



## CLINICAL PRACTICE GUIDELINE

Guideline coverage includes NICU KEMH, NICU PCH and NETS WA

# Metabolic Disorders: Inherited

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There are a large number of rare inherited disorders with a metabolic basis that can present clinically in the neonatal period. The most frequently occurring disorders are those due to defects in the metabolism of small molecules e.g. amino acids, organic acids, carbohydrates and ammonium. In addition, there are some disorders of purine and pyrimidine metabolism and some peroxisomal and lysosomal storage disorders that may also present in the newborn. The collective incidence for these disorders is approximately 1 in 2000-4000 births.

## 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 are often important findings. Some lysosomal storage disorders can present during pregnancy with foetal ascites and as hydrops foetalis.

In most cases the physical examination will not suggest a particular diagnosis as presenting signs are often non-specific e.g. poor feeding, lethargy, vomiting, dehydration, hypotonia, or seizures. However, certain features are particularly suggestive of inherited metabolic disease:

- Unusual odour
- Cataracts
- Hyperventilation secondary to unexplained metabolic acidosis
- Unexplained respiratory alkalosis
- Neurological dysfunction with respiratory alkalosis
- Dysmorphia and severe neurological dysfunction
- Peroxisomal disorders and congenital lactic acidosis
- Urea cycle defects
- Organic acidaemias
- Galactosaemia and respiratory chain defects
- Amino and organic acid disorders.

## 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.

## When the Infant is Acutely Ill the Following Investigations Should be Considered:

- Urine spot tests for glucose, ketones and reducing substances.
- Urine for amino acid and organic acid screens (ideally 2-5 mL but smaller quantities of urine are valuable).

## Additional Specific Investigations may include:

- Blood lactate and pyruvate.
- Plasma ammonium and  $\beta$ -hydroxybutyrate.
- Plasma quantitative amino acids.
- CSF lactate and amino acids. (Note: this needs to be processed promptly, ring the laboratory **prior** to taking the sample).
- A strongly positive test for urine ketones is abnormal in a neonate and suggests a possible organic acidaemia. A normal blood pH does not exclude an increased blood lactate and direct measure should be considered if there is hypoglycaemia or neurological dysfunction.

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 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  $-20^{\circ}\text{C}$ ) for potential further investigations.

Special sample collections are required if a peroxisomal or lysosomal disorder is suspected.

## 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.

Regimes should be instituted to try to induce an anabolic state and replacement of milk feeds with dextrose infusion is appropriate for most disorders i.e. amino acid, organic acid, urea cycle and carbohydrate disorders. However, this may not be appropriate for the congenital lactic acidosis, which may be exacerbated by a high carbohydrate load. More intensive treatment is sometimes also required e.g. exchange transfusion or dialysis.

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.
- New Born Blood Spot Test (Guthrie) should be collected.
- Skin (fibroblast culture) and tissues (frozen muscle and/or liver at  $-70^{\circ}\text{C}$ ) 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.

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

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