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

Paediatric Critical Care

Metabolic Disorders

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, labile glycaemic control (May be concomitant with metabolic disease)
- **Congenital heart disease:** Present with collapse e.g. coarcation aorta (as duct closes), hypoplastic left heart

Mechanism of decompensation

1) Energy insufficiency: present if delay in fuel provision or increase metabolic rate (illness)
- **Fatty acid oxidation defects (FAOD):** MCAD/VLCAD; medium/very long chain acyl-coenzyme 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-3methylgluyaryl-CoA lyase deficiency

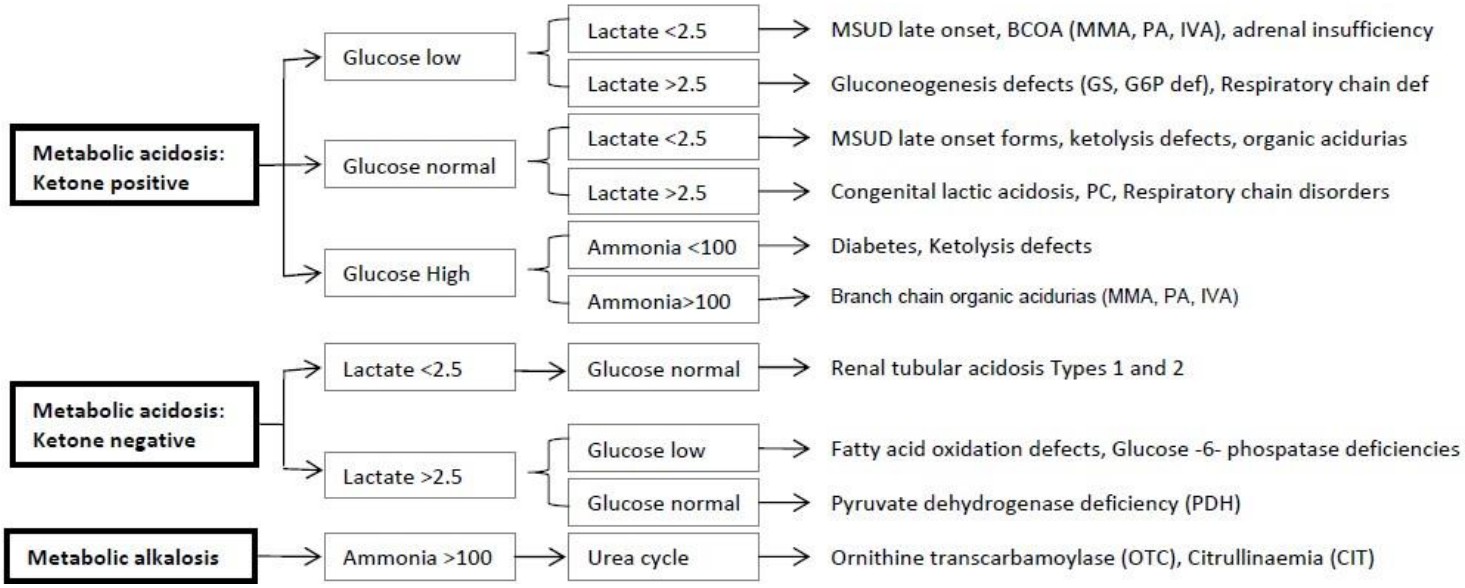
Mitochondrial disorders (MD) :(despite adequate fuel provision)
- Respiratory chain defects (RCD), congenital lactic acidosis, pyruvate dehydrogenase deficiency (PDH), pyruvate carboxylase deficiency (PC)

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

3) Failure to make complex molecules: Disordered embryogenesis; dysmorphic at birth
- **Peroxisomal disorders:** Zellweger's disease, neonatal adrenoleukodystrophy

4) Failure to break complex molecules: Progressive deterioration as storage accumulates
- **Lysosomal disorders:** Mucopolysaccharidosis (MPS), Tay Sach's disease (TS)

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



PICU Special investigations:
- **Blood:** Repeat arterial gas, lactate & ammonia
- Send acylcarnitines (FAOD), amino acids(AA/BROA)
- **Urine:** Repeat ketone dipstick, urgent organic acids for gas chromatography mass spectrometry
- **CSF:** Lactate (MD), glycine (NKH)
- **ECG, 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 irrevocable brain damage: ·Ammonia: > 350 x 4 hrs
   ·Leucine: If elevated and encephalopathic.
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[2]

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: [1]

FAOD: Glucose infusion 5-8 mg/kg/min, keep glucose >3mmol/L, carnitine (only CTD) [2]
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
MD: PDH; ketogenic diet, dichloroacetate, otherwise supportive management
AA: Stop protein intake, CVVH (hyperleucinaemia), MSUD protein formula, carnitine
BCOA: Restrict protein intake, IV rehydration, carnitine (all)[3], **B12** (MMA), glycine (IVA)
UCD: Stop protein intake, alternate pathway drugs; sodium benzoate / phenylbutyrate[4], Arginine, CVVH for hyperammonaemia, introduce low protein diet after 48-72 hours.
Prognosis if ammonia > 1000umol/L for >6hrs is POOR. Peritoneal dialysis if wt <3.5kg.

Post-mortem samples should not be taken[5]
Useful screening tests prior to death:
Save: Plasma, urine for organic acid spectrometry
Blood for chromosome/DNA store: Lithium 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)

References

1) van den Berghe, Inborn metabolic disease
2) Pierpont Am Heart J. 2000; 139:S96- S106
3) Di Donato et al, Clin Chim Acta. 1984; 139:13-21
4) Batshaw et al. J Pediatr. 2001; S46-54
5) Human Tissues act

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