Ashford and St. Peter's Hospitals
NHS Foundation Trust

HYPOGLYCAEMIA: ASSESSMENT & MANAGEMENT (NON-DIABETIC)

Author: Dr David Lim

Supervisor: Dr Sonali D'Cruz, Dr Shailini Bahl

Contact details: davidlim@nhs.net

Guideline History		
Date	**Comments**	**Approved By**
18/01/21		Paediatric Consultants

SCOPE OF GUIDELINE

This guideline is intended for the use in the management of infants >48 hours old and children who do not have a diagnosis of diabetes or other established metabolic disorder.

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PAEDIATRIC DEPARTMENT

EMERGENCY MANAGEMENT OF HYPOGLYCAEMIA

A B C (as per APLS)

Check blood glucose on gas AND **bedside blood ketones**

Hypoglycaemia = BG <2.6mmol/L (age <6 months) or <3mmol/L (age ≥6months)

Insert cannula: Hypoglycaemia screen
Put urine bag to collect next urine passed

Do not delay correction of hypoglycaemia whilst awaiting confirmation of lab glucose or if samples difficult to obtain and child is acutely unwell

No acidosis (HCO_3 ≥18mmol/L) **and** Ketones ≥0.5mmol/L **and** otherwise well (not vomiting/ drowsy)

Acidosis (HCO_3 <18mmol/L) **or** Ketones <0.5mmol/L

Unwell / Drowsy / Vomiting

Younger child: Oral dextrogel ½ tube (5g glucose) for <6 months and 1 tube (10g) for ≥6 months; <u>followed by</u> milk feed/ snack of starchy carbohydrate

Older child: Glucojuice (10-20g glucose)/ equivalent 100-150ml fruit juice

Not tolerating feed

IV access?

No

IV bolus of 10% dextrose 2ml/kg

IM glucagon (<25kg – 0.5mg ≥25kg – 1.0mg)

Unwell/ Drowsy:
Follow up with IV/IO access

IV infusion of 10% dextrose/ 0.9% NaCl at maintenance rate (if neonate: 10% dextrose)

Recheck blood glucose at 10 minutes post IV bolus/ post IM glucagon/ post oral feed

BG <2.6mmol/L:

- Ensure IV/IO access
- Give further 2ml/kg IV bolus 10% dextrose
- If 2nd bolus needed or BGs remain low, continue IV fluids and consider increasing glucose infusion rate (GIR) by increasing fluid volume (by 10% intervals) or glucose concentration (N/B central access required for concentration >12.5%)
- Monitor BG at 10-minute intervals **<u>until stable at ≥3mmol/L</u>**, then at 1-hourly intervals (if blood ketones <0.5mmol/L, aim for BG ≥3.5mmol/L)
- High GIR (>8-10mg/kg/min) may suggest hyperinsulinism
- If adrenal insufficiency suspected, inform consultant on-call – IV hydrocortisone may be required (4mg/kg, max 100mg)
- Monitor U&Es regularly whilst on IV fluids
- Seek expert opinion if metabolic or endocrine cause suspected

BG ≥2.6mmol/L:

- Continue maintenance fluids if already started
- Monitor BG at least 1 hourly **<u>until stable at ≥3mmol/L</u>** (if blood ketones <0.5mmol/L, aim for BG ≥3.5mmo/L)
- Gradually re-introduce feeds
- Check pre-feed BGs
- If pre-feed BGs not maintained ≥3mmol/L on hourly feeds, start continuous NG feeds and consider IV fluids
- If on IV fluids monitor U&Es
- Wean frequency & volume of feeds as indicated

HYPOGLYCAEMIA SCREEN

- It is vital to confirm hypoglycaemia with formal laboratory analysis, and not rely on point-of-care testing devices and blood gas analysers which are less reliable at lower BG levels
- **The most important samples (marked ** below) that need to be taken at the time of hypoglycaemia are: glucose, insulin, cortisol, lactate, free fatty acids and beta-hydroxybutyrate**
- However treatment should **not** be delayed if samples are difficult to obtain
- Print the investigation labels by searching for "paediatric hypoglycaemia screen" under "order sets" on ICE
- There are readily available and labelled "HYPO PACK"s in the department with the following: Guthrie card, Blood bottles (3 Yellow, 2 or 3 Green, 1 Grey & 1 Purple), Gas tube, Urine pot
- Ideally collect a **minimum of 7ml of blood**
- Ensure ice (packs) are ready and the lab is informed of imminent arrival of the samples

Specimen	Test	Bottle
Should be taken prior to correction of glucose		
Bedside test	Glucose **	Glucometer
	Ketones **	Ketone meter
	Blood gas **	Gas
Laboratory blood test	Glucose **	Grey (Fluor Ox) >0.5ml
	Lactate **	
	Free fatty acids **	Yellow (SST) >1.5ml – **on ice, reach lab within 15 min**
	Beta-hydroxybutyrate **	
	Cortisol **	
	Insulin **	
	C-peptide	
	Growth hormone	Yellow (SST) >0.5ml
May be taken after episode		
Laboratory blood test	U&Es	Yellow (SST) >0.5ml
	LFTs	
	FBC	Purple (EDTA) >0.5ml
	Ammonia	Green (Li Hep) >0.5ml – **on ice, reach lab within 15 min**
	Plasma amino acids	Green (Li Hep) >2ml
	Blood spot acylcarnitine *or* Plasma acylcarnitine	Guthrie blood spots x2 (ensure Guthrie card in date) *or* Green (Li Hep) >0.5ml
First urine passed after episode		
Urine dipstick	Glucose	
	Ketones	
Laboratory urine test	Urine organic acids	Universal pot 5ml
	Urine reducing substances	
Consider: Blood – Alcohol, Paracetamol, Salicylate, CRP, Blood Culture; Urine –Toxicology screen, MCS, Neuroblastoma screen		

BACKGROUND

Hypoglycaemia refers to the inadequacy of circulating blood glucose (BG), and may be associated with clinical symptoms or be asymptomatic. Clinical hypoglycaemia is defined as 'a plasma glucose concentration low enough to cause symptoms and/or sign of impaired brain function'. This glucose concentration varies from one patient to another, depending on the availability of alternative fuels and previous blood glucose concentrations. Hypoglycaemia is therefore a spectrum, and the blood glucose concentration should be interpreted together with the clinical history and concentrations of counter-regulatory hormones and intermediate metabolites.

In the majority of healthy newborns, a drop in blood glucose is expected immediately after delivery, reaching the lowest levels within 1-2 hours after birth – this is physiologically normal, and simply reflects normal metabolic adaptation to extra-uterine life. Whilst feeding is being established, alternative fuels such as ketones, pyruvate and lactate are also used by the brain; as such the otherwise healthy low-risk newborn baby in the first 2-3 days of life is probably not at risk of hypoglycaemia-associated neuronal injury, unless low blood glucose levels are prolonged or recurrent. Normal feeding is usually sufficient to support these babies through this transition. (*Separate Neonatal guideline exists for hypoglycaemia management in babies on postnatal ward and NICU)*

Biochemical hypoglycaemia is generally accepted as a laboratory blood glucose measurement of <2.6mmol/L, at which prompt investigation and treatment is required regardless the presence of symptoms. Brain glucose utilisation becomes limited at approximate blood glucose values of 3.0-3.6mmol/L, below which neuroglycopenic symptoms are triggered. Therefore beyond the neonatal period and in older children a BG value of 3mmol/L is recommended as the lower limit for hypoglycaemia.

Ketone bodies (acetoacetate and beta-hydroxybutyrate) are produced by oxidation of free fatty acids and can be utilised as an alternative energy source. Free fatty acids are released during lipolysis in the fasting state when insulin levels are low. The presence or absence of ketones during hypoglycaemia is useful in considering the diagnosis and appropriate further investigations. **In the absence of blood ketones, a higher BG limit of 3.5mmol/L must be used.**

Prolonged or recurrent hypoglycaemia, especially when associated with signs or symptoms, can cause permanent neurological damage or death. Thus prompt recognition and treatment of hypoglycaemia are essential.

The different causes of hypoglycaemia are outlined in Appendix 1.

ASSESSMENT

The following list describes typical features of hypoglycaemia but bear in mind this list is not exhaustive and **a blood glucose should be checked in any child who is unwell**.

Young infant	Older child
• Pallor • Sweating • Jitteriness • Tachypnoea • Apnoea • Hypotonia • Feeding difficulties • Irritability • Abnormal cry • Convulsions	• Anxiety • Tremor • Palpitations • Weakness • Nausea and/or vomiting • Hunger • Abdominal pain • Headache • Visual disturbance • Convulsions • Confusion • Coma

The following list highlights some important features to elicit from the history and examination.

History	Examination
• Age • Feeding history • Birth history • Birth weight • Neonatal jaundice • Neonatal hypoglycaemia • Tolerance to fasting including timing of hypoglycaemic episode and its relationship to food (i.e. how long was the fasting episode) • Ability to cope with intercurrent illness • Drug ingestion (insulin, sulphonylureas, alcohol, beta-blockers, salicylates) • Family history including parental consanguinity and neonatal/ unexpected deaths	• Growth • Dysmorphism • Features of sepsis • Hepatomegaly • Encephalopathy • Optic atrophy, cataracts, nystagmus, failure to fix and follow • Appearance of external genitalia (micropenis) • Midline defects (cleft lip, cleft palate, bifid uvula) • Skin pigmentation (gums, scars, skin creases) • Hemihypertrophy, macroglossia, omphalocele

HYPOGLYCAEMIA RESULTS LOG *(print out for patient notes)*

Specimen	Result	Interpretation
URINE		
Glucose		
Ketones		Low: fatty acid oxidation defect, hyperinsulinaemia
MCS		UTI
Reducing substances		Presence of non-glucose reducing substances suggests galactossaemia, FDPase deficiency
Amino acids Organic acids		Specific amino or organic acid disorders
Toxicology		Poisoning
BLOOD		
Glucose		Hypoglycaemia = <2.6mmol/L (in <6m) / <3mmol/L (in ≥6m)
Ketone bodies (beta-hydroxybutyrate)		Low (<0.5mmol/L): fatty acid oxidation defect, hyperinsulinaemia >1mmol/L: suspect ketotic hypoglycaemia
Lactate		High: metabolic liver disease, prolonged convulsion, GSD, sepsis, fructose-1,6-biphosphatase deficiency
Gas		Metabolic acidosis: fatty acid oxidation defect, defects in ketogenesis, sepsis, GSD, organic acidaemia
Free fatty acids		Low: fatty acid oxidation defect High: Ketotic hypoglycaemia
Acylcarnitine/ carnitine		Fatty acid oxidation defect
Ammonia		High: fatty acid oxidation defect, organic acidaemia, hyperinsulinism, liver dysfunction, urea cycle defect
Cortisol		Low: adrenal insufficiency, CAH, ACTH deficiency, hypopituitarism
Insulin & C-peptide		Abnormal (hyperinsulinism) if present even at normal lab levels if BG<2.6; if high insulin but low C-peptide consider exogenous insulin administration
Growth hormone		Low: GH deficiency, pan-hypopituitarism
Amino acids		Specific amino acid disorders
U&Es		Adrenal disorders (low Na, high K); high urea if dehydration due to prolonged vomiting
LFTs		Sepsis, liver dysfunction, metabolic disorder
Toxicology		Alcohol, paracetamol, salicylates poisoning
Blood culture		Sepsis
OTHERS:		

OTHER POINTS

- Glucagon is rarely effective in metabolic patients – refer to specific metabolic guidelines (http://www.bimdg.org.uk/site/guidelines.asp)
- Note glucagon can cause hypokalaemia, hypocalcaemia, vomiting and rebound hypoglycaemia (monitor BGs carefully)
- The presence or absence of ketones during hypoglycaemia is key in considering the diagnosis and appropriate further investigations **(see Appendix 1)**
- Non-ketotic hypoglycaemia
    - If blood ketones low/ absent and glucose requirement (glucose infusion rate) is >8-10mg/kg/min consider the diagnosis of hyperinsulinism
    - Discuss management of hyperinsulinism with the endocrine team

$$\text{Glucose infusion rate (GIR) in mg/kg/min} = \frac{\%\ \text{dextrose solution} \times \text{ml/h}}{\text{Weight (kg)} \times 6}$$

- Ketotic hypoglycaemia
    - Idiopathic ketotic hypoglycaemia
        - Most common cause of hypoglycaemia in young non-diabetic children with or without metabolic disorders or chronic conditions
        - **However this is a diagnosis of exclusion**
        - Usually precipitated by intercurrent illness with reduced oral intake and/or vomiting
    - A range of metabolic disorders can also cause hypoglycaemia with ketosis
    - If a child with a known metabolic condition presents with ketotic hypoglycaemia, refer to specific management guidelines (http://www.bimdg.org.uk/site/guidelines.asp) – speak to the metabolic team early
    - It is recommended to prevent ketotic hypoglycaemia with an 'emergency regimen' of high carbohydrate and calorie drinks with soluble glucose polymer (e.g. Maxijul, SOS, Polycal) at times of reduced intake/ increased losses – liaise with dieticians
- If cortisol deficiency is suspected, the diagnosis is established by short synacthen test
- Fasting provocation tests
    - This test may be occasionally indicated to help establish a diagnosis, especially if no investigations were performed at the time of hypoglycaemia
    - This should **NOT** be done without consulting the endocrine or metabolic team – there is a separate protocol for this
    - It is important to exclude fatty acid oxidation defects, hyperinsulinism and adrenal insufficiency (assessed by short synacthen test) before performing a controlled fast

DISCHARGE PLANNING

Prior to discharge, ensure the following have been completed:

1. A cause for the hypoglycaemia must be known
2. A reasonable time between feeds (at least 4 hours) must be safely tolerated without blood glucose falling below **3mmol/L** (or 3.5mmol/L for non-ketotic hypoglycaemia)
3. It is advisable the case is discussed with a paediatric endocrinologist before discharge
4. Ensure dietician input to agree with a written home management plan for the family
5. Ensure the family know how to treat hypoglycaemia (e.g. glucose drinks, IM glucagon)
6. Obtain blood glucose meter and ensure the family have been trained in using it
7. Prescribe any necessary medications, specialised feeds, glucose strips and lancets
8. The discharge summary for the GP should include information about treatment and blood glucose meter supplies that will need to be provided on repeat prescription
9. Arrange outpatient follow-up (+/- open access) as necessary

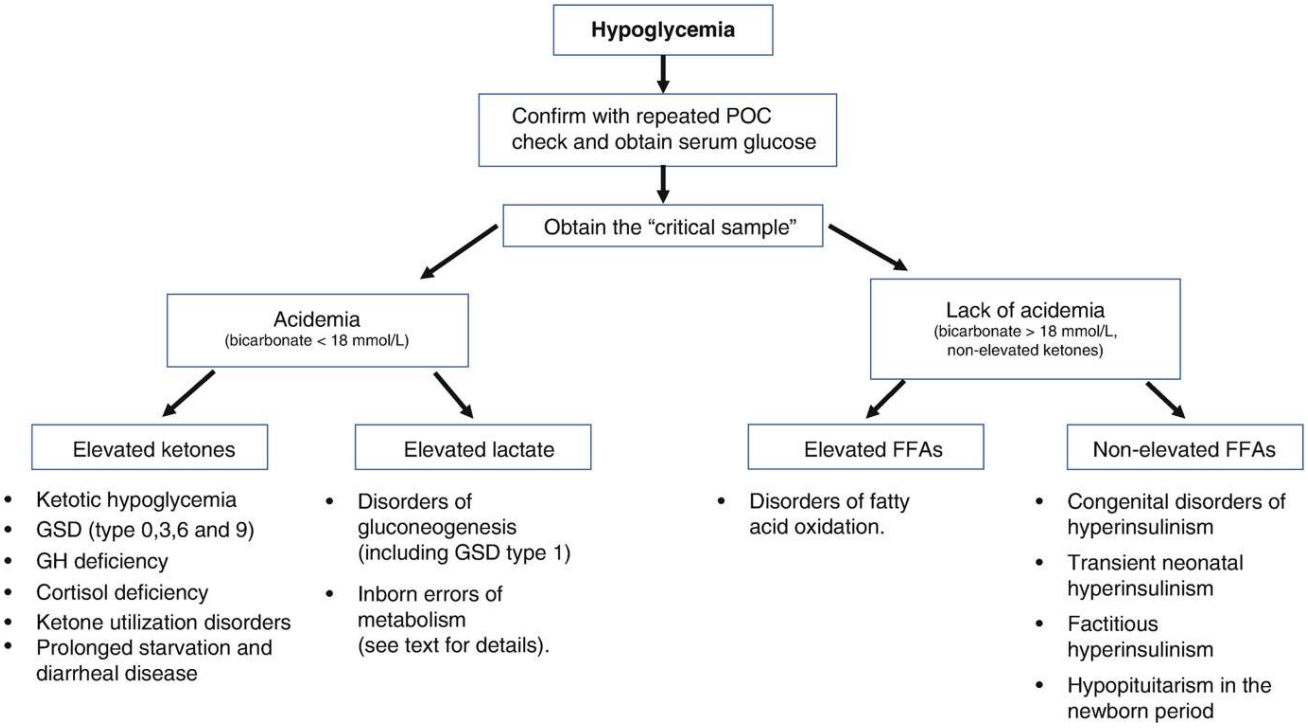
REFERENCES & SUPPORTING TRUST GUIDELINES

1. Ghosh A, et al. Recognition, assessment and management of hypoglycaemia in childhood. Arch Dis Child 2016; 101:575-580
2. Thornton PS, et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr. 2015 Aug;167(2):238-45
3. Leicester Children's Hospital (Jun 2018): Hypoglycaemia in Infants & Children (not for use in the NNU or for children diagnosed with diabetes)
4. Nottingham Children's Hospital (Jan 2020): Hypoglycaemia
5. PIER guidelines (May 2020): Investigations and Initial Management of Hypoglycaemia
6. Nyhan WL, Kölker S, Hoffmann GF. (2017) Work-Up of the Patient with Hypoglycemia. In: Hoffmann G, Zschocke J, Nyhan W (eds). Inherited Metabolic Diseases. Springer, Berlin, Heidelberg
7. St Peter's Hospital Neonatal Guidelines (Aug 2017): Prevention and Management of Hypoglycaemia in Newborns

APPENDIX 1: CAUSES OF HYPOGLYCAEMIA

Pituitary	**Pituitary:** Hypopituitarism Isolated ACTH deficiency Isolated GH deficiency **Adrenal:** Congenital adrenal hyperplasia Adrenal insufficiency **Pancreas:** Congenital hyperinsulinism (genetic mutations) Secondary hyperinsulinism (Infant of diabetic mother, IUGR, perinatal asphyxia, Rhesus disease, Beckwith-Wiedemann syndrome, idiopathic) **Thyroid:** Hypothyroidism (rare)
Metabolic	**Glycogen storage disorders:** GSD I, III, VI, IX Impaired glycogen synthesis (hepatic glycogen synthase deficiency) Impaired glycogenolysis Impaired gluconeogenesis **Fatty acid oxidation defects:** Medium chain acyl-coA dehydrogenase deficiency (MCADD) Long/ Short chain acyl-coA dehydrogenase deficiency Multiple acyl-coA dehydrogenase deficiency Carnitine deficiency Carnitine palmitoyl transferase deficiency **Carbohydrate disorders:** Defects in glucose transporters (GLUT2) Defects in gluconeogenesis (fructose-1,6-biphosphatase (FDPase) deficiency) Galactossaemia Hereditary fructose intolerance **Amino acid disorders:** Tyrosinaemia Maple Syrup Urine Disease **Organic acidaemia/aciduria:** Methylmalonic acidaemia Propionic acidaemia
Drug-induced	Insulin (exogenous) Alcohol Sulphonylurea Beta-blockers Salicylates
Miscellaneous	Liver disease Congenital heart disease Infections (gastroenteritis, sepsis, malaria)
Idiopathic ketotic hypoglycaemia	Commonest cause of hypoglycaemia after neonatal period

APPENDIX 2: ALOGRITHM FOR EVALUATION OF HYPOGLYCAEMIA



5. Guideline Governance

a. Scope

This guideline in relevant to all staff caring for all children from 0-18 years old across the emergency department, inpatient ward and outpatient department.

b. Purpose

i. This guideline aims to facilitate a common approach to the management of children. At times deviation from the guideline may be necessary, this should be documented and is the responsibility of the attending consultant.

ii. This guideline is subject to regular review to ensure ongoing evidence based practice.

c. Duties and Responsibilities

What is expected from the health care professionals using this guideline to look after children age 0-18 years old.

d. Approval and Ratification

This guideline will be approved and ratified by the Paediatric Guidelines Group.

e. Dissemination and Implementation

i. This guideline will be uploaded to the trust intranet 'Paediatric Guidelines' page and thus available for common use.
ii. This guideline will be shared as part of ongoing education within the Paediatric Department for both medical and nursing staff.
iii. All members of staff are invited to attend and give comments on the guideline as part of the ratification process.

f. Review and Revision Arrangements

a. This policy will be reviewed on a 3 yearly basis.
b. If new information comes to light prior to the review date, an earlier review will be prompted.
c. Amendments to the document shall be clearly marked on the document control sheet and the updated version uploaded to the intranet. Minor amendments will be ratified through the Paediatric Guidelines Group. A minor amendment would consist of no major change in process, and includes but is not limited to, amendments to documents within the appendices.

g. Equality Impact Assessment

Background • Who was involved in the Equality Impact Assessment
Author of guideline and Paediatric guidelines chair
Methodology • A brief account of how the likely effects of the policy was assessed (to include race and ethnic origin, disability, gender, culture, religion or belief, sexual orientation, age) • The data sources and any other information used • The consultation that was carried out (who, why and how?)
All patient and staff groups were considered
Key Findings • Describe the results of the assessment • Identify if there is adverse or a potentially adverse impacts for any equalities groups
No evidence of discrimination
Conclusion • Provide a summary of the overall conclusions
Guideline presented to consultant body at paediatric guidelines meeting and given consensus for use
Recommendations • State recommended changes to the proposed policy as a result of the impact assessment • Where it has not been possible to amend the policy, provide the detail of any actions that have been identified • Describe the plans for reviewing the assessment
Guideline to be shared, and next review will take place within specified timeframe

h. Document Checklist

To be completed (electronically) and attached to any document which guides practice when submitted to the appropriate committee for approval or ratification.

Title of the document: Hypoglycaemia: Assessment and Management (Non-diabetic)

Policy (document) Author: Dr David Lim

Executive Director:

		Yes/No/ Unsure/NA	Comments
1.	**Title**		
	Is the title clear and unambiguous?	**Y**	
	Is it clear whether the document is a guideline, policy, protocol or standard?	**Y**	
2.	**Scope/Purpose**		
	Is the target population clear and unambiguous?	**Y**	
	Is the purpose of the document clear?	**Y**	
	Are the intended outcomes described?	**Y**	
	Are the statements clear and unambiguous?	**Y**	
3.	**Development Process**		
	Is there evidence of engagement with stakeholders and users?	**Y**	
	Who was engaged in a review of the document (list committees/ individuals)?	**Y**	**Consultant body**
	Has the policy template been followed (i.e. is the format correct)?	**Y**	
4.	**Evidence Base**		
	Is the type of evidence to support the document identified explicitly?	**Y**	
	Are local/organisational supporting documents referenced?	**Y**	
5.	**Approval**		
	Does the document identify which committee/group will approve/ratify it?	**Y**	
	If appropriate, have the joint human resources/staff side committee (or equivalent) approved the document?	**N/A**	
6.	**Dissemination and Implementation**		
	Is there an outline/plan to identify how this will be done?	**Y**	
	Does the plan include the necessary training/support to ensure compliance?	**Y**	
7.	**Process for Monitoring Compliance**		
	Are there measurable standards or KPIs to support monitoring compliance of the document?	**Y**	
8.	**Review Date**		
	Is the review date identified and is this acceptable?	**Y**	
9.	**Overall Responsibility for the Document**		

		Yes/No/ Unsure/NA	**Comments**
	Is it clear who will be responsible for coordinating the dissemination, implementation and review of the documentation?	**Y**	
10.	**Equality Impact Assessment (EIA)**		
	Has a suitable EIA been completed?	Y	

Committee Approval (Neonatal Guidelines Committee)			
If the committee is happy to approve this document, please complete the section below, date it and return it to the Policy (document) Owner			
Name of Chair	**Dr Claire Mitchell**	**Date**	**30.03.2021**
Ratification by Management Executive (if appropriate)			
If the Management Executive is happy to ratify this document, please complete the date of ratification below and advise the Policy (document) Owner			
Date: n/a			