# 30 Inborn Errors of Metabolism

Inborn errors of metabolism (IEM) are disorders in which there is a block in the normal metabolic pathway that is caused by a genetic defect of a specific enzyme. The number of diseases known to be attributable to inherited defects in metabolism now exceeds 500.[1] While the diseases individually are rare, they collectively account for a significant proportion of neonatal and childhood morbidity and mortality. Diagnosis is important not only for treatment and prognostication but also for genetic counselling and antenatal diagnosis in subsequent pregnancies.

## Clinical presentation

Severe illness in the newborn, regardless of the underlying cause, tends to manifest with non-specific findings such as poor feeding, drowsiness, lethargy, hypotonia, and failure to thrive. IEM should be considered in the differential diagnosis of any sick neonate presenting with one or more of these features along with more common causes such as sepsis, hypoxicischemic encephalopathy, duct-dependent cardiac lesions, congenital adrenal hyperplasia and congenital infections (Panel 1).

**Panel 1: Clinical pointers for suspicion of IEM[2]**

- Deterioration after a period of apparent normalcy
- Parental consanguinity
- Family history of neonatal deaths
- Rapidly progressive encephalopathy and seizures of unexplained cause
- Severe metabolic acidosis
- Persistent vomiting
- Peculiar odor
- Acute fatty liver or HELLP (hemolysis, elevated liver enzymes & low platelet counts) during pregnancy: seen in women carrying fetuses with long-chain-3-hydroxyacyl-coenzyme dehydrogenase deficiency (LCHAD)

A variety of examination findings may provide a clue to the underlying IEM (Table 30.1).

**Table 30.1: Clinical pointers towards specific IEM**

| Clinical finding | Disorder |
|---|---|
| Coarse facies | Lysosomal disorders |
| Cataract | Galactosemia, Zellweger syndrome |
| Retinitis pigmentosa | Mitochondrial disorders |
| Cherry red spot | Sphingolipidosis |
| Hepatomegaly | Storage disorders, urea cycle defects |
| Renal enlargement | Zellweger syndrome,<br>Glycogen storage disorder type I |
| Eczema/alopecia | Biotinidase deficiency |
| Abnormal kinky hair | Menke's disease |
| Decreased pigmentation | Phenylketonuria |

## Patterns of presentation[2,3]

### Encephalopathy with or without metabolic acidosis

Encephalopathy, seizures, and tone abnormalities are predominant presenting features of organic acidemias, urea cycle defects and congenital lactic acidosis. Intractable seizures are prominent in pyridoxine dependency, non-ketotic hyperglycinemia, molybdenum co-factor defect and folinic-acid responsive seizures.

### Acute liver disease

This could manifest as:

*Jaundice alone*- Gilbert syndrome, Criggler-Najjar syndrome

*Hepatic failure* (jaundice, ascites, hypoglycemia, coagulopathy)- Tyrosinemia, galactosemia, neonatal hemochromatosis, glycogen storage disease type IV

*Neonatal cholestasis:* alpha-1 antitrypsin deficiency, Niemann-Pick disease type C

*Hypoglycemia:* persistent and severe hypoglycemia may be an indicator of an underlying IEM. Hypoglycemia is a feature of galactosemia, fatty acid oxidation defects, organic acidemias, glycogen storage disorders and disorders of gluconeogenesis.

### Dysmorphic features

Dysmorphic features are seen in peroxisomal disorders, pyruvate dehydrogenase deficiency, congenital disorders of

glycosylation (CDG), and lysosomal storage diseases. Some IEMs may present with nonimmune hydrops fetalis; these include lysosomal storage disorders and CDG.

### Cardiac disease

Cardiomyopathy is a prominent feature in some IEM including fatty acid oxidation defects, glycogen storage disease type II and mitochondrial electron transport chain defects.

### Investigations

Metabolic investigations should be initiated as soon as the possibility is considered. The outcome of treatment of many IEMs, especially those associated with hyperammonemia is directly related to the rapidity with which problems are detected and the appropriate management is instituted.

### First line investigations (metabolic screen)

Panel 2 summarizes the tests to be performed in all babies with suspected IEM.

**Panel 2: List of tests to be performed in all babies with suspected IEM**

1) Complete blood count (neutropenia and thrombocytopenia seen in propionic and methylmalonic acidemia)
2) Arterial blood gas and electrolytes
3) Blood glucose
4) Plasma ammonia (normal values in newborn: 90 to 150 µg/dL or 64 to 107 µmol/L)
5) Arterial blood lactate (normal values: 0.5-1.6 mmol/L)
6) Liver function tests
7) Urine ketones
8) Urine reducing substances
9) Serum uric acid (low in molybdenum cofactor deficiency)

Figure 30.1 depicts the algorithmic approach to a newborn with suspected IEM. Disease category can be diagnosed based on blood ammonia, blood gas analysis and urine ketone testing. Hyperammonemia without acidosis is caused by urea cycle defects.

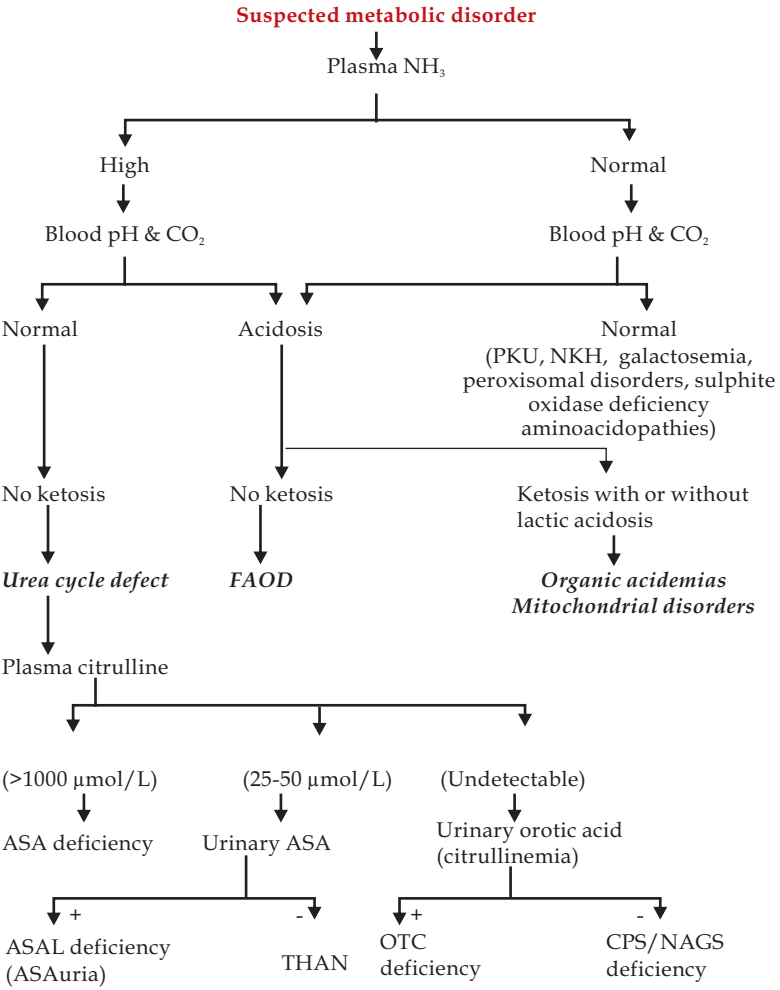


**Figure 30.1: Approach to newborn with suspected metabolic disorder**

***(FAOD: fatty acid oxidation defects, PKU: Phenylketonuria, NKH: Nonketotic hyperglycinemia, ASA: Argininosuccinic acid, OTC: Ornithine transcarbamoylase, CPS: carbamoylphosphate synthetase I; NAGS: N-acetylglutamate synthetase, THAN: transient hyperammonemia of newborn, ASAL: argininosuccinic acid lyase)***

Metabolic acidosis with or without hyperammonemia is a feature of organic acidemias and fatty acid oxidation defects.

In neonates with persistent hypoglycemia and suspected underlying IEM, presence of non-glucose reducing substances in the urine is suggestive of galactosemia. If there is no evidence of reducing substances in the urine, presence or absence of ketonuria would help diagnose the underlying condition: while the former would suggest glycogen storage diseases, gluconeogenic defects or organic acidemias, the latter (no ketonuria) would in dicate fatty acid oxidative defects, ketogenesis defects or hyperinsulinism.

Table 30.2 explains the categorization of IEM based on simple metabolic screening tests.

**Table 30.2: Categorization of neonatal IEM using metabolic screening tests**

| Acidosis | Ketosis | Lactate | Ammonia | Diagnosis |
|---|---|---|---|---|
| - | + | - | - | Maple syrup urine disease |
| + | +/- | - | +/- | Organic aciduria |
| + | +/- | + | - | Lactic acidosis |
| - | - | - | + | Urea cycle defects |
| - | - | - | - | Non-ketotic hyperglycinemia, sulfite oxidase deficiency, peroxisomal disorders, Phenylketonuria, galactosemia |

## Second line investigations (ancillary and confirmatory tests)

These tests need to be performed in a targeted manner, based on presumptive diagnosis reached after first line investigations:

1) Gas chromatography mass spectrometry (GCMS) of urine: for diagnosis of organic acidemias
2) Plasma amino acids and acyl carnitine profile by tandem mass spectrometry (TMS): for diagnosis of organic acidemias, urea cycle defects, aminoacidopathies and fatty acid oxidation defects
3) High performance liquid chromatography (HPLC): for

quantitative analysis of amino acids in blood and urine; required for diagnosis of organic acidemias and aminoacidopathies.

4) Lactate/pyruvate ratio: in cases with elevated lactate.
5) Urinary orotic acid: in cases with hyperammonemia for classification of urea cycle defect.
6) Enzyme assay: This is required for definitive diagnosis, but not available for most IEMs. Available enzyme assays include biotinidase assay in cases with suspected biotinidase deficiency (intractable seizures, seborrheic rash, alopecia); and GALT (galactose 1-phosphate uridyl transferase) assay in cases with suspected galactosemia (hypoglycemia, cataracts, reducing sugars in urine).
7) Neuroimaging: MRI may provide helpful pointers towards etiology while results of definitive investigations are pending. Some IEM may be associated with structural malformations e.g, Zellweger syndrome has diffuse cortical migration and sulcation abnormalities. Agenesis of corpus callosum has been reported in Menke's disease, pyruvate decarboxylase deficiency and nonketotic hyperglycinemia.[4] Examples of other neuroimaging findings in IEM include:
    - Maple syrup urine disease (MSUD): brainstem and cerebellar edema
    - Propionic & methylmalonic acidemia: basal ganglia signal change
    - Glutaric aciduria: frontotemporal atrophy, subdural hematomas
8) Magnetic resonance spectroscopy (MRS): may be helpful in selected disorders, e.g, lactate peak elevated in mitochondrial disorders, glycine peak in non-ketotic hyperglycinemia, leucine peak elevated in MSUD.
9) Electroencephalography (EEG): some EEG abnormalities may be suggestive of particular IEM; e.g, comb-like rhythm in MSUD, burst suppression in NKH and holocarboxylase synthetase deficiency.[5]
10) Plasma very long chain fatty acid (VLCFA) levels: elevated in peroxisomal disorders
11) Mutation analysis when available

12) CSF aminoacid analysis: CSF Glycine levels elevated in NKH, serine levels low in disorders of serine biosynthesis.

## Precautions to be observed while collecting samples

1. Should be collected before specific treatment is started or feeds are stopped, as the levels may be falsely normal if the child is off feeds.
2. Samples for blood ammonia and lactate should be transported in crushed ice and immediately tested. Lactate sample should be arterial and should be collected after 2-hour fasting in a pre-heparinized syringe. Ammonia sample is to be collected approximately after 2 hours of fasting in EDTA vacutainer. Avoid air mixing. Sample should be free flowing.
3. Detailed history including drug details should be provided to the lab (sodium valproate therapy may increase ammonia levels).

## Samples to be obtained in infant with suspected IEM when diagnosis is uncertain and death seems inevitable (Metabolic autopsy)[6]

1. Blood: 5-10 mL; frozen at -20$^0$C; both heparinized (for chromosomal studies) and EDTA (for DNA studies) samples to be taken
2. Urine: frozen at –20$^o$C
3. CSF: store at –20$^o$C
4. Skin biopsy: including dermis in culture medium or saline with glucose. Store at 4-8$^0$ C. Do not freeze.
5. Liver, muscle, kidney and heart biopsy: as indicated.
6. Clinical photograph (in cases with dysmorphism)
7. Infantogram (in cases with peroxisomal disorders and storage disorders with skeletal abnormalities)

## Treatment

In most cases, treatment needs to be instituted empirically without a specific diagnosis. The metabolic screen helps to broadly categorize the patient's IEM (e.g, urea cycle defect, organic academia, congenital lactic acidosis, etc.), based on which empirical treatment can be instituted.

## Aims of treatment

1) To reduce the formation of toxic metabolites by decreasing substrate availability (by stopping feeds and preventing endogenous catabolism)
2) To provide adequate calories
3) To enhance the excretion of toxic metabolites
4) To institute co-factor therapy for specific disease and also empirically if diagnosis not established.
5) Supportive care - treatment of seizures (avoid sodium valproate – may increase ammonia levels), ensure euglycemia and normothermia, maintain fluid, electrolyte and acid-base balance, and appropriate treatment of infections and mechanical ventilation, if required.

## Management of hyperammonemia[7,8]

1) Discontinue all feeds. Provide adequate calories by intravenous glucose and lipids. Maintain glucose infusion rate of 8-10 mg/kg/min. Start intravenous lipid at 0.5 g/kg/day (increase up to 3 g/kg/day). After stabilization, gradually add protein at 0.25 g/kg/day and increase till 1.5 g/kg/day.
2) Dialysis is the only means for rapid removal of ammonia, and hemodialysis is more effective and faster than peritoneal dialysis; however, peritoneal dialysis is more widely available and feasible in most units. Exchange transfusion is not useful.
3) Alternative pathways for nitrogen excretion:
   - Sodium benzoate (IV or oral): loading dose 250 mg/kg followed by 250 to 400 mg/kg/day in 4 divided doses (intravenous preparation is not available in India).
   - Sodium phenylbutyrate (not available in India): loading dose 250 mg/kg followed by 250 to 500 mg/kg/day
   - L-arginine (oral or IV): 300 mg/kg/day (intravenous preparation not available in India)
   - L-carnitine (oral or IV): 200 mg/kg/day
4) Supportive care: treatment of sepsis, seizures, ventilation. Avoid sodium valproate.

## Acute management of newborn with suspected organic acidemia[9]

1) Keep nil per oral; provide intravenous glucose infusion
2) Supportive care: hydration, treatment of sepsis, seizures, ventilation
3) Carnitine: 100 mg/kg/day IV or oral
4) Treat acidosis: Sodium bicarbonate 0.35 to 0.5 mEq/kg/hr (max 1 to 2 mEq/kg/hr)
5) Biotin 10 mg/day orally
6) Vitamin B 12 (Inj hydroxycobalamine) 1000 µg/day I/M (useful in B 12 responsive forms of methylmalonic acidemias)
7) Thiamine 300 mg/day (useful in thiamine-responsive variants of MSUD).
8) If hyperammonemia is present, treat as explained above

## Management of congenital lactic acidosis

1) Supportive care: hydration, treatment of sepsis, seizures, ventilation; avoid sodium valproate
2) Treat acidosis: sodium bicarbonate 0.35 to 0.5 mEq/kg/hr (max 1 to 2 mEq/kg/hr)
3) Thiamine: up to 300 mg/day in 4 divided doses
4) Riboflavin: 100 mg/day in 4 divided doses
5) Add co-enzyme Q: 5 to 15 mg/kg/day
6) L-carnitine: 50 to 100 mg/kg orally

## Treatment of newborn with refractory seizures with no obvious etiology (suspected metabolic etiology)[10]

1) If patient persists to have seizures despite 2 or 3 antiepileptic drugs in adequate doses, consider trial of pyridoxine 100 mg intravenously. If intravenous preparation not available, oral pyridoxine can be given (30 mg/kg/day).
2) If seizures persist despite pyridoxine, give trial of biotin 10 mg/day and folinic acid 15 mg/day (folinic acid responsive seizures). A trial of pyridoxal phosphate (15-30 mg/kg/day) should also be done.
3) Rule out glucose transporter defect: measure CSF and blood glucose. In glucose transporter defect, CSF glucose level is equal to or less than one-third of the blood glucose level. This disorder responds to the ketogenic diet.

## Management of asymptomatic newborn with a history of sibling death with suspected IEM

1. Baby should be kept under observation
2. One should initiate breast feeding to keep protein intake @0.25 g/kg/d and then gradually increase it to 0.5g/kg/d
3. After about 24-48 hours of initiation of feeding, basic metabolic screening including TMS should be performed.
4. Urine for GCMS should be collected and stored for further analysis depending upon the reports
5. If metabolic screen negative, then establish full feeds over a period of 2-3 days
6. The infant will need careful observation and follow-up for the first few months, as IEM may present in different age groups in members of the same family.

## Long term treatment of IEM

The following modalities are available:

*1)* Dietary treatment: This is the mainstay of treatment in phenylketonuria, maple syrup urine disease, homocystinuria, galactosemia, and glycogen storage disease type I & III. Special diets for PKU and MSUD are commercially available in the West, some of which can also be imported. These special diets are, however, very expensive, and cannot be afforded by most Indian patients. Based on the amino acid content of some common food products available in India, dietary exchanges are calculated and a low phenylalanine diet for PKU and diet low in branched chain amino acids for MSUD are being used in our center. As these are now being manufactured in India and are available at a lower cost, early and appropriate use of special diets in consultation with metabolic physician and dietician is helpful in improving the long-term outcome. Some disorders like urea cycle disorders and organic acidurias require dietary modification (protein restriction) in addition to other modalities.[11]

2) *Enzyme replacement therapy (ERT):*ERT is now commercially available for some lysosomal storage disorders.[12] However, these disorders do not manifest in the newborn period, an exception being Pompe's disease (Glycogen storage

disorder Type II)which may present in the newborn period and for which ERT though very costly is now available.

3) *Cofactor replacement therapy:* The catalytic properties of many enzymes depend on the participation of non-protein prosthetic groups, such as vitamins and minerals, as obligatory cofactors. The following co-factors may be beneficial in certain IEM:[13]
   - Thiamine: Mitochondrial disorders, thiamine responsive variants of MSUD, PDH deficiency & complex I deficiency
   - Riboflavin: Glutaric aciduria Type I, Type II, mild variants of ETF, ETF-DH, complex I deficiency
   - Pyridoxine: 50% of cases of homocystinuria due to cystathionine â-synthetase deficiency, pyridoxine dependency with seizures, xanthurenic aciduria, primary hyperoxaluria type I, hyperornithemia with gyrate atrophy
   - Cobalamin: Methylmalonic academia (*cblA, cblB),* homocystinuria and methylmalonic academia (*cblC, cblD, cblF)*
   - Folinic acid: Hereditary orotic aciduria, methionine synthase deficiency, cerebral folate transporter deficiency, hereditary folate malabsorption, Kearns-Sayre syndrome
   - Biotin: Biotinidase deficiency and holocarboxylase synthetase deficiency

Table 30.3 enlists a few commercially available preparations of common drugs used for managing IEM:

## Prevention

1) **Genetic counselling and prenatal diagnosis**: Most of the IEMs are single gene defects, inherited in an autosomal recessive manner, with a 25% recurrence risk. Therefore, when the diagnosis is known and confirmed by DNA analysis in the index case, prenatal diagnosis can be offered, wherever available for the subsequent pregnancies. The samples required are chorionic villus tissue or amniotic fluid. Modalities available are:[14]

- Substrate or metabolite detection: useful in phenylketonuria, peroxisomal defects
- Enzyme assay: useful in lysosomal storage disorders like Niemann-Pick disease, Gaucher disease
- DNA based (molecular) diagnosis: Detection of mutation in proband/ carrier parents is a prerequisite. DNA based diagnosis is the gold standard as enzyme assays and metabolite detection need an expert lab and may have borderline fetal values that may pose a diagnostic dilemma.

2) **Neonatal screening:** Tandem mass spectrometry is used for neonatal screening for IEM. Disorders which can be detected by TMS include aminoacidopathies (phenylketonuria, MSUD, homocystinuria, citrullinemia, argininosuccinic aciduria, hepatorenal tyrosinemia), fatty acid oxidation defects, organic acidemias (glutaric aciduria, propionic acidemia, methylmalonic acidemia, isovaleric acidemia). The cost of this procedure is high. The test has low specificity (implying lot of false-positives); and there are difficulties in interpretation of abnormal test results in apparently healthy infants.

**Table 30.3: Commercially available preparations of common drugs used for IEM**

| Co-factor | Trade name, formulation |
|---|---|
| Pyridoxine | Tab *Benadon* (40 mg) (Nicholas Piramal), Inj *Vitneurin* (1 ampoule contains 50 mg pyridoxine), Tab *B-long* (100 mg) |
| Pyridoxal phosphate | Tab *Tetrofol plus* (contains 25 mg pyridoxal phosphate, Elder) |
| Hydroxycobalamin (vitamin B12) | Inj Hydrox-12 (1000 mcg/mL; Neon Labs) |
| Thiamine | Tab *Benalgis* (75 mg; Franco India) |
| Riboflavin | Tab *Riboflavin* (5 mg; Shreya) |
| Biotin | Tab *Essvit* (5 mg, 10 mg; Ecopharma) |
| Carnitine | Syrup *L-Carnitor* (5 ml=500 mg), Tab *L-Carnitor* (500 mg), Inj *carnitor* (1 g/5 ml; Elder) |
| Folinic acid | Tab *Leukorin* (15 mg; Samrath) |
| Sodium benzoate | Sachet (20 g; Hesh Co.) |
| Arginine | ARG-9 Sachet (3g; Noveau Medicament) |
| Coenzyme Q | Tab *CoQ* (30 mg, 50 mg; Universal Medicare) |

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