MCN for Neonatology
West of Scotland
Neonatal Guideline

# Persistent or refractory hypoglycaemia in the neonate:

## A guideline for management

This document is applicable to all medical, nursing and midwifery staff caring for the newborn in the West of Scotland. For advice on screening for hypoglycaemia and the management of transient neonatal hypoglycaemia, staff should refer to the guideline entitled 'Hypoglycaemia: screening for and management of hypoglycaemia in the neonatal period'.

This guideline should be used for infants who require high levels of glucose intake to maintain normoglycaemia (>8mg/kg/min), or whose hypoglycaemia fails to resolve in the usual timescale of 2 days. The document should be used with reference to the appropriate pharmacy monographs.

**Contents**



**Introduction**

Transient hypoglycaemia is common in the newborn period. Cases of hypoglycaemia which are recurrent or resistant to treatment should be investigated further, because inadequate treatment can result in poor neurological outcomes (Menni et al., 2001). The most common cause of persistent hypoglycaemia is hyperinsulinism, accounting for up to 50% of cases (Dacou-Voutetakis et al., 1998). The aetiology of this condition is diverse however, and investigations should be carried out at the time of hypoglycaemia if possible.

For the purpose of this guideline, persistent hypoglycaemia is defined as being present if the patient remains hypoglycaemic for >3 days despite treatment, as detailed in the WoS Guideline entitled 'Hypoglycaemia: screening for and management of hypoglycaemia in the neonatal period'. If the neonate is requiring high infusion rates of dextrose (>10mg/kg/minute) to maintain normoglycaemia hyperinsulinism should be considered, irrespective of age.

Hypoglycaemia is severe if a glucose requirement >8mg/kg/min is required to maintain euglycaemia. Normal glucose requirements are 4-6mg/kg/min. This can be calculated using the following equations (Kuschel and Knight, 2007):

$$\text{Glucose intake (mg/kg/min)} = \frac{\text{\% Dextrose x Volume (ml/kg/day)}}{144}$$

OR

$$\text{Glucose intake (mg/kg/min)} = \frac{\text{\% Dextrose x Hourly Rate}}{\text{Weight (Kg) x 6}}$$

The following table demonstrates rates of intravenous glucose in mg/kg/minute from standard dextrose concentrations.

| **Infusion rate (ml/kg/day)** | **10% dextrose** | **12.5 % dextrose** | **15% dextrose** | **20% dextrose** |
|---|---|---|---|---|
| 60 | 4 mg/kg/min | 5 mg/kg/min | 6 mg/kg/min | 8 mg/kg/min |
| 75 | 5 mg/kg/min | 7 mg/kg/min | 8 mg/kg/min | 11 mg/kg/min |
| 90 | 6 mg/kg/min | 8 mg/kg/min | 9 mg/kg/min | 13 mg/kg/min |
| 120 | 8 mg/kg/min | 10 mg/kg/min | 13 mg/kg/min | 17 mg/kg/min |
| 150 | 10 mg/kg/min | 13 mg/kg/min | 16 mg/kg/min | 21 mg/kg/min |

For babies who are on a combination of different fluids +/- milk there is a handy online calculator at http://nicutools.org/

**History and Examination**
Initial discussion should be undertaken with the attending Neonatal Consultant.
Full clinical history and examination of the neonate should be carried out to include:

- History:
  - Maternal history of ingestion of medications which can induce hypoglycaemia, for example labetalol
  - Maternal history of diabetes
  - Feeding patterns since birth and relationship with hypoglycaemia
  - Family history of consanguinity and sudden infant death
  - History of prolonged jaundice
  - Birth weight centile (<10$^{th}$ centile)
  - Preterm (<37 weeks)
  - Severe illness e.g. sepsis, hypoxia, rhesus disease
- Examination (Robinson et al., 2009)
  - Small penis, midface abnormalities with or without prolonged jaundice suggestive of panhypopituitarism
  - Macrosomia – hyperinsulinism, infants of diabetic mothers
  - Ambiguous genitalia or virilisation or a pigmented scrotum in a Caucasian infant – congenital adrenal hyperplasia
  - Progressive liver enlargement in the first week of life – disorders of gluconeogenesis or glycogen storage disease
  - Hypotension – cortisol deficiency
  - Abnormal ear lobes, macroglossia, hemi-hypertrophy, umbilical hernia – Beckwith-Wiedemann syndrome

**Investigations**

Refractory hypoglycaemia (requiring >8mg/kg/min Glucose to maintain normoglycaemia) in the first few days after birth will usually be caused by hyperinsulinism. For such babies, the investigations outlined in bold in the table below should be prioritised. These investigations should be carried out at the time of hypoglycaemia.

Babies with persistent hypoglycaemia (more than 2 days), or with atypical presentation (babies with no clear cause for the hypoglycaemia such as maternal diabetes or beta blockers), should be discussed with the Neonatal Consultant on call and consideration given to undertaking the extended list of investigations as below.
Note that some investigations may be hard to interpret in the first few days after birth due to normal physiological hormonal changes after delivery.

If you wish to discuss which investigations are needed, discuss with the Endocrine Consultant on Call at the Royal Hospital for Children, Glasgow.

In total, you should take 2 lithium heparin blood bottles, a grey top fluoride/oxalate bottle, a blood spot card and a urine sample during hypoglycaemia and send them to Biochemistry.

These tests are performed in different laboratories throughout Glasgow. If you wish to discuss how these tests should be sent, please discuss with the On Call Biochemist.

Table 1. Investigations required for neonates with refractory or persistent hypoglycaemia at time of hypoglycaemia

| **Type of specimen and investigation** | | **How do you do it?** | **Where does it go? (GG&C)** | **Guide to interpretation** |
|---|---|---|---|---|
| **Blood** | **Glucose** | **DURING HYPOGLYCAEMIA**<br><br>**Fluoride/oxalate (grey top) bottle** | **Send to biochemistry** | **<4 days of age abnormal if <2.2mmol**<br><br>**>4 days of age abnormal if <2.6mmol** |
| **Blood** | **Capillary blood gas** | **Take in capillary tube** | **Blood gas machine** | **Metabolic acidosis in severe ketosis, lactic acidosis or organic acidaemia** |
| **Blood** | **β-hydroxybutryate and free fatty acids** | **DURING HYPOGLYCAEMIA**<br><br>**Lithium heparin bottle**<br><br>*Sample should be transported to the local laboratory & separated within 30 mins of collection,. Store frozen* | **Send to biochemistry** | **Hyperinsulinism: FFA<1.0mmol/l and FFA:β-hydroxybutyrate ratio <1.0**<br><br>**Fatty acid oxidation defect: FFA>1.0mmol/l and FFA: β-hydroxybutyrate ratio >1.4** |
| **Blood** | **Insulin and C-peptide** | **DURING HYPOCLYAEMIA**<br><br>**Lithium heparin sample**<br><br>*Samples must be collected on ice, transported to the local laboratory and separated within 30 mins of collection. Store frozen* | **Send to biochemistry** | **Insulin >2.0mU/l when hypoglycaemia present consistent with hyperinsulinism or insulinoma**<br><br>**Increased insulin with low C-peptide suggests exogenous insulin administration** |
| **Urine** | **Ketones** | **Urinalysis** | **On ward** | **Evidence of ketonuria** |

| | | | | |
|---|---|---|---|---|
| Blood | Lactate | DURING HYPOGLYCAEMIA<br><br>Fluoride/oxalate (grey top) bottle or blood gas tube | Send to biochemistry or analyse on blood gas machine | Ref range neonate 0.5-3mmol/l<br><br>Causes of high lactate:<br>• Venous stasis on sampling<br>• Tissue hypoxia and ischaemia<br>• Disorders of gluconeogenesis<br>• Glycogen storage disease type I<br>• Primary lactic acidosis (resp chain defects, pyruvate dehydrogenase deficiency) |
| Blood | Cortisol | DURING HYPOGLYCAEMIA<br><br>Lithium heparin sample | Send to biochemistry | Cortisol >250nmol/l excludes disorder of hypothalamic-pituitary axis<br><br>Cortisol 150-250nmol/l check GH level (if >6 ug/l significant pituitary pathology unlikely)<br><br>Cortisol <150nmol/l +/- GH <6 ug/l needs further investigation for pituitary/adrenal disorders |
| Blood | Growth Hormone | Lithium heparin sample | Send to biochemistry | GH level >10µg/L excludes hypopituitarism in infant <3 months of age<br><br>(Note units: 1µg/L=3mU/L) |
| Blood | Ammonia | Lithium heparin sample<br><br>*Sample should be transported to Yorkhill ASAP*<br><br>*Laboratory MUST be informed* | Send to biochemistry | <100umol/L in term infants normal<br><br><180umol/L in preterm/SGA infants<br><br>Raised in:<br>• Fat oxidation disorders<br>• Reyes syndrome<br>• Organic acidaemia (associated with hypoglycaemia and acidosis) |
| Blood | Urea and electrolytes | Lithium heparin sample | Send to biochemistry | Looking for evidence of:<br>• Severe dehydration<br>• Low K in organic acidaemia<br>• Renal disease<br>• Low Na +/- high K in adrenal disease |
| Blood | AST/ALT<br><br>CK | Lithium heparin sample | Send to biochemistry | Deranged in GSD type I, Reye's syndrome, fat oxidation defects and GSD type III |
| Blood | Thyroid function tests | Lithium heparin sample | Send to biochemistry | Low free T4 and TSH in hypopituiarism |
| Blood | Testosterone | ONLY IN MALES <4 MONTHS | Send to biochemistry | Absent normal postnatal surge of testosterone in panhypopituitarism |

| | | | | |
|---|---|---|---|---|
| | | Lithium heparin bottle | | |
| Blood | Amino acids | DURING HYPOGLYCAEMIA<br><br>Lithium heparin bottle<br><br>*Sample should be separated by local laboratory within 2hr of collection and frozen.* | Send to biochemistry | Low alanine in ketotic hypoglycaemia and starvation.<br><br>High alanine in lactic acidosis |
| Blood | ACTH | Only if cortisol response equivocal/low<br><br>Lithium heparin bottle<br><br>*Samples must be transported to local laboratory within 30 mins of collection. Store frozen* | Send to biochemistry | Ref range 7-51ng/L<br><br>Normal/low ACTH excludes adrenal pathology<br><br>High ACTH with low cortisol suggests adrenal pathology and requires Synacthen test |
| Blood | Acyl-carnitine | DURING HYPOGLYCAEMIA<br><br>Blood spots on card | Send to biochemistry | May show abnormalities in MCAD deficiency and long chain fatty acid oxidation disorders |
| Urine | Organic acids | First urine sample passed following hypoglycaemia episode. Freeze. | Send to biochemistry | Evidence of abnormalities in organic acid disorders, fatty acid oxidation defects.<br><br>Ketosis excludes endogenous hyperinsulinism. |

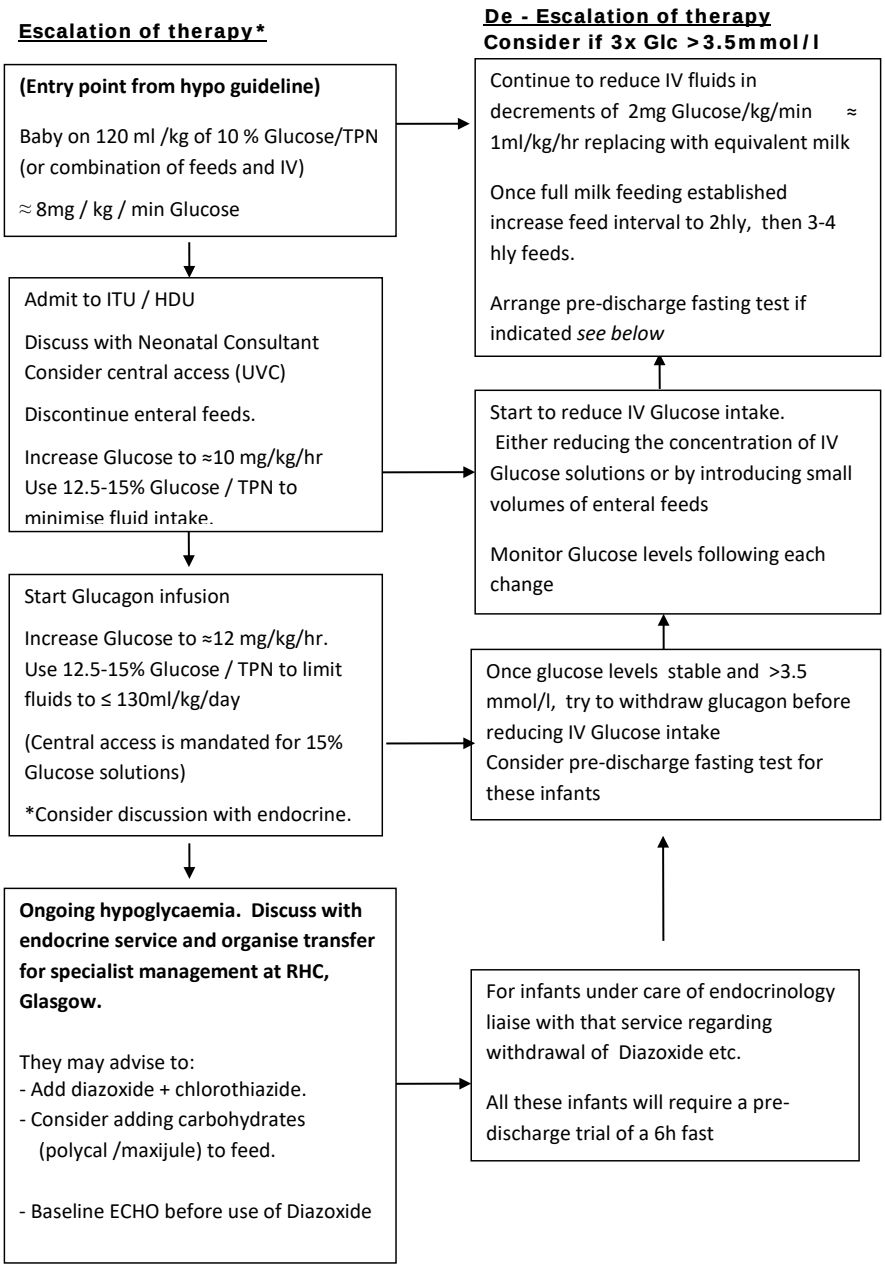
**Treatment of persistent hypoglycaemia**

Whilst investigating possible underlying causes, treatment should continue as per the WoS guideline entitled 'Hypoglycaemia: screening for and management of hypoglycaemia in the neonatal period'. If an underlying cause is identified, advice should be sought from the endocrine/metabolic team.

The aim of treatment is to maintain BM>3.0 mmol/l in the first 48h and 3.5 mmol/l thereafter, this reduces the risk of hypoglycaemia and subsequent neurological impairment.

**Treatment of refractory hypoglycaemia**

If concerns re ongoing hypoglycaemia, blood sugars should be monitored at least 4-6 hourly, ideally pre-feed. Closer monitoring will be required after any change in therapy, particularly if reduction in glucose delivery. Blood sugars should be taken using the blood gas analyser machine, as bedside BM monitors are not accurate with glucose levels <3mmol/l. There should be early consideration of central access for the neonate.




*** If unable to keep Glucose >3.0 mmol/l in the first 48h or >3.5 mmol/l thereafter, consider escalation of therapy and discussion with endocrine/metabolic team.**

**Commented [P1]:** BAPM position statement says 3.0mmol/l in first 48h and 3.5mmol/l thereafter

**Drugs which may be recommended by the Metabolic/Endocrine service.**

**For doses please see relevant pharmacy monographs**

| Drug | Prior to initiation | Route | Side effects |
|---|---|---|---|
| Glucagon | Consider central IV access | IV/IM bolus<br><br>OR<br><br>IV infusion | GI disturbance, decreased gastric acid and pancreatic enzyme production, increased myocardial contractility. |
| Diazoxide | Echocardiogram<br><br>Reduce fluids to 130ml/kg/day for at least 24 hours prior to commencement. | Oral | Pulmonary hypertension, fluid retention, hyponatraemia, heart failure, hyperuricaemia, hypertrichosis, leucopoenia, thrombocytopenia. |
| Chlorthiazide | | Oral | Electrolyte imbalance. |
| Maxijul / Polycal | | Oral | Constipation |

**Preparation for discharge**

All patients who have required medication to treat refractory hypoglycaemia should have a 'Fasting Challenge' performed prior to discharge to ensure they would tolerate a missed feed in the community. During this challenge, one of the usual 3 hourly feeds should be omitted and glucose should be monitored hourly after the scheduled omitted meal until 6 hours post feed. The following observations should also be noted on an hourly basis:

- Level of consciousness (responsive and can be roused)
- Tone (normal)
- Temperature (36.5-37.5 degrees Celsius)
- Respiration (consistently >30, <60)
- Colour (pink)

If this is satisfactory, the baby can be safely discharged. The parents should however be advised that they must feed their infant at a minimum of every 3 hours. The parents should also be advised of the symptoms to watch for which may signify hypoglycaemia (jitteriness, lethargy, high pitched cry) and to seek medical advice if they have any concerns.

NB – if the blood glucose falls below 2.6mmol/l , the baby should be fed and the fasting test abandoned. Regular 3hly feeds should be recommenced and the test repeated after an interval (interval to be determined by the medical team).

**Useful websites:**

IMD Scotland website www.imd.scot.nhs.uk

**Appendix**

1) Neonatal results sheet
2) Care plan for discharge after refractory hypoglycaemia

**References**
Dacou-Voutetakis, C., Psychou, F. and Maniati-Christidis (1998). Peristenthyperinsulinaemic hypoglycaemia of infancy: long-term results. Journal of Pediatric Endocrinology and Metabolism, 11, 131-141.
Kuschel, C. and Knight, D. (2007). Newborn Services Clinical Guideline, Fluid and Glucose Requirements. Available online at:
http://www.adhb.govt.nz/newborn/guidelines/nutrition/FluidsAndGlucose.htm

Menni, F., de Lonlay, P., Sevin, C., Touati, G. Peigne, C., Barbier, V., Nihoul-Fekete, C., Saudubray, J-M and Robert, J-J (2001). Neurologic outcomes of 90 neonates and infants with persistent hyperinsulinaemic hypoglycaemia. Pediatrics, 107, 476-479.

Robinson, P., Kirk, J., Schwahn, B., Farmer, G., Galloway, P. IMD Protocols Subgroup, Jackson, L. and Simpson, J. (2009). IMD Scotland guideline, Investigation of hypoglycaemia in neonates, infants and young children.

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**Implementation and review dates**
Implementation date 01/03/14 Latest review 03/07/20 Next review 01/07/23

**Appendix 1**

**NEONATAL HYPOGLYCAEMIA RESULTS SHEET**

| | |
|---|---|
| **NAME:**<br><br>**DATE OF BIRTH:**<br><br>**CHI NUMBER:**<br><br>**MALE/FEMALE:** | ATTACH HOSPITAL STICKER |

| | **RESULT** | | | | | | |
|---|---|---|---|---|---|---|---|
| **TEST** | **DATE** | **DATE** | **DATE** | **DATE** | **DATE** | **DATE** | **DATE** |
| Lab glucose | | | | | | | |
| Lactate | | | | | | | |
| Insulin | | | | | | | |
| C-peptide | | | | | | | |
| ALT | | | | | | | |
| AST | | | | | | | |
| CK | | | | | | | |
| TSH | | | | | | | |
| Free T4 | | | | | | | |
| Cortisol | | | | | | | |
| Ammonia | | | | | | | |
| Cortisol | | | | | | | |
| Testosterone | | | | | | | |
| Growth hormone | | | | | | | |
| Acyl-carnitine (blood spot) | | | | | | | |
| β-hydroxybutryate | | | | | | | |
| ACTH | | | | | | | |
| Serum free fatty acids | | | | | | | |
| Serum organic acids | | | | | | | |
| Serum amino acids | | | | | | | |
| Urine ketones | | | | | | | |
| Urine reducing substances | | | | | | | |
| Urine organic acids | | | | | | | |
| Other: | | | | | | | |
| Other: | | | | | | | |
| Other: | | | | | | | |
| Other: | | | | | | | |
| Other: | | | | | | | |
| Other: | | | | | | | |

**Appendix 2. Example care plan for discharge of babies who have refractory hypoglycaemia**
(please discuss with endocrine team)

## MEDICAL PLAN FOR BABY **

Baby ** makes too much **insulin**, which makes it possible for his blood glucose level to go too low. The aim of treatment is to prevent low blood glucose.

**A blood glucose less than 3 at any time could be harmful.**

**A blood glucose above 12 for a long time could be harmful.**

We aim to keep the blood glucose between 4 and 8. Low ones are most likely to happen before a feed. High ones are most likely to happen after a feed.

We have shown that, with 4 hourly feeding, a normal glucose lasts for up 6 hours after a feed, but the blood glucose *could* go too low if he misses more than 1 feed or if he vomits feeds. There is also a risk of low glucoses after shorter intervals if there is a small increase in the amount of insulin produced. It is likely that the tendency to have low blood glucose will resolve in time.

### Feeding

Baby ** is fed with ** every 4 hours.

Baby ** should not be left longer than 4 hours between feeds.

### When to check a blood glucose level

1. Every 8 hours when discharged home, with the first one before 1st feed of the day. This is when the glucose is likeliest to be lowest. For the present, the longest interval between feeds should not exceed 4 hours,
2. **At other times before feeds, if required**, and especially if any glucose has been low in the preceding 24 hour period.
3. If Baby ** is unwell, e.g. vomiting, off feeds.

**Write down all the blood glucose results in a diary or a notebook.**

### Blood Glucose Results

| | |
|---|---|
| **4-10:** | Continue the usual feeding plan. |
| **3-4:** | Give the usual feed. Repeat the blood glucose 1 hour after this feed. If it is still less than 4 seek medical advice. If it is above 4 continue the normal feeding plan and repeat the blood glucose before the next feed. |
| **< 3:** | Give a normal feed. Recheck glucose after 20 mins and consider giving an extra top-up feed with formula. |
| | **Seek medical advice.** |
| **< 2.5mmol/l:** | Try a feed only if he seems completely well. |
| | **Seek medical advice immediately/attend nearest hospital.** |
| **> 10:** | Repeat the blood glucose the same day after a feed. |

**When to seek medical advice**

1. If Baby ** has needed glucagon.
2. If blood sugar is less than 3 at any time.
3. If blood sugar is between 3 and 4 twice or more in 24 hours.
4. If blood sugar is less than 4 *and* Baby ** doesn't tolerate a feed or vomits a feed
5. If there are more than two results above 10 in any day

**Contact Numbers:**

**During working hours:**

Dr M Guftar Shaikh via secretary (0141 451 6548) or via switchboard 0141 201 0000

Endocrine Registrar via switchboard 0141 201 0000 (page 18301)

Susan McMahon Metabolic Nurse Specialist 07584159556

**Out of hours/weekends:**

On-call Endocrine consultant: via switchboard