**GUIDELINE**

# Metabolic Disorders: Inherited

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| **Scope (Staff):** | Nursing and Medical Staff |
| **Scope (Area):** | NICU KEMH, NICU PCH, NETS WA |

**Child Safe Organisation Statement of Commitment**

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

**This document should be read in conjunction with this disclaimer**

## Aim

To provide guidance on identifying and initial management of infants with inherited metabolic disorders.

## Risk

Delayed identification and implementation of correct management may increase morbidity and mortality.

## Clinical Presentation and Findings

Most infants with inherited metabolic disorders are born at or near term with normal birth weight and no abnormal features. Symptoms usually develop within the first week of life as full milk feeding is instituted. However, the time interval between birth and presentation may range from a few hours to weeks depending on the nature of the defect, the feeding regime, and the presence of other factors such as infection or surgery. Consanguinity and family history of a similar illness in siblings or unexplained deaths (especially neonatal males) or unexplained neurodevelopmental disorders are often important findings.

In most cases the physical examination will not suggest a diagnosis as presenting signs are often non-specific e.g. poor feeding, lethargy, vomiting, dehydration, hypotonia, or seizures.

A detailed clinical examination:

- Growth parameters
- Cardiorespiratory status
- Neurological status
- Odour of baby and urine

Clinical presentations of IEM in neonates

| Antenatal presentation | Neurological deterioration predominantly encephalopathy | Neurological deterioration predominantly seizures | Hypoglycemia | Liver cell failure/ cholestasis | Cardiomyopathy/ arrythmia | Dysmorphism |
|---|---|---|---|---|---|---|
| MPS VII*<br>I-cell disease*<br>CDG[0]<br>LCHADD[a] | Urea cycle disorder<br>MSUD<br>PA/MMA/IVA<br>FAOD<br>Pyruvate dehydrogenase deficiency<br>Pyruvate carboxylase deficiency<br>Respiratory chain defect | Pyridoxine responsive seizures<br>PNPO deficiency<br>Cerebral folate deficiency<br>SO deficiency<br>MOCD<br>NKH | FAOD<br>Glycogen storage disorder[#]<br>HAHI syndrome<br>Fructose 1 6 biphosphatase deficiency | Tyrosinemia<br>Galactosemia<br>Mitochondrial DNA depletion syndrome<br>Bile acid synthesis defect | FAOD<br>Respiratory chain defects | ZSD<br>CDG<br>MADD (GA-II)<br>Smith-Lemli-Opitz syndrome<br>Pyruvate dehydrogenase deficiency |

*Hydrops; [0] Cerebellar hypoplasia; [a] Maternal HELLP [#] Glycogen storage disease I and III

*CDG* Congenital disorder of glycosylation; *FAOD* Fatty acid oxidation defects; *GA II* Glutaric aciduria type II; *HAHI* Hyperammonemia hyperinsulinism syndrome; *IVA* Isovaleric acidemia; *LCHADD* Long chain acyl coA hydroxyacyl CoA dehydrogenase deficiency; *MADD* Multiple acyl-co A dehydrogenase deficiency; *MMA* Methyl malonic acidemia; *MOCD* Molybdenum cofactor deficiency; *MPS* Mucopolysaccharidosis; *MSUD* Maple syrup urine disease; *NKH* Non ketotic hyperglycinemia; *PA* Propionic acidemia; *PNPO* Pyridoxamine; *SO* Sulfite oxidase deficiency; *ZSD* Zellweger spectrum disorder

## Investigations

Most sick neonates will already have had a series of basic biochemical and haematological investigations and it is important to review the results. Unexplained hypoglycaemia, hypocalcaemia, acid-base disturbance or increased anion gap with liver, cardiac or neurological dysfunction are important clues and indicate the need for further metabolic investigations.

- Blood glucose
- Blood lactate and pyruvate
- Serum ammonia (request for urgent results especially in an unwell neonate)
    - **Hyperammonemia is a medical emergency**.
- Arterial Blood gas (primary respiratory alkalosis is a clue for high ammonia)
- A normal blood pH does not exclude an increased blood lactate and direct measure should be considered if there is hypoglycaemia or neurological dysfunction
- Serum electrolytes
- Anion gap: $(Na^+ + K^+) – (Cl^- + HCO3^-)$, normal <12mmol
- Liver function tests
- Plasma amino acids
- Plasma β-hydroxybutyrate
- Plasma carnitine and acylcarnitine profile
- Urine spot tests for glucose, ketones and reducing substances

  - A strongly positive test for urine ketones is abnormal in a neonate and suggests a possible organic acidaemia.
- Urine for amino acid and organic acid screens (ideally 2-5 mL but smaller quantities of urine are valuable)
- CSF lactate and amino acids. (Note: this needs to be processed promptly, ring the laboratory **prior** to taking the sample).

It is especially important to provide a brief clinical summary to the laboratory and include details of any medications or special diets to ensure appropriate investigations and interpretation of results are performed in a timely manner.

If the infant has an episodic illness (related to feeding) it is particularly important to collect blood and urine specimens during the acute phase as the diagnosis may be missed if specimens are collected when well. It is also useful to store all samples of plasma, urine and CSF (at -20$^{o}$C) for potential further investigations. Special sample collections are required if a peroxisomal or lysosomal disorder is suspected. Further tests may be required after discussion with a metabolic specialist.

If the illness is progressing rapidly and death seems inevitable, it is important to ensure that appropriate specimens (blood, urine, skin and tissues) are taken for biochemical analysis to enable reliable post-mortem diagnosis;

- Blood (2 mL heparinised whole blood)
- Urine (ideally 2-5 mL) should be taken pre-mortem whenever possible
- Newborn Blood Spot Test (Guthrie) should be collected
- Skin (fibroblast culture) and tissues (frozen muscle and/or liver at -70$^{o}$C) can be reliably collected up to 2-4 hours post-mortem

Contact the on-call Histopathologist to arrange appropriate collection and storage of these samples.

### Quick guide to diagnose IEM

| | Organic Acidemia | Urea cycle disorder | Fatty acid oxidation | Maple Syrup Urine Disease | Pyruvate carboxylase/ Pyruvate Dehydrogenase def |
|---|---|---|---|---|---|
| Glucose | Normal or low | Normal | Low or Normal | Low or normal | Low |
| ABG | Acidosis | Respiratory alkalosis | Normal or acidosis | Normal or acidosis | Normal or acidosis |
| Lactate | Increased | Normal | Normal or Increased | Normal | Increased |
| Ammonia | Increased | Increased | Normal or Increased | Normal | Normal or Increased |
| Ketone | Increased | Normal or Negative | Negative or low | Increased | Normal or Increased |

## Management of the Acute Situation

Whilst awaiting results of specific investigations, management is largely supportive and aims to correct electrolyte and acid-base disturbances and maintain adequate gas exchange. Early consultation with the metabolic team is recommended.

- Treat hypoglycaemia, seizures and altered conscious state.
- Treat underlying or precipitating illness e.g. sepsis.
- Stop any triggering factors i.e. stop feeds.
- Prevent catabolism by using intravenous fluids such as 10% dextrose.
- In case of metabolic acidosis, sodium bicarbonate correction may be required.
- Hyperammonemia will need urgent metabolic review and use of sodium benzoate, arginine in consultation with the metabolic team.
- More intensive treatment is sometimes also required e.g. exchange transfusion or dialysis.

For those families where a diagnosis can be made, genetic counselling and the opportunity for prenatal diagnosis in future pregnancies is significant and hence great efforts should be made to obtain important specimens especially with unwell neonates.

### References


1. Saudubray, J. M. and À. Garcia-Cazorla (2018). "Inborn Errors of Metabolism Overview: Pathophysiology, Manifestations, Evaluation, and Management." *Pediatr Clin North Am* **65**(2): 179-208
2. Balakrishnan, U. (2021). "Inborn Errors of Metabolism-Approach to Diagnosis and Management in Neonates." *Indian J Pediatr* **88**(7): 679-689. Dunne, E., et al. (2022).
3. Dunne, E., et al. (2022). "Biochemical testing for inborn errors of metabolism: experience from a large tertiary neonatal centre." *Eur J Pediatr* **181**(10): 3725-3732.
4. Clinical Practice Guidelines : Metabolic disorders (rch.org.au)
5. Saudubray, J. M., et al. (2002). "Clinical approach to inherited metabolic disorders in neonates: an overview." Semin Neonatol **7**(1): 3-15.

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