)	
Consanguinity?	
Family history (diabetes, unexplained hypoglycaemia)	
Current clinical status of baby (e.g. HIE, sepsis, polycythaemia)	
Examination findings (dysmorphism, hepatosplenomegaly, hemihypertrophy)	
Day of life hypoglycaemia identified	

Hypoglycaemia screen			
Day of life:		Day of life:	
Circumstances of hypo (e.g. spontaneous, tissued IV cannula etc)		Circumstances of hypo (e.g. spontaneous, tissued IV cannula etc)	
Glucose		Glucose	
Insulin		Insulin	
C-peptide		C-peptide	
FFA		FFA	
BHOB		BHOB	
Cortisol		Cortisol	
GH		GH	
Ammonia		Ammonia	
Blood gas		Blood gas	
Acylcarnitine profile			
Plasma amino acid		Plasma amino acid	
Urinary organic acid		Urinary organic acid	
Other		Other	

Daily updates	
Date	
Current weight	
IV glucose rate (ml/h)	
IV glucose concentration (%)	
Intravenous glucose requirement (mg/kg/min)	
Enteral feed volume	
Enteral feed frequency	
Total fluid intake (ml/kg/day)	
Frequency of BG testing	
Method of BG testing (POCT meter/gas machine)	
Medication	
Plan:	
Staff involved	