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.

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.
Paediatric Critical Care

Metabolic Disorders

**Mechanism of decomposition**

1. **Energy insufficiency**: present if delay in fuel provision or increase metabolic rate (illness)
   - Fatty acid oxidation defects (FAOD): MCD/VAHD; medium/very long chain acylcoenzyme A dehydrogenase, carnitine transport defect (CTD)
   - Glycogen storage disease (GSD): von Gierke disease (I), Pompe's disease (II)
   - Gluconeogenesis defects (GD): Glycogen syntheses (GS)/Glucose-6-phosphatase (G6P) deficiency
   - Ketolysis defects (KD): 3-hydroxy-3-methylglutaryl-CoA lyase deficiency

2. **Respiratory chain defects (RCD)**: congenital lactic acidosis, pyruvate dehydrogenase deficiency (PDH), pyruvate carboxylase deficiency (PC)

3. **Toxicity**: Symptom free period prior to clinical signs of intoxication; acute vs. chronic
   - Amino acid (AA): Maple syrup urine disease (MSUD), nonketotic hyperglycinemia (NKH)
   - Branch chain organic acidurias (BCOA): Methylmalonic aciduria (MMA), propionic aciduria (PA), isovaleric aciduria (IVA)
   - Urea cycle defects (UCD): Ornithine transcarbamoylase (OTC), citrullinaemia (CIT)
   - Sugar intolerance: Galactosaemia (GAL), hereditary fructose intolerance

4. **Metabolic diseases**: Disorders of embryogenesis: dysmorphic birth
   - Peroxisomal disorders: Zellweger's disease, neonatal adrenoleukodystrophy

5. **Disorders of intracellular trafficking**: α-1 Antitrypsin, congenital defects glycosylation (CDG)

**Parental history:**
- Consanguinous parents
- Previous SIDS/Multiple miscarriages
- Maternal illness in pregnancy e.g. HELLP, acute fatty liver
- Increased foetal movements (seizures)

**Clinical features:** varied
- Dysmorphism at birth/subsequently
- Hypotonia and lethargy
- Poor feeding +/- hypoglycaemia
- Vomiting, diarrhoea, dehydration
- Seizures, encephalopathy
- Hepatomegaly, jaundice
- Cardiac failure

**Differential diagnosis**
- **Sepsis**: metabolic acidosis, lactate, lable glycemic control (May be concomitant with metabolic disease)
- **Congenital heart disease**: Present with collapse e.g. coarctation aorta (as duct closes), hypoplastic left heart

**Metabolic acidosis: Ketone positive**
- Glucose low
- Lactate <2.5 → Glucose low
- Lactate >2.5 → Glucose normal
- Lactate 2.5 → Glucose high

**Metabolic acidosis: Ketone negative**
- Glucose low
- Lactate <2.5 → Glucose normal
- Lactate >2.5 → Glucose normal

**Metabolic alkalosis**
- Ammonia >100 → Renal tubular acidosis Types 1 and 2
- Lactate <2.5 → Glucose low
- Lactate >2.5 → Glucose normal
- Urea cycle

**Definitive treatment:**
1. Consult metabolic team at the earliest opportunity (ELCH Registrar bleep 1460)
2. Clear toxic metabolites and prevent ongoing production (promote anabolism)
3. Supplement cofactors as indicated e.g. biotin, pyridoxine, folate
4. Monitor for cerebral oedema

**Disease specific treatment:**

- **FAO**: Glucose infusion 5-8 mg/kg/min, keep glucose >3mmol/L, carnitine (only CTD)
- **GSD/GD**: Infusion of glucose to keep glucose within normal parameters (4-7 mmol/L)
- **KD**: High carbohydrate intake; PO or IV dextrose, moderate protein and fat restriction
- **PD**: ketogenic diet, dichloroacetate, otherwise supportive management
- **AA**: Stop protein intake, CVVH (hypercarcinemia), MSUD protein formula, carnitine
- **BOCA**: Restrict protein intake, IV rehydration, carnitine (all), B12 (MMA), glycine (IVA)
- **UCD**: Stop protein intake, alternate pathway drugs; sodium benzoate / phenylbutyrate, Arginine, CVVH for hyperammonaemia, introduce low protein diet after 48-72 hours.

**References**

1) van den Berge, Inborn metabolic disease
2) Pierpoint Ann Heart J. 2000; 139:596-5106
4) Batshaw et al. J Pediatr. 2001; S46-54
5) Human Tissues act

**PICU Special investigations:**
- **Blood**: Repeat arterial gas, lactate & ammonia
- **Send acylcarnitines (FAOD), amino acids (AA/BCOA)**
- **Urine**: Repeat ketone dipstick, urgent organic acids for gas chromatography mass spectrometry
- **CSF**: Lactate (MD), glycine (NKH)
- **EEG, ECHO** Cardiomyopathy (MD, FAOD, GSD II)
- **Ophthalmology**: Oil drop cataracts (GAL), cherry red spot (TS), retinopathy (MD, FAOD)
- **EEG**: Seizure disorder (NKH), encephalopathy (UCD/BCOA)
- **CT Head or MRI**: Basal ganglia changes (MD)

**Principles of continuous veno-venous haemofiltration (CVVH):**
- 1. Clear toxic metabolites: Ammonia in BCOA/UCD, Leucine in MSUD
- 2. Instigate CVVH ASAP to prevent irrecoverable brain damage: Ammonia > 350 x 4 hrs
- 3. Rapid fall of metabolites may be associated with increasing cerebral oedema
- 4. Peritoneal dialysis may be used due to size of infant and logistics but is not as effective as CVVH

**Post-mortem samples should not be taken**

**Useful screening tests prior to death:**
- **Save**: Plasma, urine for organic acid spectrometry
- **Blood for chromosome/DNA store**: Lihium, Heparin and EDTA
- **Biopsy**: Muscle (1 flash frozen sample; one saline gauze sample), Liver (2 samples flash frozen -80°C freezer), Skin fibroblasts: 1 sample into viral culture medium (pink fluid kept in PICU fridge)

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