

## *Urea cycle disorders*

# **A guide for patients, parents and families**

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## Introduction

You or your child have/had been diagnosed with a urea cycle disorder.

Initially any information regarding these types of condition is hard to understand, especially at a time when you are naturally very worried and suddenly provided with lots of medical information.

By describing this condition in booklet format, you will be able to read it at your leisure, and then write down any important questions that you may want to ask your specialist doctor, nurse or dietitian.

We're international, and we are here to help. For more information, resources or family support, contact:

National Urea Cycle Disorders Foundation

75 S. Grand Ave. | Pasadena, California 91105 | Phone: 626 578-0833

Visit us on the web at [www.nucdf.org](http://www.nucdf.org) or email us at [CureUCD@nucdf.org](mailto:CureUCD@nucdf.org)

Acknowledgements: Thank you to EIMD for sharing this booklet.

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## Metabolic function

To be a fit healthy individual, we have to feed our body regularly with food to provide energy and repair tissues.

The foods that we eat are broken down into small packages and either used for growth and repair, stored to be available for periods of starvation, or disposed of as waste. Although, this explanation describes the basic process, it is of course much more complex.

## How the body deals with protein

Foods containing protein are eggs, milk, fish, meat, cheese bread etc. During digestion, protein is broken down into smaller molecules or “building blocks” to be transported in the blood and used for growth and tissue repair.

What started as a healthy steak or a glass of milk will have now been broken down into 20 individual “building blocks” known as amino acids. These amino acids travel in the blood stream and are supplied to the cells

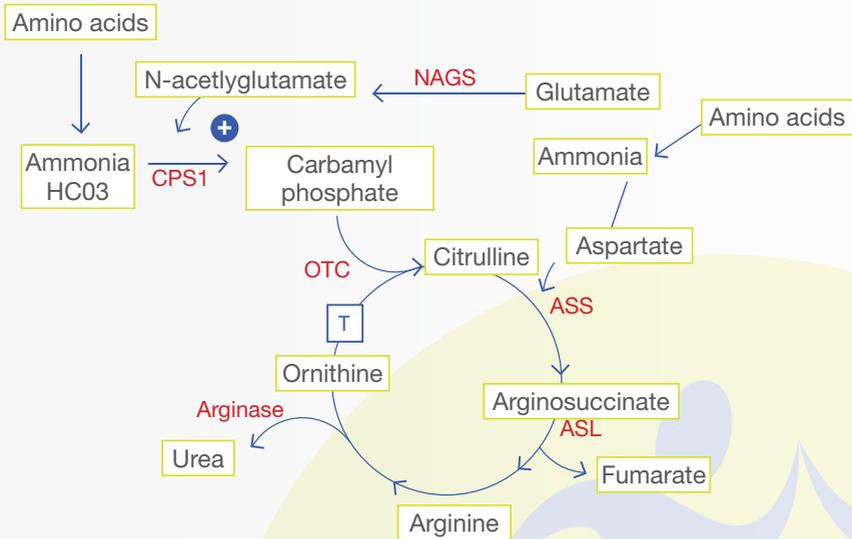
where they are needed. Generally speaking, we consume much more protein than the body needs. Therefore once we have finished with using what is needed, the excess is broken down by enzymes into smaller products, including ammonia and organic acids. The body is unable to tolerate large amounts of ammonia and organic acids; therefore a process in the liver converts these into harmless forms that can then be disposed of.



## The urea cycle

Having explained the basic function of protein metabolism, it is helpful to understand a little about the urea cycle. As previously described, the body needs a way to dispose of the ammonia. This is carried out in the liver, by a continuous process called 'the urea cycle'. As the cycle turns the toxic ammonia is changed, step by step, into urea, which is later excreted.

The urea cycle is controlled by a series of enzymes. In urea cycle disorders one of these six enzymes is not working correctly, as shown.



The urea cycle defects are:

- **NAGS** – N-acetylglutamate synthase deficiency
- **CPS1** – Carbamoyl Phosphate synthase deficiency
- **OTC** – Ornithine transcarbamylase deficiency
- **ASS** – Citrillinaemia or argininosuccinate synthase deficiency
- **ALL** – Argininosuccinic aciduria or Argininosuccinate lyase deficiency
- **Arginase** – Arginase deficiency

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## What are the symptoms?

Symptoms vary from individual to individual, and may present at different ages.

During the first week of life a **baby** can become very unwell as it can no longer rely on the mother's placenta for feeding. Once the baby is weaned and feeds are established the protein intake may exceed the capacity of the urea cycle. Babies in this situation, usually present with drowsiness, rapid breathing and vomiting. It is likely that a spell in hospital will be necessary to lower the level of ammonia in the blood and to aid the baby with breathing.



Older **children** with a urea cycle disorder, may become very ill, having had a healthy childhood with no sickness prior to this deterioration. This so-called “decompensation” may be brought about by an illness such as a cold. Sometimes a sudden increase in the amount of protein eaten eg. whilst on holiday or following a celebration, may also precipitate these types of symptoms. When the doctor takes a medical history it is common for parents to comment on faddy/fussy eating habits without being aware that their child is self-selecting a diet low in protein. It is usually the onset of acute illness and coma along with the clue in dietary history that will lead to the investigations required to diagnose a urea cycle disorder.

There is also a group of older patients, often **teenagers**, which present with chronic episodes of vomiting and drowsiness. They may require a short spell in hospital where they are given extra fluids, often through a drip directly into the vein. It is usually only after more than one admission, that a doctor is likely to become concerned and may diagnose a urea cycle disorder after further investigation.



## Treatment

### Aims of treatment

The main aim of treatment is to keep the level of ammonia in the blood down at safe levels. Several things may cause the blood ammonia to rise, these include infections or sudden increase in the amount of protein eaten. During periods of illness and infection, the body's response is to break down body stores to supply energy. As a result of this, protein is also broken down and released back into the blood stream, which in turn leads to the ammonia level going up.



### Emergency treatment during acute illnesses

If your child is feeling unwell, they should be treated with an emergency regime. An emergency regimen is necessary for every patient who has a urea cycle disorder, including those who may be mildly affected. This treatment varies from one individual to the next.

An emergency regimen is given as a high glucose energy drink e.g. Maxijul. It must be taken if your child is unwell and is unable to tolerate normal diet. It is a harmless solution, therefore, if you have commenced your child on the emergency regimen and recovery is immediate it will not have caused any side effects. By consuming these additional calories the body is prevented from breaking down its own tissues to release energy and protein as discussed above. Delay in starting can be dangerous. If you are unsure in any way, you should liaise with your local metabolic team.

The emergency regimen is prescribed to suit your child as an individual, it is regularly revised and the strength of solution increased with the child's age and weight. It is important that the instructions are followed rigidly during illness and the child is able to tolerate the right strength glucose solution given at regular intervals throughout the day and night.

Your dietitian will advise you on the emergency regimen and provide some written instructions for you.

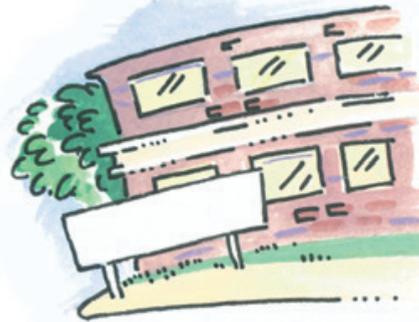


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If whilst on the emergency regimen, your child continues to vomit and it is apparent that he/she is not recovering, you must either:

- contact your local doctor and arrange for hospital admission,
- or go to casualty
- or telephone your paediatric unit (if you have an access facility that allows arranged admission).

Whilst in hospital, it will be necessary to take blood tests, to ensure that the blood chemistry is becoming normal again. One of the blood tests can measure ammonia. During phases of illness, it can easily become raised; therefore it is necessary to check it regularly.



If during hospital admission, your child is not responding well to the glucose drip, further treatments will be needed. If ammonia is allowed to rise to very high levels, drowsiness, irritability and confusion occurs, warning us that the brain is being affected. In order to prevent this occurring it may become necessary to treat with medicines through the vein. Your child may already take these medications by mouth. The medications used are called sodium phenylbutyrate, sodium benzoate and N-carbamylglutamate. (Their action is described later on in the booklet) Arginine, another medication is used to help the urea cycle work harder in removing the ammonia. If after all these medications have been introduced, your child continues to remain very sick with high ammonia in the blood stream, it will be necessary to transfer to intensive care, where a dialysis machine will be set up for the child. Dialysis works by filtering the patient's own blood through a machine removing the harmful ammonia and returning the filtered blood to the body.



## Long term treatment

### Diet

Patients that are diagnosed with a urea cycle disorder often have their dietary protein restricted, or they are advised to be a little cautious with the amount of protein they eat.

Restriction of protein is important as it reduces the workload on the urea cycle. The aim is to provide the body with sufficient protein to allow for growth and repair of tissue but at the same time reducing quantities to a level your child can tolerate. There is a tendency for the amount of protein tolerated to decrease with time because as you get older the growth rate slows.



Your dietitian will teach you how to measure protein. Using this you will be able to control and measure the amount of protein you are allowed in the diet. Measuring foods will only relate to protein-containing foods, all other foods can be eaten freely and will not need weighing.

In many instances food aversion becomes so severe that it is difficult to provide sufficient calories by mouth. In this instance use of a tube for feeding becomes essential.

Tube feeds can be given by passing a very fine tube down the nose and into the stomach. These are referred to as naso-gastric tubes. Naso-gastric tubes are not recommended for long term use. If it becomes obvious that long term tube feeding will be required, insertion of a gastrostomy tube may become necessary. A gastrostomy tube is inserted directly into the stomach and is performed under anaesthetic as a minor surgical procedure. A small plastic disc that sits just under the skin secures the gastrostomy tube. When the child is not connected to a feed, the tube is clamped and clothes are worn over the tube covering the site.

## **Liver transplantation**

Liver transplantation has been increasingly used in the management of urea cycle disorders when conventional therapies have proven difficult.

## Medication

Part of the long-term treatment to keep the ammonia levels down involves the use of a range of different medicines. The medicines are used in different combinations and are specific to the individual patient. Some patients are not on any medicines.

**ARGININE:** this is an essential amino acid located in the urea cycle. Arginine is not used in arginase deficiency. Taking extra arginine as a medication will help the urea cycle work more efficiently.

**CARGLUMIC ACID:** is also known as N-CARBAMYLGLUTAMATE: this is a medicine of choice in N-acetylglutamate deficiency (NAGS deficiency) to re-activate the urea cycle. It may also be used when a urea cycle disorder is suspected as part of the investigation process or therapy trial.

**CITRULLINE:** it can be substituted for arginine in some patients. It is not used in citrullinaemia.

**SODIUM BENZOATE:** this medicine also reduces the amount of ammonia, in a similar way to sodium phenylbutyrate.

**SODIUM PHENYLBUTYRATE:** this medicine is used to reduce the amount of ammonia in the blood.

*It is very important that you take all your medication as prescribed by your doctor.*

## How has my child got this condition?

Urea cycle disorders are usually genetic. This means that they are not brought about by anything that may have occurred during pregnancy. Genetic disorders are inherited and the pattern in which your child may have developed the condition will now be described.

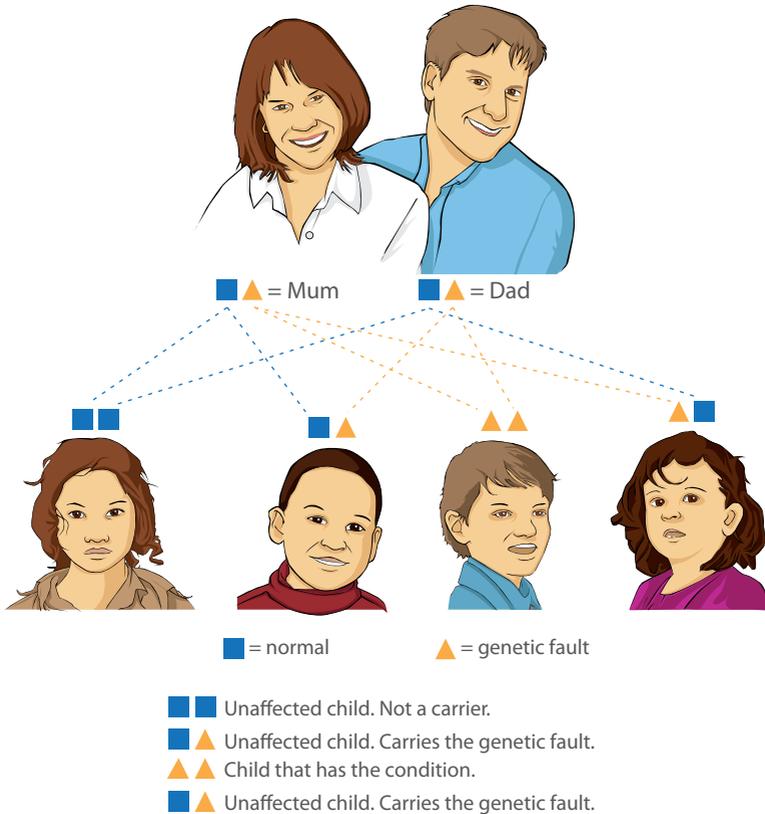
If the gene is inherited from both mum and dad it is described as autosomal recessive.

In the human body, every person carries approximately seven defects in their genetic information. If you and your partner both carry the same genetic fault, each time you get pregnant, there is a one in four chance that your baby will be born with a urea cycle disorder.



## How does this occur?

The diagram shows you how this happens.



When a child is conceived, there is no way of predicting which sperm and which egg will unite to make the baby. At conception one egg from mum and one sperm from dad is brought together to develop the foetus.

It is within the nucleus of each cell of the egg and the sperm that information called the DNA is stored on strands called chromosomes. It is this information that predicts the colour of the child's eyes, hair etc and will also carry any information that relates to a genetic disease.

## X – Linked disease

A person's gender or sex is determined by the so-called sex chromosomes. They exist in two types, X-chromosomes and Y-chromosomes. A female has 2 X-chromosomes and a male has 1 X and 1 Y.

One of the more common urea cycle disorders is called OTC, this stands for ornithine transcarbamoylase deficiency. It is inherited as an X linked disease. This means that this type of disorder is passed on from parents to baby with the X chromosome. If the baby is a female, because females have two X-chromosomes, the good X can balance out the problem with the faulty X. But because males only have one X chromosome, it can't be balanced by a normal X as in the female, and as a result in males, this disease tends to be more severe. Occasionally, a child may develop a urea cycle disorder that is not inherited. In such cases, the risk of any future children developing the disorder is extremely small. It is important with all urea cycle disorders, that a geneticist is involved, to establish whether or not the condition has evolved independently or has been inherited.

You will be offered the opportunity to meet with a geneticist to discuss your child's condition.



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## What does the future hold for my child?

As previously described, the severity of urea cycle diseases is very variable. In some cases, the condition is so mild that the specialist needs only to see the child on an annual basis. With this group of patients an annual check up allows the doctor to keep up to date with any changes that may be occurring as the patient gets older. With increasing age it may become necessary to reduce protein intake and start medication.

For those children that are more severely affected, it is important to be seen and assessed regularly by a metabolic team. It is likely that the more severely affected child will need the support of the local community service in order to have access to specialist teams in addition to the metabolic doctor. This will include special needs social workers, speech therapy, physiotherapy, community paediatricians, paediatric nurse etc.

Children that are severely affected may have learning difficulties and may therefore need assessing to ensure the education he/she receives is suitable to the child's learning ability.

## Pregnancy

Whilst urea cycle disorders are regarded as fairly serious diseases, treatments are constantly being refined, and ongoing research means that the long term outcome for patients is improving. Of course this will always depend on the type and severity of the urea cycle disorder which the individual person has.

Having a baby as a fit and healthy individual imposes a significant amount of stress and fatigue on the body. As a patient with a urea cycle disorder, the effect of a pregnancy will increase this stress level and can cause problems to both mother and child if not cared for appropriately.

It is advised that all females involved in sexual relationships be adequately protected with suitable contraception. Where possible all pregnancies should be planned and care provided pre-conceptually with your Specialist Consultant.

During your pregnancy your care will be shared between your specialist consultant and your local obstetric team. This ensures that throughout pregnancy both mother and baby are provided with the maximum support available. It is likely that you will be monitored more closely and some of the treatment, maybe the diet or medication, will be changed.



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## Travelling

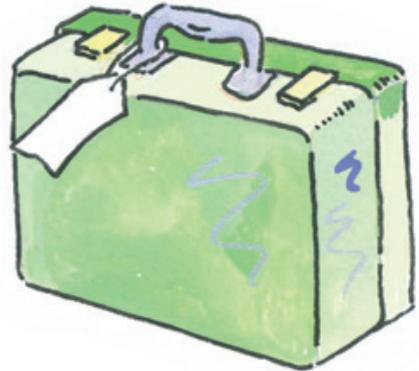


Travelling is so much part of everyday life and this should provide no barriers to the person with a urea cycle disorder. It is wise to take sensible precautions if planning an extended trip or if going abroad.

It might be sensible to just check that your destination has suitable medical facilities locally should you become ill whilst away.

It is absolutely necessary to continue with your diet and medication whilst away and to ensure that you have adequate supplies to last you for your trip.

You should carry some information regarding the nature of your illness this can be provided by your clinical team and there are some UCD emergency cards produced for this purpose which contain specific information about you condition and treatment. For longer periods abroad your medical team may be able to suggest a local doctor that could supervise your care.



## Glossary

**Acute:** sudden onset, severe

**Amino acids:** the building blocks of proteins

**Ammonia:** toxic by- product of the breakdown in protein in the body

**Chronic:** long term

**Decompensation:** a metabolic term describing onset of illness resulting in the body reverting to the breakdown of stored protein within the cells and tissue. Usually it is brought about by diarrhoea and vomiting or mild infection.

**Elimination:** the way in which the body gets rid of waste materials in urine or faeces

**Enzyme:** a chemical in the body that makes the chemical reactions proceed more quickly

**Gastrostomy:** a feeding tube which is placed directly through the stomach wall

**Intravenous:** into the blood vein

**Naso- gastric tube:** a feeding tube which goes via the nose into the stomach

**Orally:** by mouth

**Paediatrician:** a doctor who trains specifically in the care of children

**Urea:** ammonia is converted into urea it is less toxic and can be passed in the Urine