Clinical Guidance

Paediatric Critical Care: Metabolic Disorders

Summary

This guideline is for staff regarding the management of inborn errors of metabolism. It discusses treatment, differential diagnosis as well as addressing CVVH and necessary investigations when caring for these children.

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This clinical guideline has been produced by the South Thames Retrieval Service (STRS) at Evelina London for nurses, doctors and ambulance staff to refer to in the emergency care of critically ill children. This guideline represents the views of STRS and was produced after careful consideration of available evidence in conjunction with clinical expertise and experience. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient.	

Change History		
Date	Change details, since approval	Approved by
June 2023	Formatting and clarity-e.g aminoacidaemia group removed and organic acidaemia term now used throughout. Glucose replaced dextrose	PCGC

Paediatric Critical Care

Metabolic Disorders

A rare and heterogenous group of inherited conditions, typically presenting in infants/younger children but can present at any age. If clinical suspicion is high, contact tertiary metabolic team for specialist advice. If patient is clinically unstable, refer to STRS urgently.

Evelina Metabolic team: 0207 188 7188, bleep 1460 **STRS: 0207 188 5000**

Useful resources: Vademecum Metabolicum (EVM) British Inherited Metabolic Diseases Group

Clinical features
- Variable –often non-specific
- May be acute or chronic/progressive

Neonates
- Poor feeding/vomiting
- Hypotonia (or hypertonia)
- Jaundice
- Encephalopathy/seizures
- Dysmorphic features

Infants/older children
- Developmental delay/regression
- Recurrent unexplained vomiting
- Encephalopathy/seizures
- Poor growth/fussy eater
- Acute renal/liver failure
- Cardiomyopathy
- Unexplained neurological abnormalities
- Decompensation with intercurrent illness

High index of suspicion
- Consanguineous parents
- Previous SIDS/Multiple miscarriages
- Maternal illness in pregnancy e.g. HELLP, acute fatty liver
- Increased fetal movements (hiccups, seizures)

Differential diagnoses:
- Neonatal collapse
  - sepsis, cardiac
- Septic shock
- Infective encephalitis

Acute management
- Manage ABC
- Treat Seizures
- Monitor for cerebral oedema
- Early referral to STRS
- Early referral to metabolic team
- Stop feeds
- Correct electrolyte/ acid-base disturbances
- Cover for sepsis – broad spectrum antibiotic as per local policy
- Urgent transfer to tertiary centre

Glucose
- Target blood sugar 4-8 mmol/L
- Start 0.9% sodium chloride/10% glucose 2mL/kg/hr – titrate as needed to blood sugar – monitor at least hourly
- Target glucose requirement:
  - Neonates 8-10mg/kg/min
  - Older children 6-8mg/kg/min
- Glucose calculation:

$$\textit{glucose mg/kg/min} = \frac{\textit{glucose\% x mL/hr}}{\textit{weight x 6}}$$

Mechanism of decompensation

- **Disorders of intoxication**
  Often a symptom-free period prior to clinical signs of intoxication
  - Urea cycle defects (eg Ornithine transcarbamoylase/OTC deficiency, citrullinemia)
  - Organic acidaemias (eg. maple syrup urine disease, methylmalonic acidaemia, propionic acidaemia, glutaric aciduria type 1)
  - Carbohydrate disorder (eg. galactosaemia, hereditary fructose intolerance)
- **Disorders of energy metabolism**
  Often present if delay in fuel provision or increased metabolic demand (illness)
  - Fatty acid oxidation defects (eg. MCAD, VLCAD, LCHAD)
  - Carbohydrate metabolism (eg, Glycogen storage diseases,heriditary fructose 1,6 bisphosphatase deficiency)
  - Ketolysis defects
  - Mitochondrial disorders
- **Disorders of complex molecules**
  - Lysosomal storage disorders
  - Peroxisomal disorders (e.g. adrenoleukodystrophy, peroxisomal biogenesis disorders)
  - Congenital disorders of glycosylation

First line metabolic investigations:
- Blood gas - lactate, blood sugar, anion gap
- Baseline bloods – FBC, U&E, LFT, CK, INR
- Serum save
- Ammonia (correct bottle – send on ice)
- Ketones (urine & blood)

Special investigations:
- Blood spot – acyl-carnitine profile
- Plasma amino acids
- Urine – ketones, organic acids
- CSF – lactate, glucose, glycine, amino acids
- Echo/ECG – signs cardiomyopathy?
- EEG – seizure disorder? Encephalopathy?
- CT or MRI brain – basal ganglia changes?
- Ophthalmology – oil-drop cataracts, cherry-red spot, retinopathy

Useful screening tests prior to death:

1) Biopsies:
- Muscle – one flash frozen sample, one saline gauze sample
- Liver – two samples, flash frozen -80°C
- Skin fibroblasts – one sample into viral culture medium (pink fluid kept in PICU fridge at ELCH) OR saline. Store in fridge not freezer.

2) Sample saves:
- Serum save – lithium heparin
- Blood for chromosome/DNA store – lithium heparin and EDTA
- Blood spot card
- Urine for organic acid spectrometry

Metabolic disorder type	pH	Anion gap	Lactate	Glucose	Ketones	Ammonia
Urea cycle defects	N or ↑	N	N or ↑	N	N	↑↑
Organic acidaemia	↓	↑	↑	N, ↓ or ↑	↑	↑
Fatty acid oxidation defects	N or ↓	Variable	N or ↑	N or ↓	↓ or N r	N or ↑
Carbohydrate metabolism	N or ↓	N or ↑	↑	↓	N or ↑	N
Mitochondrial disorders	N or ↓	N or ↑	↑↑	N or ↓	N or ↑	N or ↑

Definitive treatment:
1. Clear toxic metabolites and prevent ongoing production
2. Promote anabolism with glucose as directed by metabolic team
3. Supplement cofactors as indicated e.g. biotin, pyridoxine, folate

Disease specific treatments:

1) Neonatal hyperammonaemia
- Renal replacement therapy
- Stop protein • Sodium benzoate • Sodium phenylbutyrate • L-arginine • Carglumic acid
- Glucose infusion +/ - intralipid

2) Organic acidaemia
- Stop protein intake. Glucose infusion ± insulin • L-carnitine • Carglumic acid

3) Fatty acid oxidation disorders
- Avoid prolonged fast. Glucose infusion NO LIPID

4) Mitochondrial disorders – use 5% glucose and 0.9% sodium chloride

Principles of CVVH (continuous veno-venous haemofiltration):
- Clear toxic metabolites:
  - Ammonia in BCOA/UCD
  - Leucine in MSUD
- **Ins**tigate CVVH ASAP to prevent irrevocable brain damage:
  - Ammonia: > 350 for more than 4 hr
  - Leucine: If elevated and encephalopathic.
- NB: rapid fall of metabolites may be associated with increasing cerebral oedema
- Peritoneal dialysis may be used due to size of infant and logistics but is not as effective as CVVH

References:

British Inherited Metabolic diseases website: BIMDG webpage

Vademecum Metabolicum website: EVM webpage