Suspected or Confirmed Congenital Hyperinsulinism: Diagnosis and Management

Title: Paediatric **Suspected or Confirmed Congenital Hyperinsulinism: Diagnosis and Management**			
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Author/s:	Dr Sarah Kiff, Consultant in Paediatric Endocrinology and Diabetes Review group: Dr Louise Bath, Consultant in Paediatric Endocrinology and Diabetes Dr Harriet Miles, Consultant in Paediatric Endocrinology and Diabetes Dr Daniela Elleri, Consultant in Paediatric Endocrinology and Diabetes Dr James Boardman, Consultant Neonatologist Jenny Carson, Lead Clinical Pharmacist		
Executive Lead:	Sarah Kiff		
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Contents

1.0 Purpose

To provide guidance for all health care professionals at NHS Lothian Paediatric Services, caring for babies with suspected or confirmed congenital hyperinsulinism.

2.0 Scope

For use by health care professionals at NHS Lothian Paediatric Services, caring for babies with congenital hyperinsulinism, or presumed congenital hyperinsulinism. The guidance should only be used in conjunction with discussion with the paediatric endocrine team.

This guideline does not apply to neonates < 48 hours of age unless specifically approved by the paediatric endocrine team. Guidance for this group is available separately.

This guideline does not apply to neonates with congenital hyperinsulinism cared for at the Simpsons Centre for Reproductive Health. Guidance for this group is available separately.

3.0 Definitions

Congenital hyperinsulinism is a condition present at birth, where inappropriately increased production of insulin results in hypoglycaemia.

4.0 Roles and responsibilities

All staff caring for a patient with congenital hyperinsulinism should follow the guideline.

5.0 Main content

Diagnosis

Diagnosis of congenital hyperinsulinism is made by the presence of:

- Non-ketotic hypoglycaemia
- Inappropriately detectable levels of insulin/c-peptide in the context of hypoglycaemia
- Glucose infusion rate of > 8 mg/kg/min to maintain normoglycaemia

$$\text{IV glucose infusion rate (mg/kg/min)} = \frac{\text{Rate of IV fluids (mL/h)} \times \text{concentration of glucose (\%)}}{6 \times \text{weight (kg)}}$$

Neonates who fulfil the above criteria of ongoing hyperinsulinism by day 5 of life should have their management discussed with the paediatric endocrine team. Earlier discussion may be required in some cases of hyperinsulinism.

Management

The following management guidelines should be followed for babies with confirmed hyperinsulinism requiring medical management.

Blood glucose testing

- Neonates with hyperinsulinism do not produce ketones as an alternative substrate and therefore are more at risk of neurological damage if blood glucose (BG) is not maintained.
- BG should therefore be maintained ≥ 3.5 mmol/L.
- Please provide all babies with a soft-touch lancet to cause minimal trauma with BG testing (available with point of care blood glucose meters).
- Ensure the foot is warm before obtaining the blood sample.
- Blood glucose should be measured on a point of care testing monitor once a diagnosis of hyperinsulinism has been made, to allow smaller size blood sampling and consistency for home monitoring.
- Whilst IV fluids are being actively weaned, blood glucose testing should be carried out 1-2 hourly.

Hypoglycaemia definition in hyperinsulinism:

Action is required if BG is < 3.5 mmol/L.

- If BG is 3.0-3.4 mmol/L, repeat BG again within 10 minutes, and if remains < 3.5 mmol/L, treat.

- If BG < 3 mmol/L, treat immediately

Hypoglycaemia treatment in hospital:

Due to the risk of rebound hypoglycaemia with more aggressive treatment, hypoglycaemia management in hyperinsulinism is individualised as described below.

Give:

EITHER: 1/3 tube (approx 5mL) of glucose 40% gel (approx 3g glucose) into mouth/cheek if the baby is able to be fed orally, followed by a small feed

OR: 1mL/kg IV 10% glucose bolus, if oral treatment is not possible, or two oral treatments have failed to resolve hypoglycaemia.

Repeat BG 10 minutes after hypoglycaemia treatment has been given. If the BG remains below 3.5 mmol/L, repeat treatment as above.

Following treatment of hypoglycaemia, consider stepping back on feed or fluid weaning plan to the point that glucose stability was last achieved (e.g. increasing IV glucose load or increasing frequency of enteral feeds).

Weaning of IV fluids in neonates with hyperinsulinism

Too rapid weaning of IV fluids can result in hypoglycaemia and inappropriate escalation of treatment. Aim to wean IV fluids every 4 hours, using the following schedule:

Blood glucose	Change to IV fluids	Comments
≥ 4 mmol/L	Reduce rate of IV glucose infusion by 1 mg/kg/min and increase milk feed by corresponding volume	Maintain total fluid intake (IV plus enteral) at 120 mL/kg/day maximum during weaning.
3.5 - 3.9 mmol/L	No action. Do not wean, until BG is ≥ 4 mmol/L	If weaning has not been possible over 24h, discuss management with endocrine team.
< 3.5 mmol/L	Treat hypoglycaemia (see above) and step back one step on IV fluid weaning plan.	If weaning has not been possible over 24h, discuss management with endocrine team.

Treatment of congenital hyperinsulinism

Congenital hyperinsulinism may either:

- be transient and resolve within a few days with no treatment other than IV glucose
- be adequately treated with feed manipulation
- require drug treatment if severe or persistent

Feeds

Options for supplementing calorie (and particularly carbohydrate) content of feeds, depending on the individual circumstances of the neonate, include:

- Fortification of breast milk for pre-term infants
- Supplementation of breast feeding with standard formula
- Use of high energy formula e.g. Infatrini or SMA High Energy (containing 10g carbs/100mL)
- Addition of vitajoule/maxijoule (glucose powder) to formula to total 10%, 12% or 14% carbohydrate as required.

Regular feeding volume should be maintained. This may necessitate use of an NG tube for top-up feeds. Diazoxide (a drug used to treat hyperinsulinism) 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, 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 be provided with high energy milk, rather than an increase in feed volume.

Drug treatment of congenital hyperinsulinism

Drug treatment for congenital hyperinsulinism should not be initiated without discussion with the paediatric endocrine team.

1. Diazoxide (see diazoxide monograph, appendix 1)

Preparation	Route	Starting dose	Maximum dose	Side effects
Diazoxide (proglycem or clinigem) 250mg/5mL (= 50mg/mL)	Oral	Give in 3 equal divided doses **Birth weight < 2kg:** 2mg/kg/day ie 0.67mg/kg 8 hourly **Birth weight 2.0 - 3.5kg**: 3mg/kg/day ie 1mg/kg 8 hourly **Birth weight > 3.5kg**: 5mg/kg/day ie 1.67mg/kg 8 hourly Dose should be rounded to the nearest 0.5mg (=0.01mL).	20 mg/kg/day (although rarely use >15mg/kg/day)	Fluid overload, pulmonary hypertension, hypertrichosis, hyperuricaemia, hypotension, leucopenia, thrombocytopenia

Normal cardiac anatomy should be confirmed by echocardiogram prior to starting diazoxide. Diazoxide should be given concurrently with diuretics. Chlorothiazide should be used first line, due to its synergistic effect on reducing insulin release.

Diazoxide dose should not be increased more frequently than every 48 hours, to allow full assessment of response. Dose escalation increments are usually around 2 mg/kg/day. If high dose diazoxide is required (> 10 mg/kg/day) chlorothiazide should be substituted for furosemide 1mg/kg twice a day and spironolactone 1mg/kg twice a day.

Before commencing diazoxide treatment, babies should be receiving a maximum of 130 ml/kg/day of fluid intake (IV fluids and feed total). An accurate fluid balance should be kept with daily weight and sodium/potassium measurement.

2. Chlorothiazide

Preparation	Route	Starting dose	Maximum dose	Side effects
Chlorothiazide 250mg/5mL (=50mg/mL)	Oral	Give in 2 divided doses 7mg/kg/day i.e. 3.5mg/kg 12 hourly	10 mg/kg/day	Hyponatraemia, hypokalaemia

3. Octreotide

Preparation	Route	Starting dose	Maximum dose	Side effects
Octreotide	- IV infusion - SC infusion - 6 hourly SC injection	5 micrograms/kg/day i.e. 1.25 micrograms/kg every 6 hours	40 micrograms/kg/day	Late onset necrotising enterocolitis Potential impact on growth Cholelithiasis

Obtain further guidance from pharmacy and endocrine team for drug preparation

4. Nifedipine

Preparation	Route	Starting dose	Maximum dose	Side effects
Will depend on clinical scenario	Oral	Give in 4 divided doses 400 micrograms/kg/day i.e. 100 micrograms/kg 6 hourly	800 micrograms /kg/day	Hypotension

There is limited evidence for the effect of nifedipine in the treatment of hyperinsulinism.

5. Glucagon

Preparation	Route	Starting dose	Maximum dose	Side effects
Glucagon 1000 micrograms/mL once reconstituted	- IV infusion - SC infusion	5 micrograms/kg/hr	10 micrograms/kg/hr	Nausea, vomiting, increases myocardial contractility

For subcutaneous infusion, further dilute reconstituted 1000micrograms/mL solution with sodium chloride 0.9% to give an infusion rate of 0.1-1mL/hour.

Change syringe of glucagon every 12 hours.

Glucagon 1mg can also be given IM or IV for emergency treatment of hypoglycaemia,but must be followed up with a continuous glucagon infusion or IV glucose due to the risk of rebound hypoglycaemia.

Genetic testing

Genetic testing for cause of hyperinsulinism is indicated if:

- Examination suggests a possible syndromic diagnosis (e.g. Beckwith-Wiedemann, Kabuki, Turner)
- There is a family history of congenital hyperinsulinism
- The baby does not respond to diazoxide treatment alone

Blood samples should be obtained from the baby and both parents and sent with the consent form from Exeter Genetics lab to the Genetics Department at the Western General Hospital for forwarding. See website for sample details:

https://www.exeterlaboratory.com/genetics/hyperinsulinism/

Please include the email address of the lead Endocrine Consultant, so results can be communicated rapidly.

Discharge planning

Discharge criteria:

Babies with congenital hyperinsulinism can be discharged when:

- Blood glucose is maintained ≥ 3.5 mmol/L on current feed and medication regimen for ≥ 24 hours
- A controlled fast has been carried out (see below)
- Parents have been trained in BG testing
- Parents have been provided with a feed and blood glucose diary (Appendix 2)
- A written hypoglycaemia management plan has been agreed with the parents (Appendix 3)
- Ongoing supplies of BG test strips, lancets and glucose 40% gel have been requested from the GP (see below)
- Follow-up has been arranged in the endocrine outpatient clinic
- A trak alert has been added (see text below). This text should also be added to the baby's neonatal discharge letter.

Trak alert:
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 ≥ 3.5 mmol/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.

Fast prior to discharge:

All babies with congenital hyperinsulinism (whether on drug treatment or not) should have a controlled fast prior to discharge to ensure their hyperinsulinism is adequately managed and they are not at high risk of hypoglycaemia if there is an unexpected delay to a feed.

- 6 hour fast for babies on 4 hourly feeds
- 4 hour fast for babies only able to tolerate 3 hourly feeds

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 < 3 mmol/L at any time, the fast should be ended and hypoglycaemia treated. If the BG is 3.0-3.4 mmol/L, repeat again in 10 minutes to see if there is a spontaneous increase in BG. If after 10 minutes the BG remains below 3.5 mmol/L, end the fast and treat the hypoglycaemia.

If a baby develops hypoglycaemia during a controlled fast, their hyperinsulinism treatment requires adjustment prior to the controlled fast being repeated at least 24 hours later.

Discharge prescription:

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

- AccuChek Performa Nano Test strips (4 boxes)
- AccuChek fastclix lancets (204)
- Glucose 40% gel (eg Glucogel ®) 3x25gs triple pack
- Medication as relevant

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.

Following discharge:

- The baby should continue to be fed with the same frequency and volume as pre-discharge (e.g. 130 mL/kg/day 4 hourly over 24h period).
- BG testing should be carried out prior to every feed.
- See appendix 1 for glucose and feed diary to be given to the family.
- The written hypoglycaemia plan should be followed if BG is < 3.5 mmol/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.

Contact details:

For communication about inpatients between neonatal and endocrine teams

Neonatal duty room	Extension	22598
Neonatal registrar	Page	1610
Endocrine registrar	Page	9187

Associated materials

Appendix 1. Diazoxide monograph
Appendix 2. Glucose and feed diary
Appendix 3. Hypoglycaemia home management plan

6.0 Evidence base

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

7.0 Stakeholder consultation

Reviewed by Paediatric and Neonatal Drugs and Therapeutics committee

8.0 Monitoring and review

Guidelines should be reviewed, as a minimum, every three years or sooner if required.