**METABOLIC DISORDERS**  
**(INBORN ERRORS OF METABOLISM)**

**RECOGNITION**
- Early recognition of inborn errors of metabolism (IEM) and prompt management are essential to prevent death or neurodisability
- Diagnosis of IEM in neonates is often delayed owing to non-specific nature of clinical presentation, and unfamiliarity with diagnostic tests
- Seek advice from local and regional clinical chemistry services

*Consider inborn errors of metabolism at same time as common acquired conditions, such as sepsis*

### Differential diagnosis

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Common conditions</th>
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| Encephalopathy without metabolic acidosis | • Urea cycle disorders  
• Maple syrup urine disease (MSUD)  
• Zellweger’s syndrome  
• Non-ketotic hyperglycaemia (NKHG)  
• Molybdenum cofactor deficiency |
| Encephalopathy with metabolic acidosis | • Organic acidaemias (propionic, methylmalonic, isovaleric)  
• Glutaric acidaemia type II |
| Liver dysfunction | • Galactosaemia  
• Tyrosinaemia  
• Neonatal haemochromatosis  
• Zellweger’s syndrome  
• α₁-antitrypsin deficiency  
• Smith-Lemli-Opitz syndrome  
• Fatty acid oxidation disorders (MCAD)  
• Congenital disorders of glycosylation – CDG 1b |
| Hypoglycaemia | • Fatty acid oxidation disorders  
• Galactosaemia  
• Glycogen storage disorders  
• Fructose-1, 6-bisphosphatase deficiency |
| Metabolic acidosis | • With raised plasma lactate  
• pyruvate dehydrogenase (PDH) deficiency  
• pyruvate carboxylase deficiency  
• respiratory chain disorders  
• organic acidaemias  
• With normal plasma lactate  
• organic acidaemias |
| Non-immune hydrops | • GM1 gangliosidosis  
• Mucopolysaccharidosis type VII and IV  
• Gaucher’s  
• Niemann-Pick A & C  
• I-Cell disease |
| Odour : maple syrup (burnt sugar) sweaty feet odour | • MSUD  
• Isovaleric acidaemia or  
• Glutaric acidaemia type II |
| Cataracts | • Galactosaemia  
• Zellweger’s syndrome |
<table>
<thead>
<tr>
<th>Congenital anomalies</th>
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<tbody>
<tr>
<td>Dislocated lens</td>
<td>• Lowe’s syndrome</td>
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<tr>
<td>Homocystinuria</td>
<td>Sulphite oxidase deficiency</td>
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<tr>
<td>Zellweger’s syndrome</td>
<td>Glutaric acidaemia type II</td>
<td>PDH deficiency</td>
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<tr>
<td>Smith-Lemli-Opitz syndrome</td>
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<tr>
<td>Congenital heart disease</td>
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<tr>
<td>* hypotonia, epicanthal folds, Brushfield spots, simian creases, large fontanelle, renal cysts</td>
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<tr>
<td>* hypertelorism, low set ears, high forehead, abdominal wall defects, large kidneys</td>
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<td>* appearance similar to fetal alcohol syndrome</td>
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<tr>
<td>* facial dysmorphism, cleft palate, poly- or syndactyly, congenital heart disease</td>
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<tr>
<td>Congenital anomalies</td>
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<tr>
<td>Agenesis of corpus callosum</td>
<td>NKHGPDH deficiency</td>
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<tr>
<td>Apnoea or periodic breathing in term infant</td>
<td>NKHG</td>
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<td>Respiratory alkalosis in a tachypnoeic baby</td>
<td>Hyperammonaemia</td>
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<td>Jaundice (particularly conjugated) and liver dysfunction</td>
<td>Galactosemia</td>
<td>Tyrosinaemia</td>
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<td>Galactosaemia</td>
<td>α₁-antitrypsin deficiency</td>
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<tr>
<td>Hypoglycaemia in a low-risk infant, or persistent/recurrent, with neurological symptoms</td>
<td>Fatty acid oxidation defects</td>
<td>Glycogen storage disorders</td>
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<tr>
<td>Galactosaemia</td>
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<tr>
<td>Metabolic acidosis with increased anion gap</td>
<td>Organic acidaemias</td>
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<tr>
<td>Persistent vomiting</td>
<td>Hyperammonaemia</td>
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<td>Hiccoughing</td>
<td>NKHG</td>
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**Specific indicators**

**Clinical context**
- Unexplained and mysterious deterioration of baby (can be as short as 12 hr but more commonly at 48 hr)

**Family history**
- Known metabolic disorders
- Unexplained neonatal or infant deaths
- Parental consanguinity

**Obstetric history**
- Acute fatty liver of pregnancy and HELLP syndrome in index pregnancy may point towards long chain fatty acid oxidation defect in neonate

**Non-specific indicators suggestive of metabolic disorder in an encephalopathic baby**
- Encephalopathy in low risk infant, or onset after period of normality
- Fluctuating consciousness and muscle tone
- Changes in muscle tone:
  - axial hypotonia with limb hypertonia
  - ‘normal’ tone in comatose baby
- Abnormal movements:
  - myoclonic or boxing movements
  - tongue thrusting
  - lip smacking
- True seizures occur late in metabolic encephalopathies except in NKHG

**INITIAL INVESTIGATIONS**
- Whenever IEM suspected, perform required investigations without delay
- Seek early advice about appropriate investigations and management from inherited metabolic diseases (IMD) team at tertiary metabolic centre
Urine
- Smell
- Ketostix: presence of large amounts of urinary ketones is always abnormal in neonates and suggests IEM, especially organic acidaemias
- Reducing substances: use Clinitest: urinary dipsticks are specific for glucose and miss galactose in babies with galactosaemia
- Freeze 15–20 mL urine for amino and organic acid analysis

Blood
- Full blood count, U&Es, Infection screen
- Glucose
- Blood gas
- Ammonia
- Lactate
- Total and conjugated bilirubin, liver function tests including clotting studies
- Acylcarnitines, including free and total carnitine
- Uric acid
- Amino acids

Imaging
- Cranial ultrasound
- Ophthalmic examination

SPECIFIC INVESTIGATIONS
Jaundice
Blood
- Galactosaemia screen (urinary reducing substances can be negative after short period of galactose exclusion)
- Ferritin
- Very long chain fatty acids
- α1-antitrypsin (quantitative)
- 7-dehydrocholesterol
- Transferrin isoelectric focusing

Urine
- Succinylacetone
- Skin (and liver) biopsy after discussion with metabolic team

Encephalopathy
- Paired blood and CSF glycine
- CSF lactate
- Very long chain fatty acid profile
- Urine for orotic acid
- Urine: Sulfitest for sulphite oxidase deficiency

Hypoglycaemia (most informative when obtained at time of hypoglycaemia)
- Plasma non-esterified fatty acids
- β-hydroxybutyrate
- RBC galactosaemia screen
- Insulin and C-peptide
- Acylcarnitine profile, free and total carnitine
- Cortisol, growth hormone
- Urine for organic acids
Post-mortem (plan how best to use these precious samples in consultation with IMD team)
- Plasma (2–5 mL), urine (10–20 mL) and CSF (1 mL) frozen at -20°C
- Red cells: blood (5 mL) in lithium heparin stored at 4°C (fridge)
- Blood (5 mL) in EDTA: stored at 4°C for DNA analysis
- Tissue biopsies
  - skin: store in viral culture medium or saline at 4°C (fridge)
  - muscle and liver: take within hour of death, snap freeze in liquid nitrogen
- Post-mortem examination

IMMEDIATE MANAGEMENT

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<tr>
<th>Commence emergency management of suspected IEM while awaiting results of initial investigations</th>
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- Attend to Airway, Breathing and Circulation; ventilate if necessary
- Omit all protein intake, including TPN and lipid
- Commence intravenous glucose infusion to provide 6–8 mg glucose/kg/min
- start insulin infusion if hyperglycaemic (>15 mmol/L) or catabolic
- if hypertonic glucose infusion necessary, insert central line
- Correct dehydration, acid-base and electrolyte disturbances
- Cover for infection
- Control seizures (avoid sodium valproate)
- Consider transfer to tertiary metabolic centre if stable and appropriate

SPECIFIC MANAGEMENT

- Must be led by IMD team
- Use following as guide to general principles of management

Neonatal hyperammonaemia: a medical emergency requiring prompt intervention to lower ammonia concentration
- Renal replacement therapy (haemofiltration more efficient than peritoneal dialysis)
- Sodium benzoate
- Sodium phenylbutyrate
- L-arginine
- L-carnitine

Organic acidaemia
- Reduce/stop protein intake
- Hypertonic glucose infusion ± insulin
- L-carnitine
- Glycine
- Biotin

Fatty acid oxidation disorders
- Avoid prolonged fast
- L-carnitine

Lactic acidosis
- Dichloroacetate
- Biotin
- L-carnitine
- thiamine
Galactosaemia
• Dietary exclusion of galactose

**For further Information on inherited metabolic diseases,**
[www.bimdg.org.uk>Guidelines> then emergency protocols and follow through]

**LOCAL CONTACT**
• For specialist advice, consult Birmingham Children’s Hospital metabolic team early