Treatment and monitoring of inborn errors of metabolism

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It is recommended that you complete training module 1 in this series, to learn about the effects of a block in a metabolic pathway before attempting this module.
Current Treatment Strategies

There are a number of strategies available to treat inherited metabolic diseases and these are often related to whether the clinical symptoms are caused by accumulation or depletion.

1 Reducing Substrate Accumulation by manipulation of diet, chelation or inhibition of biosynthesis.
2 Reducing toxic metabolites by decreasing production, facilitating transport or promoting excretion
3 Enhancing residual activity by supraphysiologival doses of cofactors and their precursors
4 Replacement of the defective enzyme by the administration of exogenous enzyme (Enzyme Replacement Therapy, ERT) or by transplantation.
5 Supplementation of a depleted metabolite by diet or by medication.
**Treatemnt Strategies**

**Accumulation of upstream metabolites may result in toxicity**

Reduce substrate accumulation:
- Dietary restriction
- Chelation therapy
- SRT

**Reduction in important metabolite e.g. glucose**

Supplement metabolites:
- Dietary replacement
- Medication

**Reduce toxic metabolites:**
- Decrease production
- Facilitate transport
- Increase excretion

**Replace deficient enzyme**
- Transplant, ERT

**Enhance residual activity:**
- Co-factor/vitamin therapy
Reduce substrate accumulation

There are three main approaches to reducing substrate levels:

1. Dietary and nutritional treatment
   (This section also discusses supplementing metabolites as this are often used in conjunction with dietary substrate restriction)

2. Chelation therapy

3. Substrate reduction therapy (SRT)
1. Dietary & Nutritional Treatment

This is an important component in the management of many inborn errors of intermediary metabolism and is used in conjunction with other medical treatments. The approach is two-fold:

a) acute/emergency management
b) long term management

All treatment requires careful monitoring to ensure no nutritional deficiency develops and that adequate growth and development is maintained.
Acute Emergency Management

The initial action is to stop or reduce intake of the potential toxic compound
- e.g. protein in urea cycle disorders

Then to promote anabolism by:

Instituting an oral carbohydrate emergency regime if the patient is able to tolerate it
To begin IV dextrose at 8-10mg/kg/min with appropriate electrolytes
To use insulin if the blood glucose is >10mmol/l

- See guidelines at www.bimdg.org.uk
Below are some examples of dietary management for specific disorders and groups of disorders.
Phenylketonuria (PKU)

PKU has a 1:10 000 incidence in the UK and is part of the UK newborn screening programme. Patients are unable to metabolise the essential amino acid phenylalanine (Phe) due to a defect in phenylalanine hydroxylase or its cofactors. Phenylalanine at high levels is neurotoxic and results in severe and progressive neurological disease.
Principles of dietary management for inborn errors of amino acid metabolism (1)

Example: Phenylketonuria (phenylalanine hydroxylase deficiency)

- Prevent the excessive accumulation of phenylalanine by strict limitation of natural protein intake in combination with use of a phenylalanine – free protein substitute
- Ensure adequate growth & development and optimal nutritional status
Principles of dietary management for IEM of amino acid metabolism (2)

Example: Phenylketonuria (phenylalanine hydroxylase deficiency)

Achieved by:

1. Restricting the Phe intake to approx 25% of the normal intake to fall within a desirable range in blood. In practice this requires a diet free of all high protein foods e.g. meat, eggs, fish.
2. Daily provision of Phe to meet the requirements from measured quantities of protein containing foods often called ‘exchanges’.
3. Provision of a Phe free protein substitute to meet the nitrogen and tyrosine requirements.
4. Maintenance of a normal energy intake by use of foods low in Phe including specially manufactured low protein foods.
5. Provision and monitoring of all vitamins and minerals to meet dietary requirements.
Principles of dietary management for inborn errors of long chain fatty acid oxidation

Example: Long chain acyl-CoA dehydrogenase deficiency

- Avoidance of fasting
- Inhibit fatty acid oxidation to avoid production of toxic metabolites by provision of frequent high carbohydrate; low fat feeds (2-3 hrly feeds during the day and continuous overnight feeds)
- Medium chain triglyceride supplementation using medium chain fatty acids to bypass the block in catabolism and supply energy
- A Carbohydrate emergency regime for periods of illness
- Supplement and monitor essential fatty acids and fat soluble vitamins which may be low in this condition due to the low fat diet.
2. Chelation Therapy: Cystinuria

- **Cystinuria** is a defect in an amino acid transporter in the intestines and renal tubules, resulting in renal loss of cystine & dibasic amino acids. Cystine is very insoluble and crystallises forming renal stones when levels in the urine are high. Cystinuria may be treated by increasing fluid intake, alkalinization of the urine and dietary modification, however sometimes chelation therapy with D-penicillamine is also required.

- **D-Penicillamine** is a chelating agent that binds with cysteine giving a mixed disulfide which is 50 times more soluble than cystine, thereby reducing the chance that crystals/stones will develop. Long-term therapy may lead to vitamin B6 deficiency; thus, supplementation is often needed.

- **Monitoring/Complications:**
  Urinary cystine levels are monitored to enable dose titration.
  Some patients do not tolerate it very well as side effects are common.
  Regular monitoring of full blood count (including white cell differential) and urine protein are important to identify pancytopenia and nephrotic syndrome respectively. Newer chelating agents such as alpha-mercaptopropionylglycine may be more appropriate in some patients.
3. Substrate Reduction Therapy (SRT)

Substrate reduction therapy is sometimes used to treat various lysosomal storage disorders. The aim is to inhibit the biosynthesis of the substrate, however great care has to be taken to ensure that there is sufficient biosynthesis for normal cell and organ development.

For example: Miglustat (also known as Zavesca)

**Indications:** This is used to treat mild to moderate type 1 Gaucher disease in patients in whom enzyme replacement therapy is not a therapeutic option (due to allergy, hypersensitivity, or poor venous access), it is also sometimes used to treat Niemann-Pick type C.

**Effects:** It has been shown to reduce spleen and liver volume and increase haemoglobin and platelet counts.

**Cautions:** It is important to monitor cognitive and neurological function in addition to growth and platelet count in Niemann-Pick type C.
Gaucher Disease - Enzyme deficiency

Gaucher disease is a lysosomal storage disorder resulting from the deficiency of Beta-glucocerebrosidase. Glucocerebroside accumulates in cells of the macrophage-monocyte system. Accumulation in the bone marrow, liver, spleen, lungs, and other organs contributes to pancytopenia, massive hepatosplenomegaly, and, at times, diffuse infiltrative pulmonary disease. See Training Module 5
Miglustat - SRT in Gaucher Disease

Miglustat (also known as Zavesca) is given orally, and inhibits the enzyme glucosylceramide synthase, which reduces the rate of synthesis of glucocerebroside and thereby reduces its accumulation.
Reduce toxic metabolites

Symptoms of many metabolic disorders are caused by the accumulation of toxic compounds. Treatment is aimed at reducing these by decreasing production, facilitating transport or promoting excretion.
Tyrosinaemia type I (Fumarylacetoacetase deficiency) is an example of an inherited metabolic disorder which is commonly treated by decreasing the production of toxic metabolites.
Tyrosine

Phenylalanine

↑Phenylalanine
↓

↑Tyrosine
↓

↑4-OH phenylpyruvate

Homogentisate

↓Maleylacetoacetate
↓Fumarylacetoacetate

NITBC inhibits this enzyme

Fumarylacetoacetase

Deficient in Tyrosinaemia type I

Fumarate & Acetoacetate

• NTBC (also known as nitisinone) – inhibits 4-OH-phenylpyruvate dioxygenase, decreasing production of succinylacetoacetate and succinyl acetone.

• Patients also need a Phenylalanine and Tyrosine restricted diet because NTBC further increases Tyrosine levels, which can crystallise in the eyes, causing damage.

• Historically, liver transplantation was commonly required to treat Tyrosinaemia type I before NTBC became available and revolutionised treatment.
Facilitate Transport of toxic metabolites

- Cystinosis is an inherited lysosomal transport defect (impaired transport of cystine out of lysosomes); in the nephropathic form, accumulation of cystine and the formation of crystals damage various organs, especially the kidneys.

- Cysteamine (also known as Cystagon) is an oral medication which converts cystine into cysteine and cysteine-cysteamine mixed disulfide, both of which are able to exit the lysosome in patients with cystinosis. This in turn reduces cystine accumulation and crystal formation.

- Leucocyte cystine measurements, taken 5 to 6 hours after dose administration, are recommended to monitor new patients once the maintenance dose is achieved.

NB: Cystine is a dimeric amino acid formed by the oxidation of two cysteine residues which covalently link (disulfide bond).
Many inherited metabolic disorders can lead to hyperammonaemia, including urea cycle defects and organic acidaemias. Ammonia is extremely neurotoxic, and both the level and time of exposure correlates inversely with outcome. It is therefore vital to reduce high levels of ammonia rapidly.

Sodium benzoate and phenylbutyrate are used to increase excretion of ammonia by providing an alternative pathway for nitrogen disposal, which is independent of the urea cycle.

Two moles of nitrogen are removed per mole of phenylbutyrate when it conjugates with glutamine, and one mole of nitrogen is removed per mole of benzoate when it conjugates with glycine.
Promoting excretion of toxic metabolites (2)

HEPATIC NITROGEN POOL

\[ \text{NH}_3 \]

\[ \text{UREA CYCLE} \]

\[ \text{Urea} \rightarrow \text{Urine} \]
Promoting excretion of toxic metabolites (3)

- HEPATIC NITROGEN POOL
  - Glutamine
    - Phenylbutyrate
    - Phenylacetate
  - Glycine
    - Benzoate
    - Hippurate
  - NH$_3$
    - UREA CYCLE
    - Urea
      - Urine
Enhance residual activity

A cofactor is an additional substance that must be associated with a particular enzyme in order for it to function. In situations where an enzyme is present but with reduced activity (rather than being totally deficient or non-functional), the residual activity may be stimulated by increasing the co-factor concentration. This may be achieved either by giving high concentrations of the cofactor itself or its precursor (usually a vitamin). Alternatively it may be possible to use cofactors/vitamins to stimulate an alternative enzyme in a related catabolic or biosynthetic pathway.
Vitamin and cofactor responsive disorders

- Some conditions may be successfully treated by augmentation of residual enzyme activity through provision of its cofactor which is often a vitamin
- Vitamin supplementation is often used alongside other dietary or medical interventions

Examples of Vitamin B12 responsive disorders:

Methylmalonic acidaemia

Examples of Vitamin B6 (pyridoxine) responsive disorders:

- Homocystinuria (cystathionine beta-synthase deficiency)
- Gyrate atrophy of the choroid and retina (ornithine keto acid transaminase deficiency)
- Primary hyperoxaluria Type I (alanine:glyoxalate transaminase deficiency)
Other vitamin responsive disorders

In some cases an accumulating metabolite may deplete the body of an important cofactor. As example of this is the inactivation of pyridoxal phosphate (active form of Vitamin B6) by alpha-amino adipate semialdehyde (α-AASA) accumulating in Pyridoxine Dependent Epilepsy (OMIM 266100) due to antiquitin deficiency.

Infants with this condition classically have a severe seizure disorder unresponsive to conventional anticonvulsant medications which improves dramatically with pyridoxine treatment.

Diagnosis is made by measurement of urinary α-AASA and mutation analysis.
Pyridoxine dependent epilepsy due to antiquitin deficiency

Accumulation of P6C leads to inactivation of pyridoxal phosphate the active cofactor of Vitamin B6
Biotinidase deficiency

- Biotin is a coenzyme of four carboxylase enzymes involved in gluconeogenesis, fatty acid synthesis and amino acid catabolism
- Biotinidase is an enzyme that recycles endogenous biotin
- In biotinidase deficiency, biotin depletion results from the inability to recycle endogenous biotin and to use free biotin from the diet
- The clinical picture is variable and may result in life-threatening metabolic derangement including metabolic acidosis, seizures, hypotonia with skin and hair abnormalities
- If diagnosis and treatment are prompt then an excellent response can be expected with regular pharmacological doses of Biotin
Replacing the deficient enzyme

Current approaches to replacing the defective enzyme include transplantation and enzyme replacement therapy.
Transplantation: A1AT deficiency

- Alpha 1-antitrypsin (A1AT) deficiency alters the configuration of A1AT and prevents its release from hepatocytes. As a result, serum levels of alpha1-antitrypsin are low (especially in Pi ZZ homozygotes). Patients can suffer from lung and/or liver disease as a result and may present at any age.
- Liver disease in babies with this disorder may improve spontaneously or may progress to cirrhotic liver failure, either in childhood or as an adult.
- It is believed to be caused by an acute response to polymerisation of Z-type protein within hepatocytes, causing damage and via fibrosis, a cirrhotic response - which carries a poor prognosis.
- Liver transplantation in indicated in cases of advanced liver disease, and can provide a cure because the alpha-1-antitrypsin protein produced is that of the donor (M-phenotype), which can be released from hepatocytes into blood in the normal way.
- A1AT deficiency is the main reason for liver transplantation in children.

<table>
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<tr>
<th>PiZZ liver</th>
<th>Donor liver</th>
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<tr>
<td>Abnormal A1AT unable to leave hepatocytes causing liver disease</td>
<td>Normal A1AT leaves hepatocytes and acts to protect lungs</td>
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There is always the risk of graft v host disease.
Enzyme replacement therapy (ERT)

- A Recombinant enzyme is given via repeated intravenous infusions to replace the deficient enzyme. They are a relatively new and expensive group of treatments, and are now available for a growing number of lysosomal storage disorders.
  - Gaucher disease (ERT: imiglucerase),
  - Fabry disease (ERT: agalsidase beta; agalsidase alpha)
  - MPS I (ERT: laronidase)
  - MPS II (ERT: idursulfase)
  - MPS VI (ERT: galsulfase)
  - Pompe disease (ERT: alglucosidase alfa)

- ERT is currently given via repeated intravenous infusions, this allows the enzyme to circulate in the blood and enter various tissues reducing many symptoms, however, it cannot cross the blood-brain barrier, which means its effects on neurological symptoms are limited.

- Clinical trials are currently taking place for MPS IV (Morquio) and MLD, with ongoing research into intrathecal preparations for MPS I and II, and chaperones to allow the recombinant enzyme to be targeted to particular tissues/organisms.

There can be problems in getting sufficient enzyme into some tissues.
ERT: eligibility

There are strict eligibility criteria regarding the use of ERT, including:

- A definite diagnosis is required and the patient must meet certain biochemical and clinical indicators, which differ internationally according to disease and protocol
- Have no medical comorbidity or disease complications that are likely to compromise the effects of treatment
- Treatment is advised as early in the disease course as possible, and in some cases only early onset disease is funded

- Guidelines on eligibility and baseline investigations can be found on the NCG website:
Gaucher Disease - Enzyme deficiency

Gaucher disease is a lysosomal storage disorder resulting from the deficiency of Beta-glucocerebrosidase. Glucocerebroside accumulates in cells of the macrophage-monocyte system.

Accumulation in the bone marrow, liver, spleen, lungs, and other organs contributes to pancytopenia, massive hepatosplenomegaly, and, at times, diffuse infiltrative pulmonary disease. See Training Module 5
**Imiglucerase – ERT in Gaucher Disease**

- **Gangliosides, Globosides**
  - Glucocerebroside
    - **Imiglucerase**
      - Enzyme Replacement Therapy
    - Ceramide glycosyl transferase
    - Ceramide
      - Galactosylcerabroside, sulphatides, sphingosine, sphingomyelin

- Also known as Cerezyme
- A recombinant analog of beta-glucocerebrosidase produced using mammalian cell culture
- Given via repeated intravenous infusions, it breaks down glucocerebroside (to glucose and ceramide) within the lysosomes of phagocytic cells in the reticuloendothelial system, thereby replacing the deficient enzyme.
Imiglucerase – ERT in Gaucher Disease

- **Indications:** Gaucher disease has an extremely variable clinical course with little correlation between genotype and disease severity. It is therefore only usually indicated in patients with type I or III Gaucher disease who exhibit related clinical signs and symptoms. Presymptomatic use is controversial.

- **Effects:** In most cases, ERT is highly effective in reversing anaemia and thrombocytopenia and reducing the spleen and liver size. However, skeletal disease is slow to respond, and pulmonary symptoms may not improve.

- **Monitoring:** Clinical examination, Imaging, U&E, LFT, ACE, Chitotriosidase, Acid phosphatase, haematology, imiglucerase antibodies

- **Complications:** Approximately 10-15% of patients with Gaucher disease treated with Imiglucerase develop antibodies to the enzyme protein, a small percentage of these develop severe allergic reactions.
Supplement metabolites

- Dietary replacement
- Prenatal Steroid therapy
Principles of dietary management for inborn errors of carbohydrate metabolism associated with hypoglycaemia

*Example: glycogen storage disease Type I, glucose 6 phosphatase deficiency*

- Avoidance of fasting
- Provision of glucose; method will vary according to age of the child/adult
  - Frequent (2-3 hourly) nasogastric tube feeding
  - Regular bolus of slow release carbohydrate e.g. cornstarch
  - Continuous overnight carbohydrate feed by nasogastric tube or gastrostomy
- High carbohydrate emergency regime during periods of illness
- Specific monitoring: growth, bone density, liver size, urate, lipids, 24 hour glucose insulin & lactate profile
Prenatal steroids: CAH

In 21-hydroxylase deficiency (classical congenital adrenal hyperplasia) patients lack the ability to synthesise cortisol. This leads to excessive androgen production, which causes virilisation of females in utero.

- Treatment with dexamethasone suppresses foetal adrenal androgen production, which partially or completely prevents virilisation.
- Unfortunately, it is contraindicated if the mother has hyperglycaemia or hypertension.

**Use:** where the foetus is known to be at risk of CAH, and DNA mutations in the family are known (allowing a prenatal genetic diagnosis to be made).
- Dexamethasone is given to the mother as it can cross the placenta freely.
- Treatment needs to be initiated early (i.e. by 7 weeks) to be successful.
- It is continued throughout pregnancy unless the foetus is shown to be male or unaffected through genetic studies of CVS tissue (10-12 weeks) or amniotic fluid (16 weeks), in which case steroid treatment is unnecessary and is stopped.

**Monitoring:** maternal plasma/urine oestriols can be measured to assess compliance and adequacy of suppression

**Post-Partum:** The baby is treated life-long with glucocorticoids and in some cases mineralocorticoids. 17-hydroxyprogesterone levels are monitored to assess adequacy.
Prenatal steroids: CAH

Treatment with glucocorticoids effectively replaces cortisol, reducing pituitary release of ACTH, thereby reducing stimulation of the adrenal glands, reducing androgen production.
## Self-Assessment Questions

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<th>False</th>
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<td>1. PKU is treated with a Phenylalanine-free diet</td>
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<td>2. NTBC can be used to reduce production of succinyl acetone in tyrosinaemia type 1</td>
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<td>3. Methylmalonic acidemia can be treated with vitamin B6 (pyridoxine)</td>
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<td>4. All patients with lysosomal storage disorders are eligible for enzyme replacement therapy (ERT)</td>
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<td>5. Prenatal treatment with steroids can reduce virilism in female babies with classical CAH</td>
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<td>6. It is important to treat hyperammonaemia quickly</td>
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## Self-Assessment Answers

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