CARE OF THE NEWBORN WITH HYPOGLYCAEMIA AND HYPERGLYCAEMIA

Background

Definition of hypoglycaemia

- Birth to 72 hours of life (term) or 96 hours of life (preterm): < 2.6 mmol/l (plasma)
- > 72 hours of life (term) or 96 hours (preterm) of life: < 3.4 mmol/l (plasma)

Aetiology

- Low glycogen stores or early depletion of the glycogen stores
- Impaired gluconeogenesis
- Hyperinsulinism or lack of counter insulinaemic hormones solely or in combination

Complications

- Plasma Glucose < 1.1 mmol/l for > 2 h cause cerebral neuronal necrosis in primates.
- Plasma Glucose < 2.6 mmol/l on > 5 single days/occasions or for > 48 h is associated with neurodevelopmental and physical growth deficits.

Prevention

- Maintenance of normal body temperature
- Early feeding within first 3 hours of life
- Prompt management of other clinical concerns

Risk Factors for Hypoglycaemia

Maternal

- Diagnosed pre-eclampsia/eclampsia or pregnancy induced or essential hypertension
- Diabetic mother (any diabetes type)
- Earlier pregnancy with a macrosomic infant (>91st centile)
- Treatment with beta adrenergic tocolytics within 7 days of delivery
- Treatment with tricyclic antidepressants or serotonin-norepinephrine reuptake inhibitors
- Treatment with beta blockers
- Substance Misuse
- Maternal glucose infusion

Neonatal

- Cord pH < 7.1
- < 37 weeks gestation
- Small for gestational age (< 9th centile) or Intrauterine Growth Restriction
- Macrosomia plus abnormal HbA1c or GTT in mother (OR > 91st percentile alone if HbA1C or GTT not done)
- Discordant twin (weight discordance > 10%)
- Hypothermia
- Infants with respiratory distress
- Delayed Feeding (e.g. feeding intolerance, lack of milk supply)
- Plethoric infant/ hyperviscosity, but also severe haemolytic disease
- Endocrine disorders: (e.g. congenital adrenal hyperplasia, adrenal insufficiency, growth hormone deficiency, pituitary disorders etc.)
- Inborn errors of metabolism: (e.g. maple syrup urine disease, organic acidaemias, disorders of carbohydrate metabolism, mitochondrial disorder, disorders of fatty acid oxidation)
- Infections (i.e. babies on IV antibiotics)
- Hypoxic-ischaemic encephalopathy or CPR at birth
- Known genetic conditions, e.g. Beckwith-Wiedemann
- Symptoms of neonatal abstinence syndrome (this can mask symptoms of hypoglycaemia)

MONITOR NEONATES WITH ANY RISK FACTOR ON THE HYPOGLYCAEMIA PATHWAY

Signs and Symptoms of Hypoglycaemia

- CNS: Irritability, jitteriness, lethargy and stupor, tremor, seizures, hypotonia
- Other: Hypothermia, apnoea, tachypnoea, poor feeding, dry nappies

MEASURE BLOOD GLUCOSE IMMEDIATELY IF HYPOGLYCAEMIA IS SUSPECTED

Measurement and Diagnosis of Hypoglycaemia

- Point-of-Care (hand-held or blood gas machine) devices are used for routine assessment of blood sugar.
- At RSCH and PRH a blood gas machine is available on TMBU and SCBU for borderline Glucose results (needs 35 microliter of blood in a capillary tube).
- Glucometer (incl. gas machine) readings are based on whole blood; hence they tend to underestimate Glucose concentrations, especially when < 2.6 mmol/l.
- Always aim to perform a plasma blood Glucose (venous sample) immediately, if the glucometer or gas machine reading is < 2.6 mmol/l (< 3.4 mmol/l).
- Be aware that raised haematocrit can impact blood glucose measurements

Investigations for Persistent Hypoglycaemia

- Glucose requirements > 8 mg/kg/min are suggestive, > 10 - 12 mg/kg/min proof, of an underlying disorder of Glucose homeostasis.
- Investigations are indicated when there is recurrent hypoglycaemia despite a Glucose intake of > 10 mg/kg/min any point in time or > 8 mg/kg/min from 72 h (96 h for preterm infants) of life onwards.
- Investigations for hypoglycaemia should be carried out while the patient is hypoglycaemic (see definitions), ideally < 2.6 mmol/l at any time. The lab can process samples with blood sugar <3.
- In the case of profound hypoglycaemia (< 1.1 mmol/l) or prolonged/repetitive hypoglycaemia despite adequate substrate administration take the following basic diagnostic specimens during a hypoglycaemic episode (during normoglycaemia many disorders can be missed):
    - Blood: FBC, plasma Glucose, Na, K, Ca, Mg, creatinine, CRP, LFT, TFT, blood gas, lactate, free-fatty acids, amino-acids, insulin/C-Peptide, growth hormone, cortisol, ammonia, ketone bodies, acylcarnitines
    - Insulin and C-peptide are processed at Guildford and run twice weekly. There is often a delay sending and approving the results. Calling the lab directly can speed things up. Short code for the hospital is *8522 and the lab extension is 4696.
    - Urine: ketones, organic acids
    - CSF: cell count, protein, Glucose in symptomatic hypoglycaemias; note: glut-1 defect can have normal plasma Glucose, but decreased CSF Glucose (CSF/plasma ratio < 0.35)
    - Genetics: Term babies with unknown cause for prolonged or profound hypoglycaemia, neonates with features suggestive of a syndrome or who are macrosomic. Does not need to be sent as part of the initial investigations for IUGR neonates

Blood bottles correct at time of writing – please check pathology website as this can change

Test	Pathology bottle	Blood (ml)	Special requirement
Glucose, Lactate	Grey top, fluoride oxalate	0.5	

Ammonia	Purple top, EDTA	0.5	Send sample on ice to lab immediately and inform biochemistry
Ketone bodies (3-hydroxybutyrate)	Green top, lithium heparin	0.5	Send sample to lab immediately (to be analysed within 30 minutes) and inform biochemistry
Amino acids	Green top, heparin preservative	0.5	
Insulin / C-peptide	Yellow top, clotted sample	0.5	On ice to lab immediately
Free fatty acids	Yellow top, clotted sample	0.5	
Cortisol, Growth hormone	Green top, lithium heparin	0.5	
Acylcarnitines	Green top, lithium heparin	0.5	Guthrie card accepted but plasma sample preferred
Genetics	Purple top, EDTA	1 - 2	Exeter lab form: http://www.exeterlaboratory.com/genetics/hyperinsulinism/

Diagnosis

Differential diagnostic approach

System of disorder	Blood gas	Lactate	Free fatty acids	Urine ketones
Endocrine	Normal	Normal	Normal - decreased	Not increased
Carbohydrate metabolism	Metabolic acidosis	Increased	Normal – (increased)	Normal – (increased)
Amino acid metabolism	Variable	Variable	Increased	Increased
Fatty acid metabolism	Variable	Increased	Increased	Not increased

Interpretation of hypoglycaemia investigations indicative of congenital hyperinsulinism

- Glucose requirements should be >8-12 mg/kg/minute (see comments above)
- Insulin has a short half-life and can be undetectable (<18 pmol/L) so should be interpreted along with a C-peptide level
- Hyperinsulinism can be diagnosed with a detectable insulin level ≥11pmol/L during a hypoglycaemic episode or a raised C-peptide level of C-peptide 94 – 300 pmol/l during a hypoglylcaemic episode. C-peptide is considered appropriately supressed if < 94 pmol/l during hypoglycaemia. Abnormal results should be discussed with the endocrine team
- Decreased free fatty acids (FFA) and normal ketone levels (B-hydroxybutyrate)

General Management of the At-Risk and Hypoglycaemic Newborn

- **Follow algorithm**
  - Monitoring can be stopped after 12 hours in newborns of diabetic mothers and large for gestational age newborns, all other newborns require monitoring for at least 24 hours
  - Never give a bolus injection of Glucose alone, it must be followed by a continuous Glucose infusion +/- milk feeds (risk of rebound hypoglycaemia).
  - Never give more than a 12.5% Glucose infusion into a peripheral vein (extravasation injury).
  - We should not give more than 20 mg/kg/min in any line, including central line – if needing more glucose than this progress to glucagon infusion / hydrocortisone (see Neonatal Drug Formulary).

- In a symptomatic newborn or a newborn with a hypoglycaemia < 1.1 mmo/l where IV access cannot be gained give Glucagon 0.1 - 0.2 mg/kg IM followed by hydrocortisone 5 - 10 mg/kg IM if still no improvement. See Neonatal Drug Formulary for details.
- Any sudden interruption of intravenous Glucose may result in profound hypoglycaemia in at risk newborns. A tissued IV cannula is an emergency and must be urgently resited.
- Do not discharge babies into community until they are at least 24 hours, maintaining their blood Glucose level and feeding well.

If a hypoglycaemia screen has been sent then the results must either be reviewed before discharge or if baby is improved and discharge planned before results are available a 6 hour fast must be performed.

- **Weaning from high Glucose concentrations and Glucagon**
  - Once Glucose concentrations have stabilised (at least 2x consecutive sugars > 2.5 mmol/l if <72 hours or > 3.3 mmol/l if >72 hours old), start weaning Glucose infusion.
  - If Glucose concentrations > 10%, reduce concentration every 12 hours before weaning volume of infusion (e.g. 20% → 15% → 12.5%).
  - Wean volume of infusion by 15 - 20 ml/kg/day (1.0 - 1.4 mg/kg/min) every 6 - 12 hours.
  - Once on 10% oral feeds may be increased overlapping with the iv fluids by increasing oral feeds as per Enteral and Parenteral Nutrition Guidance e.g. in term newborns fed 3 - 4 hrly reduce IV Glucose 1ml/h and increase feeds to give same volume i.e. 2 ml if feeding 2 hrly, 3 ml if feeding 3 hrly and 4 ml if feeding 4 hrly
  - Adjust this every other feed once blood Glucose maintained at > 2.5 mmol/l (> 3.3 mmol/l if >72 hours old) pre-feed. Do not adjust feeds faster than this even if blood Glucose stable.
  - If blood Glucose drops < 2.6 mmol/l (< 3.4 mmol/l for babies over 72 hours) at any point in weaning regime, go back to the previous feeding regime where blood Glucose was stable.
  - On full oral feeds Glucagon infusion should be reduced very slowly as per Neonatal Drug Formulary.

Management of Neonates with Congenital Hyperinsulinism

Step 1

- Discuss results with Dr Ismail (Paediatric Endocrinologist) to confirm diagnosis
- Ensure central access is in place for infusion of Glucose with concentration > 12.5%
- Provide and document Glucose requirement to maintain a stable blood Glucose > 2.5 if < 72 h (96 hours for preterms) or > 3.3 mmol/l if > 72 h (96 h) old. Once a diagnosis of hyperinsulinism is reached threshold changes to >3.8 mmol/l.
- Consider glucagon infusion while awaiting to confirm diagnosis and consider Diazoxide (Neonatal Formulary)
- Restrict total fluid volume to 120 ml/kg/day 24 hours prior to Diazoxide use
- Monitor blood Glucose hourly until normal blood Glucose values reached, then increase intervals individually according to results, but at least 4 hourly until investigations and management completed
- While awaiting hypoglycaemia screen results the neonate can be on trophic feeds

Step 2

- Ideally commence Diazoxide only once confirmed hyperinsulinism and after consultation with Dr Ismail (Paediatric Endocrinologist)
- Change blood Glucose target to 3.9 mmol/l
- Restrict to 120 ml/kg/day for 24 hours due to risk of fluid retention and heart failure before starting Diazoxide. If the neonate has a cardiac problem, discuss with cardiologist prior to commencing Diazoxide
- Initial dose Diazoxide (see Neonatal Formulary); the initial dose may need to be individualised to the patient and therefore should be discussed with Dr Ismail (Paediatric Endocrinologist)

- Commence Chlorothiazide concurrently (see Neonatal Formulary)

Step 3

- Can commence weaning of Glucose infusion once on Diazoxide for 24 hours and maintaining blood Glucose as indicated above.
- Wean Glucose infusion slowly as indicated above, as a sudden drop in Glucose concentration may cause a rebound hypoglycaemia and give a false impression of unresponsiveness to Diazoxide.
- Feeds can be commenced, while still maintaining an overall restricted fluid volume of 120 ml/kg/day.
- Discuss with the dietician and parents re. commencement of Infatrini feeds to ensure adequate growth and commence feeds as per Enteral and Parenteral Nutrition Guideline.
- Once on full enteral feeds consider reducing frequency of monitoring to pre-feed (once 3 - 4 hrly feeds).

Step 4

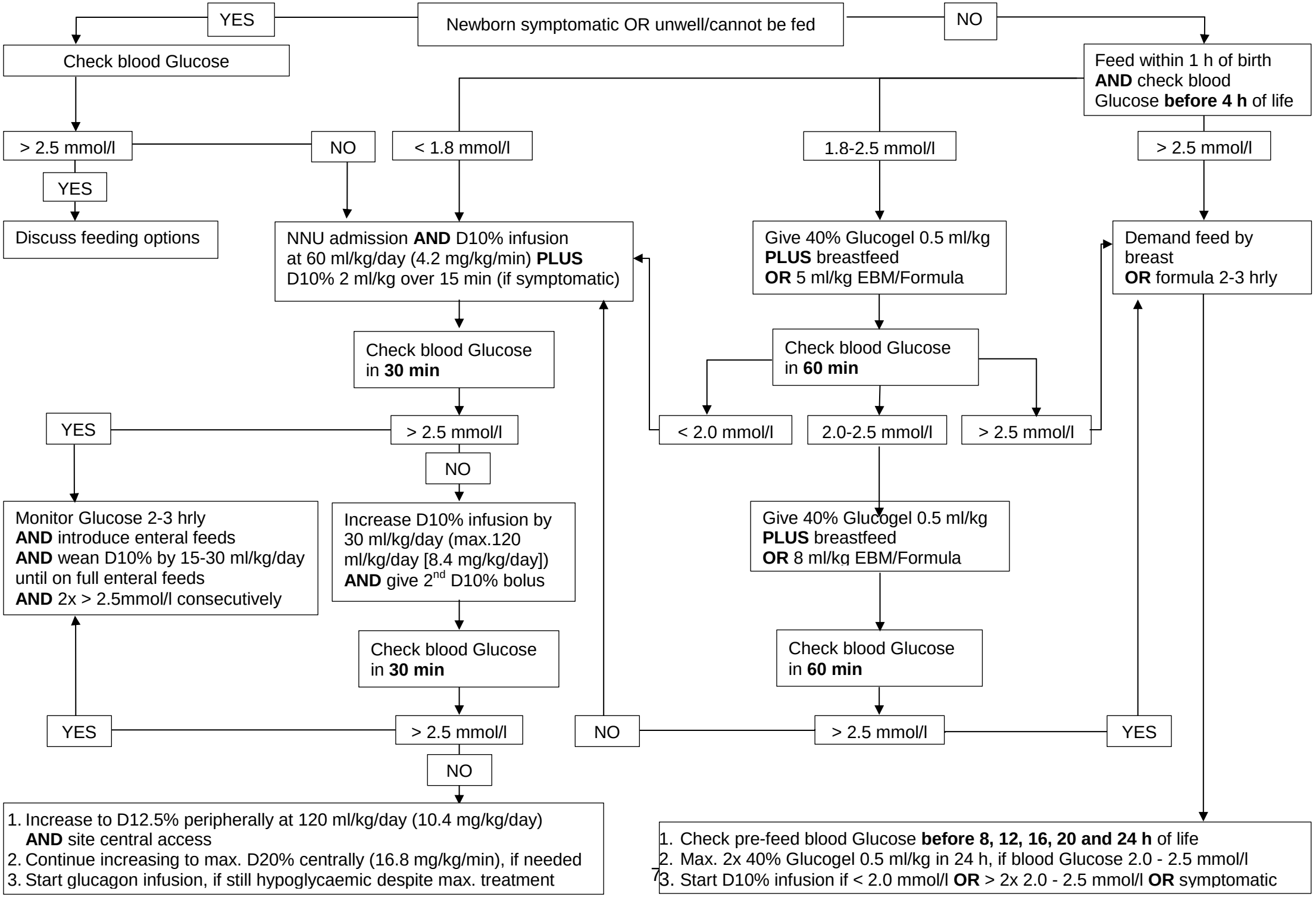
- Perform fast test prior to discharge when the infant is on full enteral feeds and has a blood Glucose maintained > 3.8 mmol/l. The fast should be carried out when central access is still in situ. This is to ensure the infant is safe to be discharged on the current dose of Diazoxide and can therefore tolerate a fast without hypoketotic hypoglycaemia and risk of brain injury:
  - Term and over 3 kg birthweight: 6 hour fast on Diazoxide and Chlorothiazide medication
  - Preterm/IUGR: 4 - 5 hour fast on Diazoxide and Chlorothiazide medication
  - Aim for blood Glucose > 3.8 mmol/l and monitor this hourly during fast. If < 3.9 mmol/l end the fast and feed the infant.
  - Take blood tests for Glucose, Insulin, fatty acids, and ketones prior to fast and at end of fast. This should be processed even if glucose normal so please call lab to arrange before sending.
  - If the patient does not tolerate the fast on their current dose of Diazoxide, this will need to be discussed with Dr Ismail (Paediatric Endocrinologist). The fast will need to be repeated to ensure they maintain their blood Glucose > 3.8 mmol/l on their planned discharge dose of Diazoxide.

Discharge planning

- Once the neonate has tolerated fast without hypoglycaemia they can be considered for discharge with the following written advice and medication for parents:
  - Test blood Glucose before a feed 3 - 4 times per day or when there is suspicion of hypoglycaemia or inter-current illness:
    - If blood Glucose < 3.9 mmol/l give feed and recheck in 15 minutes after feed
    - If blood Glucose still < 3.9 mmol/l, give Glucogel and attend Children's A & E
    - If blood Glucose < 3.9 mmol/l and unconscious call ambulance and Glucagon to be given by parents
    - If not tolerating feeds, but blood Glucose > 3.8 mmol/l, commence sips of Maxijul.
    - If not tolerating medication with inter-current illness and vomiting, test blood Glucose as above and consider attending Children's A & E
- Give a second dose of Diazoxide in a well infant with a vomit within 20 minutes of Diazoxide dose being given
- TTO Medication:
  - Diazoxide, Chlorothiazide, Glucogel, Maxijul sachets, Glucose meter and test strips, Glucagon

- Book clinic follow-up with Dr Ismail (Paediatric Endocrinologist) with a referral letter ideally for 2 months.
- Follow up in neonatal clinic until seen in Endocrine clinic.

Management of Newborn at Risk of Hypoglycaemia/Transient Hypoglycaemia



Background Hyperglycaemia

Definition of hyperglycaemia

- From Birth: > 8 mmol/l (operational threshold > 10 mmol/l) in plasma

Aetiology

- Multifactorial, in general associated with a clinical condition rather than a specific disorder of glucose metabolism
- Most common cause is high exogenous glucose infusion rates in preterm infants who are already at risk for hyperglycaemia due to decreased ability to suppress endogenous glucose production, decreased insulin response to glucose, and limited glycogen and fat stores
- A rare cause is neonatal diabetes mellitus (three different types: transient neonatal diabetes transient due to mutations of sulfonylurea receptors in > 50%, remits spontaneously in 6 months; permanent neonatal diabetes due to mutations in the genes encoding the subunit of the ATP-sensitive potassium channel most commonly; syndromic neonatal diabetes associated with syndromes like Wolfram syndrome, IPEX syndrome)

Complications

- Significantly associated increased morbidity including dehydration and electrolyte imbalance, bronchopulmonary disease, impaired immunity and increased risk of sepsis, any-grade intraventricular haemorrhage and any-stage retinopathy of prematurity in very preterm infants
- Glucose levels >10 mmol/l and longer duration of hyperglycaemia associated with increased odds of mortality
- Insulin infusion increases the risks of hypokalaemia and hypoglycaemia

Prevention

- Early enteral feeding
- Target optimal and physiologic glucose infusion rate
- Early supplementation of amino acids in TPN, leads to increase in insulin secretion
- Limit IV lipid infusion during hyperglycaemia
- Reduce/stop catecholamine infusions and glucocorticoid treatments as soon as clinically possible
- Prompt management of other clinical concerns

Risk Factors for Hyperglycaemia

- Risk increases with prematurity, growth restriction and the severity of the accompanying illness

Signs and Symptoms of Hyperglycaemia

- Generally in first week of life, usually resolves over two to three but can last up to ten days
- No specific findings related to hyperglycaemia

Diagnosis

- Repeated glucose measurements based on definition above
- Urine glucose 2+ or higher suggests osmotic diuresis
- Monitor for electrolyte disturbances and rule out sepsis
- Hyperglycaemia persisting at low glucose infusion rate (4 mg/kg/min) may indicate relative insulin deficiency or insulin resistance – check insulin and C-peptide

Management

1. Calculate glucose infusion rate in mg/kg/min
2. Reduce glucose intake slowly if > 8 mg/kg/min until reaching 4 - 6 mg/kg/min
3. Rule out other causes, e.g. sepsis, medications, if persistent hyperglycaemia despite glucose intake between 4 - 6 mg/kg/min

4. Start insulin independently through a dedicated IV line as per Neonatal Formulary and Sliding Scale
5. Correct electrolyte imbalances