How to manage a newborn with suspected metabolic disease

Always inform the neonatal consultant of any infant with suspected metabolic disease. Metabolic disease in the newborn period is rare and usually becomes apparent within 72 hours. Progressive encephalopathy is the most common form of presentation, but the onset can be subtle with poor feeding, vomiting and lethargy.

**Suspect metabolic disease in a newborn with:**
- acute or progressive encephalopathy ± seizures,
- persistent acid/base disturbance and lactic acidosis,
- persistent hypoglycaemia: please refer to the ‘Hypoglycaemia Guideline’,
- respiratory alkalosis and hyperammonaemia,
- if certain syndromes are being considered (Zellweger, Smith-Lemli-Opitz),
- cardiac disease e.g. hypertrophic cardiomyopathy and/or liver dysfunction,
- hydrops fetalis,
- a family history of SIDS, multiple miscarriages, maternal HELLP and/or consanguinity.

**Baseline metabolic emergency investigations:**

1) Obtain **Blood** samples for:
- U&E, LFT, bone profile, CRP
- Glucose and Intermediary metabolites
- Ammonia
- Blood culture
- FBC
- Coagulation
- Blood gas and lactate
- Acylcarnitine
- Plasma amino acids
- Store serum

(Total: 5 ml)

- 0.5ml Li heparin
- 0.5ml fluoride oxalate
- 0.5ml Li heparin on ice
- 1-2 ml
- 0.5ml EDTA
- capillary tube
- Guthrie card
- 0.5ml Li heparin

(out of hours contact on-call biochemist)

2) Obtain **Urine** for:
- Dipstick (pH, protein, ketones, glucose)
- Reducing substances
- Organic Acids
- Store sample

1ml
5ml
in the fridge

3) If **LP** is performed:
- MC/S
- Glucose
- Protein, amino acids, lactate
- Store CSF

0.2ml
0.2ml fluoride oxalate
0.6ml (contact 42637)
send to lab for immediate freezing

**Initial management:**

1. **Supportive care:**
   - Maintain adequate respiratory support (consider assisted ventilation early).
   - Establish secure vascular access.
   - Correct hypothermia, hypoglycaemia and dehydration.
   - Consider correcting metabolic acidosis with IV sodium bicarbonate.
   - Monitor electrolytes and blood gases.
   - Start antibiotics (sepsis is a common precursor to metabolic decompensation).

2. **Reduce load on the affected metabolic pathway:**
   - Stop all exogenous protein (this includes feeds and TPN).
   - Give IV glucose at 5-10 mg/kg/min and maintain blood sugar at 7-11 mmol/l.
   - If hyperglycaemia does occur, reduce the GIR to 4 and consider starting insulin at 0.05-1 U/kg/hr. DO NOT STOP GLUCOSE.
3. **Removal of toxic metabolites:**
- Consider giving IV Carnitine at 25 mg/kg QDS. Carnitine is an essential protein in fat metabolism. Secondary carnitine deficiency is common in many metabolic disorders, especially in organic acidaemias and fatty acid oxidation defects. Carnitine may also help directly in the removal of toxic metabolites.
- Maintain adequate urine output.
- Dialysis may be required if urine output poor, if hypernatraemic, if metabolic acidosis persistent or to directly remove toxic substrates.

**Acute management of hyperammonaemia (NH4 > 100 µmol/l):**
- Stop all exogenous protein (feeds and TPN).
- Inhibit endogenous protein catabolism: correct metabolic acidosis, maintain blood sugar between 7-11 mmol/l with IV dextrose.
- If ammonia > 150 µmol/l consider starting Sodium Benzoate (please see further information about dosing in the drug folder).
- If ammonia > 350 µmol/l, or < 400 µmol/l but with no decrease after 4 hours of IV treatment: consider dialysis.

**Investigations if death is inevitable (after detailed discussion and consent from parents):**
- Plasma: 3-5 ml lithium heparin, plasma separated and frozen.
- Whole blood: 3-5 ml EDTA for DNA analysis (not frozen).
- Whole blood: 1ml Fluoride oxalate for glucose and intermediary metabolites
- Blood spot: 4 spots on Guthrie filter paper.
- Urine: minimum 2 ml in plain sterile container.
- Skin biopsy for fibroblast culture: sterile sample from below lateral clavicle. Store in 0.9% Saline and keep refrigerated and send to cytogenetics.
- Consider CSF (freeze immediately) and tissue samples (liver, muscle).

Discuss post-mortem with parents. Remember limited post mortems can also be done. For further information regarding the presentation of specific investigations of individual disorders please see the list of contacts, table and algorithm below.

For clinical advice contact: Dr Graham Shortland (Ext 3275) (out of hours via UHW switchboard)
If Dr Shortland unavailable: Birmingham Children’s Hospital 24 hour metabolic service via 0121-3339999
Advice on lab. investigations: Dr Stuart Moat, Clinical Biochemist (Ext 43562/43560 or Bleep 5686).
Out of hours advice: On-call Medical Biochemist via UHWswitchboard.
If death is enevitable: Dr Stuart Moat (Medical Biochemist) – to confirm specific investigations required (as sample volumes are often limited).

If diagnosis of a specific metabolic condition is suspected, please refer to the the British Inherited Metabolic Disease Group (BIMDG) website: [http://www.bimdg.org.uk/site/index.asp](http://www.bimdg.org.uk/site/index.asp) for more detailed information.

References:

Dr R Hayward, Dr S Barr December 2015   To be re-evaluated December 2018
**CHECKLIST OF INVESTIGATIONS CONDUCTED**

**Baseline metabolic emergency investigations:**

<table>
<thead>
<tr>
<th>Serum:</th>
<th>Date sent</th>
<th>Result &amp; date</th>
</tr>
</thead>
<tbody>
<tr>
<td>U&amp;E, LFT, bone profile, CRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose and Intermediary metabolites</td>
<td></td>
<td></td>
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<tr>
<td>Ammonia</td>
<td></td>
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</tr>
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<td>Blood gas and lactate</td>
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<tr>
<td>Acylcarnitine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma amino acids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Store serum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anion gap: \((\text{Na} + \text{K}) - (\text{Cl} + \text{HCO}_3)\).

**Urine:**

- Dipstick (pH, protein, ketones, glucose)
- Reducing substances
- Organic Acids
- Store sample

**Lumbar puncture:**

- MC/S
- Glucose
- Protein, amino acids, lactate
- Store CSF

**Table 1 Categorisation of neonatal inborn errors of metabolism (IEM) using metabolic screening tests**

<table>
<thead>
<tr>
<th>Acidosis</th>
<th>Ketosis</th>
<th>Lactate</th>
<th>Ammonia</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Maple syrup urine disease</td>
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<tr>
<td>+</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
<td>Organic aciduria</td>
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<tr>
<td>+</td>
<td>+/-</td>
<td>+</td>
<td>-</td>
<td>Lactic acidosis</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Urea Cycle</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Non-ketotic hyperglycinaemia, sulphite oxidase deficiency, peroxisomal,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>phenylketonuria, galactosaemia</td>
</tr>
</tbody>
</table>
Algorithm for investigating suspected IEM in neonates

Plasma NH$_3$

- HIGH
- LOW

Blood pH and CO$_2$

- Normal
- acidosis

Blood pH and CO$_2$

- normal

PKU, NKH

Galactosaemia

Peroxisomal disorders

Aminoacidopathies

No ketosis

Ketosis with or without lactic acidosis

Urea cycle defect

FAOD

Plasma cirtrulline

>1000 µmol/L

25-50 µmol/L

undetectable

ASA deficiency

Urinary ASA

Urinary orotic acid

(citrullinaemia)

ASAL deficiency (ASAuria)

THAN

OTC deficiency

CPS/NAGS deficiency

Key:

FAOD fatty acid oxidation defects, PKU phenylketonuria, NKH non-ketotic hyperglycaemia, ASA argininosuccinic acid, OTC orthinine transcarbamoylase, CPS carbamoyl phosphate synthetase I, NAGS N-acetylglutamate synthetase, THAN transient hyperammonia of the newborn, ASAL argininosuccinic acid lyase.